Inclusion Criteria

Patients were going to be eligible for participation in the study if they met all of the following inclusion criteria:

1. Were male or female patients 18 years of age or older
2. Were undergoing surgery through an abdominal incision of at least 3 cm, were expected to be hospitalized for at least 36 hours, and were expected to subsequently require at least 48 hours of oral opioid therapy. Laparoscopic surgeries were not permitted. Any surgical procedure considered for inclusion in this study that did not meet the above-mentioned criteria must have been approved by Endo's Medical Monitor prior to screening.
3. Were, in the opinion of the investigator, appropriate study candidates and would not be placed at additional risk secondary to enrollment in this study and/or upon receipt of the study medication.
4. Had received short-acting analgesia post-operatively, including the following:
   - Parenteral (PCA or non-PCA) analgesia: washout of at least 45 minutes, but within 12 hours of the last dose of parenteral medication, or
   - IM analgesia: washout of at least 4 hours, but within 12 hours of last dose.
5. Had an initial pain intensity score of at least 50 mm on a 100-mm VAS and a categorical pain rating of moderate or severe on a scale of none, mild, moderate, or severe.
6. If female, were practicing abstinence or using a medically acceptable form of contraception (e.g., intrauterine device, hormonal birth control, or double barrier method). For the purpose of this study, all female patients were considered to be of childbearing potential unless they had been post-menopausal, biologically sterile, or surgically sterile (i.e., hysterectomy, bilateral oophorectomy, or tubal ligation) for more than 1 year.
7. Were not breast feeding during the study or for 48 hours after the last dose of study drug administration.
8. Were able to take oral medication.
9. Understood written and spoken English
10. Had been informed of the nature of the study and provided written informed consent.

Exclusion Criteria

Patients were going to be excluded from participation in the study if they:

1. Had a positive pregnancy test prior to dosing (females only).
2. Had a known allergy or significant reaction to opioids.
3. Had a history of chronic opioid use or opioid abuse within 6 months prior to study entry.
4. Had a history of alcohol or substance abuse within the last 3 years.
5. Had been a participant in a study of an investigational drug or device within 30 days prior to study entry.
6. Had been a previous participant in an oxymorphone clinical trial.
7. Were currently taking or had taken a monoamine oxidase inhibitor (MAOI) drug within two weeks prior to study entry.
8. Were currently taking or had taken St. John's Wort >1000 mg/day within two days prior to study entry.
9. Had used long-acting oral and parenteral analgesics (opioid, non-opioid, or non-steroidal anti-inflammatory drug [NSAID]) within 12 hours (at least 24 hours for cyclooxygenase-2 [COX-2] analgesics) prior to receiving study medication.
10. Were using the following medications for at least four weeks prior to dosing unless use was stabilized:
    - Tricyclic antidepressant drugs
    - Serotonin reuptake inhibitors
    - Amphetamines used for attention-deficit hyperactivity disorder (ADHD)
11. Had a history of seizure. (Patients with a history of juvenile febrile seizures could be included if there had been no seizure history within the past 10 years.)

10.1.2 Study 008

Summary

Study EN3203-008 was a randomized, double-blind, placebo-controlled, parallel, single- and multiple-dose (8-hour) study of oxymorphone immediate-release (IR) 5 mg in patients with mild to moderate pain following ambulatory arthroscopic knee surgery.

After outpatient knee arthroscopy, patients with mild to moderate pain (30-70 mm on a 100-mm Visual Analogue Scale) were randomized to one of the two treatment groups, oxymorphone 5 mg and placebo. Patients received the first dose at the study site and were given instructions of taking 5 mg dose as needed (PRN) but not more frequently than every hour for up to 8 hours from the time of the initial dose, and rescue analgesic of the Investigator's choice. Patients were also given take home diary to record 30-minute and hourly pain assessments and scores on Questions 3-6 of the Brief Pain Inventory (BPI) (measured prior

to each dose), and dosing information (study medication and rescue). Patients taken rescue were discontinued from the study.

Efficacy parameters included 8-hour Sum of Pain Intensity Difference (SPID) (VAS) as the primary endpoint and 6-hour SPID (VAS), hourly pain intensity differences (VAS), pain scores from Questions 3-6 of the BPI, frequency of remedication, time to rescue medication, and global evaluation of pain relief as the secondary endpoints.

Safety was evaluated by adverse events (AEs) monitoring.

A total of 122 patients were enrolled and treated, 60 in the oxymorphone IR group and 62 in the placebo group. Most patients were non-elderly (94% at ages less than 65 years) and Caucasian (84%) and half of them were female. About 70% patients had moderate pain and 30% had mild pain by a categorical scale at baseline.

The exposure ranged from one to eight doses in both treatment groups. The average exposure was approximately five doses for seven hours in the oxymorphone IR 5 mg group and four doses for five hours in the placebo group.

The discontinuation rate was 20% in the oxymorphone 5 mg group and 53% in the placebo group and was mostly due to lack of efficacy (17% in the oxymorphone 5 mg group and 48% in the placebo group). Three patients were excluded from the efficacy analyses, two for vomiting in the first hour and one for not providing a proper consent. A number of protocol deviations were identified such as incorrect start date of concomitant medications, missing start/stop dates for concomitant medication, and deviation from inclusion/exclusion criteria, but with no details provided for review.

Efficacy findings included statistically significant treatment differences in pain scores ($SPID_{0-8}$, $SPID_{0-6}$, time-specific PID over most measurements other than Hour 7), treatment difference in time to rescue (more than eight hours for oxymorphone and close to 7 hours for placebo) and in the proportion of good to excellent responses to patient global evaluation of pain relief (79% in the oxymorphone group versus 59% in the placebo group).

The most common adverse events (>5% AEs) reported from either group included nausea (28% in the oxymorphone group versus 19% in the placebo group), vomiting (13% in both groups), headache (17% in the oxymorphone group versus 8% in the placebo group), and dizziness (7% in the oxymorphone group versus 2% in the placebo group). The reporting rates of dizziness, headache, and nausea were notably higher in the oxymorphone group than the placebo group. None-fatal serious AE was reported in one patient in the placebo group and discontinuation due to AEs was reported in two patients in the placebo group, none from the oxymorphone group.

Discussion

In studying acute analgesia the most important information to be obtained is the group response to a single dose and to multiple-dose treatment with a clearly defined dosing interval between the doses, to answer the question about the effects of dose level and the effects of dosing frequency. This study by design could not answer either question. The pain measurements and time to rescue medication with no reference to dosing time and/or the amount of drug taken would not provide useful information for adequate assessment of efficacy. The safety findings suggested that the 5 mg dose is tolerated reasonably well. The exposure data suggested misinterpretation of the dosing instruction by patients as if the study drug could be taken for up to eight doses. The proposed dosing instruction of taking drug so frequently was not considered a safe practice in the use of a drug of a high misuse/abuse potential unless safe use is adequately assessed.

10.2 Line-by-Line Labeling Review

The labeling will be reviewed separately.

11 REFERENCES

The reviews and meeting minutes are all available in the electronic system of FDA.

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/s/

Christina Fang
6/22/2006 07:16:50 PM
MEDICAL OFFICER

Sharon Hertz
6/22/2006 07:51:13 PM
MEDICAL OFFICER
I concur with the recommendation for approval.

2nd Cycle Review CSS

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
CONTROLLED SUBSTANCE STAFF

Date: **June 5, 2006**

To: **Bob Rappaport, M.D., Director**
Division of Anesthesia, Analgesia and Rheumatology (HFD-170)

Through: **Deborah B. Leiderman, M.D., M.A., Director**
Silvia Calderon, Ph.D., Team Leader

From: **Geoffrey Zeldes, M.D., Pharm.D., Medical Officer**
Controlled Substance Staff (HFD-009)

Subject: **Consultation NDAs 21-610 and 21-611 for oxymorphone IR & ER**
Indication: Oxymorphone extended release tablets in 5, 10, 20 and 40 mg doses for the relief of moderate to severe pain in patients requiring continuous, around-the-clock opioid therapy for 12-hours.
Oxymorphone immediate release tablets in 5 mg and 10 mg doses for the management of moderate to severe pain where the use of an opiate is indicated.
Purpose: review the proposed RMP
Date of Submission: December 22, 2005
PDUFA Date: June 22, 2006
Sponsor: Endo Pharmaceuticals

Background

On October 8, 2003 CSS responded to a Division request for CSS consultation on the abuse liability evaluation, drug labels and the proposed Risk Management Program (RMP) for Oxymorphone immediate release and extended release tablets. The Division issued an AE letter to the Sponsor on October 10, 2003. The Sponsor has now submitted a response and CSS is requested to review the modified RMP which is included in this submission. The previous CSS consultation was used to prepare the current review. In that memo the following Conclusions and Recommendations were made:

Oxymorphone, like morphine, is a full opioid agonist that binds to mu, kappa and delta opioid receptors and is controlled under Schedule II (CII) of the Controlled Substances Act. Therefore, most of the typical physiological effects mediated through the activation of these opioid receptors should be expected. A literature search reveals that no abuse liability study or comparative assessment of the subjective effects (e.g. euphoria, liking) of oxymorphone relative to other CII opioids could be found. Based upon the

pharmacological profile the abuse liability of oxymorphone should be viewed as similar to that of morphine.

The ER formulation utilizes Penwest's TIMERx proprietary drug delivery technology. The ER product is being developed for twice-a-day dosing in patients with moderate to severe pain. TIMERx is a controlled-release technology based on an agglomerated hydrophilic matrix, which consists of the polysaccharides locust bean gum and xanthan gum.

Oxymorphone & Proposed Indication Concerns

Oxymorphone's potency is greater than morphine's but less than hydromorphone's. The oral conversion ratio is approximately 0.333 for morphine and 1.333 for hydromorphone. This places oxymorphone in the more potent opioid class.

Other comparable extended release opioid products have been labeled for use only by opioid tolerant patients. This raises both safety and abuse liability concerns when a potent long-acting opioid is used to treat chronic pain in an opioid naïve individual. This issue must be addressed both in the labeling and the RMP.

Signals from Clinical Studies

The following statement appears on Pages 6,7 of the proposed labeling for the IR form of drug (the last sentence is underlined in this review for identification purposes):

Study summaries (EN3203-004 and EN3203-005) do not indicate the basis of the highlighted statement. If there was a problem with respiratory depression with the 30 mg strength of oxymorphone that required an "unacceptably high rate of use of naloxone" in clinical trials, this risk should be addressed in the Risk Management Plan.

The following excerpt from page 11 of the proposed ER formulation labeling highlights the high dropout rate due to AEs from clinical trials seen with this product (a portion of the 3rd sentence is underlined in this review for identification purposes):

Patient Package Insert vs. MedGuide

The sponsor proposes to provide a patient package insert for the ER product and no patient info for the IR product. This is inconsistent with patient information provided for other potent extended release opioid products. The potency and dosage strengths for this product mandate a MedGuide for the ER formulation and a PPI for the IR formulation.

Summary of Proposed RMP

The Sponsor submitted a single RMP that will apply to both products, immediate and extended release oxymorphone. The revised RMP states the Sponsor is striving to improve a comprehensive RiskMAP, which aims to promote the safe and responsible use of the product while concurrently minimizing abuse, misuse, diversion, and other adverse events through appropriate drug labeling, tight controls on distribution, proactive pharmacovigilance, extensive education of healthcare professionals and sales personnel, and funding of clinically meaningful research.

The goals and objectives for the RiskMAP are to minimize the following liabilities with their product:

- Aberrant behavior such as drug abuse, misuse, and addiction in both patients and the community
- Unintentional drug overdose
- Accidental exposure
- Diversion from distribution/ manufacturing facilities
- Improper patient selection
- Fraudulent prescription activity
- Inadequate patient education

Interventions are described for:

- diversion in distribution chain

- significant increase in cases of misuse, abuse, dependence, overdose, death , or unexplained death
- IMS database identified high prescribing areas
- localized area of local pharmacy thefts

Education

1. Satellite symposia and educational programs in conjunction with professional meetings
2. National Initiative on Pain Control (NIPC); CME - accredited educational programs
3. Physician in Training and Primary Care Initiatives
4. www.Painedu.org Website and Manual
5. Development of clinical guides to opioid analgesics
6. Patient and family education
    - Pain assessment inventory
    - www.painaction.com
7. Pharmacy education promoting pharmacy-physician interactions
8. Sales Force Training
9. Tools to assist in patient selection
    - Brief screening, self-report questionnaire for patients (**S**creener and **O**piate **Assessment** for **Patients with Pain** (SOAPP)) developed in conjunction with NIDA and Harvard University.
    - Patient-physician agreement
    - Frequency of follow-up
    - Ongoing documentation for patients taking chronic opioid medication
10. Oversight of the Distribution Chain

Postmarketing surveillance

1. Inflexxion's National Addictions Vigilance Intervention & Prevention Program (NAVIPPRO) that will provide real time product specific medication data from an independent scientifically based third party.
2. Toxic Exposure Surveillance System (TESS) utilizing data compiled by the American Association of Poison Control Centers (AAPCC) which will be reviewed annually to identify product exposures.
3. Drug Abuse Warning Network (DAWN)
4. [redacted] Proportion Analysis Engine FOI act FDA data [redacted] Contractor will check safety data for various products and will report deviations in reaction frequency of oxymorphone when compared to other opioids.
5. IMS Health Xponent database
6. Quantitative Internet Surveillance Program (QISP)
7. Addiction Severity Index – Multimedia Version (ASI-MV) to identify prescription drug problems and trends

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Evaluation Plan

1. Endo Safety Review Board (ESRB) will review cases of drug abuse, drug dependence and drug overdose to detect trends in demographics and concomitant use of other products issuing quarterly reports.
2. Risk Management Team to prepare semiannual reports for the FDA
3. Risk Intervention
4. RiskMAP Semi-annual Report

Labeling

Sponsor provided chart to assist in conversion from other oral opioids to proposed product is confusing and source is not cited.

Patient Package Insert (6th grade level) for ER only (not included for IR)
Accidental overdose by children
Co-ingestion with alcohol

Black box warning (for ER form only)
Schedule II substance with abuse liability
ER oral formulation indicated for continuous use for extended period of time
Not intended for prn use
Swallow whole, if crushed could lead to rapid release and absorption of drug

For ER label – supporting studies use doses higher than will be marketed. The labeling description of these studies indicate high discontinuation rates due to adverse events, but the AEs are not described. The narrative implies that the AEs were due to non-opioid tolerance status. The label does not indicate use in opioid tolerant patients only.

Conclusions

- Oxymorphone is a potent mu opioid receptor agonist which can cause significant adverse effects at higher doses.

- Clinical studies described by the Sponsor in the proposed labeling contain safety warning signals. For example, "there was an unacceptably high rate of use of naloxone in patients receiving the OPANA 30 mg dose" and '

- The potency of the proposed 20 mg and 40 mg ER tablets could produce respiratory depression and death in an opioid naïve patient or inexperienced abuser.

- The proposed RiskMAP contains general plans but very little that is product specific. No information is given on Key Messages or how they will be conveyed to prescribers or to patients. While it is very helpful to the public health in general to have educational material on chronic pain and pain management, this does not address the risks of prescribing oxymorphone for pain.

- Neither a black box warning nor a PPI is included for the IR label.

- Not enough info on [redacted] Proportion Analysis Engine is provided.

Recommendations

- The labeling should be revised to include a Med Guide for the ER dosage form and a black box warning and PPI for the IR dosage form.

- The labeling should be revised to indicate more clearly the risks of prescribing the ER dosage form to non-opioid tolerant patients.

- The labeling should address the safety issues of high potency and high rate of adverse effects associated with oxymorphone.

- Revise the information provided to assist in conversion from other oral opioids to proposed products to a more user friendly, less confusing format with source(s) for data cited.

- The sponsor should provide more details on the [redacted] proportion analysis engine data and how it will be used to manage risk in the post-marketing surveillance plan for the proposed product.

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/s/

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6/6/2006 05:55:56 PM
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Silvia Calderon
6/6/2006 05:57:08 PM
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1ST Cycle

FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHETIC, CRITICAL CARE, AND ADDICTION DRUG PRODUCTS
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DIVISION DIRECTOR REVIEW AND BASIS FOR APPROVABLE ACTION

DATE:	October 15, 2003
DRUG:	Oxymorphone HCl Extended-Release Tablets, 5 mg, 10 mg, 20 mg and 40 mg
NDA:	21-610
NDA Code:	Type 3S NDA
SPONSOR:	Endo Pharmaceuticals, Inc.
INDICATION:	Relief of moderate to severe pain in patients requiring continuous, around-the-clock opioid therapy for an extended period of time

Endo Pharmaceuticals has submitted NDA 21-610 in support of marketing approval for their extended-release (ER) oral formulation of oxymorphone HCl, 5-mg, 10-mg, 20-mg and 40-mg tablets. An earlier immediate-release formulation of oxymorphone (Numorphan 2-mg and 5-mg tablets) was approved (NDA 11-737) in 1959. The sponsor removed that formulation from the market in 1979, purportedly for commercial reasons. Oxymorphone injectable, 1 mg/mL, for intramuscular and subcutaneous administration (NDA 11-707), and oxymorphone rectal suppositories, 2 mg and 5 mg, (NDA 11-738) were also approved in 1959 and remain on the market in the U.S.

A companion application, NDA 21-611, has been submitted by Endo for an immediate-release (IR) formulation of oxymorphone HCl. There is significant overlap between these two applications and data and information from both has been included in the overall evaluation of each application. Review of the CMC portion of this application was completed by Jila H. Boal, Ph.D. Review of the pharmacology and toxicology data presented in this application was completed by R. Daniel Mellon, Ph.D. Review of the clinical pharmacology and biopharmaceutics data in the application was completed by

David Lee, Ph.D. A statistical review and evaluation was completed by Dionne L. Price, Ph.D. Consultation on this application was obtained from the Controlled Substances Staff, the Division of Drug Marketing, Advertisement and Communications, and the Office of Drug Safety.

The sponsor has submitted four studies in support of efficacy. A detailed review of these studies was performed by Shaun M. Comfort, M.D. A detailed safety review of both the combined IR and ER Integrated Summary of Safety (ISS) was performed by Gerald Dal Pan, M.D. Sharon Hertz, M.D., medical team leader for the analgesic drug product group, provided oversight for Drs. Comfort and Dal Pan, and has provided a thorough Team Leader's Memo integrating the findings of the efficacy and safety reviews.

Efficacy:

Study EN3202-012 (012) was a multicenter, multiple-dose, randomized, placebo-controlled, double-blind, parallel-group study comparing oxymorphone (OM) ER 20 and 60 mg placebo, performed in patients with post-operative pain due to knee arthroplasty.

Following surgery, patients were placed on parenteral opioids, followed by PCA morphine or meperidine. PCA was discontinued on the morning of the day following surgery. Patients reporting pain greater than or equal to 45 mm on a 100 mm VAS pain scale or moderate to severe pain on a 4-point categorical scale within 6 hours were randomized into the trial and received the first dose of study drug. A second dose of study drug was administered 12 hours later. Rescue was provided as IV oxymorphone titrated from 0.3 mg prn by PCA, but patients were encouraged to wait at least one hour after study medication dosing before using rescue.

The primary efficacy outcome was defined as total pain relief over 0 to 8 hours (TOTPAR 0-8) based on a protocol amendment that relegated the original additional primary outcomes to secondary. The secondary outcome measures included: TOTPAR 0-4, 0-6 and 0-12, Sum of Pain Intensity Difference (SPID) 0-4, 0-6 and 0-12, time to onset of meaningful pain relief, time to re-medication, PCA oxymorphone consumption, and Patient's Global Evaluation of Study Medication. An additional secondary outcome measure was an integrated rescue PCA and pain intensity recall score.

One hundred and twenty-seven patients were randomized. One patient received 60 mg of OR ER, experienced a serious adverse event and withdrew from the study. Sixty-five patients received OM ER 20 mg and 61 placebo. Twelve patients in the OM ER group did not complete the study. Five placebo patients did not complete the full study period. While withdrawals for insufficient therapeutic effect and patient request were comparable for the two groups, 5 subjects withdrew from the OM ER group due to adverse events while only 1 subject did so in the placebo group.

The sponsor found the mean TOTPAR 0-8 to be statistically significantly better for the OM ER 20-mg group compared to placebo. Reanalysis by Dr. Price, including subjects

withdrawn for requiring rescue medication within 1 hour, confirmed this result. While the LOCF methodology was used to impute missing data, this was considered acceptable given the short duration of the study and the relatively low number of dropouts. The secondary outcome analyses were generally supportive of this result.

Study EN3202-016 (016) was a multicenter, randomized, placebo- and active-controlled, double-blind, parallel-group, randomized-withdrawal study comparing oxymorphone (OM) ER to OxyContin and placebo, performed in patients with chronic low-back pain. Patients were randomized to one of four treatment groups:

1. titrate on and remain on OM ER
2. titrate on OM ER and switch to placebo
3. titrate on and remain on OxyContin
4. titrate on OxyContin and switch to placebo

Patients were titrated on the assigned study drug at a starting dose based on their prior daily opioid dose, to a dose that resulted in the need for no more than two doses per day of rescue medication, with adequate pain control on that dose for four consecutive days. Morphine sulfate IR (15 mg q 4-6 hours, prn) was used as rescue during the first four days after stabilization. For the next 14 days, rescue was restricted to 2 doses per day.

The primary outcome variable was the change from baseline to the Hour 4 post-dose VAS pain intensity measurement at Visit 6.

Secondary outcome measures included: percent change from baseline to the Hour 4 post-dose VAS pain intensity measurement at Visit 6, mean daily pain intensity based on the categorical scale at 4 hours post-dose, pain relief from daily pain assessment at 4 hours post-dose, worst daily pain from daily pain assessments, Brief Pain Inventory, Subject's Global Assessment of Pain Medication, time to treatment failure, time to withdrawal, amount of rescue medication usage, and OM plasma levels.

Drug diversion was discovered at one of the Study Sites (23). Efficacy analyses were performed with and without this data.

Three hundred thirty patients were randomized. Fifty-three of the 166 OM ER subjects failed to complete titration, 25 due to adverse events and 7 due to lack of efficacy. In the OxyContin group, 42 out of 164 patients failed to complete titration, 26 due to adverse events and 4 due to lack of efficacy. During the treatment phase, 22 of the 80 remaining subjects in the OM ER group discontinued early, 16 due to lack of efficacy and 2 due to adverse events. Of the 80 remaining OxyContin subjects, 21 discontinued early, 13 due to lack of efficacy and 4 due to adverse events. Of the 75 patients in the placebo group, 53 discontinued early, 44 due to lack of efficacy, 5 due to adverse events.

Both the OM ER and the OxyContin groups were statistically significantly different from the placebo group on the primary outcome variable. However, all three groups demonstrated a mild worsening of pain intensity, greater in the placebo than the active

groups. The secondary outcomes were generally supportive of this finding. By Day 8, 50% of placebo patients had withdrawn due to lack of efficacy compared with 10% of either active-treatment patients.

Study EN3202-025 (025) was a multicenter, randomized, placebo-controlled, double-blind, parallel-group study comparing oxymorphone (OM) ER 10 mg, 40 mg and 50 mg to placebo (all dosed BID), performed in patients with osteoarthritis of the knee or hip. Patients with a suboptimal response to non-opioid medications and a pain intensity score in the index joint of greater than or equal to 40 mm on a 100-mm VAS were eligible for enrollment. Patients were taken off all analgesics during a 2- to 7-day washout period. They were randomized to one of the four treatment arms when their pain intensity reached 40 mm. The trial took place over two weeks. Patients randomized to 40 and 50 mg BID were treated with 20 mg BID for one week before being increased to their final dose for the second week. No rescue medication was allowed during the study.

