The protocol and its amendments had been submitted to IND 56,919 as N188 on May 14, 2004, N189 on July 12, 2004, and N194 on October 4, 2004. They were reviewed as Special Protocol Assessments by the medical reviewer, Dr. Elizabeth McNeil (DFS filing dates of the written reviews were 7/29/04, 9/1/05, and 11/29/040), and by the statistical reviewer, Dr. Dionne Price (DFS filing dates of the written reviews were 6/29/04, 8/24/04, and 11/23/04). All the agreements were incorporated into the final protocol and implemented in the study before the start of the enrollment in November 2004.

Table 10-1 Protocol

Study #	EN3202-031
Objectives	To study efficacy, dose titration regimen, dose range, and safety of oxymorphone extended release (ER) in opioid-naïve patients with chronic low back pain (LBP).
Design	Titration to effect, randomized withdrawal, double-blind, placebo-controlled, parallel, multiple-dose (28-day open-label titration period followed by double-blind treatment with twice daily dosing at individualized dose level for 12 weeks), dose range study at 29 centers in the U.S.
Sample population	Male and non-pregnant female; ≥18 years of age; **opioid naïve** (equianalgesic equivalent of ≤oxycodone 5mg/day in 14 days prior to screening); moderate to severe **chronic non-neuropathic LBP** daily for at least several hours per day for a minimum of three months prior to screening; on stable adjunct therapy (e.g., physical therapy, biofeedback therapy, acupuncture therapy, or herbal remedies) for back pain; (refer to eligibility criteria in Appendix 1 at the end of the review of the protocol)
Baseline	Initial pain score ≥50 mm on a 100 mm VAS scale
Treatment	Open-label titration: oxymorphone ER 5 mg PO q12h for two days; upward titration at increments of 5-10 mg q12h every three to seven days until stabilization (pain score ≤40 mm on same dose for three of five consecutive days immediately prior to randomization, reasonable tolerance to the dose in the same time period, having reached a minimum dose of 10 mg q12h) Double-blind treatment: oxymorphone ER at individualized fixed dose determined above or placebo q12 h for 12 weeks
Rescue and concomitant medication	Rescue medication: **not allowed in open-label phase** Rescue in double-blind phase: oxymorphone IR 5 mg q4 to 6h in first four days, dose restriction to no more than two doses/day thereafter. Other medication: anti constipation treatment throughout the study
Raw efficacy data	**Average pain of the last 24 hours** before each clinic visit (baseline, Day 4, Weeks 1, 2, 3, 4, 8, and 12) using a 100mm VAS scale **Patient's and Physician's Global** Assessments of Pain Medication on a 5-point categorical scale at screening (evaluate pre-study pain medication), baseline (evaluate oxymorphone ER during open-label titration), and 4-week, 8-week, and 12-week visit during double-blind treatment
Efficacy parameter	*Primary:* **Change in average pain intensity** (VAS) (in past 24 hours) **from baseline to final visit** *Secondary:* • Change from baseline to final visit in patient's global assessment of pain medication • Change from baseline to final visit in physician's global assessment of pain medication • Evaluation of compliance and study medication usage, time to discontinuation due to lack of efficacy
Statistical analysis	*Primary analysis:* Analysis of covariance (ANCOVA) with treatment and center as effects and screening and baseline PI as covariates; *Imputation for missing value:* • For dropouts due to an AE , screening PI (worst case) carried forward to the final visit • For dropouts due to opioid withdrawal in the placebo group, baseline PI (best case) carried forward to the final visit • For dropouts due to all other reasons last observation carried forward to the final visit.
Safety monitoring	• Adverse events (AEs) throughout the study • Vital signs at most of the clinic visits (screening, weekly visit during open-label phase, baseline and visits at Day 4, Weeks 1, 2, 3, 4, 8, and 12 during double-blind phase) • Adjective Rating Scale for Withdrawal (ARS) at screening, baseline, and visits first 4 weeks of double-blind treatment • Clinical Opiate Withdrawal Scale (COWS) assessed using the same schedule as ARS

Statistical highlights

The statistical methodology and analysis plan and related changes were presented and discussed in detail in the statistical review. Some points are mentioned below for clarification purpose.

Sample population for efficacy analyses

The pre-specified efficacy analysis population was defined as all randomized patients who received at least one dose of double-blind study medication (ITT).

Sensitivity Analyses

The Sponsor proposed sensitivity analyses using two different imputation methods that were less conservative than the original imputation with the argument that the original imputation for placebo patients dropping out due to adverse events could introduce a potential bias towards the active treatment as there might be potential overlap in the diagnosis of opioid withdrawal and other adverse events.

1. For any patient who discontinues due to an adverse event in the placebo group, the last observation instead of the screening pain score will be carried forward to the final visit.

2. For any patient who discontinues due to an adverse event in the placebo group in the first four weeks after baseline (the period in which opioid withdrawal symptoms are most likely to occur), the baseline pain score (which will reflect patient's best score) will be carried forward to the final visit.

Post hoc changes to the planned statistical analyses

Post hoc analyses were conducted for the additional efficacy endpoints, including

- Mean change from baseline in average pain intensity (VAS) by visit using the imputation rules established for the primary analyses with an additional imputation rule that a previous post-baseline value was to be used to impute a missing "intermediate" post-baseline value.

- Time to discontinuation due to all reasons using the same method of analyses as for the endpoint of time to discontinuation due to lack of efficacy

- Percentage of responders defined as at least 30% percent reduction in average pain intensity (VAS) from screening to final visit, using a chi-square test of observed values (no data imputation)

- The percent reduction at all levels ($\geq$10%, $\geq$20%, $\geq$30% ....) presented as a figure.

In the Sponsor's review of blinded data a major protocol violation was identified: failure to meet the major criterion for randomization (titration to reach a minimum of oxymorphone ER 10 mg q12h or 20 mg daily) in 13 patients. These patients were however, randomized and received the double-blind treatment although their stabilized dose level at baseline was 5 mg q12h or 10 mg daily. A Modified Intent-to-Treat (MITT) population excluding these 13 patients was used in analyses of all efficacy endpoints in addition to efficacy analyses using the ITT population.

The primary presentation of efficacy was based on MITT and the results of analyses based on both MITT and ITT populations were compared.

Results

Demographic and other baseline characteristics

The efficacy sample population consisted of 205 subjects who received double-blind treatment, with an age range of 20 to 85 years and a mean of 50 years, 90% Caucasian, 6% African American, 4% Hispanic, and 53% female. The treatment groups were approximately balanced with regard to demographic characteristics such as age (there was 8% more elderly in the active treatment group), gender, race, and weight (close to 10 lb. difference in group mean with STD of greater than 40 lb. is not considered a meaningful difference in the reviewer's opinion) and with regard to the etiology of low back pain and the baseline pain intensity (77%-82% had moderate pain and 18%-23% had severe pain at baseline).

Table 10-2 Demographics, Screening, and Randomization Characteristics (Double-Blind Period)

	Oxymorphone ER	Placebo	Total
Demographic/Statistics	(N = 105)	(N = 100)	(N = 205)
Age (yrs)			
Mean	51.3	48.1	49.7
STD	13.87	12.40	13.24
Median	50	47.5	49
Min, max	22, 85	20, 76	20, 85
Age Group, n (%)			
< 65	88 (83.8)	92 (92.0)	180 (87.8)
≥65	17 (16.2)	8 (8.0)	25 (12.2)
≥74	8 (7.6)	3 (3.0)	11 (5.4)
Race, n (%)			
African American	7 (6.7)	5 (5.0)	12 (5.9)
Caucasian	93 (88.6)	91 (91.0)	184 (89.8)
Hispanic	5 (4.8)	4 (4.0)	9 (4.4)
Gender, n (%)			
Female	59 (56.2)	50 (50.0)	109 (53.2)
Male	46 (43.8)	50 (50.0)	96 (46.8)
Stabilized Dose Level, n (%)			
High (> 30 mg daily)	50 (47.6)	48 (48.0)	
Low (≤ 30 mg daily)	55 (52.4)	52 (52.0)	
Weight (pounds)			
Mean	195.0	185.8	190.5
STD	43.38	41.58	42.66
Median	189	180	185
Min, max	100, 343	110, 334	100, 343
Etiology, n (%)			
Degenerative disc disease	34 (32.4)	28 (28.0)	62 (30.2)
Herniated disc	5 (4.8)	3 (3.0)	8 (3.9)
Osteoarthritis	26 (24.8)	29 (29.0)	55 (26.8)
Spinal stenosis	8 (7.6)	4 (4.0)	12 (5.9)
Trauma	19 (18.1)	25 (25.0)	44 (21.5)
Other	38 (36.2)	30 (30.0)	68 (33.2)
Categorical Rating of CLBP, n (%)			
Moderate	**81 (77.1)**	**82 (82.0)**	**163 (79.5)**
Severe	24 (22.9)	18 (18.0)	42 (20.5)
Average Pain Intensity (VAS)			
Mean	**70.4**	**68.3**	**69.4**
STD	12.31	11.08	11.75
Median	71	69	70
Min, max	45, 100	47, 93	45, 100

Source: Tables 7 and 8 on pages 54-57 of the report for Study 031.

In terms of the stabilized individual dosing at randomization the distribution of daily dosage was similar between the two treatment groups. Of the 105 patients assigned to the active treatment 95 (90%) were on oxymorphone ER 20 to 60 mg/day, including one third who were on 20 mg/day during the 12-week double-blind treatment.

Table 10-3 Stabilized Individual Dosing at Randomization of Double-Blind Treatment

	Oxymorphone ER (N = 105)	Placebo (N = 100)
Daily Dose (mg/day)	n (%)	n (%)
10 [a]	8 (7.6)	5 (5.0)
20	33 (31.4)	29 (29.0)
30	14 (13.3)	18 (18.0)
40	19 (18.1)	16 (16.0)
50	11 (10.5)	11 (11.0)
60	8 (7.6)	4 (4.0)
70	2 (1.9)	3 (3.0)
80	3 (2.9)	8 (8.0)
90	1 (1.0)	1 (1.0)
100	3 (2.9)	2 (2.0)
110	0	1 (1.0)
120	1 (1.0)	2 (2.0)
140	2 (1.9)	0
Statistics		
Mean	39.2	40.9
STD	26.37	25.31

[a] These patients were excluded from the efficacy analyses.
Source: Table 16 on page 84 of the report for Study 031.

Patient disposition and efficacy sample

Of the 326 patients enrolled in the study, 325 were treated during the open-label titration period. A total of 120 (37%) did not enter double-blind treatment. The dropouts included 59 (18%) due to AEs (none were opioid withdrawal AEs); 23 (7%) due to not meeting titration-stabilization criteria (not due to AEs); 14 (4%) due to withdrawal of consent (six cases were due to scheduling conflict, two cases due to fear of potential AE and fear of possible addiction, two cases due to preference for alternative treatment, three cases due to change of mind, and one case due to hand swelling); eight (3%) due to lost to follow-up; five (2%) due to protocol violation; five (2%) by investigator's opinion (four cases were due to non-compliance and one case due to fear of becoming drug dependent); four (1%) due to lack of efficacy; two (0.6%) upon Sponsor's request (one had automobile accident and one met exclusion criteria). The dropouts due to AE will be discussed in the safety review. The total dropouts due to AEs, lack of efficacy, and failure to meet titration-stabilization criteria, accounted for 26% (86/326) of patients enrolled.

Table 10-4 Patient Disposition During the Open-Label Titration Period: Number (%) of Patients

Patient Disposition	Oxymorphone ER
Entered Open-Label Titration Period	326 (100.0)
All Treated (Open-Label Titration Period) [a]	325 (99.7)
Not Treated [b]	1 (0.3)
Completed Open-Label Titration Period	205 (62.9)
Discontinued in Open-Label Titration Period [c]	120 (36.8)
Adverse Event	59 (18.1)
AE not due to opioid withdrawal	59 (18.1)
Opioid withdrawal-AE	0
Patient did not meet Titration-Stabilization criteria	23 (7.1)
Withdrew Consent	14 (4.3)
Lost to Follow-up	8 (2.5)
Investigator Opinion	5 (1.5)

Protocol Violation	5 (1.5)
>3 days of <80% compliance with study medication	1 (0.3)
Other	4 (1.2)
Lack of Efficacy	4 (1.2)
Sponsor Request	2 (0.6)
Randomized and Entered Double-Blind Treatment Period	205 (62.9)

[a] All patients who received at least one dose of the Open-Label Titration medication.
[b] Patient 031-021 was not treated according to Drug Accountability data.
[c] Reasons for discontinuation are sorted in descending order of frequency.
Note: For Patient 036-014, the reason for discontinuation was coded to AE, instead of Protocol Violation, to be consistent with the Adverse Event Case Report Form
Source: Table 3 on page 49 of the report for Study 031.

Of the 205 subjects who received double-blind treatments about 2/3 of the active treatment group and about one half of the placebo group completed the 12-week treatments. The **major reasons for dropouts** were **lack of efficacy** (11% on oxymorphone ER vs. 35% on placebo), **adverse events** (9% on oxymorphone ER vs. 8% on placebo, mostly not due to opioid withdrawal), and withdrawal of consent (7% on oxymorphone ER vs. 4% on placebo) (10 of the 11 cases were due to scheduling conflict and one by patient's preference). Dropouts due to **protocol violation** occurred in six subjects, three on oxymorphone ER and three on placebo, for non-compliance and dosing error. Of the six cases of discontinuation by Investigator's opinion or upon Sponsor's request five were due to non-compliance and one was due to conflict with scheduled surgery.

The **major differences** between the treatment groups were that remarkably more placebo patients discontinued early than active treatment (which was one of the additional efficacy endpoints) and that dropouts due to lack of efficacy in the placebo group were about three times greater than that of the active treatment group (which was a major secondary efficacy endpoint).

The group receiving oxymorphone ER in the double-blind treatment period had a lower dropout rate due to AEs (9% versus 18%) and higher dropout rate due to lack of efficacy (11% versus 1%) than the entire study population undergoing open-label titration.

All subjects who were treated and discontinued early for any reason were included in the ITT analyses of efficacy.

Of the 205 subjects randomized and treated, 13 were identified as having a major protocol violation due to a failure to meet the minimum study entry criteria for double-blind treatment. Therefore, the Sponsor defined a **Modified Intent-to-Treat (MITT)** population by excluding these 13 patients based on the review of double-blind data.

Table 10-5 Patient Disposition During the Double-Blind Treatment: Number (%) of Patients

Patient Disposition	Oxymorphone ER	Placebo	Overall
Randomized and entered double-blind treatment period	105 (100.0)	100 (100.0)	205 (100.0)
All treated patients (≥1 dose of double-blind treatment) [a]	105 (100.0)	100 (100.0)	205 (100.0)
Completed Double-Blind Treatment Period	71 (67.6)	47 (47.0)	118 (57.6)
Discontinued in Double-Blind Treatment Period	34 (**32.4**)	53 (**53.0**)	87 (42.4)
Lack of Efficacy	12 (**11.4**)	35 (**35.0**)	47 (22.9)
Adverse Event	9 (8.6)	8 (8.0)	17 (8.3)
AE not due to opioid withdrawal	8 (7.6)	6 (6.0)	14 (6.8)
Opioid withdrawal-AE	1 (1.0)	2 (2.0)	3 (1.5)
Withdrew Consent	7 (6.7)	4 (4.0)	11 (5.4)
Protocol Violation	3 (2.9)	3 (3.0)	6 (2.9)
Investigator Opinion	3 (2.9)	1 (1.0)	4 (2.0)
Other	3 (2.9)	1 (1.0)	4 (2.0)

>3 days of <80% compliance with study medication	0	2 (2.0)	2 (1.0)
Lost to Follow-up	0	1 (1.0)	1 (0.5)
Sponsor Request	0	1 (1.0)	1 (0.5)
Modified Intent-to-Treat	**97 (92.4)**	**95 (95.0)**	**192 (93.7)**

[a] All randomized patients who received at least one dose of the Double-Blind study medication.
Note: For Patient 002-001 (placebo) the reason for discontinuation has been coded to AE, instead of Sponsor Request, to be consistent with the Adverse Event Case Report Form.
Source: Table 4 on page 50 of the report for Study 031.

A total of 58/205 (28.3%) patients (37 on oxymorphone ER and 21 on placebo) who received double-blind treatments, had **protocol deviations** identified during the study, including those mentioned above. The most frequent protocol deviation was having an off-schedule visit, which occurred in 33 patients (23 on oxymorphone and 10 on placebo). The second most frequent deviation was having an incorrect visit such as missing visit (16 on oxymorphone and seven on placebo).

[Reviewer's comments: The types of protocol deviation were not considered as having a noticeable impact on the results of primary and secondary efficacy evaluations. The potential impact could only have been on the change in PI by visit (one of the additional efficacy parameters). The impact of off-schedule visit and /or missing visit had limited effect because of the relatively long time interval (one to two weeks) between the scheduled clinic visits (unlike hourly assessments) and the imputation rules for missing data specified in the data analysis plan.]

Efficacy results

Primary efficacy endpoint

The results of the primary efficacy analysis of the MIDD population revealed that from baseline to the final visit, the LS mean change in PI (VAS) from baseline was 10.6 in the oxymorphone ER group (continued on stable treatments) versus 27.7 in the placebo group (withdrew from active treatment), a statistically significant difference.

Table 10-6 Mean Average PI (VAS) and Mean Change from Baseline to Final Visit – MITT

Statistics [a]	Oxymorphone ER (N=97)	Placebo (N=95)
Average Pain Intensity		
Statistics		
Baseline (Visit 5)		
Mean (STD)	**18.5** (11.22)	**19.3** (11.26)
Minimum	1	0
Median	19.0	19.0
Maximum	48	50
Final Visit		
Mean (STD)	**29.9** (26.21)	**46.2** (27.03)
Minimum	0	0
Median	21.0	50.0
Maximum	96	96
Change from Baseline to Final Visit		
Mean (STD)	11.4 (24.39)	26.9 (27.81)
Minimum	-28	-38
Median	2.0	29.0
Maximum	76	82
LSMean ± SE	**10.6 ± 2.50**	**27.7 ± 2.53**
Treatment comparison vs. Placebo		
LSMean Difference	-17.1	--

95% CI	(-24.21, -10.04)	--
P-value	< 0.0001	--

[a] The Primary analysis used an ANCOVA model with treatment & center as effects, screening & baseline average pain intensity as covariates. The following imputation rules, for missing values, were used: Discontinued due to AE: SOCF; Discontinued due to Opioid withdrawal symptoms in placebo group: BOCF; Discontinued for all other reasons: LOCF; Patients who discontinued for all other reasons but without post-baseline pain score: SOCF.
Source: Table 11 on page 68 of the report for Study 031.

The two sensitivity analyses performed by the Sponsor provided results consistent with that of the primary analysis. The analyses used less conservative approaches for imputation of missing data than the primary analysis. The first used last observation, instead of screening pain score, carried forward to the final visit for placebo patients who discontinued due to an AE. The second used baseline score (best case), instead of screening score, carried forward to the final visit for placebo patients who discontinued due to an AE during the first four weeks after baseline.

The results of analyses of the potential interactions between the average pain intensity and demographic and screening disease characteristics showed that there were no statistically significant effects in terms of age group and age group by treatment interaction, gender and gender by treatment interaction, race and race by treatment interaction, screening pain intensity and its interaction with treatment, or stabilized dose level and its interaction with treatment.

The results of the attempted subgroup analyses by demographic and screening disease characteristics are summarized in the table below. One should be cautious in trying to conclude from the reported group mean values presented in the table. As is common in analgesic efficacy trials, the sample sizes for the subpopulations were too small to allow any valid conclusion with regard to the treatment effects on different age, gender, or ethnic groups. In the entire efficacy sample population only 25 of 205 were elderly patients, 12 of 205 were African American patients, nine of 205 were Hispanic patients, and 42 of 205 patients had severe baseline pain. Therefore, the treatment difference with respect to these subgroups could not be adequately evaluated. The subgroup sample sizes with respect to gender for the two treatment groups were similar. There was a larger treatment difference in the change in PI from baseline to the final visit in male patients (22.4) than female patients (9.5). There was also a larger treatment difference in the change in PI from baseline to the final visit in the subgroup stabilized at a higher daily dose of >30 mg (19.4) than the lower daily dose of ≤30 mg (11.5).

Table 10-7 Subgroup Analyses by Demographic and Screening Disease Characteristics

Statistics	Oxymorphone ER (N=97)			Placebo (N=95)		
Average Pain Intensity at baseline and final visit and change from baseline to final visit MEAN (±SE)						
Age Group	*< 65 (n=81)*	*≥65 (n=16)*	*≥74 (n=7)*	*< 65 (n=87)*	*≥65 (n=8)*	*≥74 (n=3)*
Baseline (Visit 5)	19.3(±1.23)	14.8(±2.90)	18.9(±4.81)	19.9(±1.21)	13.0(±3.12)	5.3(±4.33)
Final Visit	28.7(±2.79)	36.2(±7.87)	52.0(±12.47)	46.6(±2.90)	42.0(±9.89)	36.7(±17.85)
Change	9.4(±2.61)	21.4(±6.79)	33.1(±11.58)	26.7(±3.00)	29.0(±9.84)	31.3(±16.33)
Race	*Caucasian (n=85)*	*Other (n=12)*		*Caucasian (n=86)*	*Other (n=9)*	
Baseline (Visit 5)	18.7 (± 1.23)	17.3 (± 3.10)		19.3 (± 1.19)	19.8 (± 4.54)	
Final Visit	31.6 (± 2.89)	18.0 (± 5.76)		47.8 (± 2.81)	31.3 (±10.90)	
Change	12.9 (± 2.62)	0.7 (± 6.96)		28.5 (± 2.88)	11.6 (±11.67)	
Gender	*Male (n=42)*	*Female (n=55)*		*Male (n=46)*	*Female(n=49)*	
Baseline (Visit 5)	18.6 (±1.68)	18.5 (±1.56)		21.3 (±1.55)	17.6 (±1.68)	
Final Visit	27.0 (±3.64)	32.2 (±3.78)		52.0 (±3.83)	40.8 (±3.88)	
Change	8.4 (±3.48)	13.7 (±3.46)		30.8 (±4.12)	23.2 (±3.92)	
Screening PI	*Moderate (n=74)*	*Severe (n=23)*		*Moderate (n=77)*	*Severe (n=18)*	
Baseline (Visit 5)	17.7 (± 1.32)	21.1 (± 2.24)		19.9 (± 1.28)	17.1 (± 2.73)	
Final Visit	27.7 (± 2.93)	37.0 (± 5.96)		45.0 (± 3.09)	51.6 (± 6.28)	

Change	10.0 (± 2.70)	15.9 (± 5.83)	25.1 (± 3.21)	34.5 (± 6.00)
Stabilized dosage (mg/day)	*Low (≤30) (n=47)*	*High (>30) (n=50)*	*Low (≤30) (n=47)*	*High (>30) (n=48)*
Baseline (Visit 5)	17.2 (± 1.74)	19.7 (± 1.48)	18.9 (± 1.55)	19.8 (± 1.72)
Final Visit	30.6 (± 4.07)	29.3 (± 3.50)	43.7 (± 4.07)	48.7 (± 3.78)
Change	13.4 (± 3.68)	9.5 (± 3.34)	24.9 (± 4.25)	28.9 (± 3.84)

Secondary and other efficacy endpoints

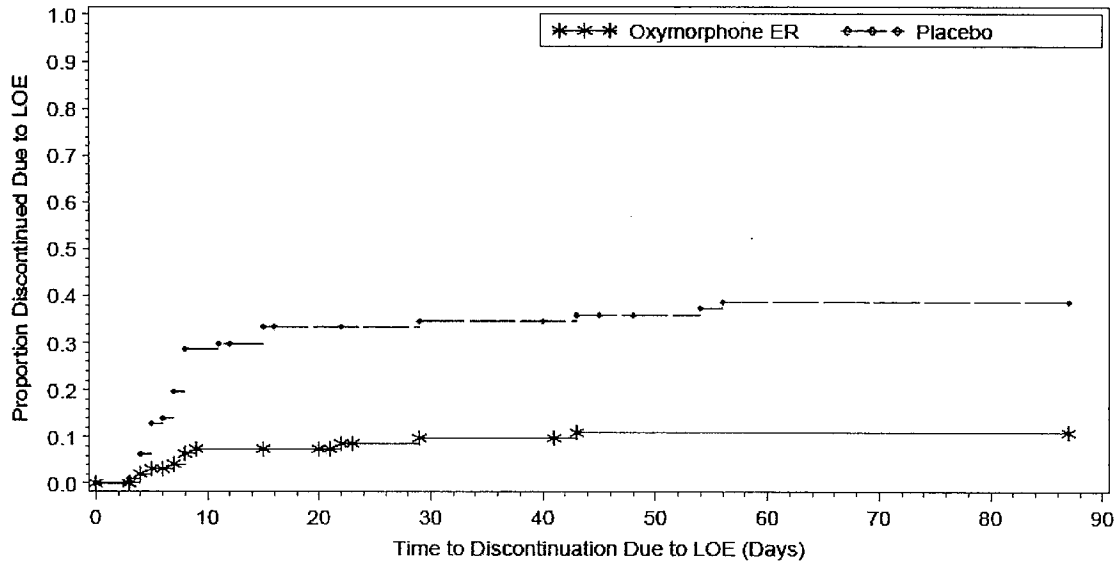
The results of secondary and additional efficacy analyses are summarized in the table below. As shown in the table, efficacy was further supported by the effect size and the level of statistical significance in the majority of the parameters tested. A smaller proportion of patients discontinued due to lack of efficacy in the oxymorphone ER group (10%) than in the placebo group (35%). Similarly, a smaller proportion of patients discontinued due to all reasons in the oxymorphone ER group (33%) than in the placebo group (55%). The proportion of patients who assessed their pain medication as good, very good, or excellent was greater in the oxymorphone ER group than in the placebo group at each visit following baseline, and was 82% versus 40%, respectively, at the final visit. Physician's global evaluation of medication followed the same trend in that the proportion evaluated as good, very good, or excellent was 83% for patients on oxymorphone ER and 37% for those on placebo. The addition of patients' stabilized dose level in the model of the primary analysis did not change the magnitude of the treatment difference. A responder analysis based on the criterion of a ≥30% reduction in average PI from screening to the final visit showed a greater proportion of responders in the oxymorphone ER group (81%) than in the placebo group (52%). The mean daily dose of rescue medication (oxymorphone IR) among patients who took rescue medication increased from 2.2 mg to 3.3 mg in the oxymorphone ER group and from 2.3 mg to 10.3 mg in the placebo group during the first four days (without dose restriction) of the double-blind treatment. For the period from Day 5 until the end of the double-blind treatment (with dose restrictions on rescue) oxymorphone ER patients took rescue less often (34 to 41% of days) than placebo patients (55 to 65% of days) on the average.

Table 10-8 Summary of Results for Secondary and Additional Efficacy Endpoints-MITT

	Oxymorphone ER (N=97)	Placebo (N=95)	P value	Study report reference
Secondary endpoints				
Time to discontinuation due to lack of efficacy (see Figure 10-1 below)			<0.0001	Fig 2, p70
Number (%) discontinued due to lack of efficacy	10/97 (10.3%)	34/95 (35.8%)		Table 14.1, p907
Patient global at final visit Proportion with good/very good/excellent	78/95 (82.2%)	34/86 (39.5%)	<0.0001	Table 13, p72
Physician global at final visit Proportion with good/very good/excellent	80/96 (83.4%)	32/87 (36.7%)	<0.0001	Table 14, p73
Additional endpoints				
Average PI by visit (see Figure 10-2 below)				Fig 3, p76
Change in PI with respect to stabilized dose level, LSMean	10.6	27.7	<0.0001	Table 18.1, p913
Percent reduction in average PI (see Figure 10-3 below)				Fig 4, p81
Responders: ≥30% reduction in PI	79/97 (81.4%)	47/91 (51.7%)	<0.0001	Fig 4, p81
Time to discontinuation due to all reasons (see Figure 10-4 below)			<0.0007	Fig 5, p82
Proportion discontinued due to all reasons	32/97 (33.0%)	52/95 (54.7%)		Table 15.1, p908
Daily rescue in first four days of double-blind treatment	↑ from 2.2 mg to 3.3 mg	↑ from 2.3 mg to 10.3 mg		Table 17, p85
% of days on rescue medication: Day 4 to final visit	34.4 - 41.2%	55.1 - 65.3%		Table 33, p4117

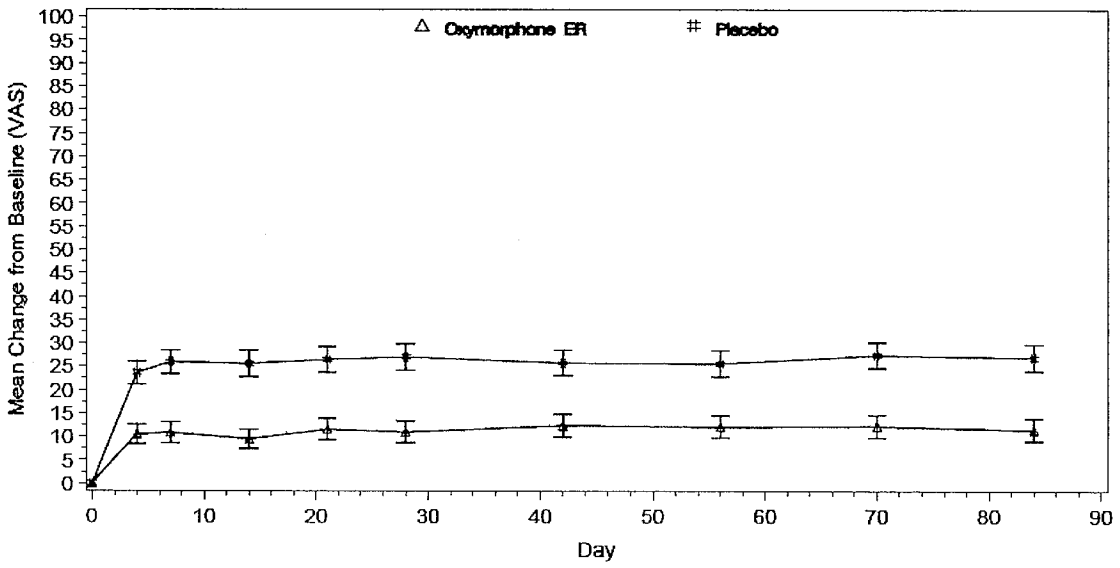
The effect size of the treatment difference in time to discontinuation due to lack of efficacy, time to discontinuation due to all reasons, and average pain intensity by visit over time during the entire course of the 12-week double-blind treatment period is presented in Figures 10-1, 10-4, and 10-2.

Figure 10-1 Time (Days) to Discontinuation Due to Lack of Efficacy (MITT, Double-Blind)



Note: p-value for treatment comparison between oxymorphone ER and placebo is <0.0001 and based on log-rank test.

