alternate analyses of the primary outcome utilizing a more inclusive population. No differences in the outcomes were found. Patient global assessment of pain relief mirrored these findings. For patients in the OM IR 20 mg group not requiring rescue medication in the first hour, the median time to rescue was nearly 5 hours. .

Summary of Safety
Safety was to be assessed from studies EN3203-004 and EN3203-005. Additional safety information was to be obtained from Study EN3202-018, Study EN3202-019 in which OM IR was used to titrate subjects prior to randomization to a modified-release opioid. Studies EN3202-017, EN3202-020, EN3202-022 which permitted the use of oxymorphone IR for rescue were intended to provide safety information, but the amount of OM IR used by patients was not documented and the effects of oxymorphone IR could not be separated from the effects of other concomitant opioids.

Safety has not been demonstrated in the clinical setting for which efficacy has been demonstrated, postoperative pain. Patients experienced a disproportionate frequency of requiring opioid antagonist treatment. Additionally, there are unanswered concerns about abnormalities of WBC count, liver function, and QTc noted during review of the safety database.

Dosing
The Sponsor's proposal for initiating dosing of oxymorphone IR with a 5 mg dose in opioid naïve subjects has not been supported by clinical studies. Equianalgesic potency with other opioids has also not been demonstrated.

An appropriate dosing interval has not been determined. The proposed dosing interval of every 6 —= hours is not supported by the clinical trial findings of more than half of study patients withdrawing from the study prior to the Hour 5 assessments in both studies. The median time to remedication during Study EN3203-004 was approximately 4 hours for the oxymorphone immediate-release 20 mg and 30 mg groups. During Study EN3203-005, median time to remedication was approximately 5 hours for the oxymorphone 20 mg dose found effective in this study. These time to remedication analyses excluded patients requiring rescue prior to 3 hours and 1 hour, respectively, suggesting the median time to remedication would have been even shorter had all patients been included.

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

FINDINGS FROM OTHER DISCIPLINES

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

REVIEW OF EFFICACY

STUDY EN3203-004:

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

The protocol provided by the Sponsor with this submission incorporated three protocol amendments. The changes attributed to each amendment are described at the end of the protocol review. This study was a multi-center, randomized, double-blind, placebo- and active-control, two-phase, multi-dose study of immediate-release oxymorphone (OM IR) and immediate-release oxycodone (OC IR). The primary objective of this study was to assess the efficacy of OM IR 10, 20, and 30 mg compared to placebo in patients with acute moderate to severe post-op pain. The secondary objectives were to evaluate the dose-response and safety of OM IR 10, 20, and 30 mg.

Three hundred patients were to be enrolled, 60 patients per treatment arm. Subjects were to be male or female, age 18 to 75 years, ASA level I-III, and to have undergone undergone total hip or knee replacement, or revision involving osteotomy. Patients were to be able to tolerate oral analgesics and were to have a baseline post-op pain intensity of moderate to severe, and $\geq$ 45 mm by VAS within 6 hours of last receiving intravenous opioids or within 9 hours of receiving intramuscular opioids. Subjects were not to have serum transaminases or creatinine more than 1.5 x the upper limit of normal, ileostomy, or chronic respiratory insufficiency. Patients were to not have used NSAIDs within 48 hours of planned surgery or monoamine oxidase inhibitor within 14 days of surgery. Corticosteroid use (except topical or inhaled) within 7 days of planned surgery.

Following surgery, patients were to be placed on IV or IM opioids. Patients able to discontinue parenteral opioids within 48 hours of surgery and who developed moderate to severe pain by categorical scale and a score of 45 mm or greater by VAS were to be enrolled and randomized. Study treatment arms were to be OM IR 10, 20, and 30 mg, oxycodone 10 mg and placebo.

Following the first dose of study mediation, patients were to be assessed at 15, 30, 45 min and 1, 1.5, 2, 3, 4, 5, 6, 7, and 8 hours, or until re-medication. The single-dose phase was to be considered complete when patients requested re-medication or completed the 8 hour assessment. Rescue medication was to be allowed at the Investigator's discretion. Patients requiring rescue within 3 hours of dosing were to be withdrawn as treatment failures.

Following completion of the single-dose phase, subjects were to enter the multiple-dose phase. Patients who had received placebo were to receive one of the four active treatments, based on the randomized treatment sequence they were originally assigned. The remainder of patients remained on their original treatment assignment. Patients were to receive study medication every 4-6 hours as needed for the remainder of the 48 hour period. The number and time of dosing were to be recorded along with other measures. Patients requesting rescue prior to 3 hours after receiving the previous dose of study medication were to be given rescue and withdrawn from the study.

Concomitant therapy to be permitted was anticonvulsants and antidepressants other than MAO inhibitors that had been stable for at least 4 weeks. No NSAIDs or COX-2 inhibitors were to be permitted. Aspirin was to be permitted for cardiovascular prophylaxis and acetaminophen for fever.

Efficacy outcome measures during the initial 8 hours were to be assessed using pain intensity (PI) by VAS and 4-point categorical scale and pain relief (PR) by 5-point categorical scale, at 15, 30, and 45 minutes and 1, 1.5, 2, 3, 4, 5, 6, 7, and 8 hours. Time to perceptible pain relief, time to meaningful pain relief, time to re-medication, and time when pain at least half-gone were to be measured by stopwatch.

During the next study period, from 8-48 hours, efficacy was to be assessed using Worst Pain Recall by VAS and 4-point categorical scale, to be measured at bedtime and waking, and Global Assessments of overall satisfaction with the pain medication taken during the study by patients and physicians.

Safety was to be evaluated by recording adverse events (AEs), physical exams, and vital signs.

The primary efficacy outcome was to be the total pain relief from 0 to 8 hours (TOTPAR 0-8) using categorical PR scores, analyzed using an ANCOVA.

The secondary efficacy outcomes during the first eight hours were to be:

- TOTPAR 0-4, TOTPAR 0-6
- Sum of pain intensity difference (SPID) with VAS and categorical scales over 0-4, 0-6, and 0-8 hour intervals.
- Proportion and time when patients first experienced 50% pain relief
- Time to onset of analgesia
- Time to re-medication

- Patient's Global Evaluation of Study Medication.

Additional secondary efficacy outcomes from eight to 48 hours were to be:

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

Exploratory analyses were performed to evaluate the dose level, dosing interval and total amount of study medication taken during the multiple dose phase when subjects were to take study medication every 4-6 hours as needed for pain for the 40 hours after the first dose.
1. Actual dose interval = Duration of multiple dose phase / number of doses.
This was to be calculated at a subject level first then averaged for each treatment group. All subjects who entered the multiple dose phase were to be included.
2. Total amount of study medication taken = Number of doses x treatment dose level.
This was to be calculated at a subject level first then averaged for each treatment group. Subjects who completed the multiple dose phase were to be included.
3. Actual dose level = Total amount of study medication taken /Actual dose level
This was to be calculated for each treatment group using the averaged values obtained from 1 and 2.

Efficacy analyses were to be performed using the Intent-to-Treat (ITT) Population which the Sponsor defined as those patients who after randomization, received the first dose of study mediation and completed the first hour of efficacy evaluation without requiring rescue or vomiting. Safety data was to be based on all randomized patients receiving at least one dose of study medication.

All statistical tests were to be two-sided, with statistical significance denoted by a p-value of 0.05 or less, unless otherwise stated. Dose response was to be performed on the primary efficacy endpoint, with a regression model using the efficacy endpoint as a dependent variable and the OM IR dose as the independent variable. Missing data due to early withdrawals was to be imputed using the last observation carry forward (LOCF).

Protocol Amendment 1, dated February 19, 2001, implemented prior to starting enrollment, removed a weight restriction, clarified the types of eligible knee and hip surgery, added the collection of vital signs during the multi-dose phase, and clarified the concomitant medications and schedule of activities, and removed inconsistencies in the 24-hour post-surgical and baseline assessments.

Protocol Amendment 2, dated May 21, 2001, was implemented after 41 patients had been enrolled. This amendment allowed for use of IV or IM opioids in the immediate postoperative period and clarified the end of multi-dose phase. The nature of these changes were unlikely to affect the analysis of efficacy.

Protocol Amendment 3, dated February 21, 2002, which was after enrollment in the study had been completed. The Sponsor reports that the amendment was implemented at the sites in December 2001 via a waiver system. This amendment permitted patients to be enrolled for revision surgery that required osteotomy, relaxed the time between post-surgery and dosing to 48 hours, permitted local laboratories for use to qualify patients, refined the population for efficacy analysis (the modified ITT population defined above), and clarified the combining of centers in the statistical analysis. The nature of these changes were unlikely to affect the analysis of efficacy.

The statistical analysis plan was amended May 9, 2002, prior to database lock and renamed the modified ITT population, efficacy evaluable population, adding the exclusion of not having significant protocol violations and permitted measures made within 5 minutes of the scheduled time during the first 2 hours, 10 minutes after the first 2 hours. Additional analyses to be analyzed using the baseline observation carried forward (BOCF) were specified along with time to analgesia defined as to be determined from time to perceptible pain relief and meaningful pain relief. The exploratory analyses of total study medication and the actual dose level removed. Pain relief (PR) and pain intensity difference (PID) at the first perceptible pain relief and meaningful pain relief were summarized.

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

RESULTS

The study was initiated December 19, 2000 and completed March 10, 2002. Patients were enrolled from 29 study sites.

Disposition:

All of the 300 patients randomized received at least the first dose of study medication. Fewer than half the enrolled patients completed the study, with the least discontinuing early from the OM IR 20 and 30 mg groups (55.9% and 55.4%, respectively). The details of disposition are in Table. The greatest number of early discontinuations were from the placebo group, 68.4%. Lack of efficacy was the most common reason for early discontinuation for all treatment groups except OM IR 20 mg. The most common reason for early discontinuation from the OM IR 20 mg group was adverse events (23.7%). This was greater than the OM IR 30 mg group which lost 15.4% of its patients due to adverse events. Most of the early discontinuations occurred during the initial 8-hour study period. Early discontinuations during the second study period (8-48 hours) were most commonly due to adverse events.

As noted in the review by Dr. Comfort, five of the 16 patients whose early discontinuations were assigned to the "Other" category were actually patients who discontinued due to lack of efficacy. Similarly, two of the patients coded as withdrawing

due to lack of efficacy withdrew due to lack of efficacy and two withdrew due to adverse events. These findings are reflected in Dr. Comfort's Table 4.2d. The patients who were recoded to lack of efficacy have been incorporated into the table below.

Table 1 Disposition of Randomized Patients

	Oxymorphone 10 mg	Oxymorphone 20 mg	Oxymorphone 30 mg	Oxycodone 10 mg	Placebo
Entire study					
Randomized	59 (100.0)	59 (100.0)	65 (100.0)	60 (100.0)	57 (100.0)
Treated patients[a]	59 (100.0)	59 (100.0)	65 (100.0)	60 (100.0)	57 (100.0)
Completed study	24 (40.7)	26 (44.1)	29 (44.6)	22 (36.7)	18 (31.6)
Discontinued	35 (59.3)	33 (55.9)	36 (55.4)	38 (63.3)	39 (68.4)
Adverse experience	4 (6.8)	14 (23.7)	10 (15.4)	4 (6.7)	4 (7.0)
Withdrew consent	3 (5.1)	1 (1.7)	1 (1.5)	1 (1.7)	1 (1.8)
Protocol violation	1 (1.7)	-	-	1 (1.7)	1 (1.8)
Lack of efficacy	23 (39.0)	12 (20.3)	23 (35.4)	28 (46.7)	33 (57.9)
Recoded lack of efficacy	24 (40.7)	12 (20.3)	25 (38.5)	29 (48.3)	
Other	4 (6.8)	6 (10.2)	2 (3.1)	4 (6.7)	-
Efficacy-evaluable[b]	51 (86.4)	51 (86.4)	57 (87.7)	55 (91.7)	44 (77.2)
Single-dose phase					
Randomized	59 (100.0)	59 (100.0)	65 (100.0)	60 (100.0)	57 (100.0)
Treated patients[a]	59 (100.0)	59 (100.0)	65 (100.0)	60 (100.0)	57 (100.0)
Discontinued	27 (45.8)	19 (32.2)	32 (49.2)	28 (46.7)	29 (50.9)
Adverse experience	2 (3.4)	5 (8.5)	8 (12.3)	-	2 (3.5)
Withdrew consent	2 (3.4)	-	1 (1.5)	-	-
Protocol violation	1 (1.7)	-	-	1 (1.7)	-
Lack of efficacy	19 (32.2)	9 (15.3)	22 (33.8)	25 (41.7)	27 (47.4)
Other	3 (5.1)	5 (8.5)	1 (1.5)	2 (3.3)	-
Multiple-dose Phase Only (Original Randomization)					
Randomized	32 (100.0)	40 (100.0)	32 (100.0)	32 (100.0)	-
Treated patients[a]	32 (100.0)	40 (100.0)	32 (100.0)	32 (100.0)	-
Discontinued	8 (25.0)	14 (35.0)	4 (12.5)	10 (31.3)	-
Adverse experience	2 (6.3)	9 (22.5)	2 (6.3)	4 (12.5)	-
Withdrew consent	1 (3.1)	1 (2.5)	-	1 (13.1)	-
Lack of efficacy	4 (12.5)	3 (7.5)	1 (3.1)	3 (9.4)	-
Other	1 (3.1)	1 (2.5)	1 (3.1)	2 (6.3)	-
Multiple-dose Phase Only (Re-Randomized)					
Randomized	6 (100.0)	8 (100.0)	7 (100.0)	7 (100.0)	-
Treated patients[a]	6 (100.0)	8 (100.0)	7 (100.0)	7 (100.0)	-
Discontinued	4 (66.7)	3 (37.5)	3 (42.9)	-	-
Adverse experience	1 (16.7)	1 (12.5)	-	-	-
Withdrew consent	-	-	1 (14.3)	-	-
Protocol violation	1 (16.7)	-	-	-	-
Lack of efficacy	2 (33.3)	2 (25.0)	2 (28.6)	-	-

Source: Sponsor's table 3, P. 44 of 4488

The Sponsor excluded 42 patients from the modified ITT population, 39 due to failure to complete the 1-hour efficacy evaluation. The three remaining patients were excluded due to concomitant use of a non-study opioid after receiving the first dose of study medication.

Demographics:
The demographic characteristics of the patients were fairly evenly spaced across treatment groups. See Dr. Comfort's Table EN3203-4.4 from the Sponsor's Table 4 (P.46 of 4488) for the demographic characteristics. The majority of patients were Caucasian (>84%) with a mean age ranging from approximately 61 to 67 years across treatment groups (range: 22.8 – 85.4 years), and a moderate baseline pain intensity score. There were fewest women in the OM IR 30 mg group (52.3%) compared to 66.1% women in each of the OM IR 10 mg and 20 mg groups. Baseline pain intensity, measured just prior to receiving study medication, varied somewhat with the OM IR 20 mg group having the most patients rating pain as severe as noted in Table 2.

Table 2 Baseline PI

	Oxymorphone 10 mg (N=59)	Oxymorphone 20 mg (N=59)	Oxymorphone 30 mg (N=65)	Oxycodone 10 mg (N=60)	Placebo (N=57)
Baseline Pain Intensity (Categorical)					
Mild	0	1 (1.7)	0	0	0
Moderate	44 (74.6)	38 (64.4)	48 (73.8)	49 (81.7)	41 (71.9)
Severe	15 (25.4)	20 (33.9)	17 (26.2)	11 (18.3)	16 (28.1)

Source: Sponsor's Table 4 (P. 46 of 4488)

The use of concomitant medications, including femoral nerve block (identified as use of local anesthetics), did not differ appreciably across treatment groups.

Efficacy Analysis Results:

Primary Efficacy Endpoints
The Sponsor's analysis of the primary efficacy outcome using the modified ITT population excluded 42 patients out of the 300 randomized, 39 of whom were excluded due to use of rescue medication or withdrawing from the study within the first one hour following dosing of study medication. At the request of Dr. Price, the statistical reviewer, the Sponsor subsequently performed a reanalysis of the primary endpoint including patients who re-medicated, and the Sponsor used a BOCF method for imputing missing data. There were fewer concerns regarding the use of LOCF for this study given the relatively small number of subjects who withdrew due to adverse events. Table 3 is reproduced from Dr. Price's review and provides the results of the original and subsequent analyses. The findings from the reanalysis are comparable to the original analysis. All three OM IR groups demonstrated statistically significantly better pain relief over the initial 8 hour period than placebo, while the oxycodone IR group did not.

Table 3 Re-Analysis of Total Pain Relief (0–8 hours)

Treatment (Number of Patients Randomized)	Statistics	Excluding patients who re-medicated within the first hour	Including patients who re-medicated within the first hour
Oxymorphone IR 10 mg (N=59)	n	51	59
	Mean	10.8	10.0
	p-value*	0.0196	0.0087
Oxymorphone IR 20 mg (N=59)	n	51	58
	Mean	12.7	11.8
	p-value*	0.0005	0.0001
Oxymorphone IR 30 mg (N=65)	n	57	64
	Mean	12.7	11.5
	p-value*	0.0003	0.0002
Oxycodone 10 mg (N=60)	n	55	59
	Mean	8.7	8.1
	p-value*	0.3331	0.1864
Placebo (N=57)	n	44	57
	Mean	7.2	6.1

* p-value is from the pairwise comparison with placebo in ANOVA.

Source: Review by Dr. Dionne Price, P. 46 of 48

Secondary Efficacy Endpoints

The Sponsor's secondary efficacy analyses were performed using the modified ITT population and were not repeated using the more inclusive population. The method for imputing missing scores was LOCF. The results are presented below.

TOTPAR 0-4 and 0-6

The table below provides the results of these analyses. The three OM IR groups all demonstrated greater pain relief over the intervals examined compared to placebo, while the oxycodone IR group did not.

Table 4 Summary of TOTPAR (Categorical) Scores

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

[a]All pairwise comparison statistical results are between corresponding active treatments and placebo.

Source: Sponsor's Table 6, P. 49 of 4488

Pain Relief (PR, Categorical) by Time Point:

The mean pain relief scores are presented in the following table. While the Sponsor did extrapolate data for the means and standard deviations, the number of subjects with data at each time point are presented. What can be seen is that starting at 45 minutes after dosing the OM IR 20 and 30 mg groups showed consistent statistically significant differences in pain relief compared to the placebo group starting at 45 minutes, the OM IR 20 and 30 mg groups had statistically significantly greater pain relief than placebo persisting through the 8 hour period. The difference in pain relief ranged from 0.4-0.8 units of the 5-point categorical scale. There were scattered time points when the OM IR 10 mg group separated from placebo, Hours 2, 3, 5, and 7. There were no differences between the OM IR 20 and 30 mg groups.

Table 5 Summary of Pain Relief for Efficacy-Evaluable Patients, Categorical Scale

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

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

[b]Based on ANOVA model including main effects for treatment, center, surgical site, and baseline pain stratification in the model.

Treatments with a common letter are not significantly different (e.g. , treatments with A and AB are not significantly different).

Note: Some patients did not have pain relief data at all time points; therefore, Ns reflect the number of patients with data at each time point not the total "N" for the efficacy evaluable population.

Source: Sponsor's Table 7, P. 52 of 4488

What can also be seen from this table is the time course for patient withdrawal. At some points, some patients may not have had data recorded, but overall the reduction in number reflects patients dropping out. Additionally, this table already excludes subjects who dropped out within the first hour for remedication. It can be seen that for the OM IR 20 and 30 mg groups fewer than half of the subjects remained after the 4-hour time period. During the single-dose period, most of the dropouts were due to lack of efficacy (n=92), rather than adverse events (n=12), supporting these dropouts were in order to remedicate. This will be important to keep in mind for consideration of the dosing interval.

Mean SPID (Categorical) at 0-4, 0-6, and 0-8 Hours:

The three OM IR groups all demonstrated statistically significantly greater SPID scores for the three time intervals analyzed. The OC IR 10 mg group did not differ statistically from the placebo group.

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

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

Source: Sponsor's Table 8, P. 53 of 4488

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

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

Pain Intensity Difference (PID, Categorical) by Time Point

The mean PID scores reflected a similar pattern of results as the mean PR scores described above. Starting at 45 minutes after dosing the OM IR 10, 20, and 30 mg groups showed for most time points statistically significant differences in PID compared to the placebo group persisting through the 8 hour period. While there were no statistically significant differences between the OM IR 20 mg and 30 mg groups and review of the mean values reveals that the PID was often greater for the OM IR 20 group compared to the OM IR 30 mg group. The oxycodone IR group did not differ statistically from placebo. The magnitude of these differences ranged from 0.2 to 1.0 units of the 5-point categorical scale. See Dr. Comfort's Table EN3203-4.9 for these values.

Sum of Pain Intensity Difference (SPID, VAS) over 0-4, 0-6, and 0-8

The mean SPID scores for all OM IR groups were statistically significantly different from the mean score for placebo. OC IR 10 mg was not statistically different from placebo.

Table 7 SPID (VAS) at 0-4, 0-6, and 0-8 for Efficacy-Evaluable Patients

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

Source: Sponsor's Table 10, P. 56 of 4488

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

Pain Intensity Difference (PID, VAS) by Time Point:

In slight contrast to the PID by categorical scale, the OM IR 10 and 30 mg groups separated from placebo with greater statistically significant differences in PID at 1.5

hours after dosing, rather than 45 minutes. The OM IR 20 mg group had a statistically significantly greater PID compared to placebo by 30 minutes. No statistically significant differences were observed between oxycodone IR 10 mg. The values are provided in the table below. The differences between placebo and the OM IR 20 mg group range from 13 to 29 mm.

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

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

Source: Sponsor's Table 11, P. 58 of 4488

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

Sum of Combined Pain Relief and Pain Intensity Difference (SPRID, Categorical)

The mean SPRID scores for all OM groups were statistically significantly different from the mean score for placebo. OC IR 10 mg was no different from placebo at all time points. See Dr. Comfort's Table EN3203-4.12 for these values.

Combined Pain Relief and Pain Intensity Difference (PRID, Categorical)

The PRID scores for the OM IR 20mg and 30 mg groups were statistically significantly different from placebo, starting at 45 minutes post-dosing. The OM IR 10 mg formulation showed a statistically significant difference in PRID over placebo starting at 2 hours after dosing. See Dr. Comfort's Table EN3203-4.13 for these values.

Proportion Pain at Least Half Gone

During the Single-Dose Phase of the study, patients were asked at each time point during the 8-hour assessment period if their pain was half gone (50% pain relief). The proportion of patients experiencing 50% pain relief was statistically significantly greater for the OM IR 10 and 20 mg groups as demonstrated in Table.

Table 9 Proportion of Patients who Experienced 50% Pain Relief (Single-Dose Phase, Efficacy-Evaluable Population

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

Source: Sponsor's Table 14, P. 63 of 4488
[a]Fisher's exact test

Median Time to Pain at Least Half Gone

The three OM IR groups had a median time of 45 minutes to pain half gone (range 15 minutes to 5 hours and 49 minutes), while the oxycodone group had a median of 32 minutes (range: 12 minutes to 7 hours) and placebo had a median of 33 minutes (range 15 and minutes to 2 hours and 33 minutes). These values were statistically significantly longer for the OM IR 10 and 20 mg groups compared to placebo.

Time to First Perceptible Pain Relief

None of the active treatment groups differed statistically from placebo, the values ranged from 15 minutes to 23 minutes.

Time to Meaningful Pain Relief

The median times to meaningful pain relief for the three OM IR groups (59 minutes to 1 hour and 5 minutes) were statistically significantly shorter than for the placebo group (1.5 hours). The median time to meaningful pain relief for the oxycodone IR group, 1 hour and 7 minutes was not statistically different from placebo.

Time to Remedication

The median times to re-medication for the OM IR 20 mg and 30 mg group(4 hours and 3 hours and 42 minutes respectively) were statistically significantly longer than placebo (3 hours and 5 minutes). The median times to remedication for the OM IR 10 mg (3 hours and 4 minutes) and oxycodone IR (3 hours and 7 minutes) were not different from placebo.

Patient's Global Evaluation of Study Medication

The OM IR 10 and 20 mg groups patient global evaluations of overall satisfaction with the pain medication were statistically significantly better than placebo as demonstrated in Table 10. The OM IR 30 mg group had the same number of Excellent ratings as Poor ratings (22.2%), but overall did not statistically differ from placebo. The distribution of the oxycodone 10 mg group ratings were very similar to placebo

Table 10 Patient Global Evaluation, Single Dose Phase, Efficacy-Evaluable Patients

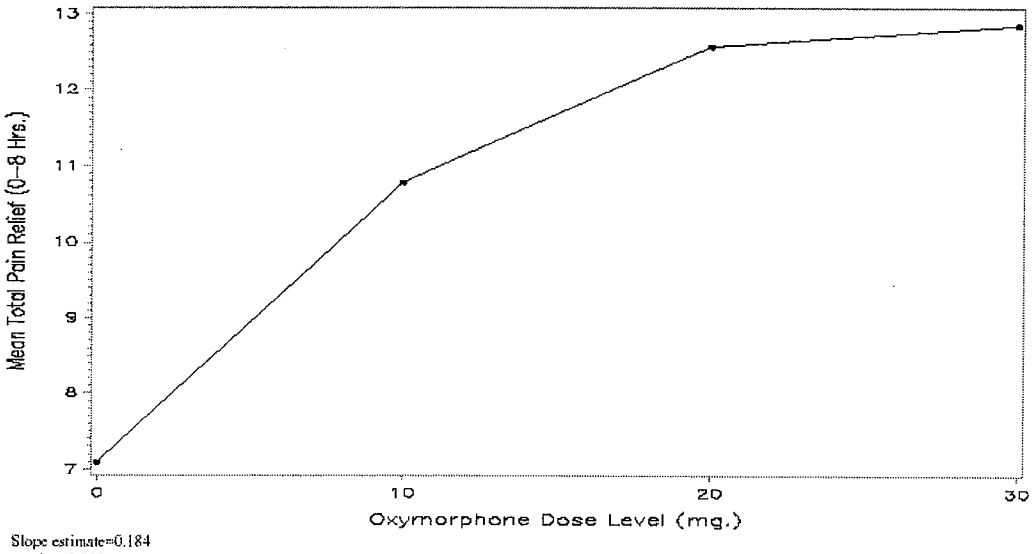
Response	Oxymorphone 10 mg (N=51)	Oxymorphone 20 mg (N=51)	Oxymorphone 30 mg (N=57)	Oxycodone 10 mg (N=55)	Placebo (N=44)
Total [1]	51 (100)	49 (100)	54 (100)	53 (100)	43 (100)
Excellent	8 (15.7)	10 (20.4)	12 (22.2)	3 (5.7)	0
Very Good	17 (33.3)	17 (34.7)	11 (20.4)	11 (20.8)	9 (20.9)
Good	11 (21.6)	16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

[1] Percentages are calculated using TOTAL as denominator, [2] All pairwise comparison p-values are based on stratified rand sum test, stratified by center and baseline pain stratification
Source: Sponsor's Table 4.9, P. 883 of 4488

Dose Response

A dose response relationship was evaluated for oxymorphone using the TOTPAR 0-8 data. The Sponsor reports a statistically significant dose response relationship. But the figure below suggest little added effect from the 30 mg dose compared to the 20 mg dose.

Figure 1. Oxymorphone dose response relationship.



Source: Sponsor's Figure 8, P. 70 of 4488.

