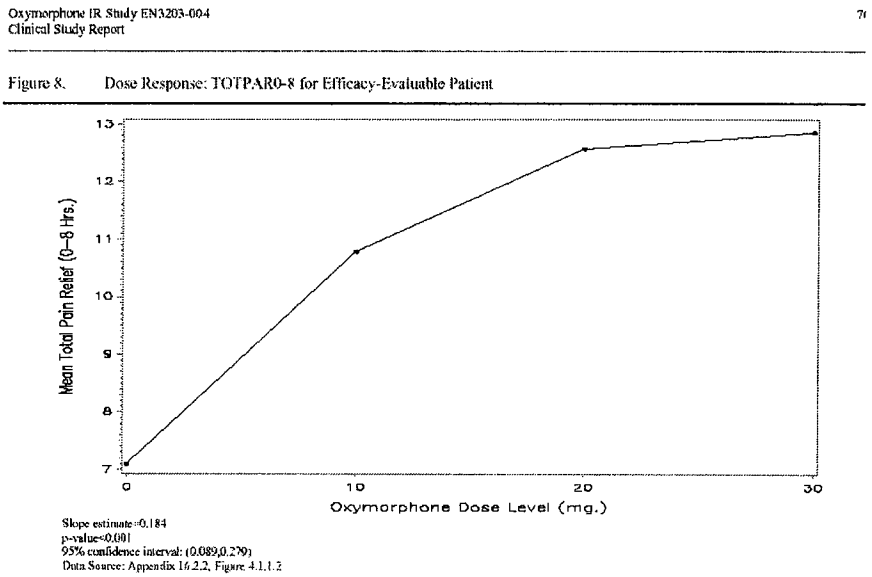
- Dose Response:
  The oxymorphone dose response efficacy assessment was studied through a regression model of the primary efficacy endpoint (TOTPAR0-8) using the arithmetic dose as the independent variable. As shown in the following figure, oxymorphone exhibited a statistically significant linear relationship that is assumed to be a dose-response relationship.

Figure EN3203-4.1 Dose Response Graph
(Data Source: Figure 8, EN3203-004 Clin Study Report, pg. 70)



Sponsor's Multi-Dose Phase Secondary Efficacy Outcomes (Active-Controlled):
The active-controlled, multi-dose phase was deemed to be inadequately designed to support efficacy (Dr. Dalpan's Protocol EN3203-004 Review 11/28/00). However, the sponsor's results are reviewed here, for completeness.

Brief Recap of Multi-Dose Phase:
Patients who tolerated the initial dose of study medication and either completed the single-dose phase through the 8-hour assessments, or re-medicated ≥ 3 hours after the first dose, entered the multiple-dose phase of the study and received blinded study medication. Patients initially randomized to the placebo group in the single-dose phase were assigned to one of the blinded active treatments during the multiple-dose phase, based upon their original randomization. All patients continued to receive study medication every 4-6 hours as needed, but not more than every 3 hours, for 48 hours after the start of the single-dose phase.

- Mean Worst Pain Scores:
  Worst pain scores were collect at Day 1 bedtime, Day 2 morning and bedtime, and Day 3 morning. These scores (categorical) were similar (ranged between 2.0 and 2.3) among active treatment groups on Day 1 and improved slightly on Days 2 and 3. The sponsor did not include tests of significance for changes in these scores. For completeness, the reviewer has included summary tables for day #1 bedtime and day #3 of the morning dose, to illustrate the change over three days.

Table EN3203-4.19 Worst Pain Score in the Multiple Dose Phase for Efficacy-Evaluable Patients (Day #1 Bedtime)

	Oxymorphone 10 mg (N=38)	Oxymorphone 20 mg (N=47)	Oxymorphone 30 mg (N=38)	Oxycodone 10 mg (N=38)
Worst Pain Score Day 1 Bedtime Dose (CAT)				
TOTAL	32	42	33	33
None - n (%)	0	1 (2.4)	2 (6.1)	0
Mild - n (%)	9 (28.1)	4 (9.5)	3 (9.1)	5 (15.2)
Moderate - n (%)	15 (46.9)	21 (50.0)	16 (48.5)	13 (39.4)
Severe - n (%)	8 (25.0)	16 (38.1)	12 (36.4)	15 (45.5)
N	32	42	33	33
Mean	2.0	2.2	2.2	2.3
Std	0.74	0.73	0.83	0.73
Worst Pain Score Day 1 Bedtime Dose (VAS)				
N	32	42	33	34
Mean	55.2	55.2	59.2	64.2
Std	28.83	29.78	26.76	26.07

Worst Pain Score (VAS) is measured using a 100 mm visual analog scale, where 0 mm = no pain and 100 mm = worst pain imaginable.
Worst Pain Score (Categorical) is measured using a four point scale, where 3 = severe, 2 = moderate, 1 = mild, and 0 = none.
Percentages are calculated using TOTAL as denominators.
Data Source: Supplemental Table 4, EN3203-004 Clin Study Report, pg. 98

Table EN3203-4.20 Worst Pain Score in the Multiple Dose Phase for Efficacy-Evaluable Patients (Day #3 Morning)

	Oxymorphone 10 mg (N=38)	Oxymorphone 20 mg (N=47)	Oxymorphone 30 mg (N=38)	Oxycodone 10 mg (N=38)
Worst Pain Score Day 1 Bedtime Dose (CAT)				
TOTAL	23	29	28	28
None - n (%)	4 (17.4)	2 (6.9)	5 (17.9)	3 (10.7)
Mild - n (%)	11 (47.8)	16 (55.2)	10 (35.7)	17 (60.7)
Moderate - n (%)	7 (30.4)	9 (31.0)	13 (46.4)	7 (25.0)
Severe - n (%)	1 (4.3)	2 (6.9)	0	1 (3.6)
N	23	29	28	28
Mean	1.2	1.4	1.3	1.2
Std Dev	0.8	0.73	0.76	0.7
Worst Pain Score Day 1 Bedtime Dose (VAS)				
N	23	29	28	28
Mean	31.2	29.3	28.3	28.9
Std Dev	23.4	21.9	24.77	23.9

Worst Pain Score (VAS) is measured using a 100 mm visual analog scale, where 0 mm = no pain and 100 mm = worst pain imaginable.
Worst Pain Score (Categorical) is measured using a four point scale, where 3 = severe, 2 = moderate, 1 = mild, and 0 = none.
Percentages are calculated using TOTAL as denominators.
Data Source: Supplemental Table 4, EN3203-004 Clin Study Report, pg. 101

It is interesting to note that the proportion of 'no' worst pain scores at day #3 are similar for both OM 10 and 30 mg, while OM 20 mg is less (4 or 17.4% & 5 or 17.9% vs. 2 or 6.9%, respectively). Note also that there was significant drop-out during this period, with the greatest proportion due to AEs (22.5% in OM 20 mg and 12.5% in OC 10 mg, respectively – from Disposition Table 4.2)

- Patient and Physician Global Evaluations of Pain Medication:
  While approximately 75-86% of patients had excellent, very good, and good evaluations of pain medication for all treatment groups on both patient's and physician's global evaluation at exit of study, it is interesting to note the distribution of scores. Subjects rated OM 10 and 30 mg with similar 'excellent' ratings of 27%, while ranking OM 20 mg much lower at 18.2%. At the same time OM 20 mg was rated as 'fair' 15.9% of the time, which was greater than either OM 10, 30, or OC 10 mg. The 'good' category appeared to be ranked equally for OM 20 mg and OC 10 mg at approximately 36% each. Interestingly, investigators rated both OM 10 over all others active treatments as 'excellent' (28.9% vs. 14% for OM 20, 24% for OM 30, and 10.5% for OC 10 mg).

Table EN3203-4.21 Global Evaluation of Pain Medication during the Multiple-Dose Phase, Efficacy Evaluable Patients

	Oxymorphone 10 mg (N=38)	Oxymorphone 20 mg (N=47)	Oxymorphone 30 mg (N=38)	Oxycodone 10 mg (N=38)
Subject Global Evaluation				
TOTAL [1]	37	44	37	38
EXCELLENT - n (%)	10 (27.0)	8 (18.2)	10 (27.0)	6 (15.8)
VERY GOOD - n (%)	10 (27.0)	16 (36.4)	12 (32.4)	14 (36.8)
GOOD - n (%)	12 (32.4)	9 (20.5)	8 (21.6)	11 (28.9)
FAIR - n (%)	-	7 (15.9)	4 (10.8)	3 (7.9)
POOR - n (%)	5 (13.5)	4 (9.1)	3 (8.1)	4 (10.5)
Physician Global Evaluation				
TOTAL [1]	38	43	37	38
EXCELLENT - n (%)	11 (28.9)	6 (14.0)	9 (24.3)	4 (10.5)
VERY GOOD - n (%)	12 (31.6)	16 (37.2)	12 (32.4)	19 (50.0)
GOOD - n (%)	8 (21.1)	14 (32.6)	10 (27.0)	7 (18.4)
FAIR - n (%)	3 (7.9)	4 (9.3)	3 (8.1)	6 (15.8)
POOR - n (%)	4 (10.5)	3 (7.0)	3 (8.1)	2 (5.3)

[1] Percentages are calculated using TOTAL as denominator.
Data Source: Table 16, EN3203-004 Clin Study Report, pg. 72

Sponsor's Exploratory Efficacy Analysis Results:

- Average Dose Interval (Multi-Dose Phase):

The sponsor performed an additional analysis of the dose interval data obtained during the multiple-dose phase (see Table 4.19 below). When the dose intervals were averaged for each patient, the longest median interval (9 hour 39 minutes) was observed in the oxymorphone IR 30 mg group. For the oxymorphone IR 10 mg and 20 mg and

oxycodone IR 10 mg groups, the median dose interval ranged from 7 hours to 7 hours 44 minutes.

Table EN3203-4.22 Average Actual Dose Interval[a] for Patients who Entered the Multiple-Dose Phase

	Oxymorphone 10 mg (N=38)	Oxymorphone 20 mg (N=48)	Oxymorphone 30 mg (N=39)	Oxycodone 10 mg (N=39)
Mean Dose Interval[b]				
N	31	39	32	34
Mean	8:28	7:52	10:01	7:41
Std	5:17	2:27	4:08	3:05
Minimum	2:45	3:32	3:00	3:37
Maximum	25:00	13:12	22:45	15:35
Minimum Dose Interval[c]				
N	31	39	32	34
Mean	6:27	5:44	7:06	5:02
Std	5:41	2:11	4:32	3:07
Minimum	2:25	2:05	3:00	1:05
Maximum	25:00	11:30	22:45	15:35
Maximum Dose Interval[d]				
N	31	39	32	34
Mean	11:22	10:42	13:58	12:12
Std	5:30	4:06	5:31	6:09
Minimum	3:05	4:10	3:00	4:00
Maximum	25:00	20:50	24:15	32:15

[a] Dose intervals are calculated as the time span (hh:mm) between adjacent doses on patient level
[b] Mean dose interval is calculated as the average dose interval per patient
[c] Minimum dose interval is calculated as the minimum dose interval per patient
[d] Maximum dose interval is calculated as the maximum dose interval per patient
Source: Table 17, EN3203-004 OM IR Study Report, pg. 73

Sponsor's Post-Hoc Analysis Results:

In addition to the planned analysis of LOCF for missing data, the analgesic efficacy endpoints also were analyzed using the Baseline Observation Carried Forward (BOCF) method for missing data. The results using the BOCF method are consistent with those using the LOCF method (see table 4.6 for comparison with the table below) for missing data. Results from a re-analysis of the primary outcome variable are shown below, for illustration. Note that all three formulations of oxymorphone IR showed a statistically significant difference when compared to placebo while oxycodone IR was not significantly different. These results are consistent with the primary outcome analysis (see table 4.6) and support the superiority of OM IR (10, 20, and 30 mg) over placebo, as measured in this situation.

In addition, Dr. Price (Biostatistics) evaluated the sponsor's data for each shorter time interval, using BOCF. The results of her efficacy re-analysis are in agreement with the Sponsor's TOTPAR significance results for the 0-4, 0-6, and 0-8 hour time intervals.