Figure 10-2 Mean Change from Baseline in Average PI (VAS) by Visit (MITT, Double-Blind)



Note: Average Pain Intensity VAS scores range from 0 mm=no pain to 100 mm=the worst pain imaginable. Error bars represent standard errors (+/-)

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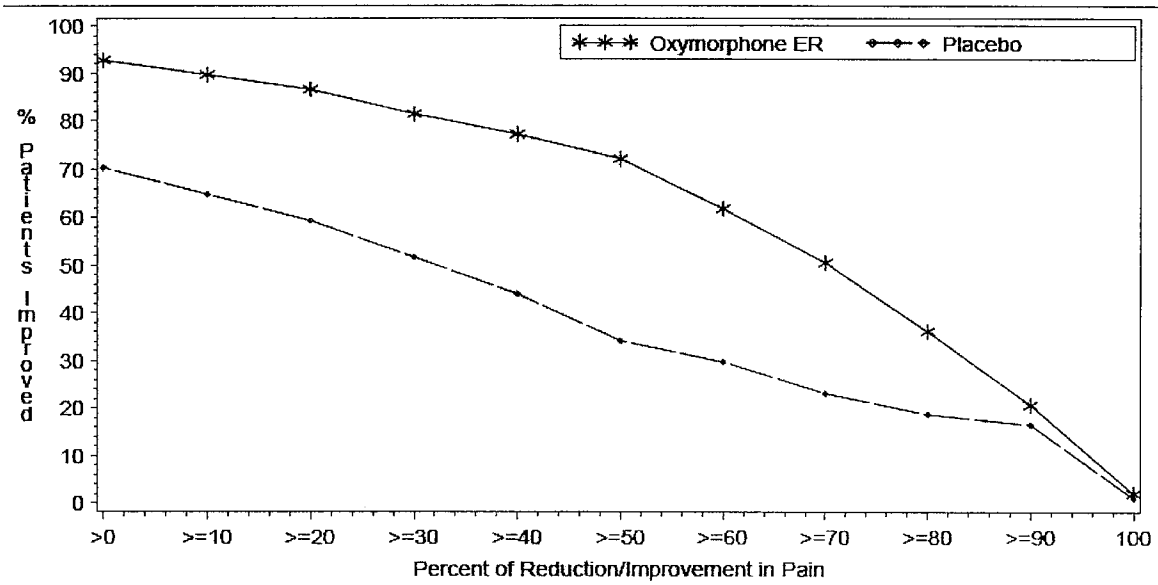
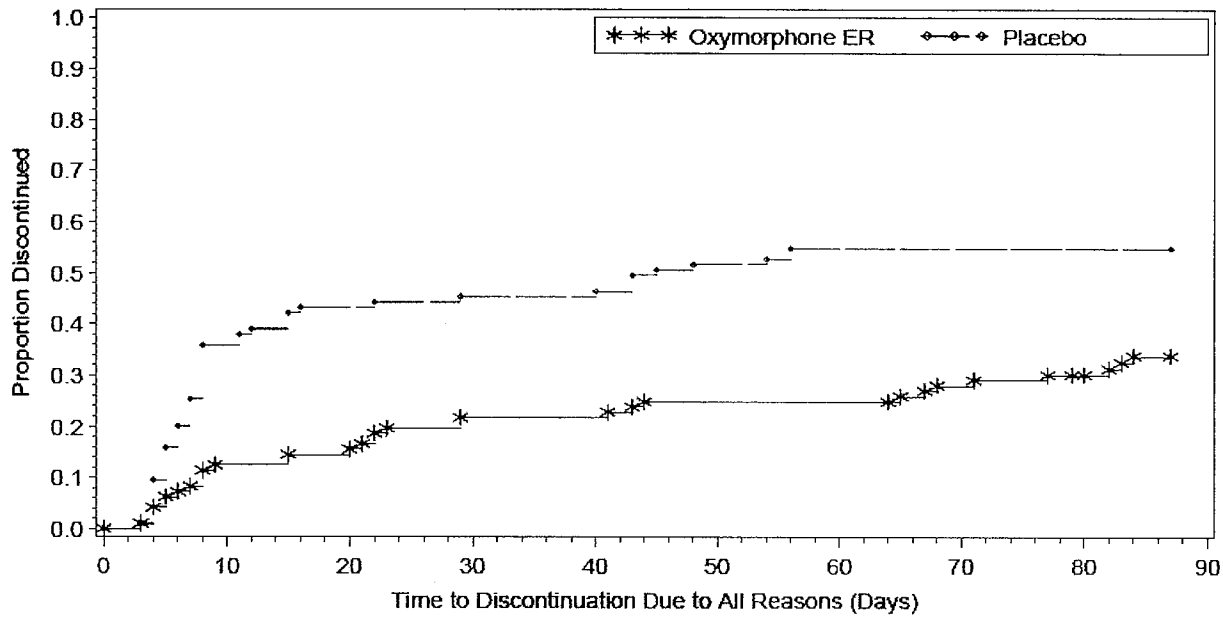
Figure 10-3 Percent Reduction in Average PI (VAS) From Screening to the Final Visit (Observed Values) (MITT, Double-Blind)



Note: No imputation rules were applied before summarizing data.

Figure 10-4 Time (Days) to Discontinuation Due to all Reasons (MITT, Double-Blind Treatment)



Note: p-value for treatment comparison between oxymorphone ER and placebo is 0.0007 and based on log-rank test.

The results of the analyses based on the entire efficacy sample consisting of all treated patients (ITT population) during the double-blind treatment were consistent with those presented for the MITT population as shown in the table below.

Table 10-9 Summary of Statistical Analysis Results (p-values) for all Efficacy Endpoints for Modified Intent-to-Treat (MITT) and Intent-to-Treat (ITT) Populations

	MITT	ITT
Primary Endpoint		
Change in Average Pain Intensity	<0.0001	<0.0001
Sensitivity Analysis 1	<0.0001	<0.0001
Sensitivity Analysis 2	0.0003	0.0001
Secondary Endpoints		
Time to Discontinuation Due to lack of efficacy	<0.0001	<0.0001
Time to Discontinuation Due to all reasons	0.0007	0.0010
Patient Global Assessment	<0.0001	<0.0001
Investigator Global Assessment	<0.0001	<0.0001

Source: Table 12 on page 69 of the report for Study 031.

Summary of Findings and Discussions

In this titration-to-effect, randomized withdrawal design study enriched for opioid naïve patients with low back pain who tolerated and responded to oxymorphone ER, the treatment differences between oxymorphone ER and placebo were clearly demonstrated in all the efficacy parameters as evidenced by the level of statistical significance and clinically meaningful effect size.

The effect of the12-week treatment was shown in the primary efficacy endpoint as the change in pain intensity from baseline to the final visit. The worsening of PI scores in the active treatment group after 12 weeks of treatment was most likely to be due to drug tolerance, a known effect of the drug class. Although the use of rescue during the double-blind treatment might have also contributed to a worsening of pain scores over the 12-week period, the restriction of its use from day four to the end of treatment had been used to minimize the confounding effects of rescue.

Efficacy was further supported by the demonstration of treatment differences in the predefined secondary endpoints, time to discontinuation due to lack of efficacy, and patient and physician global evaluation of medication. Additional supportive findings included the demonstration of treatment differences in change in PI from baseline to the final visit adjusted for stabilized dose level, time-specific measure of average PI by visit, percent reduction in average PI, proportion of responders (≥30% reduction in PI), percent discontinued due to lack of efficacy, time to discontinuation and proportion discontinued due to all reasons, and the use of rescue medication over the first four days and the percent of days used during the remainder of the 12-week double-blind treatment period.

The efficacy of oxymorphone ER was demonstrated in patients treated with stabilized individual doses at a mean daily dose of about 40 mg ranging from 10 mg to 140 mg/day (especially, in the dose range of 20 to 60mg/day).

The results obtained from the analyses of the MITT population were confirmed by re-analyses using the true ITT population.

The interpretation of the results of subgroup analyses was limited due to the small sample sizes for elderly patients, African American and Hispanic patients, and patients with severe baseline pain. The observation of a larger change in PI from baseline to the final visit in male patients (22.4) than female patients (9.5) seems to suggest a gender difference. However, the opposite result was reported in study 032. Therefore, no gender difference in treatment effects can be concluded. The data suggest a dose response of analgesic effects in that the group treated with a higher daily dose of oxymorphone ER (>30mg) showed a greater treatment difference than the group treated with a lower daily dose (≤30mg).

A major problem in using a traditional, straight parallel arm design in studying opioid-type drugs for chronic pain is the very high dropout rates due to intolerance to adverse effects and tolerance to desired therapeutic effects and consequently, the issues about how to manage a huge amount of missing data. The withdrawal design using an enriched population is one approach to address the problem upfront by eliminating the non-responders before randomization instead of waiting for them to dropout during the study. In this study, the 37% total dropout rate during the open-label titration, including an 18% dropout rate due to AEs, 7% due to failure to meet titration-stabilization criteria, and 1% due to lack of efficacy, should be taken into the consideration in trying to interpret the efficacy findings from studies with an enrichment design.

One major limitation of the titration-to-effect and withdrawal design is that it favors the active treatment arm by selecting for responders (patients able to maintain PI $\leq$40 mm for several days and in need of at least 20 mg daily of oxymorphone ER treatment without help of a rescue) and eliminating those who could not tolerate the active treatment (18% dropouts due to AEs) before the randomized withdrawal from the active treatment took place. Consequently, the study by design may overestimate benefit by showing greater treatment differences in responders than what would be expected from a more general sample population and underestimate toxicity by excluding those who can not tolerate the drug and thus have fewer reports of adverse events.

One concern in a randomized withdrawal design study of an opioid product is the risk for withdrawal symptoms in patients randomized to placebo. It may affect the integrity of the blinding and the pain evaluation. The use of rescue during the double-blind treatment in the study helped the placebo patients to taper from the active treatment and to minimize opioid withdrawal (reported in only two placebo patients during the double-blind treatment period). This helps not only to maintain the integrity of the blinding but also to reduce the dropout rates. The Sponsor attempted to minimize the confounding effect of rescue by restricting its use from Day 4 to the end of the double-blind treatment period.

Drug tolerance with the length of treatment in the opioid naïve population was suggested by the reduction of AEs (total AEs, individual AEs, and AE related early dropouts) in the 12-week double-blind treatment period in comparison to what were reported in the 4-week titration period, and by the worsening of pain from baseline to the final visit.

Conclusion

Oxymorphone ER at individualized dosage was shown to be effective in treating chronic low back pain in opioid naïve patients identified as responders who had reasonable tolerance to the medication (about 60% of the study population).

Appendix 1: Eligibility criteria for entering the open-label titration period

Inclusion Criteria

Candidates were going to be included in the study and entered into the Open-Label Titration Period if they met all the inclusion criteria listed below:

1. Were males or females 18 years of age or older – If female, must have been practicing abstinence or using a medically acceptable form of contraception (e.g., intrauterine device, hormonal birth control, or barrier method in conjunction with spermicide). For the purpose of this study, all females were considered to be of childbearing potential unless they were post-menopausal (at least 1 year since last menses), biologically sterile, or surgically sterile (i.e., hysterectomy, bilateral oophorectomy, or tubal ligation).
2. Were opioid naïve (patients taking less than the equianalgesic equivalent of 5 mg oxycodone per day during 14 days prior to the screening visit are eligible)
3. Had an initial pain intensity score of at least 50 mm on a 100-mm VAS
4. Were in good health as determined by the investigator on the basis of medical history and physical examination
5. Had moderate to severe chronic non-neuropathic (established by exclusion of neuropathic causes under Section 4.2) LBP that had been present daily for at least several hours per day for a minimum of three months prior to the screening visit
6. Kept unchanged, based on the patient's current status, any adjunct therapy for back pain, such as physical therapy, biofeedback therapy, acupuncture therapy or herbal remedies, during the period of participation of the patient
7. Provided meaningful written informed consent prior to admission to the study

Exclusion Criteria

Patients were going to be excluded from participation if they:

1. Were pregnant and/or lactating
2. Had radiculopathy, fibromyalgia, reflex sympathetic dystrophy or causalgia (complex regional pain syndrome), acute spinal cord compression, cauda equina compression, acute nerve root compression, severe lower extremity weakness or numbness, bowel or bladder dysfunction secondary to cauda equina compression, diabetic amyotrophy, meningitis, discitis, or back pain due to secondary infection or tumor
3. Could not or would not agree to stop local regional pain treatments during the study (nerve/plexus blocks or ablation, neurosurgical procedures for pain control, or inhalation analgesia). The patient must not have had a nerve/plexus block within 4 weeks of screening
4. Intended to alter their physical therapy regimen during the study. Patients who began or ended physical therapy (either home exercises or formal therapy sessions) 2 weeks prior to screening or during the study period were to be excluded from the study.
5. Had undergone surgical procedures directed towards the source of back pain within 6 months of screening
6. Had pain that was secondary to confirmed or suspected neoplasm
7. Had dysphagia or difficulty swallowing tablets or capsules, or an inability to take oral medication
8. Had a significant prior history of substance abuse or alcohol abuse
9. Had received any investigational medication within 30 days prior to the first dose of study medication, or was scheduled to receive an investigational drug other than oxymorphone during the course of the study
10. Had a previous exposure to oxymorphone
11. Had a prior history of clinically significant intolerance to oxymorphone or a known hypersensitivity to opioid analgesics
12. Had a history of seizure. Patients with a history of juvenile febrile seizures could have been included if there had been no seizure history within the past 10 years
13. Had an ileostomy or colostomy
14. Had received a monoamine oxidase (MAO) inhibitor within 14 days prior to the start of study medication
15. Had any clinically significant condition that would, in the investigator's opinion, preclude study participation
16. Would be unable to comply with the protocol, according to the investigator
17. Were unable to read, comprehend, and complete the informed consent form, questionnaires, and diaries

10.2.1 Study 032

Protocol
Study EN3202-032 was planned as a titration-to-effect, randomized withdrawal, double-blind, placebo-controlled, parallel, multiple-dose, dose range study of chronic low back pain (LBP) in opioid experienced patients. The study was planned to have two periods: an open-label titration period and a double-blind, placebo-controlled treatment period.

Eligible subjects were going to be patients with moderate to severe chronic (≥3 months duration), non-neuropathic low back pain (LBP), treated by stable, fixed dose, and around-the-clock regimen of opioid therapy for at least two weeks prior to screening.

Following screening assessments all eligible patients were planned to be started on open-label treatments with oxymorphone ER PO q12 hours at a dose approximately equivalent to their pre-study opioid requirements. Patients were also going to be allowed oxymorphone immediate release (IR) to be taken at 5 mg q4-6h as needed (prn) as a supplemental rescue pain medication for breakthrough pain. To be eligible to enter the double-blind, placebo-controlled treatment, patients were going to be required to be stabilized within four weeks of open-label treatments. Stabilization was going to be defined as reaching a tolerated dose that would provide adequate pain relief, i.e., maintaining an average pain intensity score of ≤40 mm on visual analogue scale (VAS) and not requiring more than two doses/day of oxymorphone IR as rescue, for three of five consecutive days immediately prior to randomization, and reaching a minimum dose of oxymorphone ER of 10 mg q12 hour (20 mg daily) prior to randomization. Anti-constipation medication was planned to be available throughout the study.

Patients eligible for double-blind treatment were planned to be randomized to either continue on the stabilized dose of oxymorphone ER or replace oxymorphone ER treatment with placebo. During the 12-week double-blind treatment oxymorphone IR was going to be allowed as rescue pain medication for breakthrough pain and as an aid in tapering placebo patients to prevent opioid withdrawal. The use of rescue medication was planned as oxymorphone IR 5 mg q4 to 6 hours as needed during the first four days of double-blind treatment and at most twice daily thereafter. Patients who developed intolerance or inadequate pain control to their established dose of study drug were going to be terminated from the study. Patients were to be instructed to keep a daily diary record of the total oxymorphone ER (or placebo) dose, as well as any oxymorphone IR (rescue medication) dose. During the double-blind treatment period, patients were going to return to the site for safety and efficacy assessments at Day 4 and Weeks 1, 2, 3, 4, 6, 8, 10, and 12 (±3 days).

Efficacy was planned to be assessed by the change in average pain intensity from baseline (last VAS pain score before randomization) to final study visit as the primary endpoint and by the following secondary endpoints: time to early discontinuation due to lack of efficacy, patient/physician global satisfaction with study medication, and changes in pain quality as measured by using a Pain Quality Assessment Scale.

Safety and tolerability were planned to be evaluated by adverse events (AEs), vital signs, discontinuations due to drug-related AEs (tolerability), and investigator- and patient-rated signs and symptoms of opioid withdrawal.

The protocol was submitted to IND 56,919 as N192 on September 27, 2004 and was reviewed by the medical reviewer, Dr. Elizabeth McNeil (DFS filing dates of the written reviews was 12/2/04). The study was considered a duplicate of Study 031 except that it was conducted in a different patient population (opioid experienced instead of opioid naïve population). All the agreements made under special protocol assessments for Study 031 were incorporated and implemented in the Study 032.

Table 10-10 Protocol

Study #	EN3202-032
Objectives	To study efficacy, dose titration regimen, dose range, and safety of oxymorphone extended release (ER) in opioid-experienced patients with chronic non-neuropathic low back pain (LBP)
Design	Randomized withdrawal, double-blind, placebo-controlled, parallel, multiple-dose (28-day open-label titration period followed by double-blind treatment with twice daily dosing at individualized dose level for 12 weeks), dose range study at 30 centers in the U.S.
Sample population	Male and non-pregnant female; ≥18 years of age; moderate to severe **chronic non-neuropathic LBP** present daily for at least several hours per day for a minimum of three months prior to screening; on **stable (fixed dose with reasonable tolerance) around-the-clock opioid** for LBP for at least two weeks prior to screening; with expected total daily oxymorphone ER dose in the range of 20-220 mg (equivalent to oral morphine: 60-660 mg); on stable adjunct therapy (e.g., physical therapy, biofeedback therapy, acupuncture therapy, or herbal remedies) for back pain; (refer to eligibility criteria in Appendix 1 at the end of the review of the protocol)
Baseline	Moderate to severe pain
Treatment	Open-label titration: oxymorphone ER q12h at individualized initial dose equivalent to pre-study opioid requirements and titrate to stabilization (pain score ≤40 mm on the same dose for three of five consecutive days immediately prior to randomization, reasonable tolerance to the dose in the same time period, having reached a minimum dose of 10 mg q12h, and not requesting for more than two doses of oxymorphone IR 5 mg per day as rescue medication) Double-blind treatment: oxymorphone ER at individualized fixed dose determined above or placebo q12 h for 12 weeks
Rescue and concomitant medication	Rescue medication: **oxymorphone IR 5mg q4 to 6h in open-label phase** and the first 4 days of double-blind phase; dose restriction to ≤2 doses/day after the first 4 days of double-blind phase. Other medication: anti constipation treatment throughout the study
Raw efficacy data	**Average pain of the last 24 hours** before each clinic visit (baseline, Day 4, Weeks 1, 2, 3, 4, 8, and 12) using a 100 mm VAS scale **Patient's and Physician's Global** Assessments of Pain Medication on a 5-point categorical scale at screening (evaluate pre-study pain medication), baseline (evaluate oxymorphone ER during open-label titration), and 4-week, 8-week, and 12-week visit during double-blind treatment **Pain Quality Assessment Scale** (PQAS), a 20-item, 11-point numerical scale that measures individual pain qualities and the impact of treatment on those qualities, at baseline and exit visit
Efficacy parameter	***Primary:*** **Change in average pain intensity** (VAS) (of past 24 hours) **from baseline to final visit** ***Secondary:*** • Change from baseline to final visit in patient's global assessment of pain medication • Change from baseline to final visit in physician's global assessment of pain medication • Change from baseline to final visit by Pain Quality Assessment Scale • Evaluation of compliance and study medication usage, time to discontinuation due to lack of efficacy
Statistical analysis	***Primary analysis:*** Analysis of covariance (ANCOVA) with treatment and center as effects and screening and baseline PI as covariates; ***Imputation for missing value:*** • For dropouts due to an AE, screening PI (worst case) carried forward to the final visit • For dropouts due to opioid withdrawal in the placebo group, baseline PI (best case) carried forward to the final visit • For dropouts due to all other reasons last observation carried forward to the final visit.
Safety monitoring	• Adverse events (AEs) throughout the study • Vital signs at most of the clinic visits (screening, weekly visit during open-label phase, baseline and visits at Day 4, Weeks 1, 2, 3, 4, 8, and 12 during double-blind phase) • Adjective Rating Scale for Withdrawal (ARS) at screening, baseline, and visits first 4 weeks of double-blind treatment • Clinical Opiate Withdrawal Scale (COWS) assessed using the same schedule as ARS

Statistical highlights

The statistical methodology and analysis plan and related changes were presented and discussed in detail in the statistical review. Some points are mentioned below for clarification purpose.

Sample population for efficacy analyses

The pre-specified efficacy analysis population was defined as all randomized patients who received at least one dose of double-blind study medication (ITT).

Sensitivity Analyses
The Sponsor proposed sensitivity analysis using two different imputation methods that were less conservative than the original imputation with the argument that the original imputation for placebo patient dropping out due to adverse events could introduce a potential bias towards the active treatment as there might be potential overlap in the diagnosis of opioid withdrawal and other adverse events.

1. For any patient who discontinues due to an adverse event in the placebo group, the last observation instead of the screening pain score will be carried forward to the final visit.

2. For any patient who discontinues due to an adverse event in the placebo group in the first four weeks after baseline (the period in which opioid withdrawal symptoms are most likely to occur), the baseline pain score (which will reflect patient's best score) will be carried forward to the final visit.

Post hoc changes to the planned statistical analyses
Post hoc analyses were conducted for the additional efficacy endpoints, including

- Mean change from baseline in average pain intensity (VAS) by visit using the imputation rules established for the primary analyses with an additional imputation rule that a previous post-baseline value was to be used to impute a missing "intermediate" post-baseline value.

- Time to discontinuation due to all reasons using the same method of analyses as for the endpoint of time to discontinuation due to lack of efficacy

- Percentage of responders defined as at least 30% percent reduction in average pain intensity (VAS) from screening to final visit, using a chi-square test of observed values (no data imputation)

- The percent reduction at all levels (≥10%, ≥20%, ≥30% ....) presented as a figure.

In the Sponsor's review of blinded data a major protocol violation was identified in four patients who received randomized treatments without signing the HIPAA consent form. These patients were therefore excluded from the efficacy analyses.

Results

Demographic and other baseline characteristics
The efficacy sample population consisted of 142 subjects who received double-blind treatment (one patient was randomized but not treated), with an age range of 21 to 73 years, a mean age of 47 years, 8% elderly, 86% Caucasian, 11% African American, 2% Hispanic, and 46% female. The treatment groups were approximately balanced with regard to demographic characteristics such as age, race, and weight and with regard to the baseline pain intensity (about 70% had moderate pain and 30% had severe pain at baseline). The noticeable treatment group differences were the proportion of African Americans (14% in the oxymorphone groups versus 7% in the placebo group), gender ratio (female:male ratio of 4:3 in the oxymorphone groups versus that of 1:2 in the placebo group), and disease distribution of etiology.

Table 10-11 Demographics, Screening, and Randomization Characteristics (Double-Blind Period)

Demographic/Statistics	Oxymorphone ER (N = 70)	Placebo (N = 72)	Randomized (N = 143)
Age (yrs)			

Mean	48.2	46.0	47.1
STD	11.68	11.29	11.45
Median	48	46	47
Min, max	21, 73	21, 70	21, 73
Age Group, n (%)			
< 65	64 (91.4)	67 (93.1)	132 (92.3)
≥65	6 (8.6)	5 (6.9)	11 (7.7)
Race, n (%)			
African American	10 (**14.3**)	5 (**6.9**)	15 (10.5)
Caucasian	59 (84.3)	64 (88.9)	123 (86.0)
Hispanic	1 (1.4)	1 (1.4)	3 (2.1)
Other	0	2 (2.8)	2 (1.4)
Gender, n (%)			
Female	40 (**57.1**)	24 (**33.3**)	65 (45.5)
Male	30 (**42.9**)	48 (**66.7**)	78 (54.5)
Stabilized Dose Level, n (%)			
High (>60mg daily)	31 (44.3)	35 (48.6)	
Low (20-60mg daily)	39 (55.7)	37 (51.4)	
Weight (pounds)			
Mean	200.5	191.5	195.7
STD	48.11	43.91	45.98
Median	195	197.5	196
Min, max	118, 306	95, 300	95, 306
Etiology, n (%)			
Degenerative disc disease	30 (42.9)	23 (31.9)	53 (37.1)
Herniated disc	12 (17.1)	17 (23.6)	29 (20.3)
Osteoarthritis	16 (22.9)	10 (13.9)	27 (18.9)
Spinal stenosis	2 (2.9)	0	2 (1.4)
Trauma	13 (18.6)	14 (19.4)	27 (18.9)
Other	15 (21.4)	20 (27.8)	35 (24.5)
Categorical Rating of CLBP, n (%)			
Moderate	**49 (70.0)**	**51 (70.8)**	**101 (70.6)**
Severe	21 (30.0)	21 (29.2)	42 (29.4)
Average Pain Intensity (VAS)			
Mean	67.2	71.5	69.5
STD	16.98	16.77	16.97
Median	71	73.5	71
Min, max	22, 100	14, 100	14, 100

Source of information: Tables 8 and 9 on pages 55-58 of the report for Study 032.

Dosing distribution of stabilized individual dosing at randomization for the two treatment groups are summarized in the table below. Of the 70 patients assigned to the active treatment 48 (68.6%) were on oxymorphone ER 20 to 80 mg/day and 63 (90%) had daily dosing 20 mg to 180 mg/day during the 12-week double-blind treatment.

Table 10-12 Stabilized Individual Dosing at Randomization of Double-Blind Treatment

	Oxymorphone ER (N = 70)	Placebo (N = 72)	Overall (N=142)
Daily Dose (mg/day)	n (%)	n (%)	n (%)
20	12 (17.1)	6 (8.3)	18 (12.7)
40	18 (25.7)	16 (22.2)	34 (23.9)
60	9 (12.9)	15 (20.8)	24 (16.9)
80	9 (12.9)	5 (6.9)	14 (9.9)
100	4 (5.7)	6 (8.3)	10 (7.0)
120	4 (5.7)	3 (4.2)	7 (4.9)
140	2 (2.9)	5 (6.9)	7 (4.9)
160	4 (5.7)	8 (11.1)	12 (8.5)
180	1 (1.4)	1 (1.4)	2 (1.4)

200	4 (5.7)	2 (2.8)	6 (4.2)
220	3 (4.3)	4 (5.6)	7 (4.9)
260	0	1 (1.4)	1 (0.7)
Descriptive Statistics			
Mean	80.9	93.3	87.2
Std	59.31	61.25	60.42
Min	20	20	20
Median	60	60	60
Max	220	260	260

Source: Table 16 on page 84 of the report for Study 032.

Patient disposition and efficacy sample

Of the 251 patients enrolled in the study, 250 were treated during the open-label titration period. A total of 107 (43%) did not enter double-blind treatment, including 47 (19%) due to AEs (none were opioid withdrawal AEs), 17 (7%) due to not meeting titration-stabilization criteria (not due to AEs), 15 (6%) due to withdrawal of consent (three cases were due to family reasons, three cases by personal preference, two cases due to non-compliance, two cases due to request by primary care physicians, two cases due to scheduling conflict, and three cases due to multiple reasons where lack of efficacy was part of the reason), ten (4%) due to lack of efficacy, six (2%) due to lost to follow-up, six (2%) by investigator's opinion (two cases were due to non-compliance, two cases due to lost drug, one case due to positive urine pregnancy test, and one case met exclusion criteria), four (2%) due to protocol violation, and two (0.8%) upon Sponsor's request (one case had drug dispensation issues and one had withdrawal symptoms after screening visit). The dropouts due to AE will be discussed in the review of safety. The 3 cases of dropouts due to withdrawal of consent for which lack of efficacy was part of the reason could also be counted as discontinuation due to lack of efficacy. The total dropouts due to AEs, lack of efficacy, and failure to meet titration-stabilization criteria, accounted for 31% (77/251) of patients enrolled.

Table 10-13 Patient Disposition During the Open-Label Titration Period: Number (%) of Patients

Patient Disposition	Oxymorphone ER
Entered Open-Label Titration Period	251 (100.0)
All Treated (Open-Label Titration Period) [a]	250 (99.6)
Not Treated [b]	1 (0.4)
Completed Open-Label Titration Period	143 (57.0)
Discontinued in Open-Label Titration Period [c]	107 (42.6)
Adverse Event	47 (18.7)
AE not due to opioid withdrawal	47 (18.7)
Opioid withdrawal-AE	0
Patient did not meet Titration-Stabilization criteria	17 (6.8)
Withdrew Consent	15 (6.0)
Lack of Efficacy	10 (4.0) [or 13 (5.2) see above]
Lost to Follow-up	6 (2.4)
Investigator Opinion	6 (2.4)
Protocol Violation	4 (1.6)
>3 days of <80% compliance with study medication	1 (0.4)
Other	3 (1.2)
Sponsor Request	2 (0.8)
Randomized and Entered Double-Blind Treatment Period	143 (57.0)

[a] All patients who received at least one dose of the open-label Titration medication.
[b] Patient 010-003 was not treated according to drug accountability data.
[c] Reasons for discontinuation are sorted in descending order of frequency.
Source: Table 3 on page 49 of the report for Study 032.

Of the 143 subjects who were randomized 142 received double-blind treatments, 70% patients on active treatment and 25% on placebo completed the 12-week treatments. The **major reasons for dropouts** were

lack of efficacy (11% on oxymorphone ER versus 53% on placebo) and **adverse events** (10% on oxymorphone ER versus 11% on placebo, where five of the eight cases on placebo were due to opioid withdrawal). Dropouts due to **protocol violation** occurred in three patients, two patients on oxymorphone ER (one used rescue medication >2 doses/day and one was <80% compliant with study medication), and one patient on placebo (used prohibited concomitant medication for >3 days). Of the four cases of discontinuation by Investigator's opinion, three were due to drug accountability and one due to non-compliance. One case of discontinuation upon Sponsor's request was due to loss of a controlled substance.

The **major differences** between the treatment groups were that remarkably more placebo patients discontinued early than patients on active treatment and that dropouts due to lack of efficacy in the placebo group were almost five times greater than that of the active treatment group.

The group receiving oxymorphone ER in the double-blind treatment period had lower dropout rate due to AEs (10% versus 19%) and higher dropout rate due to lack of efficacy (11% versus 5%) than the entire study population undergoing open-label titration.

All subjects who were treated and discontinued early for any reason were included in the ITT analyses of efficacy.

The Sponsor **excluded** four patients randomized and treated (one on oxymorphone and three on placebo) **from ITT efficacy analysis** because they did not sign the HIPAA consent form to have their data eligible for use.

Table 10-14 Patient Disposition During the Double-Blind Treatment: Number (%) of Patients

Patient Disposition	Oxymorphone ER	Placebo	Overall
Randomized and entered double-blind treatment period	70 (100.0)	73 (100.0)	143 (100.0)
All treated patients (≥1 dose of double-blind treatment) [a]	70 (100.0)	72 (98.6)	142 (99.3)
Not treated [b]	0	1 (1.4)	1 (0.7)
Completed Double-Blind Treatment Period	49 (70.0)	18 (24.7)	67 (46.9)
Discontinued in Double-Blind Treatment Period	**21 (30.0)**	**54 (74.0)**	75 (52.4)
Lack of Efficacy	**8 (11.4)**	**39 (53.4)**	47 (32.9)
Adverse Event	7 (10.0)	8 (11.0)	15 (10.5)
AE not due to opioid withdrawal	7 (10.0)	3 (4.1)	10 (7.0)
Opioid withdrawal-AE	0	5 (6.8)	5 (3.5)
Withdrew Consent	1 (1.4)	2 (2.7)	3 (2.1)
Protocol Violation	2 (2.9)	1 (1.4)	3 (2.1)
Investigator Opinion	2 (2.9)	2 (2.7)	4 (2.8)
Other	1 (1.4)	0	1 (0.7)
>3 days of <80% compliance with study medication	1 (1.4)	0	1 (0.7)
Lost to Follow-up	1 (1.4)	1 (1.4)	2 (1.4)
Sponsor Request	0	1 (1.4)	1 (0.7)
Used prohibited medication for >3 consecutive days	0	1 (1.4)	1 (0.7)
All treated patients (double-blind, efficacy sample[c]	**69 (98.6)**	**69 (94.5)**	**138 (96.5)**

[a] All randomized patients who received at least one dose of the double-blind study medication.
[b] Patient 023-009 was randomized but not treated according to drug accountability data.
[c] The following patients were excluded from the All Treated Patients (Double-Blind, Efficacy) population due to not signing the HIPAA consent form: 007-002 (Oxymorphone ER), 022-002 (Placebo), 022-004 (Placebo), 027-002 (Placebo).
Source: Table 4 on page 50 of the report for Study 032.

A total of 44/142 (31.0%) patients (32 on oxymorphone ER and 12 on placebo) who received double-blind treatments, had **protocol deviations** identified during the study. The most frequent protocol deviation was having an off-schedule visit, which occurred in 32 patients (26 on oxymorphone and six on placebo). The second most frequent deviation was having an incorrect visit such as missing visit, which occurred in 20 patients (17 on oxymorphone and three on placebo).

[Reviewer's comments: The types of protocol deviation were not considered as having a noticeable impact on the results of primary and secondary efficacy evaluations. The potential impact could only have been on the change in PI by visit (one of the additional efficacy parameters). The impact of off-schedule visit and missing visit had limited effect because of the relatively long time interval (one to two weeks) between the scheduled clinic visits (unlike hourly assessments) and the imputation rules for missing data specified in the data analysis plan.]

Efficacy results

Primary efficacy endpoint

The results of the primary efficacy analysis revealed that from baseline to the final visit, the LS mean change in PI (VAS)from baseline was 8.7 in the oxymorphone ER group (continued on stable treatments) versus 31.6 in the placebo group (withdrew from active treatment), a statistically significant difference.