Multi-dose Period Endpoints

The Sponsor evaluated several endpoints from the multi-dose period of the study, from hours 8 through 48. Patients receiving placebo were changed to an active treatment based on the original randomization. The data was examined in a descriptive manner including worst pain recall scores. This information is not helpful in examining the efficacy of this product. Dose intervals were calculated. The OM IR 30 mg group demonstrated the longest median dose interval of 9 hours and 39 minutes while the remaining three groups ranged from 7 hours even to seven hours and 44 minutes. This is presented in Dr. Comfort's Table EN3203-4.22. However, during this time period, patients requiring remedication prior to 3 hours since the last dose were withdrawn from the study. Additionally, patients requesting additional analgesic medication greater than 3 hours after dosing of study medication were permitted rescue of the Investigator's choice. These two study features call into question the utility of these calculated dosing intervals.

Efficacy Conclusions for EN3203-004

This was a 48-hour, single and multi-dose, placebo- and active-controlled study in patients with post-operative pain. The results of the primary efficacy endpoint, TOTPAR 0-8, along with secondary analyses of pain relief and change in pain intensity following the single dose period demonstrate that the OM IR 10, 20, and 30 mg doses were effective when compared with placebo. Effects of exclusion of patients based on the Sponsor's definition of the evaluable population were explored in additional analyses which yielded the same results. An immediate-release formulation of oxycodone was not effective when compared with placebo. Additional analyses continued to support findings of efficacy, but not consistently for the OM IR 10, 20, and 30 mg doses. The proportion of patients experiencing 50% pain relief and the median time to 50% pain relief were statistically significantly greater for the OM IR 10 and 20 mg groups

compared to placebo. Time to first perceptible pain relief did not differ between the active treatment groups and placebo while time to meaningful pain relief was statistically significantly shorter for the three OM IR groups compared to placebo. The median time to re-medication was statistically significantly longer for the OM IR 20 and 30 mg groups (4 hours and 3 hours and 42 minutes respectively) compared to placebo. Review of mean PR and PID scores at individual study time points failed to demonstrate any superiority of the OM IR 30 mg group over the OM IR 20 mg group while the data trended in favor of the OM IR 20 mg dose. The patient global evaluation of satisfaction with study medication was statistically significantly better for the OM IR 10 and 20 mg groups compared to placebo, but not for the OM IR 30 mg group.

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

Study EN3202-005
A Multicenter, Randomized, Double-Blind, Placebo- and Active-Control, Single-Dose Study of Oxymorphone IR and Oxycodone IR in Patients With Pain Following Orthopedic Surgery.

This was a multi-center, double-blind, placebo- and active-control, single dose study of oxymorphone immediate-release tablets (OM IR) and oxycodone immediate-release tablets (OC IR) in patients undergoing orthopedic surgery. The primary objective was to compare the efficacy of OM IR 10 mg and 20 mg to placebo. The secondary objectives were to compare the relative efficacy, safety, and tolerability of OM IR 10 mg and OM IR 20 mg with OC IR 15 mg and OC IR 30 mg.

Enrollment was to result in a total of 300 patients in order to achieve 60 patients per treatment arm. Patients were to be male or female, at least 18 years of age, in good general health, and were to undergo orthopedic surgery involving osteotomy. Patients were to have an initial moderate to severe pain intensity by categorical scale and at least 50 mm by VAS scale from 45 minutes to 6 hours following discontinuation of PCA analgesia. Patients were to be excluded if they had received long-acting oral or parenteral analgesics within 12 hours of study medication dosing, short-acting analgesics within 6 hours of dosing, or use of an MAO inhibitor within 2 weeks of study entry. Patients were to have no history of seizures or opioid abuse or chronic use within 6 months of the study.

Following orthopedic surgery requiring osteotomy, patients were to be started on PCA opioids as soon as possible. The PCA analgesic was to be discontinued within 24 hours and no longer than 72 hours after surgery. Subjects reporting moderate to severe pain by categorical scale and at least 50 mm by VAS from 45 minutes to 6 hours after discontinuation if the PCA were to be randomized if they fulfilled study criteria. Each patient was to receive a single dose of blinded study medication. Treatment arms were to be OM IR 10 mg, OM IR 20 mg, oxycodone IR 15 mg, oxycodone IR 30 mg, and placebo. Efficacy assessments were to be performed 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. 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.

Concomitant medications to be permitted were antiemetics given at least 4 hours prior to dosing of study drug. Continuous passive motion was to be in progress at the time of study drug dosing and was to remain constant during first four hours of study. Postoperative epidural PCA opioids were not to be allowed. There was to be a 15 minute washout after physical therapy before each evaluation. There was to be a 30 minute washout after ice before the first evaluation and further use of ice was not to be permitted.

Efficacy outcomes were to be assessed at baseline, 15, 30, and 45 minutes post dosing, and then hourly over 8 hours and were to include pain relief (PR) by VAS and 5-point categorical scale, pain intensity (PI) by VAS and 4-point categorical scale. The efficacy evaluations were to be recorded by patients in a diary. Time to perceptible pain relief and time to meaningful pain relief were to be measured using a stopwatch. Time to re-medication and time to pain at least half gone were also to be recorded. A patient global assessment on a 6-point scale was to assess how the patient rated the pain relief from study mediation was to be performed at the end of 8 hours or prior to rescue medication use.

Safety was to be evaluated by collecting adverse events, performing physical exams and vital signs.

The primary efficacy endpoint was to be the total pain relief over the eight hour study period, (TOTPAR 0-8), based on VAS PR scores. This was to be analyzed using an 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 a step-down procedure.

The secondary efficacy endpoints were to be

- TOTPAR 0-8 by categorical scale

- Sum of pain intensity difference (SPID) 0-8, 0-4, and 0-6 by VAS and categorical scales.
- TOTPAR 0-4 and 0-6 by VAS and categorical scales
- Proportion of patients experiencing pain half gone and time to pain half gone
- Time to first perceptible pain relief
- Time to onset of meaningful pain relief
- Time to remedication
- Hourly PR and PID scores
- Patient global evaluation of study medication.

The Sponsor also planned on evaluating the relative potency of OM IR and OC IR using a regression analysis of TOTPAR and SPID scores.

The primary efficacy endpoint was to be analyzed using an intent-to-treat (ITT) 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. The Sponsor planned to impute missing data from subjects withdrawing early or re-medicated after the first hour using the last observation carried forward (LOCF).

The Sponsor defined the ITT population as all patients randomized to treatment, who received the dose of study medication and completed the 1st hour efficacy evaluation. However, in Section 7.1.3 of the protocol describing the randomization phase, it also states that patients were to be considered evaluable for efficacy with the above criteria and who do not vomiting or rescue within the first hour. All patients randomized who received the one dose of study medication were to be used for safety evaluations.

Protocol Amendment 1, dated June 25, 2001, added the option of intermittent IM and non-PCA IV opioids as immediate post-op analgesia. This change would not affect the efficacy analysis.

Protocol Amendment 2, dated August 30, 2001, clarified that the washout following postoperative opioids would be 45 minutes for IV opioids, 4 hours for IM or epidural (now permitted) opioids, or 6 hours for oral opioids, but within 12 hours of discontinuation of all opioids. These changes would not affect the efficacy analysis.

Protocol Amendment 3, dated January 28, 2002, was implemented after study enrollment was completed. This amendment changed the primary efficacy endpoint from TOTPAR 0-8 using VAS data to categorical data, and 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 1st hour. The change to the definition of the ITT population was not used in the reanalysis by the Agency and did not impact the analysis of efficacy. The change in primary endpoint occurred before unblinding and was acceptable.

Additional changes were made to the statistical analysis plan, dated March 18, 2002, prior to the database lock. 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 1st hour efficacy evaluations without remedicating, vomiting or significant protocol violations. Additional analyses of the analgesic efficacy using the baseline observation carried forward (BOCF) for imputing missing data were described. These changes occurring prior to database locking were acceptable.

RESULTS

The study was begun July 18, 2001 and completed December 20, 2001. Patients were enrolled from nine study centers.

Disposition:

A total of 324 patients were randomized and received the one dose of study medication. Three hundred of the patients (92.6%) completed the study, ranging from 87.9% of placebo patients to 95.5% of the OM IR 20 mg patients. Most patients used rescue after Hour 1 and before Hour 8, ranging from 81.8% of placebo patients to 71.6% of OM IR 20 mg patients. There were few patients discontinuing due to adverse events, and few requiring rescue before the Hour 1 evaluation as detailed in Table 11.

Table 11 Study 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)	-	-
Efficacy-Evaluable Patients [2]	56 (88.9)	65 (97.0)	62 (95.4)	60 (95.2)	59 (89.4)

Source: Sponsor's Table 3, P. 38 of 2931

[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

The Sponsor's analysis population excluded twenty-two patients from the efficacy evaluable population due to remedication within the 1st hour, vomiting, or other protocol violations. These exclusions are presented in Table 12.

Table 12 Patients Excluded from the Sponsor's 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

Source: Sponsor's Table 4, P. 39 of 2931

One additional protocol violation (use of prohibited concomitant analgesic) occurred after the 2-hour efficacy evaluation and the patient was withdrawn at that point.

The baseline and demographic characteristics were comparable across treatment groups including baseline pain characteristics. The majority of patients were Caucasian, just over half were female, and the mean age was approximately 61 years. See Dr. Comfort's Table 5.3 for further details..

Use of concomitant medications, particularly opioids, was comparable across treatment groups. See Dr. Comfort's Table 5.4 for details.

Efficacy Analysis Results:

Primary Efficacy Endpoint

The Sponsor's analysis of the primary efficacy outcome using the modified ITT population excluded 22 patients out of the 324 randomized, 12 of whom were excluded due to use of rescue medication within the first one hour following dosing of study medication. As with study EN3203-004, the Sponsor was asked to perform a reanalysis of the primary endpoint including patients who re-medicated within the first hour. Table 13 is reproduced from Dr. Price's review and provides the results of the original and subsequent analyses. The findings from the reanalysis are comparable to the original analysis. The OM IR 20 mg group, but not the OM IR 10 mg group, demonstrated statistically significantly better pain relief over the initial 8 hour period than placebo. Both the oxycodone IR 15 mg and 30 mg groups were also statistically significantly superior to placebo.

Table 13 Re-Analysis of Total Pain Relief (0–8 hours)

Treatment (Number of Patients Randomized)	Statistics	Excluding patients who re-medicated within the first hour	Including patients who re-medicated within the first hour
Oxymorphone IR 10 mg	n	56	59
(N=63)	Mean	9.6	9.1
	p-value*	0.1460	0.2608
Oxymorphone IR 20 mg	n	65	66
(N=67)	Mean	12.5	12.4
	p-value*	0.0007	0.0008
Oxycodone IR 15 mg	n	62	64
(N=65)	Mean	12.7	12.6
	p-value*	0.0004	0.0006
Oxycodone IR 30 mg	n	60	62
(N=63)	Mean	12.6	12.2
	p-value*	0.0006	0.0017
Placebo	n	59	63
(N=66)	Mean	7.3	7.4

* p-value is from the pairwise comparison with placebo in ANOVA.
Source: Review by Dr. Dionne Price, P. 48 of 48

Secondary Efficacy Endpoints

The Sponsor's secondary efficacy analyses were performed using the modified ITT population and were not repeated using the more inclusive population. The method for imputing missing scores was LOCF. The results are presented below.

TOTPAR 0-4 and 0-6, Categorical Scale

The mean TOTPAR 0-4 and 0-6 analyses resulted in the same results as the TOTPAR 0-8 analysis with statistically significantly better pain relief than placebo for the OM IR 20 mg, oxycodone IR 15 mg and oxycodone IR 30 mg groups.

Table 14 Summary of TOTPAR 0-4, 0-6, and 0-8 (Categorical), Efficacy-Evaluable Patients

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

[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 in five point scale: 4 = complete, 3 = a lot, 2 = some, 1 = a little, and 0 = none.

Source: Sponsor's Table 8, P. 43 of 2831

Pain Relief (Categorical) by Time Point

From the 1-hour time point, the OM IR 20 mg and the oxycodone IR 15 mg groups demonstrated statistically significantly better pain relief than placebo. This was also true for the oxycodone 30 mg group from the 45-minute time point. The OM IR 10 mg group never separated from placebo. The magnitude of difference ranged from 0.4 to 0.9 units of a 4 point scale.

Table 15 Summary of Pain Relief (Categorical, Extrapolated), 0-8 Hours, Efficacy-Evaluable Patients

	Assessment Time Point										
Tx	**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]	0.9 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
S[a]	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	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	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
Mean	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	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	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	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
Mean	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	0.98	1.09	1.14	1.28	1.41	1.32	1.25	1.22	1.27	1.12	1.15
p-value[b]	0.211	0.889	0.137	**0.003**	**<0.001**	**<0.001**	**<0.001**	**0.002**	**0.022**	**0.010**	**0.018**

Source: Sponsor's Table 9, P. 45 of 2931

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.

Again as in Study EN3203-004, it can be seen that even excluding the patients requiring re-medication with rescue within the first hour from the table, there were substantial dropouts from the active treatments with more than half of the patients from the OM IR 20 mg, oxycodone IR 15 mg and oxycodone IR 30 mg groups out of the study by Hour 5.

TOTPAR 0-4, 0-6 and 0-8, VAS

Mean TOTPAR scores by VAS had the same pattern of results as by categorical scale with statistically significantly better pain relief for the OM IR 20 mg, oxycodone IR 15 mg and 30 mg groups. OM IR 10 mg was not statistically significant different from placebo. See Dr. Comfort's Table 5.7 for the values.

Pain Relief by VAS by Time Point

The results of the analysis of PR by VAS is similar to the results by categorical scale. The OM IR 20 mg group is statistically significantly better than placebo from the Hour 2 assessment, and the oxycodone 15 mg and 30 mg groups separate from placebo at Hour 1

and 45 minute assessments, respectively. There is no separation from placebo for the OM IR 10 mg group. See Dr. Comfort's Table EN3203-5.8 for details.

SPID by Categorical Scale and VAS

The mean SPID 0-4, 0-6 and 0-8 analyses using the categorical scale and VAS demonstrated statistically significantly greater pain intensity difference for the OM IR 20 mg, oxycodone 15 mg and 30 mg groups compared to placebo. The OM IR 10 mg group was not statistically different from placebo using categorical data, but just reaches statistical significance using the VAS data for the 0-4 hour time period. See Dr. Comfort's Tables EN3203-5.9 and 5.10 for the details.

PID by Categorical Scale

The PID detailed in the table below demonstrates the statistically significantly greater difference in pain for the OM IR 20 mg, oxycodone 15 mg and 30 mg groups compared to placebo from 45 minutes through Hour 7. There were no statistically significantly differences for the OM IR 10 mg group.

Table 16 Summary of PID 0-8 (Categorical, Extrapolated), Efficacy -Evaluable Patients

	Assessment Time Point										
	15 m	**30 m**	**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
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: Sponsor's Table 13, P 51 of 2931

[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.

PID by VAS

The findings from the PID by categorical scale analyses were replicated for the analysis using PID by VAS, with minor differences. See. Dr. Comfort's Table 5.12 for the details.

SPRID 0-4, 0-6 and 0-8 by Categorical scale and VAS

The mean SPRID scores derived from pain relief and pain intensity assessments, again demonstrated the same pattern as prior analyses. The OM IR 20 mg, oxycodone 15 mg and 30 mg groups were all statistically significantly superior to placebo, with no effect for the OM IR 10 mg group. See Dr. Comfort's Tables EN3203-5.13 and 5.15 for the details.

PRID, Categorical and VAS by Time point

This analysis revealed statistically significant improvement for the OM IR 20 mg, oxycodone 15 mg and 30 mg groups from either 45 minutes or Hour 1 through the end of the 8 hour period, compared to placebo. There was no effect for the OM IR 10 mg group. See Dr. Comfort's Tables EN3203-5.14 and 5.16 for details.

Time to First Perceptible Pain Relief

Time to first perceptible pain relief ranged from 15 to 20 minutes and did not differ statistically among any of the five treatment groups.

Time to Onset of Meaningful Pain Relief

The median time to meaningful pain relief ranged from 53 minutes to one hour and 3 minutes for the four active treatment groups, all of which were statistically significantly earlier than for placebo (8 hours).

Time to Rescue Medication

The median time to rescue medication ranged from 3 hours and 34 minutes to 4 hours and 53 minutes for the four active treatment groups, all of which were statistically significantly longer than for placebo (2 hours). This analysis excluded patients receiving rescue medication within the first hour.

Table 17 Time to Rescue Medication for Efficacy-Evaluable Patients

Treatment	Median (hh:mm)[a,b]	95% Confidence Interval
Oxymorphone IR 10 mg (N=56)	3:34 A	2:29 to 4:25
Oxymorphone IR 20 mg (N=65)	4:53 A	3:35 to 6:00
Oxycodone IR 15 mg (N=62)	4:50 A	3:47 to 5:30
Oxycodone IR 30 mg (N=60)	4:24 A	3:35 to 5:31
Placebo	2:00 B	1:39 to 2:15

Source: Sponsor's Table 22, P. 63 of 2931
a Kaplan-Meier estimate
b Log-Rank test applied as in Fisher's PLSD. Treatments with a common letter are not significantly different.

Patient's Global Assessment of Pain Relief

The patient global rating of pain relief by the study medication was consistent with prior analyses. The OM IR 20 mg, oxycodone 15 mg and 30 mg groups were all statistically significantly better than placebo. The OM IR 10 mg was not statistically different from placebo. Table demonstrates these results.

Table 18 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: Sponsor's Table 4.10, Appendix 16.2.2 P 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 Sponsor had intended to evaluate the relative analgesic potency of oxymorphone relative to oxycodone. However, there was no dose response in the oxycodone groups, resulting in no assay sensitivity; so no reliable estimation of relative potency could be made.

Evaluation of Efficacy Outcomes using 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. These analyses were comparable to the analyses using LOCF and are not represented further in this review.

Efficacy Conclusions for EN3203-005:

This single-dose double-blind, placebo-and active-control study of OM IR 10 mg, OM IR 20 mg, oxycodone 15 mg and oxycodone 30 mg demonstrated the efficacy of OM IR 20 mg as well as the two oxycodone IR doses using the primary efficacy endpoint, TOTPAR 0-8, as well as nearly all of the secondary outcome measures. There was no efficacy demonstrated for the OM IR 10 mg dose. Effects of an evaluable population excluding subjects requiring rescue medication within the first hour were explored in alternate analyses of the primary outcome utilizing a more inclusive population. No differences in the outcomes were found. Patient global assessment of pain relief mirrored these

findings. For patients in the OM IR 20 mg group not requiring rescue medication in the first hour, the median time to rescue was nearly 5 hours.

INTEGRATED REVIEW OF SAFETY

Summary of Safety Findings - Oxymorphone IR

There were no deaths attributable to use of oxymorphone IR. Serious adverse events were common, occurring in 5.16% of patients exposed to oxymorphone IR compared to 8.54% of patients exposed to oxymorphone ER. This is a relatively high rate for the oxymorphone IR group considering that the oxymorphone IR exposure was predominantly single dose trials relatively healthy subjects undergoing orthopedic surgery while the oxymorphone ER exposure represents the accumulation of events over trials lasting weeks to months in both relatively healthy patients with osteoarthritis and low back pain, as well as somewhat more ill patients with cancer.

Hypoxia and respiratory depression were particularly notable adverse events leading to study discontinuation in the oxymorphone treated patients during these postoperative studies. A review of patients requiring 1ne found 12 oxymorphone IR patients (3.6%) compared to 1 oxycodone patient (0.5%) and no placebo patients. These patients were also permitted parenteral opioid rescue medication. It appears that a manner of safe use of oxymorphone in the acute postoperative period has not yet been defined.

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

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

REVIEW OF SAFETY

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

Extent and Duration of Exposure

There were two Phase 2/3 clinical trials which used oxymorphone IR and no oxymorphone ER, in patients with acute postoperative pain, EN3203-004 and EN3203-005. There were four Phase 1 trials oxymorphone IR conducted in either healthy volunteers or subjects with hepatic or renal impairment. Additional safety information was to be obtained from Study EN3202-018 and Study EN3202-019 in which OM IR was used to titrate subjects prior to randomization to a modified-release opioid. Studies

EN3202-017, EN3202-020, EN3202-022 which permitted the use of oxymorphone IR for rescue were intended to provide safety information, but the amount of OM IR used by patients was not documented. Because patients were on other opioids concurrently or use of oxymorphone IR was not quantitated during periods of use as rescue, adverse event that may have been due to use of oxymorphone IR cannot be separated from those due to other drugs. This safety review will discuss adverse events for oxymorphone IR during Phase 2/3 as those occurring during Studies EN3203-004 and 005.

At the time of the initial NDA submission, a total of 2542 unique subjects had participated in the oxymorphone clinical development program. Of these 2108 had participated in the Phase 2/3 program, 1864 of whom had received oxymorphone ER and/or IR at some point. A total of 565 received only oxymorphone IR. The following table represents information combined from two of the tables in Dr. DalPan's review.

Table 19: Numbers of Exposures by Subset and Treatment Group and Number of Unique Participants by Subset – All Trials Including 120-Day Safety Update

		Oxymorphone			Oxycodone			
Study Group	Total[a]	ER/IR [b]	ER	IR	ER	IR	Morphine ER	Placebo
All Trials	2542	1864	1432	565	382	195	69	473
All Phase I Trials	434 (or 484)	434	343	197	0	0	0	0
All Phase II/III Trials	2108	1430	1089	368	382	195	69	473
All ER Phase II/III Trials[c]	1484	1096	1089	34	382	0	69	350
All IR Phase II/III Trials[d]	624	334	0	334	0	195	0	123
Acute Postoperative Pain Trials	751	400	66	334	0	195	0	184
EN3202-012	127	66	66	0	0	0	0	61
EN3203-004	300	204	0	204	0	67	0	57
EN3203-005	324	130	0	130	0	128	0	66
Chronic Non-malignant Pain Trials	1185	684	684	0	286	0	0	289
EN3202-015	489	240	240	0	125	0	0	124
EN3202-016	326	165	165	0	161	0	0	74
EN3202-025	370	279	279	0	0	0	0	91
Cancer Pain Trials	172	145	138	34	96	0	69	0
EN3202-017	86	63	63	0	52	0	34	0
EN3202-018	38	36	32	18	0	0	35	0
EN3202-019	48	46	43	16	44	0	0	0
Open-label Extension Trials	0	460	460	0	0	0	0	0
EN3202-020[e]	0	197	197	0	0	0	0	0
EN3202-021[f]	0	164	164	0	0	0	0	0
EN3202-022[g]	0	15	15	0	0	0	0	0

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

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

The demographic features of all subjects are presented in detail in Dr. DalPan's review.

Deaths

There were no deaths during studies EN3203-004 and EN3203-005, or during Phase 1 studies. Of the 35 deaths in the clinical development program, 34 occurred in subjects with cancer pain. Twenty-eight of the 35 deaths occurred during the open-label extension studies EN3202-020 (n=13), EN3202-021 (n=12), and EN3202-022 (n=3). Of the patients who died during these open-label extension studies, all but one had previously participated in a controlled study for cancer pain. There were seven deaths during controlled trials for cancer pain, EN3202-017 (n=4), EN3202-018 (=2), and EN3202-019 (n=1). The review of the deaths by Dr. DalPan indicated that the 34 deaths in the cancer pain subjects were most likely due to the progression of the underlying cancer. The extent to which these patients were exposed to oxymorphone IR is unclear, but there was no indication that use of oxymorphone ER or IR contributed to the death of these patients. Deaths will be explored more fully in the review of oxymorphone ER, NDA 21-610.

Serious Adverse Events

There were no non-fatal serious adverse events (SAEs) in Phase 1 clinical trials in either the ISS or the 120-Day Safety update.

Of the 368 subjects exposed to oxymorphone IR, 19 (5.16%) had at least one SAE compared to the oxymorphone ER group (8.54%). This is a relatively high rate for the oxymorphone IR group considering that the oxymorphone IR exposure was predominantly single dose trials relatively healthy subjects undergoing orthopedic surgery while the oxymorphone ER exposure represents the accumulation of events over trials lasting weeks to months in both relatively healthy patients with osteoarthritis and low back pain, as well as somewhat more ill patients with cancer.

Table 20 Incidence of SAEs in at Least two Oxymorphone -Treated Subjects

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

Data for oxymorphone are presented based on analyses of the original ISS data (ISS), the 120-Day Safety Update data, (120 Update) and the combined data (Overall). Data for the other treatment groups are from the ISS; Since there were no new data for these treatment groups, they correspond to the overall data for these treatment groups.
^N/A refers to the fact that data for this preferred term was not in the original ISS. Source: Appendix 3.143 in ISS and Appendix 1, Table 9 in 120-Day Safety Update

Discontinuations Due to Adverse Events

In Phase 2/3 IR trials, the proportion of subjects discontinuing study drug due to adverse events was higher (10.2%) in oxymorphone IR-treated subjects than in oxycodone IR-treated subjects (3.6%) and placebo-treated patients (7.4%). The top adverse events leading to study drug discontinuation in oxymorphone IR-treated subjects in Phase 2/3 studies in the original ISS include: nausea, vomiting, sedation, somnolence, coma, confusion, and respiratory depression. There are additional single reports of disorientation, mental status changes, lethargy, hypoxia, hypoventilation, and dyspnea as detailed in the table below. These events were considerably more common in the oxymorphone IR-treated patients compared to oxycodone-treated patients.

Table 21 AEs Leading to Discontinuation Occurring OM IR-Treated Subject in All Clinical Trials in the Original ISS

	Oxymorphone IR	Oxycodone IR	Placebo
Number of Subjects	334	195	95
Any Cause [c]	34 (10.2%)	7 (3.59%)	7 (7.37%)
Nausea	6 (1.80%)	1 (0.51%)	1 (1.05%)
Vomiting nos	6 (1.80%)	0 (0.00%)	3 (3.16%)
Respiratory depression	3 (0.90%)	0 (0.00%)	0 (0.00%)
Hypoventilation	1 (0.30%)	0 (0.00%)	0 (0.00%)
Hypoxia	1 (0.30%)	0 (0.00%)	0 (0.00%)
Respiratory distress	1 (0.30%)	0 (0.00%)	0 (0.00%)
Dyspnea nos	1 (0.30%)	0 (0.00%)	0 (0.00%)
Somnolence	5 (1.50%)	0 (0.00%)	0 (0.00%)
Sedation	4 (1.20%)	0 (0.00%)	0 (0.00%)
Coma nec	3 (0.90%)	0 (0.00%)	0 (0.00%)
Confusion	3 (0.90%)	0 (0.00%)	0 (0.00%)
Depressed LOC	1 (0.30%)	0 (0.00%)	0 (0.00%)
Mental status changes	1 (0.30%)	0 (0.00%)	0 (0.00%)
Lethargy	1 (0.30%)	0 (0.00%)	0 (0.00%)
Agitation	1 (0.30%)	0 (0.00%)	0 (0.00%)
Disorientation	1 (0.30%)	1 (0.51%)	0 (0.00%)
Feeling abnormal	1 (0.30%)	0 (0.00%)	0 (0.00%)
Hallucination nos	1 (0.30%)	0 (0.00%)	0 (0.00%)
Psychotic disorder nos	0 (0.00%)	0 (0.00%)	1 (1.05%)
Abdominal pain nos	1 (0.30%)	0 (0.00%)	0 (0.00%)
Ileus	1 (0.30%)	0 (0.00%)	0 (0.00%)
Constipation	1 (0.30%)	0 (0.00%)	0 (0.00%)
Myocardial infarction	1 (0.30%)	0 (0.00%)	0 (0.00%)
Hypotension nos	1 (0.30%)	0 (0.00%)	0 (0.00%)
Sweating increased	1 (0.30%)	0 (0.00%)	0 (0.00%)
Dermatitis nos	0 (0.00%)	1 (0.51%)	0 (0.00%)
Headache nos	1 (0.30%)	3 (1.54%)	0 (0.00%)
Headache nos aggravated	1 (0.30%)	0 (0.00%)	0 (0.00%)
Muscle spasms	0 (0.00%)	0 (0.00%)	1 (1.05%)
Pyrexia	0 (0.00%)	1 (0.51%)	2 (2.11%)

Source: Appendix 3.140 in the ISS

Adverse Events

Adverse events during Phase 1 studies occurred in 30.5% of oxymorphone IR treated subjects and 40.7% of oxymorphone ER treated subjects. The eight adverse events that occurred in 3.0% or more of oxymorphone (ER or IR) treated subjects were adverse events typically associated with opioid treatment (dizziness, nausea, fatigue, vomiting, constipation, euphoric mood, headache, and pruritus).

