- Functional class of OA definition for enrollment expanded from levels II-III to II-IV.
- Exclusion criteria regarding pre-study administration of steroids modified to specifically exclude subjects receiving corticosteroids in the 'non-index joint
- WOMAC index, Patient and Physician Global Impression, Quality of Life, and Sleep assessment times clarified
- Central lab used to perform pregnancy tests
- Administrative changes, changes in section numbering, etc…

7.3.1.7 SPONSOR RESULTS for EN3202-25:

Disposition:
A total of 516 patients were screened for entry into the study; 370 of these patients were enrolled and randomized. The disposition of all randomized patients is summarized in the Table 25.2a, below. The highest rates of withdrawal were seen in the OM 40 mg (58/93 or 62.4%) and OM 50 mg groups (54/91 or 59.3%). The majority of withdrawals due to AEs occurred during Week 1, when patients assigned to the OM 40 and 50 mg groups were still receiving OM 20 mg. The rate of withdrawal in the OM 10 mg group was 35.8% (34/95). The lowest rate of withdrawal was seen in the placebo group (26/91 or 28.6%), which predominately occurred during Week 1 due to lack of efficacy (15/26 or 57% of all PBO discontinuations).

Table EN3202-25.2a 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	-	1 (1.1)	-	-
During 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	-	-	1 (1.1)	-
During 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)

Data Source: Table 2, EN3202-025 Clin Study Report, pg. 48

Sponsor Analysis Population Exclusions:
The Sponsor excluded 12 patients from the ITT population due to lack of post-baseline efficacy observations and 1 patient due to 'unblinding.' An Efficacy evaluable

population was created by excluding more subjects and is not considered further in this review. The excluded ITT subjects are listed in Table 25.2b, below.

Table EN3202-25.2b Sponsor ITT Exclusions

UPID	TRTMNT	D/C REASON	EXCLUSION REASON
EN3202-025-05-005	OM 10 MG	LOST TO F/U	NO POST-BASELINE EFFICACY
EN3202-025-07-004	OM 10 MG	AE	NO POST-BASELINE EFFICACY
EN3202-025-28-013	OM 10 MG	PROTOCOL VIOL	NO POST-BASELINE EFFICACY
EN3202-025-02-008	OM 40 MG	OTHER	NO POST-BASELINE EFFICACY
EN3202-025-08-005	OM 50 MG	AE	NO POST-BASELINE EFFICACY
EN3202-025-25-007	OM 50 MG	AE	NO POST-BASELINE EFFICACY
EN3202-025-29-041	OM 50 MG	LOST TO F/U	NO POST-BASELINE EFFICACY
EN3202-025-35-008	OM 50 MG	AE	NO POST-BASELINE EFFICACY
EN3202-025-02-004	PBO	LOST TO F/U	NO POST-BASELINE EFFICACY
EN3202-025-14-004	PBO	LACK OF EFFICACY	NO POST-BASELINE EFFICACY
EN3202-025-20-005	PBO	LOST TO F/U	NO POST-BASELINE EFFICACY
EN3202-025-26-005	PBO	LACK OF EFFICACY	NO POST-BASELINE EFFICACY
EN3202-025-31-002	OM 40 MG	N/A	UNBLINDED

Source: Oxymorphone ER SAS transport data file EFFICACY.XPT and discussion with Agency Statistical Reviewer

Selected Disposition Categories:

Three categories of patient disposition were examined in detail: OTHER, PROTOCOL VIOLATION, and WITHDREW CONSENT. These categories accounted for 5 patients, as shown in Table 25.2c below. The patient withdrawn for 'OTHER' had a low hemoglobin value and was withdrawn by the investigator. This should have been coded as a withdrawal due to adverse event (AE), regardless of the causal relationship to the drug. Recoding changes disposition results slightly, with the OM ER 40 mg Week 1 AE related withdrawals changing from 38 (40.9 %) to 39 (41.9%). Three patients were listed as WITHDREW CONSENT and information on these subjects is summarized in Table 25.2d below. Note that two patients would have been more correctly coded as having discontinued due to AEs, upon examination of the CRFs. The one subject listed as withdrawn due to PROTOCOL VIOLATION (Table 25.2c) appears to be correctly coded.

Table EN3202-25.2c Selected Patient Disposition Details
(Data Source: ENDSTUDY.XPT SAS transport file)

UPID	D/C Reason	Trtmnt	D/C Detail
EN3202-025-002-008	OTHER	OM ER	PHYSICIAN DECISION-PT RANDOMIZED BASED ON PHONE CLEARENCE FROM PANIC LAB RESULT FROM LOW HGB.
EN3202-025-028-013	PROTOCOL VIOLATION	OM ER	PT. DID NOT RETURN ON TIME
EN3202-025-033-003	WITHDREW CONSENT	OM ER	
EN3202-025-033-012	WITHDREW CONSENT	OM ER	
EN3202-025-035-003	WITHDREW CONSENT	OM ER	

Table EN3202-25.2d Evaluation of 'WITHDREW CONSENT' Patients

UPID	TRTMNT	Sponsor D/C Reason	Reviewer Comments & D/C Reason
EN3202-025-033-003	OM 10 mg ER	WDC	(No AEs recorded, no other reasons listed) ***D/C due to WDC***
EN3202-025-033-012	OM 40 mg ER	WDC	OM ER (note of early termination due to arrythmia, abnl heart @ baseline, pacemaker spikes noted) ***D/C due to AE***
EN3202-025-035-003	OM ER 50 mg ER	WDC	(Data clarification states patient stopped drug due to AE of sleepiness) ***D/C due to AE***

WDC = Withdrew consent, OM = Oxymorphone, ER = Extended Release, AE = Adverse Event, D/C = Discontinued

Source: Oxymorphone ER/IR (EN3202/EN3203) Response to FDA Questions Dated August 14, 2003.

Incorporation of the recoded discontinuations changes the total disposition slightly, as illustrated in the reviewer constructed Table 25.2e below.

Table EN3202-25.2e Reviewer Re-Coded Summary 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)	53 (57)	48 (53)
WITHDREW CONSENT	-	1 (1.1)	-	-
LOST TO FOLLOW-UP	2 (2.2)	1 (1.1)	-	2 (2.2)
PROTOCOL VIOLATION	-	1 (1.1)	-	-
LACK OF EFFICACY	15 (16.5)	7 (7.4)	5 (5.4)	4 (4.4)
OTHER	-	-	-	-

Data Source: Table 2, EN3202-025 Clin Study Report, pg. 48 and Reviewer calculations

Appears This Way
On Original

Protocol Entry Criteria Violations:
Eleven of 91 (12.1%) placebo patients, 17 of 95 (17.9%) OM 10 mg patients, 12 of 93 (12.9%) OM 40 mg patients, and 11 of 91 (12.1%) OM 50 mg patients violated one or more entry criteria; all but two patients (both randomized to the OM 10 mg group, ID #s 10-010 and 12-009) were granted waivers. These were granted because the Investigator considered the patients qualified for entry into the study despite failing to meet one feature of the OA criteria (most frequently criterion 5 of the inclusion criteria: evidence of osteoarthritis). One patient (# 029-024 in the OM 50 mg group) was allowed to enter the study despite beginning treatment with Feldene® 3 days under the 3-month requirement for stable therapy. A request for a listing of the was sent to the Sponsor. The following table lists the violations and reasons for granting waivers for all 49 patients.

Table EN3202-25.2c Protocol Violators Granted Waivers for Study Entry

UPID	Protocol Violation	Reason Waiver Granted
EN3202-025-002-008	E12	History of partial gastrectomy Note: The database indicates that the subject violated exclusion criterion 12; however, exclusion criterion 16 should have been indicated.
EN3202-025-003-006	I5	Bony crepitus not palpable
EN3202-025-003-008	E2	History of fibromyalgia; inactive at study entry
EN3202-025-003-009	I5	Bony crepitus not palpable
EN3202-025-003-010	I5	Bony crepitus not palpable
EN3202-025-003-012	E2	*The documentation for granting this protocol violation waiver was unable to be source-verified at the time of this response.*
EN3202-025-004-006	I7	No x-ray within the past 12 months; new x-ray to be obtained Note: The database indicates that the subject violated inclusion criterion 7; however, inclusion criterion 5 should have been indicated.
EN3202-025-004-007	I7	No x-ray within the past 12 months; new x-ray to be obtained Note: The database indicates that the subject violated inclusion criterion 7; however, inclusion criterion 5 should have been indicated.
EN3202-025-004-014	I5	No x-ray within the past 12 months; new x-ray to be obtained
EN3202-025-004-019	I7	Washout period extended to 8 days
EN3202-025-004-021	I7	Washout period extended to 8 days
EN3202-025-005-002	I5	X-ray more than 12 months prior to Screening
EN3202-025-005-013	I5	Bony crepitus not palpable
EN3202-025-006-001	I5	Tylenol for sinus headache Note: The database indicates that the subject violated inclusion criterion 5; however, inclusion criterion 7 should have been indicated.
EN3202-025-006-009	I5	Subject was enrolled 9 days after Screening (protocol specifies 7-day window) Note: The database indicates that the subject violated inclusion criterion5; however, inclusion criterion 7 should have been indicated.
EN3202-025-008-012	E16	History of lupus erythematous; subject in complete remission at study entry
EN3202-025-008-013	E2	History of fibromyalgia; inactive at study entry
EN3202-025-009-023	I5	Bony crepitus not palpable
EN3202-025-009-023	I5	Bony crepitus not palpable
EN3202-025-009-025	I5	Bony crepitus not palpable
EN3202-025-012-010	E1 E9	History of gout; no medication for 3 years Recovered alcoholic
EN3202-025-014-002	I5	Not all 4 signs and symptoms of OA present
EN3202-025-014-003	I5	Not all 4 signs and symptoms of OA present

UPID	Protocol Violation	Reason Waiver Granted
EN3202-025-014-027	E12	Elevated CPK at Baseline
EN3202-025-017-009	NONE	This subject met all inclusion/exclusion criteria for the study; no waiver was granted. It was erroneously reported on the CRF that a waiver was granted.
EN3202-025-024-003	I5	Bony crepitus not palpable
EN3202-025-024-004	I5	Bony crepitus not palpable
EN3202-025-024-007	I5	Bony crepitus not palpable
EN3202-025-024-009	I5	Bony crepitus not palpable
EN3202-025-024-010	I5	Bony crepitus not palpable
EN3202-025-028-003	I5	No x-ray within the past 12 months; new x-ray to be obtained
EN3202-025-028-004	I5	No x-ray within the past 12 months; new x-ray to be obtained
EN3202-025-029-024	NONE	Subject not stabilized (few days short of 3 months) on Feldene therapy
EN3202-025-030-001	I5	Bony crepitus not palpable
EN3202-025-030-003	I5	Subject missed 5 out of 90 days of required analgesic treatment for OA
EN3202-025-030-004	I5	Subject missed 3 out of 90 days of required analgesic treatment for OA
EN3202-025-030-007	I5	Subject missed 6 out of 90 days of required analgesic treatment for OA
EN3202-025-030-008	E2	History of fibromyalgia; inactive at study entry
EN3202-025-030-010	I5	Subject discontinued OA medication 5 days prior to Screening
EN3202-025-030-012	E2	History of polymyalgia rheumatica; inactive at study entry
EN3202-025-030-013	I5	Subject missed 11 out of 90 days of required analgesic treatment for OA
EN3202-025-030-017	I5	Bony crepitus not palpable
EN3202-025-030-023	E2	History of inflammatory arthritis; subsided with hydroxychloroquine treatment
EN3202-025-030-026	I5	No x-ray within the past 12 months; new x-ray to be obtained
EN3202-025-030-028	I5	Bony crepitus not palpable
EN3202-025-030-029	E2	History of polymyalgia rheumatica; inactive at study entry
EN3202-025-030-032	E2	History of fibromyalgia; inactive at study entry
EN3202-025-035-001	I5	Last x-ray 13 months prior to Screening
EN3202-025-032-017	I5	Knee OA is patellofemoral rather than tibiofemoral
EN3202-025-030-034	I5	History of fibromyalgia; inactive at study entry Note: The database indicates that the subject violated inclusion criterion5; however, exclusion criterion 2 should have been indicated.

Relevant Inclusion Criteria:

I-5: Patient has osteoarthritis as defined by: Functional Class I-III; presence of typical hip and/or knee osteoarthritis joint symptoms (pain, stiffness, disability) and signs (bony crepitus); involvement of at least one hip or knee joint that has warranted daily treatment with NSAIDs, COX2 inhibitors, acetaminophen, or opioid; analgesics (including tramadol) for 90 days preceding the Screening visit and, in the opinion of the Investigator, the patient has had suboptimal response to acetaminophen, COX2, and NSAIDs; radiographic evidence (index joint) within 12 months prior to the Screening Visit of osteoarthritis in the medial and/or lateral tibiofemoral compartment of the knee (with or without patellofemoral osteoarthritis) and/or osteoarthritis in the hip as defined by at least one of the following: osteophytes, joint space narrowing, periarticular sclerosis or subchondral cysts, with a minimum of Grade II severity, as determined by a physician qualified by experience and training.

I-7: The patient must be able to discontinue NSAIDs and other analgesics (except aspirin < 325 mg QD for cardiovascular prophylaxis) during the 2- to 7-day washout period and all analgesics other than the study medication and aspirin (as above) throughout the double-blind study period.

Relevant Exclusion Criteria:

E-1: The patient has been diagnosed as having any gout, pseudo-gout or Paget disease that in the Investigator opinion would interfere with the assessment of pain and other symptoms of osteoarthritis.

E-2: The patient has been diagnosed with inflammatory arthritis or fibromyalgia.

E-9: The patient has a significant prior history of substance abuse or alcohol abuse.

E-12: The patient has AST, ALT, or creatinine >3 x the ULN at Screening, or any laboratory abnormality, which in the opinion of the Investigator would contraindicate study participation.

E-16: The patient has any clinically significant condition that would, in the Investigator's opinion, preclude study participation.

Source: Oxymorphone ER/IR (EN3202/EN3203) Response to FDA Questions Dated August 14, 2003

Demographic and Baseline Characteristics:
The treatment groups were generally comparable. The mean age of patients ranged from 60 (±11.2) years in the placebo group to 63 (±10.9) years in the OM 10 mg group (see Table 25.3a). The proportion of male patients ranged from 31.6% (30 of 95 patients) in the OM 10 mg group to 46.2% (42 of 91 patients) in the OM 50 mg group. Over 85% of the patients in each treatment group were Caucasian.

Table EN3202-25.3a Demographic Characteristics

	Placebo (N=91)	Oxymorphone 10 mg (N=95)	Oxymorphone 40 mg (N=93)	Oxymorphone 50 mg (N=91)
Age (yrs.)				
N	91	95	93	91
MEAN	60	63	62	62
STD	11.15	10.87	11.51	11.42
MIN	36	30	34	38
MAX	93	84	85	85
Sex - N (%)				
MALE	39 (42.9)	30 (31.6)	35 (37.6)	42 (46.2)
FEMALE	52 (57.1)	65 (68.4)	58 (62.4)	49 (53.8)
Race - N (%)				
CAUCASIAN	81 (89.0)	82 (86.3)	87 (93.5)	83 (91.2)
BLACK	8 (8.8)	9 (9.5)	6 (6.5)	6 (6.6)
HISPANIC	0	1 (1.1)	0	0
OTHER	2 (2.2)	3 (3.2)	0	2 (2.2)
Height (in.)				
N	91	95	92	91
MEAN	66.5	65.9	66.2	66.9
STD	3.89	3.74	4.76	4.00
MIN	59.0	57.0	54.0	59.0
MAX	78.0	74.0	78.0	76.0
Weight (lb.)				
N	91	95	92	91
MEAN	220.2	209.0	209.2	207.3
STD	55.62	50.01	52.07	48.90
MIN	114.0	116.0	104.0	110.0
MAX	425.0	360.0	350.0	353.0

Data Source: Table 3, EN3202-025 Clin Study Report, pg. 50

Baseline Characteristics:
OA characteristics were well balanced across treatment groups, however some small differences were observed. Patients with the knee identified as the "index joint" were slightly more common in the OM 40 mg group (85.0%, 79/93 patients), than the other

treatment groups: placebo (75.8%, 69/91 patients), OM 10 mg (81.1% or 77/95 patients), OM 50 mg (79.1% or72/91 patients).

Patients receiving opioid analgesic therapy just prior to "washout" were more common in the OM 40 mg group (39.8%, or 37/93 patients) compared to the other three treatment groups (ranging from 25.3% in the placebo group to 27.4% in the OM 10 mg group). Other OA features (i.e. Function class, Signs & Symptoms, etc...) appear to be similarly distributed among the different treatment groups (Table 25.3b below).

Table EN3202-25.3b Osteoarthritis Baseline Characteristics

	Placebo (N=91)	Oxymorphone 10 mg (N=95)	Oxymorphone 40 mg (N=93)	Oxymorphone 50 mg (N=91)
Index Joint				
L Knee	32 (35.2)	37 (38.9)	46 (49.5)	34 (27.4)
L Hip	4 (4.4)	9 (9.5)	6 (6.5)	9 (9.9)
R Knee	37 (40.7)	40 (42.1)	33 (35.5)	38 (41.8)
R Hip	18 (19.8)	9 (9.5)	8 (8.6)	10 (11.0)
Function OA Class				
Class II	73 (80.2)	76 (80.0)	71 (76.3)	77 (84.6)
Class III	16 (17.6)	19 (20.0)	20 (21.5)	12 (13.2)
Class IV	2 (2.2)	0	2 (2.2)	2 (2.2)
OA Signs & Symptoms				
Pain	91 (100)	95 (100)	93 (100)	91 (100)
Stiffness	91 (100)	94 (98.9)	92 (98.9)	90 (98.9)
Disability	88 (96.7)	92 (96.8)	91 (97.8)	88 (96.7)

Source: Appendix 16.2.2, Table 2.4 pg. 1 of 1, EN3202-025 Clinical Study Report

Sponsor's Efficacy Analysis Results:

Primary Efficacy Variables:

Arthritis Pain Intensity VAS Score Change from Baseline to Final Visit

The Sponsor's efficacy analysis (based on the ITT population of 357 patients) demonstrated statistically significant improvement in pain intensity in both the OM 50 and 40 mg groups at Week 2 (p=0.006 and p=0.012, respectively), compared to PBO. The OM ER 10 mg dose did not reach significance when compared to the PBO response at the end of Week 2. These statistical results are summarized in Tables 25.4a and b, below.

Table EN3202-25.4a Arthritis Pain Intensity (API)
Raw VAS Scores (in mm) for ITT Patients

	Placebo (N = 87)	Oxymorphone 10 mg (N = 92)	Oxymorphone 40 mg (N = 91)	Oxymorphone 50 mg (N = 87)
Baseline (Mean ± SD)	77 (17.5)	75.7 (14.3)	75.6 (14.8)	75.4 (15.9)
Final (Mean ± SD)	59.7 (31)	54.6 (26.7)	47.7 (32.1)	46 (30.2)

Data Source: Appendix 16.2.2, Tables 4.1.1.1 and 4.1.1.2

Table EN3202-25.4b Arthritis Pain Intensity VAS Score
Baseline to Final Visit Change for ITT Patients

	Placebo (N = 87)	Oxymorphone 10 mg (N = 92)	Oxymorphone 40 mg (N = 91)	Oxymorphone 50 mg (N = 87)
Mean±SD	-17.2±29.61	-21.0±25.44	-28.0±32.00	-29.4±31.22
LSMean±Std Error	-17.0±3.12	-21.3±3.04	-28.1±3.06	-29.2±3.12
Treatment comparison vs. Placebo				
LSMean Difference	-	-4.3	-11.1	-12.2
p-value	-	0.328	**0.012**	**0.006**
95% Confidence Interval	-	(-12.8, 4.3)	(-19.7, -2.5)	(-20.9, -3.5)

Data Source: Table 5, EN3202-025 Clin Study Report, pg. 55
LSmean=Least squares mean; SD=Standard deviation. Note: Negative change score indicates improvement

Reviewer's Primary Efficacy Re-Analysis Results:

In a study in which active treatment patients tend to drop out of the study for adverse events while patients in the placebo arm tend to drop out due to lack of efficacy, imputing missing data with LOCF results in a bias favoring the active treatment. Furthermore, this method does not accurately reflect the efficacy of the product because the scores carried forward from patients who drop out due to AEs reflect product efficacy at a dose that is intolerable. The data was reanalyzed by the Agency Statistical Reviewer, Dr. Price. This reanalysis was performed with an 'all randomized and treated' analysis population that excluded 12 subjects because of not having any post-baseline measures and 1 subject due to 'unblinding.' This results in an equivalent analysis population to the Sponsor's 357 ITT subjects. Missing data was imputed using baseline observation carried forward (BOCF). The results of the reanalysis are presented in Table 25.4c. There is no statistically significant difference comparing the oxymorphone groups with placebo.

Table EN3202-25.4c 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)

Data Source: Agency Biostatistical Reviewer

Sponsor's Secondary Variable Efficacy Analysis Results:

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

- Arthritis Pain Intensity VAS Score Analysis in Evaluable Patients
  Pairwise comparisons with the placebo group at the final visit showed a statistically significant difference between the OM 50 mg group (p=0.006) vs. PBO. There were no statistically significant differences between the OM 10 mg or 40 mg groups and PBO.