Table 10-15 Mean Average PI (VAS) and Mean Change from Baseline to Final Visit

Statistics [a]	Oxymorphone ER (N=69)	Placebo (N=69)
Average Pain Intensity		
Baseline (Visit 5) [b]	N=68	N=69
Mean (STD)	**23.9** (12.05)	**22.2** (10.75)
Minimum	0	0
Median	23.5	23.0
Maximum	57	43
Final Visit	N=69	N=69
Mean (STD)	**31.3** (23.48)	**54.5** (28.43)
Minimum	0	1
Median	24.0	62.0
Maximum	85	97
Change from Baseline to Final Visit	N=68	N=69
Mean (STD)	7.9 (20.60)	32.4 (27.00)
Minimum	-22	-23
Median	2.0	38.0
Maximum	67	88
LSMean ± SE	**8.7 ± 2.95**	**31.6 ± 2.93**
Treatment comparison vs. Placebo		
LSMean Difference	-23.0	--
95% CI	(-31.33, -14.59)	--
P-value	< 0.0001	--

[a] The Primary analysis used an ANCOVA model with treatment and center as effects, screening and baseline average pain intensity as covariates. The following imputation rules, for missing values, were used: Discontinued due to AE: SOCF; Discontinued due to Opioid withdrawal symptoms in placebo group: BOCF; Discontinued for all other reasons: LOCF; Patients who discontinued for all other reasons but without post-baseline pain score: SOCF.
[b] Oxymorphone ER patient 009-010 has a missing CRF/Visit Baseline value. BOCF=baseline observation carried forward; LOCF=last observations carried forward; SE=standard error; SOCF=screening observation carried forward
Note: Average Pain Intensity VAS scores range from 0 mm = no pain to 100 mm = the worst pain imaginable.
Source: Table 12 on page 70 of the report for Study 032.

The two sensitivity analyses performed by the Sponsor provided results consistent with that of the primary analysis. The analyses used less conservative approaches for imputation of missing data than the primary analysis. The first used last observation, instead of screening pain score, carried forward to the final visit for placebo patients who discontinued due to an AE. The second used baseline score (best case), instead of screening score, carried forward to the final visit for placebo patients who discontinued due to an AE during the first four weeks after baseline.

The results of analyses of the potential interactions between the average pain intensity and demographic and baseline disease characteristic showed that there were no statistically significant effects in terms of age group and age group by treatment interaction, gender and gender by treatment interaction, race and race by treatment interaction, screening pain intensity and its interaction with treatment, or stabilized dose level and its interaction with treatment.

The results of attempted subgroup analyses by demographic and screening disease characteristics are summarized in the table below. One should be cautious in trying to conclude from the reported group mean values presented in the table. As is common in analgesic efficacy trials the sample sizes for the subpopulations were too small to allow any valid conclusion with regard to the treatment effects on different age, gender, or ethnic groups. In the entire efficacy sample population only 11 of 142 were elderly patients, 15 of 142 were African American patients, four of 142 were Hispanic or patients of other race, and 42 of 142 patients had severe baseline pain. Therefore, the treatment difference with respect to these subgroups could not be adequately evaluated. The proportions of female to male varied in the two treatment groups, at a ratio of 4:3 for the oxymorphone group and 1:2 for the placebo group. There was a larger treatment difference in the change in PI from baseline to the final visit in female patients (29.5) than male patients (20.9). There was also a larger treatment difference in the change in PI from baseline to the final visit in the subgroup stabilized at a higher daily dose of >60 mg (31.1) than the lower daily dose of 20-60 mg (18.9).

Table 10-16 Subgroup Analyses by Demographic and Screening Disease Characteristics

Statistics	Oxymorphone ER (N=69)		Placebo (N=69)	
Average Pain Intensity at baseline and final visit and change from baseline to final visit MEAN (±SE)				
Age Group	*< 65 (n=63)*	*≥65 (n=6)*	*< 65 (n=64)*	*≥65 (n=5)*
Baseline (Visit 5)	23.3 (±1.58) (n=62)	29.2 (±2.27)	22.3 (±1.34)	20.4 (±5.64)
Final Visit	31.2 (±2.97)	33.0 (±10.07)	54.0 (±3.50)	61.6 (±16.32)
Change	8.3 (±2.62) (n=62)	3.8 (±9.01)	31.7 (±3.30)	41.2 (±16.10)
Race	*Caucasian (n=58)*	*Other (n=11)*	*Caucasian (n=61)*	*Other (n=8)*
Baseline (Visit 5)	24.8 (±1.55) (n=57)	18.9 (±3.96)	22.3 (±1.26)	21.1 (± 6.00)
Final Visit	32.2 (±3.01)	27.0 (±8.20)	56.5 (±3.47)	39.5 (±12.62)
Change	7.9 (±2.77) (n=57)	8.1 (±6.02)	34.2 (±3.47)	18.4 (± 8.04)
Gender	*Male (n=30)*	*Female (n=39)*	*Male (n=46)*	*Female(n=23)*
Baseline (Visit 5)	26.9 (±2.23)	21.4 (±1.87) (n=38)	22.2 (±1.62)	22.1 (±2.19)
Final Visit	36.6 (±4.40)	27.3 (±3.60)	52.7 (±4.19)	58.1 (±5.98)
Change	9.6 (±4.14)	6.5 (±3.08) (n=38)	30.5 (±3.87)	36.0 (±5.97)
Screening PI	*Moderate (n=49)*	*Severe (n=20)*	*Moderate (n=49)*	*Severe (n=20)*
Baseline (Visit 5)	23.2 (±1.66)	25.4 (±3.04) (n=19)	23.6 (±1.50)	18.7 (±2.42)
Final Visit	28.2 (±3.29)	39.1 (±5.20)	52.8 (±4.12)	58.7 (±6.21)
Change	4.9 (±2.71)	15.5 (±5.30) (n=19)	29.2 (±3.79)	40.0 (±6.10)
Stabilized dosage (mg/day)	*Low (20-60) (n=39)*	*High (>60) (n=30)*	*Low (20-60) (n=35)*	*High (>60) (n=34)*
Baseline (Visit 5)	23.7 (±2.19)	24.0 (±1.81) (n=29)	19.5 (±1.92)	24.9 (±1.63)
Final Visit	34.5 (±3.89)	27.3 (±4.04)	49.2 (±4.73)	60.1 (±4.84)
Change	10.8 (±3.56)	4.0 (±3.30) (n=29)	29.7 (±4.61)	35.1 (±4.60)

Secondary and other efficacy endpoints

The results of secondary and additional efficacy analyses are summarized in the table below. As shown in the table, efficacy was further supported by the effect size and the level of statistical significance in the majority of the parameters tested. A smaller proportion of patients discontinued due to lack of efficacy in the oxymorphone ER group (12%) than in the placebo group (54%). Similarly, a smaller proportion of

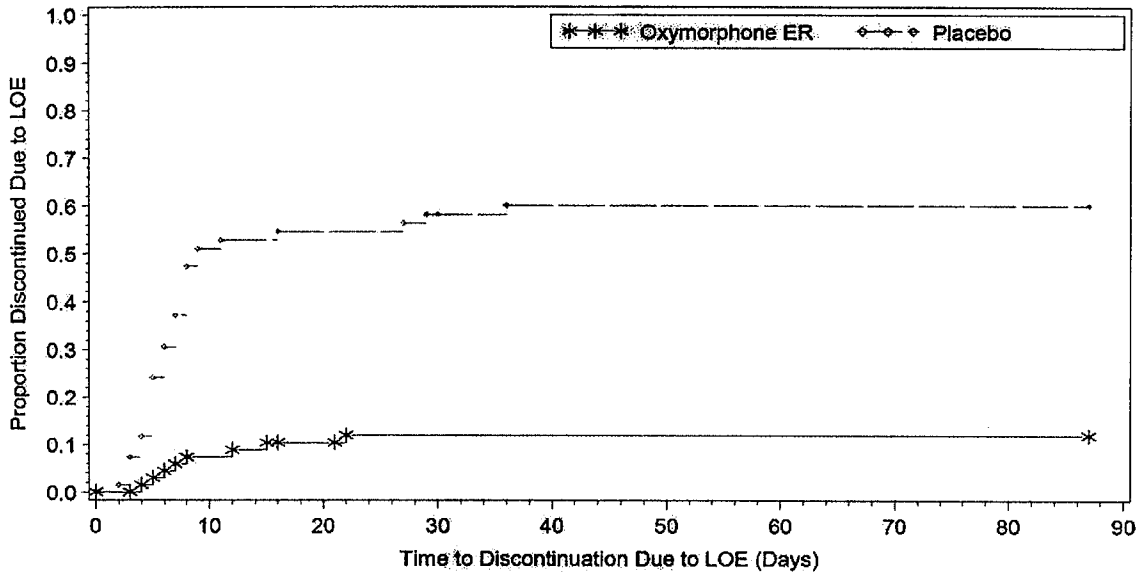
patients discontinued due to all reasons in the oxymorphone ER group (29%) than in the placebo group (74%). The proportion of patients who assessed their pain medication as good, very good, or excellent was greater in the oxymorphone ER group than in the placebo group at each visit following baseline and was 80% versus 33%, respectively, at the final visit. Physician's global evaluation of medication followed the same trend in that the proportion of evaluation as good, very good, or excellent was 85% for patients on oxymorphone ER and 28% for those on placebo. The evaluation by the Pain Quality Assessment scale revealed a much smaller change in score from baseline to final visit in patients on oxymorphone ER (5.5) than on placebo (40.5). The incorporation of patients' stabilized dose level in the model of the primary analysis did not change the magnitude of the treatment difference. A responder analysis based on the criterion of a ≥30% reduction in average PI from screening to the final visit showed a greater proportion in the oxymorphone ER group (80%) than in the placebo group (35%) that had ≥30% reduction in average pain intensity from screening to the final visit. The mean daily dose of rescue medication (oxymorphone IR) among patients who took rescue medication increased from 5.6 mg to 6.5 mg in the oxymorphone ER group and from 11.0 mg to 15.6 mg in the placebo group during the first four days (without dose restriction) of the double-blind treatment. The percentage of days over which patients took rescue in the period from Day 5 until the end of the double-blind treatment, was similar between the two treatment arms.

Table 10-17 Summary of Results for Secondary and Additional Efficacy Endpoints

	Oxymorphone ER (N=69)	Placebo (N=69)	P value	Study report reference
Secondary endpoints				
Time to discontinuation due to lack of efficacy (see Figure 10-5 below)			<0.0001	Fig 2, p71
Number (%) discontinued due to lack of efficacy	8/69, (11.6%)	37/69, (53.6%)		Table 14, p656
Patient global at final visit Proportion with good/very good/excellent	55/69 (79.7%)	22/67 (32.8%)	<0.0001	Table 13, p73
Physician global at final visit Proportion with good/very good/excellent	58/69 (84.5%)	18/65 (27.7%)	<0.0001	Table 14, p74
Change in PQAS-20 baseline to final visit LSMean	5.5	40.5	<0.0001	Table 18, p667
Additional endpoints				
Average PI by visit (See Figure 10-6 below)				Fig 3, p76
Change in PI with respect to stabilized dose level, LSMean	8.6	31.6	<0.0001	Table 19, p668
Percent reduction in average PI (see Figure 10-7 below)				Fig 4, p81
Responders: ≥30% reduction in PI	55/69 (79.7%)	23/66 (34.8%)	<0.0001	
Time to discontinuation due to all reasons (see Figure 10-8 below)			<0.0001	Fig 5, p82
Proportion discontinued due to all reasons	20/69 (29.0%)	51/69 (73.9%)		Table 15, p657
Daily rescue in first four days of double-blind treatment	↑ from 5.6 mg to 6.5 mg	↑ from 11.0 mg to 15.6 mg		Table 17, p85
% of days on rescue medication: Day 4 to final visit	61.8-70.7%	62.2-66.7%		Table 34, p697

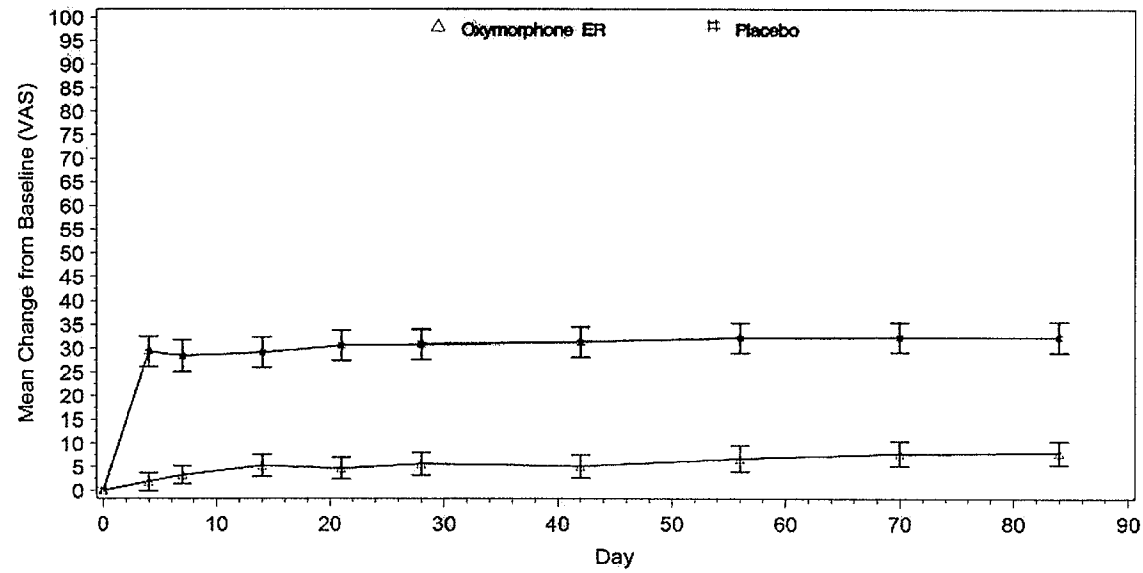
The effect size of the treatment difference in time to discontinuation due to lack of efficacy, time to discontinuation due to all reasons, and average pain intensity by visit over time during the entire course of the 12-week double-blind treatment period is presented in Figures 10-5, 10-8, and 10-6.

Figure 10-5 Time (Days) to Discontinuation Due to Lack of Efficacy (Double-Blind)



Note: p-value for treatment comparison between oxymorphone ER and placebo is <0.0001 and based on log-rank test.

Figure 10-6 Mean Change from Baseline in Average PI (VAS) by Visit (Double-Blind)



Note: Average Pain Intensity VAS scores range from 0 mm=no pain to 100 mm=the worst pain imaginable. Error bars represent standard errors (+/-)

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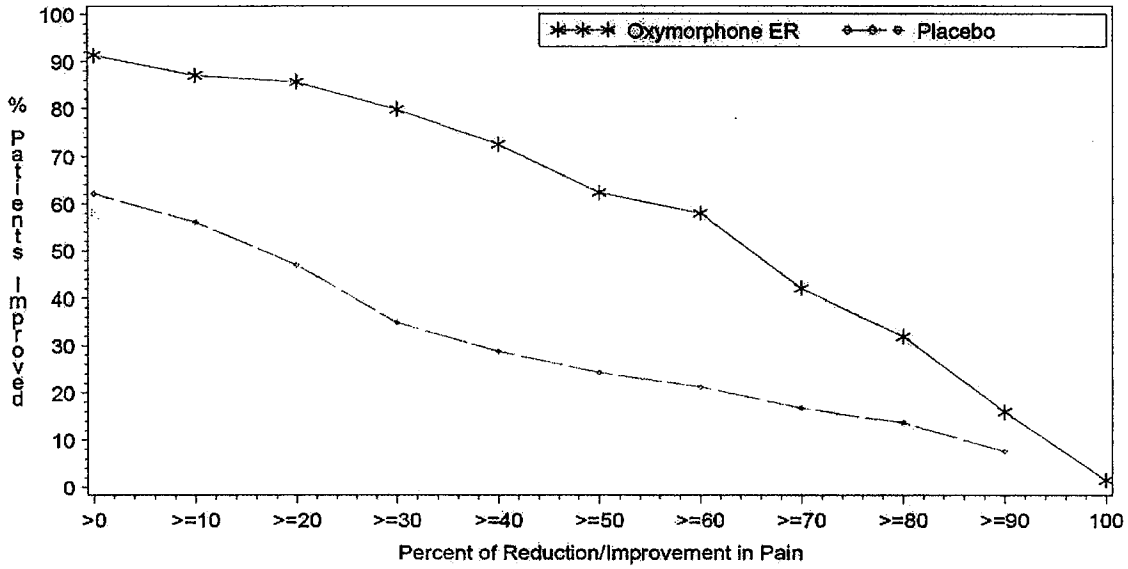
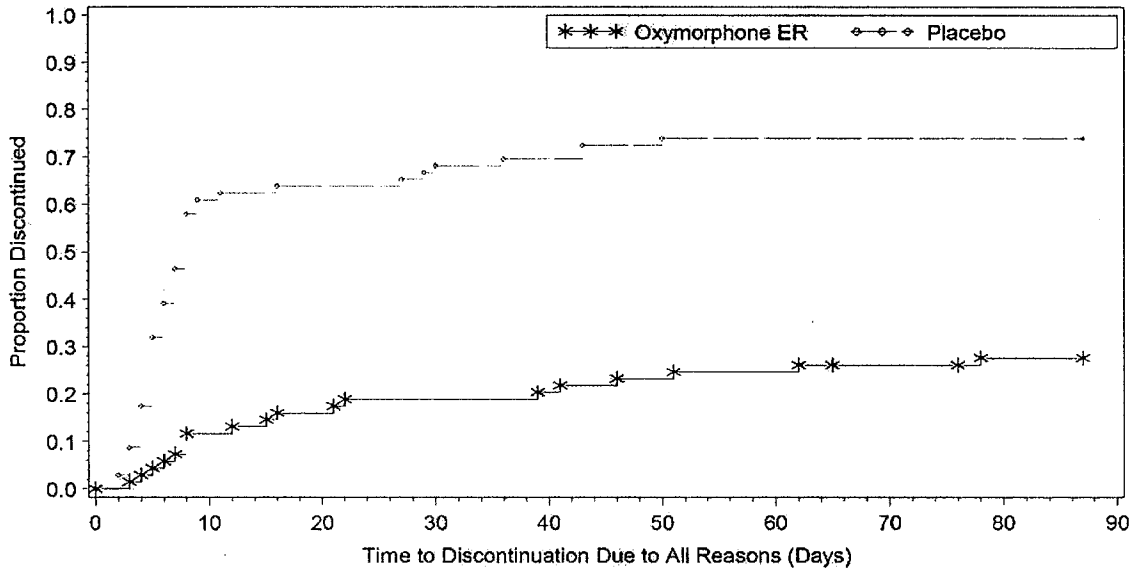
On Original

Figure 10-7 Percent Reduction in Average PI (VAS) From Screening to the Final Visit (Observed Values) (Double-Blind)



Note: No imputation rules were applied before summarizing data.

Figure 10-8 Time (Days) to Discontinuation Due to all Reasons (Double-Blind Treatment)



Note: p-value for treatment comparison between oxymorphone ER and placebo is 0.0007 and based on log-rank test.

Summary of Findings and Discussions

In this titration-to-effect, randomized withdrawal design study, enriched for opioid experienced patients with low back pain who tolerated and responded to oxymorphone ER, the treatment differences between oxymorphone ER and placebo were clearly demonstrated in all the efficacy parameters as evidenced by the level of statistical significance and clinically meaningful effect size.

The effect of the 12-week treatment was shown in the primary efficacy endpoint as a small increase in pain intensity from baseline to the final visit for the oxymorphone ER group compared to a substantial increase

in PI for the placebo group. The worsening of PI scores in the active treatment group after 12 weeks of treatment may reflect a need for a slower titration to achieve an adequate around-the-clock dose particularly in a setting of limited rescue medication. In this opioid experienced population, tolerance to a new opioid may have also played a role. Although the use of rescue during double-blind treatment might confound the efficacy results, the restriction of its use from day four to the end of treatment had been used to minimize the confounding effects of rescue.

Efficacy was further supported by the demonstration of treatment differences in the predefined secondary endpoints, time to discontinuation due to lack of efficacy, patient and physician global evaluation of medication, and pain evaluation by Pain Quality Assessment scale. Additional supportive findings included the demonstration of treatment differences in change in PI from baseline to the final visit adjusted for stabilized dose level, time-specific measure of average PI by visit, percent reduction in average PI, proportion of responders (≥30% reduction in PI), percent discontinued due to lack of efficacy, time to discontinuation and proportion discontinued due to all reasons, and the use of rescue medication over the first four days and the percent of days used during the remainder of the 12-week double-blind treatment period.

The efficacy of oxymorphone ER was demonstrated in patients treated with stabilized individual doses at a mean daily dose of about 90mg ranging from 20mg to 220mg/day (especially, in the dose range of 20 to 180mg/day).

The interpretation of the results of subgroup analyses was limited due to the small sample sizes for elderly patients, African American and Hispanic patients, and patients with severe baseline pain. The observation of a larger change in PI from baseline to the final visit in female patients (29.5) than male patients (20.9) seems to suggest a gender difference. However, the opposite result was reported in study 031. Therefore, no gender difference in treatment effects can be concluded. The data suggest a dose response of analgesic effects in that the group treated with a higher daily dose of oxymorphone ER (>60 mg) showed a greater treatment difference than the group treated with a lower daily dose (≤ 60mg).

A major problem in using a traditional, straight parallel arm design in studying opioid-type drugs for chronic pain is the very high dropout rates due to intolerance to adverse effects and tolerance to desired therapeutic effects and consequently, the issues about how to manage a huge amount of missing data. The withdrawal type design using an enriched population is one approach to address the problem upfront by eliminating the non-responders before randomization instead of waiting for them to dropout during the study. In this study, the 43% total dropout rate during the open-label titration, including an 19% dropout rate due to AEs, 7% due to failure to meet titration-stabilization criteria, and 5% due to lack of efficacy, should be taken into the consideration in trying to interpret the efficacy findings from studies with an enrichment design.

One major limitation of the titration-to-effect and withdrawal design is that it favors the active treatment arm by selecting for responders (patients able to maintain PI ≤40 mm for several days and in need of at least 20 mg daily of oxymorphone ER treatment without help of a rescue) and eliminating those who could not tolerate the active treatment (19% dropouts due to AEs) before the randomized withdrawal from the active treatment took place. Consequently, the study by design may overestimate benefit by showing greater treatment differences in responders than what would be expected from a more general sample population and underestimate toxicity by excluding those who can not tolerate the drug and thus have fewer reports of adverse events.

One concern in a randomized withdrawal design study of an opioid product is the risk for withdrawal symptoms in patients randomized to placebo. It may affect the integrity of the blinding and the pain evaluation. The use of rescue during the double-blind treatment in the study helped the placebo patients to

taper from the active treatment and to minimize opioid withdrawal (reported in five of the 73 patients assigned to placebo during the double-blind treatment period). This helps not only to maintain the integrity of the blinding but also to reduce the dropout rates. The Sponsor attempted to minimize the confounding effect of rescue by restricting its use from Day 4 to the end of the double-blind treatment period.

Drug tolerance with the continued chronic treatment in the opioid experienced population was suggested by higher dosing requirement at randomization (in comparison to what were required by opioid naïve patients in Study 031), the reduction of AEs (total AEs, individual AEs, and AE related early dropouts) during the 12-week double-blind treatment period in comparison to what were reported during the 4-week titration period, and by the worsening of pain from baseline to the final visit.

Conclusion
Oxymorphone ER at individualized dosage was shown to be effective in treating chronic low back pain in opioid experienced patients identified as responders who had reasonable tolerance to the medication (about 60% of the study population).

Appendix 1: Eligibility criteria for entering the open-label titration period

Inclusion Criteria

Candidates were going to be included in the study and entered the open-label Titration Period if they met all the inclusion criteria listed below:

1. Were males or females 18 years of age or older – If female, had to be practicing abstinence or using a medically acceptable form of contraception (e.g., intrauterine device, hormonal birth control, or barrier method in conjunction with spermicide). For the purpose of this study, all females were considered to be of childbearing potential unless they were post-menopausal (at least one year since last menses), biologically sterile, or surgically sterile (i.e., hysterectomy, bilateral oophorectomy, or tubal ligation).
2. Were in good health as determined by the investigator on the basis of medical history and physical examination.
3. Had moderate to severe chronic non-neuropathic LBP that had been present daily for at least several hours per day for a minimum of three months prior to the screening visit (Visit 1).
4. Had been on a stable around-the-clock opioid pain medication for the management of moderate to severe chronic LBP for at least two weeks prior to the Screening Visit (Visit 1). Stabilized refers to a fixed dose that balances analgesia with acceptable side effects of the opioid medication (i.e., sedation, constipation, nausea/vomiting, etc.). Stabilized does not refer to "pain free."
5. Were expected to require a total daily oxymorphone ER dose that was a minimum of 20 mg per day (oral morphine equivalent: approximately 60 mg) and would not exceed 220 mg oxymorphone ER (oral morphine requirement: approximately 660 mg)
6. Would keep unchanged, based on the patient's current status, any adjunct therapy for back pain such as physical therapy, biofeedback therapy, acupuncture therapy, or herbal remedies during the period of participation of the patient.
7. Were able to take oral medication.
8. Had provided meaningful written informed consent prior to admission to the study.

Exclusion Criteria

Patients were going to be excluded from participation if they:

1. Were pregnant and/or lactating
2. Had radiculopathy, fibromyalgia, reflex sympathetic dystrophy or causalgia (complex regional pain syndrome), acute spinal cord compression, cauda equina compression, acute nerve root compression, severe lower extremity weakness or numbness, bowel or bladder dysfunction secondary to cauda equina compression, diabetic amyotrophy, meningitis, discitis, or back pain due to secondary infection or tumor.
3. Could not or would not agree to stop local regional pain treatments during the study (nerve/plexus blocks or ablation, neurosurgical procedures for pain control, Botulinum toxin injections, or inhalation analgesia). The patient must not have had a nerve/plexus block within 4 weeks of screening (Visit 1). The patient must not have had a Botulinum toxin injection in the lower back region within 3 months of screening (Visit 1).
4. Intended to alter their physical therapy regimen during the study. Patients who began or ended physical therapy (either home exercises or formal therapy sessions) 2 weeks prior to screening or during the study period were excluded from the study.
5. Had undergone surgical procedures directed towards the source of back pain within 6 months of screening.
6. Had pain that was secondary to confirmed or suspected neoplasm.
7. Had dysphagia or difficulty swallowing tablets or capsules.
8. Had a significant prior history of substance abuse or alcohol abuse.
9. Had received any investigational medication within 30 days prior to the first dose of study medication, or were scheduled to receive an investigational drug other than oxymorphone during the course of the study.
10. Had a previous exposure to oxymorphone.
11. Had a prior history of clinically significant intolerance to oxymorphone or a known hypersensitivity to opioid analgesics.
12. Had a history of seizure. Patients with a history of juvenile febrile seizures could be included if there had been no seizure history within the past 10 years.
13. Had an ileostomy or colostomy.
14. Had received a monoamine oxidase (MAO) inhibitor within 14 days prior to the start of study medication.
15. Had any clinically significant condition that would, in the investigator's opinion, preclude study participation.
16. Were anticipated by the investigator to be unable to comply with the protocol.
17. Were unable to read, comprehend, and complete the English language informed consent form, questionnaires, and diaries.

10.3 Line-by-Line Labeling Review

The labeling will be reviewed separately.

REFERENCES

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

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Christina Fang
6/22/2006 07:05:47 PM
MEDICAL OFFICER

Sharon Hertz
6/22/2006 07:19:22 PM
MEDICAL OFFICER
I concur with the recommendation for approval.

2nd cycle

CLINICAL REVIEW

Application Type	NDA
Submission Number	21-611
Submission Code	N000
Letter Date	12-22-05, 3-28-06, 4-3-06, 5-1-06, 5-10-06, 5-23-06, 5-31-06, 6-2-06, 6-13-06, 6-14-06
PDUFA Goal Date	June 22, 2006
Reviewer Name	Christina Fang, M.D.
Review Completion Date	June 22, 2006
Established Name	Oxymorphone Immediate-Release Tablets
(Proposed) Trade Name	OPANA™
Therapeutic Class	Opioid analgesics
Applicant	Endo Pharmaceuticals Inc.
Priority Designation	3S
Formulation	Immediate-release tablets, 5 mg and 10 mg
Dosing Regimen	One oral tablet once a day
Indication	Moderate to severe acute pain
Intended Population	Adult patients in need of opioid therapy for relief of acute pain

Table of Contents

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

Oxymorphone IR (immediate-release) is recommended for approval for the relief of moderate to severe acute pain where the use of an opioid is appropriate.

The recommendation for approval is based on the acceptable benefit/risk ratio determined by evaluating the efficacy and safety data submitted in NDA 21-611.

Analgesic efficacy of oxymorphone IR 10 mg and oxymorphone IR 20 mg for the treatment of acute pain was supported by replicable positive findings from the studies of post-operative pain. The strength of evidence in support of analgesic efficacy of oxymorphone IR 10 mg and 20 mg includes a clear demonstration of multiple-dose efficacy in Study 009 and a demonstration of single-dose efficacy in all three studies for oxymorphone IR 20 mg and in one of the three studies for oxymorphone IR 10 mg.

Oxymorphone IR has a similar safety profile as the other immediate-release formulations of opioids and is considered reasonably safe to be used for the treatment of moderate to severe acute pain with a conservative starting dosage regimen of low initial dose and careful dose titration to adjust for individual's need for analgesic response and tolerance.

1.2 Recommendation on Postmarketing Actions

None.

1.2.1 Risk Management Activity

The Sponsor's proposed post-marketing Risk Management Plan (RMP) for oxymorphone products is considered acceptable in general. The additional recommendations from the Office of Drug Safety and the Controlled Substance Staff will be forwarded to the Sponsor.

1.2.2 Required Phase 4 Commitments

None.

1.2.3 Other Phase 4 Requests

There should be further studies of relative potency in comparison to the other commonly used opioids to well inform the labeling.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

In the original submission of NDA 21-610 and NDA 21-611 there were 16 Phase 1 studies and 12 Phase 2/3 studies of oxymorphone ER and IR formulations, all reviewed in detail before an approvable regulatory action was granted by the Division in October 2003. There are two new Phase 2/3 studies of the IR formulation (Studies 008 and 009) in the current submission.

1.3.2 Efficacy

The results of three trials, Studies 004, 005, and 009, are used as basis for evaluation of efficacy. The dosing regimen of 5 mg as needed (prn) and taking no more frequently than every hour for up to eight hours in Study 008, is not considered adequate in providing evidence to support efficacy.

Studies 004 and 005 had already been review in detail in the efficacy review of the original submission. They were controlled, parallel, dose response studies of post orthopedic surgical pain. Study 004 investigated 10 mg, 20 mg, and 30 mg oxymorphone doses in comparison to oxycodone 10 mg and placebo in the single-dose period and to oxycodone only in the 48-hour multiple-dose period. Study 005 was a single-dose study of 10 and 20 mg doses using oxycodone 15 and 30 mg, and placebo as controls.

Study 009 was a randomized, double-blind, placebo- and active-controlled, parallel, single- and multiple-dose (48 hours), dose response study of post-operative pain following abdominal surgery, conducted at 21 centers in the U.S.

Multiple-dose efficacy was demonstrated for oxymorphone 10 mg and 20 mg in Study 009, by the primary outcome measure as the median time to discontinuation due to all causes, as evidenced by both the level of statistical significance and clinically meaningful effect size, and supported by the secondary outcome measures, the average pain during the dosing interval, the end-of-dosing pain, and patient and physician global evaluation of study medication.

Single-dose efficacy was demonstrated for oxymorphone 20 mg by the outcome measures as time-specific pain scores (PR and PID) and summation scores (SPID and TOTPAR) in all the three studies, and for oxymorphone 10 mg in one of the three studies (Study 004). The effect sizes of the treatment differences in pain scores were relatively small. The onset of less than one hour and the single-dose duration of about four hours were shown in general. Meaningful treatment differences from placebo in onset and duration were shown only in Study 005.

1.3.3 Safety

The exposure to oxymorphone IR included 754 subjects taking at least a single dose at any dose level in the studies of oxymorphone IR and variable exposure to mostly 5mg oxymorphone IR when it was used in the studies of ER. The experience with repeated dosing at a post-operative setting included exposure to the 5 mg dose in 56 subjects (with an average of approximately five doses and an average duration of approximately seven hours) in Study 008, to the 10 mg dose in 82 subjects, to the 20 mg dose in 100 subjects, and to the 30 mg dose in 37 subjects (with an average ranging from three to five doses and an average duration of less than 24 hours) in Studies 004 and 009. Although there has been limited experience with long-term use of the IR formulation at 20 mg level the extensive experience with the use of ER formulation at much higher levels and for much longer periods (refer to the review of NDA 21-610 for detail) provides supportive evidence for drug safety.