The primary outcome variable was the change from baseline in the Arthritis Pain Intensity VAS measurement at the final visit.

Secondary outcome measures included: WOMAC Pain Subscale, WOMAC Stiffness subscale, WOMAC Physical Function Subscale, WOMAC Composite Score, Patient Global Assessment, Physician Global Assessment, incidence of withdrawal due to lack of efficacy, time to withdrawal due to lack of efficacy, sleep assessments, and the SF-36.

Three hundred and seventy patients were randomized. There were high rates of discontinuation early in the study. Most of the discontinuations (25 to 55%) from the three OM ER groups were due to adverse events. Most of the discontinuations (17%) from the placebo group were due to lack of efficacy. Withdrawals due to adverse events during the first week occurred nearly twice as often from the 40- and 50-mg OM ER groups (who were actually being treated with 20 mg at that point) compared to the OM ER 10-mg group. The number of withdrawals for adverse events remained higher in the 40- and 50-mg groups than the 10-mg group during the second week. [Table 6, page 27 of Dr. Hertz's review]

Three hundred and fifty-seven patients were included in the sponsor's ITT population. One randomized patient had been excluded due to a serious adverse event that resulted in the blind being broken. The remaining 12 patients excluded from the ITT population had no post-baseline primary efficacy assessment data.

Using a comparison of LS means and imputing data by LOCF, the sponsor found statistically significantly greater reductions in pain compared to placebo for the 40-mg and 50-mg OM ER groups, but not the OM ER 10-mg group. Due to concerns regarding the effect of the high number of dropouts due to adverse events seen in the study-drug treatment groups, Dr. Price reanalyzed the data using a more conservative population.

This population included all randomized and treated patients, and missing data was imputed using baseline observation carried forward, rather than LOCF. This reanalysis found no statistically significant differences between the OM ER groups and the placebo group. [Tables 7 and 8, page 28 of Dr. Hertz's review]

The secondary outcome analyses were supportive of the sponsor's analysis of the primary outcome measure. The review team did not perform any reanalyses of this data.

Study EN3202-015 (015) was a multicenter, randomized, active- and placebo-controlled, double-blind, parallel-group study comparing oxymorphone (OM) ER 20 mg and 40 mg to OxyContin 20 mg and placebo (all dosed BID), performed in patients with osteoarthritis of the knee or hip. Patients with a suboptimal response to non-opioid medications and a pain intensity score in the index joint of greater than or equal to 40 mm on a 100-mm VAS were eligible for enrollment. Patients were taken off all analgesics during a 2- to 7-day washout period. They were randomized to one of the four treatment arms when their pain intensity reached 40 mm. The trial took place over four weeks. Patients randomized to OM ER 20 mg BID were treated with OM ER 10 mg BID for two weeks before being increased to the final dose for two weeks. Patients randomized to OM ER 40 mg BID were treated with OM ER 20 mg BID for two weeks before being increased to the final dose for two weeks. No rescue medication was allowed during the study.

The primary outcome variables defined in the protocol were: 1) the change from baseline in the Arthritis Pain Intensity VAS measurement at the final visit, and 2) the change from baseline in the WOMAC Pain Intensity VAS subscale score at the final visit.

Secondary outcome measures included: WOMAC Stiffness subscale, WOMAC Physical Function Subscale, WOMAC Composite Score, Patient Global Assessment, Physician Global Assessment, incidence of withdrawal due to lack of efficacy, sleep assessments, and the SF-36.

Of the 491 patients randomized, 489 received at least one dose of study medication. All data from patients at Center 002 were excluded from the efficacy analyses due to the fact that drug diversion was discovered at that site. There were high rates of discontinuation during the study (overall 45%). Most of the discontinuations from the two OM ER groups (38 to 47%) and the OxyContin group (25%) were due to adverse events. Only 5% of the placebo discontinuations were due to adverse events; whereas, most of the discontinuations from the placebo group were due to lack of efficacy (27%). [Table 9, page 33 of Dr. Hertz's review]

Due to the high rate of dropouts, the sponsor excluded 94 patients from the ITT population.

Using a comparison of LS means and imputing data by LOCF, the sponsor found a statistically significantly greater reduction in pain compared to placebo for the 40-mg

OM ER group, but not the OM ER 20-mg group. Due to concerns regarding the effect of the high number of dropouts due to adverse events seen in the three study drug groups, Dr. Price reanalyzed the data using a more conservative population. This population included all randomized and treated patients, and missing data was imputed using baseline observation carried forward, rather than LOCF. This reanalysis found no statistically significant differences between the active-treatment groups and the placebo group. [Table 12, page 35 of Dr. Hertz's review]

The secondary outcome analyses were supportive of the sponsor's analysis of the primary outcome measure. The review team did not perform any reanalyses of this data.

Clinical Safety:

A total of 1432 subjects were exposed to oxmorphone ER and 565 to oxymorphone IR during the clinical development program. Two hundred and seventy-three subjects received OM ER for at least 6 months and 191 subjects for at least 12 months.

There were 35 deaths in patients. Thirty-one of these deaths occurred in patients treated with OM (29 on OM ER and 2 on OM IR). Per the sponsor, and confirmed by the review team, for all but one of those 31 patients death was attributable to progression of cancer. The one subject whose death was not attributable to cancer was a 43 year old man with a history of obesity, hypertension and osteoarthritis of the knees who had been participating in an open-label extension study for four months at the time of his death. The medical examiner attributed his death to right and left ventricular hypertrophy due to obesity. Although the toxicology report did not detect any opiates, the sponsor has noted that, "It is not likely that toxicological batteries for opiates detect oxymorphone. It is not known if the toxicological screen used by the medical examiner could have detected oxymorphone, but it is highly unlikely." Thus, a causal role for the drug can not be entirely excluded.

Although there were no serious adverse events (SAEs) in the Phase 1 studies, 8.5% of patients exposed to OM ER in the Phase 2/3 studies experienced at least 1 serious adverse event. The most common SAEs were: vomiting, chest pain, nausea, dehydration, dyspnea, abdominal pain, drug interaction and osteoarthritis aggravated. Dr. Dal Pan explored the cases of chest pain and found that they were largely non-cardiac in nature. The four cases of "drug interaction NOS" were overdoses of OM ER in post-operative patients who were also receiving OM injectable by PCA. These patients experienced severe CNS and/or respiratory effects, some requiring naloxone reversal of the opiate. The adverse events that resulted in discontinuation and the common adverse events were generally those that would be expected with an opiate analgesic and were similar in incidence across the different opiate products administered during the development program.

Dr. Dal Pan further explored the database for all administrations of naloxone as a concomitant medication. A total of 27 subjects required naloxone, 23 of who were enrolled in one of the three post-operative pain trials. Eighteen of those 23 subjects

required naloxone after receiving study treatment. The incidence of these events was higher in the OM group (4%) compared to the Oxycodone or placebo groups (2% and 1%, respectively).

Although there were only a handful of clinically significant elevations in AST, ALT or AST and ALT, no explanations were provided for these abnormalities and no follow-up information was provided. Clinically significantly low neutrophil counts with or without low total WBC counts were recorded for 6 OM ER-treated subjects and one OM IR-treated subject during the Phase 1 studies. Each subject was a healthy volunteer with normal baseline neutrophil values. No follow-up data was provided for 4 of these subjects. Two of the subjects had normal neutrophils at follow-up and one had a normal WBC count but no differential was noted.

A small number of normal volunteers in the Phase 1 studies also developed QTc prolongations post-treatment, some by as long as 100 msec. In response to the Agency's request for the source data, the sponsor found that the original ECG tracings were no longer available. Therefore, reanalysis for reading errors is not possible.

Nonclinical Safety:

Dr. Mellon has noted that OM tested positive in the *in vivo* micronucleus assay in both the rat and the mouse, and that the sponsor will need to determine the mechanism for this effect and establish the relevance of these findings to patients. Also, appropriate qualification of the impurities [redacted] or reduced specifications for these substances will be required.

In addition, Dr. Mellon notes that the carcinogenicity assessment of the [redacted] impurity should be completed, or the levels reduced to NMT [redacted]. He also recommended that a minimal genetic toxicology screen should be completed for the impurity [redacted] unless the sponsor is able to reduce the levels of this impurity to NMT [redacted]. Pending results of the genetic toxicology screen, carcinogenicity assessment of this impurity may be needed.

Biopharmaceutics:

The Applicant submitted 14 analytical and 16 clinical pharmacology reports for review. Dr. Lee has determined that these studies are adequate and sufficient in order to describe the characteristics of oxymorphone tablets and that no further biopharmaceutic studies are necessary.

Oxymorphone IR tablets exhibited 38% increase in both AUC and Cmax with food intake. ER tablets exhibited 51-58% increase in Cmax with food intake. Little to no change in AUC was observed for ER tablets. In the clinical trials oxymorphone ER was administered with or without food.

The single-dose plasma oxymorphone concentrations were approximately 36 and 45% higher in AUC and Cmax, respectively, for elderly subjects compared to young subjects. After multiple doses, plasma oxymorphone concentrations were approximately 40 and 34% higher in AUC and Cmax, respectively, for elderly subjects compared to young subjects. Dr. Lee recommended that titration of dose needs to be undertaken with caution in the elderly.

The single dose plasma oxymorphone concentrations were 19 and 43 % higher in AUC and Cmax, respectively, for women. Likewise, after multiple doses, plasma oxymorphone concentrations were 14 and 20% higher in AUC and Cmax, respectively for women.

After a single dose, renal impairment was associated with an increase in plasma oxymorphone AUC and a reduction in renal excretion of oxymorphone and its major metabolite oxymorphone-3-glucuronide. Mean oxymorphone AUC was increased by 25, 57 and 65% in mild, moderate, and severe renaly-impaired subjects, respectively. Dr. Lee recommended that titration of dose needs to be undertaken cautiously in patients with moderate and severe renal impairment.

After a single dose, individuals with moderate or severe liver disease had clinically significant increases in plasma oxymorphone concentrations (AUC was increased up to 3.7-fold [mean value] and 12.2-fold [one patient] in moderate and severe liver disease subjects, respectively). Dr. Lee recommended that titration of dose needs to be undertaken with extreme caution in moderately impaired subjects, and that oxymorphone should be contraindicated in severely impaired subjects.

Chemistry, Manufacturing and Controls:

There are numerous deficiencies involving manufacturing and quality control. These are clearly outlined in Dr. Boal's review. In addition, DMF [redacted] for oxymorphone hydrochloride is deficient. A deficiency letter has been sent to Mallinckrodt Chemical Company, Inc., the holder of the DMF.

Nomenclature:

The Division of Medication Errors and Technical Support (DMETS) in the Office of Drug Safety has reviewed the proposed proprietary names submitted by the sponsor. DMETS recommends against the use of the name Opana due to its similarity to other products based on written samples. DMETS did find the alternative prorietary name, [redacted] acceptable. However, they recommend against the use of the IR suffix for the immediate-release formulation and recommend that an appropriate suffix be used for the extended-release product, as these methods would be more consistent with standard pharmaceutical naming practices.

Abuse Liability and Risk Management:

The Office of Drug Safety, the Division of Drug Marketing, Advertising and Communications, and the Controlled Substances Staff each provided consultation regarding the sponsor's proposed Risk Management Plan for this new extended-release opiate analgesic. While the overall plan appears to address the standard elements that have been developed over the past few years, the details of these elements are lacking. Also, the plan does not include any discussion of intervention when a signal of abuse is detected.

Discussion:

The sponsor has provided preliminary evidence of efficacy in this application. Only one of the four trials submitted, Study 016 in low-back pain patients, demonstrated efficacy for the product compared to an adequate control. However, even in Study 016, the results are not clear-cut, as each of the three treatment arms showed a worsening of pain during the trial period. Study 012 was performed in an inappropriate population of post-operative patients. There were a concerning number of apparent overdose-related events in that population. Studies 025 and 015, performed in patients with osteoarthritis, failed to demonstrate efficacy when analyzed with appropriate concern for the high number of oxymorphone-treated patients who dropped out early due to intolerable adverse events. Thus, the sponsor has failed to replicate efficacy in an appropriate chronic pain population.

In addition, safety concerns related to possible hepatic, hematologic and cardiac toxicity have not been adequately addressed, and the Risk Management Plan for abuse liability is currently inadequate. There are multiple product quality and control deficiencies, and potentially genotoxic or carcinogenic impurities will need full qualification or limitation to extremely low levels.

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Action recommended by the Division: Approvable

Bob A. Rappaport, M.D.
Director
Division of Anesthetic, Critical Care and Addiction Drug Products
Office of Drug Evaluation II, CDER, FDA

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Bob Rappaport
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MEDICAL OFFICER

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FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHETIC, CRITICAL CARE, AND ADDICTION DRUG PRODUCTS
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DIVISION DIRECTOR REVIEW AND BASIS FOR APPROVABLE ACTION

DATE:	October 15, 2003
DRUG:	Oxymorphone HCl Immediate-Release Tablets, 5 mg and 10 mg
NDA:	21-611
NDA Code:	Type 3S NDA
SPONSOR:	Endo Pharmaceuticals, Inc.
INDICATION:	Analgesia for moderate to severe pain where the use of an opioid is appropriate

Endo Pharmaceuticals has submitted NDA 21-611 in support of marketing approval for their immediate-release (IR) oral formulation of oxymorphone HCl, 5-mg and 10-mg tablets. An earlier immediate-release formulation of oxymorphone (Numorphan 2-mg and 5-mg tablets) was approved (NDA 11-737) in 1959. The sponsor removed that formulation from the market in 1979, purportedly for commercial reasons. Oxymorphone injectable, 1 mg/mL, for intramuscular and subcutaneous administration (NDA 11-707), and oxymorphone rectal suppositories, 2 mg and 5 mg, (NDA 11-738) were also approved in 1959 and remain on the market in the U.S.

A companion application, NDA 21-610, has been submitted by Endo for an extended-release (ER) formulation of oxymorphone HCl. There is significant overlap between these two applications and data and information from both has been included in the overall evaluation of each application. Review of the CMC portion of this application was completed by Dominic Chiapperino, Ph.D. Review of the pharmacology and toxicology data presented in this application was completed by R. Daniel Mellon, Ph.D. Review of the clinical pharmacology and biopharmaceutics data in the application was completed by David Lee, Ph.D. A statistical review and evaluation was completed by

Dionne L. Price, Ph.D. Consultation on this application was obtained from the Controlled Substances Staff, the Division of Drug Marketing, Advertisement and Communications, and the Office of Drug Safety.

The sponsor has submitted two studies in support of efficacy. A detailed review of these studies was performed by Shaun M. Comfort, M.D. A detailed safety review of both the combined IR and ER Integrated Summary of Safety (ISS) was performed by Gerald Dal Pan, M.D. Sharon Hertz, M.D., medical team leader for the analgesic drug product group, provided oversight for Drs. Comfort and Dal Pan, and has provided a thorough Team Leader's Memo integrating the findings of the efficacy and safety reviews.

Efficacy:

The efficacy of oxymorphone HCl IR was established in two single-dose studies of post-operative pain in patients undergoing orthopedic surgical procedures.

Study EN3203-004 (004) was a multicenter, single-dose, randomized, placebo- and active-controlled, double-blind, parallel-group study comparing oxymorphone (OM) IR 10, 20 and 30 mg to oxycodone (OC) IR 10 mg and placebo, performed in patients with post-operative pain due to knee or hip arthroplasty. Following surgery, patients were placed on IV or IM opioids. Those patients who were able to discontinue parenteral opioids within 48 hours and who developed moderate to severe pain by categorical scale and by a score of 45 mm or greater on a 100 mm VAS for pain were eligible for inclusion in the study. The primary outcome variable was the total pain relief from 0 to 8 hours (TOTPAR 0-8) using categorical pain relief scores, analyzed by ANCOVA. The trial was considered complete for an individual subject when that patient either requested remedication or completed the full 8-hour period. Rescue medication was provided at the investigators' discretion and patients requiring rescue within 3 hours of dosing were withdrawn from the trial.

Following completion of the trial, subjects entered a multiple-dose phase of the study during which the patients on active treatments remained on those products, while the placebo patients were randomized to one of the four active treatments. Patients received a dose of assigned medication every 4 to 6 hours as needed for the remainder of the 48-hour study period. There was no placebo arm in this trial and no dose effect was documented for the study drug. Thus there was no internal assay sensitivity that would allow an accurate assessment of efficacy over multiple doses of the study drug and this portion of the study will not be considered further in discussion of efficacy.

Secondary outcome measures during the single-dose trial included TOTPAR 0-4 and 0-6, Sum of Pain Intensity Difference (SPID) using VAS and categorical scales over 0-4, 0-6 and 0-8 hour intervals, time to 50% pain relief, proportion of patients achieving 50% pain relief, time to onset of analgesia, time to onset of meaningful pain relief, time to remedication, and Patient's Global Evaluation of Study Medication.

Based on an amended statistical analysis plan, the sponsor used a "modified" Intent-to-Treat (ITT) population that they called the Efficacy Evaluable Population to evaluate the primary and secondary outcomes. This population included all subjects who received the dose of study medication and completed the first hour of efficacy evaluation without vomiting or requiring rescue, and who did not have any significant protocol violations. The Last Observation Carried Forward (LOCF) method was used to impute missing data.

All of the 300 randomized patients received the first dose of study medication. Fewer than half of these patients completed the trial. Dr. Comfort found that 5 patients were incorrectly coded as "Other" in the sponsor's assessment of disposition. These subjects were added to the sponsor's numbers documenting disposition as non-completers. The largest proportion of subjects dropping out of the trial in all arms were due to lack of efficacy. Dropouts for adverse events were relatively low.

The sponsor's analysis of the primary outcome excluded 42 patients, 39 of whom for use of rescue medication or for withdrawing from the study within the first one hour following dosing with study medication. At the Division's request, the sponsor reanalyzed this data including patients who re-medicated. For this reanalysis they used a Baseline Observation Carried Forward (BOCF) method for imputing missing data. The findings from the reanalysis are comparable to the original analysis.

All three OM IR groups demonstrated statistically significantly better pain relief over the 8-hour period compared to the placebo group. [Table 3, page 12 of Dr. Hertz's review] The analyses of the secondary outcome measures were generally supportive of this finding. However, there were a number of inconsistencies that raise concern regarding the efficacy of the 30-mg dose compared to the lower doses. The proportion of patients that experienced 50% pain relief and the median time to 50% pain relief were statistically significantly greater for the OM IR 10-mg and 20-mg groups compared to the placebo group. Whereas the difference between the 30-mg group and the placebo group did not reach statistical significance. Review of the mean Pain Relief and Pain Intensity scores at individual time points failed to demonstrate any superiority of the OM IR 30-mg over the OM IR 20-mg. The Patient Global Evaluation of Satisfaction with Study Medication was statistically significantly better for the OM IR 10-mg and 20-mg groups compared to the placebo-group, while the 30-mg OM IR group was not.

While time to first perceptible pain relief did not differ between any of the active-treatment groups and the placebo group, time to meaningful pain relief was statistically significantly shorter for each of the three OM IR groups compared to the placebo-group. The median time to re-medication was statistically significantly longer for the OM IR 20-mg and 30-mg groups compared to placebo, while the 10-mg group was not.

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Study EN3203-005(005) was a multicenter, single-dose, randomized, placebo- and active-controlled, double-blind, parallel-group study comparing oxymorphone (OM) IR 10 and 20 mg to oxycodone (OC) IR 15 mg and 30 mg and to placebo, performed in patients with post-operative pain due to knee or hip arthroplasty. Following surgery, patients were placed on PCA opioids. Those patients who were able to discontinue PCA opioids within 72 hours and who developed moderate to severe pain by categorical scale and by a score of 50 mm or greater on a 100 mm VAS for pain (from 45 minutes to 6 hours after discontinuation of the PCA) were eligible for inclusion in the study. The primary outcome variable was the total pain relief from 0 to 8 hours (TOTPAR 0-8) based on VAS pain relief scores, analyzed by ANOVA with effects for treatment, center and baseline pain stratification. The trial was considered complete for an individual subject when that patient either requested remedication or completed the full 8-hour period. Rescue medication was provided at the investigators' discretion and patients requiring rescue before the Hour 8 assessment were withdrawn from the trial.

Secondary outcome measures during the single-dose trial included: TOTPAR 0-8 by categorical scores, TOTPAR 0-4 and 0-6 by VAS and categorical scales, Sum of Pain Intensity Difference (SPID) using VAS and categorical scales over 0-4, 0-6 and 0-8 hour intervals, time to first perceptible pain relief, time to onset of meaningful pain relief, time to re-medication, hourly pain relief and pain intensity difference scores, and Patient's Global Evaluation of Study Medication.

Based on an amended statistical analysis plan, the sponsor used a "modified" Intent-to-Treat (ITT) population that they called the Efficacy Evaluable Population to evaluate the primary and secondary outcomes. This population included all subjects who received the dose of study medication and completed the first hour of efficacy evaluation without vomiting or requiring rescue, and who did not have any significant protocol violations. The Last Observation Carried Forward (LOCF) method was used to impute missing data.

All of the 324 randomized patients received the dose of study medication. Three hundred of those patients completed the study. However, most of the patients required rescue between Hour 1 and Hour 8, ranging from 82% of placebo patients to 72% of OM IR 20-mg patients. Few patients discontinued due to adverse events.

The sponsor's analysis of the primary outcome excluded 22 patients, 12 of whom for use of rescue medication within the first one hour following dosing with study medication. At the Division's request, the sponsor reanalyzed this data including patients who re-medicated. For this reanalysis they used a Baseline Observation Carried Forward (BOCF) method for imputing missing data. The findings from the reanalysis are comparable to the original analysis.

The OM IR 20-mg group, but not the 10-mg group, demonstrated statistically significantly better pain relief over the 8-hour period compared to the placebo group. [Table 13, page 25 of Dr. Hertz's review] The analyses of the secondary outcome measures were generally supportive of this finding. Time to perceptible pain relief ranged from 15 to 20 minutes and did not differ among any of the five treatment groups.

Time to onset of meaningful pain relief ranged from 53 minutes to 1 hour and 3 minutes for the active-treatment groups, all of which showed statistically significant differences from placebo (8 hours). Time to rescue medication ranged from 3 hours 34 minutes to 4 hours and 53 minutes for the four active-treatment groups, all of which were statistically significantly longer than placebo (2 hours), when patients receiving rescue within the first hour were excluded.

Clinical Safety:

A total of 1432 subjects were exposed to oxmorphone ER and 565 to oxymorphone IR during the clinical development program. Two hundred and seventy-three subjects received OM ER for at least 6 months and 191 subjects for at least 12 months.

No deaths occurred during the clinical development program specific to the OM IR formulation. In the combined OM ER and IR ISS there were 35 deaths in patients. Thirty-one of these deaths occurred in patients treated with OM (29 on OM ER and 2 on OM IR). Per the sponsor, and confirmed by the review team, for all but one of those 31 patients death was attributable to progression of cancer. The one subject whose death was not attributable to cancer was a 43 year old man with a history of obesity, hypertension and osteoarthritis of the knees who had been participating in an open-label extension study for four months at the time of his death. The medical examiner attributed his death to right and left ventricular hypertrophy due to obesity. Although the toxicology report did not detect any opiates, the sponsor has noted that, "It is not likely that toxicological batteries for opiates detect oxymorphone. It is not known if the toxicological screen used by the medical examiner could have detected oxymorphone, but it is highly unlikely." Thus, a causal role for the drug can not be entirely excluded.

There were no serious adverse events (SAEs) in the Phase 1 studies. Five percent of subjects in the overall program exposed to OM IR experienced at least one SAE, compared to 9% of subjects exposed to OM ER. However, according to Table 20 on page 34 of Dr. Hertz's review, each of the SAEs in IR subjects occurred in only one patient, with the exception of myocardial infarction (MI) and deep venous thrombosis (DVT), limb, each of which occurred in 3 patients, (1% of total exposed patients). Other than these 6 events, MI was only reported in 1 OC IR patient and DVT in only 1 placebo patient.