Table EN3202-25.5a Arthritis Pain Intensity
Raw VAS Scores (in mm) for Efficacy Evaluable Patients

	Placebo (N = 66)	Oxymorphone 10 mg (N = 66)	Oxymorphone 40 mg (N = 45)	Oxymorphone 50 mg (N = 50)
Baseline (± SD)	74.7 (17.5)	75.6 (14)	74.6 (12.8)	78.5 (15.1)
Final (± SD)	53.8 (30.2)	54.6 (26.5)	40.9 (29.4)	41.1 (31.4)

Data Source: Appendix 16.2.2, Tables 4.1.2.1 pages 1 and 2 of 2.

Table EN3202-25.5b Arthritis Pain Intensity VAS Score
Baseline to Final Visit Change for Efficacy Evaluable Patients

	Placebo (N = 66)	Oxymorphone 10 mg (N = 66)	Oxymorphone 40 mg (N = 45)	Oxymorphone 50 mg (N = 50)
Mean±SD	-20.9 (29.6)	-21.1 (26.3)	-33.7 (32.5)	-37.4 (32.5)
LSMean±Std Err	-21.7 (3.7)	-21.5 (3.7)	-32.2 (4.5)	-37.3 (4.3)
Treatment comparison vs. Placebo				
LSMean Difference	-	0.2	-10.5	-15.6
p-value	-	0.97	0.08	**0.006**

Data Source: Table 6, EN3202-025 Clin Study Report, pg. 57.
LSmean=Least squares mean; SD=Standard deviation. Note: Negative change score indicates improvement

- WOMAC Pain Subscale Score
  For ITT patients, pairwise comparisons with PBO at the final visit showed statistically significant differences from placebo, that increased with increasing dose (see Table 25.6 below). . The results of the analysis of the dose response relationship using WOMAC pain subscale scores for the ITT population showed a statistically significant (p=0.002) negative slope, when all doses were included in the model. Note that these results were obtained using the sponsor's ITT definition and LOCF.

- WOMAC Stiffness Subscale Score
  For ITT patients, mean changes in the OM 50 and 40 mg groups were statistically significantly different from PBO (p<0.001 and p=0.001, respectively). The OM 10 mg group did not achieve statistical significance (p=0.061) compared to PBO, at the final visit. These results are summarized in Table 25.6.

- WOMAC Physical Function Subscale Score
  For ITT patients, mean changes in each of the oxymorphone groups were statistically significantly different from PBO (p<0.001, p=0.008, and p=0.023, respectively). These results are summarized in Table 25.6.

- WOMAC Composite Index
  For ITT patients, mean changes in each of the OM groups were statistically significantly different from PBO (p<0.001, p=0.005, and p=0.017, respectively), as shown in Table 25.6 below.

Table EN3202-25.6 Baseline to Final Visit Change (mm) in WOMAC OA VAS Subscales, (ITT Population)

Variable	Time	Treatment	Difference (mm) Mean (SD)	P-value
WOMAC OA Pain Subscale	Baseline to Final	Placebo	-42.5 (123.6)	---
		OM ER 10	-83.6 (110.4)	**0.015**
		OM ER 40	-85.1 (130.2)	**0.016**
		OM ER 50	-108.0 (111.3)	**< 0.001**
WOMAC OA Stiffness Subscale	Baseline to Final	Placebo	-17.0 (44.6)	---
		OM ER 10	-29.9 (44.5)	0.061
		OM ER 40	-40.5 (61.5)	**0.001**
		OM ER 50	-48.1 (50.7)	**< 0.001**
WOMAC OA Physical Function Subscale	Baseline to Final	Placebo	-116.5 (351.3)	---
		OM ER 10	-232.9 (343.3)	**0.023**
		OM ER 40	-256.8 (379.8)	**0.008**
		OM ER 50	-310.8 (366.2)	**< 0.001**
WOMAC OA Composite Index Subscale	Baseline to Final	Placebo	-176.0 (493.0)	---
		OM ER 10	-346.4 (476.5)	**0.017**
		OM ER 40	-382.3 (549.3)	**0.005**
		OM ER 50	-461.6 (492.1)	**< 0.001**

Source: Tables 7, 8, 9, and 10 of EN3202-025 Clinical Study Report, pages 61 – 66

Note: Mean (SD) values are listed. P-values are based upon the LSMean differences and not Mean differences.

- Patient's Global Assessment of OA
  For ITT patients, the mean change in the OM 40 mg group was statistically significantly different from PBO (p=0.014), while there were no statistically significant differences between the OM 50 or 10 mg group and PBO. These results are shown in Table 25.7 below.

- Physician's Global Assessment of OA
  For ITT patients, the mean changes in the OM 50 and 40 mg groups were statistically significantly different from PBO (both p=0.025). The difference between the oxymorphone 10 mg group and PBO did not achieve statistical significance (p=0.056). These results are shown in Table 25.7 below.

- Incidence of Patient Withdrawal due to Lack of Efficacy
  Patients withdrawing from lack of efficacy decreased as the OM dose increased. Proportions of the OM 50 and 40 mg groups withdrawing due to lack of efficacy were statistically significant from placebo. There was no statistically significant difference in the proportions of OM 10 mg patients withdrawing compared to PBO.

Table EN3202-25.7 Baseline to Final Visit Change in Listed Secondary Outcome Variables, (ITT Population)

Variable	Time	Treatment	Difference (mm) Mean (SD)	P-value
Patient's Global Assessment of OA	Baseline to Final	Placebo	-15.6 (27.5)	---
		OM ER 10	-20.2 (23.9)	0.21
		OM ER 40	-25.8 (29.7)	**0.014**
		OM ER 50	-21.2 (31.1)	0.169
Physician's Global Assessment of OA	Baseline to Final	Placebo	-16.0 (26.9)	---
		OM ER 10	-24.0 (26.5)	0.056
		OM ER 40	-25.9 (31.1)	**0.025**
		OM ER 50	-26.1 (31.2)	**0.025**
Variable		**Treatment (n)**	**# Withdrawals (%)**	**P-value**
Incidence of Withdrawal due to Lack of Efficacy		Placebo (n=87)	13 (14.9)	---
		OM ER 10 (n=92)	7 (7.6)	0.138
		OM ER 40 (n=91)	5 (5.5)	**0.046**
		OM ER 50 (n=87)	4 (4.6)	**0.036**

Source: Tables 11, 12, and 13 of EN3202-025 Clinical Study Report, pages 67 – 69
Note: Mean (SD) values are listed, except for Lack of Efficacy where values are n (%). P-values are based upon the LSMean differences and not Mean differences except for Lack of Efficacy

EN3202-025 Efficacy Summary:

This 2-week, double-blind, placebo-controlled, dose-ranging study of OM ER 10, 40, and 50 mg in 240 osteoarthritis (OA) patients was submitted in support of a finding of efficacy for OM. The Sponsor's analysis of the primary outcome variable (Arthritis Pain Intensity (API) VAS score) change from baseline to the end of Week 2 demonstrated a statistically significant difference from placebo for the OM 40 and 50 mg groups. The secondary analysis also favored the 40 and 50 mg formulations, but suffered from the

same analytical flaws. Re-analysis using an all randomized population and using baseline observations carried forward (BOCF), failed to show a statistically significant difference between any of the active treatment arms and placebo.

The LOCF method for imputing data was not considered appropriate for this analysis by the Agency for two reasons. First, the differential dropout in the treatment groups, with more patients in the placebo group dropping out due to lack of efficacy and with more patients in the oxymorphone groups dropping out due to adverse events, creates bias in favor of study drug. The patients dropping out due to lack of efficacy carry forward poor scores and the patients dropping out due to AEs carry forward better scores. Additionally, patients in the 40 and 50 mg oxymorphone groups were treated with oxymorphone ER 20 mg for the first week and scores from patients who dropped out during the first week would not reflect the final assigned dose.

The primary efficacy outcome was reanalyzed using an all randomized population and using baseline observations carried forward (BOCF). This analysis failed to show a statistically significant difference between any of the active treatment arms and placebo.

In summary, the results of this study do not support a finding of efficacy for the OM 10, 40, or 50 mg doses.

7.3.1.8 Additional Supportive Studies:

Three supportive, active-controlled studies were submitted in support of efficacy. These studies were reviewed briefly for completeness, but not in detail, due to their design limitations in supporting efficacy.

Table 6.3 Oxymorphone ER Additional, Non-Placebo-Controlled, Clinical Studies

Protocol	Type	Design	Dose and Duration of Treatment	Primary Outcome	N	Reviewer Comments
3202-017	Dose equivalence, safety & efficacy; adults with Cancer pain	Open-label, sequential crossover, active controlled, multi-dose, multi-center study, 7 days on each med	OM ER 20-300 q12 hr tab MS C 15-900 q12 hr tab OC 10-600 q12 hr tab Multi-dose crossover	Change in Daily VAS Pain Intensity (PI) Assessment	86	No significant difference between PI change for MSc to OM ER vs. OC to OM ER groups
3202-018	Safety & efficacy; adults with moderate to severe cancer pain	Randomized, double-blind, Two-period crossover	Titration to optimal doses for each treatment arm: OM ER 10-100 q12 hr tab MS C 30-300 mg tab 1 wk OL titration 2 wks (1 wk/arm) crossover	24 Hr average PI score at end of each double-blind treatment period	36	OM ER and MS C not statistically comparable
3202-019	Safety & efficacy; non-inferiority design, adults with cancer pain	Randomized, double-blind, Two-period crossover; 2 week double-blind treatment period after 3-10 day screening/stabilization	Titration to optimal doses for each treatment arm: OM ER 10 – 110 OC 20 – 220 crossover	24 Hr average PI score at end of each double-blind treatment period	44	OM ER equivalence to OC?

OM = oxymorphone, OC = oxycodone or OxyContin, CR = continuous release, VAS = visual analog scale, PI = arthritis pain intensity, PI = pain intensity, hrs = hours, , MS = morphine sulfate

Data Source: Table 4.2 Clinical Trials in the Oxymorphone ER and IR Development Program, pg. 13 and EN3202-017, 018, and 019 Clinical Study Reports

7.3.1.8.1 Study EN3202-017:

Study Design:

EN3202-017 was a 1-week treatment phase (2 weeks total), multiple center, multiple dose, open- label, sequential crossover study to compare the analgesic efficacy, safety, and dose equivalence of oxymorphone ER q12h to oxycodone ER (OxyContin) q12h or morphine ER (MS Contin) q12h in outpatients with chronic cancer pain. This study planned to enroll 30 patients in four treatment sequences who already using morphine ER (30 mg/day) or oxycodone ER (20 mg/day) for chronic cancer pain. Eligible patients were to be enrolled and transferred to equianalgesic doses of MS Contin or OxyContin over a 3-day dose titration to a level of stable analgesia. Patients were to remain on their titration medication for 1 week with rescue medication available (the IR formulation of their titration medication). After one week of stable dosing, all patients were to be transferred to oxymorphone ER for 1 week at the estimated equianalgesic dose. The primary efficacy variable was to be the difference in the average daily VAS pain intensity scores measured on the last 2 days of Week 2 and Week 1, compared across treatment sequences (MS Contin to OM ER vs. OxyContin to OM ER). This was to be analyzed using an analysis population defined as all patients completing the study.

Disposition and Results:
Eighty-seven (87) patients were screened and 86 were dosed. 34 patients attained stable analgesia with morphine ER (MS Contin), with 13 subjects (38%) discontinuing treatment and 18/21 (62%) completing the study after crossing over to oxymorphone ER. The oxycodone (OxyContin) to oxymorphone sequence treatment arm had lower discontinuation rates 10/52 (19%) while taking oxycodone, and 41/52 subsequent subjects completed the oxymorphone phase. The Sponsor's analysis of the primary efficacy outcome of the study showed no statistically significant difference between the two treatment sequences in the average change in VAS pain intensity scores.

Reviewer Comments:
This study found no statistical difference between daily pain intensity scores of a morphine ER to oxymorphone ER cross-over sequence and oxycodone ER to oxymorphone ER treatment. However, this study was an open-label evaluation without placebo control. While the conclusion of no difference between treatment sequences is interesting, it is not clear that this study was designed as an actual equivalence trial capable of demonstrating 'equianalgesia' between MS Contin, OxyContin, and oxymorphone ER.

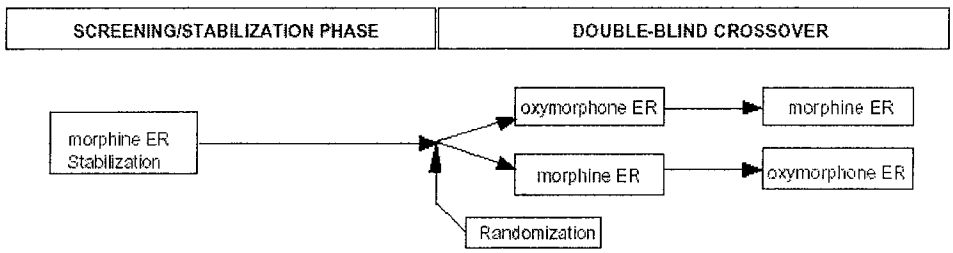
7.3.1.8.2 Study EN3202-018:

Study Design:

EN3202-018 was a 2-week treatment period, multi-center, randomized, double-blind, active-controlled, two-period crossover study to compare the analgesic efficacy of oxymorphone ER with morphine ER in outpatients with moderate to severe cancer pain. The protocol was approved on June 7, 2000. Initially, the study was initiated (9/6/00) with three phases: screening, open-label, and then a double-blind crossover. This was changed with protocol amendment #2 (6/5/01), to a two-phase study. The study was conducted in two phases with the first being a 3-10 day screening and stabilization phase to establish eligibility and document the dosage and efficacy of open-label morphine ER (MS Contin) for enrolled subjects. After a 3-day period of stable dosing, patients were eligible for randomization to the two-part (1 week each) double-blind treatment phase as shown below:

Figure EN3202-018.1 Final Study Design:
(Data Source: Figure 3, ISE Section 4 EN3202-018 Study Design, pg. 59)

Figure 3. EN3202-018: Final Study Design



The initial double-blind treatment phase dosage of each ER formulation was to be based on the total daily dose of morphine ER during the last 2 days of screening and stabilization phase. The dosage could be titrated up or down during the first 3 days of each double-blind treatment period with the goal of achieving a stable, effective dose. The primary efficacy endpoint was to be the 24-hour average pain intensity from question #5 of the Brief Pain Inventory (BPI), measured at the end of each double-blind treatment period.

Disposition and Results:

Sixty five (65) patients were screened for entry with 25 failures. Forty (40) subjects entered titration and stabilization with two discontinuing prior to treatment. Thirty eight (38) patients were dosed. Of these, 18 had at least one dose of OM IR prior to Amendment #2 (initially the study used OM IR as the titration and stabilization medication), with two discontinuing treatment before being randomized to double-blind

treatment. Twenty patients (20) entered the stabilization phase after Amendment #2 and received at least one dose of morphine ER (stabilization medication after amendment 2). Thirty six (36) patients were randomized to double-blind treatment sequences (20 patients to Sequence #1: OM ER to Morphine ER, 16 patients to Sequence #2: Morphine ER to OM ER), with two discontinuations from sequence #2. Thirty four (34) randomized patients entered the double-blind phase and comprise the ITT population. Four patients discontinued while receiving OM ER and two patients discontinued while receiving Morphine ER, leaving a total of 28 subjects completing the two double-blind crossover periods. The patient population was 36-72 years of age with 75% female patients and 86% were Caucasian. The Sponsor states there were no notable differences between treatment sequences for any demographic or baseline parameter.

The Sponsor's efficacy analysis showed that the primary outcome (average pain intensity over the last 24 hours) were not statistically comparable (i.e. the two drugs were statistically different) with statistically significant crossover sequence and treatment period effects.

Reviewer Comments:

The goal of a non-inferiority (equivalence) study is to show the treatments are NOT statistically different and that the confidence interval excludes values equal to or larger than the equivalence margin. In this case, the Sponsor fails to show equivalence in this study. Per Dr. Price (Agency Biostatistical Reviewer) even if the Sponsor had shown non-inferiority, the results would have been questionable due to the study design. Additionally, another reason for the statistical incomparability may be that morphine provided superior analgesic efficacy to oxymorphone. In summary, EN3202-018 failed to meet its primary outcome and is not capable of supporting a claim of efficacy.

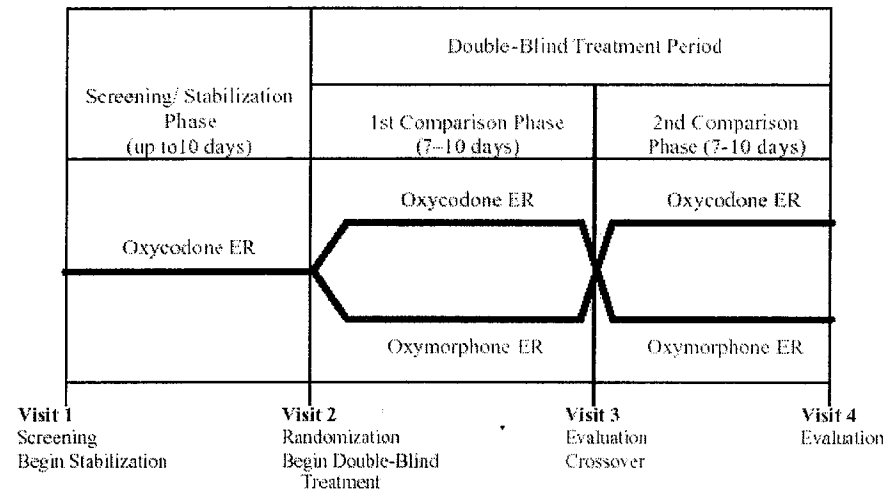
7.3.1.8.3 Study EN3202-019:

Study Design:

EN3202-019 was to be a 20 day, non-inferiority design, randomized, double-blind, multiple-dose, active-controlled, two-period, crossover study of oxymorphone ER and OxyContin in 72 opioid experienced subjects with moderate to severe cancer pain. This study went through 3 amendments (#1 and 2 occurred before any patients were randomized), with the last amendment occurring after 14 patients had been enrolled. Prior to amendment #3, the study consisted of a screening phase, an oxymorphone IR open-label titration phase, and a double-blind phase with two treatment-crossover periods. The final study design (after amendment #3) consisted of an oxycodone screening and stabilization phase followed by a double-blind treatment phase with two treatment-crossover periods. Each patient was to receive either oxymorphone ER or oxycodone ER during the first comparison phase and then was to be crossed over to the other treatment, during the second comparison phase, as illustrated in Figure 19.1 below:

Figure EN3202-019.1 Final Study Design:
(Data Source: Figure 5, ISE Section 4 EN3202-019 Study Design, pg. 62)

Figure 5. EN3202-019: Final Study Design



The screening and stabilization phase was to last from 3 to 10 days and ended with randomization. This phase was to be used to establish the eligibility of potential patients and to document the effective dose of the stabilization (oxycodone ER) regimen. Patients were to continue on OxyContin until a stable dose had been achieved for 3 days. Patients achieving stable pain control during the screening phase were to be randomized to one of two crossover sequences (oxycodone ER followed by oxymorphone ER, or oxymorphone ER followed by oxycodone ER) each lasting 7-10 days. The initial dosage of each

analgesic was to be based on the total daily dose of oxycodone ER received during the last 2 days of the screening and stabilization phase. The double-blind study medication was to be adjusted during the first 3 days of each comparison phase to establish a stable, tolerable, and effective dosage. During the double-blind treatment period, patients were to be allowed to take oral morphine sulfate q 4 to 6 hours as needed for rescue. Patients were to record all study drugs taken, rescue pain medication, and pain intensity, prior to taking rescue. The primary efficacy outcome was to be the 24-hour average pain intensity rating evaluated at the final visit in each crossover treatment phase. The analysis population was defined as all randomized subjects completing the first part of the double-blind treatment sequence, and completing at least 5 days of the second part, and having no major protocol violations.

Disposition and Results:
Fifty eight (58) patients were screened, 47 participated in the titration period, and 45 were subsequently randomized. One patient was randomized and entered double-blind treatment without completing titration; this patient was subsequently withdrawn as a protocol violator. Of the 45 patients who were randomized, 44 received at least one dose of study medication and constitute the safety population. Five randomized patients (11%) withdrew from the double-blind phase of the study. One OM ER patient (56-003) withdrew because of dysphagia and one oxycodone ER (67-006, discussed in the safety section) patient died. One dysphagia patient (67-018) was randomized to the OM ER to OC sequence, but refused to take the study medication after seeing the pill size. Another patient (67-008) completed the first phase of the double-blind treatment sequence and discontinued on the second day after crossing over to oxycodone ER. The last of the 5 discontinuations from the double-blind phase consisted of one subject (58-001, removed due to protocol violation) who received double-blinded OM ER but never was in the titration and stabilization phase.

The mean age of patients was 59 years (26 - 81 years) and the population was approximately 52% female patients and 48% male patients. Most patients were Caucasian (91%, 40/44). The majority of patients reported their baseline untreated pain intensity was of severe intensity (80%, 35/44), and the rest reported moderate intensity (21%, 9/44). Of note, inspection of the baseline characteristics showed that the OM ER to OC ER group had pain distributions of severe (90%, 19/21) and moderate intensity (9.5%, 2/21) compared to the OC ER to OM ER group (severe [69.6%, 16/23] and moderate [30.4%, 7/23]). Here, the proportion of baseline pain categories does not appear well balanced.