There were 14 new reports of deaths (13 cancer deaths and one non-cancer death), in addition to 35 deaths reviewed with the original submission, in the studies of the ER formulation. The causes of deaths were most likely attributable to complications associated with the disease progression of end-stage cancer (most cases had only 0.5-2.5 months of oxymorphone treatment preceding death) in 13 cancer deaths and attributable to community-acquired pneumonia in one non-cancer death based on the review of narratives.

In the Overall safety database serious AEs were reported in 25 (4.5%) of oxymorphone IR-treated subjects, 11 (4.0%) of oxycodone IR-treated subjects, and 9 (3.3%) of placebo subjects. In the oxymorphone IR

group the most common (0.5%) serious AEs were myocardial infarction and deep limb venous thrombosis, with 3 cases of each identified in the original ISS database. There was only one new case in the Update safety database under the category of serious cardiac AEs in a patient with tachycardia, which occurred a day after a single dose of oxymorphone IR 10 mg, spontaneously resolved, and not considered to be caused by oxymorphone IR treatment based on the review of narrative.

The Overall **dropout** rate was 42% in the oxymorphone IR group, 34% in the oxycodone IR group, and 58% in the placebo group. AEs were the second most common reason for dropouts for all the treatment groups, next to the lack of efficacy, and caused 9.9% dropouts in the oxymorphone IR group, 6.5% in the oxycodone IR group, and 8.3% in the placebo group. The most common (>1%) causes of AE-related dropouts in the oxymorphone ER group were nausea (2.5%), vomiting (2.2%), somnolence (1.1%), and sedation (1.1%), the CNS and GI systems commonly associated with the use of opioid drugs.

The cases identified as oxymorphone IR-related respiratory/CNS depression requiring naloxone treatment in the ISS database appeared to be dosage (higher dose levels and/or more frequent dosing frequency) and age related.

The incidence rates of the most common AEs were similar for the oxymorphone IR (63%) and oxycodone IR (62%) groups and much less in the placebo group (42%). The most frequently occurring AEs in patients treated with oxymorphone ER were basically events expected in opioid users: nausea (19.0%), pyrexia (14.2%), somnolence (9.3%), vomiting (9.0%), pruritus (7.9%), headache (6.8%), dizziness (excluding vertigo, 6.5%), and constipation (4.1%). Except pyrexia the same set of symptoms was identified as the most common treatment-related AEs.

Laboratory tests were not conducted in any of the new studies in the current submission. The review of laboratory findings suggested no safety signals for treatment-related decrease in WBC count, neutropenia (which were mostly due to laboratory sample mishandling), or LFT elevation.

Vital signs were recorded in the two controlled studies (031 and 032) of oxymorphone ER in the current submission to NDA 21-610. Other than a trend of small decrease in systolic and diastolic blood pressure in the first few weeks of the open-label treatment period in Study 031, there were no remarkable trends based on the changes in group mean values.

Based on the reanalysis of ECG data of the identified cases, QTc prolongation was mainly due to in treatment fluctuation because most of the QTc abnormalities were normalized upon rechallenge with the same or different oxymorphone formulations and the end-of-study measurements were normal in six of the seven cases. The ECG data from retrospective partial recollection of subjects treated in Studies 015, 020, and 025 provided no additional evidence for treatment-related QTc prolongation.

Eight cases of discontinuation due to opioid withdrawal symptoms were identified in Studies 031 and 032 of oxymorphone ER, although the group mean scores of COWS and ARS at each scheduled visit during the double-blind treatment did not show the signs of opiate withdrawal in the two treatment groups.

One case of on-study pregnancy was reported in Study 032 and ended as an elective abortion.

There were no new reports of overdose in the current submission.

There appeared to be an age-related increase in the incidence rates of dizziness, somnolence, and confusion associated with oxymorphone IR treatment. The other observed higher incidence rates of some AEs in one subpopulation versus the other were probably due to normal variations.

1.3.4 Dosing Regimen and Administration

The proposed starting dose of 10 mg to 20 mg q4-6h as needed (prn) for opioid naïve patients is supported by clinical data. A low starting dose of 5 mg is considered reasonable in initiating treatment in high risk patients. However, the proposed dosage of 5 mg q2h is not supported by substantial evidence. Dosing as frequently as every two hours should not be encouraged in the use of drugs of high abuse potential.

1.3.5 Drug-Drug Interactions

There were no new studies of drug-drug interactions in the current submission.

1.3.6 Special Populations

Elderly patients have been shown to have increased risks to oxymorphone-induced respiratory/CNS depression at higher starting doses in a post-operative setting based on the results of studies in the original submission. There was also an age-related increase in incidence rates of dizziness and somnolence. Because elderly patients are at higher risk to oxymorphone-induced drug toxicity as a result of higher levels of systemic exposure (about a 40% increase in total and maximum drug levels in comparison to younger subjects), oxymorphone treatment should be started at lower levels with gradual titration under closer supervision.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

The established name of the product is oxymorphone hydrochloride (HCL) and the proposed name is OPANA™. The excipients in the drug product formulation are lactose monohydrate (NF), Pregelatinized starch (NF), and magnesium stearate (NF). Oxymorphone HCL is a semi-synthetic opioid-receptor agonist with the proposed mechanism of action at multiple CNS sites though interaction with opioid receptors.

The proposed indication is for the relief of moderate to severe pain where the use of an opioid is appropriate.

The proposed adult dosage for opioid naïve patients is to start at 10 mg to 20 mg q4-6h as needed (prn), or to start at 5 mg q2h if necessary, followed by individualized titration based upon the individual patient's response to their initial dose, and for opioid experienced patients, to convert from other opioids.

2.2 Currently Available Treatment for Indications

The currently available treatments for the indication are mainly opioid analgesics, combination products containing an opioid as an active ingredient, and tramadol.

2.3 Availability of Proposed Active Ingredient in the United States

The currently available drug products containing the active ingredient oxymorphone are Numorphan® injection 1 mg/ml and 1.5 mg/ml by subcutaneous, intramuscular, and intravenous administration (NDA 11-707) and Numorphan® oxymorphone rectal suppositories 5 mg (NDA 11-738). Oxymorphone IR approved in 1959 was removed from the market for commercial reasons. The 2 mg and 5 mg tablets were removed after seven years of marketing and the 10 mg tablet was removed after 11 years of marketing.

2.4 Important Issues with Pharmacologically Related Products

As an opioid agonist oxymorphone has similar pharmacological effects as the other drugs of the same class as described in the product labeling for opioid drugs. The major safety issues with the use of opioids are their potential for misuse, drug abuse and addiction and the potential for respiratory depression, especially in the elderly or debilitated patients, as well as in those suffering from conditions accompanied by hypoxia or hypercapnia when even moderate therapeutic doses may dangerously decrease pulmonary ventilation. The interaction of opioids with alcohol and drugs of abuse and with other CNS depressants may cause respiratory depression, hypotension, profound sedation, or coma.

2.5 Presubmission Regulatory Activity

The original submission of NDA 21-611 for oxymorphone IR dated December 20, 2002, was granted approvable by the Division on October 15, 2003. The Sponsor was requested to address a number of clinical deficiencies, which included providing additional data, including multiple-dose data, to support the safe and effective use of oxymorphone IR in an appropriate opioid-naïve population and the safe use of the product in the postoperative setting or other appropriate clinical setting, and to support a safe and effective dosing interval, as well as additional data to address safety concerns regarding liver function, WBC count,

and QTC interval. In the subsequent interactions with the Sponsor as recorded in the meeting/teleconference minutes dated October 31, 2003, March 16, 2004, and May 25, 2004 the need for additional evidence to support efficacy, especially, efficacy and safety data to support a proper dosing interval was re-emphasized. The Sponsor's explanations for laboratory abnormality were accepted, and QTC abnormality was still a safety concern requiring further investigation. On May 6, 2004, a new protocol (Study 009) was submitted under Special Protocol Assessment (SPA) for studying short-term multiple-dose effects with focus on dosing interval, in patients with post-operative pain from abdominal surgery.

2.6 Other Relevant Background Information

There were two phase 2/3 studies of oxymorphone IR submitted in the first review cycle and both were controlled, parallel, dose response studies of post orthopedic surgical pain. Study 004 investigated 10 mg, 20 mg, and 30 mg oxymorphone doses in comparison to oxycodone 10 mg and placebo in the single-dose period and to oxycodone only in the 48-hour multiple-dose period. Study 005 was a single-dose study of 10 and 20 mg doses using oxycodone 15 and 30 mg, and placebo as controls.

The single-dose effects measured by pain scores were shown for oxymorphone IR 20 mg in both studies, for oxymorphone IR 10mg in one of the two studies (Study 004), and for oxymorphone IR 30 mg (only included in one trial).

The onset of analgesia was within one half hour in terms of perceptible relief for all the treatment groups, and about one hour in terms of meaningful relief for all the active treatments in both studies. The onset of meaningful relief was one hour for the active treatment groups versus 1.5 hours for placebo in Study 004 and one hour versus eight hours in Study 005.

The duration of single-dose effect measured by median time to remedication was about four hours for oxymorphone 20 and 30 mg doses and three hours for oxymorphone IR 10mg, oxycodone 10mg, and placebo in Study 004 and 3.5-5 hours for all the active treatment groups in comparison to two hours in placebo.

The multiple-dose efficacy could not be adequately evaluated due to limitations in study design.

Safe and efficacious use of 30 mg dose as an acute analgesia in a post-operative setting was questionable due to the findings of increased need for naloxone treatment for drug-induced CNS/respiratory depression accompanied by no additional benefits in efficacy.

Another NDA for the drug product containing the same active ingredient in different formulation submitted originally at about the same time (December 20, 2002) was NDA 21-610 for oxymorphone extended-release (ER) formulation. The two NDAs have been resubmitted on the same date. The efficacy and safety of oxymorphone ER will be reviewed separately.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

Refer to the chemistry review.

3.2 Animal Pharmacology/Toxicology

Refer to the pharmacology/toxicology review.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

Efficacy data are from Study 009 in the current submission and are supplemented by efficacy data from Studies 004 and 005 in the original submission. Safety data new to the current submission in the Update Safety database are from the two newly completed studies: Study 008 and 009. Overall safety data from all phase 2/3 studies of oxymorphone IR are also used in the safety review.

4.2 Tables of Clinical Studies

Table 4-1 Summary of Newly Completed Clinical Studies Used as Data Sources

Protocol # # of sites	Study Type	Study Design	Dates of Study	Dosage	# of subj	Mean age/range (y) (range) Gender (M, F) Race (W, NW)	Data relevance
EN3203-008 7 sites	Efficacy and safety; adults mild to moderate pain following outpatient knee arthroscopy	Multi-center, randomized, double-blind, placebo-controlled	4/17/03 – 6/27/03	OM IR 5 tab Placebo tab prn (no sooner than q1h) up to 8 hrs	122	44.8-45.0 (18-76) 52 M, 70 F 102 W, 20 NW	Safety
EN3203-009 23 sites with 22 investigators	Efficacy and safety, patients with moderate/severe pain following abdominal surgery	Randomized, double-blind, placebo- and active-controlled, single- and multiple-dose	9/1/04-8/15/05	OM IR 10 tab OM IR 20 tab OC IR 15 tab Placebo q4-6h for 48 hrs	331	42.6 (18-83) 4M, 327 F 215 W, 116 NW	Efficacy and safety

Source: Supplemental Table 2 on pages 70 to 77 of the updated safety report.

4.3 Review Strategy

Efficacy study 009 is reviewed in detail in Section 10 and the results of the three efficacy studies, Study 009 in the current submission and Study 004 and 005 in the original submission, are discussed together in Section 6. Review of safety is based on the pooled safety data from all phase 2/3 studies grouped into three categories: the Updated Safety database consisted of data from the new studies (Studies 008 and 009) in the current submission, the ISS Safety database consisted of safety data already reviewed in the first review cycle, and the Overall Safety database combining the two.

4.4 Data Quality and Integrity

Two clinical sites, Site 15 (with enrollment of 39 patients) and Site 28 (with enrollment of 52 patients) in Study 009, were selected for inspection. Inspection of Site 15 (Investigator: Neil Singla, M.D.) revealed one discrepancy in the length of time one subject participated in study 009. Inspection of Site 28 (Investigator: Keith Aqua, M.D.) revealed no discrepancy in efficacy data for protocol defined endpoints. However, several cases of protocol violation of entry criteria, inadequate documentation of medical history, and inadequate/inaccurate documentation of rescue medication were identified.

4.5 Compliance with Good Clinical Practices

The steps to ensure the accuracy and reliability of data included the selection of qualified Investigators and appropriate study centers, review of protocol procedures with the Investigators and associated personnel prior to the start of the study, and periodic monitoring visits by Sponsor personnel. Sponsor personnel reviewed CRFs for accuracy and completeness before, during, and after on-site monitoring visits; any discrepancies were resolved with the Investigator or designee, as appropriate. CRF data were entered into a clinical database by the electronic data capture system. After the resolution of data queries, the database was locked and the data transferred to the statistician.

Selective audits of four sites, Site 28 (52 patients), Site 15, (39 patients), and Site 01 and 35 (the 2 sites with 36 patients enrolled by the same Investigator, Joseph Gimbel, M.D.), with a total enrollment of 127 patients in Study 009, were performed by Endo Pharmaceuticals Inc. to evaluate compliance with Good Clinical Practice guidelines according to the requirements of Endo's Quality Assurance Audit Plan. The Sponsor provided the audit certificate in the submission.

4.6 Financial Disclosures

The financial disclosure form signed by the Sponsor certified that no financial arrangements had been made, where outcomes affects compensation, with any Principle Investigator or sub-investigators involved in the clinical studies, and that these Investigators had no proprietary, significant equity interest, or any significant payments of other sorts as defined in 21 CFR 54.2(f).

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

Refer to the clinical pharmacology review.

5.2 Pharmacodynamics

Refer to the clinical pharmacology review.

5.3 Exposure-Response Relationships

Refer to the clinical pharmacology review.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The proposed indication for the oxymorphone immediate-release formulation is for the relief of moderate to severe pain where the use of an opioid is appropriate.

6.2 Methods

There were two controlled efficacy studies, EN3202-008 and EN3202-009 submitted with the current submission. Study 008 was considered exploratory in nature because of its innovative study methodology and thus was briefly described in Section 10. The results of Study 009 are reviewed in detail in Section 10 and discussed together with the findings of the single-dose effects reported in Studies 004 and 005, which were documented in the clinical reviews of the original submission.

6.3 General Discussion of Endpoints

The efficacy endpoints in study 009 are listed below:
Primary efficacy endpoint:
Time to discontinuation due to all causes during the entire study (0-48 hours)

Secondary efficacy endpoints:

For multiple-dose phase

- Mean average pain intensity
- Mean current pain intensity
- Patient global evaluation of study medication
- Physician global evaluation of study medication

For single-dose phase

- 6-Hour Sum of Pain Intensity Differences (SPID; VAS and categorical)
- 6-Hour Total Pain Relief Scores (TOTPAR; VAS and categorical)
- Time (in hours) to First Perceptible Pain Relief
- Time (in hours) to Meaningful Pain Relief
- Hourly Pain Relief Scores
- Hourly Pain Intensity Difference Scores

Additional efficacy endpoint (post hoc analysis by request of the medical reviewer):

- Time to rescue medication or remedication in the first six hours after the initial dose

The single-dose data from previous studies (Study 004 and 005) had suggested a dosing interval of four to six hours for oxymorphone IR. With the assumption that a dosing interval of every four to six hours might work with repeated dosing, the Sponsor's strategy to optimize the response was to remove non responders by discontinue patients who wither requested rescue/remedication before the time for next dose at 4 hours, or did not need remedication within six hours from previous dose, and to use the time to discontinuation during the study as the primary efficacy endpoint. This type of primary efficacy endpoint had not been used commonly in the short-term multiple-dose analgesic trials. Most short-term studies use pain evaluation as the primary endpoint and allow rescue during the study to minimize dropouts due to lack of efficacy. The use of time to discontinuation could minimize concerns about the confounding from rescue medication and seems to be a reasonable approach when the objective is to study the dosing interval upon repeated use. The set of the secondary efficacy endpoints was considered appropriate because it included the measurements of end-of-dosing pain and patient global evaluation of the study medication. The endpoints selected originally for the evaluation of the initial dose in Study 009 did not include time to rescue/remedication as a measure of single-dose duration. Time-specific pain measurements at scheduled time points, onset, and duration together are considered the most important parameters in characterizing single-dose effects.

6.4 Study Design

Study 009 was a randomized, double-blind, placebo- and active-controlled, parallel, single- and multiple-dose (48 hours), dose response study of post-operative pain following abdominal surgery, conducted at 21 centers in the U.S.

The **design** of the trial was aimed at whether the proposed dosing interval of every four to six hour was adequate to support efficacy by using a strategy of dropping out patients who needed remedication/rescue before Hour 4 and those who did not need the next dose before Hour 6, and using time to discontinuation as the primary endpoint. There are several advantages with this approach. It selects responders by eliminating those who have too much or too little pain by the time for redosing, and it eliminates the problem in dealing with missing data in the primary analysis or dealing with confounding effects from the rescue medication.

The choice of **active control,** oxycodone IR 15 mg was considered reasonable as suggested by the results of previous studies (004 and 005), in which oxycodone IR 15 mg and 30 mg were shown to be effective but not the 10 mg dose level. The **relative potency** of oxymorphone in comparison to other approved immediate-release opioid analgesics could not be reasonably determined because of the small number of dose levels involved.

The **study population** consisting of patients with post-operative pain following abdominal surgery was appropriate in studying drugs indicated for moderate to severe pain. The inclusion/exclusion criteria defined a typical sample population eligible for acute analgesic studies.

The choice of **dose levels** (10 mg and 20 mg of oxymorphone) and dosing interval (every four to six hours) of study medication was based on the information obtained from previous controlled trials, Studies 004 and 005, in which the single-dose effects of oxymorphone 20 mg were demonstrated in both studies and that of oxymorphone 10 mg in one of the two studies. The use of flexible **dosing frequency** made it very difficult in attempts to present and interpret pain scores over time represented by 'pain curves' because of the intrapersonal and interpersonal variations in the length of actual dosing intervals. Nevertheless, the impact of flexible dosing frequency was only on periodic pain measurements, which were planned as secondary endpoints in the multiple-dose period.

The 48-hour **treatment duration** was not unusual in studying a drug to be dosed every four to six hours in a post-operative setting.

6.5 Efficacy Findings

The results of the treatment comparison between the active treatment groups and placebo are summarized in terms of multiple-dose effects (Study 009) and single-dose effects (Studies 009, 005, and 004).

Multiple-dose effects

As shown in the table below the multiple-dose effects were demonstrated for both 10 mg and 20 mg doses of oxymorphone IR, by **statistically significant treatment differences** from placebo in terms of time to discontinuation due to all causes, mean scores of average pain during the dosing interval, mean scores of end-of-dosing pain, and patient global evaluation of study medication. The treatment differences not reaching statistical significance included physician global for oxymorphone IR 10 mg, and both patient and physician global evaluations for oxycodone IR 15 mg. **Effect size** of the statistically significant treatment difference was remarkable as described below:

- The median time to discontinuation due to all causes during the entire 48-hour period (**primary endpoint**), was 13 to 15 hours longer for the oxymorphone treatment groups than for placebo (20 hours for oxymorphone IR 20 mg, 18 hours for oxymorphone IR 10 mg, and 24 hours for oxycodone IR 15 mg versus five hours for placebo).

- The average pain during the dosing interval measured by LSMean was 10 mm to 15 mm lower for the active treatment groups than for the placebo treatment (35 mm for oxymorphone IR 20 mg, 40 mm for oxymorphone IR 10 mg and oxycodone IR 15 mg treatment versus 50 mm for placebo).

- The end-of-dosing pain measured by LSMean was 13 mm to 18 mm lower for the active treatment groups than for placebo (45 mm for oxymorphone IR 20 mg, 50 mm for oxymorphone IR 10 mg, and 47 mm for oxycodone IR 15 mg versus 63 mm for placebo).

- The proportion of patients who assessed their pain medication as good, very good, or excellent at the 48-hour evaluation was at least 17% higher in the active treatment groups than the placebo group (68% for oxymorphone IR 20 mg, 62% for oxymorphone IR 10 mg, and 69% for oxycodone IR 15 mg versus 45% for placebo).

- The proportion of physicians who evaluated their patient's medication as good, very good, or excellent was 16% higher for patients in the oxymorphone ER 20 mg group than the placebo group (64% for oxymorphone IR 20 mg, 59% for oxymorphone IR 10 mg, and 63% for oxycodone IR 15 mg versus 48% for placebo).

Table 6-1 Summary of Multiple-Dose Effects in Study 009

	Oxymorphone IR 10 mg (N=81)	Oxymorphone IR 20 mg (N=81)	Oxycodone IR 15 mg (N=83)	Placebo (N=85)
Primary				
Median time to discontinuation (hour:minute) (95% CI)	**17:55 (4:30,32:35)**	**20:15 (6:00,)**	**24:05 (5:00,)**	**4:50 (3:22, 7:30)**
	p=0.0057	***p=0.0017***	***p=0.0014***	--
Secondary				
Average pain in dosing interval LSMean	39.7	35.2	39.8	50.1
	p=0.0042	***p< 0.0001***	***p=0.0042***	--
End-of-dosing pain, LSMean	49.6	44.9	47.0	63.0
	p=0.0037	***p< 0.0001***	***p=0.0005***	--
Patient global: proportion ≥good	49/79 (62.03)	52/77 (67.53)	56/81(69.14)	37/82 (45.12)
Patient global at 48 hours	***p=0.018***	***p=0.005***	*p=0.122*	--
Physician global: proportion ≥good	47/80 (58.75)	50/78 (64.10)	51/81 (62.96)	39/81 (48.15)
Physician global at 48 hours	*p=0.215*	***p=0.020***	*p=0.648*	--

Single-dose effects

Statistically significant treatment differences from placebo for the time-specific pain scores (PR and PID) and summation scores (SPID and TOTPAR) in the three studies (009, 005, and 004), were demonstrated over various time intervals for oxymorphone 20 mg in all three studies and for oxymorphone 10 mg in one of the three studies as summarized in Tables 2 and 4 below. The VAS appeared more sensitive in detecting early changes compared to placebo in Study 009, while the categorical scale appeared to be more sensitive in Studies 004 and 005.

Table 6-2 Single-Dose Effects: Summary of Time-Specific Measures

Efficacy parameter	Oxymorphone IR 10mg		Oxymorphone IR 20mg		Oxycodone IR 15mg	
	Categorical	VAS	Categorical	VAS	Categorical	VAS
Study 009						
PR	4h	None	3-6h	**0.75-6h**	3-6h	4-5h

PID	3-6h	None	3-6h	**0.75-6h**	4-6h	3-6h
Study 005						
PR	None	None	**1-8h**	**2-8h**	**1-8h**	**1-8h**
PID	None	2h	**0.75-8h**	**1-8h**	**0.75-8h**	**1-8h**
Study 004						
PR	2-3h, 5-8h	--	**0.75-8h**	--	--	--
PID	**0.75h, 2-8h**	**1.5-8h**	**0.75-8h**	**0.75, 1.5-8h**	--	--

Note: the time or time intervals included only the significant results from pairwise comparison when the overall treatment effect was significant at the specific time point.

The **effect size** for the treatment difference from placebo at the two hour scheduled measurement (which is within the time window for the maximum effect) is summarized in the table below. The effect size for the mean pain relief scores at two hours is included to provide a more complete picture of the treatment difference. The effect size for pain scores and for treatment differences in pain sores from placebo were relatively small in these studies. For example a categorical pain relief score of 2 represents some relief. The peak (2-hour value) mean PR scores was about 2 or slightly above 2 for oxymorphone IR 20 mg and oxycodone IR 15 mg and slightly below 2 for oxymorphone IR 10 mg. There was a >0.5 unit difference in PR from placebo in two of the three trials for oxymorphone IR 20 mg, in one of the three trials for oxycodone IR 15 mg, and none of the studies for oxymorphone IR 10 mg.

Table 6-3 Single-Dose Effects: Summary of Effect Size of Treatment Difference from Placebo in PR and PID at two Hours

Efficacy parameter	Oxymorphone IR 10mg		Oxymorphone IR 20mg		Oxycodone IR 15mg	
	Categorical	VAS	Categorical	VAS	Categorical	VAS
Study 009						
PR	0.2 (PR=1.9)	5.5	0.4 (PR=2.1)	**18**	0.3 (PR=2.0)	10.3
PID	0.2	6.5	0.3	**13.5**	0.2	9.3
Study 005						
PR	0.5 (PR=1.8)	10.8	**0.7** (PR=2.0)	**16.9**	**1.0** (PR=2.3)	**22.6**
PID	0.3	13.1	**0.5**	**22.9**	**0.7**	**26.7**
Study 004						
PR	0.5 (PR=1.8)	--	**0.9** (PR=2.2)	--	--	--
PID	**0.4**	**15.1**	**0.7**	**20.1**	--	--

The **effect size** for treatment differences in **summation scores**, TOTPAR and SPID was variable. The summation scores of the oxymorphone IR 20 mg group and the oxycodone IR 15 mg group were fairly consistently superior to placebo in contrast to the oxymorphone IR 10 mg group.

Table 6-4 Single-Dose Effects: Summary of Difference in Summation Scores (TOTPAR and SPID) from Placebo (LSmean)

	Oxymorphone IR 10mg		Oxymorphone IR 20mg		Oxycodone IR 15mg	
	Categorical	VAS	Categorical	VAS	Categorical	VAS
Study 009	n=80		n=80		n=83	
$TOTPAR_{0-6}$	1.8 p=0.070	14.0 p=0.614	3.5 **p=< 0.001**	86.4 **p=0.002**	2.3 **p=0.022**	41.1 **p=0.135**
$SPID_{0-6}$	1.4 **p=0.037**	39.9 p=0.080	2.2 **p=0.001**	81.3 **p< 0.001**	1.6 **p=0.019**	63.7 **p=0.005**
Study 005	n=56		n=65		n=62	
$TOTPAR_{0-6}$	1.7 p=0.145	44.4 p=0.167	3.9 **p< 0.001**	98.9 **p=0.001**	4.3 **p< 0.001**	103.4 **p=0.001**
$SPID_{0-6}$	0.9 p=0.248	45.7 p=0.087	2.7 **p< 0.001**	118.4 **p< 0.001**	3.1 **p< 0.001**	106.3 **p< 0.001**
Study 004	n=51		n=51			
$TOTPAR_{0-6}$	2.7 **p=0.018**	--	4.4 **p< 0.001**	--	--	--
$SPID_{0-6}$	2.7 **p< 0.001**	87.2 **p< 0.001**	3.9 **p< 0.001**	124.4 **p< 0.001**	--	--

The single-dose effects in terms of **onset and duration** for the three studies are summarized in the table below. The median **time to first perceptible pain relief** was less than half hour across the treatment groups (including placebo) in all three studies. The **median time to meaningful pain relief** was less than

50 minutes for all the treatment groups in Study 009. It was about one hour for all the active treatment groups in Studies 004 and 005. The half hour difference in onset of meaningful relief from placebo in Study 004 and the 7-hour difference in onset of meaningful relief from placebo in Study 005 were statistically significant. The **median time to rescue/remedication** after the initial dose (0-6 hours) was about four hours for all the treatment groups in Study 009; about five hours for oxymorphone IR 20 mg and oxycodone IR 15 mg, 3.5 hours for oxymorphone IR 10 mg, and two hours for placebo in Study 005; and four hours for oxymorphone IR 20 mg and three hours for oxymorphone IR 10 mg and placebo in Study 004. The one hour difference in duration in Study 004 and 1.5 to 3-hour differences in duration in Study 005 were statistically significant. In general, the data showed an onset of one hour or less for oxymorphone treatments and a single-dose duration of four to five hours for oxymorphone IR 20 mg and three to four hours for oxymorphone IR 10 mg.

Table 6-5 Single-Dose Effects: Summary of Onset and Duration Data from Study 009, 005, and 004

Statistics	Oxymorphone IR 10mg	Oxymorphone IR 20mg	Oxycodone IR 15mg	Placebo
Median time to first perceptible pain relief (hour:minute) (95% CI)				
Study 009	0:15 (0:12, 0:22)	0:12 (0:08, 0:15)	0:15 (0:10, 0:23)	0:15 (0:12, 0:20)
Study 005	0:15 (0:12, 0:23)	0:20 (0:16, 0:29)	0:15 (0:14, 0:22)	0:15 (0:12, 0:20)
Study 004	0:23 (0:16, 0:30)	0:15 (0:13, 0:28)	--	0:15 (0:13, 0:20)
Median time to meaningful pain relief (hour:minute) (95% CI)				
Study 009	0:40 (0:33, 1:10)	0:34 (0:25, 1:00)	0:45 (0:30, 1:39)	0:41 (0:30, 1:30)
Study 005	**1:01 (0:46, 3:00)**	**0:53 (0:46, 2:01)**	**1:03 (0:46, 2:00)**	8:00 (1:41, >8:00)
Study 004	**1:02 (0:43, 1:24)**	**0:59 (0:46, 1:28)**	--	1:30 (1:20, >8:00)
Median time to rescue/remedication (hour:minute) (95% CI)				
Study 009	4:00 (4:00, 4:10)	**4:10 (4:04, 4:50)**	**4:06 (4:00, 4:30)**	4:00 (3:55, 4:02)
Study 005	**3:34 (2:29, 4:25)**	**4:53 (3:35, 6:00)**	**4:50 (3:47, 5:30)**	2:00 (1:39, 2:15)
Study 004	3:04 (2:55, 4:02)	**4:00 (3:20, 4:35)**	--	3:05 (3:00, 3:15)

Note: statistically significant treatment differences were highlighted in the table.

The factors that might have potential impact on the study results of Studies 004 and 005 were discussed in the efficacy reviews of the original submission and will not be repeated here.

In Study 009 the treatment groups were basically balanced with regard to demographic and baseline characteristics such as age, gender, race, and baseline pain intensity. The only noticeable difference was that fewer patients had severe pain (9%) in the oxymorphone IR 20 mg group compared to the other three treatment groups (14% to 17%).

The differential dropout rate was 35% for oxymorphone IR 20 mg, 41% for oxymorphone IR 10 mg and oxycodone IR 15 mg, versus 47% for placebo in the single-dose period and about 60% in the active treatment groups versus 80% in the placebo group in the 48-hour multiple-dose period. The high dropout rates due to lack of efficacy cross the treatment groups during the first 6 hours and the entire 48-hour period were expected in a post-operative setting when rescue analgesics were not allowed during the study (patients taking rescue were designated as treatment failures). The dropout rate due to lack of efficacy in the placebo group was high as expected, 15% higher than the oxymorphone IR 20 mg group during the single-dose period and 30% higher than the oxymorphone IR 20 mg group and 20% higher than the oxymorphone IR 10 mg group during the multiple-dose period. The dropout (5-10%) due to withdrawal of consent mainly reflected the group that no longer had pain.

The protocol deviations of having remedication outside the specified windows in 17 patients and having their data included in the efficacy analyses in Study 009 are not expected to change the efficacy results dramatically because the deviation occurred in a few patients in each treatment group and because the effect size of the treatment difference in time to discontinuation due to all causes was large.

The study protocol-defined ITT population consisted of randomized patients taking at least one dose of study medication and completed at least one post dose efficacy evaluation in Study 009, which is not considered acceptable to this reviewer. Two patients, one from each of the two oxymorphone treatment groups, were excluded from single-dose analysis for not having any post-dose diary data. One patient on oxymorphone IR 10 mg was excluded from all efficacy analyses because of providing consent for the study after surgery. The exclusions were considered unacceptable but unlikely to change the study results and efficacy conclusion if data would have been reanalyzed.

Because of the relatively small sample size for the subpopulations of elderly (estimates from the group mean and standard deviation), male, non-Caucasian ethnic groups, and patients with severe pain at screening, the treatment differences with respect to these demographic and baseline characteristics could not be adequately evaluated. The efficacy results in Study 009 were basically obtained from a mostly female study population because all the study subjects except one in each treatment group were female.

6.6 Clinical Microbiology

Not applicable.

6.7 Efficacy Conclusions

The strength of evidence in support of analgesic efficacy of oxymorphone IR 10 mg and 20 mg includes a clear demonstration of multiple-dose efficacy in Study 009 and a demonstration of single-dose efficacy in all three studies for oxymorphone IR 20 mg and in one of the three studies for oxymorphone IR 10 mg.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

7.1.1 Deaths

A total of 49 deaths had been reported from all clinical trials in the oxymorphone development program. In addition to the 35 cases of deaths (34 cancer death and one non-cancer death) discussed in the safety review of the original submission, there were 14 cases of deaths reported in patients on oxymorphone treatment in the current submission. Thirteen of the 14 cases in the open-label safety studies (one case in Study 021, one case in Study 028, and 11 cases in Study 029) were cancer deaths most likely attributable to complications associated with the disease progression of end-stage cancer (most cases had only 0.5-2.5 months of oxymorphone treatment preceding deaths) based on the review of narratives. One death was reported from the study of low back pain (Study 032). The cause of death was unlikely to be related to the study drug based on the review of the narrative (refer to the safety review of NDA 21-610). No deaths were reported in any of the studies involving only the IR formulation.