Table EN3203-4.20 Total Pain Relief (TOTPAR) at 0-8 Hours, Re-Analysis using BOCF for Efficacy-Evaluable Patients

Statistics	Oxymorphone 10 mg (N=51)	Oxymorphone 20 mg (N=51)	Oxymorphone 30 mg (N=57)	Oxycodone 10 mg (N=55)	Placebo (N=44)
Descriptive					
N	51	51	57	55	44
Mean	8.4	10.9	10.0	6.1	4.5
SD	6.96	7.20	8.66	5.18	3.33
LSMean	8.3	11.0	9.9	6.1	4.5
Pairwise Comparison vs. PBO [1]					
LSMean Difference	3.8	6.6	5.4	1.6	-
StdErr	1.35	1.36	1.32	1.32	-
P-value	0.005	<0.001	<0.001	0.230	-
95% CI	(1.2, 6.5)	(3.9, 9.2)	(2.8, 8.0)	(-1.0, 4.2)	-

The Total Pain Relief (TOTPAR) at 0-8 hours is defined as the area under the pain relief (Categorical) scores over the 0-8 hour interval.
Pain Relief (Categorical) is measured on a five point scale: 4 = complete, 3 = a lot, 2 = some, 1 = a little, and 0 = none.
BOCF - baseline observation carried forward is used in handling missing data.
[1] All pairwise comparison statistical results are between corresponding active treatment and placebo. ANOVA model is used including main effects for treatment, center, surgical site and baseline pain stratification in the model.
Source: Appendix 16.2.2, Table 4.13.1.1, EN3202-004 Clinical Study Report, pg. 1 of 1.

7.3.3 Efficacy Conclusions for EN3203-004:

This 48-hour, single and multi-dose, placebo- and active-controlled study in patients with post-operative pain was intended to support a finding of efficacy for oxymorphone IR. The Sponsor's analysis of the primary outcome variable (total pain relief from 0 to 8 hours or TOTPAR8) for the single-dose phase of the study did reveal statistically significant differences from placebo for OM 10, 20, and 30 mg IR. No corresponding difference was see between placebo and oxycodone IR. Re-analysis using an 'all randomized population' and baseline observations carried forward confirmed the Sponsor's findings.

The majority of secondary outcomes favored the oxymorphone formulations over placebo, with a trend towards greater efficacy response with OM 30 mg. There were few exceptions to this trend (4 out of 18 listed secondary outcomes, not counting time varying PR, PID, and PRID). Time to First Perceptible Pain Relief' showed no statistical difference from placebo for any active treatment. The 'Proportion of Patients with Pain Half-Gone' demonstrated a statistically significant difference between the OM 10 and 20 mg groups, compared to placebo, but not for the highest dose of OM 30 mg. The 'Patient Global Evaluation of Pain Medication-Single Dose' and 'Time to 50% Pain Relief' both favored OM 10 and 20 mg over the OM 30 mg IR dose. While the explanation for these findings is not entirely clear, one possibility is that lower oxymorphone doses are better tolerated. Oxycodone IR showed no statistical difference to placebo on all secondary outcomes.

The Sponsor performed an exploratory analysis to evaluate the average dosing interval for oxymorphone IR, by averaging the time duration of multiple dosing divided by the number of doses, for individual subjects. The resulting interval varied from

approximately 7 hours and 50 minutes to 10 hours, which only roughly overlaps the proposed interval of q6 to 8 hours, and was longer than the protocol specified interval of q4 to 6 hours. In addition, substantial percentages of subjects had been withdrawn by 4 hours (approximately 50% for OM groups). These findings do not support the Sponsor's recommended dosing interval. The clinical findings and peak/trough data from single- and multi-dose PK studies of oxymorphone IR suggest a more frequent dosing interval such as every 4 hours, possibly up to every 6 hours.

In summary, all three oxymorphone formulations demonstrated a statistically significant difference to placebo as assessed by the primary efficacy endpoint and support the sponsor's claim of efficacy for the three formulations, with some evidence for a greater dose response to oxymorphone 30 mg.

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7.3.4 STUDY EN3203-005:

Title: A Multicenter, Randomized, Double-Blind, Placebo and Active Controls, Single-Dose Study of Oxymorphone IR and Oxycodone IR in Patients With Pain Following Orthopedic Surgery.

Objectives:

- Primary:
  Compare efficacy of 10 mg and 20 mg oxymorphone (OM) IR to placebo in patients with acute moderate to severe pain following orthopedic surgery

- Secondary:
  1. Compare relative analgesic efficacy of OM IR 10 mg and OM IR 20 mg with oxycodone (OC) IR 15 mg and oxycodone (OC) IR 30 mg.
  2. Compare safety and tolerability of OM IR 10 mg and OM IR 20 mg vs. OC IR 15 mg and OC IR 30 mg.

Study Design: Multicenter, randomized, double-blind, placebo and active-controlled, single-dose study with in patients having post osteotomy induced pain

Study Duration: single-dose, up to 8 hours

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

Inclusion Criteria:

- Male or female patients ≥ 18 years that were to undergo orthopedic surgery (involving osteotomy and requiring hospitalization) within 72 hours of study enrollment
- Subjects were to be in general good health
- Subjects were to have an initial moderate to severe pain intensity (PI) on a categorical scale and ≥ 50 mm on a VAS PI scale, between 45 minutes and 6 hours of PCA analgesia discontinuation.
- Women were to be of non-childbearing potential, non-lactating, and were to have a negative urine pregnancy test within 7 days before screening.
- Subjects were to be able to tolerate oral analgesics

Exclusion Criteria:

- No subjects were to have received an investigational drug within 30 days
- No subjects may have taken any of the following:
  - long-acting oral or parenteral analgesics within 12 hours of dosing
  - Short-acting parenteral/oral analgesics within 6 hours of dosing
  - MAOI use within 2 weeks or dextromethorphan containing preparation within 2 days of study entry

- No subjects were to have a history of seizures or opioid abuse or chronic use within 6 months of study

Study Design:

- Dose Selection, Concomitant Therapy and Rescue

Study Drug Dose Selection:
The selected doses of OC IR were known to have effectiveness in acute pain. OM is structurally similar to hydromorphone, which is approximately 2-4 times as potent as OC given orally. Accordingly, doses of 10 mg and 20 mg of OM IR were chosen based on relative potency.

Study Drug:
Each patient was to receive a single dose (2 capsules) of blinded study medication. Each tablet of active medication (OM IR 10 mg or OC IR 5 mg) was to be over-encapsulated to preserve blinding. Target doses of study medication were to be achieved as illustrated in Table 5.0, below.

Table EN3203-5.0 Description of Study Drug

Treatment Group	Number of Capsules		
	Oxycodone IR 15 mg	Oxymorphone IR 10 mg	Placebo
Oxymorphone IR 10 mg	0	1	1
Oxymorphone IR 20 mg	0	2	0
Oxycodone IR 15 mg	1	0	1
Oxycodone IR 30 mg	2	0	0
Placebo	0	0	2

Data Source: Table 1, EN3203-005 Clin Study Report, pg. 22

Concomitant Therapy:

- PROHIBITED – MAOI drugs within 2 weeks of dosing until completion, short-acting (except for PCA) or long-acting analgesics (opioid, non-opioid, or NSAID) for at least 6 hours prior to study dosing for the short-acting agents and 12 hours prior, for the long-acting analgesics

- ALLOWED - Zofran or other antiemetics (such as Compazine) if given at least 4 hours prior to dosing, previously started continuous passive motion (CPM) was to remain constant during 1st 4 hours of study

- OTHER – Any concomitant therapy used within 24 hours prior to surgery through 24 hours after dosing was to be reported on the CRF

Postoperative Therapy:

- PROHIBITED – epidural PCA opioids were not to be allowed

- ALLOWED – Non-epidural PCA opioids were to be allowed and recorded in each patients CRF.

Rescue Medication:

- Rescue medication was to be allowed per the investigator's choice. Subjects were to be encouraged to wait at least 2 hours before requesting rescue medication, and subjects requiring rescue before the 8-hour assessment were to be withdrawn from the study.

- Study Procedures:

1. Screening Phase:
- Inclusion and Exclusion criteria were to be assessed
- Medical history, prior and concomitant meds, vital signs, informed consent were to be obtained

2. Surgical/Post-Op Phase:
- Surgical details, procedure type, anesthesia used, pre-and post-op medications were to be recorded in each patients CRF
- Post-op PCA opioids were to be started as analgesia after surgery

3. Randomization and Treatment Phase:
- Postoperative PCA analgesia was to stopped within 24 to 72 hours of surgery
- Pain Intensity (PI) was to reach entry level (mod-severe categorical and ≥ 50 mm VAS) over the observation period of 45 mins to 6 hours (max) after stopping the patient's postoperative PCA analgesia.
- Eligible subjects were to be randomized to treatment and given two blinded capsules (single-dose) of study medication, subjects were also to be given two stopwatches with instructions on when to stop each one
- Efficacy (pain relief and pain intensity) assessments were to be assessed at 15, 30, 45, and 60 minutes post-dosing, and hourly beyond that until early withdrawal or 8 hours reached
- Subjects were to be encouraged to wait at least until 2 hours after dosing before requesting rescue medication.

4. End of Study Visit:
- Was to occur at the end of 8 hours or at early withdrawal (when requested rescue or discontinued for other reasons)
- Was to consist of global efficacy evaluation, AE assessments
- Subjects were to report AEs and concomitant meds up to 24 hours post-dosing

Table EN3203-5.1 Schedule of Protocol Assessments

			Assessment Time After Dose											
			Minutes			Hours								
Assessment	**Screening**	**Baseline[a,b]**	**15**	**30**	**45**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8 (or Rescue)**	**Exit Evaluation[c]**
Informed Consent	X													
Demographics	X													
Medical History	X	update												
Incl/Excl Criteria	X	X												
Assess Entry Criteria	X	X												
Vital Signs	X	X				X	X		X		X		X	X
Randomization		X												
Adverse Events			X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study Drug Administration		X												
Pain Evaluations:														
Current Pain Intensity (categorical/PIVAS)		X	X	X	X	X	X	X	X	X	X	X	X	
Current Pain Relief (categorical/ PRVAS)			X	X	X	X	X	X	X	X	X	X	X	
Time to Perceptible and Meaningful Pain Relief		start watches	Stop when first perceptible & meaningful relief reached											
Patient s Global Assessment													X	X

[a] After surgery.
[b]Assessment just prior to first dose.
[c]To be completed after withdrawal from study.
Data Source: EN3203-005 Clinical Study Report, Table 2, pg.25

Outcome Measures:

Efficacy (see Appendix 11.2 for detailed information regarding efficacy instruments):

1) Pain Relief (VAS and categorical scales) was to be assessed at baseline, 15, 30, and 45 minutes post dosing, and then hourly over 8 hours.
2) Pain Intensity (VAS and categorical) was to be evaluated similarly to pain relief.
3) Pain Intensity Differences, Sum of Pain Intensity Differences were to be computed from the measures assessed in 1) and 2).
4) Time to … Perceptible Pain Relief, Meaningful Pain Relief, Re-Medication, and Pain At Least Half-Gone were to be measured using stopwatch times.
5) Patient's Global Assessment of Pain Relief from the study medication (5 point categorical scale, ratings from poor (1) to excellent (5)).

Safety:

Adverse events (AEs), and vital signs (see schedule for details).

Statistical Assessment:

Primary efficacy endpoint was to be based on the intent-to-treat (ITT) patient population. All statistical tests were to be two-sided, with statistical significance denoted by a p-value of 0.05 or less, unless otherwise stated.

Primary Efficacy Variables:

- Total Pain Relief ($TOTPAR_8$, VAS): This was to be calculated as the area under the curve (AUC) of the pain relief (PR) scores from baseline (0) to 8-hours. This was to be analyzed using Analysis of Variance (ANOVA) with effects for treatment, center, and baseline pain stratification. Pair-wise comparisons between OM IR 10 mg and 20 mg to PBO were to be performed using the step-down procedure.

Secondary Efficacy Variables:

- Total Pain Relief in 0-8 hours – $TOTPAR_8$ (categorical)
- Sum of Pain Intensity Difference (SPID) with VAS and categorical scales 0-8 hours.
- 4 and 6-hour Total Pain Relief scores (TOTPAR) – (VAS and categorical)
- 4 and 6-hour Sum of Pain Intensity Differences (SPID) – (VAS and categorical)
- Proportion and time (in hours) when patients first experienced 50% pain relief
- Time to First Perceptible pain Relief
- Time to Onset of Meaningful pain Relief
- Time to Remedication
- Hourly Pain Relief (PR) and PID scores
- Patient's Global Evaluation of Study Medication.

Data Sets:

- Intent to Treat (ITT) – This was defined to be all patients randomized to treatment, took first dose, and completed the 1st hour efficacy evaluation
- Safety Population – all patients randomized and received ≥ 1 dose of study medication

Data Imputation:

- Subjects withdrawing early or re-medicated after the1st hour were to have the last observation prior to withdrawal carried forward (LOCF).

Additional Analyses:

- The relative potency of OM IR to OC IR was to be assessed using a regression analysis of the TOTPAR and SPID scores.