The Sponsor's efficacy analysis of the primary outcome shows a statistically significant difference ($p = 0.03$) between the 24-hour average pain intensity for OM ER and OC ER, using the efficacy evaluable population (37). The Sponsor analyzed the same information using the ITT population (42) and there was no statistically significant difference these groups. The Sponsor concludes that the results of this non-inferiority trial support the equivalence of OM ER with OC ER.

Reviewer Comments:
This study (EN3202-019) was a non-inferiority design that did find a significant difference in the primary outcome variable (24-hour average pain intensity) between oxymorphone ER and OxyContin ($p = 0.034$). This result favored oxymorphone. However, this trial was designed as a non-inferiority study without a pre-specified null hypothesis of superiority. This study was reviewed in 8/2000 and the method of dose assignment used in the study was noted to preclude any ability to claim superiority to OxyContin, in the event of a statistically significant difference. It is also important to note that one of the Sponsor's secondary outcomes was equivalent to the primary, with the only difference being the analysis population (the ITT population (42 subjects) was used instead of the smaller 'efficacy evaluable' population). In this case there was no statistical difference between groups ($p=0.134$) for the 24-hour pain intensity, and additionally there were no statistically significant difference on any other secondary outcomes. Given this, the finding of a statistically significant difference between OM ER and OC ER is likely spurious.

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

Study EN3202-015 was a 4-week, multi-dose, placebo- and active-controlled study in 491 randomized patients with moderate to severe osteoarthritis (OA) pain. This study was intended to support a finding of efficacy for OM. The sponsor's analysis of the primary outcome variable of Arthritis Pain Intensity VAS score, change from baseline to end of Week 3 did reveal a statistically significant difference from placebo for the OM 40 mg treatment group. However, the use of a modified intent-to-treat population and last observation carried forward for imputing missing data created a bias in favor of study drug. Reanalysis using an all randomized population with baseline observations carried forward, failed to show a statistically significant difference between any of the active treatment arms and placebo.

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

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

Study EN3202-025 was a 2-week, double-blind, placebo-controlled, dose-ranging study of OM ER 10, 40, and 50 mg in 370 randomized osteoarthritis (OA) patients, submitted in support of efficacy. The Sponsor's analysis of the primary outcome variable (Arthritis Pain Intensity (API) VAS score) change from baseline to the end of Week 2 demonstrated a statistically significant difference from placebo for the OM 40 and 50 mg groups but not for OM ER 10 mg. The secondary analysis also favored the 40 and 50 mg formulations. However, both analyses suffered from the same analytical by using the last observation carried forward method, for imputing missing data. Reanalysis using an all randomized and baseline observation carried forward (BOCF), failed to show a statistically significant difference between any of the active treatment arms and placebo. Furthermore, patients dropping out from the OM 40 and 50 groups during Week 1 had imputed data reflecting treatment on the lower titration dose, OM 20 mg bid, used during Week 1. In summary, analysis of the data using BOCF imputation does not find any statistical support for the efficacy of the OM 10, 40, or 50 mg doses compared to placebo.

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

8 INTEGRATED REVIEW OF SAFETY

Please refer to the separate Integrated Summary of Safety.

9 DOSING, REGIMEN, AND ADMINISTRATION ISSUES

- Dose Formulations:
  The Sponsor proposes oxymorphone ER in 5, 10, 20, and 40 mg tablet strengths.

- Dose Ranges:
  The Sponsor proposes a lowest starting dose of 5mg q12 hours (in opioid naïve subjects), with further dose titration based on the patient's response. However, the 5 mg IR and ER formulations were evaluated in PK studies only, therefore no conclusions regarding efficacy of 5 mg can be made. The lowest oxymorphone starting doses evaluated clinically were 10 mg ER q12 hours in opioid experienced subjects (Studies EN3202-016) and opioid naïve and experienced subjects (EN3202-

025), and 20 mg ER q12 hours in opioid naïve and experienced subjects (Study EN3202-015).

The maximum oxymorphone doses evaluated clinically were 50 mg q12 hours (EN3202-025) and 219 mg per day (EN3202-016, average dose = 66 ± 50 mg per day). It is expected that dosing will be titrated individually to achieve appropriate analgesia with minimal side effects.

- Dose Interval:
  Four adequate and well-controlled studies utilized a q12 hour dosing interval, which is the interval proposed by the Sponsor. Single dose PK evaluation of the ER formulation indicates that mean plasma half-life ranges from approximately 10 to 12 hours, with 90% of steady state trough oxymorphone concentrations achieved by the second day of dosing. There were no clinical efficacy studies to evaluate alternative intervals. Based upon the efficacy and clinical pharmacology studies, the current dosing interval appears appropriate.

- Dosing Age Groups:
  The Sponsor recommends treating patients from 18 years of age to the elderly. PK studies evaluated ER and IR oxymorphone in subjects ranging from 18 to 81 years of age and four clinical efficacy studies evaluated patients with ages ranging from 22 to 89. It is unlikely that the 18 to 22 age range will exhibit different efficacy responses to oxymorphone. Therefore, the proposed age range is acceptable. No PK or clinical data for subjects younger than 18 was submitted.

- Dosage Administration Adjustments:

  1) Hepatic Impairment: Oxymorphone is contraindicated in severe hepatic impairment, as proposed by the Sponsor. Oxymorphone demonstrated an approximate 400% increase in plasma AUC in moderately impaired subjects. For this reason, oxymorphone should be started at lower doses, titrated with extreme caution in moderately impaired patients, and titrated cautiously in mildly impaired patients.

  2) Renal Impairment: Oxymorphone should be started at lower doses and titrated cautiously in all stages of renal impairment.

  3) Age: Oxymorphone should be started at lower doses in the elderly (> 65 years of age) and titrated carefully.

  4) Gender: No specific dose adjustment is recommended for male or female patients.

  5) Food: No specific dose adjustment is recommended for taking with or without food.

- Dose Conversion from Other Oral Opioids:
  The Sponsor estimated equianalgesic dose ratios based on results from one controlled (EN3202-016) and three non-placebo controlled studies (EN3202-017, 018, and 019). The dose ratio from the controlled study showed average daily doses of oxycodone ER to oxymorphone ER of 154.8/79.4 or approximately 2 to 1. The non-controlled studies suffered from design flaws such as different usage of rescue among treatment groups, limited dose strengths of different treatments, and one was open-label. However, noting the limitations of these studies, the Sponsor did find the approximate relationship of oxycodone ER to oxymorphone ER equianalgesic ratios of 1.2 – 2x and a morphine ER to oxymorphone ER ratio of 3x. The Sponsor recommends initially converting patients from oxycodone ER and morphine ER to total daily doses of oxymorphone ER in 2:1 and 3:1 ratios, respectively. Published relative potency information is recommended for use when converting from other oral opioids.

10 USE IN SPECIAL POPULATIONS

The following discussion refers only to efficacy evaluations in subpopulations. Safety findings in special populations are discussed in a separate Integrated Review of Safety.

10.1 Evaluation of Sponsor's Gender Effects on Efficacy

Gender Effects:
The Sponsor conducted subgroup analyses of gender effects on efficacy and found a statistically significant (p=0.042) treatment by gender interaction in study EN3202-016. In the oxymorphone ER group, change from baseline in pain intensity was smaller in males (2.4 ± 20.6) than in females (14.2 ± 26.6). In the oxycodone ER group, however, change from baseline in pain intensity was larger in males (9.3 ± 24.15) than in females (2.1 ± 27.4). The Sponsor argues that this is due to magnification of the large inter-individual variability among patients, from subpopulation analysis. However, the reason for the observed differences does not appear clear.

10.2 Evaluation of Evidence for Age, Race, or Ethnicity Effects on Efficacy

Age Effects:
The Sponsor's efficacy analysis demonstrated a statistically significant interaction effect between age (p=0.026) and Pain Intensity (VAS) in one study EN3202-016. However, the Sponsor states that stratification of age into two categories (< 65 or ≥ 65 ages) resulted in unequal sample sizes of 67 and 4, respectively. Given the lack of statistically significant findings in EN3202-015 or EN3202-025, and unequal sample sizes it is likely that the finding is not clinically meaningful.

Race and Ethnicity Effects:
No separate evaluation of race or ethnicity effects on efficacy were provided. The unequal size of racial groups (1173 Caucasian patients and 141 pooled non-Caucasian patients) limited the ability to draw clinically meaningful conclusions.

10.3 Evaluation of Pediatric Program

The Sponsor proposes a pediatric development program for oxymorphone IR and ER tablets, based upon input from pediatric consultants as well as discussions with the division. The Sponsor proposes 5 clinical studies to assess oxymorphone ER and IR in ages 0 to 18. Table 9.3.1 outlines the general features of the clinical protocols. The Sponsor is also seeking Waivers or Deferrals for selected age groups and formulations based upon discussion at the July 11, 2002 pre-NDA meeting (see Table 9.3.2).

Table 9.3.1 OM IR and ER Proposed Pediatric Study Summaries

Study	Patients	Product	Duration	Dosing	Design
Study A	0-16 years N=54 Acute Pain	IR	1 day	Single dose	Open-label; ascending-dose; PK
Study B	0-16 years N=90 Acute Pain	IR; Placebo; Active comparator (MSIR)	1 day	Single dose, 3 different fixed doses	Double-blind; placebo-controlled active control; dose-ranging; PK
Study C	11-16 years N=50 Chronic Pain	IR/ER	Up to 28 days	Titration to stable pain control, then IR/ER crossover at set dose	Titration; cross-over; PK
Study D	6-16 years N=100 Chronic Pain	IR (6-16); ER (>11-16); Placebo; Activecomparator (oxycodone)	6 weeks	Fixed doses	Double-blind; placebo-controlled active controlled; PK
Study E	6-16 years N=50 Chronic Pain	IR (6- 16); ER (>11-16);	6 months	Open-label	Open-label; long term extension; PK
Data Source: Table 1, Pediatric Program, Section 9 - Other Studies and Information, NDA 21-610					

The progression of studies is to be supported by data from the OM IR and ER adult program, which guides initial dose selection for the first pediatric trial (Study A). This first study is designed to evaluate safety and effectiveness in children 0 – 16 years of age using single doses of OM IR, studied in an ascending fashion. Data from Study A will then support initiation of Study B, which will include the same pediatric population (0-16 years) using a double-blind, adequate and well-controlled, non-inferiority design with an active comparator and placebo.

The first trial with chronic pain pediatric patients (Study C) will be conducted with the older age group (>11-16 years old). This double-blind, adequate and well-controlled trial will utilize both the oxymorphone IR and ER formulations in a crossover design. After analysis of the data obtained from Study C, a second trial in chronic pain (Study D) will be conducted with both younger and older patients (6-16 years old). Study D will be a double-blind, adequate and well controlled non-inferiority trial including an active comparator and placebo, and will utilize both the IR and ER formulations, depending on the age group.

A final long-term 6-month open-label safety extension trial of studies C and D (Study E) is planned. This study allows patients with chronic pain requiring long-term chronic opioid therapy to adjust doses based on need for added efficacy or side.

Individual Study Synopses:
The Sponsor has proposed five studies (listed in Table 9.3.1 above) and has provided study synopses for evaluation. Each study is discussed briefly.

Study A –
This is an open-label ascending dose study of OM IR in 0-16 year old children with post-operative pain. Dosing is based on a mg/kg basis in children under 6 years and starts at the lowest recommended adult dose, based on potency findings in the adult studies. It is proposed that the investigator allow younger children to use parenteral Numorphan (oxymorphone 1 mg/ml) in cherry syrup. The trial design will assess progressive increasing single doses of oxymorphone IR in cohorts (each composed of 3 groups of equal numbers of 0-6, <6-11, and >11-16 year old subjects). Each successive cohort receives a doubling of the prior cohort dose. Pain is measured by using age-specific visual scales:

- Behavioral scales for children 0-6
- Color or faces scale for children 6-11
- VAS scale for children > 11.

Safety is measured by AEs, oximetry, apnea monitoring, vital signs. PK profiles are also obtained

Reviewer Comments – Study A:

- Use of parenteral Numorphan with cherry syrup may be problematic based upon Dr. Lee's discussion at the pre-NDA meeting in 2002. He stated that the PK of oral delivery of parenteral oxymorphone should be investigated in adults, before giving this to children.
- The open-label design will not provide an adequate measure of efficacy.
- It is unclear what the beginning dose will be.

Study B –
This is a double-blind, placebo-controlled, randomized, active-control evaluation of safety and efficacy of single doses of OM IR in 0-16 year old children with post-

operative pain. Dosing is based the results obtained from Study A. The investigator will allow younger children to use parenteral Numorphan (oxymorphone 1 mg/ml) in cherry syrup. The non-inferiority trial design will assess three single doses of oxymorphone IR versus morphine sulfate IR and placebo in 5 treatment groups (each consists of two cohorts of 0-6 [n=5] and >6-16 [n=15] year old subjects). Pharmacokinetic information will be obtained up to 24 hours after dosing, in order to evaluate dose response and relative comparisons to morphine. Pain is measured by using age-specific visual scales as discussed in Study A. Safety is evaluated by AEs, oximetry, apnea monitoring, vital signs. PK profiles are also obtained

Reviewer Comments – Study B:

- Use of parenteral Numorphan in cherry syrup is problematic, as discussed above.
- It is unclear if the trial objective is to show non-inferiority to morphine sulfate or to demonstrate superiority to placebo.

Study C –

This is an open-label titration to double-blind, randomized, cross-over design, safety and efficacy study that evaluates OM IR and ER in >11-16 year old children with chronic painful conditions (cancer, spine or hip degenerative disease). Dosing will be determined in the open-label phase (< 14 days) and subjects will be dosed TID or QID based on patients responses to IR treatment, and later at q12 hours with ER treatment. After dose stabilization (defined as moderate relief of pain with same dose of OM IR for 3 days), subjects will be randomized into OM IR or OM ER at the dose level determined during titration. The double-blind phase will last for 2 weeks. Pain is measured by using age-specific visual scales as discussed in Study A. Safety is evaluated by AEs and vital signs. Limited PK samples will be obtained for population PK analysis. Additional rescue will be provided using OM IR tablets.

Reviewer Comments – Study C:

- While this study may be useful in providing safety and PK information, the lack of placebo comparison precludes the ability to demonstrate efficacy.

Study D –

This is a double-blind, placebo-controlled, randomized, active control evaluation of OM IR and ER in >11-16 year old opioid experience and naïve children, with chronic pain. A non-inferiority design will assess these OM IR formulations to oxycodone IR and ER. Patients 6-11 may be randomized to IR formulations only, whereas patients > 11-16 may be randomized to ER formulations. This appears to have 5 treatment arms (OM IR [n=25], OM ER [n=25], OC IR [n=25], OC ER [n=25], and PBO [n=12]), with the placebo as part of a 'withdrawal' design. In this 6 week study, patients will be titrated to stable pain relief their initially randomized medication. At the end of titration, randomly selected patients will be withdrawn (given placebo) or continued on their respective active treatment. Rescue medication will be allowed throughout (OC or OM IR).

Pain is measured by using age-specific visual scales as discussed in Study A. Safety is evaluated by AEs and vital signs. PK samples will collected. Statistical plan to be determined.

Reviewer Comments – Study D:

- Appropriate tapering will need to be instituted for opioid naïve subjects, at the end of the study.

Study E –

This is a 6-month, open-label, safety extension trial for Studies C and D, discussed above. It will assess safety parameters and stability of dosing and pain control, in a pediatric chronic pain population. Both ER and IR formulations of OM will be used, with 6-11 year old patients limited to the IR formulation. Each patient's formulation will be based on their prior study's dosage form. Doses will be adjusted by the investigator as needed, based on acceptable clinical practice standards. Group size is to be determined. Safety is evaluated by AEs and vital signs. Statistical plan to be determined.

Reviewer Comments – Study E:

- The basic design appears reasonable, however many details are not shown in this synopsis to allow a complete evaluation.
- Opioid tapering will need to be instituted for opioid naïve subjects, at the end of the study.

Table 9.3.2 OM IR and ER Proposed Waiver or Deferral Matrix

Age Group	EN3202 (ER) Tablets	EN3203 (IR) Tablets
PreTerm	Waiver	Deferral
Newborn	Waiver	Deferral
Infant + Toddler	Waiver	Deferral
Children (2-6 yrs)	Waiver	Deferral
Children (6-11 yrs)	Waiver	Deferral
Adolescent (>11-16 yrs)	Deferral	Deferral
Data Source: Table 2, Pediatric Program, Section 9 - Other Studies and Information, NDA 21-610		

Reviewer Discussion:

- The Sponsor is seeking Waivers and Deferrals for selected age groups and formulations, as shown in Table 9.3.2. As discussed at the 7/11/02 pre-NDA

meeting, the division will honor prior agreements (10/4/00 meeting) to not require study of the ER formulation in children below 12 years of age. However, granting this waiver means that the current plan will not support a request for pediatric exclusivity. The Pediatric Written Request (PWR) has stringent requirements and requires evaluation of the extended release formulation in younger children.

- The Sponsor has modified their pediatric plan from the pre-NDA in 2002,to evaluate children below 2 years of age and eliminate crushing oxymorphone tablets (or morphine sulfate) to mix with applesauce. However, use of parenteral Numorphan in cherry syrup is still planned. In addition, the efficacy assessment is still problematic in that non-inferiority designs are planned. The division previously stated that pediatric efficacy assessment should include assay sensitivity. Based upon this the pediatric program may be inadequate to demonstrate efficacy.

11 APPENDICES

11.1 APPENDIX EN3202-015: EFFICACY ASSESSMENT INSTRUMENT DETAILS:

11.1.1 WOMAC Osteoarthritis (OA) Index:

The Western Ontario and McMaster Universities (WOMAC) Osteoarthritis index consists of questions on 3 subscales of Pain, Stiffness, and Physical Function. Each question was to be answered using a VAS (0 mm = 'very good'; 100 mm = 'very poor') scale to indicate the amount of pain, stiffness, or difficulty functioning experienced in the 'index joint.'

11.1.2 Arthritis Pain Intensity (API):

Patient's were to be asked to assess the level of osteoarthritis pain in the 'index joint' at a given visit (or since a previous visit), by marking the following VAS (0 mm = 'very good'; 100 mm = 'very poor') scale. Baseline pain had to be ≥ 40 mm on the VAS to be enrolled in the study. The Daily API was marked by patients in a similar manner on a daily basis, and was to be used as a secondary outcome variable.

11.1.3 Patient/Physician Global Assessments of Arthritis:

These two instruments are VAS (0 mm = 'very good'; 100 mm = 'very poor') scales of patient's and investigator's impressions of how the patient is affected by their arthritis on a given assessment day.

11.1.4 SF-36 Health Survey:

This is a categorical quality of life instrument, to be completed by patients before any arthritis measurements were to be performed. It includes questions regarding patient's impression of health at baseline, activities limited by health, and changes in functioning since previous assessments.

11.2 APPENDIX EN3202-016: EFFICACY ASSESSMENT INSTRUMENT DETAILS:

11.2.1 Current Pain Intensity (VAS Scale):

This is a 100 mm VAS (0 mm = 'no pain'; 100 mm = 'worst pain imaginable') in the subject diary where patients were to record their pain intensity at scheduled times.

11.2.2 Current Pain Intensity (Categorical Scale):

Subjects were to record their pain intensity by using a categorical scale in the subject diary, before each dose of study medication and 4 hours after the morning dose, as well as before taking any dose of rescue medication. Subjects were to be asked to "select the phrase that best describes the severity of pain you are experiencing right now." Pain intensity was to be measured on a four-point categorical scale as: none (0), mild (1), moderate (2), and severe (3).

11.2.3 Current Pain Relief:

This is a categorical 5-point scale (0 = 'none'; 1 = 'a little'; 2 = 'moderate'; 3 = 'a lot'; 4 = 'complete') in the subject diary where patients were to record their pain relief at scheduled times.

11.2.4 Worst Daily Pain:

This is a categorical 4-point scale (0 = 'none'; 1 = 'mild';2 = 'moderate';3 = 'severe) in the subject diary where patients were to record their worst pain intensity during the previous day, each morning.

11.2.5 Brief Pain Inventory (BPI):

This version of the BPI is a 5-item questionnaire (questions #3, 4, 5, 6, 8, and 9 of the original BPI) with 11-point categorical ratings of pain and function. Patients were to rate their pain 'at its worst over the last 24 hours', 'at its least over the last 24 hours', '... on the average', and '... right now.' Question 9 of the BPI addressed 11-point categorical ratings of general activity, mood, walking ability, normal work, social relations, sleep, and enjoyment of life.

11.2.6 Patient's & Physician's Global Assessments of Pain Medication:

These two instruments are categorical 5-point scales (1 = 'poor'; 2 = 'fair'; 3 = 'good'; 4 = 'very good'; 5 = 'excellent') where patients and the investigator were to rate their overall satisfaction with the medication's treatment of pain. In addition, the Physician scale was to also rate the medication relative to the opioid side effects experienced by the subject.