7.1.2 Other Serious Adverse Events

In the **Overall database** 25 (4.5%) oxymorphone IR-treated subjects, 11 (4.0%) oxycodone IR-treated subjects and nine (3.3%) placebo subjects experienced one or more SAE during their participation in the studies. Incidence rates for the oxymorphone ER treatment-emergent, non-fatal SAEs are presented by preferred term in the table below. The most frequently (0.4 to 0.5%) occurring individual SAEs were myocardial infarction and deep limb venous thrombosis (each reported by three subjects), followed by pneumonia, pyrexia, coma, and ileus (each reported by two subjects). In the **Update database** the new SAEs that were not reported in the original ISS database included chest pain, leukocytosis, nausea, postoperative ileus, small intestinal obstruction, tachycardia, uterine cancer, vaginal cellulitis, and vomiting (each reported by one oxymorphone IR-treated subject.

Table 7-1 Number (%) of Oxymorphone IR-Treated Patients with Non-Fatal SAEs in Descending Frequency in Phase 2/3 IR Trials

	ISS	Update	Overall
Total # patients treated with oxymorphone ER	(N = 334)	(N = 223) [a]	(N = 557)
MedDRA preferred term			
Any adverse events	18 (5.4)	7 (3.1)	25 (4.5)
Myocardial infarction	3 (0.9)	0 (0.0)	3 (0.5)
Venous thrombosis deep limb	3 (0.9)	0 (0.0)	3 (0.5)
Coma NEC	2 (0.6)	0 (0.0)	2 (0.4)
Ileus	2 (0.6)	0 (0.0)	2 (0.4)
Pneumonia NOS	1 (0.3)	1 (0.4)	2 (0.4)
Pyrexia	1 (0.3)	1 (0.4)	2 (0.4)
Adult respiratory distress syndrome	1 (0.3)	0 (0.0)	1 (0.2)
Cardiogenic shock	1 (0.3)	0 (0.0)	1 (0.2)
Chest pain NEC	0 (0.0)	1 (0.4)	1 (0.2)
Confusion	1 (0.3)	0 (0.0)	1 (0.2)
Depressed level of consciousness	1 (0.3)	0 (0.0)	1 (0.2)
Disorientation	1 (0.3)	0 (0.0)	1 (0.2)
Dyspnoea NOS	1 (0.3)	0 (0.0)	1 (0.2)
Hypotension NOS	1 (0.3)	0 (0.0)	1 (0.2)

Hypoventilation	1 (0.3)	0 (0.0)	1 (0.2)
Hypoxia	1 (0.3)	0 (0.0)	1 (0.2)
Leukocytosis	0 (0.0)	1 (0.4)	1 (0.2)
Mental status changes	1 (0.3)	0 (0.0)	1 (0.2)
Muscle contractions involuntary	1 (0.3)	0 (0.0)	1 (0.2)
Nausea	0 (0.0)	1 (0.4)	1 (0.2)
Pneumothorax NOS	1 (0.3)	0 (0.0)	1 (0.2)
Postoperative ileus	0 (0.0)	1 (0.4)	1 (0.2)
Radius fracture	1 (0.3)	0 (0.0)	1 (0.2)
Renal failure acute	1 (0.3)	0 (0.0)	1 (0.2)
Respiratory distress	1 (0.3)	0 (0.0)	1 (0.2)
Small intestinal obstruction NOS	0 (0.0)	1 (0.4)	1 (0.2)
Somnolence	1 (0.3)	0 (0.0)	1 (0.2)
Sweating increased	1 (0.3)	0 (0.0)	1 (0.2)
Tachycardia NOS	0 (0.0)	1 (0.4)	1 (0.2)
Tendon rupture	1 (0.3)	0 (0.0)	1 (0.2)
Tremor NEC	1 (0.3)	0 (0.0)	1 (0.2)
Uterine cancer NOS	0 (0.0)	1 (0.4)	1 (0.2)
Vaginal cellulitis	0 (0.0)	1 (0.4)	1 (0.2)
Vomiting NOS	0 (0.0)	1 (0.4)	1 (0.2)
Wound infection NEC	1 (0.3)	0 (0.0)	1 (0.2)

[a] New Subjects since the ISS.
Source: Table 17 on pages 180-181 of the update safety report.

The serious cardiac and respiratory AEs were mostly reported in the ISS database. There was one case of tachycardia reported from Study 009 in the Update database. The patient had a history of mitral valve prolapse and elevated blood pressure and underwent an abdominal hysterectomy. She received one dose of oxymorphone IR 10 mg. She was discontinued from the study because of use of rescue medication in less than four hours. She developed chest pain and tachycardia the second day after dropping out from the study. The event resolved spontaneously and was considered to be due to mitral valve prolapse and unlikely to be related to the study medication.

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

The disposition of subjects with respect to the treatment group of the Phase 2/3 oxymorphone IR clinical trials is summarized in the table below. In the **Overall database**, 557 subjects received oxymorphone IR, 278 subjects received oxycodone IR, and 242 subjects received placebo. Discontinuation occurred in 42% of subjects treated with oxymorphone IR, 34% of subjects treated with oxycodone IR (note: not all trials had an oxycodone arm), and 58% of subjects treated with placebo. The most frequently reported reasons for discontinuation across the treatment groups were lack of efficacy (22-24% for the active treatments versus 46% for placebo), and AEs (10% for oxymorphone IR, 7% for oxycodone IR, and 8% for placebo). The proportion of patients with early discontinuation for all the treatment groups was higher in the **Update Safety database** than in the original ISS database, mainly because of the higher rates of dropouts due to lack of efficacy.

Table 7-2 Disposition of All Subjects by Treatment Groups in Phase 2/3 Oxymorphone IR Trials

	Oxymorphone IR			Oxycodone IR			Placebo		
Patient status	ISS	Update	Overall	ISS	Update	Overall	ISS	Update	Overall
Treated	334 (100)	223 (100)	557 (100)	195 (100)	83 (100)	278 (100)	95 (100)	147 (100)	242 (100)

Complete	212 (63.5)	111 (49.8)	323 (58.0)	149 (76.4)	34 (41.0)	183 (65.8)	58 (61.1)	44 (29.9)	102 (42.1)
Discontinued	122 (36.5)	112 (50.2)	234 (42.0)	46 (23.6)	49 (59.0)	95 (34.2)	37 (38.9)	103 (70.1)	140 (57.9)
Lack of efficacy	64 (19.2)	69 (30.9)	133 (23.9)	28 (14.4)	33 (39.8)	61 (21.9)	27 (28.4)	83 (56.5)	110 (45.5)
AEs [a]	34 (10.2)	21 (9.4)	55 (9.9)	7 (3.6)	11 (13.3)	18 (6.5)	7 (7.4)	13 (8.8)	20 (8.3)
Other	24 (7.2)	22 (9.9)	46 (8.3)	11 (5.6)	5 (6.0)	16 (5.8)	3 (3.2)	6 (4.1)	9 (3.7)
Lost to follow-up							0 (0.0)	1 (0.7)	1 (0.4)

[a] This category includes patients who discontinued the study due to Adverse Event reported on either the Study Termination or Adverse Event CRF page.
Note: There were 28 patients in Study 004 who received initial placebo dose and were re-randomized to oxymorphone treatments in the multiple-dose phase of the study. They were counted here based on their last treatment received in the trial.
Source: Tables 3, 4, and 5 on pages 18 and 19 of the update safety report.

7.1.3.2 Adverse events associated with dropouts

Adverse events associated with dropouts in the oxymorphone IR treatment group in the Phase 2/3 oxymorphone IR trials are presented by preferred term in the table below. In the Overall database, 10% of oxymorphone IR-treated subjects discontinued due to an AE. AEs resulted in the discontinuation of at least three subjects (0.5%) receiving oxymorphone IR treatments were nausea (2.5%), vomiting (2.2%), somnolence (1.1%), sedation (1.1%), headache (0.7%) and coma, confusion, and respiratory depression (0.5% each, in the ISS database only).

The rates of discontinuation due to AE were similar for the original ISS and the **Update database**. The new types of AE leading to discontinuation in the Update safety database not reported in the original ISS Safety database were confusional state, incision site complication, migraine, pruritus, and rash.

Table 7-3 Number (%) of Oxymorphone IR-Treated Patients with AEs Causing Dropouts in Descending Frequency in Phase 2/3 IR Trials

	120-Day Safety	Update	Overall
Total # patients treated with oxymorphone IR	(N = 334)	(N = 223) [a]	(N = 557)
MedDRA preferred term			
Any adverse events	34 (10.2)	21 (9.4)	55 (9.9)
Nausea	6 (1.8)	8 (3.6)	14 (2.5)
Vomiting NOS	6 (1.8)	6 (2.7)	12 (2.2)
Sedation	4 (1.2)	2 (0.9)	6 (1.1)
Somnolence	5 (1.5)	1 (0.4)	6 (1.1)
Headache NOS	1 (0.3)	3 (1.3)	4 (0.7)
Coma NEC	3 (0.9)	0 (0.0)	3 (0.5)
Confusion	3 (0.9)	0 (0.0)	3 (0.5)
Respiratory depression	3 (0.9)	0 (0.0)	3 (0.5)
Abdominal pain NOS	1 (0.3)	1 (0.4)	2 (0.4)
Agitation	1 (0.3)	0 (0.0)	1 (0.2)
Confusional state	0 (0.0)	1 (0.4)	1 (0.2)
Constipation	1 (0.3)	0 (0.0)	1 (0.2)
Depressed level of consciousness	1 (0.3)	0 (0.0)	1 (0.2)
Disorientation	1 (0.3)	0 (0.0)	1 (0.2)
Dyspnoea NOS	1 (0.3)	0 (0.0)	1 (0.2)
Feeling abnormal	1 (0.3)	0 (0.0)	1 (0.2)
Hallucination NOS	1 (0.3)	0 (0.0)	1 (0.2)
Headache NOS aggravated	1 (0.3)	0 (0.0)	1 (0.2)
Hypotension NOS	1 (0.3)	0 (0.0)	1 (0.2)
Hypoventilation	1 (0.3)	0 (0.0)	1 (0.2)
Hypoxia	1 (0.3)	0 (0.0)	1 (0.2)
Ileus	1 (0.3)	0 (0.0)	1 (0.2)
Incision site complication	0 (0.0)	1 (0.4)	1 (0.2)

Lethargy	1 (0.3)	0 (0.0)	1 (0.2)
Mental status changes	1 (0.3)	0 (0.0)	1 (0.2)
Migraine NOS	0 (0.0)	1 (0.4)	1 (0.2)
Myocardial infarction	1 (0.3)	0 (0.0)	1 (0.2)
Pruritus NOS	0 (0.0)	1 (0.4)	1 (0.2)
Rash NOS	0 (0.0)	1 (0.4)	1 (0.2)
Respiratory distress	1 (0.3)	0 (0.0)	1 (0.2)
Sweating increased	1 (0.3)	0 (0.0)	1 (0.2)
Tachycardia NOS	0 (0.0)	1 (0.4)	1 (0.2)

[a] New Subjects since the ISS.
Source: Table 19 on pages 197 to 198 of the update safety report.

The most common AEs leading to discontinuation in all the treatment groups were nausea (2-3%) and vomiting (1-3%).

Table 7-4 Number (%) of Patients Discontinued due to Nausea and Vomiting in Phase 2/3 IR Trials

	Oxymorphone IR			Oxycodone IR			Placebo		
Database	ISS	Update	Overall	ISS	Update	Overall	ISS	Update	Overall
#treated	N=334	N=223	N=557	N=195	N=83	N=278	N=123	N=147	N=270
Any AE	34 (10.2)	21 (9.4)	55 (9.9)	7 (3.6)	11 (13.3)	18 (6.5)	8 (6.5)	13 (8.8)	21 (7.8)
Nausea	6 (1.8)	8 (3.6)	14 (2.5)	1 (0.5)	7 (8.4)	8 (2.9)	1 (0.8)	5 (3.4)	6 (2.2)
Vomiting	6 (1.8)	6 (2.7)	12 (2.2)	0 (0.0)	4 (4.8)	4 (1.4)	3 (2.4)	5 (3.4)	8 (3.0)

Note: The 28 patients who received both placebo and oxymorphone treatments were counted in both groups.
Source: Table 19 on pages 197 to 200 of the update safety report.

7.1.3.3 Other significant adverse events

There was one case of hypoxia and respiratory distress reported as both serious and as the cause of discontinuation from the study in the ISS database. Hypoxia and respiratory distress were not identified as serious AEs or AEs leading to discontinuation from the studies in the Update database. The issue with respiratory/CNS depression requiring naloxone treatment was discussed in the safety review of the original submission and is addressed again here. Based on the submission from the Sponsor dated September 30, 2003 a total of 15 subjects had hypoxia in Study 004, including 11 who required the naloxone treatment for respiratory/CNS depression (including three coma cases) after treatment with oxymorphone IR. Of the 11 subjects identified, seven were in the 30 mg group, four in the 20 mg group, and none in the 10 mg group. Eight of the subjects were elderly patients (seven subjects in the age range of 70 to 79 years). In comparison to Study 009, Study 004 had a similar study design, an additional higher dosing group of 30 mg (both studies had 10 mg and 20 mg doses), and permission of more frequent dosing (q4-6h and no sooner than every three hours in Study 004 versus no sooner than every four hours in Study 009). Study 004 also enrolled a much older patient population (patients post orthopedic surgery with a mean age of 62 years in Study 004 versus post abdominal surgery with a mean age of 42 years in Study 009).

7.1.4 Other Search Strategies

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

Adverse events were monitored and recorded throughout studies in study 008 and 009.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

The coding of AEs using preferred terms and categorization of AEs into system organ class by MedDRA were appropriate.

7.1.5.3 Incidence of common adverse events

In the **Overall database** AEs were reported in 349 (63%) of oxymorphone IR-treated subjects, 171 (62%) of oxycodone IR-treated subjects, and 114 (42%) of placebo subjects in the Phase 2/3 oxymorphone IR studies. The incidence of the most common AEs occurring in ≥1.5% subjects are presented by preferred term (in descending frequency in the Overall database) in the table below. The most frequently occurring treatment-emergent AEs in patients treated with oxymorphone IR were nausea (19.0%), pyrexia (14.2%), somnolence (9.3%), vomiting (9.0%), pruritus (7.9%), headache (6.8%), dizziness (excluding vertigo, 6.5%), and constipation (4.1%). The incidence rates of the most common AEs were similar for the oxymorphone IR and oxycodone IR groups and much less in the placebo group. There was a lower incidence rate of total AEs but higher incidence rates of nausea, vomiting, and headache in the **Update safety database** than in the original ISS Safety database for all the treatment groups. Hypoxia that was not considered serious was reported in eight (2.4%) subjects in the oxymorphone IR group, eight (4.1%) subjects in the oxycodone IR group, and five (4.1%) subjects in the placebo group in the ISS database and one subject in each group in the Update database.

7.1.5.4 Common adverse event tables

Table 7-5 The Most Frequent (≥1.5%) AEs Reported in All Phase 2/3 Oxymorphone IR Trials

	Oxymorphone IR			Oxycodone IR			Placebo		
Database	ISS	Update	Overall	ISS	Update	Overall	ISS	Update	Overall
#treated	N=334	N=223	N=557	N=195	N=83	N=278	N=123	N=147	N=270
Any AE	237 (71.0)	112 (50.2)	349 (62.7)	126 (64.6)	45 (54.2)	171 (61.5)	57 (46.3)	57 (38.8)	114 (42.2)
Nausea	55 (16.5)	51 (22.9)	106 (19.0)	38 (19.5)	23 (27.7)	61 (21.9)	8 (6.5)	23 (15.6)	31 (11.5)
Pyrexia	73 (21.9)	6 (2.7)	79 (14.2)	31 (15.9)	4 (4.8)	35 (12.6)	19 (15.4)	3 (2.0)	22 (8.1)
Somnolence	49 (14.7)	3 (1.3)	52 (9.3)	27 (13.8)	2 (2.4)	29 (10.4)	5 (4.1)	1 (0.7)	6 (2.2)
Vomiting NOS	26 (7.8)	24 (10.8)	50 (9.0)	13 (6.7)	8 (9.6)	21 (7.6)	5 (4.1)	14 (9.5)	19 (7.0)
Pruritus NOS	26 (7.8)	18 (8.1)	44 (7.9)	12 (6.2)	11 (13.3)	23 (8.3)	4 (3.3)	6 (4.1)	10 (3.7)
Headache NOS	10 (3.0)	28 (12.6)	38 (6.8)	8 (4.1)	6 (7.2)	14 (5.0)	1 (0.8)	11 (7.5)	12 (4.4)
Dizziness	28 (8.4)	8 (3.6)	36 (6.5)	10 (5.1)	7 (8.4)	17 (6.1)	2 (1.6)	4 (2.7)	6 (2.2)
Constipation	17 (5.1)	6 (2.7)	23 (4 .1)	14 (7.2)	2 (2.4)	16 (5.8)	1 (0.8)	2 (1.4)	3 (1.1)
Confusion	15 (4.5)	0 (0.0)	15 (2.7)	5 (2.6)	0 (0.0)	5 (1.8)	2 (1.6)	0 (0.0)	2 (0.7)
Anaemia NOS	13 (3.9)	1 (0.4)	14 (2.5)	4 (2.1)	0 (0.0)	4 (1.4)	4 (3.3)	0 (0.0)	4 (1.5)
Dry mouth	8 (2.4)	2 (0.9)	10 (1.8)	1 (0.5)	0 (0.0)	1 (0.4)	0 (0.0)	2 (1.4)	2 (0.7)
Tachycardia	7 (2 .1)	3 (1.3)	10 (1 .8)	1 (0.5)	0 (0.0)	1 (0.4)	2 (1.6)	0 (0.0)	2 (0.7)
Hypoxia	8 (2.4)	1 (0.4)	9 (1.6)	8 (4.1)	1 (1.2)	9 (3.2)	5 (4.1)	1 (0.7)	6 (2.2)

Note: The 28 patients who received both placebo and oxymorphone treatments were counted in both groups.
Source: Table 27 on pages 423 to 435 of the update safety report.

7.1.5.5 Identifying common and drug-related adverse events

The incidence rates of the most common drug-related (based on the Investigators' opinion) AEs occurring in 1.5% subjects in the Phase 2/3 oxymorphone IR studies are presented by preferred term (in descending frequency in the Overall database) in the table below. In the **Overall database**, the most frequently occurring treatment-related AEs in patients treated with oxymorphone IR were nausea (15.4%) , somnolence (8.6%), vomiting (7.0%), pruritus (6.3%), and dizziness (excluding vertigo, 5.2%). The incidence rates of the most common treatment-related AEs were similar for the oxymorphone IR and oxycodone IR treatment groups and much lower in the placebo group in general. The total AEs were

similar between the Update and ISS database with higher rates of reports of nausea, vomiting, and headache in the **Update safety database** than in the original ISS Safety database across the treatment groups.

Table 7-6 The Most Frequent (≥1.5%) Drug-Related AEs Reported in All Phase 2/3 IR Trials

	Oxymorphone IR			Oxycodone IR			Placebo		
Database	ISS	Update	Overall	ISS	Update	Overall	ISS	Update	Overall
#treated	N=334	N=223	N=557	N=195	N=83	N=278	N=123	N=147	N=270
Any adverse experience	156 (46.7)	93 (41.7)	249 (44.7)	83 (42.6)	36 (43.4)	119 (42.8)	27 (22.0)	41 (27.9)	68 (25.2)
Nausea	39 (11.7)	47 (21.1)	86 (15.4)	24 (12.3)	21 (25.3)	45 (16.2)	6 (4.9)	19 (12.9)	25 (9.3)
Somnolence	46 (13.8)	2 (0.9)	48 (8.6)	25 (12.8)	2 (2.4)	27 (9.7)	4 (3.3)	1 (0.7)	5 (1.9)
Vomiting NOS	16 (4.8)	23 (10.3)	39 (7.0)	5 (2.6)	7 (8.4)	12 (4.3)	5 (4.1)	10 (6.8)	15 (5.6)
Pruritus NOS	18 (5.4)	17 (7.6)	35 (6.3)	9 (4.6)	10 (12.0)	19 (6.8)	2 (1.6)	6 (4.1)	8 (3.0)
Dizziness (exc vertigo)	22 (6.6)	7 (3.1)	29 (5.2)	7 (3.6)	6 (7.2)	13 (4.7)	2 (1.6)	4 (2.7)	6 (2.2)
Headache NOS	5 (1.5)	17 (7.6)	22 (3.9)	3 (1.5)	4 (4.8)	7 (2.5)	1 (0.8)	8 (5.4)	9 (3.3)
Constipation	15 (4.5)	4 (1.8)	19 (3.4)	10 (5.1)	2 (2.4)	12 (4.3)	0 (0.0)	1 (0.7)	1 (0.4)
Confusion	12 (3.6)	0 (0.0)	12 (2.2)	3 (1.5)	0 (0.0)	3 (1.1)	2 (1.6)	0 (0.0)	2 (0.7)
Dry mouth	7 (2.1)	2 (0.9)	9 (1.6)	1 (0.5)	0 (0.0)	1 (0.4)	0 (0.0)	2 (1.4)	2 (0.7)
Sedation	6 (1.8)	2 (0.9)	8 (1.4)	1 (0.5)	1 (1.2)	2 (0.7)	0 (0.0)	1 (0.7)	1 (0.4)
Abdominal distension	2 (0.6)	4 (1.8)	6 (1.1)	1 (0.5)	1 (1.2)	2 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)
Hypoxia	6 (1.8)	0 (0.0)	6 (1.1)	4 (2.1)	0 (0.0)	4 (1.4)	3 (2.4)	1 (0.7)	4 (1.5)

Note: AEs included in this table occurred in >1.5% of subjects in any column. This table is sorted by Overall Total frequency in descending order.
Source: Tables 22, 23 and 24 on pages 37 and 38 of the update safety report; Tables 22a, 23a, and 24a in the submission dated May 31, 2006.

7.1.5.6 Additional analyses and explorations

Refer to the original NDA safety review.

7.1.6 Less Common Adverse Events

The incidence rates for most of the less common AEs were either similar or lower in the **Update Safety database** in comparison to the 120-Day safety database. There was noticeably higher percentage of reports of headache and flatulence in the Update Safety database than the ISS safety database.

7.1.7 Laboratory Findings

There were no laboratory tests conducted in any of the new studies in the current submission. The safety concerns with the decreased WBC count, neutropenia, and LFT elevation had been addressed by the Sponsor in the submission (meeting package) dated February 17, 2004. Of the seven cases of low WBC and neutropenia, one had a less than 10% decrease and normal end-of-study values. The other six cases had abnormally low values due to laboratory sample mishandling. Three had repeated lab tests with the results within normal range and the other three were not available for laboratory retest. Of the five cases with abnormal LFT elevations, four had elevations at a post-operative setting and had concomitant medications and/or concurrent medical conditions known to increase liver enzymes. One had LFT and GGT elevation judged by the Investigator as unlikely related to the study drug. The Sponsor's explanations were considered acceptable by the Division as documented in the meeting minutes for the meeting held on March 16, 2004.

7.1.7.1 Overview of laboratory testing in the development program

Refer to section 7.1.7 and the safety review of the original NDA.

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

Refer to section 7.1.7 and the safety review of the original NDA.

7.1.7.3 Standard analyses and explorations of laboratory data

Refer to section 7.1.7 and the safety review of the original NDA.

7.1.7.4 Additional analyses and explorations

Refer to section 7.1.7 and the safety review of the original NDA.

7.1.7.5 Special assessments

Refer to section 7.1.7 and the safety review of the original NDA.

7.1.8 Vital Signs

Vital signs were not recorded in either Study 008 or Study 009. Only two studies (031 and 032) of oxymorphone ER had vital sign measurements in the current submission. Other than a trend of small decrease in systolic and diastolic blood pressure in the first few weeks of the open-label treatment in Study 031, there were no remarkable trends based on the changes in group mean values.

7.1.8.1 Overview of vital signs testing in the development program

Refer to section 7.1.8 and the safety review of the original NDA.

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

Refer to section 7.1.8 and the safety review of the original NDA.

7.1.8.3 Standard analyses and explorations of vital signs data

Refer to section 7.1.8 and the safety review of the original NDA.

7.1.8.4 Additional analyses and explorations

7.1.8.5 Refer to section 7.1.8 and the safety review of the original NDA.

7.1.9 Electrocardiograms (ECGs)

There were no new ECG data in the current submission. According to the original NDA review there was a safety concern with QTc abnormality identified as QTc interval ≥430 msec (males) or 450 msec (females)

or a change from pre-dose of ≥30 msec reported in 11 subjects from three Phase 1 clinical trials, Studies 001, 002, and 003.

Of the 11 subjects identified four had abnormalities at baseline with no worsening on treatment. QTc abnormalities for the other seven subjects are listed in the table below. The QTc abnormalities identified after treatment with oxymorphone 20 mg tablets in the first treatment period in **Subjects 1, 2, and 5** resolved upon rechallenge with the same formulation given in the subsequent period. The QTc abnormality identified following the treatment with oxymorphone 10 mg oral solution in the third treatment period in **Subject** 7 resolved upon rechallenge with the 20 mg tablet treatment given in the fourth period. For **Subject 6**, the increase in QTc interval from 328 msec to 393 msec with 10 mg oral solution in the first treatment period did not continue upon the rechallenge with the same formulation in the second treatment period, where QTc interval was stabilized from a pre-dose value of 386 msec to a post-dose value of 385 msec. The length of the QTc interval fluctuated in an irregular pattern in the range of 367 msec and 473 msec during the three periods of treatment for **Subject 3**, for whom the abnormalities identified were the 43 msec increase from a pre-dose value of 404 msec to a post-dose value of 447 msec. Similarly, the length of the QTc interval fluctuated in an irregular pattern in the range of 382 msec and 413 msec during the four periods of treatment for **Subject 4**, for whom the abnormalities identified were the 30 msec (borderline) increase from a pre-dose value of 382 msec to a post-dose value of 412 msec. Also, all of the values for the QTc interval at the end of crossover treatments were <430 msec for six of the seven subjects.

The data did not suggest a causal relationship between the oxymorphone treatment and prolongation of QTc interval in this reviewer's opinion.

Table 7-7 Summary of QTc Interval Data: EN3202-002 and EN3202-003

				QTc (msec)		
	Subject ID	Period	Oxymorphone Treatment	Predose	Postdose	Reason for Abnormality
1	EN3202-002-001-001	1	20 mg tablet	372	476	Postdose ≥430 msec
		2	20 mg tablet	439	347	
		3	10 mg oral solution	387	364	
2	EN3202-002-001-006	1	20 mg tablet	358	491	Postdose ≥430 msec and increase from predose ≥30 msec
		2	20 mg tablet	374	356	
		3	10 mg oral solution	388	336	
3	EN3202-002-001-009	1	10 mg oral solution	408	367	
		2	20 mg tablet	473	419	
		3	20 mg tablet	404	447	Postdose ≥430 msec and increase from predose ≥30 msec
4	EN3202-003-001-002	1	20 mg tablet	386	390	
		2	20 mg tablet	382	412	Increase from predose ≥30 msec
		3	10 mg oral solution	396	391	
		4	10 mg oral solution	396	413	
5	EN3202-003-001-005	1	20 mg tablet	421	433	Postdose ≥430 msec
		2	10 mg oral solution	470	442	
		3	20 mg tablet	392	378	
		4	10 mg oral solution	388	376	
6	EN3202-003-001-012 [a]	1	10 mg oral solution	328	393	Increase from predose ≥30 msec
		2	10 mg oral solution	386	385	
7	EN3202-003-001-027	1	10 mg oral solution	352	352	
		2	20 mg tablet	342	356	
		3	10 mg oral solution	374	426	Increase from predose ≥30 msec
		4	20 mg tablet	362	358	

[a] Subject discontinued early.
Source: Table 5 on page 3746 of the safety update report.

The Sponsor performed a retrospective reanalysis of partially recollected data (not collected in the case report forms of the original submission) from Studies 015, 020, and 025 that provided the following findings though the interpretation of data was greatly limited by incomplete data and poor data quality.

- The incidences of on-study QTc prolongation judged by a baseline value of ≥430/450 msec or an increase from baseline by ≥30 msec, and on-study value of ≥500 msec were similar in the oxymorphone, oxycodone, and placebo treatment groups.

- Nearly 50% of all subjects had on-study shortening of the QTc interval (ranging from -1 to -270 msec), and about 20% who had baseline QTc prolongation of ≥ 430/450 msec subsequently had on-study QTc shortening in each treatment group.

- Of the four subjects identified as having an on-study QTc prolongation of ≥500 msec, one received placebo and three received oxymorphone treatment. Of the oxymorphone-treated patients Subject EN3202-025-011-010, had an increase from 392 msec at baseline to 505 msec at the end of the 2-week study with no cardiac AE. Subject EN3202-015-077-025 had an increase from 438 msec at baseline to 518 msec after four weeks of treatments and recovery to baseline level during the 1-year extended treatment. Subject EN3202-017-008-006 was hospitalized for an evaluation of myocardial ischemia in Study 017, who was subsequently enrolled in Study 020 and was found to have an increase from 425 msec to 501 msec after 17 days of extended treatment.

The data again did not suggest an association between the oxymorphone treatment and prolongation of QTc interval.

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

Refer to section 7.1.9 and the safety review of the original NDA.

7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

Refer to section 7.1.9 and the safety review of the original NDA.

7.1.9.3 Standard analyses and explorations of ECG data

Refer to section 7.1.9 and the safety review of the original NDA.

7.1.9.4 Additional analyses and explorations

Refer to section 7.1.9 and the safety review of the original NDA.

7.1.10 Immunogenicity

No data were available.

7.1.11 Human Carcinogenicity

There were no long-term exposure data for evaluation of human carcinogenicity.

7.1.12 Special Safety Studies

Dose dumping of oxymorphone by co-administration with alcohol was suggested by *in vivo* alcohol interaction study but not confirmed by *in vitro* dissolution test (refer to the PK review for detail).

7.1.13 Withdrawal Phenomena and/or Abuse Potential

The potential for drug abuse and dependence/withdrawal was evaluated in the safety review of the original submission and in the consultation from the Controlled Substances Staff. In the current submission there were eight cases of discontinuation due to opioid withdrawal symptoms in the double-blind treatment period, including one oxymorphone-treated patient and two placebo patients in Study 031 and five placebo patients in Study 032.

7.1.14 Human Reproduction and Pregnancy Data

One case of on-study pregnancy was reported in Study 032. Patient EN3202-032-040-013 received 17 days of open-label oxymorphone ER treatment and then was discontinued from the trial due to a positive pregnancy test. Subsequent to her termination from the trial, the Principal Investigator notified the Sponsor that the patient had an elective abortion.

Refer to pharmacology/toxicology review for the studies of genotoxicity.

7.1.15 Assessment of Effect on Growth

There were no pediatric studies.

7.1.16 Overdose Experience

There were no reports of overdose in the **Update safety database**. Refer to the safety review of the original submission for the evaluation of overdose.

7.1.17 Postmarketing Experience

Oxymorphone IR approved in 1959 was removed from the market for commercial reasons. The 2 mg and 5 mg tablets were removed after seven years of marketing and the 10 mg tablet was removed after 11 years of marketing. The search for the postmarketing reports only revealed 37 unique cases in AERS database in patients treated with intravenous and suppository formulations, which were discussed in the safety review of the original submission.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

The primary clinical safety data source was the Update Safety database consisted of data from subjects in the two trials (Studies 008 and 009) planed at the time of the 120-Day Safety data cutoff date. The safety data from the ISS Safety database were described and analyzed in the first cycle review of the original NDA submission. The Overall Safety database included the ISS Safety database and the Update Safety database. Safety data from the three safety populations (ISS, Update, and Overall) will be listed side by side, wherever applicable for comparison purpose.

7.2.1.1 Study type and design/patient enumeration

The Update safety database had data from two efficacy studies, Studies 008 and 009. Study 008 was a placebo-controlled, parallel study of oxymorphone IR 5mg taken as needed (not more frequently than every hour) for up to eight hours in patients undergoing outpatient knee arthroscopy procedure. Study 009 was a placebo- and active-controlled, parallel study of oxymorphone IR 10mg and 20mg taken every four to six hours for 48 hours in patients undergoing abdominal surgery. As shown in the table below the data set included 122 patients in Study 008 and 331 patients in Study 009.