Adverse events during the Phase 2/3 oxymorphone IR studies which occurred in 2% or more patients are presented in the table below, from Dr. DalPan's review. These were one or two dose studies. Adverse events occurred in 71.0% of oxymorphone IR-treated subjects, 64.6% of oxycodone IR-treated subjects, and 46.3% of placebo-treated subjects.

The most common adverse event was pyrexia, which may be related to the postoperative status of the patients, but was distributed unevenly between treatment groups. Aside from anemia and tachycardia, the events were typical of opioids and were similar between the oxymorphone and oxycodone groups except for hypotension, and tachycardia which occurred more frequently in the oxymorphone group.

Table 22. Adverse Events Occurring in 2% or More of Oxymorphone IR-Treated Subjects in Phase 2/3 IR Clinical Trials

	Oxymorphone IR	Oxycodone IR	Placebo
Number of Subjects N[a]	334	195	123
Any Adverse Experience[b]	237 (71.0%)	126 (64.6%)	57 (46.3%)
Pyrexia	73 (21.9%)	31 (15.9%)	19 (15.4%)
Nausea	55 (16.5%)	38 (19.5%)	8 (6.5%)
Somnolence	49 (14.7%)	27 (13.8%)	5 (4.1%)
Dizziness (exc vertigo)	28 (8.4%)	10 (5.1%)	2 (1.6%)
Pruritus NOS	26 (7.8%)	12 (6.2%)	4 (3.3%)
Vomiting NOS	26 (7.8%)	13 (6.7%)	5 (4.1%)
Constipation	17 (5.1%)	14 (7.2%)	1 (0.8%)
Confusion	15 (4.5%)	5 (2.6%)	2 (1.6%)
Anemia NOS	13 (3.9%)	4 (2.1%)	4 (3.3%)
Headache NOS	10 (3.0%)	8 (4.1%)	1 (0.8%)
Dry mouth	8 (2.4%)	1 (0.5%)	0 (0.0%)
Hypoxia	8 (2.4%)	8 (4.1%)	5 (4.1%)
Hypotension NOS	7 (2.1%)	0 (0.0%)	1 (0.8%)
Tachycardia NOS	7 (2.1%)	1 (0.5%)	2 (1.6%)

Source: Appendix 3.43 in the ISS

Hypoxia occurred in patients in all three treatment groups. There were six events of depressed respiratory function in six oxymorphone subjects during Study EN3203-004, four of whom received naloxone.

Dr. DalPan did a thorough exploration of the database for all administrations of the opiate antagonist naloxone as a concomitant medication. A total of 27 subjects in the original ISS received naloxone. Twenty-three of the 27 subjects requiring naloxone were enrolled in one of the three acute post-operative pain trials (EN3202-012, EN3203-004, and EN 3203-005). The rates of naloxone use were as follows:

Table 23 Incidence of Naloxone Use in Acute Post-Operative Pain Trials

Study Group			
EN3202-012	Oxymorphone ER N=65	Placebo N=61	
	4 (6.2%)	0 (0.0%)	
EN3203-004 and EN3203-005	Oxymorphone IR N=334	Oxycodone IR N=123	Placebo N=195
	12 (3.6%)	1 (0.5%)	0

The relatively higher rate of use of naloxone in the oxymorphone group compared to the oxycodone group raises concern about the use of oxymorphone in the postoperative setting at the doses made available during the clinical trials.

Laboratory Results

Dr. DalPan performed an extensive review of the laboratory results. One finding of interest was two oxymorphone IR-treated subjects in Study EN3203-004 who entered with normal LFTs and developed clinically significant abnormalities of both AST and ALT without significant abnormality of total bilirubin. There were no similar cases in the oxycodone or placebo groups. There were three additional case of elevations of either AST (181 U/L and 206 U/L) or ALT (118 U/L). There is no explanation for any of these events in the ISS, and no follow-up lab values or other outcome data are presented. In view of the lack of follow-up data, the clinical significance of these findings is not clear. Clinical lab data were not collected in Study EN3203-005.

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

There were no findings of concern from the review of vital signs.

Electrocardiograms

In each of the three Phase 1 studies, 12-lead ECGs were obtained at screening, at the beginning of each study period, and following the last blood collection of each study

period. Review of individual changes reveals several QTc abnormalities. This was explored by Dr. DalPan who found that five subjects had at least one post-dose value that was ≥430 msec, four of which were increased from pre-dose. Six of the 58 subjects had at least one increase post-dosing of at least 30 msec. Two of these abnormal ECGs were concerning because of QTc prolongations of over 100 msec. Following a request for additional information the Sponsor responded that the original ECG tracings are no longer available. As a result, reanalysis of these values for reading errors such as mistaken U waves, is not possible.

There have been few post-marketing adverse events reported for intravenous (NDA 11-707, approved April 2, 1959) and suppository (NDA 11-738, approved May 31, 1960) formulations of oxymorphone. These data did not contribute to an understanding of the oxymorphone ER and IR formulations.

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

Analysis of drug-demographic interactions indicates that the frequency of some adverse events, such as somnolence and dizziness, may increase with increasing age in oxymorphone ER-treated subjects. Nausea, vomiting, and headache were more frequently in women compared to men. This gender difference was not seen in placebo-treated subjects.

Oxymorphone is a mu-agonist opioid analgesic. Its abuse liability is similar to morphine. Data from the clinical trials suggest that withdrawal will occur with abrupt discontinuation. There two instances of diversion from study sites (see review of studies EN3202-015 and NE3202-016 confirming the potential for abuse of this product.

Review of Coding of Adverse Events

Adverse events were coded using the MEDRA thesaurus, version 3.0. Dr. DalPan's review of how verbatim terms were mapped to preferred terms has discovered overlapping terms used for similar adverse events. These reported terms all refer to a change in mental status – either a change in the level of arousal or a change in the content of consciousness – whose clinical features are often difficult to understand from either the reported term or the preferred term. Further review of the Sponsor's mapping of reported terms to preferred terms suggests that there may be overlap among some of the adverse events that have been mapped to the preferred terms below. These preferred terms, and their corresponding system organ classes, are listed in the table below. It is very difficult to understand the difference between some of the terms such as depressed level of consciousness and CNS depression. By coding such similar events to different terms, the frequency of what amounts to the same underlying event appears smaller.

Table 24 Frequency of Any Alteration in Mental Status in All Clinical Trials

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

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

There were several adverse events that related to poor respiratory function. Preferred terms corresponding to these events included 'respiratory acidosis', 'hypoventilation', 'respiratory distress', 'respiratory failure (exc neonatal)', and 'respiratory depression'. Review of the above table indicates that 16 events occurred in 12 subjects. Of these, six events in six subjects occurred in Study EN3203-004, a study in acute post-operative pain. Each of these six events occurred in oxymorphone IR-treated subjects. Four of these six subjects received naloxone (Subjects EM3203-004-014-038, EN3203-004-028-014, EN3203-004-030-012, and EN3203-004-030-022 [for this subject the listed reason for naloxone was somnolence). For five of these six subjects, study drug was discontinued. For four of the six subjects, the event was judged to be possibly related to study drug. One oxymorphone ER-treated subject in the Study EN3202-012, a study in acute post-operative pain that used oxymorphone, developed respiratory acidosis, requiring discontinuation of study drug. This subject also required naloxone, though the listed reason for naloxone in this subject was 'CNS depression'.

First, most of the events in the post-operative setting appears to be directly related to the study drug, and many of the subjects required naloxone to treat the event. The

observation that each of the events in the acute post-operative setting is notable, and will be addressed in the overall discussion of the risks of the drug.

To explore further potential adverse effects f opiates, the database was reviewed for all administrations of the opiate antagonist naloxone as a concomitant medication. A total of 27 subjects in the original ISS received naloxone. These subjects are summarized in the table below.

Table 25 Listing of Subjects Who Received Naloxone Treatment

Protocol	Subject ID	Study Treatment	Naloxone Treatment		
			Study Day	Dose	Reason
EN3203-004	EN3203-004-013-080	Oxymorphone IR	2	1	Lethargy
	EN3203-004-014-017	Placebo	0	1	Apnea
	EN3203-004-014-030	Oxymorphone IR	1	12	Hypoxia
	EN3203-004-014-030	Oxymorphone IR	1	12	Reverse narcotic effect
	EN3203-004-014-038	Oxymorphone IR	1	120	Respiratory depression & somnolence
	EN3203-004-015-030	Oxymorphone IR	0	0.2	Sedation narcotic reversal
	EN3203-004-015-030	Oxymorphone IR	1	0.8	Sedation narcotic reversal
	EN3203-004-019-008	Oxymorphone IR	2	0.1	Confusion; agitation; combative; decreased level of consciousness; lethargy
	EN3203-004-021-011	Oxymorphone IR	2	1.2	Obtunded
	EN3203-004-022-003	Oxymorphone IR	0	0.4	Itching
	EN3203-004-027-007	Oxymorphone IR	0	0.12	Post-op somnolence
	EN3203-004-028-007	Oxymorphone IR	1	1.6	Drowsiness unresponsiveness
	EN3203-004-028-014	Oxymorphone IR	1	2	Unresponsiveness + respiratory depression
	EN3203-004-029-022	Oxymorphone IR	0	0.2	Reversal of sedative effects
	EN3203-004-030-012	Oxymorphone IR	1	1	Respiratory depression
	EN3203-004-030-022	Oxymorphone IR	2	0.8	Somnolence
	EN3203-004-030-022	Placebo	3	0.4	Somnolence
	EN3203-004-032-001	Oxymorphone IR	1	2.6	Unresponsiveness
EN3203-005	EN3203-005-105-099	Oxycodone IR	1	unk	Increased sedation
	EN3203-005-201-020	Oxycodone IR	0	0.16	Anesthesia
	EN3203-005-301-117	Oxymorphone IR	0	0.1	Respiratory stimulus
	EN3203-005-302-022	Oxymorphone IR	1	0.2	Unresponsiveness

Review of the above table is notable for the fact that 23 of the 27 subjects requiring naloxone were enrolled in one of the three acute post-operative pain trials (EN3202-012, EN3203-004, and EN 3203-005). The majority of these subjects were receiving oxymorphone. The following table illustrates the rates of naloxone use for in two groups of post-operative pain clinical trials – Study EN3202-012, the only study to use oxymorphone ER in an acute post-operative pain trial, and Studies EN3203-004 and EN3203-005, the two studies that used oxymorphone IR in acute post-operative pain trials.

Table 26 Incidence of Naloxone Use in Acute Post-Operative Pain Trials

Study Group			
EN3202-012	Oxymorphone ER N=65	Placebo N=61	
	4 (6.2%)	0 (0.0%)	
EN3203-004 and EN3203-005	Oxymorphone IR N=334	Oxycodone IR N=123	Placebo N=195
	12 (3.6%)	2 (1.6%)	1 (0.5%)

Review of the above table indicates that naloxone was administered more frequently to both oxymorphone ER-treated subjects and to oxymorphone IR-treated subjects, relative to placebo. In addition, naloxone use occurred in a higher proportion of oxymorphone IR-treated subjects than in oxycodone IR-treated subjects. In many cases, use of study drug discontinued. In Study EN3202-012, all four oxymorphone ER-treated subjects who received naloxone required study drug discontinuation due to the adverse event that required naloxone use. In studies EN3202-004 and 005, ten subjects (nine in EN3203-004 and one in EN3203-005) had study drug discontinued in response to an adverse event that required naloxone use. All ten of these subjects were taking oxymorphone IR.

Adverse Experiences Not From Clinical Trials

The sponsor provided post-marketing adverse event data from intravenous (NDA 11-707, approved April 2, 1959) and suppository (NDA 11-738, approved May 31, 1960) formulations of oxymorphone. Fifty-four adverse events were reported for the intravenous formulation, and eight adverse events were reported for the suppository formulation. Many of the adverse events reported are typical of opiate analgesics.

A review of postmarketing data was also performed by Dr. Martin Pollock of the Division of Drug Risk Evaluation in the Office of Drug Safety. Thirty-seven unique cases were found in the AERS database that involved use of oxymorphone. Seventeen were excluded because they involved a product quality defect (n=3), or because they were reported as part of an active surveillance program for OxyContin/oxycodone (n=14). In this latter group, it is possible that the presence of oxymorphone may reflect that it is a metabolite of oxycodone. Of the remaining 20 cases, there were two deaths. One death occurred in a pediatric patient being treated for advanced cerebral leukemia. The physician reporter, felt that the death was due to the underlying disease. The second death involved a 60-year-old woman who was receiving oxymorphone injection via a patient-controlled analgesia pump (PCA) pump for 51 days prior to her death

One serious case was a 4-year-old child who underwent a tonsillectomy and adenoidectomy. The child was treated with one-half of a 2-mg suppository. The child soon thereafter became apneic, requiring intubation and naloxone. Spontaneous respiration then returned.

The post-marketing safety data provides very little additional information in the evaluation of the overall safety of oxymorphone IR and oxymorphone ER tablets.

DOSING

The Sponsor's proposal to start dosing using 5 mg tablets in opioid naïve subjects has not been studied, nor has any use of OM IR in opioid naïve outpatients.

An appropriate dosing interval has not been determined. The proposed dosing interval of every 6 — hours is not supported by the clinical trial findings of more than half of study patients withdrawing from the study prior to the Hour 5 assessments in both studies. The median time to remedication during Study EN3203-004 was approximately 4 hours for the oxymorphone immediate-release 20 mg and 30 mg groups. During Study EN3203-005, median time to remedication was approximately 5 hours for the oxymorphone 20 mg dose found effective in this study. These time to remedication analyses excluded patients requiring rescue prior to 3 hours and 1 hour, respectively, suggesting the median time to remedication would have been even shorter had all patients been included. The dosing interval of 7 to 9 hours calculated by the Sponsor from the multiple dosing period of Study EN3203-004 failed to take into account the patients withdrawn for requiring rescue medication within 3 hours of study drug dosing, or use of rescue 3 hours or more after dosing of study medication by patients continuing in the study.

The PK profile of every 6 hour dosing of OM IR demonstrates the serum concentration reaches the trough value and remains there for two hours. Simulations by the Office of Clinical Pharmacology and Biopharmaceutics indicate that dosing every 4 hours would result in accumulation with a higher steady-state C_{max} than with every 6 and every 8 hours dosing. The safety of multiple dosing at these intervals this has not been evaluated.

Dose adjustments are called for in mild to moderate hepatic impairment, titration should begin low and proceed with close clinical monitoring. Oxymorphone is highly metabolized by the liver. Use of oxymorphone should be contraindicated in severe hepatic impairment. As oxymorphone plasma concentrations were relatively higher in the setting of renal impairment, dosing of oxymorphone should be started at low doses and titrated carefully in all categories of renal impairment under close clinical supervision. Patients over age of 65 exhibited higher plasma concentrations, AUC and Cmax. Therefore, dosing in patients over the age of 65 should begin with low starting doses and titrated carefully under close clinical supervision. No dose adjustment is recommended based upon gender. There was a 38% increase in AUC and C_{max} with food intake but no dosing recommendations are suggested for food effects.

SPECIAL POPULATIONS

As described in Dr. Comfort's review. The Sponsor pooled data for the different doses of OM IR from the two clinical efficacy trials to examine the effects of gender, age and race/ethnicity. There were no consistent effects of gender.

There were 287 patients under the age of 65, 273 patients 65 years of age and older, and 103 patients 74 years of age and older. There was a small effect of increased in efficacy in patients 65 years of age and older, but this could have been related to higher exposure due to greater bioavailability in this age group.

There were too few non Caucasian subjects to adequately explore the effects of race and ethnicity on efficacy.

The Sponsor has requested a deferral for pediatric studies which is appropriate at this time.

Abuse Liability, Drug Abuse and Diversion
Oxymorphone can be expected to have an abuse liability similar to morphine and other Schedule II opioid analgesics. Reference is made to the review of NDA 21-610, oxymorphone ER, in which the occurrence of drug diversion from two study sites is described.

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/s/

Sharon Hertz
10/15/03 06:21:37 PM
MEDICAL OFFICER

1ST Cycle

FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHETIC, CRITICAL CARE, AND ADDICTION DRUG PRODUCTS
HFD-170, Room 9B-45, 5600 Fishers Lane, Rockville MD 20857 Tel:(301)827-7410

Clinical Review of Integrated Summary of Safety Data

NDA Numbers:	21-610 21-611
Products:	Oxymorphone HCl Extended-Release Tablets (NDA 21-610) Oxymorphone HCl Immediate-Release Tablets (NDA 21-611)
Sponsor:	Endo Pharmaceuticals Inc.
Proposed Indication:	"TRADEMARK is indicated for the relief of moderate to severe pain in patients requiring continuous, around-the-clock opioid therapy for an extended period of time." (NDA 21-610) "TRADEMARK is indicated for the management of moderate to severe pain when the use of an opioid is appropriate." (NDA 21-611)
Data Submitted	December 19, 2002 (NDA 21-610) December 20, 2002 (NDA 21-611)
Reviewer:	Gerald J. Dal Pan, MD, MHS
Medical Team Leader	Sharon Hertz, MD
Project Manager	Lisa Basham-Cruz

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1 INTEGRATED REVIEW OF SAFETY

1.1 Summary of Safety Findings and Safety Conclusions

1.1.1 Overview of the Safety Findings

Oxymorphone is a mu-agonist opioid analgesic being developed as an oral analgesic in an immediate-release formulation (oxymorphone IR, NDA 21-611) and in an extended-release formulation (oxymorphone ER, NDA 21-610). The Sponsor prepared a single Integrated Summary of Safety (ISS) for oxymorphone ER tablets and oxymorphone IR tablets. The Sponsor has presented data separately for the ER and IR formulations, in order to evaluate the safety profile of each formulation. In addition, the Sponsor has presented data by combining data from the two formulations in order to assess the safety of oxymorphone, regardless of the specific type of formulation

The oxymorphone clinical development program included 12 Phase 2/3 clinical trials, 10 of which used oxymorphone ER and two of which used oxymorphone IR, in patients with chronic or acute pain. In addition, there were 16 Phase 1 trials (12 with oxymorphone ER and four with oxymorphone IR), conducted in either healthy volunteers or subjects with hepatic or renal impairment. Of the Phase 2/3 ER trials, three were short-term studies (lasting less than 3 days) in patients with acute post-operative pain (EN3202-012 [oxymorphone ER], EN3203-004 [oxymorphone IR], and EN3203-005 [oxymorphone IR]). Three studies were conducted in patients with chronic non-malignant pain (EN3202-015, EN3202-016, and EN3202-025, all using oxymorphone ER). Three studies were conducted in patients with chronic cancer pain (EN3202-017, EN3202-018, and EN3202-019, all using oxymorphone ER). The six controlled trials in patients with cancer pain or chronic non-malignant pain ranged from 1 to 4 weeks in duration. The three remaining Phase 2/3 trials in the clinical development program (EN3202-020, EN3202-021, and EN3202-022) were open-label extension trials using oxymorphone ER. Subjects who completed studies EN3202-015 or EN3202-017 could receive up to 2 years of oxymorphone ER in study EN3202-020. Subjects who completed studies EN3202-016 or EN3202-019 could receive up to 1 year of oxymorphone ER in study EN3202-021. Subjects who completed study EN3202-018 could receive up to 1 year of oxymorphone ER in study EN3202-022. Subjects with cancer pain in any of these three open-label studies could also receive oxymorphone IR as rescue medication.

Safety assessments included recording of adverse events, measurement of clinical laboratory data (chemistry, hematology, and urinalysis), measurement of vital signs, and electrocardiograms. Adverse events were coded using the Medical Dictionary for Regulatory Activity (MedDRA). Not all studies included clinical laboratory data, and only a few trials included electrocardiogram data.

After data from the 120-Day Safety Update have been accounted for, the number of exposed subjects is as follows:

- The total number of unique participants in the oxymorphone clinical development program is 2542.
- The total number of unique participants in the Phase 1 studies is 434
- The total number of unique participants in all Phase 2/3 clinical trials is 2108.
- The total number of unique participants in the IR Phase 2/3 clinical trials is 624.
- The total number of unique participants in the ER Phase 2/3 clinical trials is 1484.
- The total number of unique participants in the ER Phase 2/3 clinical trials who received oxymorphone is 1089.
- The 120-Day Safety Update includes information on a total of 273 subjects who had received oxymorphone ER for at least six months and 191 subjects who had received it for at least 12 months.

In the Phase 2/3 studies presented in the original ISS, the mean age of all 2108 unique Phase 2/3 trial participants was 59.4 years (SD 12.7). Mean ages across treatment groups ranged from 54.3 years (SD

13.2) in the oxycodone ER group to 62.5 years (SD 11.8) in the oxymorphone IR group. In this group of trials, 39.2% of subjects were age 65 years or older. In these trials, 57.4% of the subjects were females, a percentage similar to the percentage of females treated with any oxymorphone (57.3%). The majority of subjects in the Phase 2/3 trials were Caucasian (88.8%), with Blacks comprising 8.1%. The demographic characteristics of subjects in the Phase 1 trials were notable for the fact that subjects generally were younger and a higher percentage were male, compared to the Phase 2/3 trials. The mean age of all 366 unique Phase 1 trial participants was 39.1 years (SD 14.0). In this group of trials, 9.8% of subjects were age 65 years or older. In the Phase 1 trials, 33.6% of the subjects were females. In this group of trials, 64.5% of subjects were Caucasian, 9.8% were Black, 35.1% were Other, and 0.5% were Asian.

Of the 35 deaths in the clinical development program, 34 occurred in subjects with cancer pain. Twenty-eight of the 35 deaths occurred during the open-label extension studies EN3202-020 (n=13), EN3202-021 (n=12), and EN3202-022 (n=3). Of the patients who died during these open-label extension studies, all but one (patient ID EN3202-015-040-007) had previously participated in a controlled study for cancer pain. Deaths during controlled trials were less common, occurring only in controlled studies for cancer pain, EN3202-017 (n=4), EN3202-018 (=2), and EN3202-019 (n=1). Review of the deaths indicated that the 34 deaths in the cancer pain subjects were most likely due to the progression of the underlying cancer. The one subject (EN3202-015-040-007) who did not have an underlying cancer was a 43-year-old Caucasian male with obesity, hypertension, and osteoarthritis of the knees. He participated in and completed Study EN3202-015, during which he received oxycodone ER, after which he enrolled in Study EN3202-020, during which he received oxymorphone 40 mg/day (total daily dose) for eight days, followed by oxymorphone 80 mg/day (total daily dose). He died suddenly about four months after entry into the open-label extension study. The medical examiner's report apparently indicated death due to right and left ventricular hypertrophy due to obesity. A toxicology report indicated the presence of caffeine, caffeine metabolites and nicotine in the blood, but not ethanol, cocaine, or opiates. In response to an Agency question, the Sponsor noted on September 4, 2003 that "It is not likely that toxicological batteries for opiates detect oxymorphone. It is not known if the toxicological screen used by the medical examiner could have detected oxymorphone, but it is highly unlikely." Review of this case suggests that information provided in the narrative and in the database is not complete, and a causal role for the drug can neither be made nor excluded with certainty.

There were no non-fatal serious adverse events (SAEs) in Phase 1 clinical trials in either the ISS or the 120-Day Safety update.

Of the 1089 subjects exposed to oxymorphone ER, 93 (8.5%) had at least one serious adverse event (SAE). Of the 368 subjects exposed to oxymorphone IR, 19 (5.16%) has at least one SAE. Rates of at least one SAE in the other treatment groups were as follows: oxycodone ER – 9/382 (2.36%), oxycodone IR – 5/195 (2.56%), morphine ER 6/69 (8.70%), and placebo 14/473 (2.96%). Comparison of rates of subjects with at least one SAE across groups is confounded by the variable durations of individual subject exposure in these groups. In particular, exposure to oxymorphone ER occurred both during controlled trials as well as during the longer duration open-label extension trials. Serious adverse events in the Phase 2/3 clinical development program occurring in four of more oxymorphone ER-treated subjects include Vomiting NOS (n=8, 0.73%), Chest pain NEC (n=7, 0.64%), Nausea (n=6, 0.55%), Dehydration (n=5, 0.46%), Dyspnoea NOS (n=5, 0.46%), Abdominal pain NOS (n=4, 0.37%), Drug interaction NOS (n=4, 0.37%), and Osteoarthritis aggravated (n=4, 0.37%). While nausea and vomiting are commonly associated with opioid use, many of the serious adverse events recorded in the oxymorphone ER-treated subjects were due in part to abdominal spread of underlying cancers, or chemotherapy treatment of the underlying cancers. The four cases of 'drug interaction NOS' are actually cases of overdoses of oxymorphone ER in subjects who received oxymorphone ER as well as oxymorphone via PCA in the acute post-operative setting in Study EN3202-012. In each case, the subjects developed severe CNS side effects and/or respiratory depression. Some required naloxone to reverse these effects. In response to these events, the study protocol for Study EN3202-102 was amended to eliminate the highest dose (60 mg). Most other serious adverse event sin the clinical development program were consistent with the spectrum of disorders that can occur in a population of chronically ill patients.

Adverse events leading to study drug discontinuation occurred frequently in the clinical development program. There was relatively high rate of discontinuations due to adverse events in oxymorphone ER-treated subjects (35.8%), oxycodone ER-treated subjects (23.6%) and morphine ER-treated subjects (31.4%) in the Phase 2/3 oxymorphone ER trials. These rates are notably higher than the corresponding rate in placebo-treated subjects (5.7%). This difference may be due, in part, to the longer duration of treatment in the oxymorphone ER-treated subjects compared to the placebo subjects. Similarly, the longer duration of treatment may explain the slightly higher rate of discontinuations due to adverse events in the oxymorphone ER-treated group compared to the oxymorphone IR-treated group. While the Sponsor has postulated this reason for the observed difference in between-group frequencies of adverse events leading to study drug discontinuation, no data (e.g., person-time analysis) has been presented in the ISS to support this hypothesis. In Phase 2/3 IR trials, the proportion of subjects discontinuing study drug due to adverse events was higher (10.2%) in oxymorphone IR-treated subjects than in oxycodone IR-treated subjects (3.6%). Across all trial subsets, the rate of discontinuation due to adverse events in placebo-treated subjects ranged from 4.5% to 7.4%.

