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
						Unknown	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	Dehydration	Oxymorphone ER/ 80 (post-treatment)	08DEC00/ 19DEC00	Severe/ Unlikely/ ./ Resolved w/o sequelae	Associated with pelvic metastases, which resulted in death. See narrative under Deaths above.
Update	EN3202-018-008-001/ EN3202-022	50/F/C	Dehydration	Oxymorphone ER/ 60	17MAY01/ 17MAY01	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.
Update	EN3202-019-071-004/ EN3202-021	57/M/C	Dehydration	Oxymorphone ER/ 120	19AUG02/ 23AUG02	Moderate/ Unlikely/ None/ Resolved w/o sequelae	This event of dehydration was associated with brain metastases, confusion, and a decreased level of consciousness (arousable to verbal stimuli.) Symptoms improved with intravenous fluids and steroids.
Update	EN3202-019-071-004/ EN3202-021	57/M/C	Dehydration	Oxymorphone ER/ 120	26AUG02/ 30AUG02	Moderate/ Unlikely/ None/ Resolved w/o sequelae	Dehydration was associated with a markedly decreased level of consciousness (which may be related to brain metastases, but it not specifically mentioned in the narrative), which responded to intravenous fluids and steroids.

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 suggests that serious cases of dehydration were often associated with vomiting, and were often related to complications of the underlying disease.

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

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	EN3202-015-019-008/ EN3202-015	58/F/C	Shortness of breath	Oxymorphone ER/ 40	12OCT99/ 14OCT99	Severe/ Unlikely/ ./ Unknown	Patient had prior history of shortness of breath and bronchospasm. Current episode required hospitalization and was treated with Albuterol inhaler. Judged to be unlikely related to study drug.
ISS	EN3202-017-008-001/ EN3202-020	67/M/C	Dyspnoea NOS	Oxymorphone ER/280	28DEC00/ 05JUL01	Moderate/ Unlikely/ ./ Resolved w/sequelae	Patients had metastatic lung carcinoma. Dyspnea occurred in the setting of left subclavian and axillary vein thrombosis, fever, and radiation dermatitis. Dyspnea was treated with guaifenesin and Tussionex, and was judged to be unrelated to study drug.
ISS	EN3202-019-050-001/ EN3202-021	72/M/C	Dyspnea	Oxymorphone ER/ 40	23JUL01/ 01OCT01	Moderate/ Unlikely/	Patient had non-small cell lung cancer. Dyspnea attributed to

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

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/o sequelae	deep venous thrombosis and pulmonary embolus.
Update	EN3202-019-060-003/ EN3202-021	61/M/C	Shortness of breath	Oxymorphone ER/ 80	18NOV01/ 06DEC01	Life Thr/ Unlikely/ None/ Resolved w/o sequelae	Patient had esophageal cancer. Shortness of breath was attributed to a pulmonary embolus and pleural effusion.
ISS	EN3202-019-067-002/ EN3202-019	48/F/C	Shortness of breath	Oxycodone ER/ 40	14SEP01/ 15SEP01	Mild/ Unlikely/ None/ Resolved w/o sequelae	Patient had breast cancer with metastases to brain, liver, and bone. Reason for dyspnea is not clear from the narrative, but she recovered and continued to take study medication.
Update	EN3202-019-067-002/ EN3202-021	48/F/C	Shortness of breath	Oxymorphone ER/ 40	12MAR02/ 15MAR02	Life Thr/ Unlikely/ Study drug discontinued/ Death	Patient had breast cancer with metastases to brain, liver, and bone. This episode of shortness of breath was associated with progression of pulmonary metastases
Update	EN3202-019-071-001/ EN3202-021	57/F/B	Shortness of breath	Oxymorphone ER/ 80	26MAR02/ 31MAR02	Moderate/ Unlikely/ None/ Resolved w/o sequelae	Patient had recurrent non-Hodgkin's lymphoma. Shortness of breath occurred after a contrast CT scan, and was associated with bacterial bronchitis.
ISS	EN3203-004-007-005/ EN3203-004	75/M/C	Shortness of breath	Oxymorphone IR/ 40	13APR01/ 13APR01	Moderate/ Possibly/ Study drug discontinued/ Resolved w/o sequelae	Patient had a history of shortness of breath and chronic atrial fibrillation. Narrative suggests that the shortness of breath may have been due to right-sided congestive heart failure and pulmonary hypertension, or alternatively, to myocardial ischemia with acute left-sided heart failure that was treated with Lasix and oxygen..