- SAP was finalized on 3/18/02 and specified additional analyses of the analgesic efficacy endpoints (TOTPAR, SPID, and SPRID for 0-8, 0-6, and 0-4 hours [categorical and VAS]; hourly pain relief scores; hourly pain intensity difference scores; and hourly combined pain relief and pain intensity difference [categorical and VAS]) using the baseline observation carried forward (BOCF) method were performed.

Protocol Amendments:
Protocol amendments were evaluated by inspecting the Sponsor supplied clinical study report summary and original protocol with amendments.

Protocol Amendment 1 (6/25/01):
- Intramuscular IM and non-PCA opioid analgesia was added to the allowed post-op medications, 9 hours was specified as time allowed for patients to develop sufficient pain after last dose of IM opioids, in order to randomize.
- Various administrative changes

Protocol Amendment 2 (8/30/01):
- Typographical errors in the designation of the strength of oxymorphone IR (10 mg) were corrected
- The upper boundaries of washout for post-operative analgesia were simplified to state that '...within 72 hours following surgery all analgesic medication will be stopped.'
- Wash-out periods for short-acting parenteral, IM (or Epidural), and oral analgesics were clarified
- Inclusion criteria #4 was amended to specifically list the short acting analgesics allowed post-operatively
- Inclusion criteria #7 (post-operative short-acting analgesia before 6 hours prior to study dosing) was removed
- Randomization phase post-op analgesia specific wash-out times clarified
- Restriction of post-operative epidural analgesics removed

Protocol Amendment 3 – (1/28/02):
- The primary efficacy variable TOTPAR8 was changed to a categorical variable (formerly used VAS score)
- The secondary efficacy variable TOTPAR8 was changed to the VAS variable (formerly was categorical)
- The ITT population was modified to include all patients who received study medication, completed the 1st hour efficacy evaluations, and were not remedicated within the first hour.

SAP Changes (3/18/02):
- The efficacy analysis population was renamed 'efficacy-evaluable' (formerly ITT in the protocol) and was clarified to include all patients who received study medication, completed the first hour efficacy evaluations without remedicating, vomiting or significant protocol violations.

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7.3.5 SPONSOR RESULTS for EN3203-005:

Disposition:

All 324 randomized patients received one dose of study medication. The distribution of randomized patients among treatment groups was similar. 300/324 patients (92.6%) completed the study and 24 of 324 patients (7.4%) withdrew. The pattern of withdrawals and discontinuations is illustrated in Table 5.2a below.

Table EN3203-5.2a Patient Disposition

	Oxymorphone 10 mg	Oxymorphone 20 mg	Oxycodone 15 mg	Oxycodone 30 mg	Placebo
Randomized	63 (100.0)	67 (100.0)	65 (100.0)	63 (100.0)	66 (100.0)
Treated Patients [1]	63 (100.0)	67 (100.0)	65 (100.0)	63 (100.0)	66 (100.0)
Completed Study	58 (92.1)	64 (95.5)	60 (92.3)	60 (95.2)	58 (87.9)
Hour 8 evaluation completed	8 (12.7)	16 (23.9)	10 (15.4)	13 (20.6)	4 (6.1)
Rescued after Hour 1, but before Hour 8 evaluation	50 (79.4)	48 (71.6)	50 (76.9)	47 (74.6)	54 (81.8)
Discontinued	5 (7.9)	3 (4.5)	5 (7.7)	3 (4.8)	8 (12.1)
Rescued prior to Hour 1 evaluation	3 (4.8)	1 (1.5)	2 (3.1)	2 (3.2)	3 (4.5)
Vomited prior to Hour 1	2 (3.2)	-	-	-	1 (1.5)
Adverse Event	-	2 (3.0)	2 (3.1)	1 (1.6)	4 (6.1)
Protocol Violation	-	-	1 (1.5)	-	-
Reviewer AEs	**2 (3.2)**	**2 (3.0)**	**2 (3.1)**	**1 (1.6)**	**5 (7.6)**
Efficacy-Evaluable Patients [2]	56 (88.9)	65 (97.0)	62 (95.4)	60 (95.2)	59 (89.4)

Source Data: Table 3. EN3203-005 OM IR Clinical Study Report, pg. 38.
[1] Treated Patients: All patients who were randomized and received study medication.
[2] Efficacy-Evaluable Patients: All patients who received study medication and completed the first-hour primary efficacy evaluation, without being re-medicated, without vomiting within the first hour, or without significant protocol violation (see Table 4 for listing of patients).
Reviewer AEs = Sponsor AEs + # Discontinued for vomiting prior to hour 1

Patients receiving placebo withdrew from the study at higher rates (8/66, or 12%) than patients receiving active treatments (range: OM 10 mg - 7.9%, OM 20 mg – 4.5%, OC 15 mg - 7.7%, and OC 30 mg – 4.8%, respectively). The most common reasons for withdrawal from the study was the use of rescue medication prior to the 1-hour evaluation (11/324 or 3.4%) and AEs (9/324 or 2.8%). This reviewer found the distinction between AE and 'vomiting prior to hour 1' problematic and combined these numbers in a row shown in bold type, within the Sponsor's disposition table. The pattern of discontinuation for reviewer re-calculated AEs was actually slightly larger (12/324 or 3.7%) than the Sponsor's total. Oxycodone had the lowest rate of discontinuation due to AEs (1.6%) compared to OM (3.0 – 3.2%) and PBO (7.6%). The category discontinued due to 'rescued prior to hour 1 evaluation', is probably a proxy for 'lack of efficacy.' Given this, OM 10 mg (4.8%) and PBO (4.5%) discontinued for this reason the most with oxycodone (1.6%) discontinuing the least.

Proportions of study completion rates show that relatively small numbers of subjects finished the full 8-hour evaluation (12.7% for OM 10, 23.9% for OM 20 mg, 15.4% for OC 15 mg, 20.6% for OC 30 mg, and 6.1% for PBO). In contrast, roughly similar proportions of the study groups required rescue medication over the course of the 8 hour evaluation (71.6 to 81.8%).

The Sponsor's analysis population was refined by excluding twenty two (22) patients from the efficacy evaluable population due to remedication within the first hour, vomiting, or other protocol violations. Table 5.2b lists the reasons for subject exclusions in detail, for comparison with Table 5.2a.

Table EN3203-5.2b Patients Excluded from the Efficacy Evaluable Population

Site ID	Patient ID	Reason	Protocol Criteria
		Placebo	
101	013	Vomited prior to 1 hour	No vomiting prior to 1 hour
104	068	Used Vioxx at 12:19 am, and dosed at 12:20 pm	Required washout of ≥24 hours
301	011	Rescued prior to 1 hour	No rescue prior to 1 hour
301	169	Rescued prior to 1 hour	No rescue prior to 1 hour
302	034	Rescued prior to 1 hour	No rescue prior to 1 hour
303	025	Rescued prior to 1 hour	No rescue prior to 1 hour
401	001	Interval between IV PCA and study dosing was >12 hours	Required interval of 45 minutes to 12 hours
		Oxymorphone IR 10 mg	
102	029	Vomited prior to 1 hour	No vomiting prior to 1 hour
105	001	Interval between IV-PCA and study dose was > 12 hours	Required interval of 45 minutes to 12 hours
201	014	Used Dilaudid IM 2 hrs. 9 min. pre-dose	Required post IM analgesia washout of at least 4 hour prior to dosing
301	151	Rescued prior to 1 hour	No rescue prior to 1 hour
301	168	Rescued prior to 1 hour	No rescue prior to 1 hour
301	179	Rescued prior to 1 hour	No rescue prior to 1 hour
302	161	Vomited prior to 1 hour	No vomiting prior to 1 hour
		Oxymorphone IR 20 mg	
303	077	Rescued prior to 1 hour	No rescue prior to 1 hour
401	002	Interval between IV-PCA and study dose was over12 hours	Required interval of 45 minutes to 12 hours
		Oxycodone IR 15 mg	
301	021	Rescued prior to 1 hour	No rescue prior to 1 hour
302	024	Rescued prior to 1 hour	No rescue prior to 1 hour
104	042	Used Demerol IM 2 hrs. 5 min. pre-dose	Required post IM analgesia washout of at least 4 hour prior to dosing
		Oxycodone IR 30 mg	
301	085	Rescued prior to 1 hour	No rescue prior to 1 hour
301	109	Rescued prior to 1 hour	No rescue prior to 1 hour
302	166	Used Celebrex at 8:00 am, and dosed at 8:46 am	Required washout of ≥24 hours

Data Source: Table 4, EN3203-005 Clin Study Report, pg. 39

Protocol Violations:

Patient (303-093) was the only protocol violator. This patient received a prohibited medication after the 2-hour efficacy assessment, and was then discontinued.

Demographic and Baseline Characteristics:

Detailed demographic data is shown in table 5.3 below. The majority of patients were female and Caucasian with a mean age ranging from 60.1 to 64.4 years across treatment groups (range: 22.5 - 91.7 years). Other demographic characteristics were similar across treatment groups (see table below).

Baseline categorical pain values were distributed in similar proportions of moderate (OM 10 mg – 68%, OM 20 mg – 64%, OC 15 mg – 69%, OC 30 mg – 73%, and PBO – 70%, respectively) and severe (OM 10 mg – 32%, OM 20 mg – 36%, OC 15 mg – 31%, OC 30 mg – 27%, and PBO – 30%, respectively) pain intensity across treatment groups.

Table EN3203-5.3 Demographics and Baseline Measures

	Oxymorphone 10 mg (N=63)	Oxymorphone 20 mg (N=67)	Oxycodone 15 mg (N=65)	Oxycodone 30 mg (N=63)	Placebo (N=66)
Age (yrs.)					
N	63	67	65	63	66
MEAN	60.8	64.4	60.4	60.1	63.5
STD	12.93	12.91	14.64	11.07	14.12
MIN	24.2	28.6	22.5	38.8	27.9
MAX	78.1	86.3	82.1	83.5	91.7
Sex - N (%)					
Male	32 (50.8)	27 (40.3)	29 (44.6)	26 (41.3)	34 (51.5)
Female	31 (49.2)	40 (59.7)	36 (55.4)	37 (58.7)	32 (48.5)
Race - N (%)					
African American	3 (4.8)	3 (4.5)	3 (4.6)	3 (4.8)	2 (3.0)
Caucasian	60 (95.2)	59 (88.1)	58 (89.2)	57 (90.5)	61 (92.4)
Native American	0	1 (1.5)	0	0	0
Hispanic or Latino	0	4 (6.0)	4 (6.2)	3 (4.8)	3 (4.5)
Height (in.)					
N	63	67	64	62	66
MEAN	67.8	67.2	66.9	67.4	67.6
STD	4.96	5.33	4.16	4.02	4.67
MIN	54.0	60.0	60.0	60.0	60.0
MAX	80.7	85.4	79.6	81.9	80.7
Weight (lb.)					
N	63	67	64	62	66
MEAN	205.1	197.7	192.1	200.8	193.9
STD	44.69	40.18	46.31	45.57	38.61
MIN	121.0	117.0	105.0	100.0	113.0
MAX	335.2	320.0	325.0	385.9	300.0
Baseline Pain Intensity (Categorical)					
Moderate	43 (68.3)	43 (64.2)	45 (69.2)	46 (73.0)	46 (69.7)
Severe	20 (31.7)	24 (35.8)	20 (30.8)	17 (27.0)	20 (30.3)

Source Data: Table 6, EN3203-005, Clinical Study Report, pg. 41.

Concomitant Medications:

The following table shows the distribution of selected concomitant medications used by patients in this study by general drug class, across the treatment groups. This reviewer selected the most common classes, focusing on analgesics. Inspection of the table shows natural opium alkaloids, cephalosporins, vitamin k antagonists, and opioid anesthetics. The distribution of medications appear to be generally equal across treatment groups and are consistent with medications used in the peri-operative setting (in this case this was the period from 24 hours prior to surgery to 24 hours post-dosing with study medication). The vitamin K antagonists and acetic acid derivatives were not clearly defined and a request was sent to the Sponsor for clarification of what these medications included. The Sponsor clarified that the Vitamin K reference was to the Vitamin K agonist warfarin. Acetic Acid Derivatives referred to toradol and keterolac.