Common adverse events leading to study drug discontinuation in oxymorphone ER-treated subjects in Phase 2/3 studies in the original ISS include nausea (12.0%), dizziness (7.37%), vomiting (6.32%), somnolence (3.35%), pruritus (2.97%), constipation (2.68%), headache (2.30%), sweating increased (1.91%), sedation (1.82%), dry mouth (1.15%), and fatigue (1.15%). These adverse events generally comprise the spectrum of adverse events commonly associated with opioid analgesics. Consistent with this observation is the observation that the rank order of adverse events for oxymorphone ER is similar to the rank order of adverse events for oxycodone ER. Morphine ER also follows the same general order, but the number of treated subjects is smaller. The rates in the oxymorphone ER and the oxycodone ER groups are also notably higher than the corresponding rates in the placebo group. The treatment-placebo difference is less obvious for the oxymorphone IR and oxycodone IR groups.

The spectrum of adverse events leading to study drug discontinuation was generally similar in the other sponsor-defined study subsets(e.g., chronic non-malignant pain studies, cancer pain studies), with the possible exception of the acute-post-operative pain trials. In the acute post-operative pain trials, the adverse events leading to discontinuation nearly all were in the central nervous system, cardiac system, or respiratory system. A single case of vomiting was the only event in the gastrointestinal system leading to study drug discontinuation in an oxymorphone ER-treated subject. Review of the adverse event data for the eight oxymorphone ER-treated subjects who discontinued study medication reveals that five of these subjects had several adverse events leading to study drug discontinuation. Four of these subjects (EN3202-012-011-004, EN3202-012-011-023, EN3202-012-018-002, and EN3202-012-019-018) each had several serious AEs that lead to study drug discontinuation. Subject EN3202-012-019-023 became non-arousable and oversedated after a single oral dose of oxymorphone ER 20 mg in the acute post-operative setting. These events were associated with a decrease in oxygen saturation and a decrease in respiratory rate. She required Narcan for the non-arousability and oversedation. An additional three oxymorphone ER-treated subjects each had one adverse event leading to study drug discontinuation: Subject EN3202-017-007 developed confusion that resulted in study drug discontinuation, Subject EN3202-018-019 developed vomiting that lead to study drug discontinuation, and Subject EN-3202-012-019-024 developed confusion that led to study drug discontinuation.

No subjects in Phase 1 studies experienced adverse events that resulted in a study medication dose change or a study medication interruption in the original ISS.

Adverse events leading to study drug interruption or dose changes occurred relatively infrequently in the Phase 2/3 studies. In all Phase 2/3 studies in the original ISS, the overall rate of study drug interruptions was 2.84% among oxymorphone ER-treated subjects and 0.82% among oxymorphone IR-treated subjects. Among oxymorphone ER-treated subjects, the most common reasons were nausea (0.57%), vomiting (0.47%), and sedation (0.38%). Most of the other adverse events resulting in study drug interruption were those that are commonly associated with opioid use. In all Phase 2/3 studies in the original ISS, the overall rate of study drug dose changes was 0.76% among oxymorphone ER-treated subjects and 0.82% among oxymorphone IR-treated subjects. Among oxymorphone ER-treated subjects, the most common reason was

sedation (0.19%). Most of the other adverse events resulting in study drug interruption were those that are commonly associated with opioid use.

Adverse events were relatively common in the Phase 1 studies, occurring in 40.7% of oxymorphone ER-treated subjects and in 30.5% of oxymorphone IR-treated subjects. Eight adverse events occurred in 3.0% or more of oxymorphone (ER or IR) treated subjects, and most were adverse events typically associated with opioid treatment (dizziness, nausea, fatigue, vomiting, constipation, euphoric mood, and pruritus). Headache also occurred in 12.6% of oxymorphone (ER or IR)-treated subjects. In general, frequencies of common adverse events were only slightly higher in oxymorphone ER-treated subjects compared to oxymorphone IR-treated subjects. Placebo or other controls are not available for comparison. As noted above, there were no serious adverse events in Phase 1 studies.

Adverse events were relatively common in the Phase 2/3 oxymorphone IR studies, occurring in 71.0% of oxymorphone ER-treated subjects, 64.6% of oxymorphone IR-treated subjects, and 46.3% of placebo-treated subjects.

The most common adverse event in this subset of studies was pyrexia, which occurred in 21.9% of oxymorphone IR-treated subjects, 15.9% of oxycodone IR-treated subjects, and 15.4% of placebo-treated subjects. The Sponsor notes in the ISS that pyrexia is frequently noted in the acute post-operative setting. Nearly all cases of pyrexia were judged to be "unlikely" related to study drug. The reason for the higher frequency of this adverse event in the oxymorphone IR-treated group relative to the two other treatment groups is not clear. Other adverse events occurring in 2% or more of oxymorphone IR-treated subjects were those that are frequently seen in patients taking opiates or in the acute post-operative setting. These included nausea, somnolence, dizziness, pruritus, vomiting, constipation, confusion, anemia, headache, dry mouth, hypoxia, hypotension, and tachycardia. For all adverse events except hypoxia, the adverse event frequency was higher in the oxymorphone IR-treated group than in the placebo-treated group. Adverse event frequencies in the oxymorphone IR-treated group were generally slightly higher than those in the oxycodone IR-treated group. While none of these between-group (i.e., oxymorphone IR versus oxycodone IR) differences was large, though there were notable between-group differences in dizziness, hypotension, and tachycardia.

Adverse events occurring in the acute post-operative setting after use of oxymorphone ER were common. Most of the adverse events seen were typical of those seen in opioid-treated subjects. Other adverse events were typical of the acute post-operative setting. Pyrexia occurred in both oxymorphone ER-treated subjects and in placebo-treated subjects, though the frequency in placebo-treated subjects was higher than in placebo-treated subjects, a pattern that is opposite to what was noted in the placebo-controlled studies of oxymorphone IR in the post-operative setting. In this setting, however, there were four subjects who had an adverse event coded to the term "drug interaction NOS". These events have been reviewed above. Briefly, each was associated with the use of a single dose of oxymorphone ER after use of oxymorphone 0.3 mg via a PCA pump as rescue medication for post-operative pain. These events were likely due to the additive effects of oxymorphone via two different routes of administration. In addition, the adverse events lethargy, sedation, and somnolence occurred in four, four, and three subjects, respectively. There was no overlap of subjects who experienced these events. Of these subjects, four required naloxone hydrochloride for reversal of the adverse event (subjects EN3202-012-011-004, EN3202-012-011-023, EN3202-012-018-002, and EN3202-012-019-023). Study drug was discontinued in each of these four subjects.

Adverse event data from the chronic non-malignant pain trials comprises data from the placebo-controlled trials in chronic non-malignant pain. Adverse events were common in this subset of trials, occurring in 86.0% of oxymorphone ER-treated subjects, 80.8% of oxycodone ER-treated subjects, and 61.2% of placebo-treated subjects. For adverse events occurring in more than 10% of oxymorphone ER-treated subjects (i.e., Nausea, Constipation, Dizziness (exc vertigo), Vomiting NOS, Pruritus NOS, Somnolence, Sweating increased, Headache NOS, and Sedation) the frequencies of these events in the oxymorphone ER group and the oxycodone ER group were higher than the frequency in the placebo group. While the overall frequencies of any adverse event was similar between the two active treatment groups, there were some notable between-group differences. Nausea, vomiting, and somnolence were more common (by at least five percentage points) in oxymorphone ER-treated subjects than in oxycodone ER-treated subjects, while

constipation, increased sweating, and sedation were more common (by at least five percentage points) oxycodone ER-treated subjects. The differences in the rates of somnolence and sedation may be due to the coding of the investigator terms to different MedDRA terms. For adverse events occurring in 2-10% of oxymorphone ER-treated subjects, the frequency of adverse events was similar between the oxymorphone ER and oxycodone ER-treated groups. The frequency of these events in both groups was generally higher than the frequency in the placebo group.

Data from the cancer pain clinical trials comprise data from the active-controlled trials in cancer pain. No placebo-controlled data in this subset were obtained. Oxymorphone IR was initially used in the titration phases of Studies EN3202-018 and EN3202-19. The overall frequency of any adverse event was similar among the oxymorphone ER, oxycodone ER, and morphine ER treatment groups. For adverse events occurring in 10% or more of oxymorphone ER-treated subjects (i.e., Constipation, Nausea, Sedation, Pruritus NOS, Dizziness (exc vertigo), Sweating increased, and Vomiting NOS), the frequency of adverse events in the oxymorphone ER treatment groups was generally similar to, or in some cases lower than, the frequency in the oxycodone ER and morphine ER treatment groups. In addition, the spectrum of adverse events occurring in 2-10% of oxymorphone ER-treated subjects was similar to the spectrum of adverse events occurring in the oxycodone ER and morphine ER-treated subjects. In general, adverse events occurring in more that 2% of oxymorphone ER-treated subjects with cancer pain were typical of these seen in an opioid-treated population.

There were several adverse events whose preferred term suggests an alteration in mental status. Preferred terms for these events included 'central nervous system depression NOS', 'coma NEC', 'confusion', 'confusion aggravated', 'delirium', 'depressed level of consciousness', 'disorientation', 'disturbance in attention NEC', 'encephalopathy NOS', 'lethargy', 'loss of consciousness NEC', 'mental impairment NOS', 'mental status changes', 'sedation', 'sedation aggravated', 'somnolence', and 'thinking abnormal NEC'. While these preferred terms specify a range of central nervous system phenomena that can vary widely in the level of arousal and the content of consciousness (i.e., coma is a distinct delirium), some events specific by preferred terms can closely resemble others, especially if the details of the events are not further specified. For example, events corresponding to the preferred terms 'sedation' and 'somnolence' may be very similar. Different investigators may use different verbatim terms to describe the same events, and these different verbatim terms are then coded to different preferred terms. To examine the overall frequency of alterations in mental status, the frequency of any alteration in mental status (i.e., the proportion of subjects who had any adverse event corresponding to any of the above preferred terms) was examined for three clinical trial subsets: all trials, all post-operative pain trials, and all chronic non-malignant pain trials. This analysis indicated that there was an overall relatively high rate of any alteration in mental status in the 'All Trials' group, especially for oxymorphone ER, oxycodone ER, and morphine ER. The rates for oxymorphone IR and oxycodone IR were lower, though comparison across formulation types (i.e. ,ER vs. IR) are confounded by the much shorter duration of exposure in the IR-treated subjects. Amongst the three ER formulations, the overall rate of any alteration in mental status were generally equal. However, the pattern of preferred terms differ among the three groups. In each of the three ER-treated groups, somnolence and sedation are the most common adverse events in this category (any alteration in mental status), and together account for the large majority of adverse events in this category. However, in oxymorphone ER-treated subjects, somnolence (13.8%) and sedation (12.0%) occur with near equal frequency. In morphine ER-treated subjects, there is a notable difference between the frequency of somnolence (4.3%) and sedation (23.2%). The clinical difference between these two preferred terms is not obvious, and the verbatim terms on the CRFs do not shed light on these differences. The most common verbatim term that coded to the preferred term 'sedation' was 'sedation'. The most common verbatim term that coded to 'somnolence' was drowsiness'. Thus, coding difference might explain some of the differences noted.

In the acute post-operative trials, which assessed subjects after one or two doses of study drug, the rates of any alteration in mental status were slightly higher in the two oxymorphone-treated groups (22.7% in the ER group and 22.8% in the IR-treated group) than in the oxycodone IR-treated group (17.9%). Each of these rates was higher than the 9.8% rate noted in the placebo group.

Several events of depressed respiratory function occurred in the clinical development program. There were 16 events that occurred in 12 subjects. Of these, six events in six subjects occurred in Study EN3203-004, a study in acute post-operative pain. Each of these six events occurred in oxymorphone IR-treated subjects. Four of these six subjects received naloxone (Subjects EM3203-004-014-038, EN3203-004-028-014, EN3203-004-030-012, and EN3203-004-030-022 [for this subject the listed reason for naloxone was somnolence]). For five of these six subjects, study drug was discontinued. For four of the six subjects, the event was judged to be possibly related to study drug. One oxymorphone ER-treated subject in the Study EN3202-012, a study in acute post-operative pain that used oxymorphone, developed respiratory acidosis, requiring discontinuation of study drug. This subject also required naloxone, though the listed reason for naloxone in this subject was 'CNS depression'.

To explore further potential adverse effects of opiates, the database was reviewed for all administrations of the opiate antagonist naloxone as a concomitant medication. A total of 27 subjects in the original ISS received naloxone. Twenty-three of the 27 subjects requiring naloxone were enrolled in one of the three acute post-operative pain trials (EN3202-012, EN3203-004, and EN 3203-005). The majority of these subjects were receiving oxymorphone. The following table illustrates the rates of post-study treatment use of naloxone in two groups of post-operative pain clinical trials – Study EN3202-012, the only study to use oxymorphone ER in an acute post-operative pain trial, and Studies EN3203-004 and EN3203-005, the two studies that used oxymorphone IR in acute post-operative pain trials.

Table. Incidence of Naloxone Use After Study Drug Administration in Acute Post-Operative Pain Trials

Study Group			
EN3202-012	Oxymorphone ER	Placebo	
	N=66	N=61	
	4 (6.1%)	0 (0.0%)	
EN3203-004 and EN3203-005	Oxymorphone IR	Oxycodone IR	Placebo
	N=334	N=195	N=123
	12 (3.6%)	1 (0.5%)	0 (0.0%)

Source: Sponsor table in information sent to Agency on September 30, 2003

Review of the above table indicates that naloxone was administered more frequently to both oxymorphone ER-treated subjects and to oxymorphone IR-treated subjects, relative to placebo. In addition, naloxone use occurred in a higher proportion of oxymorphone IR-treated subjects than in oxycodone IR-treated subjects. In many cases, use of study drug discontinued. In Study EN3202-012, all four oxymorphone ER-treated subjects who received naloxone required study drug discontinuation due to the adverse event that required naloxone use. In studies EN3202-004 and 005, ten subjects (nine in EN3203-004 and one in EN3203-005) had study drug discontinued in response to an adverse event that required naloxone use. All ten of these subjects were taking oxymorphone IR.

Among oxymorphone ER-treated subjects, the incidence rates between opioid naïve and opioid experienced subjects were somewhat higher in the opioid-naïve subjects than in the opioid experienced subjects.

Clinical laboratory tests included clinical chemistry tests, clinical hematology tests, and urinalyses.

Review of the mean and median changes from baseline to the endpoint for the Phase 2/3 ER studies indicates that, in general, the changes from baseline were small for all chemistry tests, and that he differences in the changes among the treatment groups were small and not clinically significant (see Appendix 4.31 in the ISS). One exception to this pattern is the change from baseline to the endpoint in the glucose level in oxymorphone IR-treated subjects. Twenty-three subjects were treated with oxymorphone IR in Studies EN3202-018 and EN3202-019 as part of the Phase 2/3 oxymorphone ER clinical development program. The mean baseline glucose level in the 23 oxymorphone IR-treated subjects was 115.1 mg/dL (SD 35.90). The mean endpoint glucose value was 124.6 mg/dL (SD 49.07). The mean change from baseline was 9.5 mg/dL (SD 51.19). Review of individual subject data for this group indicated

a wide range of glucose values, both pre- and post-treatment, thus accounting for the observed post-treatment increase.

Analysis of clinical chemistry data by dose at the endpoint indicates that the mean and median changes from baseline to the endpoint do not appear to be related to dose at the endpoint, and no dose-response pattern is seen. In general, the incidence of treatment-emergent abnormal lab values was similar among the treatment groups for each clinical chemistry test. In addition, the incidence of treatment-emergent clinically significant abnormal lab values was similar among the treatment groups for each clinical chemistry test. Among oxymorphone ER-treated subjects, the incidence of treatment-emergent clinically significant abnormal lab values was below 2% for alkaline phosphatase, calcium, creatinine, SGOT, SGPT, sodium, total bilirubin, triglycerides, and uric acid. The incidence of treatment-emergent clinically significant abnormal lab values was between 2% and 5% for albumin, cholesterol, GGT, and potassium. The incidence of treatment-emergent clinically significant abnormal lab values was above 5% for glucose (7.2%), and phosphorus (8.1%).

Among 860 oxymorphone ER-treated subjects with normal AST levels at baseline 4 (0.5%) developed clinically significantly high levels post-baseline. Among 845 oxymorphone ER-treated subjects with normal ALT levels at baseline, 6 (0.7%) developed clinically significantly high levels post-baseline. Review of individual clinically significant abnormal lab values indicates that the pattern of clinically significant laboratory abnormalities varied by lab test. For example, clinically significant abnormalities of AST, ALT, GGT, alkaline phosphatase, and total bilirubin occurred in a wide range of clinical studies (i.e., acute post-op studies, cancer pain trial, chronic non-malignant pain trials, open-label extension trials, and , rarely, in Phase 1 trials). In the acute post-op trials, two oxymorphone ER-treated subjects in Study EN3202-012 and two oxymorphone IR-treated subjects in Study EN3203-004 developed clinically significant abnormalities of both AST and ALT. None of these subjects had a clinically significant abnormality of total bilirubin. No subjects in other treatment groups in the acute post-op trials developed clinically significant abnormalities of both AST and ALT. In each of the above cases, the baseline values of AST and ALT were normal, and the post-baseline values of both transaminases were clinically significantly abnormal. There is no explanation for any of these events in the ISS, and no follow-up lab values or other outcome data are presented. Of note, it appears that no subjects in other treatment groups in the acute post-operative studies had clinically significant abnormalities of both AST and ALT. In view of the lack of follow-up data, the clinical significance of these findings is not clear. One other oxymorphone IR-treated subject (EN3203-004-005-012) had a clinically significantly abnormal value for ALT (118 U/L), while tow other oxymorphone IR-treated subject (EN3203-004-002-001 and EN3203-004-15-010) had clinically significantly abnormal lab values of AST (181 U/L and 206 U/L, respectively). Of note, clinical lab data were not collected in Study EN3203-005. In other clinical trial groups, abnormalities of AST and ALT occurred in many of the treatment groups, with similar elevations in AST and ALT across the treatment groups.

There was only one clinically significant case of a clinically significantly abnormal creatinine level (3.6 mg/dL in Subject EN3202-017-011-005 in open label extension study EN3202-020). There was no reported adverse event of renal insufficiency for this subject. However, the Sponsor's definition of a clinically significantly abnormal level (>3X upper limit of normal) appears to be too high, and would miss many creatinine levels in the 2.0-3.5 mg/dL range, assuming an upper limit of normal of 1.2 mg/dL.

Review of the mean and median changes from baseline to the endpoint for the Phase 2/3 ER studies indicates that, in general, the changes from baseline were small for all hematology tests, and that he differences in the changes among the treatment groups were small and not clinically significant (see Appendix 4.2 in the ISS). One exception to this pattern is the change from baseline to the endpoint in the platelet count in oxymorphone IR-treated subjects. Twenty-three subjects were treated with oxymorphone IR in Studies EN3202-018 and EN3202-019 as part of the Phase 2/3 oxymorphone ER clinical development program. The mean baseline platelet count in the 23 oxymorphone IR-treated subjects was 294.7 (x10^3/mm^3). The mean endpoint platelet count was 266.3 (x10^3/mm^3). The mean change from baseline was –28.4 (x10^3/mm^3). The small number of subjects tests may have contributed to this observation. The median change from baseline in platelet count was –4.0 (x10^3/mm^3). In general, the incidence of treatment-emergent abnormal lab values was similar among the treatment groups. In general,

the incidence of treatment-emergent clinically significant abnormal lab values was similar among the oxymorphone ER, oxycodone ER, and placebo treatment groups. Among oxymorphone ER-treated subjects, the incidence of treatment-emergent clinically significant abnormal lab values was below 2% for neutrophils, platelets, and white blood cells. The incidence of treatment-emergent clinically significant abnormal lab values was between 2% and 5% for hemoglobin. The incidence of treatment-emergent clinically significant abnormal lab values was above 5% for lymphocytes (7.0%). For lymphocytes, however, the percentage of subjects in the oxymorphone ER-treated group with a clinically significant abnormal post-baseline value was 7.0%, while the corresponding percentage in the placebo group was 2.9%.

In the Phase 1 trials, six oxymorphone ER-treated subjects and one oxymorphone IR-treated subject developed clinically significantly low neutrophil values. Each had normal neutrophil values at baseline. In some cases the clinically significantly abnormal low neutrophil count was associated with a depressed total WBC count. In other cases, there the neutrophil count was significantly low, even in the presence of a normal total WBC count. In all cases, the neutrophil count was normal at baseline. An adverse event of neutropenia was not reported for any of these subjects. It should be noted that all subjects in Study EN3202-009 received a dose of oxymorphone ER and a dose of oxymorphone IR, separated by about three weeks. In each case, the clinically significantly abnormal neutrophil count came after the second treatment (i.e., ER from some IR for others).The clinical significance of these findings is unclear. For two subjects (EN3202-009-001-001 and EN3202-009-001-019), repeat values were within the normal range. For a third subject (EN3202-009-001-028) a repeat WBC was taken and was normal (4.9), but no differential count was reported. The clinical study report for Study EN3202-009 attributes the clinically significant abnormal lab values to mishandling the lab specimens (ie, not put on ice), and notes that some samples, after they were re-drawn, were normal. However, such repeat data is not available for all subjects.

Clinically significantly low neutrophil counts occurred in all treatment groups in the cancer pain trial, and covered a wide range of low values. In the chronic non-malignant pain studies, the clinically significantly low neutrophil values were generally in the 1.200-1.499 (x10^3/mm^3) range, in both the oxymorphone ER group and in the placebo group. In the open-label extension trials, clinically significantly low neutrophil values were in the 1.00-1.499 (x10^3/mm^3 range) for the chronic non-malignant pain patients, and were in a broader range for the cancer pain patients.

The Sponsor has not analyzed any of the urinalysis data that was obtained. The sponsor notes in Section 7.3.1 of the ISS that adverse events associated with abnormal urinalysis results were infrequently reported. Among oxymorphone ER-treated subjects in the Phase 2/3 ER trials, hematuria was the most frequently reported adverse event (1.2% of subjects) associated with abnormal urinalysis results. Hematuria was reported in 0.3% of placebo-treated subjects (i.e., one subject). Other adverse events based on abnormal urinalysis results occurred in less than 1.0% of oxymorphone ER-treated subjects.

Vital signs were recorded in the clinical development program. Review of the mean and median changes from baseline to the endpoint for all Phase 2/3 studies indicates that, in general, the changes from baseline were small for all vital signs, and that the differences in the changes among the treatment groups were small and not clinically significant (see Appendix 8.2 in the ISS). The incidence of treatment-emergent clinically significant abnormal vital sign values was calculated for each treatment group in all Phase 2/3 studies (see Appendix 8.3 in the ISS). Incidences of clinically abnormal vital signs was low, generally below 3.0%. with no significant differences among the treatment groups. The one exception to this patter was the oxycodone IR treatment group. In this group, the incidence of treatment emergent clinically significant vital sign abnormalities was slightly higher than in other groups: systolic blood pressure (3.4%), diastolic blood pressure (3.7%), heart rate (2.5%), and respiration (0.3%). In the Phase 2/3 IR studies, the incidence of clinically significant vital sign abnormalities was: systolic blood pressure (3.6%), diastolic blood pressure (3.9%), heart rate (2.7%), respiration (0.3%), and temperature (1.2%). In this subset of trials, the incidence rates among oxymorphone IR-treated subjects were similar to those in oxycodone IR-treated subjects, and minimally higher than those in placebo-treated subjects. In the acute post-operative pain trials, the incidence of clinically significant vital signs abnormalities for the oxymorphone IR-treated subjects was the same as in the Phase 2/3 IR studies (the same subjects contribute to both subsets). However, the incidence rates for the oxymorphone ER-treated subjects in the acute post-operative trials

were notably high: systolic blood pressure (12.1%), diastolic blood pressure (4.5%), heart rate (12.1%), respiration (0.0%), temperature (0.0%), and weight (9.1%).

In each of the three Phase 1 studies, 12-lead ECGs were obtained at screening, at the beginning of each study period (at check-in to the study site), and following the last blood collection of each study period. Quantitative analysis of the ECG data is notable for the decline in heart rate (or ventricular rate, depending on the study). The Sponsor attributes this decline to the sedentary lifestyle that study subjects assume once they enter the research unit. Further review of the ECG data indicates that there was a slight decline in the corrected QT interval (e.g., in the Overall group [three Phase 1 studies pooled]), the mean corrected QT interval declined from 387.72 msec at pre-dose to 378.78 msec at post dose. While the mean uncorrected QT interval increased from pre-dose to post-dose (i.e., from 362.57 msec to 379.05), this increase presumably was more than offset by the decrease in heart rate, thus accounting for the decrease in mean corrected QT interval that was observed. Review of individual changes indicates several QTc abnormalities - either QTc values that were significantly prolonged (i.e. >= 430 msec for males or >=450 msec for females) or clinically significant increases in QTc from pre-dose to post-dose (i.e., >=30 msec). Of 58 subjects in three Phase 1 studies who had ECGs performed, 7 had at least one pre-dose QTc values that was >=430 msec. Each of these QTc values decreased post-dose. Five post-dose values were >=430 msec, four of which were increased from pre-dose. Six of the 58 subjects had at least one increase (from pre-dose to post-dose) of at least 30 msec. All of these ECGs were rated as 'Normal' by the investigator. The two most concerning ECGs are those of subjects EN3202-002-001-001 (whose QTc rose from a pre-treatment value of 372 msec to a post-treatment value of 476 msec) and EN3202-002-001-006 (whose QTc rose from a pre-treatment value of 358 msec to a post-treatment value of 491 msec), given the large increases in QTc values that were recorded. Review of the entire set of QTc values for all 58 subjects in these studies reveal a wide variation in both pre-treatment and post-treatment values. However, the degree to which the significantly abnormal QTc values above represent variation within the population being studies is not clear. According to the Sponsor, the original ECG tracings are no longer available. These would be helpful, since some of the apparently long QTc intervals could be the result of U waves, since the intervals were machine read.

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

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

Analysis of drug-demographic interactions indicates that the frequency of some adverse events, such as somnolence and dizziness, may increase with increasing age in oxymorphone ER-treated subjects. Nausea, vomiting, and headache were notably more frequently in females (48.9%, 28.0%, and 14.6%, respectively), compared to males (35.9%, 13.9%, and 7.0%, respectively). This gender difference was not seen in placebo-treated subjects. Among oxymorphone ER-treated subjects in the Phase 2/3 ER trials, the incidence of dizziness, somnolence, and headache were slightly higher in Caucasians (28.8%, 17.3%, and 11.6%, respectively) compared to Blacks (17.8%, 12.2%, and 6.7%, respectively). The between-race differences in these three adverse events were not noted in placebo-treated subjects.

There was no obvious association between abnormalities in albumin and bilirubin and the development of common adverse events in the Phase 2/3 trials. The Sponsor chose these lab abnormalities as markers of hepatic dysfunction, though many of these subjects had normal AST and ALT values, and most had no history of hepatic disease. The relevance of these groupings to hepatic disease is not clear, and the conclusions that can be drawn are limited. There was no obvious clinically significant drug-disease interaction between the abnormalities in renal function and the development of common adverse events in oxymorphone ER-treated subjects in the Phase 2/3 clinical trials.