The adverse events that resulted in discontinuation were those that would be expected with an opiate analgesic. However, they occurred with a significantly higher frequency in the OM IR-treated subjects (10%) compared to the OC IR-treated subjects (4%) or the placebo-treated subjects (7%). The common adverse events were generally those that would be expected with an opiate analgesic and were similar in incidence across the different opiate products administered during the development program. However, there was a relatively high incidence of pyrexia that occurred most frequently in the OM IR group, and hypotension, tachycardia and anemia also occurred more frequently in the OM IR patients compared to the OC IR and placebo patients. These abnormalities, while

likely related to the post-surgical setting, raise some concern regarding the accuracy of the sponsor's choice of relative potency of OM compared to other opiate analgesics.

Hypoxia occurred in patients in all three treatment groups. There were 6 events of depressed respiratory function in 6 OM IR subjects during Study 004. Four of those patients received naloxone. Dr. Dal Pan further explored the database for all administrations of naloxone as a concomitant medication. A total of 27 subjects required naloxone, 23 of whom were enrolled in one of the three post-operative pain trials. Eighteen of those 23 subjects required naloxone after receiving study treatment. The incidence of these events was higher in the OM group (4%) compared to the Oxycodone or placebo groups (2% and 1%, respectively).

Although there were only a handful of clinically significant elevations in AST, ALT or AST and ALT, no explanations were provided for these abnormalities and no follow-up information was provided. Clinically significantly low neutrophil counts with or without low total WBC counts were recorded for 6 OM ER-treated subjects and one OM IR-treated subject during the Phase 1 studies. Each subject was a healthy volunteer with normal baseline neutrophil values. No follow-up data was provided for 4 of these subjects. Two of the subjects had normal neutrophils at follow-up and one had a normal WBC count but no differential was noted.

A small number of normal volunteers in the Phase 1 studies also developed QTc prolongations post-treatment, some by as long as 100 msec. In response to the Agency's request for the source data, the sponsor found that the original ECG tracings were no longer available. Therefore, reanalysis for reading errors is not possible.

The sponsor's proposal to initiate dosing with 5-mg OM IR has not been studied. The safe use of OM IR in opioid-naïve outpatients has not been assessed. The sponsor's proposed dosing interval of 6 to 8 hours is not supported by the clinical trial finding that more than half of the patients withdrew before Hour 5 from each of the OM IR studies. The pharmacokinetic profile of the product is consistent with a shorter dosing interval as well.

Nonclinical Safety:

Dr. Mellon has noted that OM tested positive in the *in vivo* micronucleus assay in both the rat and the mouse, and that the sponsor will need to determine the mechanism for this effect and establish the relevance of these findings to patients. Also, appropriate qualification of the impurities, [redacted] reduced specifications for these substances will be required.

In addition, Dr. Mellon notes that the carcinogenicity assessment of the [redacted] impurity should be completed, or the levels reduced to NMT [redacted]. He also recommended that a minimal genetic toxicology screen should be completed for the impurity [redacted] unless the sponsor is able to reduce the levels of this

impurity to NMT ⟶ . Pending results of the genetic toxicology screen, carcinogenicity assessment of this impurity may be needed.

Biopharmaceutics:

The Applicant submitted 14 analytical and 16 clinical pharmacology reports for review. Dr. Lee has determined that these studies are adequate and sufficient in order to describe the characteristics of oxymorphone tablets and that no further biopharmaceutic studies are necessary.

Oxymorphone IR tablets exhibited 38% increase in both AUC and Cmax with food intake. ER tablets exhibited 51-58% increase in Cmax with food intake. Little to no change in AUC was observed for ER tablets. In the clinical trials oxymorphone ER was administered with or without food.

The single-dose plasma oxymorphone concentrations were approximately 36 and 45% higher in AUC and Cmax, respectively, for elderly subjects compared to young subjects. After multiple doses, plasma oxymorphone concentrations were approximately 40 and 34% higher in AUC and Cmax, respectively, for elderly subjects compared to young subjects. Dr. Lee recommended that titration of dose needs to be undertaken with caution in the elderly.

The single dose plasma oxymorphone concentrations were 19 and 43 % higher in AUC and Cmax, respectively, for women. Likewise, after multiple doses, plasma oxymorphone concentrations were 14 and 20% higher in AUC and Cmax, respectively for women.

After a single dose, renal impairment was associated with an increase in plasma oxymorphone AUC and a reduction in renal excretion of oxymorphone and its major metabolite oxymorphone-3-glucuronide. Mean oxymorphone AUC was increased by 25, 57 and 65% in mild, moderate, and severe renaly-impaired subjects, respectively. Dr. Lee recommended that titration of dose needs to be undertaken cautiously in patients with moderate and severe renal impairment.

After a single dose, individuals with moderate or severe liver disease had clinically significant increases in plasma oxymorphone concentrations (AUC was increased up to 3.7-fold [mean value] and 12.2-fold [one patient] in moderate and severe liver disease subjects, respectively). Dr. Lee recommended that titration of dose needs to be undertaken with extreme caution in moderately impaired subjects, and that oxymorphone should be contraindicated in severely impaired subjects.

Chemistry, Manufacturing and Controls:

There are numerous deficiencies involving manufacturing and quality control. These are clearly outlined in Dr. Chiapperino's review. In addition, the DMF holder for oxycodone has been notified that this DMF is deficient.

Nomenclature:

The Division of Medication Errors and Technical Support (DMETS) in the Office of Drug Safety has reviewed the proposed proprietary names submitted by the sponsor. DMETS recommends against the use of the name Opana due to its similarity to other products based on written samples. DMETS did find the alternative prorietary name, _____ acceptable. However, they recommend against the use of the IR suffix for the immediate-release formulation and recommend that an appropriate suffix be used for the extended-release product, as these methods would be more consistent with standard pharmaceutical naming practices.

Discussion:

The sponsor has submitted two adequate and well-controlled trials that demonstrate efficacy of their immediate-release product in a single-dose setting. Study 004 documents the efficacy of three doses (10 mg, 20 mg, and 30 mg) compared to placebo, but fails to demonstrate any advantage of the 30-mg dose over the 20-mg dose. Study 005 only demonstrates evidence of efficacy for the 20-mg dose. Thus, efficacy has only been replicated for a single dose. In addition, the lack of any data supporting sustained efficacy over multiple doses must be seen as a significant deficiency for a product that will clearly be used for more than single dosing. While the sponsor has attempted to define a dosing interval for multiple dosing in the clinical setting, their proposed interval of 6 hours is not supported by the clinical trial findings, as more than half of the subjects withdrew prior to Hour 5 in both studies. The sponsor will need to perform an additional adequate and well-controlled trial to evaluate multiple dosing in an appropriate patient population; preferably an opioid-naïve, acute-pain, outpatient population.

In addition, safety concerns related to possible hepatic, hematologic and cardiac toxicity have not been adequately addressed. There are also multiple product quality and control deficiencies, and potentially genotoxic or carcinogenic impurities will need full qualification or limitation to extremely low levels.

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Action recommended by the Division: Approvable

Bob A. Rappaport, M.D.
Director
Division of Anesthetic, Critical Care and Addiction Drug Products
Office of Drug Evaluation II, CDER, FDA

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Bob Rappaport
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MEDICAL OFFICER

FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHETIC, CRITICAL CARE, AND ADDICTION DRUG PRODUCTS

MEMORANDUM

DATE:	October 1, 2003
TO:	File, NDA 21-610
FROM:	Sharon Hertz, M.D. Team Leader, Analgesic Drug Group DACCADP
RE:	Team Leader Review of NDA 21-610, Oxymorphone Extended-Release Tablets

RECOMMENDATIONS:
The Sponsor has demonstrated a preliminary finding of efficacy for oxymorphone extended-release tablets. There is insufficient clinical study information to adequately inform the label and support marketing at this time. As a result, an approvable action is recommended. These conclusions are based on the following findings:

1. There is preliminary evidence of efficacy of oxymorphone extended-release tablets from one clinical trial of chronic pain, but two additional clinical trials of chronic pain failed to demonstrate efficacy for this product.

2. Single-dose efficacy was demonstrated in a postoperative patient population, but a high rate of use of opiate antagonists for adverse events indicate that this is not an appropriate patient population for use of this product.

3. There are unanswered safety concerns about abnormal liver function tests, WBC counts, and QTc findings.

4. Equianalgesic potency is unclear. Attempts to determine the relative analgesic potency of oxymorphone extended-release tablets and modified-release oxycodone tablets and modified-release morphine tablets were unsuccessful.

Deficiencies and Recommended Corrective Action:
An additional adequate and well controlled trial(s) is needed to provide the following information:
1. Efficacy in an appropriate patient population.

2. Address safety concerns about effects on liver function, WBC count, and QTc interval.

Although not a requirement for marketing approval, it would be useful to evaluate the relative potency of oxymorphone extended-release tablets to at least one other commonly prescribed, approved modified-release opioid.

Recommendations on Phase 4 Studies and Risk Management Steps:
There are no clinical Phase 4 recommendations at this time. Carcinogenicity will be completed as a Phase 4 commitment.

BACKGROUND
NDA 21-610, oxymorphone extended-release tablets 5, 10, 20, and 40 mg tablets, was submitted by Endo Pharmaceuticals on December 20, 2002. The proposed indication for oxymorphone extended-release tablets is for the relief of moderate to severe pain in patients requiring continuous, around-the-clock opioid therapy for an extended period of time. The results of 4 clinical trials have been submitted in support of efficacy and safety with additional safety information contributed by four active-control studies and 3 open-label extension studies.

Two trade names have been proposed by the Sponsor. The Office of Drug Safety has raised concerns about the name Opana and confusion with tincture of opium. No concerns were raised about the name _____ .

Immediate-release oxymorphone 2, 5, and 10 mg tablets were first approved by the FDA (NDA-11-737) in 1959 and marketed under the trade name Numorphan. The Sponsor reports that the oral tablets were removed from the market in 1979, for commercial reasons. Oxymorphone injectable, 1 mg/ml, for intramuscular and subcutaneous (NDA 11-707) and oxymorphone recta suppository, 2 mg and 5 mg, (NDA 11-707 and NDA 11-738) were approved by the Agency in 1959. Both products are still marketed in the US.

This Team Leader Memo was created in conjunction with the secondary review of the Medical Officer Review of Efficacy by Dr. Shaun Comfort. The statistical review of the clinical studies by Dr. Dionne Price was consulted for information concerning the Sponsor's efficacy review, as well as additional analyses requested by, and performed by Dr. Price. The Medical Officer Review of Safety by Dr. Gerald DalPan was referenced for the safety evaluation along with the Sponsor's ISS. The Clinical Pharmacology and Biopharmaceutics review by Dr. David Lee was consulted for relevant sections of this

memo. The clinical study reports in the NDA electronic document were also consulted during the secondary review process and in writing this memo.

SUMMARY OF FINDINGS

1. There is preliminary evidence of efficacy of oxymorphone extended-release tablets from one clinical trial of chronic pain, but two additional clinical trials of chronic pain failed to demonstrate efficacy for this product.

2. Single-dose efficacy was demonstrated in a postoperative patient population, but high rate of use opiate antagonists for adverse events indicate that this is not an appropriate patient population for the use of this product.

3. There are ongoing concerns about abnormal liver function tests, WBC counts and QTc findings.

4. Equianalgesic potency is unclear. An attempt to determine the relative analgesic potency of oxymorphone extended-release tablets and modified-release oxycodone tablets and modified-release morphine tablets was unsuccessful.

Summary of Clinical Studies

The Sponsor submitted the results of four placebo-controlled studies in support of efficacy, safety, and dosing recommendations for oxymorphone extended-release tablets (ER). The results of three open-label or active-controlled trials were submitted in support of safety and to establish relative potency with approved modified-release opioids. The results from three open-label studies were submitted in support of safety.

EN3202-012 was a double-blind, parallel group, placebo-controlled, multiple-dose study of oxymorphone ER. The purpose was to evaluate the efficacy and safety of a 20 mg dose of oxymorphone ER, to characterize the analgesic onset and duration of oxymorphone ER effect in a single-dose paradigm, and to evaluate the opioid dose-sparing effects of oxymorphone ER after multiple dosing in patients with acute pain following orthopedic surgery.

Efficacy was demonstrated by the primary outcome measure, mean TOTPAR 0-8, which was statistically significantly better for the oxymorphone ER 20 mg group compared to placebo. The secondary endpoints evaluating pain relief and pain intensity also favored the oxymorphone ER 20 mg group. The Integrated Rescue PCA and Pain Intensity Recall scores for 0-12 hours were statistically significantly better for oxymorphone ER 20 mg than for placebo. The PCA oxymorphone consumption was lower for the oxymorphone ER 20 mg group compared to the placebo group, with the difference in mean oxymorphone PCA consumption of 2.7 mg over 24 hours.

However, there was little support from the secondary outcome measures. There was no statistically significant difference in mean time to rescue medication, time to onset of

meaningful analgesia, time to first experiencing 50% pain relief, and median time to meaningful pain relief between the two groups. This may be due to only approximately 50% of patients in the oxymorphone ER 20 mg group and approximately 38% of patients in the placebo group ever reporting meaningful pain relief during the first 12 hours after dosing of study medication. The mean patient global evaluation score at 12 hours or early termination was statistically significantly better for the oxymorphone ER 20 mg group compared to placebo, but by a difference, 0.61 on a 5-point scale, which is of questionable clinical significance. There were a disproportionate number of subjects requiring treatment with naloxone raising concerns about safety with use of oxymorphone ER in the postoperative setting.

EN3202-015 was a double-blind, parallel group, placebo- and active-controlled, multiple-dose study of oxymorphone ER. The purpose of this 4-week study was to evaluate efficacy and safety of two doses of oxymorphone ER (20 and 40 mg) compared to placebo and OxyContin, in patients with osteoarthritis of the knee and/or hip.

The primary efficacy endpoint, change from baseline in Arthritis PI by VAS, failed to provide evidence of efficacy for the two doses of oxymorphone ER studied. The analysis by the Sponsor which imputed missing data using last observation carried forward (LOCF) for lack of efficacy and baseline observation carried forward (BOCF) for other causes, did find statistically significant differences between oxymorphone ER 40 mg compared to placebo. A reanalysis using an all treated population and BOCF method for imputing all missing data did not find any statistically significant difference between treatment groups. The latter analysis is considered the appropriate for the following reasons. Carrying forward the last observation for patients dropping out due to lack of efficacy while using BOCF for other dropouts biases in favor of the active treatment group in this situation because the reasons for early discontinuation were different based on treatment group assignment. The scores carried forward using BOCF reflect lack of efficacy for the placebo patients, while using LOCF for dropouts due to adverse events, primarily from the active treatment patients, reflect efficacy at doses that were not tolerated.

EN3202-016 was a double-blind, placebo- and active-controlled, randomized withdrawal study of oxymorphone ER. After 7-10 of double-blind titration with oxymorphone ER or OxyContin to reach a stable dose that provided satisfactory pain relief, patients were randomized to continue with current treatment or receive placebo for 18 days.

The efficacy of oxymorphone ER bid was demonstrated by the primary efficacy endpoint, change from baseline to the 4-hour post-dose VAS PI on Day 18, which was statistically significantly better for the oxymorphone ER group compared with placebo. There was a mild worsening of pain intensity for the active treatment groups, but this may reflect some of the limitations of the use of rescue medication in the study design. The secondary endpoints also supported the finding of efficacy for oxymorphone ER. These included additional analyses of pain intensity and pain relief, patient global assessment of pain medication, and time to treatment failure and mean amount of rescue medication usage.

EN3202-025 was a double-blind, dose-response, parallel-group, placebo-controlled study of 10, 40, and 50 mg doses of oxymorphone ER The purpose of this 2-week, dose-ranging study was to identify the minimum effective dose and maximum tolerable dose in patients with moderate to severe pain due to osteoarthritis.

The primary efficacy endpoint, change from baseline in Arthritis PI by VAS, failed to provide evidence of efficacy for the three doses of oxymorphone ER studied. The analysis by the Sponsor, imputing missing data using LOCF, did find statistically significant differences for oxymorphone ER 40 mg and 50 mg compared to placebo. A reanalysis using an all treated population and BOCF method for imputing missing data did not find any statistically significant difference between treatment groups. This analysis was considered appropriate for the same reasons as for Study EN3202-015. The scores carried forward using LOCF reflect lack of efficacy for the placebo patients, but efficacy at doses that were not tolerated for the active treatment groups.

The Sponsor also submitted the results of three additional studies. These studies were not appropriately designed to support efficacy, but did provide additional safety data and attempted to evaluate equianalgesic dose ratios between oxymorphone ER and oxycodone ER or morphine ER.

EN3202-017 was an open-label, crossover study of oxymorphone ER, OxyContin, and MS Contin in patients with cancer pain. The Sponsor noted that the estimation of dose ratios was subject to limitation imposed by the open-label design of the study. The allowance for dose adjustments and rescue medication may have confounded the outcome. The availability of only one strength of oxymorphone ER (20 mg) and IR (5 mg) in contrast to MS Contin and OxyContin limited the flexibility in adjusting the dose of oxymorphone, leading to a possible over-estimation of the dose of oxymorphone needed to provide equianalgesia to MS Contin and OxyContin. The Sponsor concluded that confirmation of the relative efficacy and potency needed to be obtained from a double-blind study specifically designed for this purpose.

EN3202-018 was a randomized, double-blind, crossover study intended to demonstrate analgesic equivalence between oxymorphone ER and MS Contin and determine the equianalgesic dose ratio between these two products. Descriptive summary statistics by period showed that the average pain score in Period 1 was lower for subjects who received morphine ER compared with subjects who received oxymorphone ER, while the scores were similar between treatment groups for Period 2. Subjects receiving oxymorphone ER took significantly more rescue medication. Equianalgesia between oxymorphone ER and morphine ER was not attained as oxymorphone ER and morphine ER were not statistically comparable with respect to the primary efficacy analysis. A valid dose ratio could not be calculated as there was a statistically significant sequence effect.

EN3202-019 was a randomized, double-blind, crossover study intended to demonstrate analgesic equivalence between oxymorphone ER and OxyContin and the equianalgesic

dose ratio between these two products. The primary efficacy analysis, comparing patients' ratings of average 24-hour pain intensity, did not demonstrate any differences when analyzed with the ITT population. An equianalgesic was not definitively established.

Long-term safety data was obtained from the following three studies.
EN3202-020 was an open-label study enrolling patients who completed or discontinued early from studies EN3202-015 and EN3202-017 permitting continuation of treatment with study drug for up to two years.

EN3202-021 was an open-label study enrolling patients who completed or discontinued early from studies EN3202- 016 and EN3202-019 permitting continuation of treatment with study from for up to one year.

EN3202-022 was an open-label study enrolling patients who completed or discontinued early from study EN3202- 018 permitting continuation of treatment with study for up to one year.

Summary of Safety Findings - Oxymorphone ER
At total of 1864 subjects received oxymorphone ER and/or oxymorphone IR, 1432 of whom received only oxymorphone ER and 565 only oxymorphone ER. There were 273 patients with at least 6 months exposure and 191 patients with at least 12 months exposure. There were 35 deaths in patients during studies of oxymorphone ER. Thirty-four of these deaths occurred in cancer patients without evidence that oxymorphone ER contributed to the cause of death. The one non-cancer death was attributed to ventricular hypertrophy. It is unknown if oxymorphone contributed to the cause of death as the toxicology report did not detect any opiates.

Serious adverse events were common, occurring in 8.54% of patients exposed to oxymorphone ER. The most common SAEs were as expected for an opioid, vomiting, chest pain, nausea, dehydration, dyspnea, and abdominal pain. There were several adverse events coded as drug interaction that actually represented serious events. These patients experienced the effects of over dosing of oxymorphone characterized by CNS depression and or respiratory depression after receiving oxymorphone ER in the postoperative period, and required treatment with an opiate antagonist.

The adverse events leading to study discontinuation and general adverse events were characteristic of opioids, the most frequent were nausea, dizziness, vomiting, somnolence, pruritus, and constipation.

There are outstanding concerns about several cases of clinically significant elevations in serum transaminases and clinically significant reductions in neutrophil counts with or without low total WBC counts. The absence of follow-up data or explanation for these findings leaves the clinical significance uncertain.

QTc prolongation was present in the ECGs of normal volunteers following dosing including two QTc intervals that were prolonged by over 100 msec. The clinical significance of these findings remain uncertain.

One additional concern for this product arises from the question of whether oxymorphone is routinely present as an element of drug toxicological screens. One patient who died while reportedly taking 80 mg/day of oxymorphone ER had no opiates detected by the medical examiner screen. The Sponsor noted that "It is not likely that toxicological batteries for opiates detect oxymorphone. It is not known if the toxicological screen used by the medical examiner could have detected oxymorphone, but it is highly unlikely."

Dosing

The clinical pharmacokinetic and bioavailability studies were also conducted. A dosing interval of every 12 hours has been utilized in the Study EN3203-016 in which efficacy was demonstrated and is supported by the pharmacokinetic profile of oxymorphone extended-release tablets.

Dose adjustments are called for in mild to moderate hepatic impairment, titration should begin low and proceed with close clinical monitoring. Oxymorphone is highly metabolized by the liver. Use of oxymorphone should be contraindicated in severe hepatic impairment. As oxymorphone plasma concentrations were relatively higher in the setting of renal impairment, dosing of oxymorphone should be started at low doses and titrated carefully in all categories of renal impairment under close clinical supervision. Patients over age of 65 exhibited higher plasma concentrations, AUC and Cmax. Therefore, dosing in patients over the age of 65 should begin with low starting doses and titrated carefully under close clinical supervision.

FINDINGS FROM OTHER DISCIPLINES

There were numerous deficiencies cited in the Chemistry Review by Dr. Jila Boal. No deficiencies were cited in the Clinical Pharmacology and Biopharmaceutics Review by Dr. David Lee. The Nonclinical Pharmacology and Toxicology Review by Dr. Dan Mellon identify problems with the presence of unqualified impurities including [redacted]. These impurities will need to be reduced to an acceptable level or adequately qualified. The Statistical Review by Dr. Dionne Price was is cited throughout this review.

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REVIEW OF EFFICACY

EN3202-012

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

Study EN3202-012 was a multi-center, double-blind, parallel group, placebo-controlled, multiple-dose study of oxymorphone ER. The primary objective was to evaluate the efficacy of 20 mg and 60 mg doses of oxymorphone ER compared to placebo in patients with moderate to severe postoperative pain. Secondary objectives were to compare the efficacy of the two doses of oxymorphone ER and to evaluate the safety of oxymorphone ER 20 mg and 60 mg in the setting of moderate to severe postoperative pain.

Enrollment of 175 patients was planned to result in150 patients compete the study. Patients undergoing unilateral total knee arthroplasty, ages 18 to 75 years, male or female, nonpregnant and nonlactating, free of clinically significant medical disease, and able to tolerate oral analgesics within 30 hours of completion of surgery were to be eligible for study participation. Following surgery, patients were to be permitted intermittent parenteral fentanyl, morphine, or meperidine in the immediate postoperative period, followed by PCA morphine or meperidine. On the morning of the day after surgery, the PCA opioids were to be discontinued. Previously screened and qualified patients who reported pain of ≥45 mm on a VAS or moderate to severe on a 4-point categorical scale within 6 hours were to be randomized to receive study drug consisting of oxymorphone ER 20 mg, oxymorphone 60 mg, or placebo. Study drug was to be dosed at the time pain criteria were met and once 12 hours later. Patients were to be permitted rescue doses of IV oxymorphone titrating doses from 0.3 mg as needed, by PCA, but were to be encouraged to wait at least one hour after study medication dosing. Once rescue medication was used, stopwatch assessments were to cease, but the remainder of the pain assessments were to continue through the 24 hour study period.