Table 7-8 Overview of Study Type and Design and Patient Enumeration

Protocol # Investigator(s)	Type	Design	Dates of Study	Dosage	# of subj	Demography Mean age (y) (range) Gender (M, F) Race (W, NW)
EN3203-008 7 sites	Efficacy and safety; adults mild to moderate pain following outpatient knee arthroscopy	Multi-center, randomized, double-blind, placebo-controlled	4/17/03 – 6/27/03	OM IR 5 tab Placebo tab prn (no sooner than q1h) up to 8 hrs	122	44.8-45.0 (18-76) 52 M, 70 F 102 W, 20 NW
EN3203-009 23 sites with 22 investigators	Efficacy and safety, patients with moderate/severe pain following abdominal surgery	Randomized, double-blind, placebo- and active-controlled, single- and multiple-dose	9/1/04-8/15/05	OM IR 10 tab OM IR 20 tab OC IR 15 tab Placebo q4-6h for 48 hrs	331	42.6 (18-83) 4M, 327 F 215 W, 116 NW

Source: Supplemental Table 2 on pages 70 to 77 of the updated safety report.

7.2.1.2 Demographics

In the **Overall database** subjects in the active treatment groups (oxymorphone IR and oxycodone IR) had the mean age of 55 years, about 30% elderly, about 10% age ≥74 years, and about 70% female. Placebo subjects had the mean age of 52 years, 25% elderly, 7% age ≥74 years, and 62% female. About 80% of the study subjects across the treatment groups were Caucasian. Subjects in the **Update database** had younger mean age (about 43 years) and much smaller proportions of the elderly patients, and larger proportions of female and African American than subjects in the ISS safety database.

Table 7-9 Overall Demographics for Subjects in Phase 2/3 Oxymorphone IR Trials

Treatment	Oxymorphone IR			Oxycodone IR			Placebo		
Database	ISS	Update	Overall	ISS	Update	Overall	ISS	Update	Overall
# of patients	N=334	N=223	N=557	N=195	N=83	N=278	N=123	N=147	N=270
Age (yrs)									
N	334	223	557	195	83	278	123	147	270
Mean	62.8	43.5	55.1	60.7	42.9	55.4	62.4	43.1	51.9
Std	11.80	10.99	14.89	12.56	8.92	14.18	12.29	11.62	15.32
Min, max	22, 86	18, 83	18, 86	22, 83	18, 82	18, 83	27, 91	18, 76	18, 91
< 65 years	166 (49.7)	215 (96.4)	381 (68.4)	110 (56.4)	81 (97.6)	191 (68.7)	61 (49.6)	143 (97.3)	204 (75.6)
≥ 65 years	168 (50.3)	8 (3.6)	176 (31.6)	85 (43.6)	2 (2.4)	87 (31.3)	62 (50.4)	4 (2.7)	66 (24.4)
≥74 years	67 (20.1)	1 (0.4)	68 (12.2)	27 (13.8)	1 (1.2)	28 (10.1)	19 (15.4)	1 (0.7)	20 (7.4)
Gender, n (%)									
Female	193 (57.8)	193 (86.5)	386 (69.3)	116 (59.5)	82 (98.8)	198 (71.2)	64 (52.0)	104 (70.7)	168 (62.2)
Male	141 (42.2)	30 (13.5)	171 (30.7)	79 (40.5)	1 (1.2)	80 (28.8)	59 (48.0)	43 (29.3)	102 (37.8)
Race, n (%)									
Asian	1 (0.3)	4 (1.8)	5 (0.9)	0	2 (2.4)	2 (0.7)	0	3 (2.0)	3 (1.1)
Black	25 (7.5)	40 (17.9)	65 (11.7)	15 (7.7)	18 (21.7)	33 (11.9)	7 (5.7)	18 (12.2)	25 (9.3)
Caucasian	296 (88.6)	161 (72.2)	457 (82.0)	171 (87.7)	48 (57.8)	219 (78.8)	109 (88.6)	108 (73.5)	217 (80.4)

Other	12 (3.6)	18 (8.1)	30 (5.4)	9 (4.6)	15 (18.1)	24 (8.6)	7 (5.7)	18 (12.2)	25 (9.3)
Height (in)									
N	334	-	334	193	-	193	123	-	123
Mean	68.4	-	68.4	66.5	-	66.5	66.9	-	66.9
Std	33.53	-	33.53	3.87	-	3.87	4.10	-	4.10
Min, max	54, 675	-	54, 675	57, 78	-	57, 78	57, 76	-	57, 76
Weight (lbs)									
N	334	-	334	193	-	193	123	-	123
Mean	203.0	-	203.0	197.0	-	197.0	200.2	-	200.2
Std	45.81	-	45.81	42.92	-	42.92	40.44	-	40.44
Min, max	113, 450	-	113, 450	100, 385	-	100, 385	113, 367	-	113, 367

Source: Tables 11, 12, and 13 on pages 26, 27, and 28 of the updated safety report.

7.2.1.3 Extent of exposure (dose/duration)

As summarized in the table below the overall exposure to oxymorphone IR (excluding the exposure to IR when it was used as rescue medication) was 788, including 197 subjects exposed in Phase 1 studies, 557 exposed in Phase 2/3 post-operative studies (004, 005, 008, and 009) of the IR formulation, and 34 exposed in cancer pain studies of both IR and ER formulations. The exposure to the other treatments used as controls in Phase 2/3 trials included 278 patients to oxycodone IR and 270 to placebo.

Table7-10 Summery of Exposure by Subset and Treatment Groups in Phase 2/3 IR Trials

Treatment	Oxymorphone IR			Oxycodone IR			Placebo		
Database	ISS	Update	Overall	ISS	Update	Overall	ISS	Update	Overall
All Trials	565	223	**788**	195	83	278	122	147	269
Phase 1	197	0	197	0	0	0	0	0	0
Phase 2/3	368	223	591	195	83	278	123	147	270
Phase 2/3 IR post-op pain	334	223	**557** [a]	195	83	278	123	147	270
EN3203-004	204 [a]	--	--	67 [a]	--	--	57	--	--
EN3203-005	130	--	--	128	--	--	66	--	--
EN3202-008	--	60	--	--	0	--	--	62	--
EN3202-009	--	163	--	--	83	--	--	85	--
Phase 2/3 ER cancer pain	34	0	34	0	0	0	0	0	0
EN3202-018	18								
EN3202-019	16								

[a] In Study 004, 21 placebo patients were re-randomized to one of the three oxymorphone IR treatment groups (oxymorphone IR 10 mg: six patients; oxymorphone IR 20 mg: eight patients; oxymorphone IR 30 mg: seven patients); seven placebo patients were re-randomized to oxycodone IR. These 21 patients are presented in the table under both the active (oxymorphone or oxycodone) and the placebo treatment groups.

Source: Table 50 on page 52 of the ISS, Table 2 on page 42 of the report for Study 009, and page 68 of the report for Study 008.

The exposure with respect to dose level, the status of single versus multiple dose, the number of doses per patient, and the duration of exposure is summarized in the table below. Only two acute analgesic trials (Studies 004 and 009, both were 48-hour studies) had multiple-dose exposures to ≥10mg doses in a post-operative setting. A total of 219 subjects received more than one dose of oxymorphone IR, which included 82 subjects at the 10 mg dose (n=34 in Study 004 and n= 48 in Study 009), 100 subjects at the 20 mg dose (n=47 in Study 004 and n= 53 in Study 009), and 37 subjects at the 30 mg dose (Study 004). The average number of doses was approximately five, with dosing on average every five hours, for an average duration of up to 23 hours in Study 009. The average number of doses was in a range of three to four hours, with dosing on average every seven hours, for an average duration of up to 21 hours in Study 004. There were 56 subjects with multiple-dose exposure to 5 mg doses, with an average of approximately five doses and an average duration of approximately seven hours. The multiple-dose experience with the IR formulation for the 34 subjects in cancer studies (018 and 019) varied due to the nature of study design (titration-to-effect and open-label).

Table 7-11 Summary of Exposure to Oxymorphone IR in Phase 2/3 IR Trials

Dose		Single dose	>1 dose	# of dose/ patients		Duration (hours)	
				Mean	Maximum	Mean	Maximum
5 mg	Study 008	N=60	N=56	5 doses	8 doses	7 hours	36 hours
10 mg	Study 005	N=63					
	Study 004	N=65	N=34	3 doses	11 doses	17 hours	51 hours
	Study 009	N=82	N=48	5 doses	16 doses	21 hours	80 hours
	Subtotal	***N=270***	***N=82***				
20 mg	Study 005	N=67					
	Study 004	N=67	N=47	4 doses	13 doses	21 hours	57 hours
	Study 009	N=81	N=53	5 doses	13 doses	23 hours	59 hours
	Subtotal	***N=215***	***N=100***				
30 mg	Study 004	N=72	N=37	3 doses	9 doses	16 hours	63 hours
	Total	***N=557***					

Source: Page 58 of the report for Study 005, Table 12 on page 50 of the report for Study 008, Table 18 on page 67 of the report for Study 009, and Table 1 on page 5 of the submission dated June 13, 2006.

The information on the extent of exposure to oxymorphone IR treatment by modal daily dose category is summarized in the table below. The modal daily doses taken by subjects in the Phase 2/3 oxymorphone IR studies were as the following (in descending frequency) >10 to 50 mg/day in 51% of subjects (N=285), ≤10 mg/day in 25% of subjects (N=141), >50 to 90 mg/day in 16% of subjects (N=90), and >90 mg/day in 7% of subjects (N=41). The daily dose was mainly an indicator of dosing frequency since all the multiple-dose studies had fixed dose levels and flexible dosing interval.

There were 1.7 patient-years of exposure to oxymorphone IR in the Phase 2/3 oxymorphone IR studies.

Table 7-12 Extent of Exposure by Modal Daily Dose Category – Phase 2/3 Oxymorphone IR Trials

	Oxymorphone ER dosage (mg/day) [a]				
	≤10	>10-50	>50-90	>90	Total
Duration	Number (%) of subjects on treatment				
1 - 3 Days	141 (25.3)	285 (51.2)	90 (16.2)	41 (7.4)	557 (100)
Total	141 (25.3)	285 (51.2)	90 (16.2)	41 (7.4)	557 (100)
Patient Years [b]	0.39	0.86	0.34	0.11	1.70

[a] Total duration of exposure for all trials in which a patient participated.
[b] Patient years: the total number of days in a given modal dose group divided by 365.25.
Source: Table 8 on page 22 of the updated safety report.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

Refer to the review of the original NDA.

7.2.2.1 Other studies

None.

7.2.2.2 Postmarketing experience

Oxymorphone IR approved in 1959 was removed from the market for commercial reasons. The 2 mg and 5 mg tablets were removed after seven years of marketing and the 10 mg tablet was removed after 11 years of marketing. The search for the postmarketing reports only revealed 37 unique cases in AERS database in patients treated with intravenous and suppository formulations, which were discussed in the safety review of the original submission.

7.2.2.3 Literature

Literature reports were reviewed in the safety review of the original submission. There were no new reports of AEs according to the Sponsor's most recent review of clinical literature.

7.2.3 Adequacy of Overall Clinical Experience

The exposure to oxymorphone IR included 754 subjects taking at least a single dose at any dose level in the studies of oxymorphone IR and variable exposure to mostly 5mg oxymorphone IR when it was used in the studies of ER. The experience with repeated dosing at a post-operative setting included exposure to the 5 mg dose in 56 subjects (with an average of approximately five doses and an average duration of approximately seven hours) in Study 008, to the 10 mg dose in 82 subjects, to the 20 mg dose in 100 subjects, and to the 30 mg dose in 37 subjects (with an average ranging from three to five doses and an average duration of less than 24 hours) in Studies 004 and 009. Although there has been limited experience with long-term use of the IR formulation at 20 mg level the extensive experience with the use of ER formulation at much higher levels and for much longer periods (refer to the review of NDA 21-610 for detail) provides supportive evidence for drug safety.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

Non-clinical studies were considered adequate according to the pharmacology/toxicology review.

7.2.5 Adequacy of Routine Clinical Testing

Refer to the safety review of the original NDA.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

Metabolic, clearance, and interaction workup were considered adequate according to the clinical pharmacology reviewer.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

The safety database appears to have captured most of the expected opioid-related AEs.

7.2.8 Assessment of Quality and Completeness of Data

DSI inspection discovered inadequate, inaccurate, and inconsistent data reporting in a few cases mainly involving efficacy data. The entire dataset for the treatment-emergent AEs classified as "treatment-related" was not submitted until the information was requested by the reviewer. Also, the specific information about the exposure was not submitted for Study 004 or summarized for the Overall database until the information was requested by the reviewer.

7.2.9 Additional Submissions, Including Safety Update

There are no further safety updates.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

The most frequently occurring AEs in patients treated with oxymorphone IR were nausea (19%), pyrexia (14%), somnolence (9%), vomiting (9%), pruritus (8%), headache (7%), dizziness (excluding vertigo, 7%), and constipation (4%) in all Phase 2/3 studies in the Overall database. The same set of symptoms except pyrexia was identified as the most common treatment-related AEs. The most common AEs associated with dropouts from Phase 2/3 studies of the IR formulation were nausea (3%), vomiting (2%), somnolence (1%), and sedation (1%). The incidence rates for these AEs were much lower in the placebo group. All the AEs mentioned above are known AEs associated with the use of opioid drugs.

Based on the comparison of the study designs and results of the two 48-hour analgesic studies of post-operative pain, Studies 004 and 009, and the review of original data in Study 004, the development of respiratory/CNS depression requiring the naloxone treatment in patients treated with oxymorphone IR (reported in Study 004 and not in Study 009) appeared to be associated with the compound effects of dosage pattern (about 2/3 of the cases on the higher doses of 30 mg following the dosing instruction with a dosing frequency down to three hours) and the age of the patients (mostly 70 years or older in Study 004).

The available data did not suggest treatment-related QTc prolongation or cardiac toxicity based on the findings of QTc back to normal range upon rechallenge and at the end of crossover treatment in the majority of cases reviewed and the review of serious cardiac AEs.

There was no notable safety signal for treatment-related decrease in WBC and neutrophil count (other than problems with laboratory sample mishandling) or LFT elevation.

The limited multiple-dose exposure to the IR formulation could be supplemented by the extensive exposure experience with the ER formulation.

Oxymorphone IR has a similar safety profile as the other immediate-release formulations of opioids and is considered reasonably safe to be used for the treatment of moderate to severe acute pain with a conservative starting dosage regimen of low initial dose and careful dose titration to adjust for individual's need for analgesic response and tolerance.

7.4 General Methodology

7.4.1 Pooling Data across Studies to Estimate and Compare Incidence

7.4.1.1 Pooled data vs. individual study data

All the acute studies had very short exposure (single dose in Study 005, one day in Study 008, and two days in Studies 004 and 009) and small sample size. Safety data from the individual studies had a very limited value for adequate evaluation of safety.

7.4.1.2 Combining data

The safety data from all Phase 2/3 trials are combined and grouped by the ISS safety database already reviewed before, the Update safety database with the new information, and the Overall safety database combining the two.

7.4.2 Explorations for Predictive Factors

7.4.2.1 Explorations for dose dependency for adverse findings

Refer to the safety review of the original NDA.

7.4.2.2 Explorations for time dependency for adverse findings

Refer to the safety review of the original NDA.

7.4.2.3 Explorations for drug-demographic interactions

Incidence rates for all treatment-emergent AEs occurring in 5% or more of oxymorphone ER-treated subjects in the Phase 2/3 oxymorphone ER trials are presented by age group in the table below.
In the **Overall database** there were larger percentages of reports of pyrexia, somnolence, dizziness (exc vertigo), and confusion in the elderly group than in the younger age group. There appeared to be an age-related increase in incidence rates of somnolence, dizziness, and confusion. On the other hand the percentages of reports of nausea, pruritus, and headache were lower in the elderly group than in the younger age group. There were too few elderly patients (eight in the age group of >65 years and one in the age group of ≥74 years) in the **Update safety database** to allow a reasonable comparison.

Table 7-13 The Most Frequent (≥5%) AEs by Age Group and Preferred Term in Phase 2/3 IR Trials

	ISS Safety Total			Update Total [b]			Overall Total		
	(N = 334)			(N = 223)			(N = 557)		
Age group [a]	Age < 65	Age ≥65	Age ≥74	Age < 65	Age ≥65	Age ≥74	Age < 65	Age ≥65	Age ≥74
# of subjects	166	168	67	215	8	1	381	176	68
Any AE	118 (71.1)	119 (70.8)	54 (80.6)	107 (49.8)	5 (62.5)	1 (100.0)	225 (59.1)	124 (70.5)	55 (80.9)
Nausea	34 (20.5)	21 (12.5)	11 (16.4)	49 (22.8)	2 (25.0)	0 (0.0)	83 (21.8)	23 (13.1)	81 (41.8)
Pyrexia	41 (24.7)	32 (19.0)	9 (13.4)	6 (2.8)	0 (0.0)	0 (0.0)	47 (12.3)	32 (18.2)	68 (35.1)
Somnolence	28 (16.9)	21 (12.5)	9 (13.4)	2 (0.9)	1 (12.5)	1 (100.0)	30 (7.9)	22 (12.5)	58 (29.9)
Vomiting NOS	11 (6.6)	15 (8.9)	5 (7.5)	24 (11.2)	0 (0.0)	0 (0.0)	35 (9.2)	15 (8.5)	40 (20.6)
Pruritus NOS	17 (10.2)	9 (5.4)	3 (4.5)	17 (7.9)	1 (12.5)	0 (0.0)	34 (8.9)	10 (5.7)	28 (14.4)
Headache NOS	3 (1.8)	7 (4.2)	3 (4.5)	28 (13.0)	0 (0.0)	0 (0.0)	31 (8.1)	7 (4.0)	48 (24.7)
Dizziness (exc vertigo)	12 (7.2)	16 (9.5)	7 (10.4)	8 (3.7)	0 (0.0)	0 (0.0)	20 (5.2)	16 (9.1)	11 (5.7)
Constipation	10 (6.0)	7 (4.2)	4 (6.0)	5 (2.3)	1 (12.5)	0 (0.0)	15 (3.9)	8 (4.5)	13 (6.7)
Confusion	1 (0.6)	14 (8.3)	7 (10.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	14 (8.0)	8 (4.1)

[a] Age of subject from subject youngest recorded age. This table is sorted by Overall Total frequency in descending order.
[b] New subjects since the ISS.
Source: Table 28 on page 47 of the updated safety report.

Incidence rates for all treatment-emergent AEs occurring in 5% or more of oxymorphone IR-treated subjects in the Phase 2/3 oxymorphone IR trials are presented by gender in the table below. The subpopulation size for female was more than twice of that of male in the **Overall database.** There appeared to be higher incidence rates of nausea and headache in female and higher incidence rates of pyrexia and confusion in male. The **Update safety database** had predominantly female (87%). The female subpopulation in the Update database had much lower percentages of reports of pyrexia, somnolence, dizziness, confusion, dry mouth, and constipation, and much higher percentage of report of headache than the female in the ISS database.

Table 7-14 The Most Frequent (≥5%) AEs by Gender and Preferred Term in Phase 2/3 IR Trials

	ISS Safety Total	Update Total [a]	Overall Total

	(N = 334)		(N = 223)		(N = 557)	
	Male	Female	Male	Female	Male	Female
Number of Subjects	141	193	30	193	171	386
Any Adverse Experience	97 (68.8)	140 (72.5)	15 (50.0)	97 (50.3)	112 (65.5)	237 (61.4)
Nausea	14 (9.9)	41 (21.2)	3 (10.0)	48 (24.9)	17 (9.9)	89 (23.1)
Pyrexia	38 (27.0)	35 (18.1)	0 (0.0)	6 (3.1)	38 (22.2)	41 (10.6)
Somnolence	18 (12.8)	31 (16.1)	1 (3.3)	2 (1.0)	19 (11.1)	33 (8.5)
Vomiting NOS	9 (6.4)	17 (8.8)	3 (10.0)	21 (10.9)	12 (7.0)	38 (9.8)
Pruritus NOS	9 (6.4)	17 (8.8)	1 (3.3)	17 (8.8)	10 (5.8)	34 (8.8)
Headache NOS	1 (0.7)	9 (4.7)	5 (16.7)	23 (11.9)	6 (3.5)	32 (8.3)
Dizziness (exc vertigo)	10 (7.1)	18 (9.3)	2 (6.7)	6 (3.1)	12 (7.0)	24 (6.2)
Constipation	8 (5.7)	9 (4.7)	2 (6.7)	4 (2.1)	10 (5.8)	13 (3.4)
Confusion	8 (5.7)	7 (3.6)	0 (0.0)	0 (0.0)	8 (4.7)	7 (1.8)
Dry mouth	2 (1.4)	6 (3.1)	2 (6.7)	0 (0.0)	4 (2.3)	6 (1.6)

[a] New subjects since the ISS.
Note: This table is sorted by Overall Total frequency in descending order.
Source: Table 30 on page 51 of the updated safety report.

In the **Overall database** only 65 of the 2011 (11.7%) subjects were African American and 35 of 2011 (6.3%) were classified as others. The safety data were mainly from the Caucasian population, which accounted for about 80% of the study population. Therefore, the discussion about drug-demographic interactions with respect to race is limited because of the dramatic imbalance in subpopulation size. Nevertheless, the incidence rates for all treatment-emergent AEs occurring in 5% or more of oxymorphone ER-treated subjects in the Phase 2/3 oxymorphone ER trials are presented by racial group in the table below. In the Overall database the incidence rates of dizziness (exc vertigo) and headache were about 7% reported in the Caucasian study population and none in the African American population. The incidence rates were much higher for nausea, vomiting, and flatulence and much lower for most of the other commonly occurring individual AEs in the **Update safety database** than in the 120-Day safety database for all the racial groups.

Table 7-15 The Most Frequent (≥5%) AEs by Racial Group and Preferred Term in Phase 2/3 IR Trials

	ISS Safety Total			Update Total [a]			Overall Total		
	(N = 334)			(N = 223)			(N = 557)		
	Caucasian	Black	Other	Caucasian	Black	Other	Caucasian	Black	Other
# of subjects	296	25	13	161	40	22	457	65	35
Any AE	210 (70.9)	18 (72.0)	9 (69.2)	77 (47.8)	19 (47.5)	16 (72.7)	287 (62.8)	37 (56.9)	25 (71.4)
Nausea	48 (16.2)	4 (16.0)	3 (23.1)	36 (22.4)	8 (20.0)	7 (31.8)	84 (18.4)	12 (18.5)	10 (28.6)
Pyrexia	66 (22.3)	6 (24.0)	1 (7.7)	3 (1.9)	2 (5.0)	1 (4.5)	69 (15.1)	8 (12.3)	2 (5.7)
Somnolence	40 (13.5)	4 (16.0)	5 (38.5)	2 (1.2)	0 (0.0)	1 (4.5)	42 (9.2)	4 (6.2)	6 (17.1)
Vomiting NOS	23 (7.8)	1 (4.0)	2 (15.4)	18 (11.2)	4 (10.0)	2 (9.1)	41 (9.0)	5 (7.7)	4 (11.4)
Pruritus NOS	24 (8.1)	2 (8.0)	0 (0.0)	12 (7.5)	5 (12.5)	1 (4.5)	36 (7.9)	7 (10.8)	1 (2.9)
Headache NOS	10 (3.4)	0 (0.0)	0 (0.0)	21 (13.0)	0 (0.0)	7 (31.8)	31 (6.8)	0 (0.0)	7 (20.0)
Dizziness (exc Vertigo)	26 (8.8)	0 (0.0)	2 (15.4)	7 (4.3)	0 (0.0)	1 (4.5)	33 (7.2)	0 (0.0)	3 (8.6)
Constipation	15 (5.1)	2 (8.0)	0 (0.0)	4 (2.5)	1 (2.5)	1 (4.5)	19 (4.2)	3 (4.6)	1 (2.9)
Dry mouth	6 (2.0)	1 (4.0)	1 (7.7)	2 (1.2)	0 (0.0)	0 (0.0)	8 (1.8)	1 (1.5)	1 (2.9)
Abdominal distension	3 (1.0)	0 (0.0)	1 (7.7)	1 (0.6)	0 (0.0)	3 (13.6)	4 (0.9)	0 (0.0)	4 (11.4)
Flatulence	0 (0.0)	0 (0.0)	0 (0.0)	4 (2.5)	2 (5.0)	0 (0.0)	4 (0.9)	2 (3.1)	0 (0.0)
Sweating ↑	3 (1.0)	0 (0.0)	2 (15.4)	1 (0.6)	0 (0.0)	0 (0.0)	4 (0.9)	0 (0.0)	2 (5.7)
Coma NEC	3 (1.0)	0 (0.0)	1 (7.7)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.7)	0 (0.0)	1 (2.9)
Lethargy	2 (0.7)	2 (8.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	2 (3.1)	0 (0.0)
Respiratory depression	3 (1.0)	0 (0.0)	1 (7.7)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.7)	0 (0.0)	1 (2.9)

[a] New subjects since the ISS.
Note: This table is sorted by Overall Total frequency in descending order.
Source: Table 32 on page 55 of the updated safety report.

7.4.2.4 Explorations for drug-disease interactions

Refer to the safety review of the original NDA.

7.4.2.5 Explorations for drug-drug interactions

Refer to the safety review of the original NDA.

7.4.3 Causality Determination

Most of the commonly occurring AEs were treatment-related AEs known to be associated with the use of opioid drugs. The data have limited values in identifying new safety signals due to the limited duration and number of exposure.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The proposed adult dosage for opioid naïve patients is to start at 10 mg to 20 mg q4-6h as needed (prn), or to start at 5 mg q2h if necessary, followed by individualized titration based upon the individual patient's response to their initial dose, and for opioid experienced patients, to convert from other opioids. The proposed starting dose of 10 mg to 20 mg q4-6h as needed (prn) for opioid naïve patients is supported by clinical data. A low starting dose of 5 mg is also reasonable in high risk patients. However, the proposed dosage of 5 mg q2h is not supported by substantial evidence. Dosing as frequently as every two hours should not be encouraged in the use of drugs of high abuse potential.

8.2 Drug-Drug Interactions

Refer to the safety review of the original NDA.

8.3 Special Populations

Elderly patients are at higher risks for oxymorphone treatment-related adverse events due to a higher level of systemic exposure (about a 40% increase in total and maximum drug levels in comparison to younger subjects). Elderly patients have been shown to have increased risks to oxymorphone-induced respiratory/CNS depression at higher starting doses in a post-operative setting based on the results of studies in the original submission. There was also an age-related increase in incidence rates of dizziness and somnolence. Therefore, there should be a lower starting doses, slower titration, and closer monitoring for the elderly patients.

8.4 Pediatrics

8.5 Advisory Committee Meeting

This 505(b)(2) application is not planned to be discussed at an Advisory Committee meeting.

8.6 Literature Review

Literature reports were reviewed in the safety review of the original submission. There were no new reports of AEs according to the Sponsor's most recent review of clinical literature.

8.7 Postmarketing Risk Management Plan

The Sponsor's proposed post-marketing Risk Management Plan (RMP) for oxymorphone products has been reviewed in detail in the consultation from the Office of Drug Safety (ODS). There have been several communications with the Sponsor to address the concerns. To date most of the issues have been resolved. The additional recommendations from ODS include further education in patients and HCPs about the appropriate use of oxymorphone ER, the risk associated with inappropriate use, and the differences between the IR and ER formulations, strong warning against the use with alcohol and warning about starting at higher doses of oxymorphone ER in opioid naïve patients in the labeling, inclusion of any pediatric (age 16 years or younger) use or medication error in the 15-day Alert Report, and a number of other comments about the Sponsor's pharmacovigilance and educational plans in RMP. The consultation from the Controlled Substance Staff provided additional recommendations regarding the details and the use of data analysis instrument in risk management, and a number of labeling revisions.

8.8 Other Relevant Materials

The use of the proprietary name, OPANA^{TM} ER is considered acceptable by recommendations from the Division of Medication Errors and Technical Support.

9 OVERALL ASSESSMENT

9.1 Conclusions

Analgesic efficacy of oxymorphone IR 10 mg and oxymorphone IR 20 mg for the treatment of acute pain was supported by replicable positive findings from the studies of post-operative pain. The strength of evidence in support of analgesic efficacy of oxymorphone IR 10 mg and 20 mg includes a clear demonstration of multiple-dose efficacy in Study 009 and a demonstration of single-dose efficacy in all three studies for oxymorphone IR 20 mg and in one of the three studies for oxymorphone IR 10 mg.

Oxymorphone IR has a similar safety profile as the other immediate-release formulations of opioids and is considered reasonably safe to be used for the treatment of moderate to severe acute pain with a conservative starting dosage regimen of low initial dose and careful dose titration to adjust for individual's need for analgesic response and tolerance.

The proposed starting dosing regimen of 10 mg to 20 mg every four to six hours as needed (prn) for opioid naïve patients is supported by clinical data. A low starting dose of 5 mg is reasonable in high risk patients. However, the proposed dosage of 5 mg every two hours is not supported by substantial evidence. Dosing as frequently as every two hours should not be encouraged in the use of drugs of high abuse potential.

9.2 Recommendation on Regulatory Action

Oxymorphone IR is recommended for market approval l for the relief of moderate to severe acute pain where the use of an opioid is appropriate.

9.3 Recommendation on Postmarketing Actions

None.

9.3.1 Risk Management Activity

The Sponsor's proposed post-marketing Risk Management Plan (RMP) for oxymorphone products is considered acceptable in general. The additional recommendations from the Office of Drug Safety and the Controlled Substance Staff will be forwarded to the Sponsor.

9.3.2 Required Phase 4 Commitments

None.

9.3.3 Other Phase 4 Requests

There should be further studies of relative potency in comparison to the other commonly used opioids to well inform the labeling.

9.4 Labeling Review

The labeling will be reviewed separately.

9.5 Comments to Applicant

Risk Management Plan should incorporate all the recommendations from the Office of Drug Safety and the Controlled Substance Staff. Further studies of relative potency in comparison to the other commonly used opioids should be conducted.

10 APPENDICES

10.1 Review of Individual Study Reports

10.1.1 Study 009

Protocol
Study EN3203-009 was planned as a randomized, double-blind, placebo- and active-controlled, parallel, single- and multiple-dose (48 hours), dose response study of oxymorphone immediate release (IR) in patients with moderate to severe pain following abdominal surgery.

Eligible subjects were going to be patients undergoing surgery (non laparoscopic) through an abdominal incision of at least three cm with anticipated hospitalization for at least 36 hours; anticipated need of at least 48 hours of oral opioid therapy; anticipated treatment with short-acting parenteral analgesia post-operatively with a washout within 12 hours of the last dose (washout of at least 45 minutes from IV analgesics and at least four hours from IM analgesics); anticipated conversion to oral analgesics within 30 hours following surgery.

After screening patients were planned to undergo abdominal surgery and to receive post-operative analgesics as an IV formulation (PCA or non-PCA) or IM opioid, but not epidural opioid. Within 30 hours after abdominal surgery and following a washout from post-operative analgesia, patients with moderate to severe pain on a categorical scale and pain rated $\geq$50 mm on a 100-mm visual analog scale (VAS), were planned be randomized to one of the four treatment groups to take one capsule of study medication by mouth every four to six hours (not sooner than every four hours or later than every six hours).

After completing 6-hour assessments of the initial dose in the Single-Dose Period, patients not requesting rescue/remedication in the first six hours or having requested rescue/remedication in the time window between four to six hours were going to be remedicated at Hour 6 and enter the Multiple-Dose Period. Those requesting re-medication within the first four hours were to receive a rescue medication of the Investigator's choice and to be discontinued from the study.

During the Multiple-Dose Period of 48 hours after the initial dose, patients were going to be required to complete a diary/electronic diary for dosing and pain assessments prior to each dose of the study medication. Those in need of re-medication sooner than every four hours between doses were going to be discontinued from the study, to receive a rescue medication of the Investigator's choice, and to exit the study upon the completion of the Exit Evaluation assessments.

The primary efficacy endpoint was planned to be the time to discontinuation due to all causes during the entire study. Secondary efficacy endpoints for the multiple-dose period were planned to include mean average pain intensity (PI) (the average pain during each dosing interval evaluated at the time prior to each additional dose) and mean current PI (which represented the end-of-dosing pain evaluated also at the time prior to each additional dose), and patient global and physician global evaluation of study medication (recorded at the end of 48 hours). Secondary efficacy endpoints for the single-dose period were planned to include sum of pain intensity differences (SPID), total pain relief (TOTPAR), hourly pain relief and hourly pain intensity difference (to be recorded at 15, 30, 45, and 60 minutes, 1.5 hours, 2 hours, and hourly thereafter through Hour 6 using both categorical and VAS scales), and time to the first perceptible and meaningful pain relief (by double stopwatch).