Oxymorphone is a mu-agonist opioid analgesic. Its abuse liability is similar to morphine. Data from the clinical trials suggest that withdrawal will occur with abrupt discontinuation. In addition, episodes of drug diversion at two clinical sites during the clinical development program point to a need for a risk management plan. The Sponsor has submitted a risk management plan. Review of that plan is not part of this ISS review.

1.1.2 Limitations of the Safety Evaluation

The evaluation of the safety of oxymorphone ER tablets and oxymorphone IR tablets was limited by several features of the collection, analysis, or presentation of the safety data. These limtations are summarized as follows:

- In the clinical studies of oxymorphone ER, oxymorphone IR was often used as rescue medication. Use of oxymorphone IR as rescue medication in these settings was not quantified. This lack of recording of drug use makes interpretation of adverse event data in this setting difficult. Specifically, it is impossible to determine if the addition of oxymorphone IR contributes to the development adverse events in persons taking oxymorphone ER.
- Apart from its use as rescue medication, oxymorphone IR as a single agent was studied , for the most part, exclusively in the post-operative setting. (A limited number of subjects received oxymorphone IR during titration phases in the cancer pain clinical trials of oxymorphone ER). In this setting, subjects were receiving many other acute use, short-term medications, which could confound the interpretation of safety data. In addition, this setting does not mimic the use of oxymorphone IR as treatment for acute pain on an outpatient basis.
- Some adverse events that appear to meet the regulatory definition of a serious adverse event (and the definition of a serious adverse event according to the protocol under which they occurred) were not classified as serious adverse events. For example, some of the cases of respiratory depression that required naloxone (an intervention to prevent a more serious life-threatening outcome) were not classified as a serious adverse event. The Sponsor noted, in response to a question in about this classification of adverse events as serious or not, that investigators were allowed to use their judgment to determine which events were serious. This miscoding not only effects the summary tables of incidences of serious adverse events, it also results in clinically important events not being highlighted in the ISS.
- There were several adverse events, reported by a wide range of terms on the CRFs and thus coded to a number of preferred terms, that may represent similar, or at least clinically overlapping events. These reported terms all refer to a change in mental status – either a change in the level of arousal or a change in the content of consciousness – whose clinical features are often difficult to understand from either the reported term or the preferred term. For example there are a number of serious AEs coded to the preferred terms 'Central nervous system depression', 'Coma NEC', 'Depressed level of consciousness', 'Sedation', and 'Somnolence' that, upon further review, reveal a pattern of a depressed level of consciousness that responds to naloxone. Despite the various preferred terms used to categorize these events, they appear to represent similar phenomena after review of the narratives (see review of serious adverse events below for details). Further review of the Sponsor's mapping of reported terms to preferred terms suggests that there may be overlap among some of the adverse events that have been mapped to these preferred terms. Part of this problem may lie in the MedDRA dictionary itself. The Sponsor was asked to calculate the incidence of any change in metal status.
- Several treatment-emergent clinically significant laboratory values, such as clinically significantly abnormal hepatic tests and clinically significantly abnormal neutrophil counts, were recorded at the final study visit, and have no follow-up. This lack of follow-up makes clinical interpretation of these events difficult.
- Quantitative analyses of the quantitative ECG data were limited (and were performed only in response to an Agency query during the review cycle). The Sponsor as noted to the Agency that the original tracings of these ECGs are no longer available, thus making further exploration and interpretation of some of the ECG findings difficult.

1.1.3 Safety Conclusions

Oxymorphone is mu-agonist opioid. For both the ER and IR formulations, the general clinical safety profile is typical of a mu-agonist opioid analgesic. While most of the safety profile of these drugs is expected for

an opioid analgesic, there are some unanswered questions about clinically important safety issues for both formulations.

For each of the two formulations, the most common adverse events are those typical of other opioid analgesics. The reasons for discontinuation of study drug are also typical of opioid analgesics. Review of the 35 deaths in the clinical development program indicates that progression of the underlying cancer was the reason for death in 34 of the 35 deaths. The cause of death of the single subject without cancer was attributed at autopsy to ventricular hypertrophy, though full details of this death are lacking. Many of the serious adverse events are those that would be expected in a populations of patients with either cancer or chronic osteoarthritis.

The safety profile of both formulations in the acute post-operative setting warrants comment.

First, the rationale for testing an extended-release formulation opiate in an acute post-operative setting is not clear. A long-acting agent does not allow for the changes in medication that may be needed as the patient's clinical condition changes hour by hour. Short-acting opioids in this setting provide a flexibility that long-acting opioids do not. The cases of CNS adverse events, respiratory depression, the need for naloxone in some cases, and the need to eliminate the 60 mg oxymorphone ER dose from the acute post-operative pain trials all point not only to the fact that this formulation is inappropriate for the acute post-operative setting, but also to the fact that the safety of the ER formulation in the acute post-operative setting has not been demonstrated by the single post-operative pain trial that used oxymorphone ER. Based on the available data, any label for the ER formulation should note that oxymorphone ER tables should not be used in the acute post-operative setting.

Second, the adverse events in the acute post-operative trials that used oxymorphone IR are notable for the cases of CNS events and respiratory depression that required the use of naloxone. While the short-acting nature of oxymorphone IR should make it appropriate for this setting, it may be that the optimal dose in this setting as not yet been determined, or that patient factors that influence proper dosing in this setting have not been identified. Neither the ISS nor this review attempted to explore the latter issue further. While naloxone treatment can be given to hospitalized patients who are being monitored in a post-operative setting, such treatment is not available to outpatients who are using the oxymorphone IR as outpatients. Given the high rate of naloxone use in the acute post-operative setting and the lack of significant safety data in opioid-naïve outpatients, it is not clear that the Sponsor has demonstrated the safety of oxymorphone IR as single-agent therapy in opioid-naïve outpatients.

The occurrence of clinically significant treatment-emergent neutropenia in four healthy subject in Phase 1 studies taking either oxymorphone ER or oxymorphone IR is unexplained. The occurrence of three of four cases in a single study may be due to study-specific factors (ie, mishandling of lab specimens, as the Sponsor postulates), but no data are available to support completely this hypothesis. The lack of any follow-up data makes interpretation difficult.

The occurrence of clinically significant treatment-emergent elevations in both AST and ALT in four subjects in the acute post-operative pain trials taking either oxymorphone ER or oxymorphone IR is unexplained. While many changes may happen in the post-operative setting, each of these dual hepatic enzyme elevations occurred only in oxymorphone-treated subjects. The lack of follow-up data limits the conclusions that can be made and leaves open the possibility of a potential hepatic effect of oxymorphone.

The quantitative ECG data are limited, and the conclusions that can be drawn from them are also limited. Nonetheless, the occurrence of significant QTc prolongation after treatment with oxymorphone indicates that further evaluation of the QTc interval is warranted for both the ER and IR formulations.

For the reasons given above, the safety of oxymorphone ER and oxymorphone IR tablets has not been established.

1.2 Summary of Safety Material Reviewed

The table below summarizes the clinical safety submissions to the NDAs (21-610 and 21-611) were reviewed. Each item was submitted to both NDAs.

Table. Summary of Safety Material Reviewed

Description	Type	Letter Date	Electronic Document Room Location
Original ISS		19-DEC-2002	\N_000\2002-12-19\clinstat\iss
12-Day Safety Update	SU	15-APR-2003	\N_000\2003-04-15\update
Response to FDA Questions Dated August 6, 2003	BM	13-AUG-2003	\N_000\2003-08-13\other
Response to FDA Questions Dated August 25, 2003	BM	27-AUG-2003	\N_000\2003-08-27\other
Response to FDA Questions Dated August 25, 2003	BM	29-AUG-2003	\N_000\2003-08-29\other
Response to FDA Questions Dated August 25, 2003	BM	03-SEP-2003	\N_000\2003-09-03\other
Response to FDA Questions Dated August 26, 2003	BM	04-SEP-2003	\N_000\2003-09-04\other
Response to FDA Questions Dated September 4, 2003	BM	08-SEP-2003	\N_000\2003-09-08\other
Response to FDA Questions Dated September 8, 2003	BM	11-SEP-2003	\N_000\2003-09-11\other
Response to Teleconference Discussion Held September 12, 2003	BM	17-SEP-2003	\N_000\2003-09-17\other
Response to FDA Questions Dated September 23, 2003	BM	30-SEP-2003	\N_000\2003-09-30\other

1.3 Adequacy of Exposure and Safety Assessments-

1.3.1 Overview of the Clinical Development Program and

The Sponsor has prepared a single Integrated Summary of Safety (ISS) for the two formulations of oxymorphone, oxymorphone extended release (ER) tablets and oxymorphone immediate release (IR) tablets. As will be discussed in more detail below, the Sponsor has presented data separately for the ER and IR formulations, in order to evaluate the safety profile of each formulation. In addition, the Sponsor has presented data by combining data from the two formulations in order to assess the safety of oxymorphone, regardless of the specific type of formulation.

The oxymorphone clinical development program included 12 Phase 2/3 clinical trials, 10 of which used oxymorphone ER and two of which used oxymorphone IR, in patients with chronic or acute pain. In addition, there were 16 Phase 1 trials (12 with oxymorphone ER and four with oxymorphone IR), conducted in either healthy volunteers or subjects with hepatic or renal impairment.

The following tables present an overview of the clinical trials in the oxymorphone development program. For the purpose of this overview table, the indication "clinical pharmacology" will refer to any human pharmacokinetics and bioavailability trial, and will not further specify the specific type of trial. This information can be found in the ISS and the 120-Day Safety Update tables that are the source of this composite table below.

Overview of Clinical Trials in the Oxymorphone ER and Oxymorphone IR Clinical Development Program					
Protocol No.	Development Plan ER	Development Plan IR	Indication	Does Regimen and Formulation and Duration of Treatment	Number of Subjects
3202-001	Yes	Yes	Clinical pharmacology	OM ERa 20 OM ERb 20 OM 10 solution Single dose crossover	15
3202-002	Yes		Clinical pharmacology	OM ERa 20 OM ERb 20 OM 10 solution Single dose crossover	15
3202-003	Yes		Clinical pharmacology	OM ERa 20 tab OM 10 solution Single dose crossover	15
3202-004	Yes		Clinical pharmacology	NTX/OM ER 50/20 tabs OM ER 20 tabs Single dose crossover	12
3202-005	Yes		Clinical pharmacology	NTX/OM ER 50/20 tabs Single dose	24
3202-006	Yes		Clinical pharmacology	NTX/OM ER 50/20 tabs Single/multiple dose	48
3202-007	Yes		Clinical pharmacology	Day 1 and 7 OM ER 5 tab (qd) OM ER 10 tab (qd) OM ER 20 tab (qd) OM ER 40 tab (qd) Days 3 and 6 OM ER 5 tab (bid) OM ER 10 tab (bid) OM ER 20 tab (bid) OM ER 40 (bid) Single/multiple dose crossover	24
3202-008	Yes		Clinical pharmacology	OM ER 40 tab OM IR 10 x 4 tabs Single dose crossover	28
3202-009	Yes		Clinical pharmacology	Day I OM ER 20 x 1 tab (qd) OM IR 10 x 1 tab (qd) Day 3 through 8 OM ER 20 tab (bid) OM IR 10 tab (qid) Day 9 OM ER 20 x 1 tab (qd) OM IR 10 x 2 tab (qd) Single/multiple dose crossover	28
3202-010	Yes		Clinical pharmacology	OM ER 20 tab Single dose	34
3202-011	Yes		Clinical pharmacology	OM ER 40 tab manufactured by Novartis; 2 doses OM ER 40 tab manufactured by IPC; 2 doses	24
3202-011A	Yes		Clinical pharmacology	OM ER 40 tab manufactured by Novartis; 2 doses OM ER 40 tab manufactured by IPC; 2 doses	6
3202-012	Yes	Yes	Acute post-operative pain	OM ER 20 tab Placebo Multiple dose	126
3202-015	Yes	Yes	Osteoarthritis pain	Weeks 1-2 OM ER 20 tab OM ER 20 tab OC .10 tab Placebo Weeks 3-4 OM ER 20 tab OM ER 40 tab OC .20 tab Placebo Multiple dose	

Overview of Clinical Trials in the Oxymorphone ER and Oxymorphone IR Clinical Development Program					
Protocol No.	Development Plan ER	Development Plan IR	Indication	Does Regimen and Formulation and Duration of Treatment	Number of Subjects
3202-016	Yes		Lower back pain	10-14 day Titration Period OM ER 10-110 OC ER 20-220 18-Day Double-Blind Treatment OM ER 10-110 OC ER 20-220 Placebo	329
3202-017	Yes		Cancer pain	OM ER 20-300 tab MS C® 15-900 tab OC® 10-600 tab Multiple dose crossover	86
3202-018	Yes		Cancer pain	Titration to optimal doses for each of the Trt Arms OM ER 10-100 tab MS C® 30-300 tab 1 wk OL titration 2 wks (1 wk/arm) crossover	36
3202-019	Yes		Cancer pain	Titration to optimal doses for each of the Trt Arms OM ER 10-110 tab OC® 20-220 tab Crossover	44
3202-020	Yes		Osteoarthritis and cancer pain	Completed studies 015 and 017 patients will start at dosage level from previous controlled-study; may be titrated up or down based on individual patient's pain relief and tolerability of side effects	197
3202-021	Yes		Osteoarthritis and cancer pain	Completed studies 016& 019. Optimal dose will be established during first week of dosing and may be titrated up or down based on individual patient's pain relief and tolerability of side effects	239 (164)*
3202-022	Yes		Cancer pain	Completed study 018 patients will start at dosage level from previous controlled-study; may be titrated up or down based on individual patient's pain relief and tolerability of side effects	24 (15)*
3202-025	Yes		Osteoarthritis pain	Week 1 OM ER 10 tab OM ER 20 tab OM ER 20 tab Placebo Week 2 OM ER 10 tab OM ER 40 tab OM ER 50 tab Placebo	370

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

Overview of Clinical Trials in the Oxymorphone ER and Oxymorphone IR Clinical Development Program					
Protocol No.	Development Plan		Indication	Does Regimen and Formulation and Duration of Treatment	Number of Subjects
	ER	IR			
3203-007		Yes	Clinical pharmacology	OM IR 10 tab OM IR 10 tab Single dose crossover	32
*The number outside the parentheses refers to the number in the 120-Day Safety Update. The number inside the parentheses refers to the number in the original ISS. ^These studies were submitted at the time of the 120-Day Safety Update					
Source: Based on Supplemental Tables 1 and 2 in ISS (pages 229-248), Table 4 in ISS (page 29), and Supplemental Table 1 and 2 in the 120-Day Safety Update (pages 42-66).					

There were nine Phase 2/3 controlled clinical trials in the oxymorphone development program. Three of the trials were short-term studies (lasting less than 3 days) in patients with acute post-operative pain (EN3202-012 [oxymorphone ER], EN32-3-004 [oxymorphone IR], and EN3203-005 [oxymorphone IR]). Three studies were conducted in patients with chronic non-malignant pain (EN3202-015, EN3202-016, and EN3202-025, all using oxymorphone ER). Three studies were conducted in patients with chronic cancer pain (EN3202-017, EN3202-018, and EN3202-019, all using oxymorphone ER). The six controlled trials in patients with cancer pain or chronic non-malignant pain ranged from 1 to 4 weeks in duration.

The three remaining Phase 2/3 trials in the clinical development program (EN3202-020, EN3202-021, and EN3202-022) were open-label extension trials using oxymorphone ER. Subjects who completed studies EN3202-015 or EN3202-017 could receive up to 2 years of oxymorphone ER in study EN3202-020. Subjects who completed studies EN3202-016 or EN3202-019 could receive up to 1 year of oxymorphone ER in study EN3202-021. Subjects who completed study EN3202-018 could receive up to 1 year of oxymorphone ER in study EN3202-022. Subjects with cancer pain in any of these three open-label studies could also receive oxymorphone IR as rescue medication.

1.3.2 Safety Assessments in the Clinical Development Program

The Sponsor performed a number of safety assessments in the clinical development program. The table below summarizes the safety assessments by trial. A more detailed review of the methodology for obtaining and analyzing data from specific safety assessments will be included at the beginning of each section of this safety review that deals with a particular safety assessment.

Summary of Safety Assessments		
Safety Assessment	Studies	Comments
Demographic and Baseline Characteristics	All trials	
Adverse Events	All trials	
Opioid-related Symptom Checklist	EN3202-016, EN3202-018, and EN3202-019	Checklist assessed constipation, dizziness, sedation, nausea, vomiting, sweating, and pruritus. Events were recorded on AE page only if AE was serious.
Abstinence Syndrome Assessment	EN 3202-015	Assessed using the Physical Dependence Survey whenever study medication was discontinued.
Standard Clinical Laboratory Tests	All trials except EN3203-005	Standard battery included hematology, clinical chemistry, and urinalysis. Hematology included hemoglobin, hematocrit, platelet count, white blood cell count, red blood cell count*, and WBC differential*. Standard chemistry included sodium, potassium, calcium, chloride, glucose* (random), creatinine, albumin, total protein*, blood urea nitrogen*, AST, ALT, LDH*, alkaline phosphatase*, and total bilirubin.
Creatine phosphokinase (CPK)	EN3202-012, EN3202-015, EN3202-017, EN3202-025, EN3202-020	

Summary of Safety Assessments		
Safety Assessment	Studies	Comments
Inorganic phosphorus	EN3202-012, EN3202-015, EN3202-017, EN3202-018, EN3202-025, EN3202-020	
Carbon dioxide (CO2)	EN3202-016, EN3202-018, EN3202-021, EN3203-004	
Bicarbonate	EN3202-019	
Gamma-glutamyl transpeptidase (GGT)	EN3202-016, EN3202-019, EN3202-021	
Phosphate	EN3202-016, EN3202-019, EN3202-021, EN3203-004	
Triglycerides	EN3202-016, EN3202-018, EN3202-019, EN3202-021, EN3203-004	
Total cholesterol	EN3202-016, EN3202-018, EN3202-019, EN3202-021, EN3203-004	
Uric acid	EN3202-016, EN3202-018, EN3202-019, EN3202-021, EN3203-004	
Urinalysis	All studies except EN3202-022	Standard tests included urine pH, glucose, ketones, blood, and protein
Specific gravity	EN3202-012, EN3202-015, EN3202-016, EN3202-017, EN3202-018, EN3202-020, EN3202-021, EN3203-004	
Bilirubin	EN3202-012, EN3202-015, EN3202-016, EN3202-017, EN3202-019, EN3202-025, EN3202-020, EN3202-021, EN3203-004	
Urobilinogen	EN3202-016, EN3202-018, EN3202-019, EN3202-021, EN3203-004	
Microscopy	EN3202-016, EN3202-018, EN3202-019, EN3202-021	
Vital Signs	All trials except EN3202-022	Included systolic and diastolic blood pressure and heart rate
Respiratory Rate	EN3202-012, EN3202-016, EN3202-018, EN3202-019, EN3202-025, EN3202-021, EN3203-004, and EN3203-005	
Body Temperature	EN3202-016, EN3202-018, EN3202-021, EN3203-004, and EN3203-005	
Body Weight	EN3202-012, EN3202-015, EN3202-017, EN3202-018, EN3202-019 and EN3202-020	
Electrocardiogram	Baseline and final: EN3202-015, EN3202-025, EN3202-020 Post-baseline only if clinically indicated: EN3202-016, EN3202-018, and EN3202-019	
*Not performed in EN3202-022. Absolute neutrophil counts were obtained n EN3202-018 and EN3202-022		
Source: Based on summary in ISS Section 2.2		

The above assessments are generally acceptable for clinical trials of opioid analgesic agents.

1.3.3 Extent and Duration of Exposure

Because a unique individual could participate in more than one trial (e.g., a controlled Phase2/3 trial followed by an open-label Phase 2/3 trial) or could receive more than one study treatment in a trial (e.g., both oxymorphone ER and oxymorphone IR in a single trial), or a combination of the above, the Sponsor used two methods to summarize the number of trial participants. First, the number of unique trial participants was counted according the last treatment received in the first trial in which they participated. This number indicates the number of unique participants in the entire clinical development program. Second, the Sponsor counted the numbers of trial participants according to all trial treatments received, including during run-in periods, in all trials. In this method, each subject is counted once for each treatment received. This summary therefore provides the number of subjects exposed to each treatment. The Sponsor has used each of these two methods to summarize the number of subjects in the clinical development program.

In addition to summarizing the number of participants in all trials, the Sponsor has identified eight other subsets of studies and subjects of interest and has applied these summaries to these subsets:

- All Phase 2/3 trials
- Oxymorphone ER Phase 2/3 trials
- Oxymorphone IR Phase 2/3 trials
- Acute post-operative pain trials
- Chronic non-malignant pain trials
- Cancer pain trials
- Open-label extension trials
- All Phase 1 trials

At the time of the initial NDA submission, a total of 2474 unique subjects had participated in the oxymorphone clinical development program. Of these 2108 had participated in the Phase 2/3 program; of these, 1398 received oxymorphone ER and/or IR at some point. A total of 142 of these subjects received oxymorphone ER for at least 6 months (180 days), and 75 received oxymorphone ER for at least one year (365 days). The Sponsor has summarized exposure by treatment received and study type in ISS Table 5, which is reproduced below:

Table: Numbers of Exposures by Subset and Treatment Group and Number of Unique Participants by Subset – All Trials

		Oxymorphone			Oxycodone			
Study Group	Total[a]	ER/IR[b]	ER	IR	ER	IR	Morphine ER	Placebo
All Trials	2474	1764	1332	565	382	195	69	473
All Phase I Trials	366	366	275	197	0	0	0	0
All Phase II/III Trials	2108	1398	1057	368	382	195	69	473
All ER Phase II/III Trials[c]	1484	1064	1057	34	382	0	69	350
All IR Phase II/III Trials[d]	624	334	0	334	0	195	0	123
Acute Postoperative Pain Trials	751	400	66	334	0	195	0	184
EN3202-012	127	66	66	0	0	0	0	61
EN3203-004	300	204	0	204	0	67	0	57
EN3203-005	324	130	0	130	0	128	0	66
Chronic Non-malignant Pain Trials	1185	684	684	0	286	0	0	289
EN3202-015	489	240	240	0	125	0	0	124
EN3202-016	326	165	165	0	161	0	0	74
EN3202-025	370	279	279	0	0	0	0	91
Cancer Pain Trials	172	145	138	34	96	0	69	0
EN3202-017	86	63	63	0	52	0	34	0
EN3202-018	38	36	32	18	0	0	35	0
EN3202-019	48	46	43	16	44	0	0	0
Open-label Extension Trials	0	376	376	0	0	0	0	0
EN3202-020[e]	0	197	197	0	0	0	0	0
EN3202-021[f]	0	164	164	0	0	0	0	0
EN3202-022[g]	0	15	15	0	0	0	0	0

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

Source: Sponsor Table 5 in ISS.

Of the 2474 subjects in the clinical development program, the majority (2108, 85.2%) participated in the Phase 2/3 studies, while 366 (14.2%) participated in the Phase 1 studies. Of the 2474 subjects who participated in the clinical development program described in the original ISS, 1764 received an oxymorphone product. Of the subjects receiving at least one dose of an oxymorphone product, 1332 received oxymorphone ER and 565 received oxymorphone IR. In Phase 1 studies, a total of 366 subjects received an oxymorphone product, 275 of whom received oxymorphone ER and 197 of whom received oxymorphone IR. In Phase 2/3 studies, a total of 1398 subjects received an oxymorphone product, 1057 of whom received oxymorphone ER and 368 of whom received oxymorphone IR. Among the Phase 2/3 trial groups, 684 subjects were treated with oxymorphone (all oxymorphone ER) in chronic non-malignant pain trials, 400 subjects were treated with oxymorphone (66 with oxymorphone ER and 334 with oxymorphone IR) in acute post-operative pain clinical trials, and 145 subjects were treated with oxymorphone (138 with oxymorphone ER and 34 with oxymorphone IR) in cancer pain trials. At the time of the original ISS submission, 376 subjects had participated in open-label extension studies, all of whom received oxymorphone ER.

At the time of NDA submission, five clinical studies were ongoing. These included three open-label Phase 2/3 oxymorphone ER studies (EN3202-020, EN3202-021, and EN3202-022) and two Phase 1 drug interaction clinical trials (EN3202-0326 and EN3202-027). In the 120-day Safety Update, submitted on April 15, 2003, the Sponsor provided an update on the status of the studies. The in-life portion of studies EN3202-020 and EN3202-022 are complete, and clinical study reports are being prepared. Study EN3202-021 is still ongoing. The two Phase 1 drug interaction studies have been completed, and complete clinical study reports were included in the 120-Day Safety Update. Data from all five trials has been added to the 120-Day Safety Update. For the three Phase 2/3 clinical trials, data have been integrated with the Phase 2/3 data from the ISS. For the Phase 2/3 clinical trials, the Sponsor has provided three analysis populations for the 120-Day Safety Updated: 1) The ISS Analysis population, an exact replica of the relevant section for the ISS data set, 2) the 120-Day Safety Update population, which includes additional data on 151 subjects who were included in the original NDA and data on 84 additional subjects who were not included in the original NDA, and 3) the Overall population, which includes the relevant sections of the ISS updated with the new data from the three open-label Phase 2/3 studies. Data from the two additional Phase 1 studies were taken directly from the completed clinical study reports for these studies. These Phase 1 data were not further integrated.

The following table, a replica of Sponsor Table 1 in the 120-Day Safety Update, ISS, summarizes the additional patient data from the Phase 2/3 studies that were incorporated into the 120-Day Safety Update.

Number of Subjects Included in the 120-Day Safety Update

		Subjects Included in 120-Day Safety Update		
Study Number	Number of Subjects Included in NDA	Number of Subjects Included in NDA with Additional Data	Number of New Subjects Not Included in NDA	Overall Total Number of Subjects Included in 120-Day Safety Update
EN3202-020	197	30	0	197
EN3202-021	164	113	75	239
EN3202-022	15	8	9	24
TOTAL	376	151	84	460

Source: Sponsor Table 1 in the 120-Day Safety Update.

The Sponsor notes that of the 84 new subjects in 120-Day Safety Update, 52 had received oxymorphone ER in one of the other oxymorphone clinical trials. Thus, these were not new unique exposures to oxymorphone ER. The remaining 32 subjects were new unique exposures to oxymorphone who had received either placebo, morphine, and/or oxycodone in one of the controlled trials (EN3202-016, EN3202-018, or EN3202-019). Thus, the overall number of unique exposures to oxymorphone ER is 1089 (1057 from the NDA and 32 new unique exposures in the 120-Day Safety Update).

After data from the 120-Day Safety Update have been accounted for, the number of exposed subjects is as follows:

- The total number of unique participants in the oxymorphone clinical development program is 2542 (2474 included in the original NDA and 68 included in the 120-Day Safety Update).
- The total number of unique participants in the Phase 1 studies is 434 (366 included in the original NDA and 68 included in the 120-Day Safety Update).
- The total number of unique participants in all Phase 2/3 clinical trials is 2108 (2108 included in the original NDA and no new patients in the 120-Day Safety Update).
- The total number of unique participants in the IR Phase 2/3 clinical trials is 624 (624 included in the original NDA and no new patients in the 120-Day Safety Update).
- The total number of unique participants in the ER Phase 2/3 clinical trials is 1484 (1484 included in the original NDA and no new patients in the 120-Day Safety Update).
- The total number of unique participants in the ER Phase 2/3 clinical trials who received oxymorphone is 1089 (1057 included in the original NDA and 32 new patients in the 120-Day Safety Update).
- There were no new exposures to oxycodone ER, oxycodone IR, morphine ER, or placebo in the 120-Day Safety Update.