Pain intensity (PI) was to be measured by VAS and categorical scale. Pain relief was to be measured by categorical sale. Measures were to be taken at baseline, 15, 30, 45 minutes, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10 and 12 hours after administration of study drug and immediately prior to the first dose of rescue medication. Average PI was also to be recorded at those times. Additional measures were to be time when pain was half gone, time to onset and time to meaningful pain relief, and amount of PCA oxymorphone used during the 24 hour treatment period. Average pain intensity since first dose by recall was to be recorded at 12 and 24 hours post-dose, or at study termination. A global evaluation ("How would you rate the study medication you received for pain?") was to be completed at 12 and 24 hours post-dose. Adverse event reporting was to occur throughout the study period. Vital signs and collection of blood for laboratory evaluation were to be collected at screening, baseline, and study termination.

All statistical tests were to be performed as two-tailed tests, and all effects were to be considered statistically significant if $p \leq 0.05$. Primary and secondary efficacy analyses

were to be conducted 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 to be applied to least square means resulting from the ANCOVA model. Survival analysis methods were to be utilized for the time-to-event secondary variable analyses.

The Sponsor initially planned two primary efficacy analyses, a standard analgesic evaluation and a PCA opioid dose sparing evaluation. An efficacy analysis population was defined for the former as randomized patients who received study drug and completed the first hour of observation without receiving rescue during that time. For the latter, the efficacy analysis population was defined as randomized patients who received at least the first dose of study medication and completed the 12-hour efficacy evaluation.

There were initially multiple primary efficacy variables described. See Protocol Amendment 3 for changes.
Standard Acute Pain Analgesic Evaluation:

- Total Pain Relief (TOTPAR): 0-4, 0-6, 0-8, and 0-12 hours.
- 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 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, 0-6, and 0-24 hours. This result was to be analyzed using ANOVA with treatment and center as factors.
- PCA Oxymorphone Consumption at 0-6, 0-12, 12-24, and 0-24 hours:
- Patient global evaluation at 12 and 24 hours or early termination

Secondary Efficacy Variables:
Standard Analgesic Evaluation

- SPID by VAS at 0-4, 0-6, 0-8, and 0-12 hours
- Time-specific pain intensity difference from baseline (PID) (VAS and categorical scales)
- Pain relief (PR) at the post-dose time points
- Sum of pain relief and pain intensity difference on the categorical scale (PRID) at post-dose time points
- Peak pain intensity difference (PPID), the highest PID score achieved at any time during the evaluation period
- Peak pain relief (PPR), the highest PR score achieved at any time during the evaluation period
- Summed PRID scores (SPRID) at 0-4, 0-6, 0-8, and 0-12 hour time intervals
- Time to perceptible pain relief (stopwatch)

- Time to onset of analgesia defined as the time of change from previous assessment in PID (categorical) ≥ 1
- Time to first experienced 50% pain relief
- Number of patients experiencing 50% pain relief

PCA-Opioid Dose Sparing Analgesic Evaluation:
- Pain intensity recall (VAS) scores for average pain since previous assessment at 0-6, 6-12, and 0-12 hours
- Pain intensity recall (VAS) scores for average pain since first dose at 12 and 24 hours

Post-hoc analyses included a comparison of PCA oxymorphone dose and the integrated rescue PCA and pain recall scores between treatments using ANOVA with treatment and center as factors, and a reordering of the Patient Global Evaluation of Efficacy scale.

In Protocol Amendment 1(October, 1999), the Sponsor removed the 60 mg dose of oxymorphone ER due to an "increased likelihood" of adverse events, increased the range of surgical procedures beyond total knee arthroplasty, added guidelines for control of patient movement during the study period, added a set of opioid dose sparing evaluations immediately prior to the first dose of rescue, added respiratory rate to the vital signs, increased the upper age of eligibility to 80 years, permitted long-acting local anesthetics (e.g. bupivicaine), added for the arousal of sleeping patients for vital sign and pain assessments, and added prophylactic antiemetics. PCA opioid was to be continued for a minimum of 12 hours if patients were receiving passive continuous motion. Other extraneous movements were to be avoided for the first 2 hours after dosing and kept to a minimum thereafter. Inclusion criteria were amended to include a baseline pain intensity (BPI) $\geq$ 45 mm on the VAS and moderate to severe on the categorical scale, within six hours of PCA discontinuation. As only one patient received the 60 mg dose prior to this amendment, there were no effects on the outcome of the study for the 20 mg dose of oxymorphone.

In Protocol Amendment 2 (December, 1999), the Sponsor reduced the starting dose of IV oxymorphone from 0.3 mg to 0.2 mg and broadened the abnormal lab inclusion criterion from >1.5X to >2 X the upper limit of normal for serum transaminases. The number of subjects enrolled was increased to 125 to achieve 100 evaluable patients. This amendment provided for improved safety and did alter the quality or validity of the efficacy outcome measures.

In Protocol Amendment 3 (July, 2000), the Sponsor increased the demand dose lock-out for rescue PCA oxymorphone from 6 to 10 minutes. The final sample size calculation was based on the primary comparison of oxymorphone ER versus placebo for TOTPAR 0-8 hours. The Sponsor identified the primary efficacy variable for the Standard Acute Pain Evaluation TOTPAR 0-8. TOTPAR and SPID at 0-4, 0-6, and 0-12, time to re-medication, time to meaningful pain relief, and patient global evaluation were changed to secondary efficacy variables. The integrated rescue PCA and pain intensity recall score at 0-6 and 0-24 hours, PCA oxymorphone consumption, and patient global evaluation at 12 and 24 hours were to be secondary efficacy variables. The change in PCA dosing

improved safety without effecting the validity of outcome measures. The alterations to the statistical analysis plan occurred prior to unblinding of the data and was in response to comments from the Agency.

Amendment 4 (March, 2001) was prior to locking the database and included excluding a group of patients from the efficacy evaluable population because of entry criteria violations, specified that centers with missing patients in one treatment group were to be combined with the smallest center that had patients in both treatment groups, and that LOCF was to be the method of imputing missing data.

RESULTS

The study took place from September, 1999 through November, 2000. Fourteen investigators enrolled patients at 14 centers.

Disposition

Of the 223 patients screened, 127 patients were randomized. One patient received 60 mg of oxymorphone ER. This patient experienced a serious adverse event (SAE) and withdrew from the study. Of the remaining 126 patients, 65 received oxymorphone ER 20 mg and 61 received placebo. Twelve patients (18%) from the oxymorphone ER 20 mg group did not complete the study, seven withdrew before 12 hours, and five withdrew during the subsequent 12 hours. An additional two subjects completed the 24 hour interval but did not take the second dose and so are not counted among the 12 who discontinued. Five placebo patients (8%) did not complete the 24 hour study period, two withdrawing in the first 12 hours, three the second 12 hours. Five withdrawals from the oxymorphone ER 20 mg group were due to serious and non-serious AEs, compared to one placebo patient. Withdrawals due to insufficient therapeutic effect and patient request were comparable for the two groups.

Table 1 Disposition of Patients

		OM ER 60	OM ER 20	Placebo
Randomized		1[a]	65	61
Completed				
	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 (1.5%)	1 (1.6%)

Source: Sponsor's Table 10.1 Clinical Study Report, Page 36 of 157.
[a]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.

No patients were excluded from safety or efficacy evaluations due to protocol violations.

The demographic characteristics did not differ between the two treatment groups.

Efficacy Analysis Results

Standard Analgesic Evaluation Results

The mean TOTPAR 0-8 was statistically significantly better for the oxymorphone ER 20 mg group compared to placebo (11.26 vs. 8.09, respectively, p=0.0057) using the Sponsor's efficacy population of 104 patients. A reanalysis by Dr. Dionne Price using a true ITT population (N=126), which included subjects withdrawn for requiring rescue medication within the first hour, confirmed this finding. These results from Dr. Price's review are presented in Table 2. Missing data was imputed using the last observation carried forward (LOCF). This method was considered acceptable for this analysis given the short duration of the study and the relatively small number of dropouts.

Table 2 Total Pain Relief 0–8, All Randomized (LOCF), standard analgesic evaluation

	Total Pain Relief at 8 hours
OCR 20 (N=65)	9.65 (8.6)
Placebo (N=61)	6.79 (7.0)
LS Mean Difference	3.81
p-value	0.005
95% CI	(1.18, 6.43)

OCR = Oxymorphone ER
Mean values and accompanying standard deviations are shown for each treatment arm.
Source: Review by Dr. Dionne Price, Table 4.

The TOTPAR 0-4, 0-6, and 0-12 were also statistically significantly better for the oxymorphone ER 20 mg group compared to placebo. See Table EN3202-12.6 in Dr. Comfort's review.

The secondary analyses for the standard analgesic endpoints were conducted using the same evaluable population as the primary endpoint. Reanalyses were not performed using a the full ITT population. The mean SPID by categorical scale at 0-4, 0-6, 0-8, and 0-24 hours all favored oxymorphone ER 20 mg over placebo and the differences were statistically significant by the Sponsor's analysis. See Table EN3202-12.8 in Dr. Comfort's review for these values. The mean SPID by VAS at 0-4, 0-6, 0-8, and 0-24 hours also all favored oxymorphone ER 20 mg over placebo as presented in Table EN 3202-12.9 in Dr. Comfort's review.

There was no difference in mean time to rescue medication between the two groups (1 hour 54 minutes vs. 1 hour 59 minutes, oxymorphone ER 20 mg and placebo groups respectively).

The median time to meaningful pain relief was approximately 3 hours for oxymorphone ER 20 mg and more than 12 hours for placebo and yet this difference failed to reach statistical significance. Only approximately 50% of patients in the oxymorphone ER 20 mg group and approximately 38% of patients in the placebo group ever reported meaningful pain relief during the first 12 hours after dosing of study medication.

The time to onset of meaningful analgesia (change in categorical scale of ≥ 1) was 33 minutes for the oxymorphone ER 20 mg group compared to 45 minutes for the placebo group. This difference did not reach statistical significance.

The time to first experiencing 50% pain relief was approximately 1 one hour for the oxymorphone ER 20 mg group compared to 1.5 hours for the placebo group. This difference did not reach statistical significance. Approximately 60% of oxymorphone ER 20 mg patients and approximately 56% of placebo patients achieved 50% PR throughout the 12 hour period of assessment.

The number of patients experiencing 50% pain relief for the oxymorphone ER 20 mg was greater than for the placebo group 1.5 hours (43.4% vs. 23 %, respectively, p=0.0169). This difference only reached statistical significance again at Hours 3 and 6, failed to differ between treatment groups at Hours 2, 4, 5, 7, 8, 10, and 12.

The mean patient global evaluation score at 12 hours or early termination was 3.25 for the oxymorphone ER 20 mg group and 3.86 for the placebo group. The Sponsor notes this was a statistically significant difference, but a mean difference of 0.61 on a 5-point scale is of questionable clinical significance.

The mean PID scores by VAS at each assessment time for oxymorphone ER 20 mg were higher than those for placebo at each assessment time, and the differences between the treatment groups were statistically significant at the 30-minute and 1.5-hour through 12-hour assessments. See Dr. Comfort's Table EN3202-12.13. The mean PID scores by categorical scale were statistically significantly greater for the oxymorphone ER 20 mg group than the placebo group from Hour 3 through Hour 10. See Dr. Comfort's Table EN3202-12.15 and 12.16 for these details.

Pain relief (PR) by 5-point categorical scale was approximately 0.4 units higher for oxymorphone ER 20 mg at hours 2 and 3, and then remained approximately 0.5 units higher for oxymorphone ER 20 mg (approximately 1.4) compared to placebo (approximately 0.9) from hours 4 through 7.

The remainder of the secondary endpoints favored the oxymorphone ER 20 mg group over placebo. These are reviewed in detail in Dr. Comfort's review.

<u>PCA-Opioid Dose Sparing Evaluation:</u>
According to the Sponsor's analysis, the Integrated Rescue PCA (IR-PCA) and Pain Intensity Recall (PIR) scores for 0-12 hours were statistically significantly better for oxymorphone ER 20 mg than for placebo (-21.0 vs. 19.5 respectively, p=0.001). Similar

difference occurred for the 0-6 and 0-24 hour intervals. See Dr. Comfort's Table EN3202-12.7 for the values. A reanalysis by Dr. Dionne Price using an all randomized and treated population of 126 patients confirmed the results from the Sponsor's analysis using an evaluable population of 104 patients.

PCA oxymorphone consumption at 0-6, 0-12, 12-24, and 0-24 hour time intervals were lower for the oxymorphone ER 20 mg group compared to the placebo group. These values are provided in the following table. The difference in mean oxymorphone consumption by PCA scores over the 0-24 hour period was 2.7 mg. The oral bioavailability of oxymorphone is approximately 10%, so that when considering mean values, the amount of PCA sparing was comparable to the amount of oral oxymorphone administered.

Table 3 PCA Oxymorphone Consumption (mg) at 0-6, 0-12, 12-24, and 0-24 Hour Time Intervals. ITT Population for PCA-Opioid Dose Sparing Evaluation

Time Interval	OCR 20	Placebo	Inferential Statistics	
	(N=58)	(N=58)	Source	p-value
0-6 Hours				
N	50	54	Treatment [1]	0.0842
Mean	1.59	1.88	Site [1]	0.0086
Standard Deviation	1.571	1.449	Treatment*Site [2]	0.7136
0-12 Hours				
N	50	54	Treatment [1]	0.0187 *
Mean	3.07	3.98	Site [1]	0.0133 *
Standard Deviation	2.901	2.666	Treatment*Site [2]	0.5014
12-24 Hours				
N	50	54	Treatment [1]	0.0312 *
Mean	2.20	3.95	Site [1]	0.0010 ***
Standard Deviation	2.204	7.089	Treatment*Site [2]	<.0001 ***
0-24 Hours				
N	50	54	Treatment [1]	0.0104 *
Mean	5.28	7.93	Site [1]	0.0007 ***
Standard Deviation	4.747	8.812	Treatment*Site [2]	0.0008 ***

Source: Sponsor's Table 11.18, P. 70 or 157.
*, **, ***: P-value significant at level 0.05, 0.01, or 0.001 respectively.
[1] From two-way analysis of variance with treatment and pooled investigational site as factors.
[2] From two-way analysis of variance with treatment, pooled investigational site, and their interaction as factors.

The patient global evaluation analyses at 12 and 24 hours or early termination were also calculated for the patient population used in the opioid sparing analysis by the Sponsor. There was no difference from the analysis presented above.

The mean pain intensity recall (VAS) scores for average pain since previous assessment at 0-6, 6-12, and 0-12 hours were approximately 10 points higher for the placebo group than oxymorphone ER 20 mg group for the three specified time intervals. See Dr. Comfort's Table EN3203-12.29 for the values.

Patients getting oxymorphone ER 20 mg did not experience fewer AEs than placebo patients. Nine patients in oxymorphone ER 20 mg group had SAEs, vs. 5 in placebo.

Summary

Efficacy was demonstrated for the oxymorphone ER 20 mg group. The primary outcome measure, mean TOTPAR 0-8 was statistically significantly better for the oxymorphone ER 20 mg group compared to placebo by the Sponsor's evaluation of an evaluable population and a reanalysis of an ITT population by Dr. Price. The secondary endpoints evaluating pain relief and pain intensity also favored the oxymorphone ER 20 mg group.

There was no statistically significant difference in mean time to rescue medication, time to onset of meaningful analgesia, and time to first experiencing 50% pain relief between the two groups. The median time to meaningful pain relief, although approximately 3 hours for oxymorphone ER 20 mg and more than 12 hours for placebo, also failed to reach statistical significance. This may be because only approximately 50% of patients in the oxymorphone ER 20 mg group and approximately 38% of patients in the placebo group reported meaningful pain relief during the first 12 hours after dosing of study medication. The number of patients experiencing 50% pain relief only differed for the two groups at 3 out of 7 time points.

The mean patient global evaluation score at 12 hours or early termination was statistically significantly better for the oxymorphone ER 20 mg group compared to placebo, but with a difference of 0.61 on a 5-point scale, is of questionable clinical significance.

The Integrated Rescue PCA and Pain Intensity Recall scores for 0-12 hours were statistically significantly better for oxymorphone ER 20 mg than for placebo by the Sponsor's analysis of an evaluable population and by a reanalysis using an ITT population. The PCA oxymorphone consumption was lower for the oxymorphone ER 20 mg group compared to the placebo group, with the difference in mean oxymorphone PCA consumption of 2.7 mg over 24 hours.

EN3202-016

Evaluation of the Efficacy and Safety of Numorphan® CR (Oxymorphone HCl Controlled-release) Compared to Placebo and OxyContin® (Oxycodone HCl Controlled Release) in Subjects with Chronic Low Back Pain

EN3202-016 was a double-blind, placebo- and active-controlled randomized withdrawal study of oxymorphone ER. The final protocol provided incorporated the three protocol amendments and so are included in the review that follows. The primary objective of the study was to evaluate the analgesic efficacy and safety of Oxymorphone ER compared to placebo in subjects with moderate to severe chronic low back pain who require opioid pain therapy. The secondary objectives were to establish an efficacious dose range, compare the analgesic efficacy and safety of OxyContin to placebo, and compare the

safety of Oxymorphone ER to OxyContin in subjects with moderate to severe chronic low back pain.

Enrollment was to be 240 male and nonpregnant, nonlactating female patients, ages 18 to 75 years of age, with the diagnosis of moderate to severe chronic lower back pain, not scheduled for surgery, and not related to cancer. The diagnosis was to have been confirmed by radiological examination or by attestation by the investigator to confirm study participation was not an attempt to acquire opioids inappropriately. Patients were to be on a stable, fixed dose of opioid for at least three days prior to enrollment, requiring less than 220 mg/day of oxymorphone (660 mg oral morphine equivalents). LBP was to be present for greater than 15 days/month and more than several hours/day, for at least 2 months. Patients were to be in good general health without clinically significant concomitant disease and on stable (X2 weeks) medications for concomitant illnesses. Adjunctive therapies for back pain were permitted as long as they were stable for at least 2 weeks prior to enrollment and were expected to remain stable. Patients with unsettled litigation, Worker's Compensation cases, or Social Security benefit determinations were to be excluded. Ongoing local regional pain treatment was to exclude patients as was related back surgery within 2 months.

Patients were to be randomized to one of four treatment groups: titrate on and remain on oxymorphone ER, titrate on oxymorphone ER and change to placebo, titrate on and remain on OxyContin, titrate on OxyContin and change to placebo. Study drug was to be administered every 12 hours. Patients were to titrate on the assigned study drug at a starting dose based on their prior total daily opioid dose. Patients were to be titrated to a dose that results in the need for no more than two doses/day of rescue medication use, with adequate pain control on the same dose, for four consecutive days. Morphine sulfate IR (15 mg) was to be the rescue medication during titration (q 4-6 hours, as needed) and the later treatment phase. Once a stable dose was achieved, patients were to enter the next study period during which, based on initial randomization, they either continued on study drug or received placebo for 18 days. Study drug dose was not to be changed during this period. During the first 4 days of the double-blind treatment phase, unrestricted rescue medication was to be permitted (q 4-6 hours, as needed), but for the next 14 days, rescue was to be restricted to a maximum of 2 doses per day. Subjects requiring more analgesic were to be discontinued from study participation.

No nonstudy opioids were to be permitted during the study including cough suppressants. No dextromethorphan was to be permitted. Daily aspirin for cardiovascular prophylaxis, and as needed doses of short acting NSAIDs or acetaminophen were to be permitted for management of fever.

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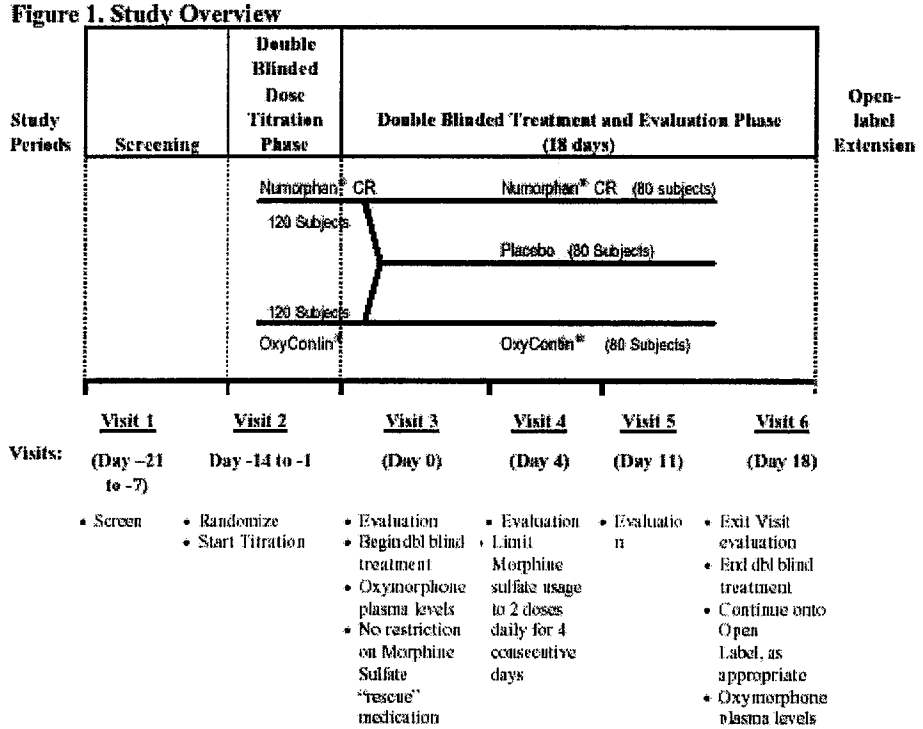
Figure 1. Study Overview



Source: Sponsor's Figure 1, Final Study Report EN3202-016, p. 101 of 6257

Patients were to record the following outcome measures three times each day in diaries received at Visits 2-5:

1. Daily Pain Intensity Assessments (VAS and categorical scale,4-point scale, prior to each dose and 4 hours after the morning dose)
2. Daily Pain Relief Assessments (prior to each dose and 4 hours after the morning dose, and prior to rescue doses)
3. Worst Daily Pain (prior to each morning dose, 4-point scale)
4. Blinded Study Medication Usage
5. Supplemental Pain Medication Usage
6. Timing of meal in relation to study drug dose

Weekly visits to the investigator were to include the following safety assessments and analgesic efficacy assessments:

1. Subject's Global Evaluation (overall satisfaction with analgesic effects and opioid side effects experienced on a 5-point scale)
2. Physician's Global Evaluation of study pain medication
3. Evaluation of compliance and rescue medication usage
4. Brief Pain Inventory - questions 3-6, 8 and 9
5. Opioid Side Effects - seven specific questions
6. Oxymorphone plasma levels at Visits 3 and 6

A physical exam and blood for laboratory evaluation were to be performed at baseline and study termination. Vital signs were to be collected at each visit. An ECG was to be performed at baseline and as needed with adverse events.