11.3 APPENDIX EN3202-012: EFFICACY ASSESSMENT INSTRUMENT DETAILS:

11.3.1 ASA Physical Status Classification System:

Assignment of a physical status classification (PS-1 through PS-6) is based on the physical condition of the patient independent of the planned operation:

PS-1	A normal healthy patient
PS-2	A patient with mild systemic disease that results in no functional limitation
PS-3	A patient with mild systemic disease that results in functional limitation
PS-4	A patient with severe systemic disease that is a constant threat to life
PS-5	A moribund patient who is not expected to survive without the operation
PS-6	A declared brain-dead patient whose organs are being removed for donor purposes

11.3.2 Pain Intensity (VAS):

This is a 100 mm VAS (0 mm [left-hand end of scale] = 'no pain'; 100 mm [right-hand end of scale] = 'extreme pain'). Patients were to indicate their level of pain by making a vertical mark on the line, in response to the statement:

> "My pain at this time is." The VAS score was equal to the distance (in mm) from the left-hand end of the scale to the patient's mark.

11.3.3 Pain Intensity Categorical Scale:

Patients were to complete the following statement:

> "My pain at this time is" using the scale: None = 0, Mild = 1, Moderate = 2, or Severe = 3.

11.3.4 Pain Relief:

Patients were to complete the following statement:

> "My relief from starting pain is" using the scale: None = 0, A little = 1, Some = 2, A lot = 3, or Complete = 4.

11.3.5 Pain at least Half Gone:

Patients were to complete the following statement:

> "My starting pain is at least half gone" using No = 1 or Yes = 2.

11.3.6 Patient's Recall of Pain (Serial Assessments):

Patients were to complete the following statement, "My average (usual) pain since the last pain recording has been" using a VAS scale (VAS anchors: "No Pain" on the left and

"Extreme Pain" on the right). At baseline, the statement to be answered was to be phrased, "My average (usual) pain over the past hour has been."

11.3.7 Patient's Recall of Pain (Last 12 or 24 Hours):
Patients were to complete the following statement, "My average (usual) pain since I first took my study medication has been" using a 100 mm VAS scale (VAS anchors: "No Pain" on the left and "Extreme Pain" on the right).

11.3.8 Time to Perceptible Pain Relief:
Study personnel were to start a stopwatch for each patient at the time of the first dose of study medication. The patient was to stop the stopwatch when they felt any pain relieving effect of the drug according to the following instructions:

> "I would like you to stop the stopwatch when you first feel any pain relieving effect whatsoever from the drug. This does not necessarily mean you feel completely better, although you might, but when you first feel any differences in the pain that you have had."

11.3.9 Time to Meaningful Pain Relief:
Study personnel were to start a second stopwatch for each patient at the time of the first dose of study medication. The patient was to stop the second stopwatch when the pain relief felt was meaningful according to the following instructions:

> "I would like you to stop the stopwatch when you have meaningful pain relief, that is, when the relief from the pain is meaningful to you."

11.3.10 Patient's Global Evaluation of the Study Medication:
Patients were to complete the following statement at 12 and 24 hours post dosing, just prior to receiving the 1st rescue dose, or at early termination:

> "How would you rate the study medication you received for pain?" using the scale Poor = 5, Fair = 4, Good = 3, Very Good = 2, or Excellent = 1.

11.3.11 Integrated Rescue PCA and Pain Intensity Recall Score:
This is a derived variable based upon Silverman and O'Conner's 1993 (Anesth Analg 1993;77:168-70) that allows a way of integrating visual analog scale (VAS) pain scores and rescue amounts of analgesics (such as morphine in the original paper). For example, the following data is abstracted from the 1993 paper:

Table 1. Raw Scores and Ranks for Pain and Morphine Use

Group	Pain		Morphine use	
	Score	Rank	(mg/h)	Rank
Ketorolac				
1	4	14.5	2.4	15.5
2	3	10	1.7	10
3	2	5	0.9	6
4	2	5	1.8	11.5
5	0	1	0	1
6	2	5	0.3	2
7	5	18.5	2.7	17
8	4	14.5	2.4	15.5
9	3	10	1.1	7
10	3	10	1.8	11.5
11	3	10	1.3	8
Nonketorolac				
1	1	2	0.8	5
2	2	5	5.0	22
3	6	21.5	3.9	21
4	5	18.5	2.3	14
5	5	18.5	1.5	9
6	3	10	0.7	4
7	2	5	0.5	3
8	4	14.5	3.5	20
9	4	14.5	2.1	13
10	5	18.5	2.9	19
11	6	21.5	2.8	18

Visual analog scale scores and morphine use and the derived subject ranks for 22 consecutive postlaminectomy patients based upon data obtained in continuing Human Investigation Committee-approved assessments of ketorolac tromethamine (intramuscularly, at 6-h intervals, with first dose intraoperatively) as an adjunct to patient-controlled analgesia (morphine 1.5 mg/dose, 6 min lockout interval). Visual analog scale scores obtained on morning of first postoperative day; morphine use reported as hourly use as of this time.

With the VAS score as the 1st of the 2 variables to be assessed, the following steps may be performed:

- Rank the subjects (n=22) in the combined treatment groups according to their VAS scores; ties are assigned the average of the ranks that the tied observations would have if there were no ties (e.g. the pain scores of 4 are all assigned an average of 14.5).
- Determine the mean rank of the control plus treated subjects: $(n + 1)/2 = 11.5$
- Express the difference of each treated subject's VAS rank from 11.5 as a percentage of 11.5 (i.e. percent difference).
- Perform the above steps for morphine use.
- Add the percent differences for the two variables on a per-subject basis to proved an integrated percent difference.
- The individual and summated percent differences can now be compared with statistical tests or plotted on a graph.

Using this method converts the data for each variable to a commons scale, thereby allowing for further statistical comparisons.

11.4 APPENDIX EN3202-025: EFFICACY ASSESSMENT INSTRUMENT DETAILS:

11.4.1 Functional Class of Osteoarthritis (OA):

Class I Complete functional capacity with ability to carry on all usual duties without handicaps.

Class II Functional capacity adequate to conduct normal activities despite handicap of discomfort or limited mobility of one or more joints.

Class III Functional capacity adequate to perform only a few or none of the duties of usual occupation or of self care.

Class IV Largely or wholly incapacitated with patient bedridden or confined to a wheelchair, permitting little or no self care.

11.4.2 Arthritis Pain Intensity (VAS):

This is a 100 mm VAS (0 mm [left-hand end of scale] = 'no pain'; 100 mm [right-hand end of scale] = 'extreme pain'). Patients were to indicate their OA pain by making a vertical mark on the line, in answer to the question: "Overall, how much pain have you experienced in your study joint since your last visit?" Subjects were to have had at least a $\geq$ 40 mm baseline VAS score to qualify for randomization.

11.4.3 WOMAC Osteoarthritis (OA) Index:

The Western Ontario and McMaster Universities (WOMAC) Osteoarthritis index consists of 3 subscales, pertaining to Pain, Joint Stiffness, and Physical Function, respectively. Each subscale has questions that were to be answered using a VAS (0 mm = 'none'; 100 mm = 'extreme') scale to indicate the amount of pain, stiffness, or difficulty functioning experienced in the 'index joint.' Patient were instructed to answer the appropriate questions regarding pain, stiffness, and physical function relative to their last visit.

11.4.4 Patient's Global Assessment of Arthritis:

Patients were to be asked, "Considering all the ways your arthritis condition affects you, i.e. pain, stiffness and limitation of activity, how are you doing today?" Patients were to indicate their response on a 100 mm VAS scale (0 mm [left-hand end of scale] = 'very good'; 100 mm [right-hand end of scale] = 'very poor').

11.4.5 Physician's Global Assessment of Arthritis:

Physicians were to be asked, "How is the patient doing today?" Physicians were to indicate their response on a 100 mm VAS scale (0 mm [left-hand end of scale] = 'very good'; 100 mm [right-hand end of scale] = 'very poor').

11.4.6 Quality of Life Assessment:

Quality of life was to be assessed using the SF-36 Health Survey. Patients were to complete this before any arthritis assessments were to be performed.

11.4.7 Patient's Assessment of Sleep:

Patient's were to be asked to respond to questions regarding the impact of their pain upon sleep. The patient was to answer questions with a VAS scale (0 mm [left-hand end of scale] = 'never'; 100 mm [right-hand end of scale] = 'always'). Questions were of the form:

- Since your last visit, how often have you had trouble falling asleep because of pain?
- Since your last visit, how often have you needed sleeping medication to help you fall asleep?
- Since your last visit, how often have you been awakened by pain during the night?
- Since your last visit, how often have you been awakened by pain in the morning?
- Since your last visit, how would you rate the overall quality of your sleep? Note that this question answers using a VAS scale with 0 mm = 'excellent' and 100 mm = 'very poor.'

11.5 Appendix: Useful Statistical Terms and Definitions:

11.5.1 ANOVA:

Analysis of Variance (ANOVA) is a statistical method that allows comparisons of ≥ 2 treatment groups and estimates of treatment effects to be adjusted for other possible factors such as race, gender, treatment center, etc... (Source: Day S., Dictionary for Clinical Trials, 1999, pg. 5)

11.5.2 ANCOVA:

Analysis of Covariance (ANCOVA) is a statistical method related to ANOVA. It allows for comparisons of ≥ 2 treatment groups and estimates of treatment effects to be adjusted for other factors (e.g. race, gender, treatment center, etc...) and covariates (e.g. baseline pain status, etc...). (Source: Day S., Dictionary for Clinical Trials, 1999, pg. 5)

11.5.3 Least Squares Means:

The estimated mean of a variable obtained from an ANOVA or ANCOVA linear model. It is the adjusted mean after adjusting for any other factors and covariates in the model. (Source: Day S., Dictionary for Clinical Trials, 1999, pg. 99)

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/s/

Shaun Comfort
9/26/03 04:16:18 PM
MEDICAL OFFICER

Oxymorphone ER Clinical Review

Sharon Hertz
10/15/03 06:24:45 PM
MEDICAL OFFICER
I do not fully concur with this review. See Team Leader memo for summary of efficacy and integration with safety.

1ST Cycle

NDA 21.611 CLINICAL REVIEW

FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHETIC, CRITICAL CARE, AND ADDICTION DRUG PRODUCTS
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MEDICAL OFFICER'S DRAFT REVIEW OF CLINICAL DATA

NDA # (serial):	**21,611**
Related IND(s):	**56,919 & 58,602**
Drug Name (generic):	**Numorphan IR (Oxymorphone HCL)**
Sponsor:	**Endo Pharmaceuticals, Inc.**
Indication:	**Short term management of acute/moderate to severe pain**
Type of Submission:	**NDA**
Date of Receipt (CDR):	**20DEC02**
Date of Review:	**15JAN03 to 17SEP03**
Material Reviewed:	**Electronic NDA Submission Documents**
Reviewer:	**Shaun M. Comfort, M.D.**
Team Leader:	**Sharon Hertz, M.D.**
Project Manager:	**Lisa Basham-Cruz**

Clinical Review for NDA 21-611

EXECUTIVE SUMMARY

Appears This Way
On Original

EXECUTIVE SUMMARY

1 RECOMMENDATIONS:

1.1 Recommendations on Approvability:

The Sponsor has demonstrated the efficacy of oxymorphone immediate-release based on the following conclusions:

1) The Sponsor has demonstrated efficacy of Oxymorphone (OM) immediate-release (IR) doses of 20 and 30 mg, in the treatment of post-operative pain in two adequate, and well-controlled, clinical trials of OM in knee and/or total hip replacement, and orthopedic surgery.

2) The efficacy findings for both the 20 and 30 mg doses were clinically and statistically significantly different from placebo.

3) The efficacy findings for the 20 and 30 mg doses were supported by the majority of secondary outcome measures in the supporting clinical studies.

1.2 Recommendations on Phase 4 Studies and Risk Management Steps:

There are no clinical Phase 4 recommendations at this time. Carcinogencity will be completed as a Phase 4 commitment. The Sponsor's Risk Management Plan is reviewed and discussed in a separate document.

1.3 Deficiencies and Recommended Corrective Action:

There are no current clinical deficiencies warranting corrective action at this time.

2 SUMMARY OF CLINICAL FINDINGS:

2.1 Brief Overview of Clinical Program

The Sponsor has submitted NDA 21-611 in support of oral oxymorphone hydrochloride immediate release (IR) 5 and 10 mg tablets. Oxymorphone is a semi-synthetic opioid analgesic proposed for treatment of moderate to severe pain where the use of an opioid is appropriate. Two trade names have been proposed at the time of this writing Opana and ——— but no name has been chosen at the time of this writing.

Two pivotal studies examined single and multiple doses of oxymorphone IR in 624 patients with post-operative pain following total hip or knee replacement and orthopedic surgery. The following sections discuss the efficacy and safety findings.

2.2 Efficacy

Two adequate and well-controlled pivotal trials were submitted in support of efficacy for oxymorphone immediate-release, identified as EN3203-004 and EN3203-005.

Study EN3203-004 was a 48-hour, single and multi-dose, placebo- and active-controlled study in 300 patients with post-operative pain following knee or hip replacement. The Sponsor's analysis of the primary outcome variable (total pain relief from 0 to 8 hours or TOTPAR8) for the single-dose phase of the study revealed statistically significant differences from placebo for OM 10, 20, and 30 mg IR. Re-analysis by the Agency Biostatistical Reviewer confirmed the Sponsor's findings. The majority of secondary outcomes favored the oxymorphone formulations over placebo, with a trend towards greater efficacy response with OM 30 mg.

Study EN3203-005 was an 8-hour multicenter, randomized, double-blind, placebo- and active- controlled, single-dose study of oxymorphone IR (10 and 20 mg formulations) and oxycodone IR (15 and 30 mg formulations) in 324 patients with postoperative pain due to osteotomy. The Sponsor's analysis of the primary outcome variable of Total Pain Relief from 8 hours demonstrated a statistically significant difference from placebo for the OM 20 mg treatment group, but not for the OM 10 mg group. The secondary outcomes also favored the OM 20 mg dose, but not the 10 mg formulation. The Sponsor's efficacy findings were confirmed by the Agency re-analysis of the efficacy data.

In Summary, the Sponsor's investigations support the efficacy of oxymorphone IR versus placebo. There appears to be a greater efficacy response at higher doses (20 and 30 mg) with inconsistent efficacy at 10 mg (positive in one trial and negative in another). The evidence of two trials taken together suggests that 20 mg is the minimally effective dose, in this post-operative setting.

2.3 Safety

The review of safety and all relevant safety conclusions and recommendations is discussed in a separate Integrated Summary of Safety document.

2.4 Dosing

The Sponsor proposes oxymorphone IR in 5 and 10 mg tablet strengths, with higher doses determined by individual patient needs. The Sponsor proposes a starting dose of 5mg (in opioid naïve subjects), with further dose titration based on the patient's response. However, the 5 mg IR and ER formulations were evaluated in PK studies only, therefore no conclusions regarding efficacy of 5 mg can be made. The lowest oxymorphone IR starting dose evaluated clinically was 10 mg (Studies EN3203-004 and –005), which demonstrated inconsistent efficacy. Based upon this the minimally consistent effective dose appeared to be 20 mg IR, in the post-operative pain setting. The maximum oxymorphone IR doses evaluated clinically was 30 mg (EN3203-004).

The Sponsor proposes a dose interval of q 6 ——— However, this interval was not supported by the clinical trials with greater than 50% of subjects discontinuing after four hours of treatment, , in the single-dose post-operative pain study. Evaluation of the multiple dose PK parameters for IR oxymorphone indicates that the plasma oxymorphone level reaches a stable trough at approximately 4 hours, which lasts for the subsequent two hours, following dosing every 6 hours (Refer to the Biopharmaceutics Review for further detail). Based upon these PK results, a q 4 to 6 hour dosing is recommended.

The Sponsor states that oxymorphone is appropriate for patients from 18 years of age and older. PK studies evaluated ER and IR oxymorphone in subjects ranging from 18 to 81 years of age and the two clinical efficacy studies evaluated patients with ages ranging from 22 to 91. Based upon these exposures the proposed age range appears acceptable.

Dosage Adjustments:
Several disease and age related situations require contraindication, caution, and/or consideration of dose adjustment.

1) Hepatic Impairment: Oxymorphone is contraindicated in severe hepatic impairment, as proposed by the Sponsor. Oxymorphone demonstrated an approximate 400% increase in plasma AUC in moderately impaired subjects. For this reason, oxymorphone should be started at lower doses, titrated with extreme caution in moderately impaired patients, and titrated cautiously in mildly impaired patients.

2) Renal Impairment: Oxymorphone should be started at lower doses and titrated cautiously in all categories of renal impairment.

3) Age: Oxymorphone should be started at lower doses in the elderly (> 65 years of age) and titrated cautiously.

2.5 Special Populations

Gender Effects:
Subgroup analyses of gender effects on efficacy shows slight differences between male and female patient efficacy outcomes, across all treatment groups. These differences were small in magnitude (approximately 11% difference in primary outcome for EN3203-004), lacked a consistent pattern, and were also observed in placebo patients. These observations suggest that this finding is not clinically meaningful, however the Sponsor did not perform statistical comparisons of the results.

Age Effects:
Several efficacy outcomes were pooled from studies EN3203-004 & EN3203-005. There was slightly better pain relief for each of the three treatment arms, OM IR, OC IR, and PBO for patients ≥ 65 years of age relative to younger patients. This observation was noted across treatment arms, including placebo. PK studies of oxymorphone found that

the single-dose and steady-state plasma concentrations were approximately 40% higher in elderly patients (≥ 65 years of age) relative to younger subjects. This may account for some of the difference observed for oxymorphone, although it would not explain the similar findings in placebo patients. A complete explanation for this finding is not known.

Race and Ethnicity Effects:
There were too few non-Caucasian patients to analyze the effects of race or ethnicity.

Pediatrics:
The Sponsor has provided a proposal for pediatric development intended to fulfill the guidance outlined by the Best Pharamceuticals for Children Act and the Pediatric Rule. The sponsor has requested a deferral for pediatric studies of oxymorphone IR.

CLINICAL REVIEW

3 INTRODUCTION AND BACKGROUND

3.1 Proposed Indication:

The current indication proposed for this product is analgesia for moderate to severe pain where the use of an opioid is appropriate.

3.2 Oxymorphone Regulatory History:

Please refer to the Regulatory History section of NDA 21-610 (Oxymorphone ER) as this section involves both oxymorphone formulations.

4 CLINICALLY RELEVANT FINDINGS FROM CHEMISTRY, ANIMAL PHARMACOLOGY AND TOXICOLOGY, MICROBIOLOGY, BIOPHARMACEUTICS, STATISTICS, AND/OR OTHER CONSULTANT REVIEWS

4.1 Chemistry

4.1.1 Drug, Trade Name, and Drug Class:

Oxymorphone hydrochloride immediate-release (IR) tablet is a semi-synthetic opioid mu-receptor agonist analgesic. The Sponsor proposes 5 mg and 10 mg tablet strengths for oral administration. Two trade names have been proposed at the time of this writing: Opana and ———. In a review by the Division of Medication Errors and Technical Support of the Office of Drug Safety, the trade name Opana was not recommended because of concerns about possible errors due to the availability of tincture of opium. There were no objections to the tradename ———.

4.1.2 Clinically Relevant CMC Findings:

Please refer to the Chemistry Review.

4.2 Animal Pharmacology and Toxicology

Please refer to the Pharmacology and Toxicology Review.

4.3 Biopharmaceutics

A total of 14 clinical PK and bioavailability studies have been conducted to support the development and labeling of this modified-release opioid product. The following information is derived from the sponsor's clinical pharmacology summaries, proposed label, and the Division Biopharmaceutics Review, where applicable.

Absorption

Following oral administration oxymorphone IR is with a mean absolute bioavailability of 10.8%. The extent of absorption (AUC) was comparable between IR and ER tablets. The rate of absorption (Cmax) was higher (approximately 35%) for IR tablets, compared with

ER tablets. The significance of increased Cmax with IR tablets may not warrant dosage adjustment. Summary oxymorphone IR pharmacokinetic parameters are shown in Table 3.1.1 below, taken from the Sponsor's draft label.

Table 3.1.1 Oxymorphone IR Pharmacokinetic Parameters, (Mean ± SD)

Regimen	Dosage	Cmax (ng/mL)	AUC (ng·hr/mL)	T ½ (hr)
Single Dose	5 mg	1.10 ± 0.55	4.48 ± 2.07	7.25 ± 4.40
	10 mg	1.93 ± 0.75	9.10 ± 3.40	7.78 ± 3.58
	20 mg	4.39 ± 1.72	20.07 ± 5.80	9.43 ± 3.36
Multiple Dose[a]	5 mg	1.73 ± 0.62	4.63 ± 1.49	NA
	10 mg	3.51 ± 0.91	10.19 ± 3.34	NA
	20 mg	7.33 ± 2.93	21.10 ± 7.59	NA

NA = not applicable
[a] Results after 5 days of q6h dosing.
Source: Table 1, Oxymorphone Draft Label, pg. 3, 4/15/03 submission

Food Effects:
Oxymorphone IR tablets exhibited a 38% increase in both AUC and Cmax, with food intake. The ER formulation exhibited a 53% increase in Cmax with food intake, but no change in AUC was observed. Oxymorphone was taken with and without food in clinical efficacy trials. The results of the food effect studies indicate that oxymorphone can be dosed irrespective of relationship to meals.

Dose Linearity, Proportionality, and Steady-State PK
Oxymorphone IR and ER tablets exhibited dose proportionality (testing 5 mg up to 40 mg) with both single and multiple doses. No accumulation was observed after multiple administration of IR tablets every 6 hours and ER tablets every 12 hours.