Table: Numbers of Exposures by Subset and Treatment Group and Number of Unique Participants by Subset for Selected Subsets After Inclusion of 120-Day Safety Update Information

		Oxymorphone			Oxycodone			
Study Group	Total[a]	ER/IR[b]	ER	IR	ER	IR	Morphine ER	Placebo
All Trials	2542	1864	1432	565	382	195	69	473
All Phase I Trials	434	434	343	197	0	0	0	0
All Phase II/III Trials	2108	1430	1089	368	382	195	69	473
All ER Phase II/III Trials[c]	1484	1096	1089	34	382	0	69	350
All IR Phase II/III Trials[d]	624	334	0	334	0	195	0	123
Open-label Extension Trials	0	460	460	0	0	0	0	0
EN3202-020[e]	0	197	197	0	0	0	0	0
EN3202-021[f]	0	239	239	0	0	0	0	0
EN3202-022[g]	0	24	24	0	0	0	0	0

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

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

At the time of the ISS submission, 142 subjects had received oxymorphone ER for at least 6 moths (180 days), and 75 had received oxymorphone ER for at least one year (365 days). The 120-Day Safety Update includes information on total of 273 subjects who had received oxymorphone ER for at least six months and 191 subjects who had received it for at least 12 months.

In many of the Phase 2/3 studies, opioid rescue medications were allowed to supplement the study medication. The table below, based on Sponsor's Table 4 in the ISS, lists the study medications and the rescue medication for each Phase 2/3 trial.

Sponsor Table 4. Trial and Rescue Medications by Trial

Trial Number	Indication	Study Medications	Rescue Medications
Oxymorphone IR Trials			
EN3202-012	Acute post-operative pain	Placebo Oxymorphone ER 20 mg	Oxymorphone IV
EN3202-015	Osteoarthritis pain	Placebo Oxymorphone ER 20, 40 mg Oxycodone CR 10, 20 mg	N/A
EN3202-016[a]	Lower back pain	Placebo Oxymorphone ER Oxycodone CR	Oral morphine sulfate
EN3202-017[b]	Cancer pain	Oxycodone CR or morphine CR (per. 1) Oxymorphone ER (per. 2)	Oxycodone IR or morphine IR Oxymorphone IR (per. 2)
EN3202-018[c]	Cancer pain	Oxymorphone ER 10, 20, 40 mg Morphine ER 30, 60, 120 mg	Oxycodone IR
EN3202-019[a,c]	Cancer pain	Oxymorphone ER 10, 20, 40 mg Oxycodone CR 20, 40, 80 mg	Oral morphine sulfate
EN3202-020[a,d]	Osteoarthritis and cancer pain	Oxymorphone ER	Oxymorphone IR (cancer pain subjects only)
EN3202-021[a,e]	Osteoarthritis and cancer pain	Oxymorphone ER	Oxymorphone IR
EN3202-022[a,f]	Cancer pain	Oxymorphone ER	Oxymorphone IR
EN3202-025	Osteoarthritis pain	Placebo Oxymorphone ER 10, 40, 50 mg	N/A
Oxymorphone IR Trials			
EN3203-004	Acute post-operative pain	Placebo Oxymorphone IR 10, 20, 30 mg Oxycodone IR 10 mg	N/A
EN3203-005	Acute post-operative Pain	Placebo Oxymorphone IR 10, 20 mg Oxycodone IR 15, 30 mg	N/A

[a]Trial medication flexibly dosed
[b]Sequential crossover trial.
[c]Crossover trial.
[d]Open-label extension trial for subjects in EN3202-015 and EN3202-017.
[e]Open-label extension trial for subjects in EN3202-016 and EN3202-019.
[f]Open-label extension trial for subjects in EN3202-018.
CR=controlled release; ER=extended release; IR=immediate release; IV=intravenous; N/A=not applicable; per=period.
Source: Sponsor Table 4 in ISS

Review of the above table indicates that in many of the Phase 2/3 ER trials, an additional opioid agent (e.g., oxymorphone IR, morphine, oxycodone) was also given. Oxymorphone IR was offered for breakthrough pain to subjects receiving oxymorphone ER in EN3202-017, to all cancer pain subjects in EN3202-020, and to all subjects in EN3202-021 and EN3202-022. In study EN3202-017, rescue medication use was recorded in dosing diaries. Dosing diaries were not used in EN3202-020, EN3202-021 or EN3202-022. Scheduled doses of oxymorphone IR, along with associated start and stop dates, were recorded in the CRFs. Dispensing and accountability of rescue medication were recorded by site personnel on drug accountability CRFs in all relevant trials. The use of rescue medication was not accounted for in the analysis of safety data, because dosing diaries were not used. The Sponsor notes that "in studies where oxymorphone IR was used as rescue medication, this use comprised only a small fraction of the assigned study medication (oxymorphone ER) dose. For example, in study EN3202-017, the average daily dose of oxymorphone ER was approximately 90-130 mg while the average daily dose of oxymorphone IR given as rescue comprised only 14% of the total daily exposure to oxymorphone (study medication + rescue)." (See Sponsor's response to FDA questions, dated August 13, 2003).

1.4 Demographic Characteristics of the Study Population

Demographic characteristics, including age, gender and race, were recorded for all subjects. Height and weight were recorded as part of the physical examination. Descriptive statistics of these variables were calculated for the "All Trials" population as well as for the eight other clinical trial subsets. Because of differences in the study population in the various trials that comprise the ISS, comparisons across subsets were not performed.

1.4.1 Demographic Characteristics of the All Trials Population

The demographic features of all subjects enrolled all clinical trials of oxymorphone (N=2474) is presented in Table 13 of the ISS, which is reproduced below.

ISS Table 13. Demographic Characteristics – All Trials

Demographic Characteristic	Total[a] [c]	Oxymorphone			Oxycodone		Morphine ER	Placebo
		ER/IR[b]	ER	IR	ER	IR		
Age (years)	2474	1764	1332	565	382	195	69	473
< 65 years [N(%)]	1611 (65.1%)	1202 (68.1%)	941 (70.6%)	386 (68.3%)	288 (75.4%)	110 (56.4%)	51 (73.9%)	281 (59.4%)
>= 65 years[N(%)]	863 (34.9%)	562 (31.9%)	391 (29.4%)	179 (31.7%)	94 (24.6%)	85 (43.6%)	18 (26.1%)	192 (40.6%)
>= 74 years[N(%)]	303 (12.2%)	199 (11.3%)	132 (9.9%)	70 (12.4%)	35 (9.2%)	27 (13.8%)	2 (2.9%)	63 (13.3%)
(range)	(18-93)	(18-89)	(18- 89)	(18-86)	(21-88)	(22-83)	(30-80)	(26-93)
Mean (SD)	56.4 (14.8)	54.9 (15.3)	54.2 (15.0)	52.1 (17.7)	54.3 (13.2)	60.7 (12.6)	56.8 (11.0)	59.8 (12.4)
Gender [N(%)]								
FEMALE	1333 (53.9%)	924 (52.4%)	681 (51.1%)	274 (48.5%)	195 (51.0%)	116 (59.5%)	50 (72.5%)	270 (57.1%)
MALE	1141 (46.1%)	840 (47.6%)	651 (48.9%)	291 (51.5%)	187 (49.0%)	79 (40.5%)	19 (27.5%)	203 (42.9%)
Race [N(%)]								
CAUCASIAN	2108 (85.2%)	1479 (83.8%)	1119 (84.0%)	455 (80.5%)	345 (90.3%)	171 (87.7%)	60 (87.0%)	422 (89.2%)
BLACK	206 (8.3%)	152 (8.6%)	118 (8.9%)	44 (7.8%)	24 (6.3%)	15 (7.7%)	8 (11.6%)	36 (7.6%)
OTHER	156 (6.3%)	129 (7.3%)	92 (6.9%)	63 (11.2%)	13 (3.4%)	9 (4.6%)	1 (1.4%)	15 (3.2%)
ASIAN	4 (0.2%)	4 (0.2%)	3 (0.2%)	3 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Height(in)	2454	1748	1317	563	371	193	67	473
(range)	(48-675)	(48-675)	(48-78)	(54- 675)	(48-77)	(57-78)	(54-75)	(57-78)
Mean (SD)	66.8 (12.9)	67.0 (15.1)	66.8 (4.18)	67.8 (25.9)	66.8 (4.33)	66.5 (3.87)	65.4 (4.29)	66.7 (3.89)
Weight(lbs)	2458	1753	1321	564	372	193	68	473
(range)	(79-450)	(84-450)	(84-427)	(112-450)	(84-340)	(100-385)	(79-330)	(110-425)
mean (SD)	194 (48.1)	192 (48.3)	192 (49.0)	188 (43.3)	188 (47.6)	197 (42.9)	179 (48.5)	202 (47.8)

Note: Subjects are counted in more than one treatment group depending on treatments received
[a] Total number of unique subjects
[b] Either or both Oxymorphone formulations
[c] Subjects in study EN3202-011A are not counted since they were previously treated in study EN3202-011
Source: Sponsor Table 13 in ISS

The mean age of all trial participants was 56.4 years (SD 14.8). Subjects' ages ranged form 18 years to 93 years. The mean age of subjects receiving any oxymorphone was 54.9 years (SD 15.3). Subjects receiving either oxycodone IR or placebo were, on average, slightly older than other subjects (means ages 60.7 years [SD 12.6] and 59.8 [12.4], respectively). Subjects who received these two study treatments were enrolled exclusively in Phase 2/3 clinical trials. The mean ages across the other treatment groups were similar.

Among all trial participants, the proportion of subjects age 65 years or older was 34.9%, while the proportion age 74 years or older was 12.2%. Across the treatment groups, the proportion of subjects age 65 years or older was highest in the oxycodone IR and placebo groups (43.6% and 40.6%, respectively). The oxycodone ER group had the lowest proportion of subjects age 65 years or older (24.6%). Nearly a third (31.9%) of subjects who received any oxymorphone were age 65 years or older, while 11.3% of subjects receiving any oxymorphone were age 74 years or older.

Among all trial participants, 53.9% were female, and 46.1% were male. Among all subjects receiving any oxymorphone, 52.4% were female. The proportion of females receiving oxycodone IR, morphine ER, and placebo were somewhat higher (59.5%, 72.5%, and 57.1% respectively).

Of the 2474 unique participants, 85.2% were Caucasian, 8.3% were Black, 6.3% were 'Other', and 0.2% were Asian. The percentage of Blacks ranged from 6.3% in the oxycodone ER group to 11.6% in the morphine ER group. The percentage of 'Other' ranged from 1.4% in the morphine ER group to 11.2% in the oxymorphone IR group. The makeup of the 'Other' group is not clear. Case Report Forms for some of the studies had an option to indicate Hispanic as well as a separate option for 'Other', with further specification of the latter. The reason for including Hispanics as 'Other' is not clear.

The average height of all trial participants was 66.8 inches (SD 12.9). There were no notable differences in average height across the various treatment groups. Of note, the upper most height was an improbable 675 inches. Subject EN3203-004-007-005 has a height entered into the database as 675 inches. Review of that subject's CRFs indicates that height appears to have been recorded as 67.5 inches, though there was no place on the pre-printed form for a decimal point.

The average weight of all trial participants was 194 pounds (SD 48.1). Across the treatment groups, the average weights ranged from 179 (SD 48.5) in the morphine ER group to 202 (SD 47.8) in the placebo group. Within each treatment group, the range of weights was wide.

1.4.2 Demographic Characteristics of Defined Subsets

1.4.2.1 All Phase 2/3 Trials

The demographic characteristics of subjects who received treatments other than oxymorphone in the Phase 2/3 subjects were identical to those in all trials (see Sponsor Table 14 in the ISS).

The mean age of all 2108 unique Phase 2/3 trial participants was 59.4 years (SD 12.7). Mean ages across treatment groups ranged from 54.3 years (SD 13.2) in the oxycodone ER group to 62.5 years (SD 11.8) in the oxymorphone IR group. In this group of trials, 39.2% of subjects were age 65 years or older.

In the Phase 2/3 trials, 57.4% of the subjects were females, a percentage similar to the percentage of females treated with any oxymorphone (57.3%). The majority of subjects in the Phase 2/3 trials were Caucasian (88.8%), with Blacks comprising 8.1%.

1.4.2.2 Phase 2/3 Oxymorphone ER Trials

The demographic characteristics of subjects in the Phase 2/3 oxymorphone ER clinical trials were generally similar to those in all Phase 2/3 clinical trials (see Sponsor Table 15 in the ISS).

The mean age of all 1484 unique Phase 2/3 oxymorphone ER clinical trial participants was 58.3 years (SD 12.7). Mean ages across treatment groups ranged from 54.3 years (SD 13.2) in the oxycodone ER group to 59.6 years (SD 11.4) in the oxymorphone IR group. In this group of trials, 35.5% of subjects were age 65 years or older.

In the Phase 2/3 oxymorphone ER clinical trials, 57.5% of the subjects were females, a percentage similar to the percentage of females treated with any oxymorphone (57.1%). In this group of trials, 89.0% of subjects were Caucasian, 8.4% were Black, 2.5% were Other, and 0.1% were Asian. Only 2.9% of subjects receiving oxymorphone IR were Black; the remaining were Caucasian.

1.4.2.3 Phase 2/3 Oxymorphone IR Trials

The demographic characteristics of subjects in the Phase 2/3 oxymorphone IR clinical trials were generally similar to those in all Phase 2/3 clinical trials, though trial participants were somewhat older on average than in other clinical trial groups (see Sponsor Table 16 in the ISS). No subjects received oxymorphone ER, oxycodone ER or morphine ER in this group of trials.

The mean age of all 624 unique Phase 2/3 oxymorphone ER clinical trial participants was 62.1 years (SD 12.2). Mean ages across treatment groups ranged from 60.7 years (SD 12.6) in the oxycodone IR group to 62.8 years (SD 11.8) in the oxymorphone IR group. In this group of trials, 48.1% of subjects were age 65 years or older.

In the Phase 2/3 oxymorphone IR clinical trials, 57.2% of the subjects were females, a percentage similar to the percentage of females treated with oxymorphone IR (57.8%). In this group of trials, 88.3% of subjects were Caucasian, 7.2% were Black, 4.3% were Other, and 0.2% were Asian.

1.4.2.4 Acute Post-Operative Pain Trials

The demographic characteristics of subjects in the acute post-operative pain trials were generally similar to those in the Phase 2/3 oxymorphone IR trials, since the acute post-operative pain studies and the oxymorphone IR studies differed only by the inclusion of subjects in trial EN3202-012 in the former group (see Appendix 2.5 of ISS). In that trial, subjects received either oxymorphone ER (n=66) or placebo (n=61).

The mean age of all 751 unique acute post-operative pain trial participants was 62.7 years (SD 11.8). Mean ages across treatment groups ranged from 60.7 years (SD 12.6) in the oxycodone IR group to 65.1 years (SD 8.27) in the oxymorphone ER group. In this group of trials, 50.3% of subjects were age 65 years or older.

In the acute post-operative pain trials, 57.5% of the subjects were females, a percentage similar to the percentage of females treated with any oxymorphone (58.5%). In this group of trials, 88.1% of subjects were Caucasian, 8.0% were Black, 3.7% were Other, and 0.1% were Asian.

1.4.2.5 Chronic Non-malignant Pain Trials

The demographic characteristics of subjects in the chronic non-malignant pain trials were generally similar to those in the Phase 2/3 oxymorphone ER trials (see Sponsor Table 17 in ISS).

The mean age of all 1185 unique chronic non-malignant pain trial participants was 57.8 years (SD 12.8). Mean ages across treatment groups ranged from 53.8 years (SD 13.2) in the oxycodone ER group to 58.5

years (SD 12.9) in the oxymorphone ER group. In this group of trials, 34.1% of subjects were age 65 years or older.

In the chronic non-malignant pain trials, 56.9% of the subjects were females, a percentage similar to the percentage of females treated with oxymorphone ER (57.7%). In this group of trials, 89.5% of subjects were Caucasian, 8.3% were Black, 2.2% were Other, and 0.1% were Asian.

1.4.2.6 Cancer Pain Trials

The demographic characteristics of subjects in the cancer pain trials were generally similar to those in the Phase 2/3 oxymorphone ER trials (see Sponsor Table 18 in ISS).

The mean age of all 172 unique cancer pain trial participants was 56.5 years (SD 12.3). Mean ages across treatment groups ranged from 55.9 years (SD 13.3) in the oxycodone ER group to 59.6 years (SD 11.4) in the oxymorphone IR group. In this group of trials, 26.2% of subjects were age 65 years or older.

In the cancer pain trials, 60.5% of the subjects were females, a percentage similar to the percentage of females treated with oxymorphone ER (59.3%) and oxymorphone IR (58.7%). In this group of trials, 87.2% of subjects were Caucasian, 11.0% were Black, and 1.7% were Other.

1.4.2.7 Open-label Extension Trials

The demographic characteristics of subjects in the open-label extension trials were generally similar to those in the Phase 2/3 oxymorphone ER trials (see Appendix 2.8 in ISS), except that the average age of participants in the open-label studies was slightly younger than in all Phase 2/3 oxymorphone ER trials. The only study medication in these trials was oxymorphone ER.

The mean age of all 376 unique open-label extension trial participants was 53.4 years (SD 12.3). In this group of trials, 21.5% of subjects were age 65 years or older.

In the open-label extension trials, 55.6% of the subjects were females. In this group of trials, 89.9% of subjects were Caucasian, 7.2% were Black, 2.7% were Other, and 0.3% were Asian.

1.4.2.8 All Phase 1 Trials

The demographic characteristics of subjects in the Phase 1 trials were notable for the fact that subjects generally were younger and a higher percentage were male, compared to the Phase 2/3 trials (see Appendix 2.9 in the ISS).

The mean age of all 366 unique Phase 1 trial participants was 39.1 years (SD 14.0). In this group of trials, 9.8% of subjects were age 65 years or older.

In the Phase 1 trials, 33.6% of the subjects were females. In this group of trials, 64.5% of subjects were Caucasian, 9.8% were Black, 25.1% were Other, and 0.5% were Asian.

1.4.2.9 120-Day Safety Update

The 120-Day Safety Update presents updated demographic characteristics for the Phase 2/3 oxymorphone ER trials, reflecting the addition of 32 new unique subjects receiving oxymorphone in the open-label clinical trials who had received another study medication in the controlled trials prior to participation in the open-label trials. (Of the 84 subjects for whom additional Phase 2/3 information was submitted in the 120-Day Safety Update, 32 were new unique exposures to oxymorphone ER; 52 had previously received oxymorphone ER in other trials.) The table below, a reproduction of Sponsor Table 5 in the 120-Day Safety

updates, presents demographic information for participants in the Phase 2/3 ER trials from the original ISS, the 120-Day Safety Update, and the Overall populations.

Table. Demographic Characteristics – Phase 2/3 ER Trials in the ISS, 120-Day Safety Update, and Overall

Demographic Characteristics	ISS Total (a)	120 - Day Safety Update Total	Overall Total (a)
Age (years)	1057	84	1089
< 65 years [N(%)]	702 (66.4)	73 (86.9)	731 (67.1)
>= 65 years [N(%)]	355 (33.6)	11 (13.1)	358 (32.9)
>= 74 years [N(%)]	121 (11.4)	4 (4.8)	121 (11.1)
(range)	(26 - 89)	(24 - 77)	(24 - 89)
mean (SD)	57.8 (12.7)	50.8 (12.4)	57.4 (12.8)
Gender [N(%)]			
FEMALE	603 (57.0)	40 (47.6)	619 (56.8)
MALE	454 (43.0)	44 (52.4)	470 (43.2)
Race [N(%)]			
CAUCASIAN	941 (89.0)	72 (85.7)	968 (88.9)
BLACK	90 (8.5)	9 (10.7)	93 (8.5)
OTHER	25 (2.4)	3 (3.6)	27 (2.5)
ASIAN	1 (0.1)	0 (0)	1 (0.1)
Height (in)	1043	82	1075
(range)	(48 - 78)	(58 - 77)	(48 - 78)
mean (SD)	66.7 (4.3)	67.4 (4.4)	66.7 (4.3)
Weight (lbs)	1047	83	1079
(range)	(84 - 427)	(100 - 310)	(84 - 427)
mean (SD)	199.1 (51.7)	183.4 (46.2)	198.6 (51.6)

(a) Total number of unique subjects using demographic values from a subject's first study.
Source: Sponsor Table 5 in the 120-Day Safety Update.

Review of the above table indicates no significant differences between the original ISS Phase 2/3 ER population and the Overall Phase 2/3 ER population.

For the Phase 1 trial population, the 120-Day Safety Update provided demographic information on the two individual Phase 1 studies submitted in the ISS. The table below summarizes the demographic data from those trials.

Table. Demographic Characteristics of Subjects in Phase 1 Studies EN3202-026 and EN3202-027

Demographic Characteristics	EN3202-026	EN3202-027
Age (years)	80	85
(range)	(19-55)	(18-55)
Mean (SD)	39	40
Gender [N(%)]		
FEMALE	30 (38%)	35 (41%)
MALE	50 (63%)	50 (59)
Race [N(%)]		
CAUCASIAN	28 (35%)	40 (47%)
BLACK	11 (14)	12 (14%)
HISPANIC	40 (50%)	33 (39%)
ASIAN	1 (1%)	0
Weight (lbs)		
(range)	(102-206)	(103-220)
mean (SD)	162	156

Source: Information taken from Section 4.2 of 120-Day Safety Update

Review of the above table indicates that the demographic characteristics of subjects in these two Phase 1 studies are similar to those in the other Phase 1 studies.

1.5 Adverse Events

1.5.1 Review of Coding of Adverse Events

The Sponsor used the Medical Dictionary for Regulatory Activity (MedDRA), Version 3.0, to assign all adverse events to a body system (ie, system organ class) and a preferred term. Appendix 10.1 of the ISS provides the mapping of the adverse event terms reported on the case report forms (CRFs) to the MedDRA terms. Overall, the mapping of the reported terms to the preferred terms appears appropriate. There are, however, several adverse events, reported by a wide range of terms on the CRFs and thus coded to a number of preferred terms, that may represent similar, or at least clinically overlapping events. These reported terms all refer to a change in mental status – either a change in the level of arousal or a change in the content of consciousness – whose clinical features are often difficult to understand from either the reported term or the preferred term. For example there are a number of serious AEs coded to the preferred terms 'Central nervous system depression', 'Coma NEC', 'Depressed level of consciousness', 'Sedation', and 'Somnolence' that, upon further review, reveal a pattern of a depressed level of consciousness that responds to naloxone. Despite the various preferred terms used to categorize these events, they appear to represent similar phenomena after review of the narratives (see review of serious adverse events below for details). Further review of the Sponsor's mapping of reported terms to preferred terms suggests that there may be overlap among some of the adverse events that have been mapped to the preferred terms below. These preferred terms, and their corresponding system organ classes, are listed in the table below.

Selected MedDRA Preferred Terms	
System Organ Class	Preferred Term
General disorders and administration site conditions	Lethargy
	Mental status changes
Nervous system disorders	Central nervous system depression NOS
	Coma NEC
	Depressed level of consciousness
	Disturbance in attention NEC
	Encephalopathy NOS
	Judgement impaired
	Loss of consciousness NEC
	Mental impairment NOS
	Sedation
	Sedation aggravated
	Somnolence
Psychiatric disorders	Confusion
	Confusion aggravated
	Delirium
	Disorientation
	Thinking abnormal NEC

Review of the above table indicates that all of the preferred terms refer to some sort of alteration in mental status. While many of the preferred terms themselves refer to specific clinical entities (ie, 'coma' as a clinical entity is distinct from 'delirium'), the reported terms on the CRFs are often less precise, and there is thus the possibility that there is overlap among the clinical entities indicated by the reported terms. The implications of this coding will be reviewed in the discussion of adverse events below.

1.5.2 Deaths

The Sponsor reports that a total of 35 deaths occurred during the clinical development program. Twenty-five deaths were reported in the original ISS; the 120-day safety update reported an additional 10 deaths.

Of the 35 deaths in the clinical development program, 34 occurred in subjects with cancer pain. Twenty-eight of the 35 deaths occurred during the open-label extension studies EN3202-020 (n=13), EN3202-021 (n=12), and EN3202-022 (n=3). Of the patients who died during these open-label extension studies, all but one (patient ID EN3202-015-040-007) had previously participated in a controlled study for cancer pain. Deaths during controlled trials were less common, occurring only in controlled studies for cancer pain, EN3202-017 (n=4), EN3202-018 (=2), and EN3202-019 (n=1).

Of the seven patients who died during the controlled clinical trials, one was receiving oxymorphone ER, two were receiving morphine ER, one was receiving oxycodone ER, and two were receiving oxymorphone IR. (Subject EN3202-018-011-002 is counted as a death under two treatments, oxymorphone IR and morphine ER. The adverse event of dysphagia, which resulted in death, occurred during the oxymorphone IR period of the study, while disease progression, which also resulted in death, occurred during the morphine ER period of the study. For this reason, the death is counted under two treatments.) The following table summarizes patients who died during controlled trials:

Table. Summary of Patients Who Died During Controlled Clinical Trials in the Oxymorphone Clinical Development Program

Protocol	Patient ID	A/G/R	Treatment	Dose	Preferred Term	Verbatim Term
EN3202-017	EN3202-017-008-007	79/M/C	Oxymorphone ER	80	Concomitant disease progression	Concomitant disease progression
	EN3202-017-010-002	54/F/C	Oxycodone ER	160	Concomitant disease progression	Death secondary to progressive lymphoma
	EN3202-017-011-003	65/F/C	Oxycodone ER	200	Cardio-respiratory arrest	Cardiopulmonary arrest
					Concomitant disease progression	Concomitant disease progression
	EN3202-017-013-001	44/F/C	Morphine ER	120	Concomitant disease progression	Concomitant disease progression
EN3202-018	EN3202-018-011-002	72/F/C	Morphine ER	120	Concomitant disease progression	Advancement of disease state
			Oxymorphone IR	150	Dysphagia	Difficulty swallowing
	EN3202-018-020-001	69/F/C	Oxymorphone IR	95	Concomitant disease progression	Advance disease
EN3202-019	EN3202-019-067-006	54/M/C	Oxycodone ER	40	Confusion	Confusion
					Metastases to brain	Brain mets
					Pain NOS	Uncontrollable pain
					Pneumonia NOS	Pneumonia

Source: Appendix 2, Listing 7 in the 120-Day Safety Update

Review of the narratives, CRFs, and other information in the database is notable for the following:

Patient EN3202-017-008-007, a 79-year-ol man, was being treated for cancer (narrative notes "small cell lung carcinoma", CRFs note "non-small cell carcinoma" of the liver with spinal metastases) who had received oxycodone ER in the first period of the study (20 mg q12h which was increased to 40 mg q12h). In the second period, he received oxymorphone ER, initially 40 mg q12h for two days, followed by an increase to 40 mg q12h. He completed the study according to protocol on May 22, 2000. On [redacted] he was hospitalized with confusion, disorientation, dysphoria, abnormal gait, and severe pain. He was treated with a variety of medications for pain (the narrative and CRF do not delineate this further), and was discharged on [redacted]. On [redacted] he died of disease progression. The investigator judged the relationship of this death to study drug as "unlikely".