The primary efficacy analysis was to be the change from baseline to the 4-hour post-dose VAS PI at Visit 6. The secondary measures of efficacy were to be:

- Percentage change from baseline to the 4-hour post-dose VAS pain intensity at Visit 6
- Mean daily pain intensity based on the categorical scale at 4 hours post-dose
- Pain Relief from daily pain assessment at 4 hours post-dose
- Worst Daily Pain from daily pain assessments
- Brief Pain Inventory (pain intensity, pain relief and pain interference items)
- Subject's Global Assessment of Pain Medication
- Physician's Global Assessment of Pain Medication
- Time to treatment failure
- Time to withdrawal
- Amount of rescue medication usage
- Oxymorphone plasma levels

The sample size calculation was based on the primary efficacy variable of change from baseline in the VAS score for pain intensity at 4 hours after dosing, at the end of the Double-Blind Treatment Phase. By using these data from a previous study in which the treatment difference between oxymorphone ER and placebo was 15 mm on the VAS scale, with a pooled standard deviation of 31.6., it was calculated that a sample size of 70 subjects per treatment group, 210 subjects total, would be required for this study, based on a two-sided, two-sample t-test at a significance level of 5% with 80% power. An estimated total of 240 subjects, 80 per group, were to be randomized to allow for early dropouts. This number was increased to 330 subjects in order to compensate for an unexpectedly large number of dropouts during titration.

The actual protocol amendments as submitted to the IND were not provided but were summarized by the Sponsor. Protocol Amendment 1 was instituted on June 27, 2001, four months after the first subjects were enrolled in the study. Amendment 1 described the required timing of study visits in greater detail, specified that that blood samples for oxymorphone concentrations at Visit 6 should be collected only from compliant subjects, clarified inclusion and exclusion criteria, and several baseline and efficacy statistical analyses were described in greater detail than in the original protocol. This amendment did not alter the evaluation of efficacy.

Protocol Amendment 2 was instituted on May 7, 2002, when the majority of subjects had completed the study. This amendment extended the maximum allowable length of the Double-Blind Dose Titration Phase from 10 days to 14 days. In addition, Amendment 2 removed the third 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") and changed the wording describing the analysis of treatment-by-center interaction. As most patients had already been enrolled at the time of

this amendment, and the database had not been unblinded, these changes did not interfere with the analysis of efficacy.

Protocol Amendment 3, dated August 21, 2002, was instituted after all subjects had completed the study but before the data were unblinded. This amendment described a new primary efficacy endpoint as the change from baseline to last visit rather than the PI measure at the last visit. The previous statistical analysis a two-way ANOVA with treatment and center as factors in the model was replaced by an ANCOVA with treatment and center as effects and baseline pain intensity as a covariate. The secondary efficacy analysis of percentage change from baseline to Visit 6 was added, and mean daily PI based on VAS was removed. Additional statistical modifications were also incorporated.

Amendment 3 added the comparison of baseline VAS pain intensity scores between placebo subjects who had received titration with oxymorphone ER and placebo subjects who had received titration with OxyContin in an attempt to verify that these groups were equivalent in baseline scores and could therefore be pooled for the primary efficacy analysis.

The analysis planned for time to treatment failure and time to withdrawal was originally described generally as "survival analysis methods," while Amendment 3 specified these methods as the Kaplan-Meier method and the log rank test. Amendment 3 introduced an additional analysis to be performed upon the concentration of oxymorphone in plasma, the correlation coefficient between oxymorphone concentration in plasma and current pain intensity (VAS).

The changes to the planned analysis in Amendment 3 were incorporated before unblinding of the data, and so were acceptable for the analysis of efficacy.

The SAP was finalized on August 23, 2002, after the study was completed, but prior to unblinding the data. The SAP indicated that because the time of rescue medication dosing was not recorded during the titration phase, the baseline VAS score from the 4-hour evaluation would be used in all cases, whether or not the subject took rescue medication. As described in the SAP, two subjects (26-003 and 26-013) who were found to have taken medications prohibited by the protocol were also excluded as protocol violators from both modified ITT populations.

Post Hoc Analyses

The primary efficacy variable was summarized by gender within each treatment group. In the survival analysis, the secondary efficacy variables time to treatment failure and time to withdrawal were combined into a single variable, time to discontinuation because of lack of efficacy.

Fisher's exact test was used for the AE comparisons instead of the Chi Square and the Kruskal-Wallis test was used for the laboratory comparisons.

The protocol stated that for vital signs, all values outside of the pre-defined normal range would be highlighted in the individual subject listings. This was not done. However, out-

of-range laboratory values were flagged in the individual subject listings, although this was not mentioned in the protocol.

In addition to baseline comparability analyses specified in the SAP, for the two titration subgroups that were randomized to placebo, comparability analyses were performed throughout the double-blind treatment period.

RESULTS

The study was initiated on February 26, 2001 and completed on July 26, 2002. Patients were enrolled from 26 study centers. Drug diversion was discovered from Site 23. As a result, efficacy analyses were performed both with and without the inclusion of data from Site 23 and presented in the study report, but all results supporting the efficacy objectives of the protocol are based on data excluding Site 23. All demographic and safety analyses, however, were performed including the Site 23 data.

Disposition

Three hundred and thirty patients were randomized to treatment. Disposition is detailed in Table 4. Of the 166 patients in the oxymorphone ER titration group, 53 (32%) failed to complete titration. According to the Sponsor, 25 of these patients withdrew due to adverse events, and seven due to lack of efficacy. Of the 164 patients in the OxyContin titration group, 42 (27%) failed to complete titration. Twenty six of these patients withdrew due to AEs and four due to lack of efficacy. Further details of the disposition of these patients are provided in the review by Dr. Comfort, including recoding of some of these patients following review of the pertinent CRFs. Table EN3202-16.13b provides these values.

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Table 4 Patient Disposition

	Oxymorphone ER	OxyContin	Placebo	Total
Subject Disposition	(n)	(n)	(n)	(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
Modified ITT population[c] without Site 23 data	71	75	67	213

Source: Sponsor's Table 7, P 44 of 6257

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

*b*One subject (12-012) randomized to OxyContin/Placebo group withdrew during titration without taking any study drug, 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.

Once patients entered the treatment phase, there were a notable number of early terminations. Of the 80 patients remaining on oxymorphone ER, an additional 22 subjects discontinued early, 16 due to lack of efficacy and none due to adverse events. Of the 80 patients remaining on OxyContin, 21 patients discontinued early, 13 did so due to lack of efficacy and two due to AEs. Of the 75 patients who were switched to placebo, 53 discontinued early, 44 due to lack of efficacy, none due to adverse events.

Demographic characteristics did not differ appreciably between treatment groups, including years with back pain.

The Sponsor defined evaluable population excluded 98 of the 235 subjects entering the treatment phase. Inclusion in this population required that subjects had efficacy data from Week 3. The Sponsor's modified ITT population excluded the 18 subjects from Site 23 and included all randomized subjects, who completed the Dose Titration Phase, received at least one dose of study medication, and had at least one visual analog scale (VAS) pain intensity assessment completed during the Double-Blind Treatment Phase. The four additional subjects excluded did not have efficacy measurements following study drug administration.

Primary Efficacy Endpoint
The primary efficacy analysis was to be the change from baseline to the 4-hour post-dose VAS PI at Visit 6. Given that this was a withdrawal design, ideally for a treatment that was effective over the course of the study, there would be little change or improvement characterized by a lower score and an negative value for change. Both the oxymorphone and OxyContin groups were statistically significantly different from placebo (8.0 and 6.6 respectively vs. 26.6, p=0.0001 for both comparisons). The positive values represents a mild worsening of pain intensity for the active treatment groups, and a greater worsening for the placebo group. The primary endpoint was reanalyzed by Dr. Dionne Price and confirmed the Sponsor's findings. No differences were found between the two active treatment groups.

Secondary Efficacy Endpoints
The percentage change from baseline to the 4-hour post-dose VAS pain intensity at Final Visit also demonstrated statistically significant change between each active treatment group compared to placebo. However, the results were more favorable for OxyContin, with a 67% change, than for oxymorphone ER with a 112.7% change. The placebo group had a 188.5% change over the duration of the study. These results appear different from the absolute change reported for the primary analysis because rather than using the percent change of mean scores, the percent change of individual scores were determined then means calculated. These results also suggest either a greater number of oxymorphone ER patients had worsened pain intensity or that the oxymorphone ER patients had a greater degree of worsening than the OxyContin patients.

Rather than analyze the mean daily pain intensity based on the categorical scale at 4 hours post-dose the Sponsor analyzed number of subjects in each pain intensity category. The values revealed a greater proportion of patients in the mild category and fewer in the severe category for the active treatments compared with placebo. These values are presented in Dr. Comfort's Table 3202-16.7. There was little difference for the none and moderate categories.

The categorical PR at 4 hours post-dose was measured daily and the data for the final day of treatment was presented in the study report. The Sponsor analyzed the number of subjects in each category and the results show a greater number of placebo patients with scores of none and a little and the active treatments with a greater number of patients scoring moderate and a lot.

The change from baseline in Worst Daily Pain by 4-point categorical scale from daily pain assessments for the last day of treatment reveals a worsening of 0.1 unit compared for the two active treatments compared to a worsening of 0.5 units for placebo.

The Brief Pain Inventory questions, worst pain in last 24 hours, least pain in last 24 hours, average pain in last 24 hours, and pain right now, are measured on a 0-10 point scale. The results trended in favor of the two active treatments, but none of the mean differences between groups exceeded 0.9.

The results of the BPI percent pain relief in last 24 hours demonstrated greater pain relief for the oxymorphone ER and OxyContin (56.8 and 54.1%, respectively) compared to placebo (39.1%).

The patient global assessment of pain medication revealed a greater number of ratings of poor among placebo (50.7% vs. 18.3 and 16.0% for oxymorphone ER and OxyContin, respectively). There were many more reports of very good and good (60.5% and 58.7% for oxymorphone ER and OxyContin, respectively, categories combined) compared to placebo (20.9%). There was no difference for the category of excellent which was chosen by few patients from any group.

The results from the physician global assessment of pain medication was similar to the results from patient reported global.

Time to treatment failure separated the placebo group from the active treatments by Day 2. The Sponsor highlights that by Day 8, 50% of placebo patients had withdrawn due to lack of efficacy compared with approximately 10% of either oxymorphone ER or OxyContin patients. The median time to treatment failure (withdrawal due to lack of efficacy) was more than 18 days for the active groups, and 8 days for the placebo group.

The mean amount of rescue medication usage was statistically significantly different from Visits 3 to 4, 25.5 and 24.4 mg for the oxymorphone ER and OxyContin groups, respectively, compared with 34.8 mg for the placebo group, as shown in the table below. During this time period a maximum of 60 mg or morphine IR was permitted (four doses). From Visits 4 to 5 and 5 to 6, there was no difference between treatment groups (mean of approximately 14 mg/day for each of the three groups), even though the maximum permitted dosage was 30 mg/day. (Note, the amount of rescue use by some patients exceeded the maximum permitted by the protocol from Visit 4 to 5 for all three groups and from Visit 5 to 6 for the placebo group).

Table 5 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		

Source: Sponsor's Table 20, P. 60 of 6257
*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.

Peak and trough oxymorphone plasma levels did not change from Visit 3 to Visit 7 for those patients remaining on oxymorphone ER.

Summary of EN3202-016
The efficacy of oxymorphone ER bid was demonstrated in this double-blind, placebo- and active-control, randomized withdrawal study. The primary efficacy analysis, the change from baseline to the 4-hour post-dose VAS PI at Visit 6 (Day 8) was statistically significantly better for the OM ER group compared with placebo. Similar findings occurred for the OxyContin group. There was a mild worsening of pain intensity for the active treatment groups, but this may reflect some of the limitations of the use of rescue medication in the study design.

The secondary endpoints also supported the finding of efficacy for OM ER. These included additional analyses of pain intensity and pain relief, patient global assessment of pain medication, and time to treatment failure and mean amount of rescue medication usage.

Brief Pain Inventory questions, worst pain in last 24 hours, least pain in last 24 hours, average pain in last 24 hours, and pain right now trended in favor of OM ER.

EN3202-025
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 (OA) of the Knee and/or Hip

EN3202-025 was a double-blind, dose-response, parallel-group, placebo-controlled study of 10, 40, and 50 mg doses of oxymorphone ER The primary objective purpose of this 2-week, dose-ranging study was to identify the minimum effective dose and maximum tolerable dose in patients with moderate to severe pain due to osteoarthritis. Amendment 1 was incorporated into the original protocol and is included in this review.

Enrollment was to total 330 patients in anticipation of 220 patients completing. Patients were to be greater than 18 years of age, male or female, in good general health. Patients were to have Functional Class II to IV OA of the knee or hip, a diagnosis of OA based on typical hip or knee symptoms of pain, stiffness or disability with bony crepitus, and radiographic evidence within 12 months. Patients were to have OA warranting daily treatment with NSAIDs, COX2 inhibitors, acetaminophen, or opioids for 90 days prior to screening, with suboptimal response to NSAIDs, COX2 inhibitors, and acetaminophen. Patients were to have had a PI in the index joint of ≥40 mm by VAS and were to be able to discontinue prior NSAIDS and analgesics during the 2-7 day washout period. Patients were to be excluded from study participation if they had other rheumatologic diagnoses, had surgery at the index joint within 2 months or was anticipated to need surgery, prior

joint replacement of the index joint, use of corticosteroids by any route at any site within one month, or in the index joint within 2 months, viscosupplementation of the index joint within 6 months. Additional exclusion criteria were to include LFTs or creatinine more than 3 x the upper limit of normal, history of seizure, ileostomy or colostomy.

After screening, patients were to be taken off all prior analgesics during a 2 to 7 day washout period. Upon reaching a PI of 40 mm by VAS, were to be randomized for the double-blind period. Treatment arms were to be oxymorphone ER 10 mg bid, 40 mg bid, 50 mg bid and placebo for two weeks. Patients randomized to oxymorphone ER 40 mg bid and 50 mg bid were to begin on 20 mg bid for one week and then increase to their respective final doses for the second week. No rescue medication was to be permitted during the study.

No concomitant analgesics were to be permitted except aspirin $\leq$ 325mg/day for cardiovascular prophylaxis was to be allowed. No MAO inhibitors were to be permitted. Antidepressants and anticonvulsants were not to be permitted started during the study. Ongoing and unchanged adjunctive therapies were to be permitted. No regional pain treatments were to be used during the study.

The outcome measures were to be:

- WOMAC Osteoarthritis Index - 3 subscales, joint pain, joint stiffness, and physical function. Each subscale consisted of questions rated on a 100 mm VAS. For joint pain, patients rate pain walking on a flat surface, going up or down stairs, in bed at night, sitting or lying, and standing upright. For the joint stiffness, patients rate stiffness on first awakening and after resting later in the day. For physical function, patients rate degree of difficulty with 17 activities including ascending and descending stairs, rising from sitting, bending to floor.
- Arthritis pain intensity was to be an assessment of pain by VAS over the prior week.
- Patient Global Assessment of arthritis (VAS): Considering all the ways arthritis affects you, how are you doing today?
- Physician Global Assessment (VAS): How is the patient doing today?
- SF-36
- Sleep assessment: 4 questions by VAS, how often patient has had trouble falling asleep because of pain, needed sleeping medication to fall asleep, been awakened by pain during the night, awakened by pain in the morning, and overall quality of sleep.

Safety was to be assessed using ECGs, clinical labs, and physical examination obtained at screening and Visit 4 or early termination. Vital signs and adverse events were to be measured at each study visit.

The ITT population was defined as all randomized patients who took at least one dose of study medication and provided primary efficacy measures at baseline and at least once post-baseline.

The primary efficacy variable was to be the change in Arthritis PI score at final visit from baseline.

The secondary efficacy variables were to be:

- WOMAC Pain subscale
- WOMAC Stiffness subscale
- WOMAC Physical function subscale
- WOMAC Composite score
- Patient Global assessment
- Physician Global assessment
- Incidence of withdrawal due to lack of efficacy
- Time to withdrawal due to lack of efficacy
- Sleep assessments
- SF-36

Post hoc analyses were:

- Summaries and analyses of all efficacy variables at the Week 1 visit. This was in order to compare treatment with oxymorphone ER 10 mg and oxymorphone ER 20 mg with placebo
- Analyses for a dose response relationship using the Arthritis PI and WOMAC pain subscale score
- Exploratory analyses of efficacy in opioid naive and opioid experienced patients using the Arthritis PI and WOMAC pain subscale score
- No responder analysis was conducted
- Details of the analysis of the QOL variables, the sleep assessments and SF-36, were not included in the statistical plan. Each sleep assessment and SF-26 Physical and Mental Component Summary scores were analyzed during pairwise comparisons
- Incidence rates of AEs causing withdrawal for opioid naïve and opioid experienced patients, all patients, by treatment group.
- Shift tables for laboratory tests were presented with the worst post-baseline result rather than at Weeks 1 and 2.

RESULTS

The study was initiated July, 2001 and completed April 2002. Patients were enrolled from 33 study sites.

Disposition

A total of 516 patients were screened, 370 of whom were enrolled and randomized. There were high rates of early discontinuation from the oxymorphone ER 40 mg (62.4%) and oxymorphone ER 50 mg (59.3%) groups compared to the oxymorphone ER 10 mg group (35.8%) and placebo group (28.6%). The details of patient disposition are provided in the following table. Most of the withdrawals in the oxymorphone ER groups were due to AEs while in the placebo group most of the withdrawals were due to lack of efficacy. The withdrawals due to adverse events during Week 1 were nearly twice as common from the oxymorphone ER 40 and 50 mg groups (40.9% and 37.4%, respectively) while these patients were receiving 20 mg bid, compared to the oxymorphone ER 10 mg group (23.2%). There were more withdrawals due to AEs

during Week 2, 14% for both the oxymorphone ER 40 and 50 mg groups when the remaining patients started to receive the full dose, while only an additional 2% withdrew during Week 2 from the oxymorphone ER 10 mg group. Withdrawals due to lack of efficacy were similar during Week 1 for all three oxymorphone ER groups.

Table 6 Patient disposition

	Placebo N (%)	Oxymorphone 10 mg, n (%)	Oxymorphone 40 mg, n (%)	Oxymorphone 50 mg, n (%)
Treated	91 (100.0)	95 (100.0)	93 (100.0)	91 (100.0)
Completed study	65 (71.4)	61 (64.2)	35 (37.6)	37 (40.7)
Discontinued	26 (28.6)	34 (35.8)	58 (62.4)	54 (59.3)
Adverse experience	9 (9.9)	24 (25.3)	51 (54.8)	47 (51.6)
During week 1	9 (9.9)	22 (23.2)	38 (40.9)	34 (37.4)
During week 2	-	2 (2.1)	13 (14.0)	13 (14.3)
Withdrew consent	-	1 (1.1)	1 (1.1)	1 (1.1)
During week 1	-	-	1 (1.1)	-
During week 2	-	1 (1.1)	-	1 (1.1)
Lost to follow-up	2 (2.2)	1 (1.1)	-	2 (2.2)
During week 1	2 (2.2)	1 (1.1)	-	1 (1.1)
During week 2	-	-	-	1 (1.1)
Protocol violation (Week 1)	-	1 (1.1)	-	-
Lack of efficacy	15 (16.5)	7 (7.4)	5 (5.4)	4 (4.4)
During week 1	14 (15.4)	4 (4.2)	5 (5.4)	4 (4.4)
During week 2	1 (1.1)	3 (3.2)	-	-
Other (week 1	-	-	1 (1.1)	-
Intent-to-treat	87 (95.6)	92 (96.8)	91 (97.8)	87 (95.6)
Efficacy-evaluable	66 (72.5)	66 (69.5)	45 (48.4)	50 (54.9)

Source: Sponsor's Table 2, p. 48 of 5004

The Sponsor's ITT population consisted of 357 of the 370 randomized patients. One patient was excluded from the ITT when it was necessary to break the blind when hospitalized for CNS depression after receiving three doses of study medication (oxymorphone ER 20 mg). The remaining 12 patients excluded from the ITT population (four placebo patients, three oxymorphone ER 10 mg patients, two oxymorphone ER 40 mg patients, and three other oxymorphone ER 50 mg patients) were excluded because they had no post-baseline primary efficacy assessment data.

Baseline demographic characteristics were balanced across the treatment groups.

Primary Efficacy Endpoint

The Sponsor performed analyses on an efficacy population and an ITT population. The efficacy population analyses are not considered further. The Sponsor's ITT population consisted of 357 patients as noted in Disposition.

The primary efficacy analysis was the change in Arthritis PI from baseline to final visit. Using a comparison of least square (LS) means and imputing missing data by LOCF, there were statistically significantly greater reductions in pain compared to placebo for the 40 mg and 50 mg oxymorphone ER groups (p=0.006 and p=0.012, respectively), but not the oxymorphone ER 10 mg group. The change in PI for the oxymorphone ER 10 mg group was nearly the same magnitude as the change for the placebo group.

When the mean Arthritis PI VAS scores were reviewed without imputed data, the change in score from baseline to final visit are still largest for the oxymorphone ER 40 mg and 50 mg groups. However, the number of patients available to contribute data reflects the high dropout rate, particularly during Week 2. (The numbers in Table 6 are not comparable to Table 7 because with the ITT population, any patients with values during Week 1 were counted, not just those that completed the week as were counted for disposition). The amount of change in pain score did not change substantially from Week 1 to Week 2 for the oxymorphone ER 40 mg and 50 mg groups even though these patients received a lower titration dose (20 mg bid) during Week 1.

Table 7 Arthritis Pain Intensity VAS Score, ITT Population

	Observed value				Change from baseline			
	Placebo	10 mg	40 mg	50 mg	Placebo	10 mg	40 mg	50 mg
Visit/Statistics	(N=87)	(N=92)	(N=91)	(N=87)	(N=87)	(N=92)	(N=91)	(N=87)
Baseline (Visit 2)								
N	87	92	91	87	-	-	-	-
MEAN	76.9	75.7	75.6	75.4	-	-	-	-
STD	17.47	14.34	14.75	15.94	-	-	-	-
W 1 (Visit 3)								
N	87	92	91	86	87	92	91	86
MEAN	64.9	51.7	45.7	48.6	-11.9	-24.0	-29.9	-26.8
STD	28.41	29.03	31.40	29.77	27.49	26.11	29.42	28.96
W 2 (Visit 4)								
N	66	67	46	50	66	67	46	50
MEAN	53.8	54.3	40.2	41.1	-20.9	-21.3	-33.8	-37.4
STD	30.22	26.35	29.38	31.38	29.60	26.17	32.12	32.46
Final Visit (LOCF)								
N	87	92	91	87	87	92	91	87
MEAN	59.7	54.6	47.7	46.0	-17.2	-21.0	-28.0	-29.4
STD	30.94	26.68	32.11	30.18	29.61	25.44	32.00	31.22

Source: Sponsor's Appendix 16.2.2, Table 4.1.1.1, P. 396 of 5004

The data was reanalyzed by Agency Biostatistician, Dr. Dionne Price, using a more conservative population, all randomized and treated patients (n=369). Missing data was imputed using baseline observation carried forward (BOCF). The results of the reanalysis presented in Table 8 are from Dr. Price's review (Table 9). There is no statistically significant difference for any of the comparisons of the oxymorphone ER groups and placebo.

Table 8 Arthritis Pain Intensity VAS Score Baseline to Final Visit Change

	Placebo	Oxymorphone 10 mg	Oxymorphone 40 mg	Oxymorphone 50 mg
Mean (SD)	-15.9 (27.3)	-15.5 (24.2)	-17.1 (28.4)	-21.5 (30.8)
LSMean (Std Err)	-15.9 (2.91)	-15.9 (2.86)	-17.0 (2.87)	-21.2 (2.94)
Treatment vs. Placebo LSMean Difference		0.04	-1.12	-5.29
p-value		0.9922	0.7854	0.2036
95% CI		(-8.03, 8.11)	(-9.21, 6.97)	(-13.47, 2.88)

A bias results from using last observation to impute missing data when the reasons for early discontinuation are different based on treatment group assignment. Placebo patients

dropped out primarily due to lack of efficacy (16.5% for the placebo group, 4-7% for the oxymorphone ER groups), while patients in the oxymorphone ER groups dropped primarily due to adverse events (>50% for the oxymorphone ER 40 and 50 mg groups, <10% for the placebo group). As a result, the scores carried forward using LOCF reflect lack of efficacy for the placebo patients, but efficacy at doses that were not tolerated for the active treatment groups.