Metabolism
Oxymorphone is metabolized principally in the liver by oxidation and glucuronidation to form two major metabolites: oxymorphone-3-glucuronide and 6-OH-oxymorphone. The Sponsor states that the pharmacologic activity of the glucuronide metabolite has not been evaluated and 6-OH-oxymorphone has been shown in animal studies to have bioactivity.

Excretion
Less than 1% of the administered oxymorphone dose is excreted unchanged in the urine.

Drug Interactions:
In vitro studies in human recombinant human liver microsomes and hepatocytes indicate that oxymorphone does not inhibit the activity of CYP450 1A2, 2C19, 2D6, or 2E1. However 2C9 and 3A4 inhibition was observed at supra-clinical concentrations (inhibitory concentration was 300- to 1000- fold and 10,000-fold higher, respectively, than the expected clinical concentration). The Sponsor states that two clinical drug

interaction studies are ongoing to further investigate the effects on CYP450 2C9 and 3A4.

Renal Impairment
Single doses of oxymorphone 20 mg ER showed progressive increases in plasma oxymorphone AUC and Cmax, as renal function declined (by 25, 57, and 65% in mild, moderate, and severe impairment respectively), but the elimination half-life appeared unaffected by renal impairment. In agreement with the Biopharmaceutics Review, dose titration should be undertaken cautiously in moderate to severe renally impaired patients.

Hepatic Impairment
Single doses of oxymorphone 20 mg ER tablets produced clinically significant increases in plasma oxymorphone concentrations (mean AUC increased up to 3.7x and 12.2x in moderate and 1 severe liver disease patient, respectively). Individuals with mild liver disease did not appear to have a significant AUC increase (approx. 1.5x) and t1/2 was unchanged across all three groups. In agreement with the Biopharmaceutics Review, oxymorphone should be contraindicated in severe hepatic impairment and dose titration must be undertaken with extreme caution in patients with moderate hepatic impairment.

Age and Gender Findings
Study EN3202-006 was conducted to evaluate single and multi-dose oxymorphone PK characteristics in 48 healthy adults divided in four groups, based on age (18-40 and > 65) and gender. The single-dose and steady-state plasma concentrations of oxymorphone were approximately 40% higher in elderly subjects (> 65 years of age) than in young subjects (20 to 40 years of age). Steady-state plasma oxymorphone concentrations were slightly higher (14 and 20 % increase in AUC and Cmax, respectively, for all gender) in women than in men. In addition, the mean oxymorphone AUC in elderly females was greater than in elderly males by approximately 26%; and the AUC in young females were greater than in young males by approximately 24%. The Sponsor states that no gender related differences were observed when the PK results were normalized for body weight. In summary, caution should be used in dose titration of elderly patients.

Pharmacodynamics:
There is no exposure-response relationship information for IR tablets. The Sponsor stated that they did not observe any exposure-response relationship for ER tablets. However, additional analysis (by Division Biopharmaceutics reviewer) suggests a trend of decreasing pain intensity when oxymorphone concentration increases.

4.4 Biostatistics
Please refer to the Biostatistical Review.

4.5 Controlled Substance
Please refer to the separate Controlled Substance and Risk Management Plan Review documents.

5 DESCRIPTION OF CLINICAL DATA AND SOURCES:

5.1 Overall Data

The primary data source was the two placebo-controlled studies submitted in support of efficacy of the immediate-release (IR) oxymorphone formulation (EN3203-004 and 005). These studies are reviewed in detail in the clinical sections below. Clinical pharmacology studies (EN3202-001, 002, 006, and 007) are reviewed in detail within the biopharmaceutics review. Additional scientific literature was provided in support of the NDA, although this was not used as part of this review.

5.2 Tables Listing the Clinical Trials

The clinical development plan included trials evaluating both the extended-release (ER) and immediate-release (IR) formulations of oxymorphone. This NDA (21-611) specifically evaluates the efficacy of the IR formulation. As both development programs ran simultaneously, the following table lists all the clinical studies performed, along with numbers of patients and basic design features. Note that all placebo-controlled pivotal trials are in bold type to distinguish them from clinical pharmacology, open-label, and active-controlled studies.

Table 5.2 Clinical Trials in the Oxymorphone ER and IR Development Program

Protocol No.	Development Plan		Study Type	Does Regimen and Formulation and Duration of Treatment	N
	ER	IR			
3202-001	Yes	Yes	Clinical pharmacology	OM ERa 20, OM ERb 20 OM 10 solution, Single dose crossover	15
3202-002	Yes		Clinical pharmacology	OM ERa 20, OM ERb 20 OM 10 solution, Single dose crossover	15
3202-003	Yes		Clinical pharmacology	OM ERa 20 tab, OM 10 solution, Single dose crossover	15
3202-004	Yes		Clinical pharmacology	NTX/OM ER 50/20 tabs OM ER 20 tabs, Single dose crossover	12
3202-005	Yes		Clinical pharmacology	NTX/OM ER 50/20 tabs, Single dose	24
3202-006	Yes		Clinical pharmacology	NTX/OM ER 50/20 tabs, Single/multiple dose	48
3202-007	Yes		Clinical pharmacology	Day 1 and 7 OM ER 5, 10, 20, and 40 tab (qd) Days 3 and 6 OM ER 5, 10, 20, and 40 tab (bid) Single/multiple dose crossover	24
3202-008	Yes		Clinical pharmacology	OM ER 40 tab, OM IR 10 x 4 tabs Single dose crossover	28
3202-009	Yes		Clinical pharmacology	Day I OM ER 20 x 1 tab (qd), OM IR 10 x 1 tab (qd) Day 3 through 8 OM ER 20 tab (bid), OM IR 10 tab (qid) Day 9 OM ER 20 x 1 tab (qd), OM IR 10 x 2 tab (qd), Single/multiple dose crossover	28
3202-010	Yes		Clinical pharmacology	OM ER 20 tab, Single dose	34
3202-011	Yes		Clinical pharmacology	OM ER 40 tab manufactured by Novartis; 2 doses OM ER 40 tab manufactured by IPC; 2 doses	24
3202-011A	Yes		Clinical pharmacology	OM ER 40 tab manufactured by Novartis; 2 doses OM ER 40 tab manufactured by IPC; 2 doses	6
3202-012	**Yes**	**Yes**	**Phase III, Acute post-operative pain, placebo-controlled**	**OM ER 20 tab, Placebo, Multiple dose**	**127**

Protocol No.	Development Plan		Study Type	Does Regimen and Formulation and Duration of Treatment	N
	ER	IR			
3202-015	**Yes**	**Yes**	**Phase III, Osteoarthritis pain, placebo-controlled**	**Weeks 1-2** **OM ER 20 tab, OM ER 20 tab, OC .10 tab, Placebo** **Weeks 3-4** **OM ER 20 tab, OM ER 40 tab, OC .20 tab, Placebo,** **Multiple dose**	**489, 491 Rand**
3202-016	**Yes**		**Phase III, Lower back pain, placebo-controlled**	**10-14 day Titration Period** **OM ER 10-110, OC ER 20-220** **18-Day Double-Blind Treatment** **OM ER 10-110, OC ER 20-220, Placebo**	**329, 330 Rand**
3202-017	Yes		Cancer pain	OM ER 20-300 tab, MS C® 15-900 tab OC® 10-600 tab, Multiple dose crossover	86
3202-018	Yes		Cancer pain	Titration to optimal doses for each of the Trt Arms OM ER 10-100 tab, MS C® 30-300 tab 1 wk OL titration, 2 wks (1 wk/arm) crossover	36
3202-019	Yes		Cancer pain	Titration to optimal doses for each of the Trt Arms OM ER 10-110 tab, OC® 20-220 tab, Crossover	44
3202-020	Yes		Osteoarthritis and cancer pain	Completed studies 015 and 017 patients will start at dosage level from previous controlled-study; may be titrated up or down based on individual patient's pain relief and tolerability of side effects	197
3202-021	Yes		Osteoarthritis and cancer pain	Completed studies 016& 019. Optimal dose will be established during first week of dosing and may be titrated up or down based on individual patient's pain relief and tolerability of side effects	239 (164) *
3202-022	Yes		Cancer pain	Completed study 018 patients will start at dosage level from previous controlled-study; may be titrated up or down based on individual patient's pain relief and tolerability of side effects	24 (15)*
3202-025	**Yes**		**Phase III, Osteoarthritis pain, placebo-controlled**	**Week 1** **OM ER 10 tab, OM ER 20 tab, OM ER 20 tab, Placebo** **Week 2** **OM ER 10 tab, OM ER 40 tab, OM ER 50 tab, Placebo**	**370**
EN3202-026^	Yes		Clinical pharmacology	Group A : OM ER (3 × 20 mg PO q12h Days 1-14 am) plus NTX (2 × 50 mg PO Day –1 and 50 mg PO q24h Days 1-14) Group B: OM ER (10 mg PO q12h Days 1-3; 20 mg PO q12h Days 4-14 am; 10 mg PO q12h Days 14 pm-17 am; and 5 mg PO q12h Days 17 pm-18 am) Group C : rifampin (2 × 300 mg PO q24h Days 1-14) Group D: NTX (2 × 50 mg PO Day –1 and 50 mg PO q24h Days 1-14) Group E: untreated All Groups: CYP450 3A4 probe 3 μ Ci [^{14}C N-methyl] erythromycin ~0.03 mg IV push and midazolam HCl syrup 2 mg/mL PO (SD, am, Day -1, Day 7, and Day 14)	80
EN3202-027^	Yes		Clinical pharmacology	Group A: OM ER (3 × 20 mg PO q12h Days 1-14 am) plus NTX (2 × 50 mg PO Day –1 and 50 mg PO q24h Days 1-14) Group B: OM ER (10 mg PO q12h Days 1-3; 20 mg PO q12h Days 4-14 am; 10 mg PO q12h Days 14 pm-17 am; and 5 mg PO q12h Days 17 pm-18 am) Group C: rifampin (2 × 300 mg PO q24h Days 1-14) Group D: NTX (2 × 50 mg PO Day -1 and 50 mg PO q24h Days 1-14) Group E: untreated control All Groups: tolbutamide (SD 500 mg PO, am, Day -1, Day 7, and Day 14)	85

Protocol No.	Development Plan		Study Type	Does Regimen and Formulation and Duration of Treatment	N
	ER	IR			
3203-001	Yes	Yes	Clinical pharmacology	OM 10 tab, OM 10 soln OM 1 IV, Single dose crossover	9
3203-002		Yes	Clinical pharmacology	OM IR 10 tab, OM 10 soln, OM IR 1 x 10 tab OM IR 2 x 5 tabs, Single dose crossover, fasting, 7 day washout	30
3203-004	**Yes**	**Yes**	**Phase III, Acute post-operative pain, placebo-controlled**	**OM IR 10 tab, OM IR 20 tab, OM IR 30 tab, OC IR 10 tab, Placebo, Single/multiple dose**	**300**
3203-005	**Yes**	**Yes**	**Phase III, Acute post-operative pain, placebo-controlled**	**OM IR 10 tab, OM IR 20 tab, OC IR 15 tab, OC IR 30 tab, Placebo tab, Single dose**	**324**
3203-006		Yes	Clinical pharmacology	NT/OM IR 50/5, NT/OM IR 50/10 tab NT/OM IR 50/10 tab, Single/multiple dose crossover	24
3203-007		Yes	Clinical pharmacology	OM IR 10 tab, OM IR 10 tab Single dose crossover	32

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

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

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

5.3 Postmarketing Experience

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

5.4 Literature Review

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

6 CLINICAL REVIEW METHODS:

6.1 How the Review was Conducted

Studies EN3202-004 and 005 submitted in support of a finding of efficacy were reviewed in detail. An extensive review of the study protocols, study reports, and patient summaries was performed. The case report forms (CRFs) and case report tabulations (CRTs) were consulted to further evaluate patient disposition, to confirm the sponsor's efficacy analysis, and to perform additional efficacy analyses.

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

6.2 Overview of Materials Consulted in Review

Primary review material (PDF text files and SAS transport data files) was provided in electronic format by the sponsor. In addition to the electronic NDA, prior protocol reviews were also consulted. This material was principally used to document the regulatory and administrative history of this product's development.

6.3 Overview of Methods Used to Evaluate Data Quality and Integrity

The Sponsor states that data were entered from the CRF using a double-blind entry procedure with quality control audits conducted on 100% of critical variables for all patients. In addition, 100% of data were reviewed for a randomly selected sample of 10% of the patients. The SAS datasets were compared visually, field-by-field, with the paper CRF. Any discrepancies were either resolved or explained on an "Audit Finding Worksheet."

Study disposition results, efficacy results, and selected data tables were compared to Sponsor supplied SAS listings, SAS CRTs, and CRFs whenever possible, as part of the efficacy review. Inconsistencies, missing or unclear information resulted in requests for clarifications, additional data, and/or CRFs from the Sponsor to resolve all review questions.

6.4 Were Trials Conducted in Accordance with Accepted Ethical Standards

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

6.5 Evaluation of Financial Disclosure

The sponsor submitted certification with a Form 3454 for the Principle Investigators and their sub-investigators for six studies: EN3203-001, 002, 004, 005, 006 and 007. One study (EN3203-001) was started before the initiation of the financial disclosure requirements.

All investigator sites (#45) had financial disclosure forms (FDFs) returned from all participants. There were no disclosures of any financial arrangements that would create a conflict of interest or result in the need to exclude the results from any study sites.

7 INTEGRATED REVIEW OF EFFICACY

7.1 Brief Statement of Conclusions

Two adequate and well-controlled pivotal trials were submitted in support of efficacy for oxymorphone immediate-release. These were identified as EN3203-004 and EN3203-005 as shown in Table 7.1 below.

Table 7.1 NDA 21-611 Pivotal Studies

Protocol	Type	Design	Dose and Duration of Treatment	Primary Outcome	N	Reviewer Comments
3203-004	Safety & efficacy; drug vs. placebo; adults with moderate to severe pain following total hip or knee surgery	Randomized, double-blind, placebo-controlled, parallel group, single/multiple dose, 48 hour duration	Single-Dose: 0-8 Hours: OM IR 10 mg, OM IR 20 mg, OM IR 30 mg, OC IR (Percolone) 10 mg, Placebo Multi-Dose: 8-48 Hours: OM IR 10 mg q4-6 hrs, OM IR 20 mg q4-6 hrs, OM IR 30 mg q4-6 hrs, OC IR (Percolone) 10 mg	Single-Dose Phase: Total Pain Relief (TOTPAR8)	300	Achieved primary with LOCF and BOCF
3203-005	Safety & efficacy; drug vs. placebo; adults with moderate to severe pain following orthopedic surgery	Randomized, double-blind, placebo-controlled, parallel group, single-dose trial	Single-Dose: 0-8 Hours: OM IR 10 mg, OM IR 20 mg, OC IR 15 mg, OC IR 30 mg, Placebo	Total Pain Relief (TOTPAR8)	324	Achieved primary with LOCF and BOCF
Data Source: Table 5.2, NDA 21-611 Review, pg. 14, and EN3203-004 and 005 Clin Study Report information						

Study EN3203-004 was a 48-hour, single and multi-dose, placebo- and active-controlled study in 300 patients with post-operative pain.. The Sponsor's analysis of the primary outcome variable (total pain relief from 0 to 8 hours or TOTPAR8) for the single-dose phase of the study revealed statistically significant differences from placebo for OM IR 10, 20, and 30 mg . Re-analysis by the Agency Biostatistical Reviewer confirmed the Sponsor's findings. The majority of secondary outcomes favored the oxymorphone formulations over placebo, with a trend towards greater efficacy response with OM 30 mg. Evaluation of the average dosing interval calculation shows intervals ranging from 7 to 10 hours, but subjects were permitted rescue medication. In summary, all three oxymorphone IR doses demonstrated a statistically significant difference to placebo and support the sponsor's claim of efficacy for the three formulations, but do not support the Sponsor's proposed dosing interval.

Study EN3203-005 was an 8-hour multicenter, randomized, double-blind, placebo- and active- controlled, single-dose study of oxymorphone IR (10 and 20 mg formulations) and oxycodone IR (15 and 30 mg formulations) in 324 patients with postoperative pain due to osteotomy. This study was intended to support a finding of efficacy of oxymorphone. The Sponsor's analysis of the primary outcome variable of Total Pain

Relief from 0 to 8 hours demonstrated a statistically significant improvement compared with placebo for the OM 20 mg treatment group, but not for the OM 10 mg group. The secondary analysis also favored the OM 20 mg dose, but not the lowest 10 mg formulation. Oxycodone 15 and 30 mg IR doses were statistically different from placebo in the primary and secondary analyses. The Sponsor's efficacy findings were confirmed by Dr. Price (Agency Biostatistical Reviewer) in a re-analysis of the efficacy data. The results of EN3203-005 support the sponsor's claim of analgesic efficacy of the oxymorphone IR 20 mg formulation compared to placebo.

In Summary, two adequate and well-controlled studies in post-operative pain support the single-dose efficacy of oxymorphone IR 20 and 30 mg versus placebo.

7.2 General Approach to Review of the Efficacy of the Drug

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

7.3 Detailed Review of Trials by Indication

7.3.1 STUDY EN3203-004:

Title: Multi-Center, Randomized, Double-Blind, Placebo-Controlled, Parallel-group, Dose-Ranging Comparison of the Analgesic Efficacy and Safety of Numorphan IR (Oxymorphone HCL Immediate-Release), Percolone, and Placebo in patients with Postsurgical Pain Following Orthopedic Total Hip and Knee Replacement.

Objectives:

- Primary:
  Assess efficacy of three doses (10, 20, and 30 mg) of immediate-release (IR) oxymorphone (OM) vs. placebo (PBO) in patients with acute moderate to severe post-op pain.
- Secondary:
  1. Evaluate dose-response and analgesic efficacy of 10, 20, and 30 mg OM IR
  2. Compare safety of 3 dose-levels of OM IR to 10 mg oxycodone (OC - Percolone) IR and PBO

Study Design: Multi-center, randomized, double-blind, placebo and active controlled, 2-phase, multi-dose study of OM IR and OC IR

Study Duration: up to 48 hours (includes an initial 8-hour single-dose phase followed by a multiple dose phase)

Population: Enroll 300 patients in order to achieve 60 patients per treatment arm

Inclusion Criteria:

- Male or female patients, 18 to 75 years of age
- Women were to be of non-childbearing potential, non-lactating, and were to have a negative serum pregnancy test at screening.
- Patients were to meet the criteria for Physical Status Classification System levels I-III of the American Society of Anesthesiologists (ASA) (see Appendix 11.1 for details and definition)
- Patients were to have undergone total hip or knee replacement, or revision (provided they had prior osteotomy performed)
- Patients were to have no contraindications to the study medications and no other painful physical conditions confounding evaluation of postoperative pain.
- Patients were to have the ability to tolerate oral analgesics based on the presence of bowel sounds, absence of significant nausea or vomiting, and tolerability of fluids.
- Patients were to have baseline post-op moderate to severe pain intensity on a 100 mm visual analog scale (VAS) and were to have $\geq$ 45 mm within 6 hours of receiving intravenous (IV), or 9 hours after last intramuscular (IM) opioid.

Exclusion Criteria:

- Receiving an investigational drug within 30 days of the current study
- AST, ALT, or Serum Creatinine > 1.5 x upper limit of the normal range (ULN) at screening
- The patient was found to have an ileostomy or evidence of GI stasis or chronic respiratory insufficiency
- Use of NSAIDs (except Vioxx or Celebrex) within 48 hrs of planned surgery or monoamine oxidase inhibitor (MAOI) use within 14 days of surgery
- Corticosteroid use (except topical, inhaled or intraarticular (IA) route) within 7 days of planned surgery
- Prior analgesic, EtOH, or opioid abuse within 180 days prior to study

Study Design:

Screening visit (Day -14):
Potential patients were to be assessed for study eligibility, have their informed consent obtained, and undergo normal preoperative evaluation at this time.

Post Surgery (Day 0):
Pre-screened post-operative patients were to be placed on opioid analgesia (could be intravenous (IV) or intramuscular (IM)) and this was to be stopped within 48 hours, for patients able to take oral medication. Eligible patients who then developed moderate to severe pain measured as pain intensity ≥ 45 mm on a 100 mm VAS scale, were to be randomized to one of 5 possible treatments:

1. OM IR 10 mg
2. OM IR 20 mg
3. OM IR 30 mg
4. OC IR 10 mg (Percolone)
5. PBO

Treatment Phase (up to 48 hours):

Single-Dose Phase (0 - 8 hours):

- Baseline vital sign measurements and pain assessments (VAS and categorical) were to be taken
- Patients were to receive 1st dose of randomized study medication
- Efficacy assessments were to be taken just prior to the 1st dose and at 15, 30, 45 min and 1, 1.5, 2, 3, 4, 5, 6, 7, and 8 hours, or until re-medication
- The single-dose phase was to be completed when either of the following occurred:
  1. The patient was to request re-medication (if ≤ 3 hours after 1st dose, they exited study as treatment failures)
  2. The patient completed the 8-hour assessment

Multi-Dose Phase (8 - 48 hours):

Subjects that completed the single dose phase, tolerated the initial dose of study medication and did not require re-medication before 3 hours after the initial dose of study drug were to enter the multiple dose phase.