Table EN3203-5.4 Concomitant Medications Used

MEDICATIONS	Oxymorphone 10 mg (N=63) n (%)	Oxymorphone 20 mg (N=67) n (%)	Oxycodone 15 mg (N=65) n (%)	Oxycodone 30 mg (N=63) n (%)	Placebo (N=66) n (%)
NATURAL OPIUM ALKALOIDS	63 (100.0)	65 (97.0)	65 (100.0)	62 (98.4)	64 (97.0)
CEPHALOSPORINS AND RELATED SUBSTANCES	53 (84.1)	57 (85.1)	56 (86.2)	55 (87.3)	58 (87.9)
OPIOID ANESTHETICS	49 (77.8)	53 (79.1)	50 (76.9)	55 (87.3)	53 (80.3)
VITAMIN K ANTAGONISTS	35 (55.6)	37 (55.2)	35 (53.8)	35 (55.6)	37 (56.1)
PHENYLPIPERIDINE DERIVATIVES	35 (55.6)	39 (58.2)	29 (44.6)	34 (54.0)	38 (57.6)
SOFTENERS, EMOLLIENTS	31 (49.2)	32 (47.8)	29 (44.6)	25 (39.7)	29 (43.9)
ACETIC ACID DERIVATIVES AND RELATED SUBSTANCES	25 (39.7)	24 (35.8)	29 (44.6)	28 (44.4)	33 (50.0)
OTHER GENERAL ANESTHETICS	28 (44.4)	31 (46.3)	24 (36.9)	22 (34.9)	24 (36.4)
BENZODIAZEPINE DERIVATIVES	21 (33.3)	25 (37.3)	28 (43.1)	25 (39.7)	29 (43.9)

Source: Supplemental Table 1.0, EN3203-005 OM IR Clinical Study Report, pg 79.

Sponsor's Efficacy Analysis Results:

Primary Efficacy Variables:

The Sponsor's analysis using the efficacy evaluable population and LOCF for imputed scores is presented in Table 5.5, which lists the mean total pain relief scores (TOTPAR, categorical) over 4, 6, and 8 hours of this single-dose study. The mean TOTPAR scores for the OM IR 20-mg group, OC IR 15 mg group and OC IR 30 mg group were all statistically significantly different when compared to placebo. The OM IR 10-mg group was not statistically significantly different from placebo. Note that the pairwise comparison p-values are based upon the least squares mean differences, as shown in the lower half of Table 5.5.

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Table EN3203-5.5 Summary of TOTPAR (Categorical) Scores at 0-4, 0-6, and 0-8 Hour Time Intervals for Efficacy-Evaluable Patients

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

Source: Table 8. EN3203-005 Clin Study Report, pg. 43.

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

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

Reviewer Primary Efficacy Re-Analysis Results:

Patients requiring rescue medication and then having their last efficacy observations carried forward (LOCF), may have resulted in inflated efficacy findings for the proposed formulation. For this reason, Dr. Dionne Price (Agency Biostatistics Reviewer) evaluated the Sponsor's efficacy data using the baseline observation carried forward (BOCF) for imputed data. The sponsor also re-performed the primary efficacy analysis using this definition, as a post-hoc analysis. Dr. Price's findings were in agreement with sponsor's conclusions, that the analgesic efficacy endpoints resulting from BOCF were consistent with the results using LOCF.

Sponsor's Efficacy Analysis for Secondary Variables:

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

- Categorical TOTPAR at 0-4 and 0-6 Hour time intervals:
  The mean TOTPAR scores for the OM IR 20-mg group were statistically significantly different from placebo at both 0-6 and 0-4 hour time intervals. However, the OM IR 10-mg mean TOTPAR scores were not statistically significantly different from placebo at these time intervals. Mean TOTPAR scores for both the oxycodone IR 15- and 30-mg groups were statistically significantly from placebo at both 0-6 and 0-4 hour time. See Table 5.5 for result details.

- Pain Relief (Categorical) by Time Point:
  Table 5.6 summarizes the pain relief (categorical scores) over the 8-hour assessment period. LOCF was used for patients who withdrew early. Linear interpolation was applied when missing data occurred between scheduled assessment time. The OM IR 20-mg group showed a consistent statistically significant difference from the placebo group from one to 8 hours. A similar trend also was shown for OC IR 15 mg starting at 1 hour and OC IR 30 mg starting at 45 minutes post-dose. There was no statistical difference between oxymorphone IR 20 mg and either of the OC IR groups, over the time period studied. OM IR 10 mg was not statistically significant different from placebo. In addition, an interesting observation is that substantial percentages of subjects had discontinued from the study by 4 hours in all treatment groups (54% for OM 10, 46% for OM 20, 47% for OC 15, 40% for OC 30, and 81% for placebo).

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Table EN3203-5.6 Summary of Pain Relief (Categorical, Extrapolated) Over 0-8 Hours for Efficacy-Evaluable Patients

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

Source: Table 9, EN3203-005 OM IR Clin. Study Report, pg. 45.

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

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

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

- VAS Total Pain Relief (TOTPAR) at 0-4, 0-6, and 0-8 Hour time intervals: Mean TOTPAR scores, derived from visual analog scale (VAS) pain relief assessment, for the five treatment groups are shown in Table 5.7. The OM IR 20-mg group and both OC IR groups (15 and 30 mg) were statistically significantly different from placebo at all three (0-8, 0-6, and 0-4 hour) time intervals. OM IR 10 mg was not statistically significant different from placebo.

Table EN3203-5.7 TOTPAR (VAS) at 0-4, 0-6, and 0-8 Hours for Efficacy-Evaluable Patients

	TOTPAR		
Treatment/Analysis Factor	**0-4 Hour**	**0-6 Hour**	**0-8 Hour**
Mean (±SD)			
Oxymorphone IR 10 mg (N=56)	145.2 (±113.49)	200.1 (±166.96)	244.6 (±216.58)
Oxymorphone IR 20 mg (N=65)	171.3 (±117.40)	250.1 (±182.16)	312.0 (±236.69)
Oxycodone IR 15 mg (N=62)	184.9 (±114.70)	258.6 (±171.45)	314.0 (±223.18)
Oxycodone IR 30 mg (N=60)	194.4 (±126.30)	275.4 (±192.85)	337.1 (±252.62)
Placebo (N=59)	113.3 (±111.25)	154.2 (±160.22)	187.7 (±202.58)
Pairwise Contrast with Placebo[a]			
Oxymorphone IR 10 mg			
LS Mean Difference	31.1	44.4	54.9
StdErr	21.32	32.06	41.37
P-value	0.146	0.167	0.186
95% CI of Difference	(-10.9, 73.1)	(-18.7, 107.5)	(-26.5, 136.3)
Oxymorphone IR 20 mg			
LS Mean Difference	59.7	98.9	128.4
StdErr	20.50	30.83	39.79
P-value	0.004	0.001	0.001
95% CI of Difference	(19.4, 100.1)	(38.2, 159.6)	(50.1, 206.7)
Oxycodone IR 15 mg			
LS Mean Difference	71.0	103.4	124.7
StdErr	20.72	31.15	40.21
P-value	<0.001	0.001	0.002
95% CI of Difference	(30.2, 111.8)	(42.1, 164.7)	(45.5, 203.8)
Oxycodone IR 30 mg			
LS Mean Difference	80.4	120.1	147.8
StdErr	20.90	31.42	40.56
P-value	<0.001	<0.001	<0.001
95% CI of Difference	(39.2, 121.5)	(58.2, 181.9)	(68.0, 227.6)

Source: Table 10, EN3203-005 Clin Study Report, pg. 46.
[a]All pairwise comparison statistical results are between corresponding active treatment and placebo. ANOVA model is used including main effects for treatment, center, and baseline pain stratification in the model.
Total Pain Relief (TOTPAR) is defined as the area under the pain relief (VAS) scores over corresponding time interval.
Pain Relief (VAS) is measured in 100 mm scale: 0 mm=no relief and 100 mm=total relief.

- Pain Relief (Categorical) by Time Point:

  Table 5.8 summarizes pain relief (VAS) over 0 to 8 hours. OM IR 20 mg was statistically significantly different from placebo over the 8-hour time period starting at 2 hours post-dose. The same trend also was observed for OC IR 15 mg group (starting at 1 hour post-dose) and for OC IR 30 mg group, starting at 45 minutes post-dose up to 8 hours post-dose. OM IR 10 mg was not statistically significant different from placebo. There were no statistically significant differences between the OM IR 20 mg and the OC IR groups.

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Table EN3203-5.8 Summary of Pain Relief (VAS, Extrapolated) Over 0-8 Hours for Efficacy-Evaluable Patients

	Assessment Time Point										
Treatment	**15 min**	**30 min**	**45 min**	**1 hr**	**2 hr**	**3 hr**	**4hr**	**5 hr**	**6 hr**	**7 hr**	**8 hr**
Oxymorphone IR 10 mg											
n	54	55	55	54	41	33	25	18	12	8	7
Mean[a]	19.6 A	31.8 A	41.5 AB	41.1 AB	44.5 BC	37.4 B	35.5 B	34.1 BC	31.6 AB	30.8 AB	29.9 AB
SD[a]	25.13	30.66	34.19	36.31	37.43	36.49	36.53	37.10	36.27	35.91	34.95
Oxymorphone IR 20 mg											
n	63	62	63	63	47	40	33	29	23	18	16
Mean[a]	17.8 A	32.8 A	43.4 AB	44.9 AB	50.6 AB	51.3 A	48.8 A	47.3 A	42.4 A	40.4 A	39.2 A
SD[a]	20.21	32.35	35.60	34.25	36.40	37.30	38.13	38.63	36.71	35.77	34.95
Oxycodone IR 15 mg											
n	61	62	61	60	52	44	33	29	18	13	10
Mean[a]	17.8 A	30.9 A	44.7 AB	51.9 A	56.3 AB	54.4 A	49.7 A	43.6 AB	40.2 A	39.8 A	40.5 A
SD[a]	21.78	30.62	34.94	36.09	35.98	36.80	37.04	37.69	38.16	37.79	38.52
Oxycodone IR 30 mg											
n	60	60	59	60	48	38	36	25	20	17	12
Mean[a]	23.7 A	34.9 A	49.8 A	53.5 A	57.9 A	56.9 A	52.2 A	44.8 AB	42.7 A	37.7 A	36.7 AB
SD[a]	29.27	32.33	35.94	36.63	40.24	39.88	39.95	37.73	37.23	36.13	35.47
Placebo											
n	59	58	59	59	34	20	15	11	9	5	3
Mean[a]	25.4 A	31.8 A	33.4 B	33.5 B	33.7 C	30.7 B	28.6 B	26.1 C	26.5 B	23.7 B	25.1 B
SD[a]	25.09	29.15	30.60	33.58	37.36	35.26	34.90	32.77	33.26	31.51	32.07
Treatment p-value[b]	0.270	0.965	0.127	**0.011**	**0.002**	**<0.001**	**0.001**	**0.005**	**0.036**	**0.034**	0.063

Source: Table 11 EN3203-005 OM IR Clin Study Report, pg. 48.
[a]Mean and Standard Deviation are based on extrapolated data.
[b]Based on ANOVA model including main effects for treatment, center, and baseline pain stratification in the model.
Treatments with a common letter are not significantly different (e.g. treatments with A and AB are not significantly different).
Sample sizes (n) are not extrapolated.

- Sum of Pain Intensity Difference (SPID, Categorical) Over 0-8 Hrs:

Mean SPID (categorical) scores for the five treatment groups are shown below. The OM IR 20-mg group and the OC IR groups were statistically significantly different from placebo at all three (0-8, 0-6, and 0-4 hour) time intervals. OM IR 10 mg was not statistically significant different from placebo.

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Table EN3203-5.9 SPID (Categorical) at 0-4, 0-6, and 0-8 Hours for Efficacy -Evaluable Patients

Treatment/Analysis Factor		SPID 0-4 Hour	SPID 0-6 Hour	SPID 0-8 Hour
Mean (±SD)				
Oxymorphone IR 10 mg (N=56)		2.0 (±2.68)	2.4 (±3.94)	2.6 (±5.43)
Oxymorphone IR 20 mg (N=65)		2.9 (±2.67)	4.1 (±4.20)	4.9 (±5.44)
Oxycodone IR 15 mg (N=62)		3.3 (±3.30)	4.4 (±5.11)	5.0 (±6.68)
Oxycodone IR 30 mg (N=60)		3.3 (±2.75)	4.5 (±4.20)	5.3 (±5.56)
Placebo (N=59)		1.1 (±2.41)	1.3 (±3.46)	1.2 (±4.26)
Pairwise Contrast with Placebo[a]				
Oxymorphone IR 10 mg				
	LS Mean Difference	0.7	0.9	1.1
	StdErr	0.50	0.76	0.99
	P-value	0.141	0.248	0.247
Oxymorphone IR 20 mg				
	LS Mean Difference	1.6	2.7	3.5
	StdErr	0.48	0.73	0.95
	P-value	<0.001	<0.001	<0.001
Oxycodone IR 15 mg				
	LS Mean Difference	2.1	3.1	3.7
	StdErr	0.49	0.74	0.96
	P-value	<0.001	<0.001	<0.001
Oxycodone IR 30 mg				
	LS Mean Difference	2.1	3.1	3.9
	StdErr	0.49	0.74	0.97
	P-value	<0.001	<0.001	<0.001

Source: Table 12 EN3203-005 OM IR Clinical Study Report, pg. 49.
[a]All pairwise comparison statistical results are between corresponding active treatment and placebo. ANOVA model is used including main effects for treatment, center, and baseline pain stratification in the model
Pain intensity (Categorical) is measured using a four point scale, where 3 = severe, 2 = moderate, 1 = mild, and 0 = none.
Pain intensity difference at each time point is calculated as the baseline pain intensity score minus the pain intensity score at that time point.
The Sum of Pain Intensity Difference (SPID) is defined as the area under the pan intensity difference (categorical) scores over time

- Sum of Pain Intensity Difference (SPID, VAS) Over 0-8 Hrs:
  Mean SPID (VAS) scores for the five treatment groups are shown below. The OM IR 20-mg group and the OC IR groups were statistically significantly different from placebo at all three time intervals (0-8, 0-6, and 0-4 hour). The mean SPID score for the OM IR 10-mg group was significantly different from placebo only at the initial 0-4 hour interval.