The Sponsor's secondary analyses were performed using the same methodology as the primary analysis, in particular, using LOCF for imputed data. As the reanalysis of the primary efficacy variable using BOCF failed, the secondary analyses were not reanalyzed.

The secondary analyses by the Sponsor demonstrated statistically significant improvement from baseline in the WOMAC Pain subscale, and Physical Function subscale, and Composite score for the oxymorphone ER 10 mg, 40 mg, and 50 mg groups compared to the placebo group. Statistically significant changes from baseline were demonstrated for the WOMAC Stiffness Subscale for the oxymorphone ER 40 mg and 50 mg groups. The Patient Global assessment was only better compared to placebo for the oxymorphone ER 40 mg group, while the Physician Global demonstrated better scores of the oxymorphone ER 40 mg and 50 mg groups.

The incidence of withdrawal due to lack of efficacy was 13.9% for the placebo group which according to the Sponsor's analysis was statistically significantly greater than the 5.5% incidence for the oxymorphone ER 40 mg group and the 4.6% incidence for 50 mg group but not compared to the 7.6% incidence for the 10 mg group. The Sponsor did not include analyses for the time to withdrawal due to lack of efficacy, sleep assessments or SF-36. Given the failure of the reanalysis of the primary efficacy outcome, these secondary analyses were not pursued further.

Summary of EN3202-025

The primary efficacy endpoint, change from baseline in Arthritis PI by VAS failed to provide evidence of efficacy for the three doses of oxymorphone ER studied. The analysis by the Sponsor utilizing an ITT population excluding patients who dropped out without a post treatment assessment, and imputing missing data using LOCF did find statistically significant differences between oxymorphone ER 40 mg and 50 mg compared to placebo. A reanalysis by Dr. Price using an all treated population and BOCF method for imputing missing data did not find any statistically significant difference between treatment groups. A bias results from using last observation to impute missing data because the reasons for early discontinuation were different based on treatment group assignment. Placebo patients dropped out primarily due to lack of efficacy (16.5% for the placebo group, 4-7% for the oxymorphone ER groups), while patients in the oxymorphone ER groups dropped primarily due to adverse events (>50% for the oxymorphone ER 40 and 50 mg groups, <10% for the placebo group). As a result, the scores carried forward using LOCF reflect lack of efficacy for the placebo patients, but efficacy at doses that were not tolerated for the active treatment groups.

EN3202-015
Double-blind, Placebo-Controlled, Parallel Group, Dose Ranging Comparison of the Efficacy and Safety of CR Oxymorphone (Numorphan CR), Controlled-release Oxycodone (OxyContin) and Placebo in the Treatment of OA of the Knee and/or Hip

EN3202-015 was a double-blind, parallel group, placebo- and active-controlled, multiple-dose study of oxymorphone ER. The primary objectives were to compare the analgesic efficacy of Numorphan (OM ER) 20 mg and 40 mg with placebo, and to compare the safety and tolerability of OM ER 20 mg and 40 mg with OxyContin 20 mg. The secondary objectives were to compare the efficacy of OM ER 20 mg with Oxymorphone ER 40 mg, and to compare the efficacy of Oxymorphone ER with OxyContin 20 mg.

Enrollment was to ensure 240 evaluable patients. Inclusion criteria were to be men and women, age 40 years or older, in good general health. A diagnosis of osteoarthritis was to have been made by typical joint symptoms, radiographic evidence within 6 months, involvement of one hip or knee warranting treatment with NSAIDs, acetaminophen, or opioid analgesics for 75 of prior 90 days. Patients were to have had a suboptimal response to acetaminophen and NSAIDS therapy, or previously received an opioid analgesic. Baseline pain intensity by VAS was to be $\geq$ 40 mm. Patients were to be excluded from study participation if they had any other inflammatory arthritis, gout, or other pain syndrome, had a need for surgery at the index joint within 2 months or was anticipated to need surgery during the study period, use of corticosteroids by any route at any site within one month, or in the index joint within 2 months, viscosupplementation of the index joint within 6 months. Additional exclusion criteria were to include LFTs more than 1.5 x the upper limit of normal, elevated creatinine beyond the upper limit of normal, history of seizure, ileostomy or colostomy, or use of an MAO inhibitor within 14 days.

Permitted concomitant medications were to include stable prior antidepressants, aspirin up to 325 mg/day for cardiovascular prophylaxis. Acetaminophen up to 2000 mg/day was to be permitted for reasons other than OA, and was not to be used within 24 hours of an assessment.

After a two to seven day washout of prior analgesics, patients were to be randomized to one of the four treatment arms. The treatment arms were to be OM ER 20 bid, OM ER 40 mg bid (titrated from 20 mg bid x 2weeks), OxyContin 20 mg bid (titrated from 10 bid x2 weeks), and placebo. Study visits were to take place at the end of Weeks 1, 2, 3, and 4, or upon early termination. Study drug use was to cease at the end of study Week 4. Patients were to use non-opioid analgesics until the final study visit, at the end of Week 5, when a physical dependence questionnaire was to be completed.

The outcome measures were to be:

- WOMAC Osteoarthritis Index - 3 subscales, joint pain, joint stiffness, and physical function. Each subscale consisted of questions rated on a 100 mm VAS. For joint pain, patients rate pain walking on a flat surface, going up or down stairs, in bed at

night, sitting or lying, and standing upright. For the joint stiffness, patients rate stiffness on first awakening and after resting later in the day. For physical function, patients rate degree of difficulty with 17 activities including ascending and descending stairs, rising from sitting, bending to floor.

- Arthritis pain intensity was to be an assessment of pain by VAS over the prior week.
- Patient Global Assessment of arthritis (VAS): Considering all the ways arthritis affects you, how are you doing today?
- Physician Global Assessment (VAS): How is the patient doing today?
- SF-36
- Patient's Assessment of Nausea - by VAS, assessing nausea over the prior week
- Patient's Assessment of Drowsiness- by VAS, assessing drowsiness over past week
- Sleep assessment: 4 questions by VAS, how often patient has had trouble falling asleep because of pain, needed sleeping medication to fall asleep, been awakened by pain during the night, awakened by pain in the morning, and overall quality of sleep.
- Physical Dependence Assessments - Since your last visit, have you experienced any of the following?: body aches, diarrhea, nervousness or restlessness, runny nose, sneezing, tremors or shivering, gooseflesh, loss of appetite, trouble with sleeping, increased sweating, increased yawning, weakness, increased heart rate or fever - mild, moderate or severe

Safety assessments were to include physical exam at screening and Week 5 or early termination. Vital signs were to be recorded at each study visit. ECGs were to be performed at screening and Week 4 or early termination.

The ITT population was defined as all randomized patients who had efficacy information recorded at the baseline and the Week 1 (or later) visit, the first primary efficacy variable data collection point on treatment. The ITT_2 population was defined as all randomized patients who had Arthritis Pain Intensity data at baseline and at least one post-baseline assessment.

Sample size was based on ability to provide 90% power to detect a 64 mm difference in the WOMAC pain subscale (maximum of 500 mm), or a 15 mm difference in the Arthritis PI VAS.

The Sponsor was planning to impute missing data using LOCF unless patients drop out due to lack of efficacy prior to the Week 1 visit, then BOCF was to be used.

The Sponsor planned two primary efficacy analyses, the change in Arthritis PI from baseline to final visit, and the change in WOMAC Pain Intensity VAS subscale score from baseline to final visit, both at Week 3.

The secondary efficacy analyses were to be:

- WOMAC Stiffness subscale
- WOMAC Physical Function subscale
- WOMAC Composite score
- Patient Global Assessment

- Physician Global Assessment
- Incidence of withdrawal due to lack of efficacy
- SF-36
- Sleep Assessments

Safety assessments were to include physical exam at screening and Week 5 or early termination. Vital signs were to be recorded at each study visit. ECGs were to be performed at screening and Week 4 or early termination.

Protocol Amendment No. 1, dated December 1, 1999, made allowance for enrolling up to 480 patients to ensure 240 evaluable patients, and changed the upper limit for AST and ALT abnormality to 2 x the ULN from 1.5, and to 1.5 x ULN for creatinine from >ULN. The nature of these changes did not adversely influence the analysis of efficacy.

RESULTS

The study was initiated July, 1999 and completed May, 2000. Patients were enrolled from 31 study centers.

Data from Center 002 were excluded from the efficacy analyses because results from this group of subjects could have been compromised by drug diversion that occurred at this site. The Sponsor notified the FDA that the study coordinator at this center was diverting study drug by enrolling herself and friends into the study.

Disposition:

Of the 491 patients randomized, 489 received at least one dose of study medication. There was a large number of dropouts from the trial, 222 patients (45.2%). The greatest number of dropouts was from the Oxymorphone ER 40 mg group (56.2%), followed by Oxymorphone ER 20 mg (47.9%). Forty percent of the OxyContin patients dropped out and the fewest patients dropped out from the placebo group (37%). Most of the dropouts from the active treatment groups were due to adverse events, 47.1% from the Oxymorphone ER 40 mg group, 38.0% from the Oxymorphone ER 20 mg group, 24.8% from the OxyContin 20 mg group, and only 4.8% from the placebo group. In contrast, the dropouts due to lack of efficacy were most common from the placebo group (27.4%) followed by the OxyContin group (10.4%), the oxymorphone ER 40 mg group (7.4%), and the oxymorphone ER 20 mg group (4.1%).

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Table 9 Study Disposition

	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.

Source: Sponsor's Table 10.1, P.40/1007

The Sponsor defined the ITT population as those patients receiving therapy and having the post-treatment assessment at the Week 1 visit. Due to the high number of dropouts, 94 patients were excluded from the ITT population. This represented 41 patients from the Oxymorphone ER 40 mg group, 33 from the Oxymorphone ER 20 mg group, 14 from the OxyContin group, and 6 from the placebo group. The Sponsor also defined an ITT_2 population which included all randomized patients who had baseline and one post-baseline assessment.

Baseline and demographic characteristics did not differ between groups. See Dr. Comfort's Table EN3202-15.5 for details.

Primary Efficacy Endpoint

The analysis of the change in Arthritis PI VAS score from baseline to final visit performed by the Sponsor revealed a statistically significant improvement for the Oxymorphone ER 40 mg group compared to placebo, but not for either the Oxymorphone ER 20 mg or OxyContin 20 mg groups.

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Table 10

Table 11.1: Mean at Baseline and LS Mean Change from Baseline in Arthritis Pain Intensity (VAS) – ITT Population Excluding Center 2

	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.

Source: Sponsor's Table 11.1, P. 47/1007

The table below reveals PI scores for the Arthritis PI VAS. Only 56% and 58% of subjects included in the Sponsor's analysis population were still participating in the study at Week 3 for the oxymorphone 40 mg and 20 mg groups, respectively. This represents only 34% of the patients originally randomized to the oxymorphone 40 mg group and 40% of the patients originally randomized to the oxymorphone ER 20 mg group.

Table 11 Raw Arthritis PI Scores (VAS, ITT Population excluding Site #002)

	Mean API in mm, (SE)		
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

Source: Appendix 15.3, Table 4.1.1.1, P. 91 of 1641

The primary efficacy variable was reanalyzed by Dr. Price using a more conservative population, all randomized patients, and missing data was imputed using BOCF regardless of reason for early study withdrawal. As can be seen in the table below from Dr. Price's review, there were no statistically significant differences between the treatment groups and placebo.

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Table 12 Mean Change in Arthritis PI (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)			

A bias can result from using last observation to impute missing data when the reasons for early discontinuation are different based on treatment group assignment. Placebo patients dropped out primarily due to lack of efficacy, while patients in the oxymorphone ER groups dropped primarily due to adverse events. As a result, the scores carried forward using LOCF reflect lack of efficacy for the placebo patients, but efficacy at doses that were not tolerated for the active treatment groups. Using BOCF for dropouts due to lack of efficacy and LOCF for all other dropouts further exaggerates these differences.

The Sponsor's secondary analyses were all performed using the same methodology as the primary analysis and suffer from the same methodological problems as described for the Arthritis PI analysis above. The Sponsor's analyses revealed statistically significantly greater reductions the WOMAC Pain Intensity subscale for the Oxymorphone ER 40 mg and 20 mg groups compared to placebo, but not for the OxyContin group. The analysis of the WOMAC Stiffness subscale revealed statistically significant improvement of the Oxymorphone ER 20 mg group compared to placebo. The analysis of the WOMAC Physical Function subscale and Composite score demonstrated statistically significant improvements for the Oxymorphone ER 40 mg and Oxymorphone ER 20 mg groups compared to placebo.

The Sponsor's analyses for the Global assessments, Sleep Assessments and SF-36 were also flawed due to the methodology for selecting the analysis population and method of imputation of missing data. The Patient Global Assessment revealed statistically significant improvements for the Oxymorphone ER 20 mg and 40 mg groups at Week 3 compared to placebo and for the Oxymorphone ER 40 mg group at Week 4. The Physician Global Assessment demonstrated statistically significant improvements for all three active treatment compared to placebo at Weeks 3 and 4.

The incidence of withdrawal due to lack of efficacy was statistically significantly lower for the three active treatment groups compared to placebo. The results for the Sleep Assessments and SF-36 were inconsistent over Weeks 3 and 4.

Summary of EN3202-015
There was a very large number of dropouts from the trial, 222 patients (45.2%). Forty-seven percent of the patients in the oxymorphone ER 40 mg group dropped out due to adverse events and 38.0% from the oxymorphone ER 20 mg group, compared to only 4.8% from the placebo group. In contrast, 27.4% of placebo patients dropped out due to lack of efficacy compared to 7.4% the oxymorphone ER 40 mg patients and 4.1% of the oxymorphone ER 20 mg patients.

The primary efficacy endpoint, change from baseline in Arthritis PI by VAS failed to provide evidence of efficacy for the two doses of oxymorphone ER studied. While the analysis by the Sponsor and imputing missing data using LOCF for lack of efficacy and BOCF for other causes, did find statistically significant differences between oxymorphone ER 40 mg compared to placebo, a reanalysis by Dr. Price using an all treated population and BOCF method for imputing missing data for all causes did not find any statistically significant difference between treatment groups. The latter analysis is considered the appropriate for the following reasons. Carrying forward the last observation for patients dropping out due to lack of efficacy while using BOCF for other dropouts biases in favor of the active treatment group in this situation because the reasons for early discontinuation were different based on treatment group assignment. As a result, the scores carried forward using BOCF reflect lack of efficacy for the placebo patients, while using LOCF for dropouts primarily for the active treatment patients reflect efficacy at doses that were not tolerated for the active treatment

Other studies
EN3202-017
Title: Open-Label, Sequential Crossover Evaluation of the Analgesic Dose Equivalence, Efficacy and Safety of Controlled-Release Oxymorphone (Numorphan CR) Relative to Controlled-Release Oxycodone (OxyContin) and Controlled-Release Morphine (MS Contin) in Patients With Cancer Pain

This was an open-label, crossover study comparing oxymorphone ER with OxyContin and MS Contin in patients with chronic cancer pain. The primary objectives of this study were to compare the analgesic efficacy and tolerability of oxymorphone ER to both extended-release morphine (MS Contin) and to extended-release oxycodone (OxyContin). The secondary objectives of the study were to compare the analgesic dose equivalence and safety of extended-release oxymorphone to both extended-release morphine (MS Contin) to extended-release oxycodone (OxyContin).

Enrollment was planned to result in 30 patients assigned to each of two treatment arms. Patients were to have been using at least 30 mg of extended-release morphine or 20 mg extended-release oxycodone, or the analgesic equivalent, and were to be transferred to MS Contin or OxyContin given q12h. Patients were to be stabilized, requiring $\leq$3 rescue doses of an opioid/day, averaged over 3 consecutive days) within two weeks. Rescue

medication was to be an immediate-release formulation of the same opioid. At the completion of the titration period, patients were to remain on the treatment for 7 days.

After seven days, patients were to switch to oxymorphone ER for 7 days at an estimated equianalgesic dose with adjustment as needed. Rescue was to be oxymorphone IR.

Assessments were to measure pain, nausea, and drowsiness

Results
The study was initiated October, 1999 and completed August, 2000. Patients were enrolled from 16 study centers. Eighty seven patients were screened, and 86 patients received study medication. Fifty-two patients entered the study on or transferred to OxyContin, 42 of whom remained in the study long enough to enter the oxymorphone ER treatment period. Thirty-four entered on, or transferred to MS Contin, 21 of whom remained in the study long enough to enter the oxymorphone period.

The Sponsor noted that the estimation of dose ratios was subject to limitation imposed by the open-label design of the study. The allowance for dose adjustments and rescue medication may have confounded the outcome. The availability of only one strength of oxymorphone ER (20 mg) and IR (5 mg) in contrast to MS Contin and OxyContin limited the flexibility in adjusting the dose of oxymorphone, which may have lead to an over-estimation of the dose of oxymorphone needed to provide equianalgesia to MS Contin and OxyContin. The Sponsor concluded that confirmation of the relative efficacy and potency needed to be obtained from a double-blind study specifically designed for this purpose.

EN3202-018
Title: A Randomized, Double-Blind, Two-Period Crossover Trial Comparing the Safety and Effectiveness of Numorphan CR (oxymorphone controlled-release tablets) and MS Contin (morphine sulfate controlled-release tablets) for the Relief of Moderate to Severe Pain in Patients with Cancer

The objectives of this study were to compare the efficacy and safety of oxymorphone ER tablets and MS Contin tablets in subjects with moderate to severe pain due to cancer, and to determine an approximate dosage ratio for conversion from other opioids to oral oxymorphone ER.

Patients were to be over 18 years of age with moderate to severe chronic cancer pain who required the use of World Health Organization (WHO) Step 3 analgesics (i.e., strong opioids) were eligible to enter the study.

The initial protocol called for screening, open-label titration with oxymorphone IR, and double-blind crossover treatment. Each subject's morphine ER dose was based on a 3:1 fixed ratio of morphine to oxymorphone. Following a protocol amendment, the design was changed to a screening/stabilization phase to determine the total daily dosage

requirement of morphine ER, and a double-blind treatment with random assignment to oxymorphone ER or morphine ER.

The primary efficacy endpoint was the 24-hour average pain intensity by BPI score at the end of each double-blind treatment period for the efficacy evaluable population. There were several other efficacy endpoints measuring PI and PR by categorical scale, use of rescue, patient and investigator global pain relief assessments, Karnofsky performance status scores, determination of the oxymorphone ER equivalent dose, and oxymorphone PK/PD relationship.

RESULTS

The study took place from March 2001 – March 2002, with patients from 25 study centers. Fifty subjects were planned but only 40 enrolled. Thirty-eight patients had titration/stabilization dosing data (20 received oxymorphone IR and 18 received morphine ER); 36 were randomized (20 to Sequence 1 and 16 to Sequence 2.

Descriptive summary statistics by period showed that the average pain score in Period 1 was lower for subjects who received morphine ER compared with subjects who received oxymorphone ER, while, the scores were similar between treatment groups for Period 2. Subjects receiving oxymorphone ER took significantly more rescue medication. Equianalgesia between oxymorphone ER and morphine ER was not attained as oxymorphone ER and morphine ER were not statistically comparable with respect to the primary efficacy analysis. A valid dose ratio could not be calculated as there was a statistically significant sequence effect. Overall, there were no apparent clinically relevant differences in the incidence or severity of AEs between treatment groups.

EN3202-019

Title: A Randomized, Double-Blind, Two-Period Crossover Study Comparing the Efficacy, Safety and Tolerability of Numorphan CR (Oxymorphone HCl, Controlled Release) and OxyContin (Oxycodone HCl, Controlled Release) in Cancer Patients Who Require Chronic Opioid Treatments

The objective of this study was to compare the efficacy, safety and tolerability of oxymorphone ER and oxycodone ER, in subjects with moderate to severe pain because of cancer, and to determine the approximate dosage ratio for conversion of subjects to oxymorphone ER from pre-study opioid analgesics or OxyContin

Patients were to be over 18 years of age, with a diagnosis of cancer accompanied by moderate to severe pain that required chronic treatment with opioid analgesics. Patients were originally to complete an initial titration/stabilization period to establish an effective and tolerable dose of oxymorphone IR, and after a protocol amendment to begin the study with stabilization on OxyContin. Patients then received either double-blind oxymorphone ER or OxyContin for 7 to 10 days followed by a crossover to the alternate treatment for 7-10 days. Morphine sulfate was to be the rescue medication.

The study was initiated March 2001 and completed March 2002. Patients were enrolled from 13 centers. Enrollment was planned to randomize 72 subjects, 45 were actually randomized.

The primary efficacy measure, analgesic efficacy, was evaluated by using the 24-hour average pain intensity rating, BPI Question 5, from the final visit of each comparison phase of the Double-Blind Treatment Period in the efficacy-evaluable population of subjects. Multiple secondary measures were planned.

Efficacy

The primary efficacy analysis, comparing patients' ratings of average 24-hour pain intensity, failed to demonstrate a significant treatment effect favoring oxymorphone ER using the ITT population.

The equivalent dose of oxymorphone ER relative to OxyContin was calculated by evaluating the amount of the two drugs averaged over the last two days of each crossover period. While subjects used twice as much oxymorphone ER as OxyContin, the lack of adequately controlled efficacy data precludes confirmation that these doses were comparably effective.

INTEGRATED ANALYSIS OF SAFETY

Summary of Safety Findings - Oxymorphone ER

At total of 1864 subjects received oxymorphone ER and/or oxymorphone IR, 1432 of whom received oxymorphone ER and 565 oxymorphone ER. There were 273 patients with at least 6 months exposure and 191 patients with at least 12 months exposure. There were 35 deaths in patients during studies of oxymorphone ER. Thirty-four of these deaths occurred in cancer patients without evidence that oxymorphone ER contributed to the cause of death. The one non-cancer death was attributed to ventricular hypertrophy. It is unknown if oxymorphone contributed to the cause of death. The toxicology report did not detect any opiates, but the Sponsor noted that it is possible that the toxicological screen used by the medical examiner might not have been capable of detecting oxymorphone.

Serious adverse events were common, occurring in 8.54% of patients exposed to oxymorphone ER. The most common SAEs were as expected for an opioid, vomiting, nausea, dehydration, dyspnea, abdominal pain. Chest pain was among the most common and represented symptoms expected in postoperative and cancer patient populations. There were several events coded as drug interaction however, that represented serious events. These patients actually experienced overdoses characterized by CNS depression and or respiratory depression after receiving oxymorphone ER in the postoperative period. These patients received oxymorphone in the postoperative period and required treatment with an opioid antagonist.

The adverse events leading to study discontinuation and general adverse events were characteristic of opioids, the most frequent were nausea, dizziness, vomiting, somnolence, pruritus, and constipation.

There are concerns involving clinically significant elevations in serum transaminases clinically significant reductions in neutrophil counts with or without low total WBC counts. The absence of follow-up data or explanation leaves the clinical significance of these findings as uncertain.

QTc prolongation was present in the ECGs of normal volunteers following dosing including two QTc intervals that were prolonged by over 100 msec. The Sponsor was unable to access the original ECG tracings so that reanalysis of these recordings was not possible. The clinical significance of these findings remain uncertain.

There was diversion of study drug at two sites reported by the Sponsor and confirmed by DSI audits.

One additional concern for this product arises from the question of whether oxymorphone is routinely present as an element of drug toxicological screens. One patient who died while reportedly taking 80 mg/day of oxymorphone ER had no opiates detected by the medical examiner screen. The Sponsor noted that "It is not likely that toxicological batteries for opiates detect oxymorphone. It is not known if the toxicological screen used by the medical examiner could have detected oxymorphone, but it is highly unlikely."