- Prior PBO patients (in the single-dose phase) were to cross over to one of the active blinded treatments, based on the randomized treatment sequence they were originally assigned
- Patients were to receive study medication every 4-6 hours prn, but not more than q 3hr for up to 48 hours. The number and time of study medication doses were to be recorded
- During the multiple-dose phase, patients were to recall their worst intensity of pain during the day, at bedtime and worst intensity of pain during the night, each morning upon awakening. Other assessments are shown in the schedule of activities, included below.
- Patients requesting additional analgesia prior to 3 hours after receiving the previous dose of study medication were to be given rescue, complete an exit evaluation then exit the study

Table EN3203-4.0a Treatment Sequences

Sequence	Double-Blind Medication	
	Single-Dose Phase	Multiple-Dose Phase
AA	10 mg Numorphan IR	10 mg Numorphan IR
BB	20 mg Numorphan IR	20 mg Numorphan IR
CC	30 mg Numorphan IR	30 mg Numorphan IR
DD	10 mg Percolone	10 mg Percolone
EA, EB, EC, ED	Placebo	10, 20, 30 mg Numorphan IR or 10 mg Percolone

*A, B, and C= 10, 20 and 30 mg Numorphan IR respectively, D= 10 mg Percolone, E= Placebo

Data Source: Figure 5: Treatment Sequences, EN3202-004 Protocol, pg. 32 of 48.

- Dose Selection, Concomitant Therapy and Rescue

Study Drug, Dose Selection, and Interval:

1. The selected dose of immediate-release (IR) oxycodone had been shown effective in the treatment of acute and chronic pain. The dose of oxycodone was given as combinations of three over-encapsulated tablets of 5 mg or placebo, as shown in Table 4.0b, below.

2. The doses of oxymorphone IR were selected, based on available efficacy and safety data on IV PCA oxymorphone use in the post-operative setting. Each dose was to be given as 3 capsules. Total daily doses of active oxymorphone (between 10 and 30 mg) were achieved by varying the number of active OM 10 mg IR (3 tabs for a 30 mg dose) over-encapsulated tablets, as shown in Table 4.0b below.

Table EN3203-4.0b Description of Study Medication

	Contents of Each Capsule		
Treatment Group	**Capsule #1**	**Capsule #2**	**Capsule #3**
Oxymorphone IR 10 mg	Oxymorphone IR 10 mg	Placebo	Placebo
Oxymorphone IR 20 mg	Oxymorphone IR 10 mg	Oxymorphone IR 10 mg	Placebo
Oxymorphone IR 30 mg	Oxymorphone IR 10 mg	Oxymorphone IR 10 mg	Oxymorphone IR 10 mg
Oxycodone IR 10 mg	Oxycodone IR 5 mg	Oxycodone IR 5 mg	Placebo
Placebo	Placebo	Placebo	Placebo

Data Source: Table 1, EN3202-004 Clin Study Report, pg. 23

3. The dosing interval was to be approximately every 4-6 hours as needed, but not more than every 3 hours, until 48 hours after the start of the Single-Dose Phase.

Post-Operative Analgesia:

- ALLOWED – IV or IM opioids up to 48 hours after surgery.

Concomitant Therapy:

- RESTRICTED – Anticonvulsants prior to 4 weeks of dosing, long acting NSAIDs or COX-2 Inhibitors (stopped ≥ 24 hrs before dosing), tranquilizers, muscle relaxants, and antihistamines (other than Benadryl) from 4 hours prior to stopping initial opioid pain meds until study completion.

- ALLOWED - Antidepressants were allowed if the patient was on a stable dose throughout the study. Additionally, ASA for prophylaxis, femoral nerve block, APAP for fever, diphenhydramine for pruritis, Zofran or other antiemetic after 2 hrs of study dose were to be allowed.

Rescue Medication:

- Rescue medication was to be allowed per the investigator's choice. Patients requiring analgesia prior to 3 hours post dosing with the study drug were to be treated and then removed as "treatment failures."

Table EN3203-4.1 Schedule of Protocol Assessments

Assessment	Visit 1	Visit 2 (Hospital)														
	Pre-Treatment	Single-Dose Phase												Multiple-Dose Phase	
		After First Dose														
	Screening	Baseline (day after surgery)	15"	30"	45"	1h	1.5h	2h	3h	4h	5h	6h	7h	8h or rescue or re-med.	Dose every 4-6 hrs prn until 48	Exit Evaluation[d]
Informed Consent	X															
Demographics	X															
Medical History	X	update														
Physical Exam	X															X
Assess Entry Criteria	X	X														
Vital Signs	X	X				X		X		X		X		X	X	X
Clinical Laboratory	X															X
Randomization		X														
Adverse Events			X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study Drug Administration		X													X	
Pain Assessments:																
Current Pain Intensity		X[a]	X	X	X	X	X	X	X	X	X	X	X	X		
Current Pain Relief			X	X	X	X	X	X	X	X	X	X	X	X		
Pain 50% Gone			X	X	X	X	X	X	X	X	X	X	X	X		
Time to Perceptible and Meaningful Pain Relief		start watches	Stop when perceptible & meaningful relief reached													
Worst Pain															X[b]	
Patient's Global Evaluation														X	X[c]	
Physician's Global Evaluation															X[d]	

[a]Assess just prior to first dose
[b]Assess in the morning when the patient wakes up and at bedtime
[c]To be completed at end of the Multiple-Dose Phase
[d]To be completed after the last dose of Multiple-Dose Phase medication or withdrawal from the study
Data Source: Table 2, EN3202-004 Clin Study Report, pg. 27

Outcome Measures:

Efficacy (see Appendix 11.1 for detailed efficacy instrument descriptions):

Single-Dose Phase:

1) Pain Intensity (VAS and categorical scales) was to be assessed at 12 timepoints (15, 30, and 45 minutes and 1, 1.5, 2, 3, 4, 5, 6, 7, and 8 hours) over 8 hours.
2) Pain Relief (5 point categorical scale) was to be assessed at 12 timepoints (15, 30, and 45 minutes and 1, 1.5, 2, 3, 4, 5, 6, 7, and 8 hours) after the first study dose, over 8 hours.
3) Time to … Perceptible Pain Relief, Meaningful Pain Relief, Re-Medication, and Pain At Least Half-Gone were to be measured at the time subjects reported pain relief, meaningful pain relief, pain half gone, and the time of re-medication using stopwatch times.

Multi-Dose Phase:

1. Worst Pain Recall (100 mm VAS and 4-point categorical scale) was to be measured at bedtime and at waking
2. Subject and the investigator were to provide a categorical global rating of the study medication, based upon their overall satisfaction with the pain medication taken during the study.

Safety:

Adverse events (AEs), physical exams (PEx),vital signs, and clinical labs (see schedule for details).

Statistical Assessment:

Primary efficacy endpoint was to be based on the single-dose phase of the study using a modified intent-to-treat population. All statistical tests were to be two-sided, with statistical significance denoted by a p-value of 0.05 or less, unless otherwise stated. Dose response was to be performed on the primary efficacy endpoint, with a regression model using the efficacy endpoint as a dependent variable and the OM IR dose as the independent variable.

Primary Efficacy Variables:

- Total Pain Relief (**$TOTPAR_8$**): This was defined to be the area under the curve (AUC) of the 5-point categorical Pain Relief (PR) scores from baseline (0) to 8-hours during the single-dose phase. This was to be analyzed using an Analysis of Covariance (ANCOVA).

Secondary Efficacy Variables:

Single-Dose Phase:

- Total pain relief at the 0-4 and 0-6 hour intervals – $TOTPAR_4$, $TOTPAR_6$, defined similarly to the primary efficacy variable

- Sum of pain intensity difference (SPID) with VAS and categorical scales over 0-4, 0-6, and 0-8 hour intervals.
- Proportion and time (in hours) when patients first experienced 50% pain relief
- Time to onset of analgesia
- Time (in hours) to re-medication
- Patient's Global Evaluation of Study Medication.

Multiple-Dose Phase:

- Worst Pain:
  - during the day: VAS and categorical (collected at bedtime)
  - during the nighttime: VAS and categorical (collected in the morning)
- Patient and physician's global evaluation of study Medication.

Data Sets:

1. Intent-to-Treat (ITT) Population – This was to be all patients randomized to treatment, receiving the 1st dose, and completing the 1-hour primary efficacy evaluation without being re-medicated or vomiting.

2. Safety Population – Was to be all patients randomized and receiving ≥ 1 dose of study medication

Missing Data:
In general, the last observation carry forward (LOCF) method was to be used to impute missing data for early withdrawals.

Exploratory Analyses:
During the multiple dose phase, subjects were to take study medication every 4-6 hours as needed for pain for 48 hours after the first dose. The amount of study medication taken was to be analyzed to calculate the actual dose level and dosing interval using the following definition:

Actual Dose Interval = Duration of Multiple Dose Phase / Number of Doses

Post-Hoc Analyses:
In addition to the planned analysis of Last Observation Carried Forward (LOCF) for missing data, the analgesic efficacy endpoints also were analyzed using the Baseline Observation Carried Forward (BOCF) method, for missing data.

Protocol Amendments:

Amendment 1 - (2/19/01) [implemented prior to starting enrollment]:

- Removed weight restriction, clarified knee/hip surgery, excluded unstable antidepressant or anticonvulsant patients
- Vital sign collection added during multi-dose phase, concomitant medications clarified, schedule of activities clarified

- Schedule of Activity and 24-hour post-surgical and baseline assessment inconsistencies clarified

Protocol Amendment 2 - (5/21/01) [implemented after 41 patients enrolled]:

- Post-op analgesia changed to allow IV (PCA or non-PCA) or IM opioids, end of multi-dose phase clarified
- 9 hours specified as the required time after last dose of IM opioids within which subjects had to develop moderate to severe pain, to be randomized.

Protocol Amendment 3 – (2/21/02):

Implemented after enrollment completed via a waiver system implemented at study sites in Dec. 2001.

- Revision surgery allowed, time between post-surgery and dosing increased to 48 hours
- Small centers missing subjects in ≥ one treatment group will be pooled with the smallest center with subjects in all 5 treatment groups.
- The primary efficacy analysis population was clarified to be a Modified ITT defined as subjects receiving the 1st dose of study medication and completing the 1 hour primary efficacy evaluation without being remedicated or vomiting.
- If necessary, local laboratories were to be used to qualify subjects, on a case by case basis. Duplicate samples were to be sent to the central lab for verification.

SAP Changes:

An amendment to the final statistical analysis plan was issued (5/9/02), prior to database lock:

- Modified Intent-to-Treat population was renamed an 'efficacy evaluable' population and was additionally changed to include patients within the original modified ITT population and also did not have significant protocol violations.
- Handling of missing and off-schedule data evaluations was clarified
- Additional analyses and efficacy endpoints specified using the baseline observation carried forward (BOCF) on TOTPAR, sum of combined pain relief and pain intensity difference scores (SPRID), and SPID efficacy variables.
- Time to Analgesia measurement was to be determined from the measurement of 'time to perceptible pain relief' and 'meaningful pain relief.'
- The exploratory analyses in the multiple-dose phase were modified. The total study medication and the actual dose level were not calculated. Pain relief (PR) and pain intensity difference (PID) at the first perceptible pain relief and meaningful pain relief were summarized.

7.3.2 SPONSOR RESULTS for EN3203-004:

Disposition:

All of the 300 patients randomized, received ≥ 1 dose of study medication in the single-dose phase of the study. The distribution of randomized patients among treatment groups was similar. A total of 165/300 patients (55%) completed the single-dose phase of the study and 135/300 patients (45%) withdrew. OM 10, 20, and 30 mg patients dropped out at 46, 32, and 49%, respectively, compared to 46.7 % for the OC 10 mg group and 51% for PBO patients with 'lack of efficacy' accounting for the majority of discontinuations (32.2, 25.3, 33.8, 42, and 47.4 % respectively for OM 10, 20, 30, OC 10, and PBO). AEs accounted for the second most common reason for discontinuation, particularly in the oxymorphone groups (3.4, 8.5, and 12.3 % in the OM 10, 20, and 30 mg groups compared to 3.5% in PBO).

Table EN3203-4.2a Disposition of Randomized Patients

	Oxymorphone 10 mg	Oxymorphone 20 mg	Oxymorphone 30 mg	Oxycodone 10 mg	Placebo
Entire Study					
Randomized	59 (100.0)	59 (100.0)	65 (100.0)	60 (100.0)	57 (100.0)
Treated Patients[a]	59 (100.0)	59 (100.0)	65 (100.0)	60 (100.0)	57 (100.0)
Completed Study	24 (40.7)	26 (44.1)	29 (44.6)	22 (36.7)	18 (31.6)
Discontinued	35 (59.3)	33 (55.9)	36 (55.4)	38 (63.3)	39 (68.4)
ADVERSE EXPERIENCE	4 (6.8)	14 (23.7)	10 (15.4)	4 (6.7)	4 (7.0)
WITHDREW CONSENT	3 (5.1)	1 (1.7)	1 (1.5)	1 (1.7)	1 (1.8)
PROTOCOL VIOLATION	1 (1.7)	-	-	1 (1.7)	1 (1.8)
LACK OF EFFICACY	23 (39.0)	12 (20.3)	23 (35.4)	28 (46.7)	33 (57.9)
OTHER	4 (6.8)	6 (10.2)	2 (3.1)	4 (6.7)	-
Efficacy-Evaluable[b]	51 (86.4)	51 (86.4)	57 (87.7)	55 (91.7)	44 (77.2)
Single-Dose Phase					
Randomized	59 (100.0)	59 (100.0)	65 (100.0)	60 (100.0)	57 (100.0)
Treated Patients[a]	59 (100.0)	59 (100.0)	65 (100.0)	60 (100.0)	57 (100.0)
Discontinued	27 (45.8)	19 (32.2)	32 (49.2)	28 (46.7)	29 (50.9)
ADVERSE EXPERIENCE	2 (3.4)	5 (8.5)	8 (12.3)	-	2 (3.5)
WITHDREW CONSENT	2 (3.4)	-	1 (1.5)	-	-
PROTOCOL VIOLATION	1 (1.7)	-	-	1 (1.7)	-
LACK OF EFFICACY	19 (32.2)	9 (15.3)	22 (33.8)	25 (41.7)	27 (47.4)
OTHER	3 (5.1)	5 (8.5)	1 (1.5)	2 (3.3)	-
Multiple-Dose Phase Only (original randomization)					
Randomized	32 (100.0)	40 (100.0)	32 (100.0)	32 (100.0)	-
Treated Patients[a]	32 (100.0)	40 (100.0)	32 (100.0)	32 (100.0)	-
Discontinued	8 (25.0)	14 (35.0)	4 (12.5)	10 (31.3)	-
ADVERSE EXPERIENCE	2 (6.3)	9 (22.5)	2 (6.3)	4 (12.5)	-
WITHDREW CONSENT	1 (3.1)	1 (2.5)	-	1 (3.1)	-
LACK OF EFFICACY	4 (12.5)	3 (7.5)	1 (3.1)	3 (9.4)	-
OTHER	1 (3.1)	1 (2.5)	1 (3.1)	2 (6.3)	-
Multiple-Dose Phase Only (re-randomized)					
Randomized	6 (100.0)	8 (100.0)	7 (100.0)	7 (100.0)	-
Treated Patients[a]	6 (100.0)	8 (100.0)	7 (100.0)	7 (100.0)	-
Discontinued	4 (66.7)	3 (37.5)	3 (42.9)	-	-
ADVERSE EXPERIENCE	1 (16.7)	1 (12.5)	-	-	-
WITHDREW CONSENT	-	-	1 (14.3)	-	-
PROTOCOL VIOLATION	1 (16.7)	-	-	-	-
LACK OF EFFICACY	2 (33.3)	2 (25.0)	2 (28.6)	-	-

Data Source: Table 3, EN3203-004 Clin Study Report, pg. 44

[a]Treated Patients: Patients who are randomized to treatment and who take at least one dose of study medication.

[b]Efficacy-Evaluable Patients: Patients who received the first dose of study medication and completed the one-hour primary efficacy evaluation, without being re-medicated, without vomiting within the first hour, or without significant protocol violation.

164 patients entered the multiple-dose phase of the study (this includes 28 patients who were re-randomized from placebo to active medication), 46 (28%) patients discontinued from the study prior to completion of 48 hours. The most common reason for withdrawal from the multiple-dose phase of the study was adverse events (19/164 or 11.6%) followed by lack of efficacy (17/164 or 10.4%). The greatest frequency of AEs occurred in the OM 10 mg group (10/48 or 20.8%) followed by OC 10 mg (4/39 or 10.3%). Lack of efficacy was most frequent in the OM 10 mg (6/38 or 15.8%) and 20 mg (5/48 or 10.4%) dose formulations.

Other:
This category was explored in some detail for both the single and multiple dose phases of the study, using the sponsor supplied case report tabulations (CRTs). Table 4.2b lists the 16 treated patients and their corresponding reasons for discontinuation. For example, EN3203-004-25-005 (OM 10 mg) was withdrawn because of 'requesting rescue before 3 hours.' Patient # 27-007 (OM 10 mg) did not request re-medication within 9 hours of the multi-dose phase of the study. In the multi-dose 20 mg oxymorphone group "other" consisted of # 09-011 (OM 20 mg) "transferred to rehab", # 08-014 and # 08-020 "required no additional pain meds 8 hours after single dose", etc... Two patients (#s 25-006 and 26-002) in the OM 30 mg group were coded as "other" after "requesting rescue prior to 3 hours" and "discharged home" respectively. Evaluation of this category shows that two of the above listed subjects (# 25-005 and 25-006) should have been coded as withdrawal due to 'Lack of Efficacy.' Thus, this category for oxymorphone should be increased by 2 in the disposition table.

Table EN3203-4.2b Discontinued Treated Patients Listed as: OTHER
(Data Source: ENDSTUDY.XPT SAS Transport Analysis Data File)

PATID	CLASS	DESCRIPTION
EN3203-004-08-014	OTHER	REQUIRED NO ADDITIONAL PAIN MED 8 HOURS AFTER SINGLE DOSE
EN3203-004-08-020	OTHER	NO ADDITIONAL PAIN MED REQUESTED BY 8 HOURS PAST SINGLE DOSE
EN3203-004-08-021	OTHER	PATIENT DISCHARGED FROM HOSPITAL.
EN3203-004-09-011	OTHER	TRANSFERRED TO REHAB
EN3203-004-13-016	OTHER	PATIENT COULD NOT SWALLOW PILL
EN3203-004-13-049	OTHER	ANOTHER OPIVCD ANALGESIC GIVEN IN MULTI-DOSE PHASE
EN3203-004-13-062	OTHER	PT. REQUIRED RESCUE MEDICATION
EN3203-004-13-074	OTHER	REQUIRED RESCUE MEDICATION FOR PAIN RELIEF.
EN3203-004-25-004	OTHER	RESCUED PRIOR TO 3 HOURS
EN3203-004-25-005	OTHER	REQUESTED RESCUE MEDICATIONS PRIOR TO 3 HOURS
EN3203-004-25-006	OTHER	REQUESTED RESCUE MEDICATION PRIOR TO 3 HOUR
EN3203-004-26-002	OTHER	DISCHARGED TO HOME
EN3203-004-26-005	OTHER	CRC ERROR
EN3203-004-26-010	OTHER	DISCHARGED
EN3203-004-27-006	OTHER	DID NOT REQUEST REMEDICATION WITHIN 8HR
EN3203-004-27-007	OTHER	PT. DID NOT REQUEST STUDY MEDICINE WITHIN 8 HR

Withdrew Consent:
The sponsor supplied CRTs were examined to find more detail on these 7 subjects. When no additional comments were found, a request was sent to the sponsor for the associated CRFs. Evaluation of the supplied CRFs allowed construction of Table 4.2c,

shown below. Several patients should have been coded as withdrawing due to lack of efficacy (2) or from AEs (2). Three subjects appear to be coded appropriately.

Table EN3203-4.2c Discontinued Patients Listed as: Withdrew Consent
(Data Source: ENDSTUDY.XPT SAS Transport Analysis Data File and Endo Response to Request for Information, submitted 8/21/03)

UPID	Treatment	D/C Reason	Recoded D/C Reason	Reviewer Comments
EN3203-004-003-021	OM 10 mg	Withdrew Consent	LOE	Subject w/d after 4 hrs, PI also listed lack of efficacy at time of withdrawal
EN3203-004-007-003	OM 30 mg	Withdrew Consent	AE	Subject w/d after 8 hrs, some nausea and itching, PI states pt. W/d consent but AEs were present
EN3203-004-008-018	PBO	Withdrew Consent	No Change	Subject w/d after 3 hours, no AEs, no other information on why stopped, LOE possible but cannot be sure without other info
EN3203-004-008-019	OM 10 mg	Withdrew Consent	AE	Subject w/d, AEs of fever & post-op anemia present
EN3203-004-008-023	OM 10 mg	Withdrew Consent	No Change	Subject w/d after 1.5 hrs, no AEs, no other info to change classification
EN3203-004-013-087	OC 10 mg	Withdrew Consent	LOE	Subject w/d after 3 hrs, global assessment of med rated poor, had sore throat? LOE
EN3203-004-020-006	OM 20 mg	Withdrew Consent	No Change	Completed 8 hours, AE: mild Pruritis experienced, did not go on to multi-dose. PI aksed to clarify D/C reason and listed 'withdrew consent'

Recoding subjects originally listed as withdrawing due to 'other' or 'withdrew consent' changes the study disposition frequencies, as shown in Table 4.2d below. This can be contrasted to the Sponsor's disposition results in Table 4.2a.