The other three patients who died during Study EN3202-017 were treated with either Oxycodone ER (Patients EN3202-017-010-002 with lymphocytic B cell lymphoma with breast and leg metastases, and EN3202-017-011-003 with right kidney transitional cell lymphoma with lung metastases) or Morphine ER (Patient EN3202-017-013-001 with breast cancer metastatic to liver and bone). The two oxycodone ER-treated patients received no oxymorphone, having each died before the end of the oxycodone ER period. In addition, each died at least a few days after the last dose of study medication. Patient EN3202-017-013-001 also never received oxymorphone, having discontinued from the study due to inadequate pain relief and worsening ascites. She died about one month after discontinuation. Review of study data and narratives for these three patients supports concomitant disease progression as the cause of death and further supports the investigators' judgement that study medication (ie, oxycodone ER or morphine ER) was unlikely related to the deaths.

Patient EN3202-018-011-002, a 72-year-old woman with ovarian cancer and malignant pleural effusions, was initially treated with increasing doses of oxymorphone IR during the titration phase of the study, which began on June 1, 2001. Doses ranged from 60 mg/day to 160 mg/day. On June 6, she developed dysphagia. She was then randomized to morphine ER, which she began on June 11. Doses ranged from 180 to 480 mg/day. She discontinued study participation on June 15, due to an adverse event due to the dysphagia and

vomiting. Disease progression was noted on June 18, though no details of its manifestations are provided. She died [redacted]. The investigator judged the dysphagia and vomiting as possibly related to study medication, but judged the disease progression as unlikely related to study medication. Because the dysphagia, which resulted in death, developed during the oxymorphone IR period, and the disease progression developed as she discontinued from the morphine ER period, the death is counted both in the oxymorphone IR and morphine ER treatment groups.

Patient EN3202-018-020-001, a 69-year-old woman with lung cancer, began treatment with oxymorphone IR on May 22, 2001, with doses ranging from 10 to 105 mg/day [redacted] later, concomitant disease progression was noted, requiring hospitalization. On May 31, she was randomized to oxymorphone ER, and received daily doses of 50 to 100 mg/day. She received this treatment for 8 days, and withdrew because of lack of efficacy [redacted]. She died [redacted] after completing therapy with oxymorphone ER. The death was judged to be unlikely related to study medication.

Patient EN3202-019-067-006, a 54-year-old man with lung cancer metastatic to bone and brain, was stabilized during the titration/stabilization phase on oxycodone ER at an average daily dose of 40 mg/day. He was then randomized to the oxycodone ER/oxymorphone ER sequence, and was provided with a supply of study medication. On the day of randomization, however, he developed confusion, brain metastases, pain, and pneumonia, and died. Because his study medication was not returned, the extent of exposure to study medication at the time of death is not known. The investigator judged this death as unlikely related to study medication.

After review of the above deaths in controlled clinical trials, it appears that deaths in oxymorphone-treated patients are similar to those in patients treatment with other opiate analgesics (oxycodone and morphine). In each case, concomitant disease progression or a complication of the underlying cancer appears to be the cause of death. In some cases, death occurred after study medication had been stopped.

Twenty-eight of the 35 of deaths in the oxymorphone clinical development program occurred during open-label extension trials. Study medication in each of these trials was oxymorphone ER. The table below summarizes these deaths.

Table. Summary of Patients Who Died During Open-Label Extension Clinical Trials in the Oxymorphone Clinical Development Program

Protocol	Patient ID	A/G/R	Treatment	Dose	Preferred Term	Verbatim Term
EN3202-020	EN3202-015-040-007	42/M/C	Oxymorphone ER	80	Ventricular hypertrophy	Ventricular hypertrophy
	EN3202-017-008-001	67/M/C	Oxymorphone ER	240	Concomitant disease progression	Concomitant disease progression
				280	Hypoxia	Hypoxia
	EN3202-017-008-002	51/M/C	Oxymorphone ER		Concomitant disease progression	Concomitant disease progression
	EN3202-017-008-003	50/F/C	Oxymorphone ER	171	Concomitant disease progression	Concomitant disease progression
	EN3202-017-008-006	69/M/C	Oxymorphone ER	120	Concomitant disease progression	Concomitant disease progression
					Abdominal pain NOS	Abdominal pain
					Haematemesis	Haematemesis
					Nausea	Nausea
					Pancreatitis NOS	Pancreatitis
					Vomiting NOS	Vomiting
	EN3202-017-011-004	30/F/C	Oxymorphone ER		Concomitant disease progression	Concomitant disease progression
					Dyspnoea NOS	Dyspnoca
					Pyrexia	Pyrexia
	EN3202-017-011-005	59/F/C	Oxymorphone ER	40	Fluid overload	Fluid overload
					Cardiac failure congestive	Congestive heart failure
					Concomitant disease	Concomitant disease progression

Table. Summary of Patients Who Died During Open-Label Extension Clinical Trials in the Oxymorphone Clinical Development Program

Protocol	Patient ID	A/G/R	Treatment	Dose	Preferred Term	Verbatim Term
					progression	
					Multi-organ failure	Multiorgan failure
					Pleural effusion	Pleural effusion
	EN3202-017-013-002	64/M/B	Oxymorphone ER	40	Concomitant disease progression	Concomitant disease progression
	EN3202-017-013-004	65/F/C	Oxymorphone ER	80	Sepsis NOS	Septicemia
					Concomitant disease progression	Concomitant disease progression
					Pain exacerbated	Increased pain due to fall
	EN3202-017-014-001	59/M/C	Oxymorphone ER		Concomitant disease progression	Lung cancer disease progression fatality
	EN3202-017-014-002	53/M/C	Oxymorphone ER		Coronary artery disease NOS	Coronary artery disease
	EN3202-017-015-003	48/F/C			Coronary artery disease NOS	CAD (autopsy finding)
	EN3202-017-016-016	53/F/C	Oxymorphone ER		Concomitant disease progression	Concomitant disease progression
EN3202-021	EN3202-019-050-001	72/M/C	Oxymorphone ER	40	Concomitant disease progression	Primary disease progression
					Metastases to brain	Brain metastases
	EN3202-019-056-001	64/M/C	Oxymorphone ER	80	Anxiety NEC	Anxiety
					Concomitant disease progression	Progression of liver metastasis
					Excessive bronchial secretion	Respiratory secretions
					Oral Candidiasis	Oral Candidiasis
	EN3202-019-060-002	79/F/C	Oxymorphone ER	60-	Swelling NOS	Lump-right calvarium
					Breath sounds decreased	Decreased breath sounds
				120	Concomitant disease progression	Disease progression (liver cancer with metastases)
					Loin pain	Bilateral flank pain
					Neurogenic bladder	Narcotic bladder
					Anxiety NEC	Anxiety
					Rectal disorder NOS	Rectal lesions
					Tenesmus	Painful defecation
	EN3202-019-060-003	61/M/C	Oxymorphone ER		Concomitant disease progression	Concomitant disease progression
	EN3202-019-067-002	48/F/C	Oxymorphone ER	40	Concomitant disease progression	Disease progression breast cancer
					Dyspnoea NOS	Shortness of breath
	EN3202-019-067-012	77/M/C	Oxymorphone ER	40	Concomitant disease progression	Disease progression cancer
					Confusion	Confusion
	EN3202-019-067-013	77/M/C	Oxymorphone ER		Myocardial infarction	Myocardial infarction
	EN3202-019-067-014	52/F/C	Oxymorphone ER	80	Concomitant disease progression	Disease progression
	EN3202-019-067-016	60/F/C	Oxymorphone ER	40	Concomitant disease progression	Disease progression lung cancer
	EN3202-019-069-003	64/F/C	Oxymorphone ER	360	Concomitant disease progression	Progression of disease
					Thrombocytopenia	Thrombocytopenia
	EN3202-019-071-004	57/M/C	Oxymorphone ER	120	Metastases to brain	Brain metastases
	EN3202-019-074-001	64/M/C	Oxymorphone ER	100	Concomitant disease progression	Disease progression
					Jaundice NOS	Icteric conjunctiva
					Jaundice NOS	Jaundice
					Weight increased	Weight gain

Table. Summary of Patients Who Died During Open-Label Extension Clinical Trials in the Oxymorphone Clinical Development Program

Protocol	Patient ID	A/G/R	Treatment	Dose	Preferred Term	Verbatim Term
EN3202-022	EN3202-018-011-007	63/F/C	Oxymorphone ER	20	Fatigue	Fatigue
	EN3202-018-018-002	57/F/C	Oxymorphone ER	60-120	Joint effusion	Right knee effusion
					Abdominal pain NOS	Abdominal pain
					Concomitant disease progression	Progressive metastatic esophageal cancer
					Vision blurred	Blurred vision
					Anaemia NOS	Severe anemia
	EN3202-018-018-004	53/F/C	Oxymorphone ER	40-100	Concomitant disease progression	Progressive metastatic breast cancer
					Pain NOS	Intense pain

Source: Appendix 2, Listing 7 in 120-Day Safety Update

Of these 28 patients who died in an open-label extension trial, only one patient did not have cancer. The remaining 27 patients each had an underlying cancer and each had participated in a controlled trial for cancer pain prior to enrollment in the open-label extension study.

Patient EN3202-015-040-007 was the only patient to die in an open-label extension study who did not have cancer. He was a 43-year-old Caucasian male with obesity, hypertension, and osteoarthritis of the knees. He also had a past history of cellulitis, mild depression, pneumonia as a child, and NSAID gastropathy. He participated in and completed Study EN3202-015, during which he received oxycodone ER, with total daily doses ranging from 10 mg/day to 40 mg/day. He then enrolled in Study EN3202-020, during which he received oxymorphone 40 mg/day (total daily dose) for eight days, followed by oxymorphone 80 mg/day (total daily dose). He began Study EN3202-015 on February 28, 2000, and escalated to the oxymorphone 80 mg/day total daily dose on March 6, 2000. Blood pressure at study entry was 140/92. An EKG was not performed at study entry. Physical examination at study entry was notable for obesity and moderate tenderness of the right medial toe joint. No baseline signs or symptoms were noted. Concomitant medication included Zestril 10 mg po q AM at study entry for hypertension (he had been on it for about 4 years). The dose was changed to 20 mg po q AM on June 19, 2000. Blood pressure on April 10, 2000 was 146/89, and on May 8, 2000 it was 130/86. On June 19, blood pressure was 148/88. On July 27, 2000, the blood pressure was 130/80. A 12-lead EKG at that time was reported as normal. On July 27, 180 20-mg oxymorphone ER tables were dispensed. He died on [redacted]. The investigator listed "death secondary to natural causes" on the adverse event form. The medical examiner's report apparently indicated death due to right and left ventricular hypertrophy due to obesity. In a Data Management Query Form, the Sponsor asked the investigator if the ventricular hypertrophy would be a more appropriate adverse event than "death secondary to natural causes". The investigator responded that it would not be. Nonetheless, the adverse event database contained "ventricular hypertrophy". The Sponsor, in a response of September 4, 2003 to an Agency question, noted that MedDRA coding dose not permit an outcome (e.g., death) as an adverse event term. Thus, the Sponsor used "ventricular hypertrophy" as the adverse event term. The investigator judged the relationship of the death to the study drug as "unlikely". The Sponsor's narrative further notes that the "manner of death was natural". It also notes that a toxicology report indicated the presence of caffeine, caffeine metabolites and nicotine in the blood, but not ethanol, cocaine, or opiates. In response to an Agency question, the Sponsor noted on September 4, 2003 that "It is not likely that toxicological batteries for opiates detect oxymorphone. It is not known if the toxicological screen used by the medical examiner could have detected oxymorphone, but it is highly unlikely." Review of this case suggests that information provided in the narrative and in the database is not complete, and a causal role for the drug can neither be made nor excluded with certainty.

Of the 27 patients with cancer who died in an open-label extension study, 24 experienced progression of the underlying disease, which was listed as an adverse event leading to death.

Review of several cases indicates that the progression of the underlying disease was the most likely cause of death. For most subjects, all adverse events resulting in death were judged by the investigator to be

unlikely related to study drug. The table below summarizes all subjects for whom the judged relationship of all adverse events resulting in death was "unlikely". It should be noted that the summaries below are very brief summaries, principally of the underlying cancer and the events leading up to death. Most of the subjects had other concomitant medical conditions in addition to the underlying cancer. These conditions, as well as the multiple medications that most subjects were taking, are not summarized in the table below. This information can be found in the patient narratives that the Sponsor has submitted, as well as in the medical history, adverse event, and concomitant medication data that the Sponsor has submitted.

Table. Summary of Patients Who Died During Open-Label Extension Clinical Trials in the Oxymorphone Clinical Development Program Whose Death Was Judged to be Unlikely Related to Study Drug

Protocol Patient ID	A/G/R	Underlying Cancer Information	Description of Selected Adverse Events	Reviewer Comments
EN3202-020				
EN3202-017-008-001	67/M/C	Non-small cell lung cancer with pneumothorax and probable post-obstructive pneumonia 3 months before death	Terminal events included respiratory failure and hypoxia, with continued right lung collapse, left-sided infiltrate, and possible endobronchial obstruction. Patient was alert but confused at final admission. Required IV analgesia for pain control.	Concomitant disease progression appears to be the cause of death.
EN3202-017-008-002	51/M/C	Lung carcinoma (Pancoast tumor) diagnosed 23 years prior to study entry, previously treated with chemotherapy and radiation therapy. Course complicated by radiation-induced anemia.	About 7 weeks prior to death, patient was admitted with increased shoulder pain (attributed to MRI-documented tumor infiltration of the brachial plexus and adjacent thoracic spine) an hypotension., attributed to hypovolemia. Chronic anemia and pre-renal azotemia also were noted.	Patient discontinued from study on November 22, 2000 because of inability to keep appointments. He died of progressive carcinoma (per narrative's description of the death certificate) [redacted]
EN3202-017-008-003	50/F/C	Breast carcinoma, with brain and pleural metastases on September 15, 2000. Treatment included steroids, radiation, thoracocentesis (malignant cells confirmed) and chemotherapy.	Patient was re-admitted [redacted] with recurrent pleural effusion, requiring removal of 2 liters of fluid, chest tube insertion, pleurodesis, and bleomycin therapy. Chest tube removed on [redacted] Some mental confusion noted. She was discharged from the hospital on [redacted]	Patient died on [redacted] with death certificate listing disease progression as the cause of death. Date of last dose of study medication is not known.
EN3202-017-011-004	30/F/C	Spindle cell sarcoma of the cervical spine, treated with surgical removal and chemotherapy	Patient began study treatment on April 10, 2000. She developed pneumonia on June 3, with resolution by June 12. She entered hospice care, and decided to withdraw from the study on August 2. Patient developed pyrexia and dyspnea on August5. She died on [redacted]	Investigator attributes death to metastatic disease progression.
EN3202-017-011-005	59/F/C	Recurrent non-Hodgkin's lymphoma, treated with chemotherapy, biological therapy, radiation therapy, and bone marrow transplant complicated by pulmonary fibrosis, congestive heart failure and urinary retention.	Patients was admitted for chemotherapy on [redacted], she developed congestive heart failure, hypoxemia, and a left pleural effusion was found. Study medication was stopped and IV morphine was started for pain control. On May 23, renal insufficiency requiring renal dose dopamine.	Patient died on [redacted] of multi-organ failure and disease progression.
EN3202-017-013-002	64/M/B	Prostate cancer with brain metastases	Patient was admitted with loss if consciousness on [redacted] and was found to have bleeding into the brain parenchyma due to metastatic tumor. He discontinued study participation at that time. He required intrancranial pressure relief via burr hole and craniotomy for subdural hematoma and dural tumor removal. Mental status improved, but repeat CT revealed fresh blood in the brain. He became obtunded and was discharged to home for terminal care.	Patient died on [redacted], of disease progression.
EN3202-017-	65/F/C	Breast cancer treated	Patient began oxymorphone ER 40 mg bid on	Patient died on [redacted]

Table. Summary of Patients Who Died During Open-Label Extension Clinical Trials in the Oxymorphone Clinical Development Program Whose Death Was Judged to be Unlikely Related to Study Drug

Protocol Patient ID	A/G/R	Underlying Cancer Information	Description of Selected Adverse Events	Reviewer Comments
013-004		with surgery, chemotherapy and radiation therapy, with pleural metastases and methotrexate-induced cirrhosis	January 21, 2000. On February 13 at 4:00 am, she fell while getting out of bed. Source documents (ER report and SAE report) give conflicting information on the use of rescue medication. Because of increased pain after this fall, she was hospitalized on [redacted]. Study medication was stopped on February 17. She became bacteremic (thought due to a urinary tract source)and hypotensive, requiring transfer to the ICU and antibiotics.	sepsis and disease progression. NOTE: The Serious Adverse Experience Report dated April 26, 2000 changed the judged relationship of the fall to "Suspected". However, the adverse event listings (e.g. Appendix 10.3 in the ISS) list the judged relationship of "Fall" to study drug as "unlikely". The reason for this discrepancy is not clear.
EN3202-017-014-001	59/M/C	Lung cancer, COPD, and multiple other medical problems	Patient began oxymorphone ER on March 6, 2000. He was hospitalized on [redacted] for non-healing skin ulcers and cellulitis, and treated with antibiotic with some improvement. The last dose of study drug was given on June 17.	The patient died [redacted] of progressive disease.
EN3202-017-014-002	53/M/C	Pharyngeal carcinoma with mouth and throat metastases.	Patient began oxymorphone ER on March 13, 2000. Last dose of study medication was on September 13.	Patient died on [redacted] The Medical Examiner's Death Certificate noted coronary artery disease as the cause of death. No prior cardiac history other than hypertension.
EN3202-017-015-003	48/F/C	Pancreatic cancer	The patient began oxymorphone ER on February 22, 2000. On [redacted] she was found unresponsive and taken to a hospital, where a cerebrovascular accident (left-sided paralysis)and hyperglycemia (blood glucose=470 mg/dL) were noted. Study medication was stopped. Severe carotid stenosis was noted, as were cardiac left ventricular hypertrophy and sinus tachycardia. On [redacted] she developed a brainstem stroke.	The patient died [redacted] The narrative notes that the autopsy determined that the cause of death was a stroke. The adverse event listing notes that coronary artery disease was found at autopsy, and lists this as the adverse event resulting in death. The adverse event (reported term) 'Fatal stroke – brain stem' has an outcome of 'unknown' and not 'death'.
EN3202-017-016-016	53/F/C	Ovarian cancer	The patient began oxymorphone ER on July 6, 2000. Clinical course was complicated by PICC line and Port-A-Cath site infections in November 2000. On November 6, 2000, pelvic metastases were noted along with bilateral hydronephrosis. Nausea, vomiting, and dehydration necessitated re-admission on [redacted]. Esophageal ulcerations were noted. There was concern over bowel obstruction.	The patient was discharged to home hospice care on [redacted]. She died on [redacted]. The cause of death was determined to be ovarian cancer.
EN3202-021				
EN3202-019-050-001	72/M/C	Non-small cell lung cancer with underlying chronic obstructive pulmonary disease (COPD)	Clinical course complicated by deep vein thrombosis (DVT) and pulmonary embolus August 29, 2001), COPD exacerbation (September 6-October 9), recurrent DVT (September 26), falling and dehydration (October 5), brain metastases, and coumadin-related coagulopathy.	He died on [redacted] of progressive disease.
EN3202-019-056-001	64/M/C	Metastatic colon cancer	Clinical course complicated by progression of liver metastases, resulting in "being almost comatose". Some confusion, but no other adverse events , were considered "possibly" related to study drug.	He did of progressive disease [redacted]
EN3202-019-060-002	79/F/C	Adenocarcinoma of unknown origin with metastases to liver	She received chemotherapy, but refused other forms of treatment. She was receiving palliative care via hospice at study entry.	She died about six weeks after study entry of progressive disease.
EN3202-019-060-003	61/M/C	Esophageal cancer, treated with surgery,	Clinical course complicated by pulmonary embolus, left-sided pleural effusion, asymptomatic	Patient died suddenly at home, after electing only palliative

Table. Summary of Patients Who Died During Open-Label Extension Clinical Trials in the Oxymorphone Clinical Development Program Whose Death Was Judged to be Unlikely Related to Study Drug

Protocol Patient ID	A/G/R	Underlying Cancer Information	Description of Selected Adverse Events	Reviewer Comments
		radiation therapy, and radiation therapy	ventricular tachycardia, and coumadin-related coagulopathy	care. No autopsy was performed. There was clinical concern that he may have had a pulmonary embolus.
EN3202-019-067-002	48/F/C	Breast cancer metastatic to brain, lung, liver, and bone, treated with chemotherapy and radiation therapy	Patient began open-label oxymorphone ER 10 mg po bid on September 18, 2001. On March 12, 2002, she developed progressive shortness of breath, and was found to have progression of pulmonary metastases. She opted for palliative care, switched from oral oxymorphone ER to morphine sulfate infusions for pain.	She died on [redacted] of progressive disease.
EN3202-019-067-012	77/M/C	Renal cell carcinoma metastatic to back, lung, and hypopharynx, treated with chemotherapy and radiation therapy	Prior clinical course complicated by T11 lytic lesion and paraplegia. He began study medication on December 7, 2002, at a dose of oxymorphone ER 10 mg po bid and oxymorphone IR tables 5 mg 2-3 times per day. On December 17, his family noted some confusion, judged by the investigator to be probably related to study drug. Dehydration and hyperkalemia were treated. Progressive metastatic pulmonary disease was noted. On December 18, his renal function deteriorated (creatinine=2.9). e was discharged to home on [redacted].	The patient died on [redacted] of advanced renal cancer. The Sponsor notes that the deteriorating renal function may have lead to accumulation of oxymorphone or its metabolites, which could in turn have resulted in confusion.
EN3202-019-067-013	77/M/C	Stage IV non-Hodgkin's lymphoma, treated with chemotherapy	Patient had a history of atherosclerotic heart disease. Patient entered open-label study on December 2001. Last dose of study drug was March 14, 2002.	The patient died of a "massive heart attack" (per narrative) on [redacted], attributed to his concurrent cardiac disorder and lymphoma.
EN3202-019-067-014	52/F/C	Hepatocellular carcinoma treated with chemotherapy	Patient had pain due to malignancy-related hepatic congestion. She entered the open-label study on December 24, 2001 on oxymorphone ER 20 mg po bid. She was admitted to the hospital on August 4, 2002 for management of increasing pain and hospice care, with decreasing oral intake. Jaundice was noted. The last dose of study drug was on August 4, 2002.	She died on [redacted] of progressive disease.
EN3202-019-067-016	60/F/C	Metastatic lung cancer to brain, treated with radiation therapy	Patient entered open-label study on January 11, 2002. On February 25, she developed increasing pain, and stopped study medication. She was switched to morphine. Two days later, brain metastases were noted.	She died on [redacted], of progressive disease, about one month after stopping study medication.
EN3202-019-069-003	64/F/C	Metastatic small cell lung cancer	Patient entered the open-label study on December 3, 2001. On May 1, 2020, she developed increasing pain, due to bone metastases. Her last dose of study medication was on June 13, 2002, when she was switched to Duragesic patch and morphine. Her condition deteriorated further, resulting in jaundice and thrombocytopenia.	She died on [redacted] due to metastatic lung cancer progression.
EN3202-019-071-004	57/M/C	Non-small cell lung cancer treated with chemotherapy	Patient entered open-label study on April 11, 2002 taking oxymorphone ER 30-60 mg po bid and was receiving second-line chemotherapy with taxotere. Clinical course was complicated by a right internal jugular venous thrombosis (June 3) and atrial fibrillation (June 9). On August 6 he developed mental status changes. Brain metastases were found and he was treated with cranial radiation. Mental status changes recurred and dehydration developed (August 19). He was given intravenous fluids and steroids, with improvement. Decreased level of consciousness again recurred (August 24) and it was decided he would be treated only with comfort measures (August 26).	He died on [redacted] due to brain metastases.
EN3202-019-074-001	64/M/C	Rectal cancer metastatic to liver and lungs, treated with chemotherapy.	He began open-label study medication on March 26, 2002. In the one month prior to this, his metastatic cancer had progressed. He was referred for hospice	He died on [redacted] of metastatic cancer progression.

Table. Summary of Patients Who Died During Open-Label Extension Clinical Trials in the Oxymorphone Clinical Development Program Whose Death Was Judged to be Unlikely Related to Study Drug

Protocol Patient ID	A/G/R	Underlying Cancer Information	Description of Selected Adverse Events	Reviewer Comments
			care on April 8, received his last dose of study medication on April 10, and was transferred to hospice on April 11.	
EN3202-022				
EN3202-018-011-007	63/F/C	Lung cancer with liver metastases, lower back pain, upper back metastases to shoulder and right hip.	Required increase in dose from 20 mg /day at study entry to 60 mg/day due to increasing pain 37 days after study entry, she discontinued due to lack of efficacy and disease progression.	She died [redacted] after discontinuing study medication.
EN3202-018-018-002	57/F/C	Esophageal cancer with adrenal and lung metastases	Multiple AEs related to underlying cancer and to opioid-related events (constipation, sedation, nausea, and vomiting). She required increasing doses of study medication.	She died [redacted] after discontinuing study medication
EN3202-018-018-004	53/F/C	Breast cancer with skin metastases	Multiple AEs related to underlying cancer and to opioid-related events (e.g., constipation, nausea, vomiting, sedation, dizziness, and pruritus). She required increasing doses of study medication.	She died [redacted] after discontinuing study medication.

Source: Appendix 2, Listing 7 in the 120-Day Safety Update and the Patient Narratives

For six patients who died in the open-label extension clinical trials, the investigator judged at least one adverse event whose outcome was death as "possibly" or "probably" related to the study drug, oxymorphone ER.

Patient EN3202-017-008-006, a 69-year-old man with primary lung carcinoma with liver metastases, as well as renal and adrenal gland carcinoma (possibly metastatic from the lung primary) treated with chemotherapy, right lung lobe resection, right nephrectomy and right adrenal gland removal, as well as coronary artery disease, began oxymorphone ER on May 5, 2000. The last dose of study drug was administered on May 28, 2000. On that day, he was admitted to the hospital for nausea and vomiting and abdominal pain. He was thought to have pancreatitis. A CT scan the next day revealed diffuse metastases within the liver, pelvic ascites, and a pancreatic mass, possibly tumor or a pseudocyst. On June 6, fluid was drained from the right pleura, but it recurred by June 8. Mild diffuse interstitial lung disease was noted at that time. On June 9, he was transferred to a nursing unit for pain control and comfort measures. He died on [redacted]. The death was attributed to disease progression. The investigator judged the hematemesis and nausea as "possibly" related to study drug. The abdominal pain, pancreatitis, and disease progression, however, were judged to be "unlikely" related to study drug.

Patient EN3202-018-018-002, a 58-year old Caucasian woman with esophageal cancer with adrenal and lung metastases, gastroesophageal reflux (GERD) and hiatal hernia, Raynaud's syndrome, difficulty walking secondary to leg edema, bronchitis, bronchospasm, and sarcoidosis entered the open-label study on June 8, 2001. Multiple AEs related to underlying cancer and to opioid-related events (constipation, sedation, nausea, and vomiting, all of which were judged to be probably related to study medication). She required increasing doses of study medication. On July 30, she developed abdominal pain, judged to be possibly related to study medication. It is not clear if she was treated for this pain. This event was recorded as ongoing at the time of her death, and is also listed as an adverse event whose outcome was death. On August 1, she developed blurred vision, judged to be unlikely related to study medication. Progressive esophageal carcinoma was diagnosed on August 27. She then developed anemia (august 30), discontinued study medication (September 2), and died from progression of her cancer on [redacted].