REVIEW OF SAFETY

The Sponsor submitted a single Integrated Summary of Safety (ISS) for oxymorphone ER tablets and oxymorphone IR tablets. This review will focus on the safety of oxymorphone ER. Dr. DalPan has provided an extensive review of the safety data. Sections of his review are summarized below.

EXTENT AND DURATION OF EXPOSURE

The oxymorphone clinical development program included 10 Phase 2/3 clinical trials of oxymorphone ER in patients with chronic and acute pain. In addition, there were 12 Phase 1 trials with oxymorphone ER, conducted in either healthy volunteers or subjects with hepatic or renal impairment. Of the Phase 2/3 ER trials, one was a single dose study in patients with acute post-operative pain, three were multi-dose studies in chronic non-malignant pain, and three were multi-dose studies chronic cancer pain with oxymorphone IR as rescue, ranging from one to four weeks in duration. There were three additional open-label extension trials of 1 or 2 years duration.

An individual could have participated in more than one trial or could have received more than one study treatment in a trial (e.g., both oxymorphone ER and oxymorphone IR in a single trial), or a combination of the above The Sponsor summarized study participants in two ways, the number of unique trial participants was counted according the last treatment received in the first trial in which they participated, and number of subjects participating in each trial so that each subject is counted once for each treatment received.

The number of unique patients are summarized in the table below created from two tables in Dr. DalPan's review.

Table 13 Numbers of Exposures by Subset and Treatment Group and Number of Unique Participants by Subset – All Trials Including 120-Day Safety Update

		Oxymorphone			Oxycodone			
Study Group	Total[a]	ER/IR [b]	ER	IR	ER	IR	Morphine ER	Placebo
All Trials	2542	1864	1432	565	382	195	69	473
All Phase I Trials	434	434	343	197	0	0	0	0
All Phase II/III Trials	2108	1430	1089	368	382	195	69	473
All ER Phase II/III Trials[c]	1484	1096	1089	34	382	0	69	350
All IR Phase II/III Trials[d]	624	334	0	334	0	195	0	123
Acute Postoperative Pain Trials	751	400	66	334	0	195	0	184
EN3202-012	127	66	66	0	0	0	0	61
EN3203-004	300	204	0	204	0	67	0	57
EN3203-005	324	130	0	130	0	128	0	66
Chronic Non-malignant Pain Trials	1185	684	684	0	286	0	0	289
EN3202-015	489	240	240	0	125	0	0	124
EN3202-016	326	165	165	0	161	0	0	74
EN3202-025	370	279	279	0	0	0	0	91
Cancer Pain Trials	172	145	138	34	96	0	69	0
EN3202-017	86	63	63	0	52	0	34	0
EN3202-018	38	36	32	18	0	0	35	0
EN3202-019	48	46	43	16	44	0	0	0
Open-label Extension Trials	0	460	460	0	0	0	0	0
EN3202-020[e]	0	197	197	0	0	0	0	0
EN3202-021[f]	0	164	164	0	0	0	0	0
EN3202-022[g]	0	15	15	0	0	0	0	0

[a] Total Number of unique subjects
[b] Either or both Oxymorphone formulations
[c] EN3202-012,EN3202-015,EN3202-016,EN3202-017,EN3202-018,EN3202-019, EN3202-020,EN3202-021,EN3202-022,EN3202-025
[d] EN3203-004,EN3203-005
[e] Open-label extension study for EN3202-015,EN3202-017
[f] Open-label extension for EN3202-016,EN3202-019
[g] Open-label extension for EN3202-018

Source: Sponsor Table 5 in ISS and 120-Day Safety Updated, and Response to FDA Questions, Dated August 13, 2003.

At the time of 120-Day Safety Update includes information on total of 273 subjects who had received oxymorphone ER for at least six months and 191 subjects who had received it for at least 12 months.

In all but two of the 10 Phase 2/3 studies, opioid rescue medications were permitted. The amount of opioid used was recorded for these trials and there is no means to separate the contributions of the oxymorphone ER and the immediate-release opioids to the adverse events recorded.

The demographic characteristic are well presented in Dr. DalPan's review. The mean age of Phase 2/3 oxymorphone study participants was 58.3 years. In this group of trials, 35.5% of subjects were age 65 years or older. More than half of the subjects were female, 57.5% and 89.0% of subjects were Caucasian.

Deaths

Of the 35 deaths in the clinical development program, 34 occurred in subjects with cancer pain. Twenty-eight of the 35 deaths occurred during the open-label extension and seven during the active controlled trials. Review of the deaths indicated that the 34 deaths in the cancer pain subjects were most likely due to the progression of the underlying cancer. These events are fully described in Dr. DalPan's review.

The one subject whose death was not attributable to cancer was a 43 year old man (EN3202-015-040-007) with a history of obesity and hypertension. The patient had a history of osteoarthritis if of the knees and had completed study EN3202-015, and had been participating in the open-label extension, EN3202-020 for four months at the time of his death. The patients dose of oxymorphone ER was 80 mg/day at the time of his death. The patient died suddenly, his death was attributed to right and left ventricular hypertrophy due to obesity in the medical examiner's report. The toxicology report did not detect any opiates. In response to a request for additional information, the Sponsor noted that "It is not likely that toxicological batteries for opiates detect oxymorphone. It is not known if the toxicological screen used by the medical examiner could have detected oxymorphone, but it is highly unlikely." A causal role for the drug can neither be made nor excluded with certainty.

Serious Adverse Events

There were no non-fatal serious adverse events (SAEs) in Phase 1 clinical trials.

Of the 1089 subjects exposed to oxymorphone ER in Phase 2/3 trials, 93 (8.5%) had at least one serious adverse event (SAE). The most common SAEs were vomiting, chest pain, nausea, dehydration, dyspnea, abdominal pain, drug interaction, and osteoarthritis aggravated. The four cases of 'drug interaction NOS' were cases of overdoses of oxymorphone ER in subjects who also received oxymorphone PCA in the acute post-operative setting in Study EN3202-012. In each case, the subjects developed severe CNS side effects and/or respiratory depression. Some required naloxone to reverse these effects. These are described in detail later in the review. Most of the remainder of SAEs were consistent with opioid adverse events and events that can be expected in a study population consisting of both fairly sick patients with cancer pain and patients with relatively well patients with osteoarthritis. The incidence of SAEs in at least 2 patients treated with oxymorphone ER are presented in the table below, modified from Dr. DalPan's review.

Appears This Way
On Original

Table 14 Incidence of SAEs Occurring in at Least Two Oxymorphone-Treated Subjects in Overall Phase 2/3 Clinical Development Program

	Oxymorphone		Oxycodone		Morphine	
	ER	IR	ER	IR	ER	Placebo
MEDRA Preferred Term						
Number of subjects exposed	1089	368	382	195	69	473
Number (%) of subjects with ≥1 SAE	93 (8.54%)	19 (5.16%)	9 (2.36%)	5 (2.56%)	6 (8.70%)	14 (2.96%)
Vomiting nos.	8 (0.73%)	0 (0.00%)	1 (0.26%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Chest pain nec	7 (0.64%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Nausea	6 (0.55%)	0 (0.00%)	1 (0.26%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Dehydration	5 (0.46%)	0 (0.00%)	1 (0.26%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Dyspnea nos	5 (0.46%)	1 (0.27%)	1 (0.26%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Abdominal pain nos	4 (0.37%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Drug interaction nos	4 (0.37%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Osteoarthritis aggravated	4 (0.37%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Atrial fibrillation	3 (0.28%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.21%)
Back pain	3 (0.28%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Depressed loc	3 (0.28%)	1 (0.27%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Hypotension nos	3 (0.28%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Pain in limb	3 (0.28%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.21%)
Pneumonia nos	3 (0.28%)	1 (0.27%)	1 (0.26%)	1 (0.51%)	0 (0.00%)	1 (0.21%)
Urinary retention	3 (0.28%)	1 (0.27%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Urinary tract infection nos	3 (0.28%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Venous thrombosis deep limb	3 (0.28%)	3 (0.82%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.21%)
Arthralgia	2 (0.18%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.21%)
Cellulitis	2 (0.18%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
CNS depression nos	2 (0.18%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Cerebrovascular accident nos	2 (0.18%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
COPD exacerbated	2 (0.18%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.45%)	0 (0.00%)
Concomitant disease progression	2 (0.18%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Confusion	2 (0.18%)	1 (0.27%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Diarrhea nos	2 (0.18%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Gastroenteritis nos	2 (0.18%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Hepatic encephalopathy	2 (0.18%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Hypocalcaemia	2 (0.18%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Myocardial infarction	2 (0.18%)	3 (0.82%)	0 (0.00%)	1 (0.51%)	0 (0.00%)	0 (0.00%)
Pain exacerbated	2 (0.18%)	N/A^	N/A	N/A	N/A	N/A
Pancreatitis nos	2 (0.18%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Pulmonary embolism	2 (0.18%)	0 (0.00%)	1 (0.26%)	1 (0.51%)	0 (0.00%)	0 (0.00%)
Pyrexia	2 (0.18%)	1 (0.27%)	0 (0.00%)	1 (0.51%)	1 (1.45%)	0 (0.00%)
Respiratory failure (exc neonatal)	2 (0.18%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Somnolence	2 (0.18%)	1 (0.27%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.21%)

^N/A refers to the fact that data for this preferred term was not in the original ISS. The rate of the AE for any treatment groups whose vale is N/A is therefore 0%.

Source: Appendix 3.143 in ISS and Appendix 1, Table 9 in 120-Day Safety Update

Of the 21 SAEs that were cardiac-related, 11 occurred in the oxymorphone group. Twelve of the 21 non-fatal serious AEs in this category occurred in the three trials in the post-operative setting (EN3202-012, EN3203-004, and EN3203-005). The investigators did not attribute most of these to study drug except SVT in one patient on oxymorphone

ER. The arrhythmia occurring in the context of hypotension that may have been opioid related as it responded to treatment with naloxone.

Discontinuations due to Adverse Events

In the Phase 1 trials, seven oxymorphone ER-treated subjects discontinued due to adverse events. Nausea, vomiting, headache, and dizziness were experienced by several subjects. Additional adverse events were pain in limb, hypoglycemia, toothache with right cheek swelling, hypertension, fainting, combativeness, altered mental status, and signs and symptoms of withdrawal.

The most common adverse events leading to study drug discontinuation in oxymorphone ER-treated subjects during Phase 2/3 trials were nausea, dizziness, vomiting, somnolence, pruritus, and constipation. These are consistent with known opioid-related events. The following table from Dr. DalPan's review provides this information in detail.

Table 15. Frequency of AEs Leading to Study Drug Discontinuation in Four or More Oxymorphone ER-Treated Subjects in All Clinical Trials, Original ISS

	Oxymorphone			Oxycodone		Morphine	Placebo
MEDRA Preferred Term	ER/IR	ER	IR	ER	IR	ER	
Number of Treated Subjects	1523	1045	478	276	195	35	445
Nausea	131 (8.60%)	125 (12.0%)	6 (1.26%)	32 (11.6%)	1 (0.51%)	5 (14.3%)	8 (1.80%)
Dizziness (exc vertigo)	78 (5.12%)	77 (7.37%)	1 (0.21%)	14 (5.07%)	0 (0.00%)	3 (8.57%)	4 (0.90%)
Vomiting NOS	72 (4.73%)	66 (6.32%)	6 (1.26%)	15 (5.43%)	0 (0.00%)	3 (8.57%)	7 (1.57%)
Somnolence	40 (2.63%)	35 (3.35%)	5 (1.05%)	4 (1.45%)	0 (0.00%)	1 (2.86%)	1 (0.22%)
Pruritus NOS	31 (2.04%)	31 (2.97%)	0 (0.00%)	8 (2.90%)	0 (0.00%)	1 (2.86%)	2 (0.45%)
Constipation	29 (1.90%)	28 (2.68%)	1 (0.21%)	12 (4.35%)	0 (0.00%)	1 (2.86%)	1 (0.22%)
Headache NOS	25 (1.64%)	24 (2.30%)	1 (0.21%)	7 (2.54%)	3 (1.54%)	0 (0.00%)	1 (0.22%)
Sweating increased	22 (1.44%)	20 (1.91%)	2 (0.42%)	6 (2.17%)	0 (0.00%)	1 (2.86%)	3 (0.67%)
Sedation	23 (1.51%)	19 (1.82%)	4 (0.84%)	8 (2.90%)	0 (0.00%)	1 (2.86%)	2 (0.45%)
Dry mouth	12 (0.79%)	12 (1.15%)	0 (0.00%)	2 (0.72%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Fatigue	12 (0.79%)	12 (1.15%)	0 (0.00%)	1 (0.36%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Abdominal pain NOS	12 (0.79%)	10 (0.96%)	2 (0.42%)	2 (0.72%)	0 (0.00%)	0 (0.00%)	1 (0.22%)
Confusion	13 (0.85%)	10 (0.96%)	3 (0.63%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Insomnia NEC	8 (0.53%)	8 (0.77%)	0 (0.00%)	1 (0.36%)	0 (0.00%)	0 (0.00%)	1 (0.22%)
Diarrhea NOS	8 (0.53%)	7 (0.67%)	1 (0.21%)	1 (0.36%)	0 (0.00%)	0 (0.00%)	1 (0.22%)
Lethargy	8 (0.53%)	7 (0.67%)	1 (0.21%)	2 (0.72%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Weakness	6 (0.39%)	6 (0.57%)	0 (0.00%)	4 (1.45%)	0 (0.00%)	1 (2.86%)	1 (0.22%)
Disorientation	6 (0.39%)	5 (0.48%)	1 (0.21%)	0 (0.00%)	1 (0.51%)	0 (0.00%)	0 (0.00%)
Euphoric mood	5 (0.33%)	5 (0.48%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Drug interaction NOS	4 (0.26%)	4 (0.38%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Dyspnea NOS	5 (0.33%)	4 (0.38%)	1 (0.21%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.22%)
Hallucination NOS	5 (0.33%)	4 (0.38%)	1 (0.21%)	0 (0.00%)	0 (0.00%)	1 (2.86%)	0 (0.00%)
Rigors	4 (0.26%)	4 (0.38%)	0 (0.00%)	3 (1.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Tremor NEC	5 (0.33%)	4 (0.38%)	1 (0.21%)	2 (0.72%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Urinary retention	4 (0.26%)	4 (0.38%)	0 (0.00%)	1 (0.36%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Vision blurred	4 (0.26%)	4 (0.38%)	0 (0.00%)	2 (0.72%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

Source: Appendix 3.140 in the ISS

The range of adverse events leading to discontinuation were similar across the outpatient studies, but as Dr. DalPan points out in his review, adverse events leading to study discontinuation in patients from postoperative pain trials were more commonly events involving the central nervous system, cardiac system, or respiratory system. A single case

of vomiting was the only event in the gastrointestinal system leading to study drug discontinuation in an oxymorphone ER-treated subject. Of the eight oxymorphone ER-treated in study EN3202-012, two experienced confusion, one over sedation with respiratory depression and hypoxia requiring treatment with an opioid antagonist, and one experienced vomiting.

Adverse Events

Adverse events were relatively common in the Phase 1 studies, occurring in 40.7% of oxymorphone ER treated subjects and in 30.5% of oxymorphone IR treated subjects. These are detailed below in the table from Dr. DalPan's review. Most of these adverse events are consistent with the known effects of opioids. The occurrence of palpitations is unusual.

Table 16. Adverse Events Occurring in 1% or More of Oxymorphone (ER/IR)-Treated Subjects in Phase 1 Clinical Trials

	Oxymorphone		
	ER/IR	ER	IR
Any Adverse Experience[c]	133 (36.3%)	112 (40.7%)	60(30.5%)
Dizziness (exc vertigo)	53 (14.5%)	39 (14.2%)	35 (17.8%)
Headache NOS	46 (12.6%)	35 (12.7%)	14 (7.1%)
Nausea	42 (11.5%)	32 (11.6%)	19 (9.6%)
Fatigue	34 (9.3%)	28 (10.2%)	17 (8.6%)
Vomiting NOS	24 (6.6%)	16 (5.8%)	12 (6.1%)
Constipation	11 (3.0%)	11 (4.0%)	0 (0.0%)
Euphoric mood	12 (3.3%)	11 (4.0%)	4 (2.0%)
Pruritus NOS	11 (3.0%)	9 (3.3%)	5 (2.5%)
Feeling of relaxation	8 (2.2%)	8 (2.9%)	0 (0.0%)
Somnolence	7 (1.9%)	7 (2.5%)	0 (0.0%)
Abdominal pain NOS	5 (1.4%)	5 (1.8%)	0 (0.0%)
Arthralgia	5 (1.4%)	5 (1.8%)	0 (0.0%)
Feeling hot	5 (1.4%)	5 (1.8%)	1 (0.5%)
Vision blurred	4 (1.1%)	4 (1.5%)	0 (0.0%)
Back pain	3 (0.8%)	3 (1.1%)	0 (0.0%)
Dry mouth	6 (1.6%)	3 (1.1%)	4 (2.0%)
Palpitations	4 (1.1%)	3 (1.1%)	1 (0.5%)
Rigors	3 (0.8%)	3 (1.1%)	0 (0.0%)
Sweating increased	3 (0.8%)	3 (1.1%)	0 (0.0%)
Chest pain NEC	3 (0.8%)	2 (0.7%)	1 (0.5%)
Dermatitis NOS	3 (0.8%)	2 (0.7%)	1 (0.5%)
Dyspepsia	2 (0.5%)	2 (0.7%)	0 (0.0%)
Feeling jittery	2 (0.5%)	2 (0.7%)	0 (0.0%)
Hiccups	2 (0.5%)	2 (0.7%)	0 (0.0%)
Hypertension NOS	2 (0.5%)	2 (0.7%)	0 (0.0%)
Muscle cramps	2 (0.5%)	2 (0.7%)	0 (0.0%)
Pain in limb	2 (0.5%)	2 (0.7%)	0 (0.0%)
Paresthesia NEC	4 (1.1%)	2 (0.7%)	2 (1.0%)

Source: Appendix 3.128 in the ISS

Adverse events were common in the Phase 2/3 oxymorphone IR studies, occurring in 71.0% of oxymorphone ER treated subjects, 64.6% of oxymorphone IR treated subjects, and 46.3% of placebo-treated subjects. As can be seen in the table below, modified from

Dr. DalPan's review, the adverse events occurring in at least 5% of patients were consistent with those expected of an opioid.

Table 17. Adverse Events Occurring in 5% or More of Oxymorphone ER-Treated Subjects in Phase 2/3 Clinical Trials

	Oxymorphone			Oxycodone		Morphine	
	ER/IR	ER*	IR	ER	IR	ER	Placebo
Number of Subjects N[b]	1398	1089	368	382	195	69	473
Any Adverse Experience[c]	1178	976	262	300	126	53	282
	(84.3%)	(89.6%)	(71.2%)	(78.5%)	(64.6%)	(76.8%)	(59.6%)
Nausea	515	400	63	128	38	26	71
	(36.8%)	(45.9%)	(17.1%)	(33.5%)	(19.5%)	(37.7%)	(15.0%)
Constipation	415	434	25	143	14	23	64
	(29.7%)	(39.9%)	(6.8%)	(37.4%)	(7.2%)	(33.3%)	(13.5%)
Dizziness (exc vertigo)	279	280	34	85	10	17	37
	(20.0%)	(24.2%)	(9.2%)	(22.3%)	(5.1%)	(24.6%)	(7.8%)
Pruritus NOS	268	256	30	79	12	16	46
	(19.2%)	(23.5%)	(8.2%)	(20.7%)	(6.2%)	(23.2%)	(9.7%)
Vomiting NOS	258	232	28	53	13	13	28
	(18.5%)	(21.9%)	(7.6%)	(13.9%)	(6.7%)	(18.8%)	(5.9%)
Somnolence	226	179	49	39	27	3	19
	(16.2%)	(16.4%)	(13.3%)	(10.2%)	(13.8%)	(4.3%)	(4.0%)
Sweating increased	173	199	14	71	5	13	39
	(12.4%)	(18.3%)	(3.8%)	(18.6%)	(2.6%)	(18.8%)	(8.2%)
Sedation	167	188	15	76	1	16	38
	(11.9%)	(17.3%)	(4.1%)	(19.9%)	(0.5%)	(23.2%)	(8.0%)
Headache NOS	131	129	11	44	8	3	27
	(9.4%)	(11.8%)	(3.0%)	(11.5%)	(4.1%)	(4.3%)	(5.7%)
Dry mouth	84	81	8	26	1	0	1
	(6.0%)	(7.4%)	(2.2%)	(6.8%)	(0.5%)	(0.0%)	(0.2%)
Diarrhea NOS	62	68	1	15	0	3	18
	(4.4%)	(6.2%)	(0.3%)	(3.9%)	(0.0%)	(4.3%)	(3.8%)

*Updated from 120 Safety Update

Source: Appendix 3.15 in the ISS

Patients Requiring Opioid Antagonists

Dr. DalPan did a thorough exploration of the database for all administrations of the opiate antagonist naloxone as a concomitant medication. A total of 27 subjects in the original ISS received naloxone. Twenty-three of the 27 subjects requiring naloxone were enrolled in one of the three acute post-operative pain trials (EN3202-012, EN3203-004, and EN 3203-005). The rates of naloxone use are detailed in Table 18. The incidence of use of naloxone in postsurgical patients receiving oxymorphone ER was 6.2%.

Table 18 Incidence of Naloxone Use in Acute Post-Operative Pain Trials

Study Group			
EN3202-012	Oxymorphone ER N=65	Placebo N=61	
	4 (6.1%)	0 (0.0%)	
EN3203-004 and EN3203-005	Oxymorphone IR N=334	Oxycodone IR N=123	Placebo N=195
	12 (3.6%)	1 (0.5%)	0

The four subjects in the oxymorphone ER group from the preceding table who had an adverse event coded to the term "drug interaction NOS", but these were actually overdoses. Each of these events occurred following use of a single dose of oxymorphone ER and several doses of PCA hydromorphone. The details are provided in the following table modified from Dr. DalPan's review.

Table 19. Summary of Serious Adverse Events of Drug Interaction

Subject ID/	Age/ Gender/ Race	Treatment/ Dose (mg)	Reviewer Comments
EN3202-012-011-004/	73/F/C	Oxymorphone ER/ 60	Patient had undergone left knee arthroplasty. Oxymorphone ER 60 mg was given at 9:00. Rescue doses of 0.3 mg PCA oxymorphone were given 1.5 and 2 hours later. By 11:00 am, the patient was disoriented and confused..
EN3202-012-011-023/ EN3202-012	71/M/C	Oxymorphone ER/ 20	Patient underwent right knee arthroplasty. He received seven doses of rescue medication (0.3 mg PCA oxymorphone iv) between 7:45 am and 1:47 PM. He developed severe lethargy "barely ...able to answer simple questions"), supraventricular tachycardia, and hypotension (as low as 88/51). Patient was withdrawn from the study, and administered Narcan.
EN3202-012-018-002/ EN3202-012	65/M/C	Oxymorphone ER/ 20	Patient underwent right knee arthroplasty. He was randomized to oxymorphone ER 20 mg, and received a single dose. He received ten doses of rescue medication (0.2 mg PCA oxymorphone iv) between 10:47 am and 7:00 PM. He developed severe sedation with respiratory acidosis and depressed oxygen saturation. Patient was withdrawn from the study, and administered Narcan
EN3202-012-019-018/ EN3202-012	72/F/C	Oxymorphone ER/ 20	Type II diabetes mellitus who received a single 20 dose of oxymorphone ER after right knee arthroplasty. She began to feel "hot" and became agitated, with a decline in mental status. Blood glucose levels were high (low 300s). She was given Ativan. The narcotics were held, with improvement in the mental status.