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Table EN3203-5.10 SPID (VAS) at 0-4, 0-6, and 0-8 Hours for Efficacy -Evaluable Patients

Treatment/Analysis Factor		SPID 0-4 Hour	SPID 0-6 Hour	SPID 0-8 Hour
Mean (±SD)				
Oxymorphone IR 10 mg (N=56)		75.1 (±95.15)	90.4 (±144.78)	98.9 (±195.82)
Oxymorphone IR 20 mg (N=65)		112.4 (±94.16)	159.8 (±147.48)	193.4 (±192.08)
Oxycodone IR 15 mg (N=62)		114.5 (±100.28)	148.3 (±156.78)	163.7 (±209.45)
Oxycodone IR 30 mg (N=60)		116.6 (±87.82)	155.8 (±131.13)	178.5 (±168.42)
Placebo (N=59)		36.6 (±83.92)	40.7 (±124.51)	39.6 (±159.15)
Pairwise Contrast With Placebo[a]				
Oxymorphone IR 10 mg				
	LS Mean Difference	35.9	45.7	54.2
	StdErr	17.35	26.56	34.78
	P-value	0.040	0.087	0.121
Oxymorphone IR 20 mg				
	LS Mean Difference	75.1	118.4	153.0
	StdErr	16.69	25.54	33.45
	P-value	<0.001	<0.001	<0.001
Oxycodone IR 15 mg				
	LS Mean Difference	77.0	106.3	122.3
	StdErr	16.86	25.81	33.80
	P-value	<0.001	<0.001	<0.001
Oxycodone IR 30 mg				
	LS Mean Difference	78.5	113.0	136.0
	StdErr	17.01	26.03	34.09
	P-value	<0.001	<0.001	<0.001

Source: Table 14, EN3203-005 OM IR Clin. Study Report, pg. 52
[a]All pairwise comparison statistical results are between corresponding active treatment and placebo. ANOVA model is used including main effects for treatment, center, and baseline pain stratification in the model.
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 at each time point is calculated as the baseline pain intensity score minus the pain intensity score at that time point.
The Sum of Pain Intensity Difference (SPID) is defined as the area under the pan intensity difference (VAS) scores over corresponding time interval.

- Pain Intensity Difference (PID, Categorical) Over 0-8 Hrs:
  Table 5.11 summarizes the pain intensity difference (PID, categorical) over the 8-hour efficacy assessment period. OM IR 20 mg was statistically significantly different from the placebo group, starting at 45 minutes post-dose. A similar pattern was observed for the OC IR groups starting at 45 minutes, with the exception of the OC IR 30-mg group (which was not significantly different from PBO at 8 hours). OM IR 10 mg was not statistically significant different from placebo. There was no statistically significant difference between OM IR 20 mg and the OC IR groups over the time period.

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Table EN3203-5.11 Summary of Pain Intensity Difference (Categorical, Extrapolated) Over 0-8 Hours for Efficacy -Evaluable Patients

Treatment	Assessment Time Point										
	15 min	30 min	45 min	1 hr	2 hr	3 hr	4hr	5 hr	6 hr	7 hr	8 hr
Oxymorphone IR 10 mg											
n	54	55	55	54	41	33	25	18	12	8	7
Mean[a]	0.4 A	0.5 A	0.7 AB	0.7 BC	0.7 BC	0.6 B	0.5 B	0.4 B	0.4 B	0.4 BC	0.4 BC
SD[a]	0.59	0.64	0.81	0.79	0.80	0.91	0.85	0.91	0.92	0.97	0.95
Oxymorphone IR 20 mg											
n	63	62	63	63	48	40	34	29	23	18	16
Mean[a]	0.2 A	0.5 A	0.8 A	0.9 AB	0.9 AB	0.9 A	0.9 A	0.9 A	0.8 A	0.7 A	0.7 A
SD[a]	0.50	0.73	0.82	0.79	0.85	0.90	0.94	0.93	0.90	0.89	0.85
Oxycodone IR 15 mg											
n	62	62	61	61	52	44	33	29	19	13	10
Mean[a]	0.3 A	0.6 A	0.9 A	1.0 A	1.1 A	1.0 A	0.9 A	0.7 A	0.7 A	0.6 AB	0.6 AB
SD[a]	0.59	0.75	0.83	0.98	0.98	0.99	1.05	1.07	1.03	1.04	1.06
Oxycodone IR 30 mg											
n	60	60	59	60	48	38	36	25	20	17	12
Mean[a]	0.3 A	0.6 A	0.9 A	0.9 A	1.0 A	1.0 A	0.9 A	0.7 A	0.7 A	0.6 AB	0.6 ABC
SD[a]	0.68	0.71	0.81	0.84	0.86	0.89	0.89	0.81	0.82	0.81	0.79
Placebo											
n	59	58	59	59	34	20	15	11	9	5	3
Mean[a]	0.4 A	0.5 A	0.5 B	0.5 C	0.4 C	0.4 B	0.3 B	0.3 B	0.3 B	0.2 C	0.3 C
SD[a]	0.58	0.62	0.70	0.73	0.75	0.72	0.68	0.64	0.70	0.62	0.63
Treatment p-value[b]	0.643	0.633	**0.042**	**0.004**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**0.008**	**0.018**	**0.038**

Source: Table 13, EN3203-005 OM IR Clin. Study Report, pg 51.
[a]Mean and Standard Deviation are based on extrapolated data.
[b]Based on ANOVA model including main effects for treatment, center, and baseline pain stratification in the model.
Treatments with a common letter are not significantly different (e.g. treatments with A and AB are not significantly different).
Sample sizes (n) are not extrapolated.

- Pain Intensity Difference (PID, VAS) Over 0-8 Hrs:
  Table 5.12 presents a summary of pain intensity difference (PID, VAS) over the 8-hour efficacy assessment period. OM IR 20 mg and both OC IR groups (15 and 30 mg) were consistently statistically significantly different from placebo (starting at 45 minutes, 1 hour, and 45 minutes post-dose, respectively). OM IR 10 mg was not significantly different from placebo, with exception of the 2-hour post-dose timepoint. There were no statistically significant differences between the OM IR 20 mg group and either OC IR group.

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Table EN3203-5.12 Summary of Pain Intensity Difference (VAS, Extrapolated) Over 0-8 Hours for Efficacy-Evaluable Patients

Treatment	Assessment Time Point										
	15 min	30 min	45 min	1 hr	2 hr	3 hr	4hr	5 hr	6 hr	7 hr	8 hr
Oxymorphone IR 10 mg											
n	54	55	55	54	41	33	25	18	12	8	7
Mean[a]	9.1	18.9	25.8	23.5	24.8	18.7	16.3	14.3	13.0	12.9	12.6
	AB	A	AB	BC	B	B	B	B	BC	BC	BC
SD[a]	18.90	25.15	28.69	28.40	29.96	30.30	30.43	31.92	31.68	31.19	30.93
Oxymorphone IR 20 mg											
n	63	62	63	63	48	40	34	29	23	18	16
Mean[a]	6.9	17.6	29.4	31.9	34.6	35.9	33.1	31.1	27.4	25.2	24.1
	B	A	A	AB	A	A	A	A	A	A	A
SD[a]	14.60	24.49	29.66	27.96	28.72	30.98	32.43	31.26	29.97	29.64	29.22
Oxycodone IR 15 mg											
n	61	62	61	60	52	44	33	28	19	13	10
Mean[a]	11.5	19.1	27.7	33.2	38.4	34.3	30.7	24.9	22.2	21.6	21.5
	AB	A	AB	AB	A	A	A	A	AB	AB	AB
SD[a]	17.92	25.51	27.57	29.20	29.65	29.96	32.87	33.66	35.36	35.21	35.80
Oxycodone IR 30 mg											
n	60	60	59	60	48	38	36	25	20	17	12
Mean[a]	13.4	20.9	30.5	36.7	35.8	34.7	30.9	25.4	24.8	20.7	19.7
	AB	A	A	A	A	A	A	A	A	AB	AB
SD[a]	22.43	23.62	27.09	26.46	28.37	29.71	28.76	27.89	27.52	28.38	28.45
Placebo											
n	59	58	59	59	34	20	15	11	9	5	3
Mean[a]	13.8 A	16.9 A	17.5 B	16.0 C	11.7 C	10.1 B	8.36 B	8.69 B	8.68 C	7.64 C	7.75 C
SD[a]	19.95	23.72	26.20	27.49	26.62	25.07	24.76	24.76	25.69	24.54	24.63
Treatment p-value[b]	0.182	0.922	0.106	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**0.002**	**0.009**	**0.016**

Source: Table 15, EN3203-005 Clin Study Report, pg. 54.

*a*Mean and Standard Deviation are based on extrapolated data.
*b*Based on ANOVA model including main effects for treatment, center, and baseline pain stratification in the model.
Treatments with a common letter are not significantly different (e.g. treatments with A and AB are not significantly different).
Sample sizes (n) are not extrapolated.

- Sum of Combined Pain Relief and Pain Intensity Difference (SPRID, Categorical) Over 0-8 Hrs:

  Mean SPRID (categorical) scores, derived from categorical pain relief and pain intensity assessments, for the five treatment groups are shown in Table 5.13. The mean SPRID scores for OM IR 20 mg and both OC IR groups were statistically significantly different compared with placebo at all three (0-8, 0-6, and 0-4 hour) time intervals. However, OM IR 10-mg group did not show a significant difference from placebo.

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Table EN3203-5.13 SPRID (Categorical) at 0-4, 0-6, and 0-8 Hour Time Intervals for Efficacy -Evaluable Patients

	SPRID		
Treatment/Analysis Factor	**0-4 Hour**	**0-6 Hour**	**0-8 Hour**
Mean (±Std)			
Oxymorphone IR 10 mg (N=56)	7.8 (±6.55)	10.3 (±9.51)	12.4 (±12.66)
Oxymorphone IR 20 mg (N=65)	9.7 (±6.73)	14.0 (±10.48)	17.2 (±13.54)
Oxycodone IR 15 mg (N=62)	10.8 (±7.31)	14.9 (±11.15)	17.8 (±14.56)
Oxycodone IR 30 mg (N=60)	10.6 (±7.06)	14.8 (±10.92)	18.0 (±14.47)
Placebo (N=59)	5.6 (±6.24)	7.3 (±8.84)	8.5 (±10.80)
Pairwise Contrast with Placebo[a]			
Oxymorphone IR 10 mg			
LS Mean Difference	1.9	2.6	3.4
StdErr	1.25	1.88	2.44
P-value	0.122	0.168	0.166
Oxymorphone IR 20 mg			
LS Mean Difference	4.0	6.6	8.6
StdErr	1.20	1.81	2.35
P-value	**<0.001**	**<0.001**	**<0.001**
Oxycodone IR 15 mg			
LS Mean Difference	5.1	7.4	9.1
StdErr	1.21	1.83	2.37
P-value	**<0.001**	**<0.001**	**<0.001**
Oxycodone IR 30 mg			
LS Mean Difference	4.9	7.3	9.2
StdErr	1.23	1.85	2.39
P-value	**<0.001**	**<0.001**	**<0.001**

Source: Table 16, EN3203-005 Clin. Study Report, pg. 55.

[a]All pairwise comparison statistical results are between corresponding active treatment and placebo. ANOVA model is used including main effects for treatment, center, and baseline pain stratification in the model.
Pain Relief (Categorical) is measured using a five point scale, where 4=complete, 3=a lot, 2=some, 1=a little and 0 = none.
Pain Intensity (Categorical) is measured in a four point scale, where 3=severe, 2=moderate, 1=mild and 0=none. Pain intensity difference at each time point is calculated as the baseline pain intensity score minus the pain intensity score at that time point.
The Sum of Combined Pain Relief and Pain Intensity Difference (SPRID) is defined as the area under the sum of pain relief and pain intensity difference (categorical) scores over corresponding time interval.