Table EN3203-4.2d Entire Study Reviewer Recoded Disposition

	Oxymorphone 10 mg	Oxymorphone 20 mg	Oxymorphone 30 mg	Oxycodone 10 mg	Placebo
Entire Study					
Randomized	59 (100.0)	59 (100.0)	65 (100.0)	60 (100.0)	57 (100.0)
Treated Patients[a]	59 (100.0)	59 (100.0)	65 (100.0)	60 (100.0)	57 (100.0)
Completed Study	24 (40.7)	26 (44.1)	29 (44.6)	22 (36.7)	18 (31.6)
Discontinued	35 (59.3)	33 (55.9)	36 (55.4)	38 (63.3)	39 (68.4)
ADVERSE EXPERIENCE	5 (8.5)	14 (23.7)	11 (16.9)	4 (6.7)	4 (7.0)
WITHDREW CONSENT	1 (1.7)	1 (1.7)	-	-	1 (1.8)
PROTOCOL VIOLATION	1 (1.7)	-	-	1 (1.7)	1 (1.8)
LACK OF EFFICACY	24 (40.7)	12 (20.3)	25 (38.5)	29 (48.3)	
OTHER	4 (6.8)	6 (10.2)	-	4 (6.7)	-
Data Source: Tables 4.2a, 4.2b, and 4.2c, NDA 21-611 Clinical Review					

Protocol Violations and Exclusions from the Efficacy Analysis:

Protocol deviations and exclusion of patients from the efficacy analyses were determined prior to unblinding. Patients were excluded from the efficacy evaluable population due to lack of completion of the 1-hour primary efficacy assessment and significant protocol violations. Six (6) patients were included in the efficacy evaluable population with partial data. The following tables illustrate the exclusion categories. Forty-two (42)

randomized and treated subjects were excluded from the Sponsor's final ITT (efficacy-evaluable) population.

Table EN3203-4.3a ITT Population (Efficacy Evaluable) Exclusions

	Oxymorphone 10 mg	Oxymorphone 20 mg	Oxymorphone 30 mg	Oxycodone 10 mg	Placebo	Total
Entire Study	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Randomized	59 (100.0)	59 (100.0)	65 (100.0)	60 (100.0)	57 (100.0)	300
Treated Patients	59 (100.0)	59 (100.0)	65 (100.0)	60 (100.0)	57 (100.0)	300
Excluded from ITT:	8 (13.6)	8 (13.6)	8 (13.6)	5 (8.3)	13 (22.8)	42
Failure to complete 1-hr efficacy assessment	8 (13.6)	7 (11.9)	7 (10.8)	4 (6.7)	13 (22.8)	39
Protocol Violation		1 (1.7)	1 (1.5)	1 (1.7)		3
Efficacy-Evaluable	51 (86.4)	51 (86.4)	57 (87.7)	55 (91.7)	44 (77.2)	258

Source: Supplemental Table 1., EN3203-004 Clin Study Report, pg. 91

Three subjects were excluded for protocol violations. Examination of the sponsor's supplemental table shows that each case was due to use of another opioid:

- Patient # 13-016 – PCA pump was not discontinued prior to dosing
- Patient # 08-027 - " "
- Patient # 19-002 – Patient was using OxyContin concurrently

Table EN3203-4.3b Patients Included in the Efficacy-Evaluable Population with Partial Data

Site ID	Patient ID	Action	Reason
		Placebo	
09	021	Only the first hour efficacy assessment was included in analysis	Scheduled Hour 1 data was 10 minutes beyond 1 hour (dosing time: 8:40, Hour 1 data at 9:50)
08	006	Only the first hour efficacy assessment was included in analysis	Patient re-medicated 1 hour 8 minutes after dosing and had post 1-hour data but out of window for 8 minutes
13	078	Only the first hour efficacy assessment was included in analysis	Scheduled Hour 1 data was 33 minutes beyond 1 hour
		Oxymorphone IR 10 mg	
08	023	Only the first hour efficacy assessment will be included in analysis	No Hour 1 data.
		Oxymorphone IR 20 mg	
09	003	Only the first hour efficacy assessment will be included in analysis	Scheduled Hour 1 data was 6 minutes earlier than 1 hour (dosing time: 06:21, Hour 1 data at 07:15)
		Oxycodone IR 10 mg	
32	001	Only the first hour efficacy assessment will be included in analysis	Scheduled Hour 1 data was 15 minutes beyond 1 hour (dosing time: 11:10, Hour 1 data at 12:25)

Data Source: Supplemental Table 2, EN3203-004 Clin Study Report, pg. 92

Inclusion Criteria Violations:
Four of 57 (7.0%) placebo patients, 7 of 59 (11.9%) OM IR 10 mg patients, 9 of 59 (15.3%) OM IR 20 mg patients, 14 of 65 (21.5%) OM IR 30 mg patients, and 8 of 60 (13.3%) OC IR 10 mg patients violated ≥ 1 of the entry criteria. All but five patients (2 each in the OM IR 10 mg and 30 mg groups and 1 in the placebo group) were granted waivers by the Sponsor. In all cases, the violations were considered insufficient to warrant exclusion. The Sponsor's supplementary Listing 10 of Appendix 16.4 showed subjects and inclusion criteria status, by treatment. Examination of the patient listings shows that the majority of violations granted exceptions were for the following reasons:

- Inclusion Criteria #2 (22 exceptions granted) - "The subject's age is between the ages of 18 and 75 years."

- Inclusion Criteria #9 (14 exceptions granted) – Per the Sponsor this criterion underwent 3 amendments with the final wording:

  "The patient underwent primary total hip or total knee replacement surgery, *or revision surgery provided the patient has an osteotomy (per Amendment 3)*, and had a moderate to severe postoperative pain score >45 mm on a100 mm VAS within 6 hours *for patients receiving IV, or 9 hours after the last IM opioid pain medication dose (per Amendment 2)*. Patients who underwent unilateral condylar replacement were not to be enrolled."

- Inclusion Criteria #3 (acceptable weight for study) and #5 (subjects is physical status 1 to 3 in the ASA physical status classification) – accounted for 2 total exceptions

Detailed descriptions of the violations of criteria #9 were not found in the sponsor listings or CRTs and this information was requested from the Sponsor. The requested information showed that some patients were granted waivers for inclusion because protocol amendments to this criterion were pending and then later given IRB approval. The Sponsor supplied the following table of the fourteen subjects granted waivers.

Table EN3203-4.3c Patients Granted Waivers to Inclusion Criteria #9

UPID	Treatment (Single-Dose Phase)	Protocol Violation
EN3203-004-013-004 patient should be listed as EN3203-004-013-*044*	OM 10 mg	Left total knee revision involving osteotomy
EN3203-004-027-007	OM 10 mg	IV PCA was extended; subject required revision surgery due to the complications of the hip replacement.
EN3203-004-003-017	OM 30 mg	Bilateral knee replacement
EN3203-004-003-022	OM 30 mg	Bilateral knee arthroplasty
EN3203-004-013-077	OM 30 mg	Right hip revision arthroplasty involving osteotomy
EN3203-004-014-011	OM 30 mg	IV or IM morphine used instead of PCA
EN3203-004-020-026	OM 30 mg	Bilateral knee replacement
EN3203-004-027-002 patient should be listed as EN3203-004-027-*022*	OM 30 mg	Screening three weeks prior to surgery (Note: This is not a violation of inclusion 9 but deviation from the protocol requirement that surgery be done within 14 days of screening.)
EN3203-004-030-003	OM 30 mg	Unicompartmental knee revision involving osteotomy
EN3203-004-027-009	OC 10 mg	IV PCA was extended
EN3203-004-031-008	OC 10 mg	Left hip arthroplasty involving osteotomy
EN3203-004-020-027	PBO	Right knee replacement was a revision
EN3203-004-027-005	PBO	Hip revision involving osteotomy
EN3203-004-020-014	PBO	Patient received IM morphine instead of PCA

(Data Source: Endo Response to Request for Information, submitted 8/21/03

Database Errors:

Review of the database prior to conducting the statistical analyses, disclosed one error. One patient (EN3203-004 # 07-005) had height incorrectly listed as 675 inches. The corresponding CRF was evaluated and the patient's height was actually 67.5 inches but the decimal point was incorrectly entered into the CRF. This error does not appear to significantly effect the efficacy results.

Demographic and Baseline Characteristics:

Demographics:

The majority of patients were female and Caucasian with a mean age ranging from approximately 61 to 67 years across treatment groups (range: 22.8 – 85.4 years), and a moderate baseline pain intensity score. The different treatment groups appeared roughly comparable.

Table EN3203-4.4 Demographics for Treated Patients

	Oxymorphone 10 mg (N=59)	Oxymorphone 20 mg (N=59)	Oxymorphone 30 mg (N=65)	Oxycodone 10 mg (N=60)	Placebo (N=57)
Age (yrs.)					
N	59	59	65	60	57
MEAN	63.9	66.5	61.5	62.8	62.4
STD	11.03	9.97	11.57	12.11	9.93
Sex - N (%)					
MALE	20 (33.9)	20 (33.9)	31 (47.7)	23 (38.3)	25 (43.9)
FEMALE	39 (66.1)	39 (66.1)	34 (52.3)	37 (61.7)	32 (56.1)
Race - N (%)					
CAUCASIAN	52 (88.1)	50 (84.7)	55 (84.6)	51 (85.0)	48 (84.2)
BLACK	5 (8.5)	7 (11.9)	6 (9.2)	8 (13.3)	5 (8.8)
HISPANIC	1 (1.7)	2 (3.4)	3 (4.6)	1 (1.7)	3 (5.3)
ASIAN	0	0	1 (1.5)	0	0
OTHER	1 (1.7)	0	0	0	1 (1.8)
Height (in.)					
N	59	58	65	60	57
MEAN	66.4	65.9	67.0	66.8	66.8
STD	4.11	3.79	3.74	4.44	4.08
Weight (lb.)					
N	59	59	65	60	57
MEAN	205.8	199.2	207.8	199.5	207.6
STD	49.81	53.37	44.89	37.66	41.64
Baseline Pain Intensity (Categorical)					
Mild	0	1 (1.7)	0	0	0
Moderate	44 (74.6)	38 (64.4)	48 (73.8)	49 (81.7)	41 (71.9)
Severe	15 (25.4)	20 (33.9)	17 (26.2)	11 (18.3)	16 (28.1)

Data Source: Table 4, EN3203-004 Clin Study Report, pg. 46
Note: Patient 07-005 (oxymorphone IR 20 mg) is excluded from the summary of height due to a data entry error of 675 inches.

Baseline Comparability:
The distribution of baseline VAS and categorical pain intensity were similar across treatment groups (Table EN3203-4.5). Baseline pain data and post-op analgesia used are summarized in the following table.

Table EN3203-4.5 Postoperative Screening/Baseline Data for Treated Patients

	Oxymorphone 10 mg (N=59)	Oxymorphone 20 mg (N=59)	Oxymorphone 30 mg (N=65)	Oxycodone 10 mg (N=60)	Placebo (N=57)
Method of opioid pain medication management					
PCA PUMP	54 (91.5)	54 (91.5)	59 (90.8)	56 (93.3)	50 (87.7)
IV	2 (3.4)	1 (1.7)	2 (3.1)	1 (1.7)	2 (3.5)
IM	3 (5.1)	4 (6.8)	4 (6.2)	3 (5.0)	5 (8.8)
Pain intensity score (VAS) when post-operative analgesia stopped					
n	21	22	26	25	19
Mean	36.3	37.2	43.7	39.1	42.1
Std	21.30	20.96	26.72	25.57	22.31
Time (hh:mm, from end of post-operative analgesia) when pain assessment					
n	59	58	65	60	57
Minimum	0:00	0:01	0:00	0:00	0:00
Median	0:45	1:01	0:40	0:40	0:45
Maximum	4:30	8:35	5:15	6:45	7:55
Pain intensity score (VAS) when criteria[a] met					
n	59	59	65	60	57
Mean	62.9	62.7	64.5	60.5	62.4
Std	12.54	14.95	16.48	13.68	13.21
Categorical pain intensity score when criteria met					
Moderate	46 (78.0)	43 (72.9)	48 (73.8)	50 (83.3)	46 (80.7)
Severe	12 (20.3)	15 (25.4)	17 (26.2)	10 (16.7)	11 (19.3)

Data Source: Table 5, EN3203-004 Clin Study Report, pg. 47

[a]Pain intensity must have been at least 45 mm VAS to be eligible for dosing with study medication.

Sponsor's Efficacy Analysis Results:

Primary Efficacy Variables:

The Sponsor's analysis using the Efficacy-Evaluable (renamed from modified ITT population) and LOCF for imputed scores is presented in Table 4.6. This table lists the mean TOTPAR0-8 scores along with pair-wise comparisons of the least squares means, and associated p-values, for the five treatments. The Sponsor's results show mean TOTPAR0-8 scores for all oxymorphone IR groups were statistically significantly different from placebo. Oxycodone IR 10 mg showed no statistically significant difference compared to placebo.

Reviewer Primary Efficacy Analysis Results:

Dr. Dionne Price (Agency Biostatistical Reviewer) re-analyzed the sponsor's primary efficacy data using an 'all randomized and treated' analysis population and baseline observations carried forward (BOCF). The sponsor also performed a re-analysis of the efficacy data using a revised definition of the efficacy-evaluable population and both a BOCF and LOCF data imputation strategy. Dr. Price stated that the efficacy outcomes remain essentially unchanged and she is in general agreement with the sponsor's results.

Table EN3203-4.6 Summary of TOTPAR (Categorical) Scores for Efficacy-Evaluable Patients

Treatment/Analysis Factor	TOTPAR 0-4 Hour	TOTPAR 0-6 Hour	TOTPAR 0-8 Hour
Mean (±SD)			
Oxymorphone 10 mg (N=51)	6.1 (±3.47)	8.6 (±5.44)	10.8 (±7.37)
Oxymorphone 20 mg (N=51)	7.3 (±3.49)	10.2 (±5.41)	12.6 (±7.46)
Oxymorphone 30 mg (N=57)	7.0 (±4.38)	10.1 (±6.81)	12.8 (±9.22)
Oxycodone 10 mg (N=55)	5.0 (±3.44)	6.9 (±5.01)	8.7 (±6.59)
Placebo (N=44)	4.5 (±2.93)	5.8 (±4.33)	7.1 (±5.83)
Pairwise Contrast with Placebo[a]			
Oxymorphone 10 mg			
LS Mean Difference	1.6	2.7	3.6
P-value	**0.034**	**0.018**	**0.020**
Oxymorphone 20 mg			
LS Mean Difference	3.0	4.4	5.5
P-value	**<0.001**	**<0.001**	**<0.001**
Oxymorphone 30 mg			
LS Mean Difference	2.5	4.1	5.5
P-value	**<0.001**	**<0.001**	**<0.001**
Oxycodone 10 mg			
LS Mean Difference	0.5	1.0	1.5
P-value	0.501	0.351	0.333

Data Source: Table 6, EN3203-004 Clin Study Report, pg. 49

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

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

Sponsor's Secondary Efficacy Analysis Results:

The Sponsor's secondary efficacy analyses were performed using the same patient population and method for imputing missing scores (LOCF) as the primary efficacy analyses. The results are presented below. Re-analyses were not performed by this reviewer or by the statistical reviewer.

Single-Dose Phase Secondary Efficacy Outcomes:

- TOTPAR at 0-4, 0-6, and 0-12 Hour time intervals:
  These results are shown above in Table EN3203-4.6, along with the primary variable at 8 hours. The mean TOTPAR scores for all oxymorphone IR groups were statistically significantly higher than the mean score for placebo. Oxycodone IR 10 mg (Percolone) was not statistically significantly different from placebo.

- Pain Relief (PR, Categorical) by Time Point:
  The categorical PR over the 8-hour period is the basis for calculating the primary efficacy variable TOTPAR. Statistics at each time point were based on extrapolated data where LOCF was used for patients who withdrew early. The results are summarized in Table 4.7 below. The OM IR 20 and 30 mg groups showed consistent statistically significant differences in pain relief compared to

the placebo group starting at 45 minutes after dosing (except at 1.5 hours for the OM IR 30 mg group). OM IR 10 mg and OC IR 10 mg did not differ statistically from placebo. In addition, an interesting observation is that substantial percentages of subjects had discontinued from the study by 4 hours in all treatment groups (55% for OM 10, 39% for OM 20, 46% for OM 30, 69% for OC 10, and 81% for placebo). Note that the most frequent reason for discontinuing during the single dose phase was 'lack of efficacy.'

Table EN3203-4.7 Summary of Pain Relief for Efficacy-Evaluable Patients

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

Data Source: Table 7, OM IR Study Report, pg. 52.
[a]Mean and Standard Deviation are based on extrapolated data.
[b]Based on ANOVA model including main effects for treatment, center, surgical site, and baseline pain stratification in the model.
Treatments with a common letter are not significantly different (e.g. , treatments with A and AB are not significantly different).
Sample sizes (n) are not extrapolated.
Note: Some patients did not have pain relief data at all timepoints; therefore, Ns reflect the number of patients with data at each timepoint not the total "N" for the efficacy evaluable population.

- Mean SPID (Categorical) at 0-4, 0-6, and 0-8 Hours:
  The mean sum of pain intensity difference (SPID) scores for all OM IR groups were statistically significantly different from placebo. The OC IR 10 mg formulation was not statistically different from placebo.

Table EN3203-4.8 SPID at 0-4, 0-6, and 0-8 Hours for Efficacy-Evaluable Patients

Treatment/Analysis Factor	SPID (CAT) 0-4 Hour	SPID (CAT) 0-6 Hour	SPID (CAT) 0-8 Hour
Mean (±SD)			
Oxymorphone 10 mg (N=51)	2.4 (±2.66)	3.2 (±4.06)	3.6 (±5.51)
Oxymorphone 20 mg (N=51)	3.4 (±2.62)	4.6 (±4.10)	5.5 (±5.62)
Oxymorphone 30 mg (N=57)	2.9 (±2.85)	4.0 (±4.51)	4.9 (±6.11)
Oxycodone 10 mg (N=55)	1.4 (±2.29)	1.4 (±3.33)	1.3 (±4.37)
Placebo (N=44)	0.9 (±2.26)	0.5 (±3.39)	0.1 (±4.54)
Pairwise Contrast with Placebo[a]			
Oxymorphone 10 mg			
LS Mean Difference	1.6	2.7	3.6
P-value, 95% CI	**0.001 (0.6, 2.6)**	**<0.001 (1.3, 4.2)**	**<0.001 (1.7, 5.6)**
Oxymorphone 20 mg			
LS Mean Difference	2.5	3.9	5.1
P-value, 95% CI	**<0.001 (1.5, 3.5)**	**<0.001 (2.4, 5.4)**	**<0.001 (3.1, 7.1)**
Oxymorphone 30 mg			
LS Mean Difference	2.1	3.7	4.9
P-value, 95% CI	**<0.001 (1.2, 3.1)**	**<0.001 (2.2, 5.1)**	**<0.001 (2.9, 6.9)**
Oxycodone 10 mg			
LS Mean Difference	0.6	1.0	1.3
P-value, 95% CI	0.237 (-0.4, 1.5)	0.195 (-0.5, 2.4)	0.200 (-0.7, 3.2)

Data Source: Table 8, EN3203-004 OM IR Study Report, pg. 53

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

The Sum of Pain Intensity (SPID, Categorical) is defined as the area under curve of pain intensity difference from baseline over the corresponding time interval. Pain intensity (Categorical) was measured using a 4-point scale, where 3 = severe, 2 = moderate, 1 = mild, and 0 = none. Pain intensity differences at each time point are calculated as the baseline pain intensity score minus the pain intensity score at that time point.

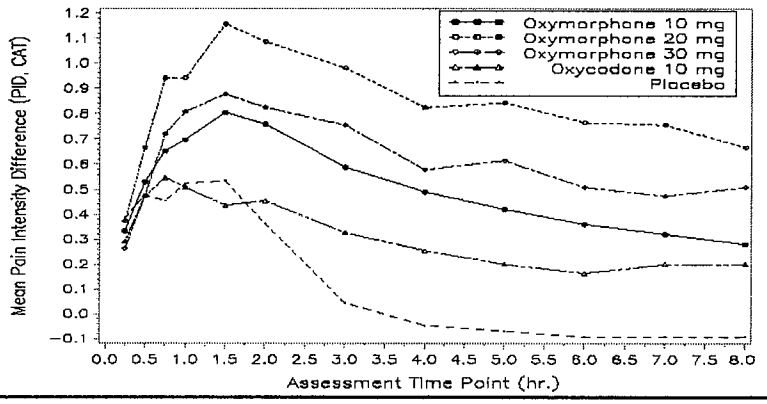
- Pain Intensity Difference (PID, Categorical) by Time Point:
  There was a statistically significant difference in pain intensity difference for all the oxymorphone IR treatment groups compared to placebo, starting at 45 minutes post dose. No statistically significant difference was seen at 1 hour for the oxymorphone IR 10 and 30 mg groups, and at 1.5 hours for the oxymorphone 10 mg group. OC IR did not differ statistically from placebo.