Patient EN3202-018-018-004, a 53-year-old Caucasian woman with breast cancer, who had a history of multiple medical problems, entered the open-label study on June 22, 2001 taking oxymorphone ER 20 mg po bid. She developed multiple opioid-related adverse events (constipation, nausea, vomiting, sedation, dizziness, and pruritus, all of which were judged to be probably related to study drug). On August 21, she

developed severe pain, for which she was given Vioxx (rofecoxib) 50 mg orally. On October 3, she was reported to have moderate progression of her skin metastases. On October 11, she developed hypoesthesia of her feet associated with lymphedema, for which she was given prednisone 5 mg and levofloxacin for prevention of infection. On October 15, her study mediation was increased to 50 mg po q 12 h. On October 23, she discontinued study medication due to disease progression, and switched to morphine sulfate and methadone. She died of progression of her cancer on [redacted] after discontinuing study medication. The pain was listed as an adverse event that was probably related to study drug (the rationale for this determination is not stated) whose outcome was death.

Patient EN3202-019-056-001, a 64-year-old man with colon cancer and multiple other medical problems entered the open-label study on May 31, 2001 taking oxymorphone ER 40 mg po bid. Two weeks earlier, on May 17, he was found to have increasing liver function tests, interpreted by his physician as a progression of liver metastases. On May 21 he developed confusion. On June 3, he became progressively weaker, anxious, and had increased bronchial secretions. By June 6, he was "almost comatose", but did squeeze a hand to command. The confusion was judged to be possibly related to study medication and was listed as an adverse event whose outcome was death. He died [redacted].

Patient EN3202-019-060-002, a 79-year-old Caucasian woman with advanced adenocarcinoma of unknown primary with liver metastases. She received chemotherapy, but refused other therapies for this cancer. She also had a history of coronary artery disease and hypothyroidism., and was on multiple medications. At study entry on July 26, she was under hospice care receiving palliative therapy for pain and other symptoms secondary to chemotherapy. She received oxymorphone ER 60 mg po bid form July 26 until her death from metastatic progression of disease [redacted]. Bilateral flank pain and neurogenic bladder are two adverse events that were judged to possibly related tot study drug whose outcome was listed as death.

Patient EN3202-019-067-012, a 77-year-old Caucasian man with metastatic renal cell carcinoma to the back, lung and hypopharynx, had received chemotherapy and radiation therapy for his cancer. He also had a lytic lesion at T11 and was paraplegic. He began study medication on December 7, 2002, at a dose of oxymorphone ER 10 mg po bid and oxymorphone IR tables 5 mg 2-3 times per day. On December 17, his family noted some confusion, judged by the investigator to be probably related to study drug. Dehydration and hyperkalemia were treated. Progressive metastatic pulmonary disease was noted. On December 18, his renal function deteriorated (creatinine=2.9). e was discharged to home[redacted]. The patient died [redacted] of advanced renal cancer. The Sponsor notes that the deteriorating renal function may have lead to accumulation of oxymorphone or its metabolites, which could in turn have resulted in confusion. The confusion was listed as an adverse event that was judged to be probably related to study drug and whose outcome was death.

Review of all of the deaths supports the conclusion that the deaths in the 34 subjects with cancer were related to progression of the underlying disease. While some of the subjects with cancer had adverse events judged by the investigator to be possibly or probably related to study medication which then had death as an outcome, a careful review of the narratives and the other information in the study database indicates that these events were not the cause of death. In each of these cases, the available information indicates that the cause of death was the progression of the underlying cancer. The single subject without cancer who died appears to have died of cardiac disease (ventricular hypertrophy) though there are few details of his death

1.5.3 Non-fatal Serious Adverse Events

1.5.3.1 Non-fatal Serious Adverse Events in Phase 1 Clinical Trials

1.5.3.2 Non-fatal Serious Adverse Events in Phase 2/3 Clinical Program

The following discussion will summarize the SAE profile for all SAEs in the overall Phase 2/3 clinical trials program, which combines data from the ISS and the 120-Day Safety Update. Data for oxymorphone IR, oxycodone ER, oxycodone IR, morphine ER, and placebo were taken from the ISS. Data for oxymorphone ER were taken from the 120-Day Safety Update. Data for any oxymorphone exposure (ie, either oxymorphone ER or oxymorphone IR) were summarized in the ISS but not in the 120-Day Safety Update (see Appendix 1, Table 9 in the 120-Day Safety Update).

Of the 1089 subjects exposed to oxymorphone ER, 93 (8.5%) had at least one SAE. Of the 368 subjects exposed to oxymorphone IR, 19 (5.16%) has at least one SAE. Rates of at least one SAE in the other treatment groups were as follows: oxycodone ER – 9/382 (2.36%), oxycodone IR – 5/195 (2.56%), morphine ER 6/69 (8.70%), and placebo 14/473 (2.96%) (Appendix 3.143 in ISS and Appendix 1, Table 9 in the120-Day Safety Update). Comparison of rates of subjects with at least one SAE across groups is confounded by the variable durations of individual subject exposure in these groups. In particular, exposure to oxymorphone ER occurred both during controlled trials as well as during the longer duration open-label extension trials.

Among patients in controlled trials for chronic non-malignant pain, 12/684 (1.75%) treated with oxymorphone ER, 4/286 (1.40%) treated with oxycodone ER, and 1/239 (0.35%) treated with placebo developed at least one serious AE (Appendix 3.143 in ISS). Among patients in controlled trials for cancer pain, 3/138 (2.17%) treated with oxymorphone ER, 1/34 (2.94%) treated with oxymorphone IR, 5/96 (5.21%) treated with oxycodone ER, and 6/69 (8.70%) treated with morphine developed at least one serious AE (Appendix 3.143 in ISS). In each of the these two clinical trials subsets, the incidence of at least one serious AE in patients treated with oxymorphone ER was similar to the incidence in the other treatment groups. The generally higher incidence rates in all treatment groups in the cancer pain clinical trials compared to the corresponding rates in the non-malignant pain clinical trials may be due to the underlying disease.

The following table presents the incidence rates of all serious AEs occurring in two or more oxymorphone treated subjects in the overall Phase 2/3 clinical development program.

Table. Incidence of Non-Fatal Serious Adverse Events Occurring in at Least Two Oxymorphone-Treated Subjects in Overall Phase 2/3 Clinical Development Program

	Oxymorphone				Oxycodone			
	ER			IR	ER	IR	Morphine ER	Placebo
MedDRA Preferred Term	ISS*	120-Update*	Overall*	Overall*	Overall*	Overall*	Overall*	Overall*
Number of subjects exposed	1057	235	1089	368	382	195	69	473
Number (%) of subjects with at least one SAE	73 (6.91%)	18 (7.66%)	93 (8.54%)	19 (5.16%)	9 (2.36%)	5 (2.56%)	6 (8.70%)	14 (2.96%)
Vomiting NOS.	5 (0.47%)	2 (0.85%)	8 (0.73%)	0 (0.00%)	1 (0.26%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Chest pain NEC	4 (0.38%)	3 (1.28%)	7 (0.64%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Nausea	3 (0.28%)	2 (0.85%)	6 (0.55%)	0 (0.00%)	1 (0.26%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Dehydration	4 (0.38%)	1 (0.43%)	5 (0.46%)	0 (0.00%)	1 (0.26%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Dyspnoea NOS	3 (0.28%)	1 (0.43%)	5 (0.46%)	1 (0.27%)	1 (0.26%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Abdominal pain NOS	2 (0.19%)	2 (0.85%)	4 (0.37%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Drug interaction NOS	4 (0.38%)	0 (0.00%)	4 (0.37%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Osteoarthritis aggravated	4 (0.38%)	0 (0.00%)	4 (0.37%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Atrial fibrillation	2 (0.19%)	1 (0.43%)	3 (0.28%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.21%)
Back pain	1 (0.09%)	2 (0.85%)	3 (0.28%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Depressed level of consciousness	1 (0.09%)	2 (0.85%)	3 (0.28%)	1 (0.27%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Hypotension NOS	3 (0.28%)	0 (0.00%)	3 (0.28%)	1 (0.27%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Pain in limb	2 (0.19%)	1 (0.43%)	3 (0.28%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.21%)
Pneumonia NOS	2 (0.19%)	1 (0.43%)	3 (0.28%)	1 (0.27%)	1 (0.26%)	1 (0.51%)	0 (0.00%)	1 (0.21%)
Urinary retention	3 (0.28%)	0 (0.00%)	3 (0.28%)	1 (0.27%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Urinary tract infection NOS	3 (0.28%)	0 (0.00%)	3 (0.28%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Venous thrombosis deep limb	3 (0.28%)	0 (0.00%)	3 (0.28%)	3 (0.82%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.21%)
Arthralgia	0 (0.00%)	2 (0.85%)	2 (0.18%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.21%)
Cellulitis	2 (0.19%)	0 (0.00%)	2 (0.18%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Central nervous system depression NOS	2 (0.19%)	0 (0.00%)	2 (0.18%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Cerebrovascular accident NOS	2 (0.19%)	0 (0.00%)	2 (0.18%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Chronic obstructive airways disease exacerbated	2 (0.19%)	0 (0.00%)	2 (0.18%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.45%)	0 (0.00%)
Concomitant disease progression	1 (0.09%)	1 (0.43%)	2 (0.18%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Confusion	2 (0.19%)	0 (0.00%)	2 (0.18%)	1 (0.27%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Diarrhoea NOS	1 (0.09%)	1 (0.43%)	2 (0.18%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Gastroenteritis NOS	1 (0.09%)	1 (0.43%)	2 (0.18%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Hepatic encephalopathy	2 (0.19%)	0 (0.00%)	2 (0.18%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Hypokalaemia	1 (0.09%)	1 (0.43%)	2 (0.18%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Myocardial infarction	2 (0.19%)	0 (0.00%)	2 (0.18%)	3 (0.82%)	0 (0.00%)	1 (0.51%)	0 (0.00%)	0 (0.00%)
Pain exacerbated	0 (0.00%)	2 (0.85%)	2 (0.18%)	N/A^	N/A	N/A	N/A	N/A
Pancreatitis NOS	2 (0.19%)	0 (0.00%)	2 (0.18%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Pulmonary embolism	1 (0.09%)	1 (0.43%)	2 (0.18%)	0 (0.00%)	1 (0.26%)	1 (0.51%)	0 (0.00%)	0 (0.00%)
Pyrexia	1 (0.09%)	1 (0.43%)	2 (0.18%)	1 (0.27%)	0 (0.00%)	1 (0.51%)	1 (1.45%)	0 (0.00%)
Respiratory failure (exc neonatal)	1 (0.09%)	1 (0.43%)	2 (0.18%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Somnolence	2 (0.19%)	0 (0.00%)	2 (0.18%)	1 (0.27%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.21%)

*Data for oxymorphone are presented based on analyses of the original ISS data (ISS), the 120-Day Safety Update data (120 Update),and the combined data (Overall). Data for the other treatment groups are from the ISS. Since there were no new data for these treatment groups, they correspond to the overall data for these treatment groups.

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

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

Review of the above table is notable for the fact that no single adverse event occurred more frequently than 0.73% of oxymorphone ER-treated subjects in the overall dataset. The following analysis of serious AEs will focus on the overall data, with limited attention to differences between the ISS and the 120-Day Safety Update.

The most common serious AE in oxymorphone- ER-treated subjects was vomiting. A total of 9 subjects developed at least one serious non-fatal case of vomiting in the Phase 2/3 clinical trial program. Eight of these subjects developed the vomiting while taking oxymorphone ER, while the ninth subject developed it while taking oxycodone ER. This subject (EN3202-017-008-006) also had a serious AE of vomiting while on oxymorphone ER but this case was associated with death (see section on Deaths above) and is therefore not represented in the count of non-fatal cases of vomiting in oxymorphone- ER-treated subjects.

Table. Summary of Non-Fatal Serious Adverse Events of Vomiting

Source	Subject ID/ Protocol	Age/ Gender/ Race	AE Verbatim Name	Treatment/ Dose (mg)	AE Onset Date/ AE End Date	Severity/ Relationship/ Action Taken/ Outcome	Reviewer Comments
ISS	EN3202-015-075-010/ EN3202-015	53/M/B	Vomiting	Oxymorphone ER/ 40	24MAR00/ 28MAR00	Severe/ Unlikely/ ./ Unknown	Patient had OA and depression. Vomiting resulted in hyopnatremia (116 meEq/L), hypokalemia (2.4 mEq/L), and hypochloremia (116 mEq/L). Required hospitalization dehydration. Investigator attributed nausea and vomiting to depression.
ISS	EN3202-017-008-006/ EN3202-017	69/M/C	Vomiting	Oxycodone ER/ 80	19APR00/ 19APR00	Mild/ Possibly/ ./ Resolved w/sequelae	Patient began oxycodone ER on April 17. Two days later nausea and vomiting began. Not known if action was taken, but event resolved that day. Judged possible related to study drug.
ISS	EN3202-017-008-006/ EN3202-017	69/M/C	Vomiting	Oxycodone ER/ 80	21APR00/ 28APR00	Severe/ Unlikely/ ./ Resolved w/sequelae	This episode of nausea and vomiting developed one day after starting carboplatin and Taxol. Dehydration and fecal impaction required hospitalization. Judged to be unlikely related to study drug.
ISS	EN3202-017-010-001/ EN3202-020	56/M/C	Protracted vomiting	Oxymorphone ER/ 40	20MAY00/ 26MAY00	Severe/ Unlikely/ ./ Resolved w/sequelae	Patient required hospitalization for protracted vomiting, diarrhea, dehydration, and hypokalemia (level not reported) about 4 months after beginning oxymorphone ER and IR treatment and about one week after receiving Lupron treatment. Required Inapsine and Reglan.
ISS	EN3202-017-016-016/ EN3202-020	53/F/C	Vomiting NOS	Oxymorphone ER/ 80 (post-treatment)	08DEC00/ 19DEC00	Severe/ Unlikely/ ./ Resolved w/sequelae	Associated with pelvic metastases, which resulted in death. See narrative under Deaths above.
Update	EN3202-018-005-005/ EN3202-022	44/F/C	Vomiting	Oxymorphone ER/ 80	05JAN02/ 08JAN02	Severe/ Unlikely/ None/ Resolved w/o sequelae	Vomiting was attributed recent steroid use for brain metastases. She stopped study drug for three days, and then resumed it without further SAEs.
Update	EN3202-018-008-001/ EN3202-022	51/F/C	Vomiting	Oxymorphone ER/ 60	15MAY01/ 16MAY01	Severe/ Possibly/ None/ Resolved w/o sequelae	Vomiting was associated with dehydration, and required Phenergan. Study drug was temporarily interrupted, but she was able to resume it without further SAEs.
ISS	EN3202-018-008-001/ EN3202-022	50/F/C	Vomiting	Oxymorphone ER/ 60	15MAY01/ 16MAY01	Severe/ Possibly/	See above

Table. Summary of Non-Fatal Serious Adverse Events of Vomiting

Source	Subject ID/ Protocol	Age/ Gender/ Race	AE Verbatim Name	Treatment/ Dose (mg)	AE Onset Date/ AE End Date	Severity/ Relationship/ Action Taken/ Outcome	Reviewer Comments
						None/ Resolved w/o sequelae	
ISS	EN3202-018-025-001/ EN3202-018	65/F/C	Vomiting	Oxymorphone ER/ 0	04DEC01 /04DEC01	Severe/ Unlikely/ None/ Continuing	Symptoms of nausea, vomiting, and hepatic encephalopathy developed 2 days after stopping oxymorphone ER
Update	EN3202-019-071-001/ EN3202-021	57/F/B	Vomiting	Oxymorphone ER/ 80	06FEB02/ 08FEB02	Mild/ Unlikely/ None/ Resolved w/o sequelae	Vomiting developed after receiving Baro CAT, a contrast medium for CT scanning. Symptoms resolved with intravenous hydration, and she was able to continue on study drug.
Update	EN3202-019-071-003/ EN3202-021	46/F/B	Vomiting	Oxymorphone ER/ 80	30AUG02/ 13SEP02	Moderate/ Unlikely/ None/ Resolved w/o sequelae	This episode of vomiting was associated with nausea and shortness of breath. She had a left pleural effusion, requiring thoracentesis. Nausea and vomiting were treated symptomatically and with intravenous fluids.
Update	EN3202-019-071-003/ EN3202-021	46/F/B	Vomiting	Oxymorphone ER/ .	15OCT02/ 04NOV02	Moderate/ Unlikely/ None/ Resolved w/o sequelae	Intractable nausea and vomiting occurred after chemotherapy

Source: Appendix 10.6 in the ISS and Appendix 2, Listing 6 in the 120-Day Safety Update and Patient Narratives

Review of the above table indicates that certain cases of vomiting are associated with dehydration and electrolyte disorders, especially in patients treated with chemotherapy for the underlying cancer. In addition, the rationale for the attribution of the nausea and vomiting in Subject EN3202-015-075-010 to depression, and not to the oxymorphone treatment, is not clear. Although the judged relationship of some of these events to the vomiting episodes is listed as "unlikely" a contributory role for oxymorphone can not be excluded.

The second most common serious AE in oxymorphone- ER-treated subjects was chest pain. A total of 7 subjects developed at least one serious non-fatal case of chest pain in the Phase 2/3 clinical trial program, each of whom was taking oxymorphone ER. The table below summarizes these cases.

Table. Summary of Non-Fatal Serious Adverse Events of Chest Pain

Source	Subject ID/ Protocol	Age/ Gender/ Race	AE Verbatim Name	Treatment/ Dose (mg)	AE Onset Date/ AE End Date	Severity/ Relationship/ Action Taken/ Outcome	Reviewer Comments
ISS	EN3202-015-016-004/ EN3202-020	71/M/C	Atypical chest pain	Oxymorphone ER/ 40	03APR00/ 07APR00	Severe/ Unlikely/ ./ Resolved w/sequelae	Patient discontinued oxymorphone ER on March 30 because of vomiting. On [redacted] he developed chest pressure with left arm radiation and blurred vision. He was hospitalized. Myocardial infarction was ruled out based on normal cardiac enzymes and EKG. Chest pain was attributed to costochondritis.
Update	EN3202-015-064-023/ EN3202-020	68/F/C	Chest pain	Oxymorphone ER/ 40	04APR02/ 05APR02	Severe/ Unlikely/ ./ .	Patient reported that a prior cardiac catheterization revealed an 80% stenosis. Chest pain developed with elevated blood pressure (212/106), and was relieved with nitroglycerin. ECG, CPK, and troponin did not suggest an acute MI, though she was felt to have angina.
ISS	EN3202-015-069-005/ EN3202-020	73/F/C	Intermittent chest pain	Oxymorphone ER/ 59	22MAR00/ 23MAR00	Mild/ Unlikely/ ./ Resolved w/o sequelae	Patient was diagnosed with coronary artery disease in [redacted], about one month after starting oxymorphone ER. About [redacted] later, she was admitted tot he hospital with acute chest pain. It is not clear from the narrative if a new MI was diagnosed, though EKG showed an old MI. Anti-anginal medications were adjusted. She continued on study medication for another 9 months.
ISS	EN3202-016-007-002/ EN3202-016	45/M/C	Chest pain	Oxymorphone ER/ 10	19APR01/ 19APR01	Moderate/ Possibly/ Study drug discontinued/ Resolved w/o sequelae	Patient developed chest pain after the first dose of oxymorphone ER 10mg on the first day of titration, along with abdominal pain and diaphoresis. He was hospitalized. Where increased CPK and CPK-MB were noted (values not reported), which resolved the next day. He discontinued study medication, and al symptoms resolved. No specific diagnosis was made. The investigator attributed the chest pain and increased CPK as possibly related to study drug.
ISS	EN3202-016-010-001/ EN3202-021	73/M/C	Chest pain	Oxymorphone ER/100	14MAY01/ 16MAY01	Severe/ Unlikely/ ./ Resolved w/o sequelae	An extensive cardiac evaluation, including a normal cardiac angiogram, was performed. A cardiac etiology was ruled out.
Update	EN3202-016-021-025/ EN3202-021	38/M/C	Chest pain	Oxymorphone ER/160	30JUN02/ 30JUN02	Severe/ Possibly/ None/ Resolved w/o sequelae	Chest pain occurred with minimal activity and no vigorous exertion. ECG, and CXR revealed no active cardiopulmonary disease. Other cardiac testing, not specified in

Table. Summary of Non-Fatal Serious Adverse Events of Chest Pain

Source	Subject ID/ Protocol	Age/ Gender/ Race	AE Verbatim Name	Treatment/ Dose (mg)	AE Onset Date/ AE End Date	Severity/ Relationship/ Action Taken/ Outcome	Reviewer Comments
							the narrative, was negative for coronary artery disease. A cardiac etiology was ruled out. Symptoms resolved. Although the event was judged to be possibly related to study drug, he was able to continue study drug,.
Update	EN3202-019-071-002/ EN3202-021	36/F/B	Chest pain	Oxymorphone ER/200	11JUL02/ 19JUL02	Moderate/ Unlikely/ None/ Resolved w/o sequelae	Right-sided chest wall pain was associated with right upper quadrant abdominal pain. Hepatomegaly was noted. Events were attributed to metastatic colon cancer.

Source: Appendix 10.6 in the ISS and Appendix 2, Listing 6 in the 120-Day Safety Update and Patient Narratives

The case of chest pain with elevated CPK and CPK-MB in subjects EN3202-016-007-002 is lacking in many details, and thus a causal relationship of these events to oxymorphone ER can not be excluded. Overall, these chest pain events comprise a diverse group of events (cardiac events, probable musculoskeletal events, and pain related to metastatic cancer). These heterogeneous events can be expected in the heterogeneous patient population in the oxymorphone clinical development program.

The third most common serious AE in oxymorphone ER-treated subjects was nausea. A total of 6 oxymorphone ER-treated subjects and one oxycodone ER-treated subject developed at least one serious non-fatal case of nausea in the Phase 2/3 clinical trial program, each of whom was taking oxymorphone ER. The table below summarizes these cases.

Table. Summary of Non-Fatal Serious Adverse Events of Nausea

Source	Subject ID/ Protocol	Age/ Gender/ Race	AE Verbatim Name	Treatment/ Dose (mg)	AE Onset Date/ AE End Date	Severity/ Relationship/ Action Taken/ Outcome	Reviewer Comments
ISS	EN3202-015-075-010/ EN3202-015	53/M/B	Nausea	Oxymorphone ER/ 40	24MAR00/ 01APR00	Severe/ Unlikely/ ./ Unknown	Patient had OA and depression. Vomiting resulted in hyopnatremia (116 meEq/L), hypokalemia (2.4 mEq/L), and hypochloremia (116 mEq/L). Required hospitalization dehydration. Investigator attributed nausea and vomiting to depression.
ISS	EN3202-017-008-006/ EN3202-017	69/M/C	Nausea	Oxycodone ER/ 80	19APR00/ 19APR00	Mild/ Possibly/ ./ Resolved w/sequelae	Patient began oxycodone ER on April 17. Two days later nausea and vomiting began. Not known if action was taken, but event resolved that day. Judged possible related to study drug.
ISS	EN3202-017-008-006/ EN3202-017	69/M/C	Nausea	Oxycodone ER/ 80	21APR00/ 28APR00	Severe/ Unlikely/ ./ Resolved w/sequelae	This episode of nausea and vomiting developed one day after starting carboplatin and Taxol. Dehydration and fecal impaction required hospitalization. Judged to be unlikely related to study drug.
ISS	EN3202-017-016-016/ EN3202-020	53/F/C	Nausea	Oxymorphone ER/ 80 (post-treatment)	08DEC00/ 19DEC00	Severe/ Unlikely/ ./	Associated with pelvic metastases, which resulted in death. See narrative under

Table. Summary of Non-Fatal Serious Adverse Events of Nausea

Source	Subject ID/ Protocol	Age/ Gender/ Race	AE Verbatim Name	Treatment/ Dose (mg)	AE Onset Date/ AE End Date	Severity/ Relationship/ Action Taken/ Outcome	Reviewer Comments
						Resolved w/sequelae	Deaths above.
Update	EN3202-018-005-005/ EN3202-022	44/F/C	Nausea	Oxymorphone ER/ 80	05JAN02/ 08JAN02	Severe/ Unlikely/ None/ Resolved w/o sequelae	Nausea and vomiting were attributed recent steroid use for brain metastases. She stopped study drug for three days, and then resumed it without further SAEs.
ISS	EN3202-018-025-001/ EN3202-018	65/F/C	Nausea	Oxymorphone ER/ 0	04DEC01/ 04DEC01	Severe/ Unlikely/ None/ Continuing	Symptoms of nausea, vomiting, and hepatic encephalopathy developed 2 days after stopping oxymorphone ER
Update	EN3202-019-071-001/ EN3202-021	57/F/B	Nausea	Oxymorphone ER/ 80	06FEB02/ 08FEB02	Mild/ Unlikely/ None/ Resolved w/o sequelae	Nausea and vomiting developed after receiving Baro CAT, a contrast medium for CT scanning. Symptoms resolved with intravenous hydration, and she was able to continue on study drug.
Update	EN3202-019-071-003/ EN3202-021	46/F/B	Nausea	Oxymorphone ER/ 80	30AUG02/ 13SEP02	Moderate/ Unlikely/ None/ Resolved w/o sequelae	This episode of nausea and vomiting were associated with shortness of breath. She had a left pleural effusion, requiring thoracentesis. Nausea and vomiting were treated symptomatically and with intravenous fluids.

Source: Appendix 10.6 in the ISS and Appendix 2, Listing 6 in the 120-Day Safety Update and Patient Narratives

Review of the above table indicates that the serious cases of nausea were diverse in origin, and were often associated with the underlying disease The rationale for the investigator's attribution of nausea and vomiting to depression in Subject NE3202-015-075-010 is not clear.

Serious adverse events of dehydration and dyspnea each occurred in five oxymorphone ER-treated subjects. These cases are summarized below.

Table. Summary of Non-Fatal Serious Adverse Events of Dehydration

Source	Subject ID/ Protocol	Age/ Gender/ Race	AE Verbatim Name	Treatment/ Dose (mg)	AE Onset Date/ AE End Date	Severity/ Relationship/ Action Taken/ Outcome	Reviewer Comments
ISS	EN3202-015-075-010/ EN3202-015	53/M/B	Nutritional dehydration	Oxymorphone ER/ 20	27MAR00/ 04APR00	Severe/ Unlikely/ ./ Unknown	Patient had OA and depression. Vomiting resulted in hyopnatremia (116 meEq/L), hypokalemia (2.4 mEq/L), and hypochloremia (116 mEq/L). Required hospitalization dehydration. Investigator attributed nausea and vomiting to depression.
ISS	EN3202-017-008-006/ EN3202-017	69/M/C	Dehydration	Oxycodone ER/ 80	21APR00/ 28APR00	Severe/ Unlikely/ ./ Resolved w/sequelae	This episode of nausea and vomiting developed one day after starting carboplatin and Taxol. Dehydration and fecal impaction required hospitalization. Judged to be unlikely related to study drug.
ISS	EN3202-017-010-001/ EN3202-020	56/M/C	Dehydration	Oxymorphone ER/ 40	20MAY00/ 26MAY00	Moderate/ Unlikely/ ./	Patient required hospitalization for protracted vomiting, diarrhea, dehydration, and