Safety and tolerability were planned to be evaluated by monitoring adverse events (AEs) throughout the study.

The protocol and its amendments had been submitted to IND 58,602 as N091 on May 6, 2004, N092 on July 1, 2004, and N093 on August 24, 2004. They were reviewed as special protocol assessments by the medical reviewer, Dr. Elizabeth McNeil (DFS filing dates of the written reviews were 6/21/04, 12/2/04, 9/10/04, and 7/6/05), and by the statistical reviewer, Dr. Dionne Price (DFS filing dates of the written reviews were 6/16/04 and 8/16/04).

The key features of the protocol for Study 009 are summarized in the table below.

Table 10-1 Protocol

Study #	EN3203-009
Objectives	To study efficacy, dose response, tolerability, and safety of oxymorphone immediate release (IR) in patients with moderate to severe pain following abdominal surgery.
Design	Randomized, double-blind, placebo- and active-controlled, parallel, single- and multiple-dose (48 hours), dose response study at 21 centers in the U.S
Sample population	Male and non-pregnant female; ≥18 years of age; undergoing surgery (non laparoscopic) through an abdominal incision of at least 3 cm; anticipated hospitalization for at least 36 hours; anticipated in need of at least 48 hours of oral opioid therapy; had received short-acting parenteral analgesia post-operatively and had washout within 12 hours of last dose (washout ≥45 minutes from IV analgesics and ≥4 hours from IM analgesics); able to convert to oral analgesics within 30 hours following surgery
Baseline	Moderate to severe pain by a categorical scale and ≥50 mm on a 100-mm VAS within the required time periods.
Treatment	Oxymorphone IR 10 mg, Oxymorphone IR 20 mg, oxycodone IR 15 mg, or placebo q4-6h for 48 hours. Note: patients rescue within four hours after initial dose are not eligible for repeated dosing; patients request remedication sooner than every four hours or have no need for additional treatment in the 4-6h redosing window will be discontinued
Rescue and concomitant medication	Rescue medication of investigator's choice for patients discontinued from the study after requesting remedication within four hours of the initial dose or of any additional dose; Aspirin (≤325 mg/day) for prevention of thrombosis or potential emboli; Acetaminophen (≤650 mg over the duration of the study) for fever; Diphenhydramine only for pruritus or as a sleep aid, stable antidepressant, other medication needed for concurrent conditions not expected to interfere with the response to study medication
Raw efficacy data	Single dose: PI and PR using both categorical and 100-mm VAS scales at 15, 30, and 45 minutes and 1, 1.5, 2, 3, 4, 5, and 6 hours after the initial dose and prior to rescue; time to first perceptible PR and time to meaningful PR by using two stopwatches; time to rescue medication Multiple dose: current PI using a VAS scale prior to each dose; average pain since last dose using a VAS scale prior to each additional dose; patient's global and physician's global evaluation of study medication on a 5-point categorical scale at the end of the 48-hour treatment
Efficacy parameter	***Primary:*** Time to discontinuation due to all causes during the entire study ***Secondary:*** **Multiple dose** • Mean average pain intensity • Patient global evaluation of study medication • Mean current pain intensity • Physician global evaluation of study medication **Single dose** • 6-Hour Sum of Pain Intensity Differences (SPID; VAS and categorical) • 6-Hour Total Pain Relief Scores (TOTPAR; VAS and categorical) • Time (in hours) to First Perceptible Pain Relief • Hourly Pain Relief Scores • Time (in hours) to Meaningful Pain Relief • Hourly Pain Intensity Difference Scores
Statistical analysis	ITT: randomized patients taking ≥1 dose of study medication and completed ≥1 post dose efficacy evaluation Primary analysis: median time by Kaplan-Meier estimate; pairwise comparison by log-rank test and p-values evaluation by a Step-down procedure
Safety monitoring	Adverse events (AEs) throughout the study

Statistical Highlights

The statistical methodology and analysis plan and related changes were presented and discussed in detail in the statistical review. Some points are mentioned below for clarification purpose.

Sample population for efficacy analysis

The pre-specified efficacy analysis population was defined as all randomized patients who received at least one dose of double-blind study medication (ITT) and completed one post-dose efficacy evaluation.

Primary Analyses

The primary efficacy endpoint, time to discontinuation due to all causes was estimated using Kaplan-Meier method and analyzed using log-rank test. Pairwise comparisons were performed and p-values were evaluated using the Step-down procedure (between oxymorphone IR 20 mg and placebo and then between oxymorphone IR 10 mg and placebo).

Missing data management in the secondary analyses

The average of all available pain scores for each patient (collected immediately prior to each additional dose on a q4-6h dosing schedule), including those discontinued early, was used for calculating mean pain intensity scores in the 48-hour multiple-dose period.

Data from missing or off-schedule (outside the window specified by ±5 minutes of the scheduled time points during the first hour and ±10 minutes of the scheduled time points after one hour) evaluations in the 6-hour single-dose period were handled in the following manner :

- For patients who discontinued early or took the second dose of study medication prior to completion of the initial six hours of assessments, BOCF method was used for discontinuation due to AEs and LOCF method was used for discontinuation due to all other reasons.
- Data for missing evaluations at other time points were interpolated linearly, where possible.
- For TOTPAR and SPID, missing data at Hour 6 were imputed as specified above, and actual time was used in the calculation.
- For hourly data analysis, time windows as specified above were used to adjust actual time to scheduled time and data were imputed at each scheduled time point where missing data occur.

Post hoc changes to the planned statistical analysis of the secondary endpoints

- The graphic displays of the mean average and current pain intensity by number of doses and by dosing time interval, respectively, as originally planned in the protocol, was not presented.
- Instead of average PI, time-weighted average PI was used for the first six hours in the calculation of the mean average PI in multiple-dose analyses for those who discontinued prior to Hour 6.
- The windows for scheduled evaluations were redefined as within five minutes of the scheduled time points during the first two hours of the study and within 10 minutes of the scheduled time points after two hours.
- The method of BOCF/LOCF for missing data imputation was explained further as the following:
  - For PR, a score of zero was used in the BOCF method for discontinuation due to an AE.
  - For patients who took a second dose, only the LOCF method was applied to PR and PI.
  - For patients who took a second dose prior to completion of the initial 6 hours of assessments, the LOCF method was used to carry the last pain score collected in the Single-Dose Period to Hour 6.

[Reviewer's comments: The ITT population should be all randomized patients who received at least one dose of double-blind treatment regardless the status of the post dose evaluation. The issue was not raised in the Special Protocol Assessment. Only two patients, one on oxymorphone IR 10 mg and one on oxymorphone IR 20 mg, were excluded from the analyses of single-dose effect for not having any post-dose

diary data. All the subjects treated with study medication were included in the primary analyses, except one patient on oxymorphone IR 10 mg, who was excluded because of late consent.

The graphic displays of the mean PI by number of doses and by dosing time interval would be very difficult to interpret because of the flexible dosing induced variation in dosing time, dosing frequency, total number and amount of daily dose, etc., for the same individual and/or between individuals.]

Results

Demographic and other baseline characteristics

The study sample population consisted of 331 subjects enrolled in the study (330 received the study medication), with an age range of 18 to 83 years and a mean of 43 years. Of the 331 subjects 65% were Caucasian, 21% were African American, 8% were Hispanic, 3% were Asian, and most were (98.8%) female. The treatment groups were approximately balanced with regard to demographic characteristics such as age, gender, and race and with regard to the baseline pain intensity (PI) with a group mean of 62 to 65 on a 100 mm VAS scale. By the categorical scale most patients had moderate pain (83% to 91% in various treatment groups) at baseline. There were fewer patients with severe pain (9%) in the Oxymorphone IR 20 mg group compared to the other 3 treatment groups (14% to 17%).

Table 10-2 Demographics and Baseline Characteristics – All Treated Patients

Characteristics	Oxymorphone IR 10 mg (N=82)	Oxymorphone IR 20 mg (N=81)	Oxycodone IR 15 mg (N=83)	Placebo (N=85)	Total (N=331)
Age (years)					
n	82	81	83	85	331
Mean	42.8	43.2	42.9	41.8	42.6
SD	8.83	9.98	8.92	9.62	9.32
Minimum	21.0	23.0	18.0	23.0	18.0
Maximum	68.0	83.0	82.0	68.0	83.0
Gender, n (%)					
Male	1 (1.22)	1 (1.23)	1 (1.20)	1 (1.18)	4 (1.21)
Female	**81 (98.78)**	**80 (98.77)**	**82 (98.80)**	**84 (98.82)**	**327 (98.79)**
Race, n (%)					
Caucasian	52 (63.41)	57 (70.37)	48 (57.83)	58 (68.24)	215 (64.95)
Black	20 (24.39)	17 (20.99)	18 (21.69)	15 (17.65)	70 (21.15)
Hispanic	6 (7.32)	4 (4.94)	8 (9.64)	7 (8.24)	25 (7.55)
Asian	2 (2.44)	2 (2.47)	2 (2.41)	3 (3.53)	9 (2.72)
Hawaiian	0 (0.00)	0 (0.00)	1 (1.20)	0 (0.00)	1 (0.30)
Latino	1 (1.22)	0 (0.00)	1 (1.20)	0 (0.00)	2 (0.60)
Native American	0 (0.00)	0 (0.00)	1 (1.20)	0 (0.00)	1 (0.30)
Other	1 (1.22)	1 (1.23)	4 (4.82)	2 (2.35)	8 (2.42)
Baseline PI (categorical), n (%)					
Moderate	69 (84.15)	74 (**91.36**)	69 (83.13)	73 (85.88)	285 (86.10)
Severe	13 (15.85)	7 (**8.64**)	14 (16.87)	12 (14.12)	46 (13.90)
Baseline Pain Intensity (VAS)					
n	82	81	83	85	331
Mean	**62.4**	**64.3**	**65.3**	**64.2**	**64.1**
SD	10.00	11.19	13.01	11.38	11.45
Minimum	50.0	50.0	50.0	48.0	48.0
Maximum	97.0	90.0	96.0	100.0	100.0

Note: Baseline pain intensity (VAS) is measured using a 100 mm visual analog scale, where 0 mm = no pain and 100 mm = the worst pain imaginable.
Source: Table 3 on page 44 of the report for study 009.

Patient disposition and efficacy sample

Of the 331 subjects who received study medication more than 50% completed the single-dose period and about 40% in the active treatment groups versus <20% in the placebo group completed the 48-hour multiple-dose period.

The **major reasons for dropouts** were **lack of efficacy** (26% to 41%) and **adverse events** (5% to 6%) in the single-dose period and lack of efficacy (31% to 62%), adverse events (9% to 17%), and withdrawal of consent (5% to 11%) in the 48-hour multiple-dose period. The reasons for withdrawal of consent for the 25 dropout cases (including five cases in the single-dose period) included that patients were no longer in need of pain medication (13 cases), not want the pain medication (nine cases), not want to complete the study assessments (one case), no longer interested in study participation (one case), and no reason provided (one case). Three subjects dropped out due to **protocol violations**, one in each of the three treatment groups (oxymorphone 10 mg and 20 mg groups and placebo group), for either dosing early or dosing with the wrong medication.

The **remarkable differences** between the treatment groups were that fewer patients on oxymorphone IR 20 mg and more patients on placebo discontinued early due to lack of efficacy than the other two active treatment groups in both the single-dose and the 48-hour multiple-dose periods. There was a dose response in adverse events between the oxymorphone 20 mg and 10 mg dose levels (17% AE versus 9%) during the 48-hour evaluation period.

Of the patients who received study medication one patient in the oxymorphone IR 10 mg group was excluded from the **ITT population for primary efficacy analysis** because of providing consent for the study after surgery. Two patients, one from each of the two oxymorphone treatment groups, were excluded from the **ITT population for secondary efficacy analyses** for not having any post-dose diary data (refer to the protocol-defined ITT population described in the section of statistical highlights).

Table 10-3 Patient Disposition – All Randomized Patients

Patient Disposition n (%)	Oxymorphone IR 10 mg (N=82)	Oxymorphone IR 20 mg (N=81)	Oxycodone IR 15 mg (N=83)	Placebo (N=85)	Total (N=331)
Randomized	82	81	83	85	331
All Treated Patients	82 (100.00)	81 (100.00)	83 (100.00)	85 (100.00)	331 (100.00)
Multiple-Dose Period (0-48 Hours)					
Completed treatment Period	31 (37.80)	32 (39.51)	34 (40.96)	15 (**17.65**)	112 (33.84)
Discontinued	**51 (62.20)**	**49 (60.49)**	**49 (59.04)**	**70 (82.35)**	219 (66.16)
Lack of Efficacy	34 (41.46)	25 (**30.86**)	33 (39.76)	53 (**62.35**)	145 (43.81)
Adverse Event	7 (**8.54**)	14 (**17.28**)	11 (13.25)	11 (12.94)	43 (12.99)
Withdrew Consent	9 (10.98)	7 (8.64)	4 (4.82)	5 (5.88)	25 (7.55)
Protocol Violation	1 (1.22)	1 (1.23)	0 (0.00)	1 (1.18)	3 (0.91)
Withdrew by Investigator	0 (0.00)	1 (1.23)	0 (0.00)	0 (0.00)	1 (0.30)
Other	0 (0.00)	1 (1.23)	1 (1.20)	0 (0.00)	2 (0.60)
Intent-to-Treat Patients	81 (98.78)	81 (100.00)	83 (100.00)	85 (100.00)	330 (99.70)
Single-Dose Period (0-6 Hours)					
Completed treatment Period	48 (58.54)	53 (65.43)	49 (59.04)	45 (52.94)	195 (58.91)
Discontinued	**34 (41.46)**	**28 (34.57)**	**34 (40.96)**	**40 (47.06)**	136 (41.09)
Lack of Efficacy	29 (35.37)	21 (**25.93**)	27 (32.53)	35 (**41.18**)	112 (33.84)
Adverse Event	5 (6.10)	4 (4.94)	4 (4.82)	4 (4.71)	17 (5.14)
Withdrew Consent	0 (0.00)	1 (1.23)	3 (3.61)	1 (1.18)	5 (1.51)
Withdrew by Investigator	0 (0.00)	1 (1.23)	0 (0.00)	0 (0.00)	1 (0.30)
Other	0 (0.00)	1 (1.23)	0 (0.00)	0 (0.00)	1 (0.30)
Intent-to-Treat Patients	80 (97.56)	80 (98.77)	83 (100.00)	85 (100.00)	330 (99.70)

Source: Table 2 on page 42 of the report for study 009.

Ten treated patients (four patients on oxymorphone 10 mg, three on oxymorphone 20 mg, two on oxycodone 15 mg, and four on placebo) had minor violations of the inclusion/exclusion criteria but were included in the efficacy analysis. A total of 17 patients (four on oxymorphone 10 mg, six on oxymorphone 20 mg, four on oxycodone 15 mg, and three on placebo) had deviations from the specified dosing interval, which included having a mean dosing interval of less than four hours in four patients (one on oxymorphone 10 mg, one on oxycodone 15 mg, and two on placebo) and dosing beyond six hours at more than one occasion in the other 13 patients. The Sponsor provided explanations for the patients who exceeded the maximum dosing time as "the result of patients self-medicating after discharge from the hospital" and "clinical study staff failing to require the patients to dose at the specified time (i.e., the patient was sleeping, etc.)."

[Reviewer's comments: It would be interesting to see the results of efficacy re-analyses with the time to discontinuation corrected to the earliest time in the 17 cases when dosing was outside the four to six-hour time window. However, the results are not expected to change dramatically because the deviation occurred in a few patients in each treatment group and because there was a substantial treatment difference in time to discontinuation due to all causes.]

Exposure

The exposure information is summarized in the table below. About half of the patients took five doses in the active treatment groups in comparison to two doses in the placebo group. The mean duration of exposure was close to one day in the active treatment groups in comparison to the mean duration of exposure close to half day in the placebo group. The mean and the median dosing interval were between four and five hours as expected since those who did not re-dose in the window of every four to six hours should have been discontinued by the protocol. The 17 patients who had deviated dosing interval as mentioned above expanded the actual dosing interval to a wider range from 27 minutes to 16 hours.

Table 10-4 Exposure During the Multiple-Dose Period

	Oxymorphone IR 10 mg (N=81)	Oxymorphone IR 20 mg (N=81)	Oxycodone IR 15 mg (N=83)	Placebo (N=85)
Exposure				
Actual Number of Doses Taken, n (%)				
Dose 1	82 (100.00)	81 (100.00)	83 (100.00)	85 (100.00)
Dose 2	48 (58.54)	53 (65.43)	49 (59.04)	45 (52.94)
Dose 3	43 (52.44)	47 (58.02)	46 (55.42)	32 (37.65)
Dose 4	42 (51.22)	44 (54.32)	45 (54.22)	22 (25.88)
Dose 5	41 (50.00)	42 (51.85)	44 (53.01)	22 (25.88)
Dose 6	39 (47.56)	35 (43.21)	39 (46.99)	18 (21.18)
Dose 7	32 (39.02)	35 (43.21)	37 (44.58)	17 (20.00)
Dose 8	32 (39.02)	33 (40.74)	36 (43.37)	15 (17.65)
Dose 9	31 (37.80)	32 (39.51)	34 (40.96)	15 (17.65)
Dose 10	20 (24.39)	20 (24.69)	24 (28.92)	9 (10.59)
Dose 11	14 (17.07)	11 (13.58)	16 (19.28)	7 (8.24)
Dose 12	8 (9.76)	5 (6.17)	8 (9.64)	4 (4.71)
Dose 13	4 (4.88)	1 (1.23)	2 (2.41)	1 (1.18)
Dose 14	1 (1.22)	0 (0.00)	1 (1.20)	0 (0.00)
Dose 15	1 (1.22)	0 (0.00)	1 (1.20)	0 (0.00)
Dose 16	1 (1.22)	0 (0.00)	0 (0.00)	0 (0.00)
Maximal Number of Doses Per Patient				
N	82	81	83	85
Mean	5.4	5.4	5.6	3.4
SD	4.51	4.20	4.52	3.56
Duration of Exposure (hr:min)				
N	82	81	83	85

Mean	21:34	22:53	23:09	11:38
SD	22:18	21:30	22:40	17:17
Minimum	0:00	0:00	0:00	0:00
Median	14:57	20:09	19:55	4:00
Maximum	79:40	59:05	84:00	52:05
Dose Interval Average Per Patient				
Dose Interval (hr:min)				
N	48	53	49	45
Mean	5:01	5:10	5:04	4:36
SD	0:47	0:43	0:52	0:40
Minimum	3:49	4:00	3:59	3:55
Median	4:58	5:12	4:56	4:20
Maximum	6:44	6:47	8:38	6:30

Source: Table 18 on page 67 of the report for study 009.

Efficacy results

Primary efficacy endpoint (48-hour)

The results of time to discontinuation due to all causes per treatment group during the entire 48-hour period are summarized in the table below with the graph displayed in Figure 10-1. The median time to discontinuation due to all causes during the entire 48-hour period was about 20 hours for the oxymorphone IR 20 mg, 18 hours for oxymorphone IR 10 mg, 24 hours for oxycodone IR 15 mg, and five hours for the placebo group. The treatment differences from pairwise comparison between each of the three active treatment groups and placebo were statistically significant by log-rank test. Differences among the three actives treatment groups were not statistically significant.

Table 10-5 Time (hour:minutes) to Discontinuation Due to All Causes–Multiple-Dose Period

Statistics	Oxymorphone IR 10 mg (N=81)	Oxymorphone IR 20 mg (N=81)	Oxycodone IR 15 mg (N=83)	Placebo (N=85)
Descriptive				
Minimum	0:20	0:05	0:30	0:15
Maximum	48:00	48:00	48:00	48:00
Median (95% CI) [a]	**17:55 (4:30,32:35)**	**20:15 (6:00,)**	**24:05 (5:00,)**	**4:50 (3:22, 7:30)**
Pairwise Comparison [b]				
Oxymorphone IR 20mg	0.6946	-	-	-
Oxycodone IR 15mg	0.6479	0.9487	-	-
Placebo	***0.0057***	***0.0017***	***0.0014***	-

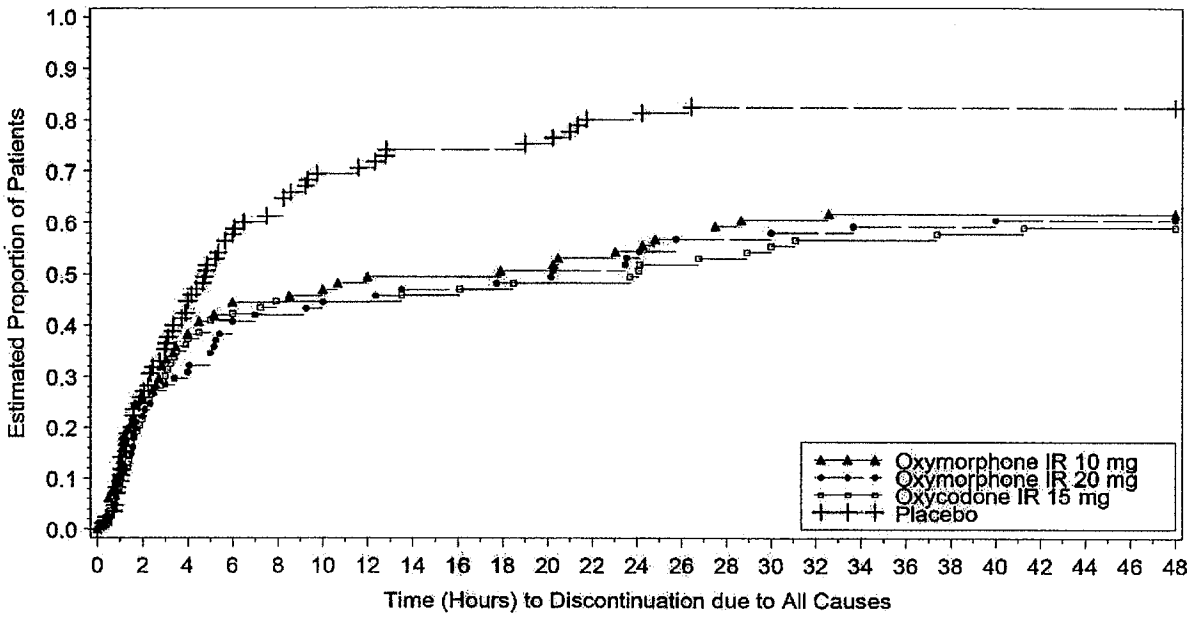
[a] Median was calculated using the Kaplan-Meier Estimate.

[b] All pairwise comparisons were performed using a Log-Rank test.

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

Source: Table 6 on page 47 of the report for study 009.

Figure 10-1 Time (Hours) to Discontinuation Due to All Causes–Multiple-Dose Period (0-48 Hours)



Source: Figure 2 on page 48 of the report for study 009.

Secondary efficacy endpoints

Multiple-dose effects (0-48 hours): mean average pain intensity

The mean scores for average pain intensity (PI) (the average pain during each dosing interval evaluated at the time prior to each additional dose) are summarized in the table below. The average pain intensity during the dosing interval by LSMean was 35 mm for oxymorphone IR 20 mg, 40 mm for oxymorphone IR 10 mg and oxycodone IR 15 mg treatments, and 50 mm for placebo. The mean scores for average pain intensity were 10 mm to 15 mm lower for the active treatment groups than for placebo and the treatment differences based on pairwise comparison were statistically significant.

Table 10-6 Summary of Mean Average Pain Intensity (VAS) – Multiple-Dose Period (0-48 Hours)

Statistics	Oxymorphone IR 10 mg (N=81)	Oxymorphone IR 20 mg (N=81)	Oxycodone IR 15 mg (N=83)	Placebo (N=85)
n	80	80	83	85
Mean	38.9	35.2	40.2	50.5
SD	24.70	26.26	23.72	23.28
Minimum	1.0	0.0	3.9	1.6
Median	39.8	30.7	41.4	51.0
Maximum	94.2	90.3	92.6	100.0
LSMean	39.7	35.2	39.8	50.1
Pairwise Comparison with Placebo [a]				
LSMean Difference	-10.5	-15.0	-10.3	-
StdErr	3.63	3.62	3.59	-
P-value	***0.0042***	***< 0.0001***	***0.0042***	-
95% CI	(-17.63, -3.33)	(-22.09, -7.83)	(-17.42, -3.28)	-

[a] All pairwise comparison statistical results are between corresponding active treatment and placebo. ANCOVA model is used including main effects for treatment, center, and baseline pain intensity (VAS) as covariate in the model.

Note: Average Pain Intensity (VAS) is measured using a 100 mm visual analog scale, where 0 mm = no pain and 100 mm = the worst pain imaginable.

Source: Table 7 on page 49 of the report for study 009.

Multiple-dose effects (0-48 hours): mean current pain intensity

The mean scores for current pain intensity (which represented the end-of-dosing pain evaluated at the time prior to each additional dose) are summarized in the table below. The current (end-of-dosing) PI by LSMean was 45 mm for oxymorphone IR 20 mg, 50 mm for oxymorphone IR 10 mg, 47 mm for oxycodone IR 15 mg, and 63 mm for placebo. The mean scores for current PI were 13 mm to 18 mm lower for the active treatment groups than for placebo and the treatment differences based on pairwise comparison were statistically significant.

Table 10-7 Summary of Mean Current Pain Intensity (VAS) – Multiple-Dose Period (0-48 Hours)

Statistics	Oxymorphone IR 10 mg (N=81)	Oxymorphone IR 20 mg (N=81)	Oxycodone IR 15 mg (N=83)	Placebo (N=85)
n	80	80	83	85
Mean	48.8	45.0	47.5	63.3
SD	30.86	32.62	29.59	29.18
Minimum	1.0	0.0	0.0	0.0
Median	46.1	36.2	46.3	70.0
Maximum	99.0	100.0	100.0	100.0
LSMean	49.6	44.9	47.0	63.0
Pairwise Comparison with Placebo				
LSMean Difference	-13.4	-18.1	-15.9	-
StdErr	4.57	4.56	4.52	-
P-value	***0.0037***	***< 0.0001***	***0.0005***	-
95% CI	(-22.37, -4.38)	(-27.03, -9.09)	(-24.84, -7.06)	-

Source: Table 8 on page 50 of the report for study 009.

Multiple-dose effects (0-48 hours): patient and physician global evaluation of study medication

The patient global and physician global evaluation of study medication at the end of study are summarized in the two tables below. The statistically significant treatment differences from placebo based on pairwise comparison were shown in patient global for the two oxymorphone treatments and in physician global for the oxymorphone IR 20 mg treatment only.

Table 10-8 Patient Global Evaluation of Study Medication

Statistics	Oxymorphone IR 10 mg (N=81)	Oxymorphone IR 20 mg (N=81)	Oxycodone IR 15 mg (N=83)	Placebo (N=85)
Total, n (%) [1]	79 (100.00)	77 (100.00)	81(100.00)	82 (100.00)
Excellent	22 (27.85)	25 (32.47)	19(23.46)	11 (13.41)
Very Good	15 (18.99)	20 (25.97)	20(24.69)	9 (10.98)
Good	12 (15.19)	7 (9.09)	17(20.99)	17(20.73)
Fair	9 (11.39)	9 (11.69)	7(8.64)	18 (21.95)
Poor	21 (26.58)	16 (20.78)	18(22.22)	27 (32.93)
Pairwise Comparison [2]				
Oxymorphone IR 20mg	0.986	-	-	-
Oxycodone IR 15mg	0.455	0.150	-	-
Placebo	***0.018***	***0.005***	*0.122*	-

[1] Total is the number of patients with a non-missing patient global evaluation of study medication at the end of study. Percentages are calculated using Total as denominator.

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

Source: Table 12 on page 574 of the report for study 009.

Table 10-9 Physician Global Evaluation of Study Medication

Statistics	Oxymorphone IR 10 mg (N=81)	Oxymorphone IR 20 mg (N=81)	Oxycodone IR 15 mg (N=83)	Placebo (N=85)
Total, n (%)	80 (100.00)	78 (100.00)	81 (100.00)	81 (100.00)
Excellent	26 (32.50)	32 (41.03)	21 (25.93)	17 (20.99)
Very Good	13 (16.25)	13 (16.67)	19 (23.46)	10 (12.35)
Good	8 (10.00)	5 (6.41)	11 (13.58)	12(14.81)

Fair	12 (15.00)	12 (15.38)	13 (16.05)	20 (24.69)
Poor	21 (26.25)	16 (20.51)	17 (20.99)	22 (27.16)
Pairwise Comparison				
Oxymorphone IR 20mg	0.232	-	-	-
Oxycodone IR 15mg	0.716	0.061	-	-
Placebo	*0.215*	***0.020***	*0.648*	-

Source: Table 13 on page 575 of the report for study 009.

The proportions of patient global and physician global evaluation of study medication rated as good, very good, and excellent are summarized in the table below. The proportion of good to excellent responders was 62 to 69% in the active treatment groups versus 45% in the placebo group for patient global and 59 to 64% in the active treatment groups versus 48% in the placebo group for physician global.

Table 10-10 Summary of the Proportions of Good to Excellent Responders

Proportion of good to excellent responders	Oxymorphone IR 10 mg	Oxymorphone IR 20 mg	Oxycodone IR 15 mg	Placebo
Patient global	49/79 (62.03)	52/77 (67.53)	56/81(69.14)	37/82 (45.12)
Physician global	47/80 (58.75)	50/78 (64.10)	51/81 (62.96)	39/81 (48.15)

Source: Two tables above.

Single-dose effects (0-6 hours): time-specific pain measurements

As shown in the table below statistically significant differences from placebo based on pairwise comparison of time-specific pain measurements were shown consistently only for the oxymorphone IR 20 mg treatment. The oxycodone IR 15 mg treatment performed better than placebo in the later half of the evaluation period, 3-6 hours or 4-6 hours, the time period with increased dropouts and use of imputed data. The difference in effect size corresponding to the statistically significant treatment difference was about 0.5 to 0.8 unit for PR-categorical, 12 to 18 mm for PR-VAS, 0.3 to 0.5 unit for PID-categorical, and 10 to 30 mm for PID-VAS (refer to Tables 10-15 to 10-18 attached to the end of study review). The four graphs of the time-specific pain measurements plotted against time (refer to Figures 10-2 to 10-5) provided visual impression of the effect size of the treatment difference. These relatively small effect size of treatment differences appeared to be multi-factorial, a high placebo response (especially during the first three hours) on top of small effect size of active treatments, e.g., the maximum group mean PR score was 2.2 for the oxymorphone IR 20 mg treatment, 2.0 for the oxycodone IR 15 mg treatment, and 1.9 for the oxymorphone IR 10 mg treatment, where a PR=2 represented only some pain relief.

Table 10-11 Time-Specific Pain Measurements (PR and PID) - First Six Hours after Initial Dose

Pairwise comparison with placebo: statistically significant difference at the scheduled evaluation time					
Efficacy parameter	Effect size corresponding to stat. sign. differences	Oxymorphone IR 10 mg (N=81)	Oxymorphone IR 20 mg (N=81)	Oxycodone IR 15 mg (N=83)	Source of information
PR-categorical	≥0.5 unit	4h	3-6h	3-6h	Table 13, Fig 5
PR-VAS	≥12 mm		**0.75-6h**	4-5h	T Table 14, Fig 6
PID-categorical	≥0.3 unit	3-6h	3-6h	4-6h	Table 15, Fig 7
PID-VAS	≥10 mm		**0.75-6h**	3-6h	Table 16, Fig 8

Note: the time or time intervals included only the significant results from pairwise comparison when the overall treatment effect was significant at the specific time point.

Single-dose effects (initial dose): onset

As shown in the table below there were basically no treatment differences in terms of either the median time to first perceptible pain relief or the median time to meaningful pain relief. An early onset of about 15 minutes by perceptible PR and about 45 minutes by meaningful PR were reported across the treatment groups.