Table EN3203-4.9 PID (Categorical) over 0-8 Hours for Efficacy-Evaluable Patients

	Assessment Time Point											
Treatment	**15 min**	**30 min**	**45 min**	**1 hr**	**1.5 hr**	**2 hr**	**3 hr**	**4 hr**	**5 hr**	**6 hr**	**7 hr**	**8 hr**
Oxymorphone 10 mg												
n	51	50	49	50	43	38	36	23	14	12	9	3
Mean[a]	0.3	0.5	0.7	0.7	0.8	0.8	0.6	0.5	0.4	0.4	0.3	0.3
	A	A	AB	AB	AB	AB	BC	AB	BC	AB	B	AB
SD[a]	0.65	0.64	0.71	0.81	0.80	0.91	0.94	0.95	0.88	0.85	0.87	0.83
Oxymorphone 20 mg												
n	51	51	51	50	43	41	40	31	22	19	13	12
Mean[a]	0.4	0.7	0.9	0.9	1.2	1.1	1.0	0.8	0.8	0.8	0.8	0.7
	A	A	A	A	A	A	A	A	A	A	A	A
SD[a]	0.63	0.79	0.73	0.79	0.84	0.84	1.01	1.03	1.01	0.99	0.99	0.95
Oxymorphone 30 mg												
n	56	57	57	56	45	40	36	30	22	17	11	11
Mean[a]	0.3	0.5	0.7	0.8	0.9	0.8	0.8	0.6	0.6	0.5	0.5	0.5
	A	A	AB	AB	A	A	AB	AB	AB	A	AB	A
SD[a]	0.52	0.57	0.75	0.90	0.93	0.95	0.96	0.98	1.00	0.98	0.98	1.02
Oxycodone 10 mg												
n	55	53	54	55	44	37	32	17	12	6	5	3
Mean[a]	0.3	0.5	0.5	0.5	0.4	0.5	0.3	0.3	0.2	0.2	0.2	0.2
	A	A	BC	C	C	BC	CD	BC	CD	BC	BC	BC
SD[a]	0.53	0.66	0.74	0.74	0.76	0.77	0.82	0.82	0.85	0.81	0.80	0.80
Placebo												
n	43	44	41	41	36	32	27	8	1	2	1	0
Mean[a]	0.4	0.5	0.5	0.5	0.5	0.4	0.0	0.0	-0.1	-0.1	-0.1	-0.1
	A	A	C	BC	BC	C	D	C	D	C	C	C
SD[a]	0.49	0.55	0.66	0.76	0.86	0.81	0.81	0.78	0.73	0.71	0.71	0.71
Treatment p-value[b]	0.820	0.448	**0.010**	0.044	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**

Data Source: Table 9, EN3203-004 Clin Study Report, pg. 55
[a]Mean and Standard Deviation are based on extrapolated data.
[b]Based on ANOVA model including main effects for treatment, center, surgical site, and baseline pain stratification in the model.
Treatments with a common letter are not significantly different (e.g. treatments with A and AB are not significantly different).
Sample sizes (n) are not extrapolated.
Note: Some patients did not have pain relief data at all timepoints; therefore, 'n' reflects the number of patients with data at each timepoint not the total N for the efficacy evaluable population.

Figure EN3203-4.2 Summary of Pain Intensity Difference (Categorical) over 0-8 Hours for Efficacy Evaluable Patients



- Sum of Pain Intensity Difference (SPID, VAS) over 0-4, 0-6, and 0-8 Hrs:
  The mean SPID scores for all OM groups were statistically significantly different from the mean score for placebo. OC IR 10 mg was not statistically different from placebo.

Table EN3203-4.10 SPID (VAS) at 0-4, 0-6, and 0-8 Hours for Efficacy-Evaluable Patients

Treatment/Analysis Factor	SPID (VAS) 0-4 Hour	SPID (VAS) 0-6 Hour	SPID (VAS) 0-8 Hour
Mean (±SD)			
Oxymorphone 10 mg (N=51)	88.9 (±75.92)	116.2 (±111.44)	134.9 (±147.94)
Oxymorphone 20 mg (N=51)	113.9 (±93.09)	156.7 (±138.29)	189.9 (±182.39)
Oxymorphone 30 mg (N=57)	95.4 (±89.20)	136.0 (±141.47)	167.7 (±191.80)
Oxycodone 10 mg (N=55)	47.1 (±83.42)	49.8 (±112.96)	49.1 (±140.28)
Placebo (N=44)	39.5 (±67.27)	31.4 (±91.93)	20.9 (±117.56)
Pairwise Contrast with Placebo[a]			
Oxymorphone 10 mg			
LS Mean Difference	51.6	87.2	117.4
StdErr	17.11	25.07	32.59
P-value	**0.003**	**<0.001**	**<0.001**
Oxymorphone 20 mg			
LS Mean Difference	75.1	124.4	166.8
StdErr	17.21	25.21	32.78
P-value	**<0.001**	**<0.001**	**<0.001**
Oxymorphone 30 mg			
LS Mean Difference	59.5	108.5	150.9
StdErr	16.80	24.60	31.99
P-value	**<0.001**	**<0.001**	**<0.001**
Oxycodone 10 mg			
LS Mean Difference	10.2	20.9	31.1
StdErr	16.78	24.59	31.96
P-value	0.546	0.395	0.331

Data Source: Table 10, EN3203-004 Clin Study Report, pg. 56
[a]All pairwise comparison statistical results are between corresponding active treatment and placebo. The ANOVA model is used including main effects for treatment, center, surgical site, and baseline pain stratification in the model.

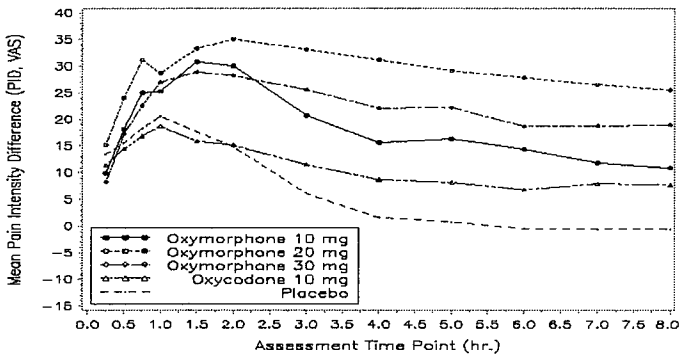
- Pain Intensity Difference (PID, VAS) by Time Point:
  All OM IR groups showed a consistently statistically significant difference in PID scores compared to the placebo group, starting at 1.5 hours after dosing. No statistically significant difference between oxycodone IR 10 mg and placebo was observed during the entire 8-hour assessment period.

Table EN3203-4.11 PID (VAS) over 0-8 Hours for Efficacy-Evaluable Patients

	Assessment Time Point											
Treatment	**15 min**	**30 min**	**45 min**	**1 hr**	**1.5 hr**	**2 hr**	**3 hr**	**4 hr**	**5 hr**	**6 hr**	**7 hr**	**8 hr**
Oxymorphone 10 mg												
n	51	50	49	50	43	37	36	23	14	12	9	3
Mean[a]	9.8	18.1	25.0	25.3	30.8	30.0	20.7	15.6	16.3	14.4	11.8	10.9
	A	AB	AB	A	A	A	BC	BC	BC	BC	BC	BC
SD[a]	20.10	20.24	21.42	24.67	25.94	27.62	25.51	26.61	26.74	25.36	24.74	23.66
Oxymorphone 20 mg												
n	51	51	51	50	43	41	40	31	22	19	13	12
Mean[a]	15.2	24.0	31.1	28.6	33.3	35.0	33.1	31.1	29.1	27.8	26.5	25.5
	A	A	A	A	A	A	A	A	A	A	A	A
SD[a]	21.89	24.81	26.14	26.44	28.62	27.80	30.70	30.24	30.37	29.90	29.10	28.98
Oxymorphone 30 mg												
n	56	57	57	56	45	40	36	30	21	16	10	10
Mean[a]	8.2	17.2	22.5	27.0	28.9	28.2	25.6	22.1	22.2	18.7	18.8	18.9
	A	AB	AB	A	A	A	AB	AB	AB	AB	AB	AB
SD[a]	15.59	18.25	23.62	25.86	27.10	28.74	29.12	31.73	31.82	32.14	32.56	32.55
Oxycodone 10 mg												
n	55	53	54	55	44	36	32	17	12	6	5	3
Mean[a]	11.4	14.4	16.8	18.7	15.8	15.1	11.5	8.7	8.1	6.8	7.9	7.7
	A	B	B	A	B	B	CD	CD	CD	CD	CD	CD
SD[a]	19.47	23.85	24.82	26.90	28.65	29.77	27.74	27.33	27.27	26.91	27.15	26.89
Placebo												
n	43	44	41	41	36	32	27	8	1	2	1	0
Mean[a]	13.4	15.6	18.3	20.6	17.6	14.9	6.1	1.6	0.8	-0.5	-0.6	-0.6
	A	B	B	A	B	B	D	D	D	D	D	D
SD[a]	14.34	16.11	20.41	20,89	22.52	23.83	25.92	23.75	22.20	21.93	21.88	21.88
Treatment p-value[b]	0.432	0.129	**0.017**	0.218	**0.002**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**

Data Source: Table 11, EN3203-004 Clinical Study Report, pg. 58
[a]Mean and Standard Deviation are based on extrapolated data.
[b]Based on ANOVA model including main effects for treatment, center, surgical site, and baseline pain stratification in the model.
Treatments with a common letter are not significantly different (e.g. treatments with A and AB are not significantly different).
Sample sizes (n) are not extrapolated.

Figure EN3203-4.3 Summary of Pain Intensity Difference (VAS) over 0-8 Hours for Efficacy Evaluable Patients



- Sum of Combined Pain Relief and Pain Intensity Difference (SPRID, Categorical): The mean SPRID scores for all OM groups were statistically significantly different from the mean score for placebo. OC IR 10 mg was no different from placebo at all time points (see table 4.12).

Table EN3203-4.12 SPRID (Categorical) at 0-4, 0-6, and 0-8 Hour Time Intervals for Efficacy Evaluable Patients

Treatment/Analysis Factor	SPRID (CAT) 0-4 Hour	SPRID (CAT) 0-6 Hour	SPRID (CAT) 0-8 Hour
Mean (±SD)			
Oxymorphone 10 mg (N=51)	8.5 (±5.76)	11.8 (±8.77)	14.4 (±11.81)
Oxymorphone 20 mg (N=51)	10.7 (±5.72)	14.8 (±8.94)	18.1 (±12.24)
Oxymorphone 30 mg (N=57)	9.9 (±6.87)	14.1 (±10.75)	17.8 (±14.52)
Oxycodone 10 mg (N=55)	6.4 (±5.30)	8.3 (±7.62)	10.0 (±9.87)
Placebo (N=44)	5.4 (±4.51)	6.3 (±6.47)	7.2 (±8.46)
Pairwise Contrast with Placebo[a]			
Oxymorphone 10 mg			
LS Mean Difference	3.2	5.5	7.2
P-value	**0.007**	**0.003**	**0.003**
Oxymorphone 20 mg			
LS Mean Difference	5.4	8.3	10.6
P-value	**<0.001**	**<0.001**	**<0.001**
Oxymorphone 30 mg			
LS Mean Difference	4.6	7.8	10.4
P-value	**<0.001**	**<0.001**	**<0.001**
Oxycodone 10 mg			
LS Mean Difference	1.1	2.0	2.7
P-value	0.356	0.253	0.243

Data Source: Table 12, EN3203-004 Clin Study Report, pg. 59
Pain Relief was measured on a 5-point scale: 4 = complete, 3 = a lot, 2 = moderate, 1 = a little, and 0 = none. Pain intensity (Categorical) was measured using a 4-point scale, where 3 = severe, 2 = moderate, 1 = mild, and 0 = none.
Pain intensity differences at each time point were calculated as the baseline pain intensity score minus the pain intensity score at that time point.

- Combined Pain Relief and Pain Intensity Difference (PRID, Categorical):
  The PRID scores for the OM IR 20mg and 30 mg groups were statistically significantly different from placebo, starting at 45 minutes post-dosing. The OM IR 10 mg formulation showed a statistically significant difference in PRID over placebo starting at 2 hours after dosing.

Table EN3203-4.13 Summary of Combined Pain Relief and Pain Intensity Difference (PRID, Categorical, and Extrapolated) over 0-8 Hours for Efficacy-Evaluable Patients

	Assessment Time Point											
Treatment	**15 min**	**30 min**	**45 min**	**1 hr**	**1.5 hr**	**2 hr**	**3 hr**	**4 hr**	**5 hr**	**6 hr**	**7 hr**	**8 hr**
Oxymorphone 10 mg												
n	51	50	49	50	43	38	36	23	14	12	9	3
Mean[a]	1.2	1.8	2.2	2.3	2.7	2.6	2.2	1.9	1.8	1.6	1.5	1.4
	A	A	BC	AB	AB	AB	BC	AB	BC	B	AB	AB
SD[a]	1.39	1.43	1.61	1.84	1.87	1.98	2.02	2.06	2.01	1.83	1.95	1.84
Oxymorphone 20 mg												
n	51	51	51	50	43	41	40	31	22	19	13	12
Mean[a]	1.3	2.1	2.9	2.9	3.4	3.2	3.0	2.7	2.6	2.4	2.4	2.2
	A	A	A	A	A	A	A	A	A	A	A	A
SD[a]	1.37	1.71	1.69	1.74	1.86	1.76	2.24	2.18	2.14	2.08	2.07	2.02
Oxymorphone 30 mg												
n	55	57	57	56	45	40	36	30	21	17	10	11
Mean [a]	1.1	1.8	2.5	2.8	2.8	2.8	2.6	2.1	2.2	2.0	1.9	1.9
	A	A	AB	A	A	A	AB	AB	AB	AB	AB	AB
SD[a]	1.22	1.42	1.76	2.19	2.22	2.18	2.25	2.29	2.31	2.25	2.28	2.31
Oxycodone 10 mg												
n	55	53	54	55	44	37	32	17	12	6	5	3
Mean[a]	1.1	1.6	1.9	2.0	1.8	2.0	1.7	1.4	1.4	1.3	1.4	1.4
	A	A	C	B	C	BC	CD	BC	CD	BC	BC	BC
SD[a]	1.32	1.58	1.65	1.69	1.73	1.73	1.85	1.70	1.78	1.69	1.66	1.66
Placebo												
n	43	44	41	41	36	32	27	8	1	2	1	0
Mean[a]	1.3	1.7	1.8	1.9	2.0	1.7	1.1	0.8	0.8	0.7	0.7	0.7
	A	A	C	B	BC	C	D	C	D	C	C	C
SD[a]	1.09	1.16	1.30	1.45	1.85	1.72	1.67	1.51	1.38	1.29	1.29	1.29
Treatment p-value[b]	0.909	0.392	**0.002**	**0.018**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**0.002**

Data Source: Table 13, EN3203-004 Clin Study Report, pg. 62

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

[b]Based on ANOVA model including main effects for treatment, center, surgical site, and baseline pain stratification in the model. Treatments with a common letter are not significantly different (e.g. treatments with A and AB are not significantly different). Sample sizes (n) are not extrapolated.

- Proportion and Time When Patient's Pain was at least Half-Gone:
  The median time and proportion (in %) of patients experiencing 50% pain relief for the OM IR 10 and 20 mg groups differed statistically from PBO (see Table 4.14) whereas the OM IR 30 mg and OC groups did not (see below).

Table EN3203-4.14 Proportion of Patients who Experienced 50% Pain Relief (Single-Dose Phase, Efficacy-Evaluable Population)

	Oxymorphone			Oxycodone	
	10 mg	20 mg	30 mg	10 mg	Placebo
N (%) patients with 50% pain relief	42 (82.4)	46 (90.2)	44 (77.2)	38 (69.1)	26 (59.1)
Treatment contrast (vs. placebo) p-value[a]	**0.022**	**<0.001**	0.081	0.398	-

Data Source: Table 14, EN3203-004 Clin Study Report, pg. 63
[a]Fisher's exact test

- Time to First Perceptible Pain Relief:
  None of the active treatment groups differed significantly from placebo, as illustrated below. Note that the ranges of median times are very similar across all treatment groups (15 minutes to 23 minutes).

Table EN3203-4.15 Time (hrs) to Perceptible Pain Relief (Efficacy-Evaluable Population)

Treatment	Median (hh:mm) [a,b]	95% Confidence Interval[c]
Oxymorphone 10 mg	0:23 A	0:16 to 0:30
Oxymorphone 20 mg	0:15 A	0:13 to 0:28
Oxymorphone 30 mg	0:16 A	0:15 to 0:30
Oxycodone 10 mg	0:16 A	0:12 to 0:27
Placebo	0:15 A	0:13 to 0:20

Data Source: Figure 5, EN3203-004 Clin Study Report, pg. 64
[a]Kaplan-Meier estimate (c.f. Miller, Survival Analysis, page 75)
[b]Log-Rank test applied as in Fisher's PLSD. Treatments with a common letter are not significantly different
[c]Method of Simon & Lee. Cancer Treat Rep 66: 37-42, 1982

- Time to Meaningful Pain Relief:
  The median times to meaningful pain relief for the OM IR groups (approximately 1 hour) demonstrated a statistically significant difference from the placebo group (1.5 hours). However, this median difference appears to be limited to less than 30 minutes.

Table EN3203-4.16 Time (hrs) to Meaningful Pain Relief (Efficacy-Evaluable Population)

Treatment	Median (hh:mm) [a,b]	95% Confidence Interval[c]
Oxymorphone 10 mg	1:02 B	0:43 to 1:24
Oxymorphone 20 mg	0:59 B	0:46 to 1:28
Oxymorphone 30 mg	1:05 B	0:45 to 1:30
Oxycodone 10 mg	1:07 AB	0:48 to 1:45
Placebo	1:30 A	1:20 to >8:00

Data Source: Figure 6, EN3203-004 Clin Study Report, pg. 66
[a]Kaplan-Meier estimate (c.f. Miller, Survival Analysis, page 75)
[b]Log-Rank test applied as in Fisher's PLSD. Treatments with a common letter are not significantly different

[c]Method of Simon & Lee. Cancer Treat Rep 66: 37-42, 1982

- Time to Remedication:
  The median times to re-medication for the OM IR 20 mg and 30 mg groups were > 3 hours 40 minutes (statistically significantly different from placebo) compared to approximately 3 hours for other groups. The OM IR 10 mg and OC IR 10 mg groups did not differ from placebo. Table 4.17 illustrates the results. Note that the median time was actually less in the OM IR 30 mg group compared to the smaller 20 mg oxymorphone group.

Table EN3203-4.17 Time (hrs) to Re-Medication (Efficacy-Evaluable Population)

Treatment	Median (hh:mm) [a,b]	95% Confidence Interval[c]
Oxymorphone 10 mg	3:04 BC	2:55 to 4:02
Oxymorphone 20 mg	4:00 BD	3:20 to 4:35
Oxymorphone 30 mg	3:42 AB	3:00 to 4:40
Oxycodone 10 mg	3:07 CD	2:12 to 3:26
Placebo	3:05 C	3:00 to 3:15

Data Source: Figure 7, EN3203-004 Clin Study Report, pg. 68
[a]Kaplan-Meier estimate
[b]Log-Rank test applied as in Fisher's PLSD. Treatments with a common letter are not significantly different
[c]Method of Simon & Lee, 1982

- Patient's Global Evaluation of Study Medication:
  The oxymorphone IR 10 and 20 mg were rated as statistically significantly different when compared with placebo. No statistically significant between-treatment-group differences were observed. It is interesting to observe that the OM IR 20 mg distribution of 'Good' and 'Very Good' ratings (32.7 and 34.7 %, respectively) are actually greater than the OM IR 20 mg treatment group (24.1 and 22.2 %, respectively).

Table EN3203-4.18 Patient Global Evaluation of Pain Medication (Single Dose Phase) for Efficacy-Evaluable Patients

Response	Oxymorphone 10 mg (N=51)	Oxymorphone 20 mg (N=51)	Oxymorphone 30 mg (N=57)	Oxycodone 10 mg (N=55)	Placebo (N=44)
Total [1]	51 (100)	49 (100)	54 (100)	53 (100)	43 (100)
Excellent	8 (15.7)	10 (20.4)	12 (22.2)	3 (5.7)	0
Very Good	17 (33.3)	17 (34.7)	11 (20.4)	11 (20.8)	9 (20.9)
Good	11 (21.6)	16 (32.7)	13 (24.1)	15 (28.3)	11 (25.6)
Fair	5 (9.8)	1 (2.0)	6 (11.1)	10 (18.9)	11 (25.6)
Poor	10 (19.6)	5 (10.2)	12 (22.2)	14 (26.4)	12 (27.9)
Pairwise Comparisons [2]					
Oxymorphone 20 mg	0.921	-	-	-	-
Oxymorphone 30 mg	0.965	0.668	-	-	-
Oxycodone 10 mg	0.125	0.277	0.336	-	-
Placebo	0.017	0.018	0.058	0.151	-

[1] Percentages are calculated using TOTAL as denominator, [2] All pairwise comparison p-values are based on stratified rand sum test, stratified by center and baseline pain stratification
Source: Appendix 16.2.2, Table 4.9, EN2303-004 OM IR Clinical Study Report, pg. 1 of 1