- Combined Pain Relief and Pain Intensity Difference (PRID, Categorical) by Timepoint:

  Table 5.14 summarizes the combined pain relief and pain intensity difference (SPRID, categorical) over the 8 hour efficacy assessment period. OM IR 20 mg and the OC IR groups were consistently statistically significantly different when compared with the placebo group starting at 1 hour and 45 minutes post-dose, respectively. OM IR 10 mg was not statistically significantly different from placebo.

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Table EN3203-5.14 Summary of Combined PR and PI Difference (Categorical, Extrapolated) Over 0-8 Hours for Efficacy -Evaluable Patients

	Assessment Time Point										
Treatment	**15 min**	**30 min**	**45 min**	**1 hr**	**2 hr**	**3 hr**	**4hr**	**5 hr**	**6 hr**	**7 hr**	**8 hr**
Oxymorphone IR 10 mg											
n	54	55	55	54	41	33	25	18	12	8	7
Mean[a]	1.3 AB	1.9 A	2.4 AB	2.3 BC	2.5 BC	2.1 B	1.8 B	1.7 B	1.6 BC	1.6 AB	1.6 AB
SD[a]	1.51	1.64	1.96	2.00	2.04	2.14	2.07	2.15	2.15	2.24	2.16
Oxymorphone IR 20 mg											
n	63	62	63	63	47	40	34	29	23	18	16
Mean[a]	1.0 B	1.8 A	2.5 AB	2.7 AB	2.9 AB	2.9 A	2.8 A	2.7 A	2.4 A	2.3 A	2.2 A
SD[a]	1.25	1.82	2.05	1.96	2.04	2.17	2.26	2.23	2.14	2.09	2.00
Oxycodone IR 15 mg											
n	62	62	61	61	52	44	33	29	19	13	10
Mean[a]	1.2 AB	1.9 A	2.7 A	3.1 A	3.4 A	3.1 A	2.8 A	2.5 A	2.3 AB	2.2 A	2.2 A
SD[a]	1.42	1.80	1.98	2.20	2.19	2.25	2.31	2.36	2.32	2.34	2.37
Oxycodone IR 30 mg											
n	60	60	59	60	48	38	36	25	20	17	12
Mean[a]	1.3 AB	2.1 A	2.8 A	3.0 A	3.2 A	3.2 A	2.9 A	2.4 A	2.3 A	2.1 A	2.1 A
SD[a]	1.68	1.76	2.00	2.02	2.23	2.26	2.32	2.12	2.11	2.07	2.03
Placebo											
n	59	58	59	59	34	20	15	11	9	5	3
Mean[a]	1.5 A	1.8 A	1.9 B	1.8 C	1.7 C	1.6 B	1.4 B	1.3 B	1.3 C	1.1 B	1.2 B
SD[a]	1.43	1.60	1.75	1.90	2.07	1.96	1.84	1.77	1.87	1.63	1.68
Treatment p-value[b]	0.304	0.882	0.081	**0.002**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**0.010**	**0.008**	**0.016**

Source: Table 17, EN3203-005 Clin. Study Report, pg.57
[a]Mean and Standard Deviation are based on extrapolated data.
[b]Based on ANOVA model including main effects for treatment, center, and baseline pain stratification in the model.
Treatments with a common letter are not significantly different (e.g. treatments with A and AB are not significantly different).
Sample sizes (n) are not extrapolated.

- Sum of Combined Pain Relief and Pain Intensity Difference (SPRID, VAS) Over 0-8 Hrs:
  Mean SPRID (VAS) scores, derived from VAS pain relief and pain intensity assessments, for the five treatment groups are shown in Table 5.15. The mean SPRID scores for OM IR 20-mg group and both OC IR groups were statistically significantly different when compared with placebo at all three time intervals (0-8, 0-6, and 0-4 hours). However, the oxymorphone IR 10-mg group did not show a statistically significant difference compared with the placebo group.

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Table EN3203-5.15 SPRID (VAS) at 0-4, 0-6, and 0-8 Hour Time Intervals for Efficacy -Evaluable Patients

	SPRID		
Treatment/Analysis Factor	**0-4 Hour**	**0-6 Hour**	**0-8 Hour**
Mean (±SD)			
Oxymorphone IR 10 mg (N=56)	220.3 (±201.11)	290.4 (±296.93)	343.5 (±389.07)
Oxymorphone IR 20 mg (N=65)	283.3 (±206.25)	409.3 (±321.18)	504.7 (±415.72)
Oxycodone IR 15 mg (N=62)	299.4 (±210.73)	407.6 (±321.03)	480.0 (±420.78)
Oxycodone IR 30 mg (N=60)	311.1 (±210.68)	431.2 (±318.65)	515.7 (±413.31)
Placebo (N=59)	150.0 (±184.58)	194.9 (±265.26)	227.3 (±331.10)
Pairwise Contrast With Placebo[a]			
Oxymorphone IR 10 mg			
LS Mean Difference	67.0	90.0	108.7
StdErr	37.66	56.81	73.29
P-value	0.076	0.114	0.139
Oxymorphone IR 20 mg			
LS Mean Difference	134.5	216.7	280.7
StdErr	36.22	54.64	70.49
P-value	**<0.001**	**<0.001**	**<0.001**
Oxycodone IR 15 mg			
LS Mean Difference	148.0	210.4	249.1
StdErr	36.60	55.21	71.22
P-value	**<0.001**	**<0.001**	**<0.001**
Oxycodone IR 30 mg			
LS Mean Difference	158.8	233.0	283.6
StdErr	36.92	55.69	71.84
P-value	**<0.001**	**<0.001**	**<0.001**

Source: Table 18, EN3203-005 Clin. Study Report, pg. 58.
[a]All pairwise comparison statistical results are between corresponding active treatment and placebo. ANOVA model is used including main effects for treatment, center, and baseline pain stratification in the model.
Pain Relief (VAS) is measured using a 100 mm visual analog scale (VAS), where 0 mm= no relief and 100 mm=total relief.
Pain Intensity (VAS) is measured using a 100 mm visual analog scale (VAS), where 0 mm=no pain and 100 mm=worst pain imaginable.
Pain intensity difference at each time point is calculated as the baseline pain intensity score minus the pain intensity score at that time point.
The Sum of Combined Pain Relief and Pain Intensity Difference (SPRID) is defined as the area under the sum of pain relief and pain intensity difference (VAS) scores over corresponding time interval.

- Combined Pain Relief and Pain Intensity Difference (PRID, VAS) by Timepoint: Table 5.16 summarizes combined pain relief and pain intensity differences (PRID, VAS) over the 8-hour efficacy assessment period. OM IR 20 mg and OC IR 30 mg groups were consistently statistically significantly different compared with the placebo group starting at 45 minutes post-dose. A statistically significant difference compared with placebo started at 1 hour post-dose for OC IR 15 mg. OM IR 10 mg was not statistically significant different from placebo.

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Table EN3203-5.16 Summary of Combined PR and PI Difference (VAS, Extrapolated) Over 0-8 Hours for Efficacy -Evaluable Patients

	Assessment Time Point										
Treatment	**15 min**	**30 min**	**45 min**	**1 hr**	**2 hr**	**3 hr**	**4hr**	**5 hr**	**6 hr**	**7 hr**	**8 hr**
Oxymorphone IR 10 mg											
n	54	55	55	54	41	33	25	18	12	8	7
Mean[a]	28.7	50.8	67.3	64.6	69.3	56.2	51.8	48.3	44.6	43.7	42.6
	AB	A	AB	BC	BC	B	B	BC	BC	BC	BC
SD[a]	41.20	52.36	60.68	62.07	65.34	63.99	64.88	66.32	64.92	64.23	62.91
Oxymorphone IR 20 mg											
n	63	62	63	63	47	40	33	29	23	18	16
Mean[a]	24.7	50.4	72.8	76.8	85.1	87.2	81.7	78.4	69.7	65.6	63.3
	B	A	A	AB	AB	A	A	A	A	A	A
SD[a]	31.72	53.98	63.56	59.64	63.07	66.25	68.59	67.94	64.01	62.58	61.30
Oxycodone IR 15 mg											
n	61	62	61	60	52	44	33	28	18	13	10
Mean[a]	29.2	50.0	72.4	85.2	94.7	88.6	80.4	68.9	63.2	62.1	62.8
	AB	A	AB	AB	A	A	A	AB	AB	AB	AB
SD[a]	37.25	53.15	60.50	63.55	63.91	65.18	68.09	69.17	71.01	70.36	71.83
Oxycodone IR 30 mg											
n	60	60	59	60	48	38	36	25	20	17	12
Mean[a]	37.1	55.9	80.3	90.2	93.6	91.6	83.1	70.2	67.6	58.4	56.5
	AB	A	A	A	A	A	A	AB	A	AB	AB
SD[a]	50.27	53.20	61.18	60.52	66.80	67.49	66.88	63.04	62.02	61.39	60.71
Placebo											
n	59	58	59	59	34	20	15	11	9	5	3
Mean[a]	39.2 A	48.7 A	50.9 B	49.5 C	45.4 C	40.8 B	36.9 B	34.8 C	35.2 C	31.4 C	32.8 C
SD[a]	42.50	50.41	54.78	57.70	61.33	57.61	56.67	53.70	55.44	51.93	53.20
Treatment p-value[b]	0.225	0.961	0.106	**0.002**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**0.006**	**0.011**	**0.021**

Source: Table 19, EN3203-005 Clin. Study Report, pg. 60
*a*Mean and Standard Deviation are based on extrapolated data.
*b*Based on ANOVA model including main effects for treatment, center, and baseline pain stratification in the model.
Treatments with a common letter are not significantly different (e.g. ,treatments with A and AB are not significantly different).
Sample sizes (n) are not extrapolated.

- Time to First Perceptible Pain Relief:

  Time to first perceptible pain relief for the five treatment groups is shown in Table 17. The median time to the first perceptible pain relief for all treatment groups was similar, ranging from 15-21 minutes post-dose. The difference between each of the active treatment groups compared with placebo was not statistically significant.

Table EN3203-5.17 Time (hour:minutes) to First Perceptible Pain Relief for Efficacy-Evaluable Patients

Treatment	Median (hh:mm)[a,b]	95% Confidence Interval[c]
Oxymorphone IR 10 mg	0:15 A	0:12 to 0:23
Oxymorphone IR 20 mg	0:20 A	0:16 to 0:29
Oxycodone IR 15 mg	0:15 A	0:14 to 0:22
Oxycodone IR 30 mg	0:21 A	0:15 to 0:31
Placebo	0:15 A	0:11 to 0:16

Source: Table 20, EN3203-005 Clin. Study Report, pg. 61.
[a]Kaplan-Meier estimate
[b]Log-Rank test applied as in Fisher's PLSD. Treatments with a common letter are not significantly different.
[c]Method of Simon & Lee, 1982

- Time to Onset of Meaningful Pain Relief:

Time to meaningful pain relief for the five treatment groups is shown in Table 18. The median times to onset of meaningful pain relief for the oxymorphone IR and oxycodone IR groups (approximately 1 hour) were statistically significantly different when compared with placebo (8 hours). There were no statistically significant differences among the active groups in time to meaningful pain relief.

Table EN3203-5.18 Time (hour:minutes) to Meaningful Pain Relief for Efficacy-Evaluable Patients

Treatment	Median (hh:mm)[a,b]	95% Confidence Interval[c]
Oxymorphone IR 10 mg	1:01 A	0:46 to 3:00
Oxymorphone IR 20 mg	0:53 A	0:46 to 2:01
Oxycodone IR 15 mg	1:03 A	0:46 to 2:00
Oxycodone IR 30 mg	1:01 A	0:45 to 1:30
Placebo	8:00 B	1:41 to >8:00

Source: Table 21, EN3203-005 Clin Study Report, pg. 62.
[a]Kaplan-Meier estimate
[b]Log-Rank test applied as in Fisher's PLSD. Treatments with a common letter are not significantly different.
[c]Method of Simon & Lee, 1982

- Time to Rescue Medication:
  Time to rescue medication for the five treatment groups is given in Table 19. The median times to rescue medication for the oxymorphone IR and oxycodone IR treatment groups were statistically significant longer (ranging from 3 hours 34 minutes to 4 hours 53 minutes) compared with placebo (2 hours). There were no statistically significant differences among the active treatment groups.