Source: Appendix 2, Listing 6 in the 120-Day Safety Update and Patient Narratives

In response to the events in Subject EN3202-012-011-004, the 60 mg oxymorphone ER dose was eliminated from the study. Subsequent protocol amendments reduced the PCA oxymorphone dose and increased the demand dose lock-out period.

Additional adverse events of lethargy, sedation, and somnolence occurred in four, four, and three subjects, respectively. Dr. DalPan reviewed the ISS dataset and found that these represented 12 individual patients, four of whom required naloxone hydrochloride for reversal of the adverse event, and for whom study drug was discontinued.

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Table 20. Adverse Events Occurring in Two or More of Oxymorphone ER-Treated Subjects in Study EN3202-012

Preferred Term	Oxymorphone ER N=65	Placebo N=61
At least one adverse event	52 (85.0%)	48 (78.7%)
Nausea	19 (29.2%)	12 (19.7%)
Pyrexia	14 (21.5%)	18 (29.5%)
Dizziness (exc vertigo)	8 (12.3%)	3 (4.9%)
Pruritus NOS	8 (12.3%)	8 (13.1%)
Confusion	3 (4.6%)	3 (4.9%)
Drug interaction NOS	3 (4.6%)	0 (0.00%)
Insomnia NEC	4 (6.2%)	1 (1.64%)
Lethargy	4 (6.2%)	0 (0.00%)
Sedation	4 (6.2%)	3 (4.9%)
Somnolence	3 (4.6%)	4 (6.6%)
Hypotension NOS	3 (4.6%)	1 (1.64%)
Vomiting NOS	3 (4.6%)	6 (9.8%)
Dry mouth	2 (3.1%)	0 (0.00%)
Hemoglobin decreased	2 (3.1%)	0 (0.00%)
Headache NOS	2 (3.1%)	2 (3.3%)

Source: Sponsor Table 5.21 in Appendix 16.2.2 of Study EN3202-012 Study Report

Selected Adverse Events

Ten events of 'Palpitations' occurred in eight subjects who received oxymorphone ER and in one subject who received oxymorphone IR. All of these events were judged to be non-serious. The clinical significance of this finding is uncertain.

Ten events of drug withdrawal occurred in nine subjects who received oxymorphone ER. study drug discontinuation. Drug withdrawal was also reported for one subject who received placebo and for two subjects who received oxycodone ER. There was little information provided for these events.

There were many mapped terms used to represent various degrees of mental status, including the use of synonyms. This can result in the appearance of a fewer number of events, as they are spread across the different terms. Some examples include somnolence and sedation, confusion, disorientation, thinking abnormal and encephalopathy. These are detailed below in the table by Dr. DalPan. Because some of these may have occurred in the same patient, more than one term may have been used to represent the underlying event, adding the frequencies as was done below likely represents an over-reporting, but the point can still be made that these events were more common than would appear by review of any one term.

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Table 21 Frequency of Any Alteration in Mental Status in All Clinical Trials

Clinical Trial Subset	Oxymorphone			Oxycodone		Morphine ER	Placebo
Preferred Term	ER/IR	ER	IR	ER	IR		
All Clinical Trials							
Number of Subjects Exposed	1764	1332	565	382	195	69	473
Any alteration in mental status	468 (26.5%)	391 (29.4%)	85 (15.0%)	124 (32.5%)	35 (17.9%)	20 (29.0%)	63 (13.3%)
Somnolence	233 (13.2%)	184 (13.8%)	49 (8.7%)	39 (10.2%)	27 (13.8%)	3 (4.3%)	19 (4.0%)
Sedation	167 (9.5%)	160 (12.0%)	15 (2.7%)	76 (19.9%)	1 (0.5%)	16 (23.2%)	38 (8.0%)
Confusion	32 (1.8%)	17 (1.3%)	15 (2.7%)	6 (1.6%)	5 (2.6%)	0 (0.0%)	5 (1.1%)
Disorientation	18 (1.0%)	15 (1.1%)	3 (0.5%)	3 (0.8%)	1 (0.5%)	1 (1.4%)	1 (0.2%)
Disturbance in attention nec	12 (0.7%)	12 (0.9%)	0 (0.0%)	3 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Lethargy	16 (0.9%)	12 (0.9%)	4 (0.7%)	3 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Mental impairment NOS	5 (0.3%)	5 (0.4%)	0 (0.0%)	1 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Depressed loc	8 (0.5%)	4 (0.3%)	4 (0.7%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)
Mental status changes	7 (0.4%)	4 (0.3%)	3 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Sedation aggravated	3 (0.2%)	3 (0.2%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	1 (0.2%)
CNS depression NOS	2 (0.1%)	2 (0.2%)	0 (0.0%)	1 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Loss of Consciousness	2 (0.1%)	2 (0.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Confusion aggravated	1 (0.1%)	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Encephalopathy NOS	1 (0.1%)	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Thinking abnl nec	1 (0.1%)	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Coma nec	4 (0.2%)	0 (0.0%)	4 (0.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Delirium	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)

Review of the above table is notable for the overall relatively high rate of any alteration in mental status in the 'All Trials' group, especially for oxymorphone ER, oxycodone ER, and morphine ER. The rates for oxymorphone IR and oxycodone IR were lower, though comparison across formulation types (i.e. ER vs. IR) are confounded by the much shorter duration of exposure in the IR-treated subjects.

Adverse Events by Dose

The adverse events were reviewed by dose at first occurrence. There is no pattern describing the dose and occurrence of these events, even though the dose range is wide, from less than 10 mg to more than 90 mg/day. This could be due to the development of tolerance to these adverse events over time, in subjects ultimately requiring higher doses.

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Table 22. Treatment-Emergent AEs by Dose (mg/day) at First Occurrence, Occurring in ≥ 5% of Oxymorphone ER treated subjects, All ER Phase 2/3 Trials

	Oxymorphone ER Dose					
MEDRA preferred term	<=10 mg	>10-29 mg	>29-50 mg	>50-70 mg	>70-90 mg	>90 mg
Nausea [a]	223	467	656	90	221	178
	43 (19.3%)	130 (27.8%)	214 (32.6%)	9 (10.0%)	25 (11.3%)	37 (20.8%)
Constipation [a]	223	472	647	81	219	160
	23 (10.3%)	112 (23.7%)	143 (22.1%)	15 (18.5%)	55 (25.1%)	48 (30.0%)
Dizziness (exc vertigo) [a]	223	481	695	99	268	199
	21 (9.4%)	68 (14.1%)	117 (16.8%)	4 (4.0%)	18 (6.7%)	21 (10.6%)
Pruritus nos [a]	223	482	685	95	256	190
	13 (5.8%)	59 (12.2%)	112 (16.4%)	11 (11.6%)	20 (7.8%)	27 (14.2%)
Vomiting nos [a]	223	484	703	104	262	197
	14 (6.3%)	52 (10.7%)	123 (17.5%)	5 (4.8%)	16 (6.1%)	22 (11.2%)
Somnolence [a]	223	486	707	115	268	203
	10 (4.5%)	46 (9.5%)	94 (13.3%)	2 (1.7%)	16 (6.0%)	9 (4.4%)
Sweating inc. [a]	223	479	704	92	271	195
	15 (6.7%)	36 (7.5%)	68 (9.7%)	9 (9.8%)	13 (4.8%)	25 (12.8%)
Sedation [a]	223	479	694	83	276	188
	15 (6.7%)	37 (7.7%)	56 (8.1%)	8 (9.6%)	19 (6.9%)	25 (13.3%)
Headache nos [a]	223	490	717	114	290	209
	5 (2.2%)	28 (5.7%)	58 (8.1%)	4 (3.5%)	12 (4.1%)	13 (6.2%)
Dry mouth [a]	223	491	712	113	294	216
	2 (0.9%)	25 (5.1%)	28 (3.9%)	3 (2.7%)	10 (3.4%)	8 (3.7%)
Diarrhea nos [a]	223	491	720	115	295	219
	0 (0.0%)	8 (1.6%)	29 (4.0%)	4 (3.5%)	13 (4.4%)	7 (3.2%)

[a] Total number of subjects at risk

Adverse Events in Opioid Naïve and Opioid Experienced Subjects

There was little difference in the frequency of adverse events for opioid naïve and opioid experienced patients in the Phase 2/3 trials for the more common adverse events of nausea, constipation, dizziness, vomiting, pruritus, and sweating increased.

Laboratory Tests

Dr. DalPan did a thorough review of laboratory values. There were no notable changes in serum chemistry values. Among oxymorphone ER-treated subjects with normal baseline values, there were four patients who developed clinically significantly levels elevations of AST and six with developed clinically significant elevations of ALT. There were two subjects who received oxymorphone ER in the postoperative period with clinically significant elevations in both ALT and AST, representing elevations of 5 to 10 fold. No follow-up or explanations for these findings were provided so the clinical significance of these findings remains uncertain. The only case of notable elevation in serum creatinine occurred in a cancer patient. Again, no additional information was provided.

Clinically significantly low neutrophil counts with or without low total WBC counts were recorded for six oxymorphone ER-treated subjects and one oxymorphone IR-treated subject during the Phase 1 trials following the second of two doses separated by three weeks. Each was a healthy volunteer and each had normal neutrophil values at baseline. No follow-up WBC or neutrophil counts are reported for any of these subjects. The clinical significance of these findings is unclear.

There were no clinically significant patterns of changes in vitals signs other than the cases of respiratory depression and hypotension reported previously

Dr. DalPan provided a detailed review of the ECG analysis. In each of the three Phase 1 studies, 12-lead ECGs were obtained at screening, at the beginning of each study period, and following the last blood collection of each study period. Review of individual changes reveals several QTc abnormalities among subjects exposed to oxymorphone IR. This was explored by Dr. DalPan who found that five subjects had at least one post-dose value that was ≥430 msec, four of which were increased from pre-dose. Six of the 58 subjects had at least one increase post-dosing of at least 30 msec. Two of these abnormal ECGs were concerning because of QTc prolongations of over 100 msec. Following a request for additional information the Sponsor responded that the original ECG tracings are no longer available. As a result, reanalysis of these values for reading errors such as mistaken U waves, is not possible.

There was limited ECG data from the Phase 2/3 studies. ECGs were only performed in Studies EN3202-015, EN3202-020, and EN3202-025. No quantitative analysis was performed by the Sponsor. A shift table was submitted and is reproduced from Dr. DalPan's review below. This table reveals two patients with missing ECGs on study entry (presumed normal) developed clinically significant abnormal ECGs. These abnormalities were left ventricular systolic dysfunction, a depressed ejection fraction (30-35%), sclerodegenerative changes of the aortic valve; and biatrial enlargement, left ventricular hypertrophy, and repolarization abnormalities. Three patients with abnormal but not clinical significant ECGs on study entry, developed clinically significant changes, but according to Dr. DalPan, the nature of the changes are unclear and would require a review of the recordings for clarification.

Table 23 ECG Data in Phase 2/3 Clinical Trials

Baseline	Normal	Abnormal Not CS [c]	Abnormal CS [c]	Total
Normal	220 (73.3%)	78 (26.0%)	2 (0.7%)	300
Abnormal not CS [c]	54 (20.5%)	206 (78.3%)	3 (1.1%)	263
Abnormal CS [c]	0 (0.0%)	3 (60.0%)	2 (40.0%)	5
Total	274	287	7	568

CS = Clinically Significant

Source: Appendix 8.30 in the ISS

Adverse Experiences Not From Clinical Trials

Post-marketing adverse event data are available for intravenous (NDA 11-707, approved April 2, 1959) and suppository (NDA 11-738, approved May 31, 1960) formulations of oxymorphone. These data did not contribute to an understanding of the oxymorphone ER and IR formulations.

Drug-Drug Interactions

No major clinically significant drug-drug interactions were noted in the clinical trials.

Withdrawal Effects
While the Sponsor reports that physical dependence was assessed in Study EN3202-015 using a Physical Dependence Survey, this instrument has not been not validated. The Sponsor concludes that the results from this test would be uncertain.

Six oxymorphone ER-treated subjects and two oxycodone ER-treated subjects had adverse events mapped to drug withdrawal syndrome. Two of these events occurred in Study EN3202-016, in which subjects were re-randomized to placebo treatment after stabilization on double-blind treatment with oxymorphone ER or oxycodone ER.

Overdose
As described in Dr. DalPan's review, there was one accidental overdose by a patient who mistakenly took four tablets instead of one, for one dose. The subject contacted the study site as was monitored. No adverse events were noted. Several cases of patients requiring naloxone for oversedation or respiratory depression in the postoperative setting have been described.

Drug Abuse and Abuse Liability
Oxymorphone is a mu-agonist opioid analgesic and it's abuse liability can be expected to be similar to morphine. Data from the clinical trials suggest that withdrawal will occur with abrupt discontinuation. There were two episodes of drug diversion at two clinical sites during the clinical development program as described in the review of efficacy by Dr. Shaun Comfort and summarized by Dr. DalPan, reproduced below:

> 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.

Additional Concerns
Additional concern about the ability to follow post-marketing events for this product stem from comments the Sponsor made when questioned about the lack of detectable oxymorphone levels in a study patient who died. The Sponsor noted that "It is not likely that toxicological batteries for opiates detect oxymorphone. It is not known if the toxicological screen used by the medical examiner could have detected oxymorphone, but it is highly unlikely."

DOSING

A dosing interval of 12 hours is supported by the finding of efficacy in study EN3202-016 and by the pharmacokinetic profile of OM ER. The effects of dosing during a high fat meal were less than observed for immediate-release oxymorphone formulations, indicating that these effects were limited by the ER characteristics of the formulation. There was no sign of dose dumping following dosing with a high fat meal.

Dose adjustments are called for in mild to moderate hepatic impairment, titration should begin low and proceed with close clinical monitoring. Oxymorphone is highly metabolized by the liver. Use of oxymorphone should be contraindicated in severe hepatic impairment. As oxymorphone plasma concentrations were relatively higher in the setting of renal impairment, dosing of oxymorphone should be started at low doses and titrated carefully in all categories of renal impairment under close clinical supervision.

Patients age 65 and older exhibited approximately 40% higher plasma concentrations, even after dosing was normalized by weight. Dosing in these patients begin with low starting doses and titrated carefully under close clinical supervision. No dose adjustments are called for based on gender.

SPECIAL POPULATIONS

There were too few non Caucasian subjects to adequately explore the effects of race and ethnicity on efficacy. Among oxymorphone ER-treated subjects in the Phase 2/3 ER trials, the incidence of dizziness, somnolence, and headache were slightly higher in Caucasians compared to Blacks, but the relatively small proportion of Blacks (8%) makes the clinical significance of this difference uncertain.

There were too few subjects over the age of 65 years to provide a meaningful evaluation of the effects of age on efficacy in the only trial supporting the proposed indication, EN3202-016. The frequency of some adverse events, such as somnolence and dizziness, may increase with increasing age in oxymorphone ER-treated subjects..

There were no consistent effects of gender on efficacy. Nausea, vomiting, and headache were notably more frequently in females (48.9%, 28.0%, and 14.6%, respectively), compared to males (35.9%, 13.9%, and 7.0%, respectively). This gender difference was not seen in placebo-treated subjects

The Sponsor has requested a waiver for pediatric studies. A waiver is not appropriate, but a deferral pending greater experience in adults is acceptable at this time.

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/s/

Sharon Hertz
10/15/03 04:27:08 PM
MEDICAL OFFICER

MEMORANDUM

DATE:	October 1, 2003
TO:	File, NDA 21-611
FROM:	Sharon Hertz, M.D. Team Leader, Analgesic Drug Group DACCADP
RE:	Team Leader Review of NDA 21-611, Oxymorphone Immediate-Release Tablets

RECOMMENDATIONS:

The Sponsor has demonstrated preliminary findings of efficacy of oxymorphone immediate-release tablets but has not performed sufficient clinical investigations to adequately inform the label and support marketing at this time. As a result, an approvable action is recommended. These conclusions are based the following findings:

1. The efficacy of oxymorphone immediate-release 20 mg tablets was demonstrated during two single-dose studies of postoperative pain due to orthopedic surgery involving osteotomy. Efficacy of the oxymorphone 10 mg dose was not replicated.

2. While efficacy of the oxymorphone 30 mg dose was demonstrated in one study, no benefit over the 20 mg dose was found based on pain intensity and pain relief outcome measures. Additionally, patients global ratings of satisfaction were lower for the oxymorphone immediate-release 30 mg dose compared to the 20 mg dose.

3. Multiple-dose efficacy has not been demonstrated due to limitations in the study designs.

4. An appropriate dosing interval has not been determined. The proposed dosing interval of every 6 ⁓ hours is not supported by the clinical trial findings. More than half of study patients withdrew prior to the Hour 5 assessments in both studies. The result of conservative analyses of median time to remedication was 4 to 5 hours.

5. Equianalgesic potency is unclear. An attempt to determine the relative analgesic potency of oxymorphone immediate-release and oxycodone immediate-release was unsuccessful.

6. A means for safe use in the postoperative setting has not been established, and safety in an outpatient setting has not been adequately studied. Additional safety concerns include abnormalities reported for liver function tests, WBC count, and QTc interval.

Recommendations on Phase 4 Studies:
There are no clinical Phase 4 recommendations at this time.

Deficiencies and Recommended Corrective Action:
An additional adequate and well controlled trial(s) is needed to provide the following information:
1. Safe and effective use in an appropriate opioid naïve population (s), including data on multiple dosing.

2. Safe manner of use in the postoperative setting.

3. A safe and effective dosing interval.

4. Address safety concerns about effects abnormalities reported for liver function tests, WBC count, and QTc interval.

BACKGROUND
NDA 21-610, oxymorphone immediate-extended tablets 5, 10, 20, and 40 mg tablets, was submitted by Endo Pharmaceuticals on December 20, 2002. The proposed indication for oxymorphone immediate-release (OM IR) tablets is analgesia for moderate to severe pain where the use of an opioid is appropriate. The results of two clinical trials have been submitted in support of efficacy and safety with additional safety information contributed by studies of oxymorphone extended-release tablets in which OM IR had been used during titration phases or as rescue medication.

Two trade names have been proposed by the Sponsor. The Office of Drug Safety has raised concerns about the name Opana and confusion with tincture of opium. No concerns have been raised about the name ' ——.

Immediate-release oxymorphone (Numorphan 2 and 5 mg tablets) was first approved by the FDA (NDA-11-737) in 1959 . The Sponsor reports that the oral formulation was removed from the market in 1979, for commercial reasons. Oxymorphone injectable, 1 mg/ml, for intramuscular and subcutaneous (NDA 11-707) and oxymorphone recta

suppository, 2 mg and 5 mg, (NDA 11-707 and NDA 11-738) were approved by the Agency in 1959. Both products are still marketed in the US.

This Team Leader Memo was created in conjunction with the secondary review of the Medical Officer Review of Efficacy by Dr. Shaun Comfort. The Statistical Review of the clinical studies by Dr. Dionne Price was consulted for information concerning the Sponsor's efficacy review, as well as additional analyses requested by, and performed by Dr. Price. The Medical Officer Review of Safety by Dr. Gerald DalPan was referenced for the safety evaluation along with the Sponsor's ISS. The Clinical Pharmacology and Biopharmaceutics review by Dr. David Lee was consulted for relevant sections of this memo. The clinical study reports in the NDA electronic document were also consulted during the secondary review process and in writing this memo.

SUMMARY OF FINDINGS

1. The efficacy of oxymorphone immediate-release 20 mg tablets was demonstrated during two single-dose studies of postoperative pain due to orthopedic surgery involving osteotomy. Efficacy of the oxymorphone 10 mg dose was not replicated.

2. While efficacy of the oxymorphone 30 mg dose was demonstrated in one study, no benefit over the 20 mg dose was found based on pain intensity and pain relief outcome measures. Additionally, patients global ratings of satisfaction were lower for the oxymorphone immediate-release 30 mg dose compared to the 20 mg dose.

3. Multiple dose efficacy has not been demonstrated due to limitations in the study designs.

4. An appropriate dosing interval has not been determined. The proposed dosing interval of every 6— hours is not supported by the clinical trial findings of more than half of study patients withdrawing from the study prior to the Hour 5 assessments in both studies. The median time to remedication during Study EN3203-004 was approximately 4 hours for the oxymorphone immediate-release 20 mg and 30 mg groups. During Study EN3203-005, median time to remedication was approximately 5 hours for the oxymorphone 20 mg dose found effective in this study. These time to remedication analyses excluded patients requiring rescue prior to 3 hours and 1 hour, respectively, suggesting the median time to remedication would have been even shorter had all patients been included. Simulations by the Office of Clinical Biopharmaceutics indicate that dosing every 4 hours results in accumulation with a higher steady-state C_{max} than with every 6 and every 8 hours dosing. The safety of multiple dosing at these intervals this has not been evaluated.

5. Equianalgesic potency is unclear. An attempts to determine the relative analgesic potency of oxymorphone immediate-release and oxycodone immediate-release during Study EN3203-005 was unsuccessful.

Summary of Clinical Trials

Study EN3203-004 was a 48-hour, single and multi-dose, placebo- and active-controlled study in 300 patients with post-operative pain due to knee or hip total or partial arthroplasty involving osteotomy. The results of the primary efficacy endpoint, TOTPAR 0-8, along with secondary analyses of pain relief and change in pain intensity following the single dose period demonstrate that the OM IR 10, 20, and 30 mg doses were effective when compared with placebo. Effects of exclusion of patients based on the Sponsor's definition of the evaluable population were explored in additional analyses which yielded the same results. An immediate-release formulation of oxycodone was not effective when compared with placebo. Additional analyses continued to support findings of efficacy, but not consistently for the OM IR 10, 20, and 30 mg doses. The proportion of patients experiencing 50% pain relief and the median time to 50% pain relief were statistically significantly greater for the OM IR 10 and 20 mg groups compared to placebo. Time to first perceptible pain relief did not differ between the active treatment groups and placebo while time to meaningful pain relief was statistically significantly shorter for the three OM IR groups compared to placebo. The median time to re-medication was statistically significantly longer for the OM IR 20 and 30 mg groups compared to placebo. Review of mean PR and PID scores at individual study time points failed to demonstrate any superiority of the OM IR 30 mg group over the OM IR 20 mg group while the data trended in favor of the OM IR 20 mg dose. The patient global evaluation of satisfaction with study medication was statistically significantly better for the OM IR 10 and 20 mg groups compared to placebo, but not for the OM IR 30 mg group.

The nature of the study design during the multi-dose period precludes drawing conclusions about efficacy during this portion of the study. The Sponsor also attempted to determine the dosing interval of OM IR during this study period. The analysis of the dosing interval performed by the Sponsor suggests a dosing interval of 7 to 9 hours. However, this analysis fails to account for subjects being withdrawn from the study for requiring rescue medication within 3 hours of study medication dosing, and for subjects receiving rescue medication after 3 hours of study medication dosing. Further support that the dosing interval for OM IR is not 7 to 9 hours comes from the finding that more than half of the study patients on OM IR 10 mg withdrew from the study by Hour 4 and for patients on OM IR 20 mg and 30 mg, by Hour 5.

Study EN3203-005 was a single-dose, double-blind, placebo-and active-control study of oxymorphone IR 10 mg, oxymorphone IR 20 mg, oxycodone 15 mg, and oxycodone 30 in 324 patients with postoperative pain due to orthopedic procedures involving osteotomy. The results support a finding of efficacy for oxymorphone IR 20 mg as well as the two oxycodone IR doses using the primary efficacy endpoint, TOTPAR 0-8, as well as nearly all of the secondary outcome measures. There was no efficacy demonstrated for the oxymorphone IR 10 mg dose. Effects of an evaluable population excluding subjects requiring rescue medication within the first hour were explored in