Table 10-12 Summary of Median Time to First Perceptible Pain Relief and to Meaningful Pain Relief

Statistics	Oxymorphone IR 10 mg (N=81)	Oxymorphone IR 20 mg (N=81)	Oxycodone IR 15 mg (N=83)	Placebo (N=85)
Time to first perceptible pain relief				
Descriptive				
Minimum	0:01	0:01	0:02	0:15
Maximum	6:00	6:00	6:00	48:00
Median (95% CI) [a]	**0:15 (0:12, 0:22)**	**0:12 (0:08, 0:15)**	**0:15 (0:10, 0:23)**	**0:15 (0:12, 0:20)**
Pairwise Comparison [b]				
Oxymorphone IR 20mg	0.252	-	-	-
Oxycodone IR 15mg	0.875	0.329	-	-
Placebo	*0.836*	*0.356*	*0.960*	-
Time to meaningful pain relief				
Descriptive				
Minimum	0:04	0:05	0:01	0:04
Maximum	6:00	6:00	6:00	6:00
Median (95% CI) [a]	**0:40 (0:33, 1:10)**	**0:34 (0:25, 1:00)**	**0:45 (0:30, 1:39)**	**0:41 (0:30, 1:30)**
Pairwise Comparison [b]				
Oxymorphone IR 20mg	0.343	-	-	-
Oxycodone IR 15mg	0.700	0.185	-	-
Placebo	*0.690*	*0.179*	*0.990*	-

[a] Median is calculated using the Kaplan-Meier Estimate
[b] All pairwise comparisons were performed using a Log-Rank test.
Source: Tables 22 and 23 on pages 584 and 585 of the report for study 009.

[Reviewer's comments: The time to onset was treated as a censored value and assigned a score of six for those who did not experience an onset of pain relief (regardless the status of request of rescue/remedication) in the first six hours.]

Single-dose effects (initial dose): duration

The duration was defined as the median time to requesting rescue/remedication during the first six hours after the initial dose, including the request made in the window of four to six hours when patients were asked to wait until Hour 6 to get the second dose of study medication. As shown in the table below the duration of single-dose effect was about four hours in all the treatment groups.

Table 10-13 Median Time to Rescue Medication/Remedication - First Six Hours after Initial Dose

Statistics	Oxymorphone IR 10 mg (N=81)	Oxymorphone IR 20 mg (N=81)	Oxycodone IR 15 mg (N=83)	Placebo (N=85)
Descriptive				
n	81	80	83	85
Minimum	0:20	0:31	0:30	0:15
Maximum	6:00	6:00	6:00	6:00
25% quartile (95% CI) [a]	2:36 (1:31, 4:00)	3:53 (1:42, 4:00)	2:55 (1:52, 4:00)	1:59 (1:20, 3:20)
Median (95% CI) a	**4:00 (4:00, 4:10)**	**4:10 (4:04, 4:50)**	**4:06 (4:00, 4:30)**	**4:00 (3:55, 4:02)**
75% quartile (95% CI) [a]	5:04 (4:15, 5:50)	5:15 (5:00, 6:00)	5:15 (4:35, 5:59)	4:20 (4:05, 4:54)
Pairwise Comparison [b]				
Oxymorphone IR 20mg	0.180	-	-	-
Oxycodone IR 15mg	0.469	0.544	-	-
Placebo	0.126	***0.004***	***0.024***	-

[a] Calculated using the Kaplan-Meier Estimate;
[b] All pairwise comparisons were performed using a Log-Rank test.
Source: Table 1 in the submission on May 1, 2006.

[Reviewer's comments: The data and data analysis for median time to requesting rescue/remedication during the first six hours after the initial dose were not submitted with the current application dated December 22, 2005. The information was made available upon the reviewer's request. Interestingly, very

small numerical differences of 6-10 minutes (4:06 for oxycodone IR 15 mg versus 4:00 for placebo; 4:10 for oxymorphone IR 20 mg versus 4:00 for placebo) were shown to be statistically significant.]

Single-dose effects (initial dose): derived pain scores

Time-weighted summation of pain scores over the first six hours of evaluation of the initial dose are briefly summarized in the table below with details presented in Table 10-19 in Appendix. Statistically significant differences from placebo were shown in all four summation scores for oxymorphone IR 20 mg, three of four summation scores (except $TOTPAR_{0-6}$, VAS) for oxycodone IR 15 mg, and only in one of four summation scores ($SPID_{0-6}$, categorical) for oxymorphone IR 10 mg.

Table 10-14 Summary of the Time-Weighted Summation of Pain Scores

Pairwise comparison with placebo with respect to LSMean difference: p value				
	Oxymorphone IR 10 mg (N=81)	Oxymorphone IR 20 mg (N=81)	Oxycodone IR 15 mg (N=83)	Source of information
$SPID_{0-6}$ (categorical)	***0.037***	***0.001***	***0.019***	Table 9, p51
$SPID_{0-6}$ (VAS)	*0.080*	***< 0.001***	***0.005***	Table 10, p52
$TOTPAR_{0-6}$ (categorical)	*0.070*	***< 0.001***	***0.022***	Table 11, p53
$TOTPAR_{0-6}$ (VAS)	*0.614*	***0.002***	*0.135*	Table 12, p54

Summary of Findings and Discussions

In this placebo- and active-controlled, parallel, 48-hour study of oxymorphone IR dosed every four to six hours for post-operative pain the multiple-dose effects were demonstrated for both 10 mg and 20 mg doses and single-dose effects for 20 mg dose only.

For oxymorphone IR 20 mg treatment, multiple-dose effects were shown in the primary outcome measure as the median time to discontinuation due to all causes, as evidenced by both the level of statistical significance and clinically meaningful effect size. The multiple-dose efficacy was supported by the secondary outcome measures, the average pain during the dosing interval, the end-of-dosing pain, and patient and physician global evaluation of study medication. The findings were supported by the demonstration of single-dose effects in time-specific pain scores (PR and PID) and summation scores (SPID and TOTPAR) derived from measured pain scores. The single-dose effects were also shown in terms of onset of less than one hour (12 minutes by median time to perceptible relief and 34 minutes by median time to meaningful relief) and duration of slightly over four hours, though there were no meaningful treatment differences from placebo in onset and duration due to a high placebo response of unknown reasons.

For oxymorphone IR 10 mg treatment, multiple-dose effects were shown in the primary outcome measure as the median time to discontinuation due to all causes, as evidenced by both the level of statistical significance and clinically meaningful effect size. The multiple-dose efficacy was supported by the secondary outcome measures, the average pain during the dosing interval, the end-of-dosing pain, and patient and physician global evaluation of study medication. However, the single-dose effects were not shown by the measurement of time-specific pain scores and summation scores. The single-dose onset was shown to be less than one hour (15 minutes by median time to perceptible relief and 40 minutes by median time to meaningful relief) and the single-dose duration was shown to be four hours, though neither was meaningfully different from placebo due to a high placebo response.

The design of the trial was aimed at whether the proposed dosing interval of every four to six hour was adequate to support efficacy by using a strategy of dropping out patients who needed remedication/rescue before Hour 4 and those who did not need the next dose before Hour 6, and using time to discontinuation as the primary endpoint. There are several advantages with this approach. It selects responders by

eliminating those who have too much or too little pain by the time for redosing, and it eliminates the problem in dealing with missing data in the primary analysis or dealing with confounding effects from the rescue medication.

The high dropout rates due to lack of efficacy cross the treatment groups during the first 6 hours and the entire 48-hour period were expected in a post-operative setting when rescue analgesics were not allowed during the study (patients taking rescue were designated as treatment failures). The dropout rate due to lack of efficacy in the placebo group was high as expected, 15% higher than the oxymorphone IR 20 mg group during the single-dose period and 30% higher than the oxymorphone IR 20 mg group and 20% higher than the oxymorphone IR 10 mg group during the multiple-dose period. The dropout (5-10%) due to withdrawal of consent mainly reflected the proportion of the group that no longer had pain.

Because the flexible dosing frequency of every four to six hours was allowed in the study, the intrapersonal and interpersonal variation in the length of actual dosing intervals made it very difficult in trying to present and interpret pain scores over time (the 'pain curves').

The relatively small effect size of the treatment differences from placebo in pain scores during the single-dose period, especially during the first three hours, appeared to be attributable to a combination of high placebo response and low response to active treatments as shown on the pain curves. The high placebo response was also suggested by the result of onset and duration measurements that placebo behaved as an active treatment for having an early onset and a duration of four hours.

The results of summation scores, SPID and TOTPAR, were basically consistent with those of the time-specific measurements of pain scores for oxymorphone 10 mg and 20 mg treatments. The effect size varied and was difficult to be interpreted clinically. It is interesting to see that statistically significant treatment difference between oxycodone IR and placebo in summation scores corresponded to significant separation in time-specific measurements only in last half of the evaluation period, during which the group mean pain scores were driven by missing data since only about a quarter of patients on oxycodone and about 10-15% placebo patients provided actual pain scores at Hours 5 and 6. This supports the argument that the summation scores may be biased against the treatment group that has earlier dropouts.

Conclusion

Oxymorphone IR 20 mg given every four to six hours was shown to be effective in treating acute post-operative pain in patients undergoing abdominal surgery based on the single-dose effects and multiple-dose effects demonstrated in clinical trials. Multiple-dose effects were demonstrated for oxymorphone IR 10 mg and were not supported by single-dose outcome measures.

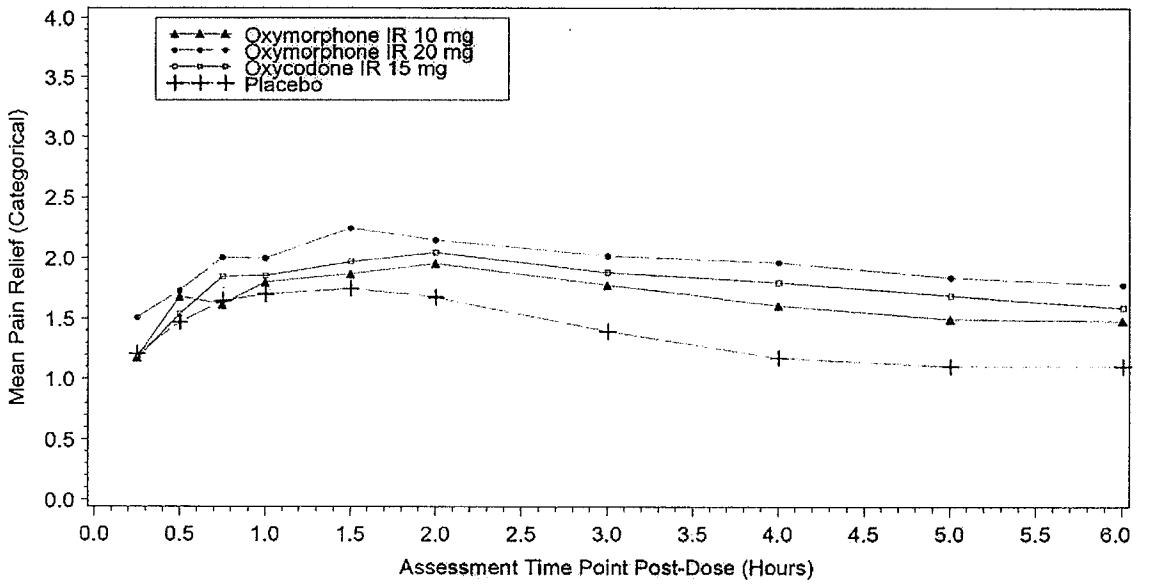
Appendix

Table 10-15 Summary of Pain Relief (PR, Categorical) Over Time in Single-Dose Period (0-6 Hours)

	Assessment Time Point Post-Dose									
Treatment/Statistics	15 min	30 min	45 min	1 hr	1.5 hr	2 hr	3 hr	4 hr	5 hr	6 hr
Oxymorphone IR 10 mg (N=81)										
n[a]	78	77	73	69	62	55	55	41	21	4
Mean[a]	1.2	1.7	1.6	1.8	1.9	1.9	1.8	1.6	1.5	1.5
SD[a]	1.19	1.28	1.23	1.30	1.31	1.37	1.41	1.37	1.32	1.34
Pairwise Comparisons[b]	A	A	A	A	AB	AB	AB	B	AB	AB
Oxymorphone IR 20 mg (N=81)										
n[a]	79	80	78	74	70	62	56	49	24	9
Mean[a]	1.5	1.7	2.0	2.0	2.2	2.1	2.0	2.0	1.8	1.8
SD[a]	1.21	1.29	1.29	1.26	1.31	1.40	1.42	1.49	1.41	1.39
Pairwise Comparisons[b]	B	A	B	A	B	B	B	B	B	B
Oxycodone IR 15 mg (N=83)										
n[a]	83	81	79	72	68	63	57	47	21	8
Mean[a]	1.2	1.5	1.8	1.8	2.0	2.0	1.9	1.8	1.7	1.6
SD[a]	1.13	1.12	1.26	1.33	1.36	1.46	1.44	1.47	1.43	1.41
Pairwise Comparisons[b]	A	A	AB	A	AB	AB	B	B	B	B
Placebo (N=85)										
n[a]	84	82	83	76	64	61	55	37	9	4
Mean[a]	1.2	1.5	1.6	1.7	1.7	1.7	1.4	1.2	1.1	1.1
SD[a]	1.03	1.14	1.26	1.30	1.34	1.33	1.20	1.14	1.09	1.09
Pairwise Comparisons[b]	AB	A	AB	A	A	A	A	A	A	A
Treatment p-value[c]	0.108	0.506	0.135	0.484	0.081	0.125	0.018	0.002	0.002	0.007
Baseline Pain Intensity p-value[c]	0.552	0.147	0.016	0.007	0.009	0.051	0.051	0.035	0.018	0.038
Root Mean Square Error[c]	1.04	1.14	1.19	1.25	1.29	1.33	1.31	1.32	1.26	1.25

*a*Sample sizes (n) are not extrapolated. Mean and Standard Deviation are based on LOCF or BOCF data based on missing data handling rules.
*b*Treatments with the same letter are not significantly different (e.g. Treatments with A and AB are not significantly different).
*c*Based on ANCOVA model with treatment and center as effects and baseline pain intensity (VAS) as covariate.
Note: Pain relief (categorical) is measured on a five point scale: 4 = complete, 3 = a lot, 2 = some, 1 = a little, and 0 = none.

Figure 10-2 Mean of PR (Categorical) at 0-6 Hours by Time Point in Single-Dose Period



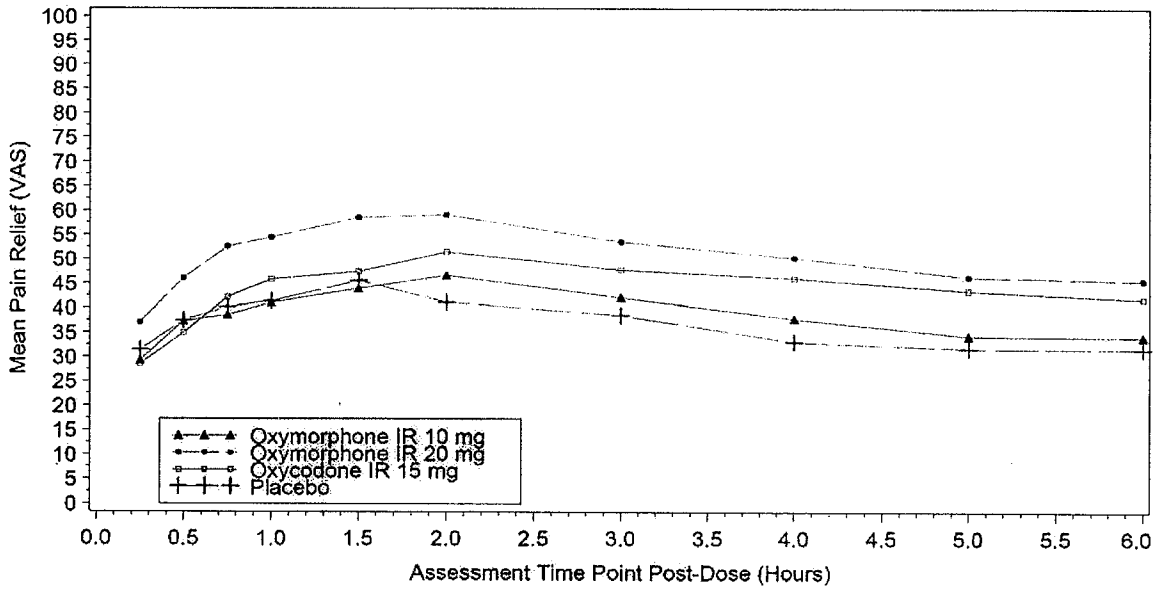
Pain relief (categorical) is measured on a five-point scale: 4 = complete, 3 = a lot, 2 = some, 1 = a little, and 0 = none.

Table 10-16 Summary of Pain Relief (VAS) Over Time in Single-Dose Period (0-6 Hours)

	Assessment Time Point Post-Dose									
Treatment/Statistics	15 min	30 min	45 min	1 hr	1.5 hr	2 hr	3 hr	4 hr	5 hr	6 hr
Oxymorphone IR 10 mg (N=81)										
n [a]	78	76	73	70	62	56	55	41	21	4
Mean [a]	29.2	37.3	38.6	41.0	43.9	46.6	42.1	37.8	34.2	34.0
SD [a]	29.95	34.35	34.02	34.72	37.22	38.19	37.46	36.55	35.29	35.38
Pairwise Comparisons [b]	A	AB	A	A	A	A	A	AB	AB	A
Oxymorphone IR 20 mg (N=81)										
n [a]	79	79	77	73	69	62	56	49	24	9
Mean [a]	37.1	46.1	52.6	54.4	58.5	59.1	53.5	50.3	46.3	45.5
SD [a]	33.06	35.45	36.62	36.34	36.57	38.49	38.88	40.06	38.65	38.21
Pairwise Comparisons [b]	A	B	B	B	B	B	B	C	C	B
Oxycodone IR 15 mg (N=83)										
n [a]	82	82	79	72	68	63	57	47	21	8
Mean [a]	28.5	34.9	42.2	45.8	47.4	51.4	47.8	46.0	43.4	41.8
SD [a]	31.74	31.89	33.87	36.36	37.17	38.71	38.35	39.06	38.00	37.70
Pairwise Comparisons [b]	A	A	AB	AB	AB	AB	AB	BC	BC	AB
Placebo (N=85)										
n [a]	84	83	83	76	64	61	55	37	10	4
Mean [a]	31.5	37.4	40.2	41.4	45.5	41.1	38.5	33.0	31.7	31.6
SD [a]	29.43	32.11	35.30	36.19	35.35	34.99	34.59	33.57	32.79	32.75
Pairwise Comparisons [b]	A	AB	A	A	A	A	A	A	A	A
Treatment p-value [c]	0.202	0.130	0.032	0.042	0.033	0.012	0.038	0.012	0.023	0.040
Baseline Pain Intensity p-value [c]	0.948	0.263	0.060	0.065	0.033	0.144	0.244	0.141	0.091	0.122
Root Mean Square Error [c]	28.64	31.43	33.06	34.13	35.11	36.06	35.47	36.16	35.15	34.86

aSample sizes (n) are not extrapolated. Mean and Standard Deviation are based on LOCF or BOCF data based on missing data handling rules.
bTreatments with the same letter are not significantly different (e.g., Treatments with A and AB are not significantly different).
cBased on ANCOVA model with treatment and center as effects and baseline pain intensity (VAS) as covariate.
Note: Pain relief (VAS) is measured on a 100 mm visual analog scale, where 0 mm = no relief and 100 mm = total relief.

Figure 10-3 Mean of PR (VAS) at 0-6 Hours by Time Point in Single-Dose Period



Note: Pain relief (VAS) is measured on a 100 mm visual analog scale, where 0 mm = no relief and 100 mm = total relief.

Table 10-17 Summary of Pain Intensity Difference (PID, Categorical) Over Time in Single-Dose Period

	Assessment Time Point Post-Dose									
Treatment/Statistics	15 min	30 min	45 min	1 hr	1.5 hr	2 hr	3 hr	4 hr	5 hr	6 hr
Oxymorphone IR 10 mg (N=81)										
n [a]	78	77	73	69	62	56	55	41	21	4
Mean [a]	0.4	0.6	0.5	0.6	0.7	0.7	0.5	0.4	0.3	0.3
SD [a]	0.60	0.81	0.80	0.81	0.84	0.95	0.99	0.99	0.94	0.94
Pairwise Comparisons [b]	A	A	A	AB	AB	AB	B	B	B	B
Oxymorphone IR 20 mg (N=81)										
n [a]	79	80	78	73	70	62	56	49	24	9
Mean [a]	0.5	0.6	0.8	0.8	0.9	0.8	0.7	0.6	0.5	0.5
SD [a]	0.69	0.83	0.83	0.82	0.91	0.99	0.96	1.03	0.94	0.91
Pairwise Comparisons [b]	A	A	B	B	B	B	B	B	B	B
Oxycodone IR 15 mg (N=83)										
n [a]	83	82	79	72	68	63	57	47	21	8
Mean [a]	0.4	0.5	0.7	0.8	0.7	0.7	0.6	0.5	0.4	0.4
SD [a]	0.65	0.70	0.78	0.85	0.90	0.97	0.99	0.97	0.87	0.84
Pairwise Comparisons [b]	A	A	AB	AB	AB	AB	AB	B	B	B
Placebo (N=85)										
n [a]	84	82	83	76	64	61	55	37	10	4
Mean [a]	0.4	0.5	0.6	0.5	0.5	0.5	0.3	0.1	0.1	0.1
SD [a]	0.66	0.73	0.84	0.89	0.91	0.95	0.87	0.80	0.77	0.77
Pairwise Comparisons [b]	A	A	AB	A	A	A	A	A	A	A
Treatment p-value [c]	0.805	0.439	0.066	0.084	0.061	0.094	0.028	0.013	0.015	0.020
Baseline Pain Intensity p-value [c]	0.510	0.113	0.454	0.857	0.771	0.122	0.270	0.247	0.241	0.230
Root Mean Square Error [c]	0.61	0.73	0.77	0.80	0.85	0.91	0.90	0.91	0.84	0.83

*a*Sample sizes (n) are not extrapolated. Mean and Standard Deviation are based on LOCF or BOCF data based on missing data handling rules.
*b*Treatments with the same letter are not significantly different (e.g., Treatments with A and AB are not significantly different).
*c*Based on ANCOVA model with treatment and center as effects and baseline pain intensity (VAS) as covariate.
Note: Pain intensity (categorical) is measured using a four point scale, where 3 = severe, 2 = moderate, 1 = mild, and 0 = none.
Pain Intensity Difference (PID) at a time point is calculated as baseline pain intensity score minus pain intensity score at that time point.

Figure 10-4 Mean of PID (Categorical) at 0-6 Hours by Time Point in Single-Dose Period

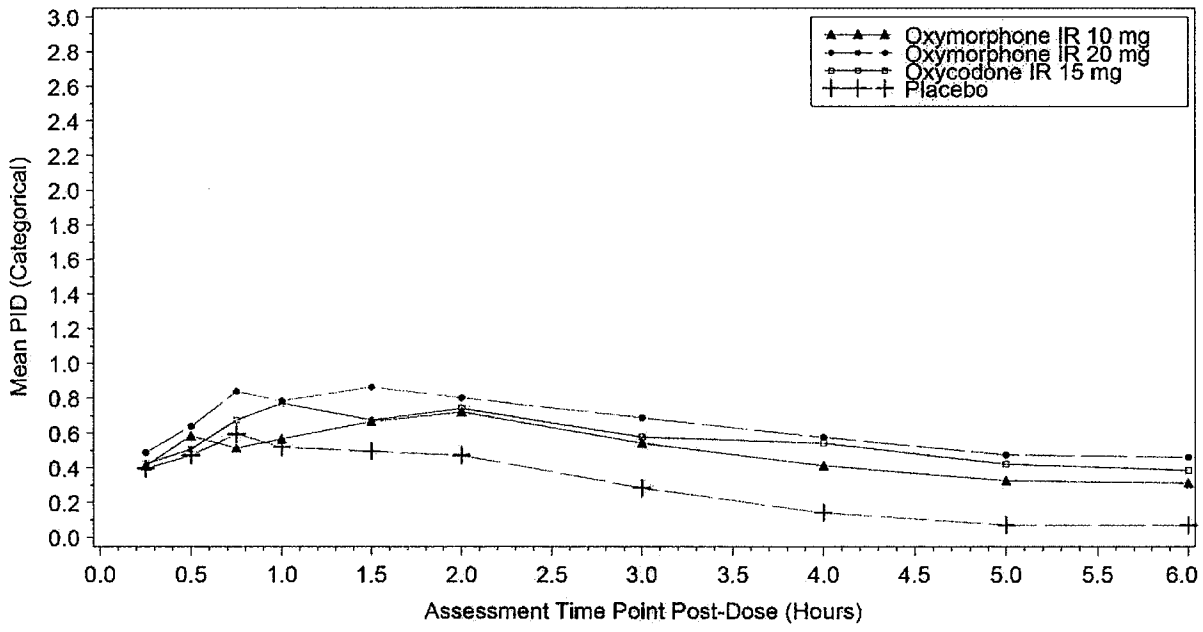


Table 10-18 Summary of PID (VAS) Over Time in Single-Dose Period (0-6 Hours)

	Assessment Time Point Post-Dose									
Treatment/Statistics	15 min	30 min	45 min	1 hr	1.5 hr	2 hr	3 hr	4 hr	5 hr	6 hr
Oxymorphone IR 10 mg (N=81)										
n [a]	79	77	73	70	62	56	55	51	21	13
Mean [a]	13.1	18.8	19.3	19.8	24.7	24.2	17.0	10.1	8.2	6.5
SD [a]	18.26	25.95	26.99	26.88	27.89	31.46	33.90	32.72	31.17	30.17
Pairwise Comparisons [b]	A	A	A	A	AB	AB	AB	AB	AB	AB
Oxymorphone IR 20 mg (N=81)										
n [a]	79	79	77	73	69	62	56	55	30	14
Mean [a]	18.9	24.9	29.9	30.7	31.1	31.2	26.8	20.4	14.9	11.9
SD [a]	20.63	25.29	26.60	28.27	30.82	32.09	32.63	34.97	32.95	30.61
Pairwise Comparisons [b]	A	A	B	B	B	B	B	BC	B	B
Oxycodone IR 15 mg (N=83)										
n [a]	82	82	79	72	68	63	57	51	22	14
Mean [a]	14.2	19.9	23.4	27.9	25.9	27.0	23.2	22.0	15.3	13.9
SD [a]	20.86	23.49	27.01	27.85	29.90	32.72	33.59	34.10	33.47	32.80
Pairwise Comparisons [b]	A	A	AB	AB	AB	AB	B	C	B	B
Placebo (N=85)										
n [a]	84	83	83	76	64	61	55	48	12	4
Mean [a]	15.2	18.5	20.0	20.3	18.2	17.7	11.3	3.7	0.2	-0.6
SD [a]	21.63	25.37	27.95	28.95	30.61	30.87	30.55	28.71	26.50	25.95
Pairwise Comparisons [b]	A	A	A	A	A	A	A	A	A	A
Treatment p-value [c]	0.269	0.311	0.047	0.029	0.041	0.037	0.010	<0.001	0.006	0.010
Baseline Pain Intensity p-value [c]	0.002	0.004	0.033	0.034	0.050	0.020	0.032	0.023	0.006	0.002
Root Mean Square Error [c]	18.96	23.98	25.73	26.71	28.34	30.06	30.51	31.21	29.57	28.21

*a*Sample sizes (n) are not extrapolated. Mean and Standard Deviation are based on LOCF or BOCF data based on missing data handling rules.
*b*Treatments with the same letter are not significantly different (e.g., Treatments with A and AB are not significantly different).
*c*Based on ANCOVA model with treatment and center as effects and baseline pain intensity (VAS) as covariate.
Note: Pain intensity (VAS) is measured using a 100 mm visual analog scale, where 0 mm = no pain and 100 mm = worst pain imaginable. Pain Intensity Difference (PID) at a time point is calculated as baseline pain intensity score minus pain intensity score at that time point

Figure 10-5 Mean of PID (VAS) at 0-6 Hours by Time Point in Single-Dose Period

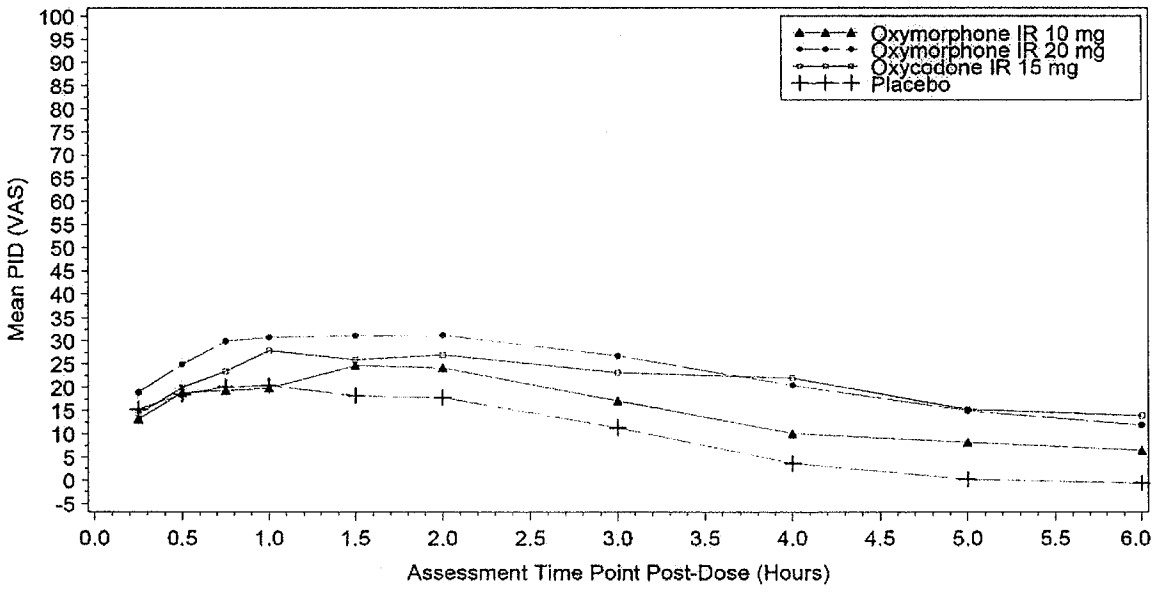


Table 10-19 Time-Weighted Summation of Pain Scores over the First Six Hours

Statistics	Oxymorphone IR 10 mg (N=81)	Oxymorphone IR 20 mg (N=81)	Oxycodone IR 15 mg (N=83)	Placebo (N=85)
$SPID_{0-6}$ (categorical)				
Mean	3.0	3.9	3.4	1.7
SD	4.61	4.89	4.56	4.10
Minimum	-5.9	-5.6	-5.9	-5.7
Median	2.6	3.6	4.0	1.1
Maximum	13.6	15.8	13.5	12.9
LSMean	3.1	3.9	3.3	1.7
Pairwise Comparison with Placebo a				
LSMean Difference	1.4	2.2	1.6	-
StdErr	0.67	0.67	0.66	-
p-value	***0.037***	***0.001***	***0.019***	-
95% CI	(0.08, 2.72)	(0.89, 3.52)	(0.26, 2.87)	-
$SPID_{0-6}$ (VAS)				
Mean	93.3	139.0	126.9	57.1
SD	154.3	164.5	162.3	141.3
Minimum	-192	-273	-197	-230
Median	92.5	151.8	137.6	36.0
Maximum	436.6	480.1	502.6	493.7
LSMean	97.9	139.3	121.7	58.0
Pairwise Comparison with Placebo a				
LSMean Difference	39.9	81.3	63.7	-
StdErr	22.72	22.65	22.46	-
p-value	*0.080*	***< 0.001***	***0.005***	-
95% CI	(-4.83, 84.58)	(36.72, 125.87)	(19.48, 107.86)	-
$TOTPAR_{0-6}$ (categorical)				
Mean	10.0	11.6	10.5	8.1
SD	6.71	7.06	7.16	6.00
Minimum	0.0	0.0	0.0	0.0
Median	9.8	12.2	11.2	7.6
Maximum	23.0	23.7	22.0	20.5
LSMean	10.0	11.7	10.4	8.2
Pairwise Comparison with Placebo a				
LSMean Difference	1.8	3.5	2.3	-
StdErr	1.00	1.00	0.99	-
p-value	*0.070*	***< 0.001***	***0.022***	-
95% CI	(-0.15, 3.78)	(1.55, 5.47)	(0.33, 4.21)	-
$TOTPAR_{0-6}$ (VAS)				
Mean	234.4	303.9	260.6	216.9
SD	181.9	196.1	194.4	171.5
Minimum	0.0	0.0	0.0	
Median	214.4	339.9	282.5	209.4
Maximum	578.3	590.7	566.9	578.4
LSMean	232.8	305.1	259.8	218.7
Pairwise Comparison with Placebo [a]				
LSMean Difference	14.0	86.4	41.1	-
StdErr	27.77	27.68	27.45	-
p-value	*0.614*	***0.002***	*0.135*	-
95% CI	(-40.62, 68.65)	(31.91, 140.86)	(-12.91, 95.10)	-

[a] All pairwise comparison statistical results are between corresponding active treatment and placebo. ANCOVA model is used including main effects for treatment, center, and baseline pain intensity (VAS) as covariate in the model.