Table EN3203-5.19 Time to Rescue Medication for Efficacy-Evaluable Patients

Treatment	Median (hh:mm)[a,b]	95% Confidence Interval[c]
Oxymorphone IR 10 mg	3:34 A	2:29 to 4:25
Oxymorphone IR 20 mg	4:53 A	3:35 to 6:00
Oxycodone IR 15 mg	4:50 A	3:47 to 5:30
Oxycodone IR 30 mg	4:24 A	3:35 to 5:31
Placebo	2:00 B	1:39 to 2:15

Source: Table 22, EN3203-005 Clin. Study Report, pg. 63
[a]Kaplan-Meier estimate
[b]Log-Rank test applied as in Fisher's PLSD. Treatments with a common letter are not significantly different
[c]Method of Simon & Lee, 1982

- Patient's Global Assessment of Pain Relief:
  Patients rated their global assessment of pain relief provided by the study medication as excellent, very good, good, fair, or poor. This summary is based on the category frequency counts by treatment group, using the total efficacy-evaluable patients providing this assessment (within each treatment group) as the denominator. The OM IR 20 mg and both OC IR groups were statistically significantly different compared with placebo. In addition, a significant between-

treatment-group statistical difference was observed favoring OC IR 30 mg over OM IR 10 mg.

Table EN3203-5.20 Subject Global Assessment of Pain Relief for Efficacy-Evaluable Patients

Response	Oxymorphone 10 mg (N=56)	Oxymorphone 20 mg (N=65)	Oxycodone 15 mg (N=62)	Oxycodone 30 mg (N=60)	Placebo (N=59)
Total [1]	**56**	**65**	**62**	**60**	**59**
Poor	15 (26.8)	14 (21.9)	10 (16.1)	14 (23.3)	24 (40.7)
Fair	8 (14.3)	6 (9.4)	7 (11.3)	2 (3.3)	10 (16.9)
Good	11 (19.6)	13 (20.3)	13 (21.0)	13 (21.7)	15 (25.4)
Very Good	18 (32.1)	20 (31.3)	20 (32.3)	16 (26.7)	7 (11.9)
Excellent	4 (7.1)	11 (17.2)	12 (19.4)	15 (25.0)	3 (5.1)
Pairwise Comparisons [2]					
Oxymorphone 20 mg	0.223	-	-	-	-
Oxycodone 15 mg	0.256	0.619	-	-	-
Oxycodone 30 mg	0.034	0.404	0.485	-	-
Placebo	0.149	**0.015**	**0.001**	**< 0.001**	-

Source: Table 4.10, Appendix 16.2.2 of the EN3203-005 Clin Study Report, Page 1 of 1
[1] Percentages are calculated using TOTAL as denominator
[2] All pairwise comparison p-values are based on stratified rank sum test, stratified by center and baseline pain

Additional Analyses:

- Analgesic Potency of OM IR Relative to OC IR:
  The analgesic potency of oxymorphone relative to oxycodone was estimated using a parallel line assay for six efficacy endpoints (TOTPAR8 [categorical and VAS]; SPID8 [categorical and VAS]; and SPRID8 [categorical and VAS]). The relative potency estimates of OM to OC ranged from 0.59 to 1.11 for all analgesic measures considered. A smaller lambda (shown below) represents greater sensitivity of the assay (i.e., 1 or less). The lambda for all parameters was very large, ranging from 11.65 to 153.1. Due to the lack of dose response in the oxycodone groups, there was no assay sensitivity; therefore, estimation of relative potency is not valid.

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Table EN3203-5.21 Analgesic Potency Estimates of Oxymorphone Relative to Oxycodone for Efficacy-Evaluable Patients

	Relative Potency	95% Confidence Interval	Lambda
TOTPAR 8 Hours			
Categorical	0.59	0.14 - 2.47	153.1
VAS	0.73	0.26 - 2.04	35.80
SPID 8 Hours			
Categorical	0.72	0.29 - 1.81	24.87
VAS	1.11	0.55 - 2.23	11.65
SPRID 8 Hours			
Categorical	0.65	0.22 - 1.97	47.27
VAS	0.9	0.39 - 2.07	18.27

Source Data: Table 23, EN3203-005 Clin Study Report, pg. 65.

Lambda: assay precision was measured with lambda which was calculated by dividing the square root of the ANOVA error mean square by the common slope.

TOTPAR 8 Hours: total pain relief during the 8 hours efficacy assessment

SPID 8 Hours: sum of pain intensity difference during the 8 hours efficacy assessment

SPRID 8 Hours: composite score of SPID and TOTPAR during the 8 hours efficacy assessment

- Evaluation of Efficacy Outcomes using Baseline Observation Carried Forward (BOCF):

  In addition to the planned analysis of LOCF for missing data, the primary analgesic efficacy endpoints also were analyzed using the BOCF method for missing data. The results using the BOCF method are consistent with those using the LOCF method for missing data, as presented in Table 5.22 below. The primary efficacy for OM 20 mg and both OC IR formulations is still statistically significantly different from PBO at 8 hours. Consistent with the efficacy evaluable conclusions, OM IR 10 mg was not significantly different from PBO at 8 hours..

Table EN3203-5.22 Total Pain Relief (TOTPAR, BOCF, Categorical) at 0-8 Hours for Efficacy-Evaluable Patients

Statistics	Oxymorphone 10 mg (N=56)	Oxymorphone 20 mg (N=65)	Oxycodone 15 mg (N=62)	Oxycodone 30 mg (N=60)	Placebo (N=59)
		Descriptive			
Mean	7.9	10.7	10.8	10.9	5.5
LS Mean	7.2	8.91	8.14	8.79	6.51
		Pairwise Comparisons with PBO [1]			
LS Mean Difference	2.3	5.3	5.2	5.4	-
Std Error	1.5	1.4	1.5	1.5	-
P-value	0.125	**< 0.001**	**< 0.001**	**< 0.001**	-

Source: Table 4.12.1, Appendix 16.2.2 of the EN3203-005 Clin Study Report, Page 1 of 1

Pain Relief (Categorical) is measured on a five point scale: 4 = complete, 3 = a lot, 2 = some, 1 = a little, and 0 = none.
BOCF - baseline carried forward is used in handling missing data.

7.3.6 Efficacy Conclusions for EN3203-005:

This was an 8-hour multicenter, randomized, double-blind, placebo- and active-controlled, single-dose study of oxymorphone IR (10 and 20 mg formulations) and oxycodone IR (15 and 30 mg formulations) in patients with postoperative pain due to osteotomy. This study was intended to support a finding of efficacy of oxymorphone. The Sponsor's analysis of the primary outcome variable of Total Pain Relief (TOTPAR, categorical) from 0-8 hours did reveal a statistically significant difference from placebo for the OM 20 mg treatment group, but not for the OM 10 mg group. The secondary analysis also favored the OM 20 mg dose, but not the 10 mg formulation. Oxycodone 15 and 30 mg IR doses were also statistically different from placebo in the primary and secondary analyses. The Sponsor's efficacy findings were confirmed by Agency re-analysis of the efficacy data using an 'all randomized and treated' population with baseline observations carried forward.

The 10 mg oxymorphone dose did not show a statistical difference from placebo on all primary and secondary outcome variables, with the exception of the time specific pain intensity difference (PID, VAS), the 4 hour SPID (VAS scale), Time to Meaningful Pain Relief, and Time to Rescue Medication (4 positive findings in 28 different measures of efficacy). This consistent finding of no difference from placebo does not support the Sponsor's claim that the OM 10 mg formulation is the minimally effective dose.

In summary, the results of EN3203-005 support the sponsor's claim of analgesic efficacy of the oxymorphone IR 20 mg formulation compared to placebo and this appears to be the minimally effective dose in post-operative pain.

7.4 Efficacy Conclusions:

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

Study EN3203-004 was a 48-hour, single and multi-dose, placebo- and active-controlled study in 300 patients with post-operative pain following knee or hip replacement. The Sponsor's analysis of the primary outcome variable (total pain relief from 0 to 8 hours) for the single-dose phase of the study demonstrated statistically significant differences from placebo for OM IR 10, 20, and 30 mg. No corresponding difference was seen between placebo and oxycodone IR. Re-analysis using an 'all randomized population' and baseline observations carried forward confirmed the Sponsor's findings. The majority of secondary outcomes favored the oxymorphone doses over placebo, with a trend towards greater efficacy response with OM IR 30 mg. Calculation of the average dosing interval demonstrated frequencies ranging from 7 to 10 hours, which does not support the proposed dosing interval. In addition, there was a large proportion of drop outs by 4 hours in this study.

Study EN3203-005 was an 8-hour multicenter, randomized, double-blind, placebo- and active- controlled, single-dose study of oxymorphone IR (10 and 20 mg doses) and

oxycodone IR (15 and 30 mg formulations) in 324 patients with postoperative pain due to osteotomy. The Sponsor's analysis of the primary outcome variable of Total Pain Relief (TOTPAR, categorical) from 0-8 hours demonstrated a statistically significant difference from placebo for the OM 20 mg treatment group, but not for the OM 10 mg group. The secondary analysis also favored the OM 20 mg dose, but not the 10 mg formulation. Oxycodone 15 and 30 mg IR doses were also statistically different from placebo in the primary and secondary analyses. The Sponsor's efficacy findings were confirmed by Agency re-analysis of the efficacy data using an 'all randomized and treated' population with baseline observations carried forward. The results of EN3203-005 support the efficacy of the oxymorphone IR 20 mg formulation compared to placebo. The 20 mg OM IR dose also appears to be the minimally effective dose. The OM IR 10 mg formulation efficacy was consistently indistinguishable from placebo, in this post-operative pain population.

In summary, the Sponsor's investigations support the efficacy of oxymorphone IR 20 mg and 30 mg tablets with a failure to replicate the findings of efficacy of the 10 mg dose in the patient population studied.

8 INTEGRATED REVIEW OF SAFETY

Please refer to the separate Integrated Summary of Safety review document.

9 DOSING, REGIMEN, AND ADMINISTRATION ISSUES

- Dose Formulations:
  The Sponsor proposes oxymorphone IR in 5 and 10 mg tablet strengths.

- Dose Ranges:
  The Sponsor proposes a lowest starting dose of 5mg (in opioid naïve subjects), with higher doses determined by the patient's response. However, both the 5 mg IR and ER formulations were evaluated in PK studies only, therefore no conclusions regarding efficacy of 5 mg can be made. The lowest oxymorphone IR starting dose evaluated clinically was 10 mg IR (Studies EN3203-004 and –005). The minimally consistent effective dose appeared to be 20 mg IR.

  The maximum oxymorphone IR dose evaluated clinically was 30 mg (EN3203-004). It is expected that dosing will be titrated individually to achieve appropriate analgesia with minimal side effects.

- Dose Interval:
  One adequate and well-controlled study (EN3203-004) examined multiple doses of oxymorphone IR, and attempted to estimate a dose interval. The resulting average time between doses does not support the Sponsor's proposed q6 ——— interval. This issue was discussed with the Division Biopharmaceutics Reviewer. In addition, substantial percentages of subjects had been withdrawn by 4 hours (approximately 50% for OM groups) in both pivotal studies. Overall, the peak/trough data from

single- and multi-dose PK studies of oxymorphone IR and ER (Refer to Biopharmaceutics Review for further detail) suggests a more frequent dosing interval is necessary. Based upon this information q 4 to 6 hour dosing interval is recommended.

- Dosing Age Groups:
  The Sponsor recommends treating patients from 18 years of age to the elderly. PK studies evaluated ER and IR oxymorphone in subjects ranging from 18 to 81 years of age and two clinical efficacy studies evaluated patients with ages ranging from 22 to 91. It is unlikely that the 18 to 22 age range will exhibit different efficacy responses to oxymorphone. Therefore, the proposed age range is acceptable. No PK or clinical data for subjects younger than 18 were submitted.

- Dosage Administration Adjustments:

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

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

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

  4. Gender: No specific dose adjustment is recommended based upon gender.

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

- Dose Conversion from other Oral Opioids:
  The Sponsor estimated relative potency based on combined selected efficacy outcomes from EN3203-004 and EN3203-005. The relative potencies ranged between 1.48 and 1.74 over 8 hours (TOTPAR, SPID, and SPRID efficacy variables). The Sponsor notes that the potency ratios were statistically significantly greater than one (i.e. 95% CI is > 1) for the SPID and SPRID variables, but not for pain relief (TOTPAR). In addition, the relative potency assessment in EN3203-005 was not valid due to lack of oxycodone dose response, per the Sponsor. However, based upon the pooled analysis of efficacy outcomes, the Sponsor recommends initially converting patients from oxycodone IR to oxymorphone IR using a 2:1 ratio. Published relative potency information is recommended for use when converting from other oral opioids.

10 USE IN SPECIAL POPULATIONS

10.1 Evaluation of Sponsor's Gender Effects

The Sponsor conducted subgroup analyses of gender effects on efficacy by pooling data for all doses of oxymorphone IR, oxycodone IR, and placebo from studies EN3203-004 and EN3203-005. Slight differences were observed between male and female patient efficacy outcomes. These differences were small in magnitude (approximately 11% difference in primary outcome for EN3203-004), lacked a consistent pattern, and were observed in placebo patients. The reason for the observed differences is unknown and the small magnitude suggests this finding is not clinically meaningful. Overall, the Sponsor's analysis of possible gender effects appears reasonably adequate, with both sexes well represented in the populations studied (245 male and 315 female patients). However, statistical comparisons between groups would have been helpful.

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

Age Effects:

Several efficacy outcomes were pooled from studies EN3203-004 & EN3203-005. There was slightly better pain relief for each of the three treatment arms, OM IR, OC IR, and PBO for patients ≥ 65 years of age relative to younger patients. This observation was noted for all three treatment arms including placebo. The Sponsor did not indicate that this analysis was adjusted for body weight or other factors. In addition, the Sponsor did not perform statistical comparisons between age and treatment groups. PK studies of oxymorphone found that the single-dose and steady-state plasma concentrations were approximately 40% higher in elderly patients (≥ 65 years of age) relative to younger subjects. This may account for some of the difference observed for oxymorphone, although it would not explain the similar findings for oxycodone IR and placebo.

Race and Ethnicity Effects:

There were too few non-Caucasian patients to analyze the effects of race or ethnicity.

10.3 Evaluation of Pediatric Program

Please refer to the Pediatric Program evaluation in NDA 21-610 (Oxymorphone ER) as this section involves both oxymorphone formulations.

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11 APPENDICES

11.1 EN3203-004: EFFICACY ASSESSMENT INSTRUMENTS

11.1.1 American Society of Anesthesiologists Physical Status Classification System:

Assignment of a physical status classification is based on the physical condition of the subject independent of the planned operation:

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

11.1.2 Current Pain Relief (VAS):

Subjects record their intensity of pain on a 100 mm visual analog scale (VAS). The 100 mm VAS will be bounded on the left by "no pain" and on the right by "the worst pain imaginable". The subject will be instructed to "place a single vertical mark across the line which best indicates the amount of pain you are having right now". The score will be the distance in mm from the left end of the VAS to the point where the mark crosses the line.

11.1.3 Current Pain Relief (Categorical):

At each timepoint, patients each patient will record their current pain relief unless the subject requests re-medication. Pain relief will also be recorded prior to remedication or rescue, and when each stopwatch is stopped for the assessment of perceptible pain relief and meaningful pain relief. Subjects will be asked to "Select the phrase that best describes how much pain relief your pain medication is providing right now". Pain relief will be measured on a five point categorical scale as: none (0), a little (1), moderate (2), a lot (3), or complete (4).

11.1.4 Time to Perceptible Pain Relief:

The time to perceptible pain relief is the time from the administration of study medication to the time when subject first begins to feel any pain relief from the study medication. The subject will be instructed to "Stop one stopwatch when you first begin to feel any pain relief or any improvement in the pain that you had prior to taking the study medication." When the subject stops the stopwatch for perceptible pain relief, the subject will assess and record his/her current intensity of pain and pain relief respectively. Time to Meaningful Pain Relief:

11.1.5 Time to Meaningful Pain Relief:

The time to meaningful pain relief is the time from the administration of study medication to the time when the subject first begins to feel their pain relief is meaningful

to them. The subject will be instructed to "Stop the stopwatch when you first feel that the relief from the pain is meaningful to you." When the subject stops the stopwatch for meaningful relief, the subject will assess and record his/her current intensity of pain and pain relief, respectively.

11.1.6 Time to Re-Medication:
During the Single Dose Phase, the time to re-medication will be recorded as the exact time a subject requests additional analgesia.

11.1.7 Pain at Least Half Gone:
As an estimate of the proportion and time when subjects experience 50% pain relief, subjects will be asked to evaluate when their pain is reduced by 50%. During the Single Dose Phase each subject will assess whether their pain was reduced by 50% since the beginning of treatment at 15, 30 and 45 minutes and 1, 1.5, 2, 3, 4, 5, 6, 7, and 8 hours after the first dose of study medication or until the patient requests re-medication. This assessment will also be recorded prior to re-medication or rescue, and when each stopwatch is stopped for the assessment of perceptible pain relief and meaningful pain relief. The subject will be asked at each of the above times, "Is the level of pain that you felt at the start at least half gone." The subject will respond yes or no.

11.1.8 Worst Pain:
During the Multiple Dose Phase subjects will recall at bedtime their worst intensity of pain during the day and recall their worst intensity of pain during the nighttime when they wake up in the morning. Worst pain will be captured with a 100 mm VAS and 4 point categorical scale similar to Pain Intensity:

- 4-point categorical scale – "none(0), mild(1), moderate(2), and severe(3)"
- VAS – 100 mm scale bounded on the left by "no pain" and on the right by "the worst pain imaginable."

11.1.9 Subject's Global Evaluation of Study Medication:
At the end of the Single Dose Phase and Multiple Dose Phase, each subject will make an overall assessment of the study medication. Subjects will be asked, "Please rate your overall satisfaction with the pain medication you took during the study". The subject will rate the effectiveness on a five point categorical scale as: poor (1), fair (2), good (3), very good (4), or excellent (5).

11.1.10 Physician's Global Evaluation of Study Medication:
At the end of the Single-Dose Phase and Multiple-Dose Phase , the investigator will be asked to rate their satisfaction with the study medication that the patient received. This will be performed similarly to 11.1.9.

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11.2 EN3203-005: EFFICACY ASSESSMENT INSTRUMENTS

11.2.1 Pain Relief (VAS):

At each timepoint, patients were to be asked to rate their current pain relief on a 100-mm VAS, bounded on the left by "none" and on the right by "complete relief." Patients were to be asked, "How much pain relief do you have now compared to immediately prior to taking the study medicine?" Patients were to be instructed to make a vertical mark on the line to indicate their pain relief. The study coordinator was to use a standard metric ruler supplied by the Sponsor to measure the distance in millimeters (0 to 100) from the left side of the scale to the patient's vertical mark and was to record this number on the appropriate CRF.

11.2.2 Pain Relief (Categorical):

At each timepoint, patients were to record their current pain relief relative to baseline in response to being asked, "How much pain relief do you have now compared to immediately prior to taking the study medicine?" (Check one) None (0), A little (1), Some (2), A lot (3), Complete (4).

11.2.3 Pain Intensity (VAS):

At each timepoint, patients were to be asked to rate their current pain intensity on a 100-mm VAS, bounded on the left by "none" and on the right by "worst possible pain." Patients were to be asked, "How much pain do you have now?" Patients were to make a vertical mark on the line to indicate their pain relief. The study coordinator was to use a standard metric ruler to measure the distance in millimeters (0 to 100) from the left side of the scale to the patient's vertical mark and was to record this number on the appropriate CRF.

11.2.4 Pain Intensity (Categorical):

At each timepoint, patients were to record their current pain intensity in response to being asked, "How much pain do you have now?" (Check one) None (0), A little (1), Some (2), A lot (3), Severe pain (4).

11.2.5 Time to Onset of 1st Perceptible Pain Relief:

The time to perceptible pain relief is the time from the administration of study medication to the time when the subject first begins to perceive pain relief. Subjects were to be instructed to stop the stopwatch when they first perceived relief.

11.2.6 Time to Meaningful Pain Relief:

The time to meaningful pain relief is the time from the administration of study medication to the time when the subject first begins to feel pain relief that is meaningful. Subjects were to be instructed to stop the 2nd stopwatch when they felt meaningful relief.

11.2.7 Time to Re-Medication:
This was to be calculated by determining the number of minutes between the time study medication was taken and the time rescue analgesia was taken. Subjects not taking rescue were to be assigned a score of 8.

11.2.8 Patient's Global Evaluation of Study Medication:
At the end of 8 hours or the time rescue medication is administered, patients were to provide a global evaluation of pain relief since baseline. The patient was to be asked, "How do you rate the pain relief you obtained from the study medication?" (Circle one): Excellent (5), Very Good (4) , Good (3) , Fair (2) , Poor (1)

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11.3 Appendix: Useful Statistical Terms and Definitions:

11.3.1 ANOVA:

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

11.3.2 ANCOVA:

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

11.3.3 Least Squares Means:

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

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Oxymorphone IR Clinical Review

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Refer to the Team Leader Memo for final comments on conclusions and recommendations.

1ST Cycle Review

MEMORANDUM **DEPARTMENT OF HEALTH AND HUMAN SERVICES**
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: June 19, 2003

TO: Bob A. Rappaport, M.D., Acting Director
Division of Anesthetic, Critical Care and Addiction Drug Products, HFD-170

THROUGH: Mark Avigan, M.D., Acting Director
Office of Drug Safety, Division of Drug Risk Evaluation, HFD-430

Toni Piazza-Hepp, Pharm.D., Acting Director
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FROM: Mary Willy, Ph.D., M.P.H., Epidemiologist
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SUBJECT: Consult: Review of Oxymorphone HCL CR and IR Risk Management Plan
PID#: D030188

I. EXECUTIVE SUMMARY

This is the Office of Drug Safety (ODS) memorandum on a proposed outline for a risk management plan (RMP) for Oxymorphone from Endo Pharmaceuticals. The Division of Anesthetic, Critical Care, and Addiction Drug Products (HFD-170) requested ODS to review and comment on the elements of the plan. Currently, the sponsor's proposal is lacking sufficient detail to allow a complete evaluation. The sponsor needs to provide a clear description of their objectives, program components and evaluation plan so that it can be evaluated by ODS.

II. BACKGROUND

The sponsor submitted a risk management plan as part of the NDA documentation received on December 19, 2002. Oxymorphone (14-hydroxoydihydromorphinone) is a semisynthetic opioid agonist that is structurally related to morphine and modulates pain by acting with specificity at the mu opioid-receptor sites in the CNS. The drug was first approved in 1959 and an immediate release oral form was marketed in the early 1960s. The immediate release form was voluntarily removed from the market for "commercial" reasons in the 1970s (the 2mg and 5mg tablets were

removed after 7 years of marketing and the 10mg tablets were removed after 11 years). Endo currently has approval for injectable and rectal suppository dosage forms of oxymorphone.

Oxymorphone ER is intended for the relief of moderate to severe pain in patients requiring continuing pain relief for extended periods of time. The sponsor expects the drug to have a similar abuse liability to "other strong opioid analgesics."

III. SUMMARY of RISK MANAGEMENT PLAN

The RMP includes a listing of educational programs planned for different groups. Reference is made to pharmacy, patient and family educational pamphlets and risk management "kits." A reference is made to a Screening for Opiate Addiction Potential Tool (SOAP), a patient assessment instrument that is being developed by a team from Harvard University, Brigham and Women's Hospital and Inflexxion (a consulting company) to identify patients that might have more "problems" during treatment. Another component of the RMP is post marketing surveillance, but the methods used for identifying cases of drug abuse and the goals of surveillance and monitoring programs are not described in detail. The sponsor describes a plan to "view safety data on all pharmaceutical products...for signal generation." The last component of the RMP is labeling which is provided in a separate attachment and will not be addressed in this review.

IV. COMMENTS on RISK MANAGMEMENT PLAN

The sponsor has provided a limited description of their RMP. The plan is missing a list of specific goals, objectives and an evaluation plan. In addition, detailed information about how the proposed SOAP tool will be implemented (including a time line and how practitioners will be introduced to the system) and the objectives for introducing that tool has not been provided. There is minimal information about how the sponsor will collect post marketing information about abuse and diversion. Although the signal generation plan can be a useful tool, by itself it does not constitute a complete postmarketing surveillance program. The surveillance for abuse and diversion is complex and one that requires a multi-faceted approach. The sponsor should be requested to provide a description of anticipated data sources for surveillance, the frequency with which updates from these sources will be obtained, types of analyses that will be performed on these data, and a rationale as to why these particular data sources were chosen for surveillance (strengths and weaknesses, etc.) Finally, a detailed intervention plan and a description of the RMP evaluation plan should be provided.

V. CONCLUSIONS

The sponsor's RMP for oxymorphone requires additional information and development. Although there is no Agency guidance for the sponsor to reference, they might refer to the FDA risk management concept paper that was discussed at a public forum this spring (1). The RMP provided by the sponsor does not provide a clear description of their objectives, program components or evaluation plan.

REFERENCES

1. Risk management concept paper, March 3, 2003. www.fda.gov/cder/meeting/groupIIfinal.pdf

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