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

Four serious adverse events of 'Drug Interaction' were reported, all from a single study (EN3202-012).

Table. Summary of Non-Fatal Serious Adverse Events of Drug Interaction

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	EN3202-012-011-004/ EN3202-012	73/F/C	Drug interaction	Oxymorphone ER/ 60	29SEP99/ 01OCT99	Severe/ Probably/ Study drug discontinued/ Unknown	Patient had undergone left knee arthroplasty [redacted]. [redacted] PCA morphine was stopped at 5:00 am on September 29. Oxymorphone ER 60 mg was given at 9:00. Rescue doses of 0.3 mg PCA oxymorphone were given 1.5 and 2 hours later. By 11:00 am, the patient was disoriented and confused. All PCA and narcotics were stopped at 3:00 PM. The study blind was broken (pt. was taking oxymorphone ER 60 mg).
ISS	EN3202-012-011-023/ EN3202-012	71/M/C	Drug interaction	Oxymorphone ER/ 20	22FEB00/ 22FEB00	Severe/ Probably/	Patient underwent right knee arthroplasty [redacted].

Table. Summary of Non-Fatal Serious Adverse Events of Drug Interaction

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
						Study drug discontinued/ Unknown	PCA morphine was stopped at 5:00 am on February 22. He was randomized to oxymorphone ER 20 mg, and received a single dose. He received seven doses of rescue medication (0.3 mg PCA oxymorphone iv) between 7:45 am and 1:47 PM. He developed severe lethargy "barely ...able to answer simple questions"), supraventricular tachycardia, and hypotension (as low as 88/51). Patient was withdrawn from the study, and administered Narcan, with substantial, though not complete, resolution of mental status changes.
ISS	EN3202-012-018-002/ EN3202-012	65/M/C	Drug interaction	Oxymorphone ER/ 20	06JUL00/ 06JUL00	Moderate/ Probably/ Study drug discontinued/ Unknown	Patient underwent right knee arthroplasty [redacted]. He was randomized to oxymorphone ER 20 mg, and received a single dose. He received ten doses of rescue medication (0.2 mg PCA oxymorphone iv) between 10:47 am and 7:00 PM. He developed severe sedation with respiratory acidosis and depressed oxygen saturation. Patient was withdrawn from the study, and administered Narcan, with gradual improvement and resolution of each of the serious adverse events.
ISS	EN3202-012-019-018/ EN3202-012	72/F/C	Drug interaction	Oxymorphone ER/ 20	12JUL00/ 13JUL00	Moderate/ Probably/ Study drug discontinued/ Unknown	Patient with hypertension, mild cardiomyopathy, hyperlipidemia, Type II diabetes mellitus who received a single 20 dose of oxymorphone ER after right knee arthroplasty. She began to feel "hot" and became agitated, with a decline in mental status. Blood glucose levels were high (low 300s). She was given Ativan. A neurologist diagnoses an encephalopathy secondary to medication. The narcotics were held, with improvement in the mental status.

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

In response to the confusion, disorientation, and drug interaction (oxymorphone ER and PCA oxymorphone) in Subject EN3202-012-011-004, the 60 mg oxymorphone ER dose was eliminated from the study (Protocol Amendment 1). Subsequent protocol amendments reduced the PCA oxymorphone dose form 0.3 mg to 0.2 mg (Protocol Amendment 2) and increased the demand dose lock-out period of PCA oxymorphone rescue from six minutes to 10 minutes (Protocol Amendment 3) (See Section 9.8 of Study EN3202-012 Clinical Study Report for full details). Each o the above four cases of "drug interaction" resulted in some form of mental status change. In each of the above cases the investigator judged the relationship of the study medication to the serious AE as "probable". In the cases of subject EN3202-012-019-018, the mental status changes appear to have preceded the Ativan. Of note, each of these cases occurred in the post-operative setting, suggesting that a long-acting oxymorphone in the setting of shorter acting opioid narcotic rescue medications may predispose to encephalopathy.

Non-fatal serious AEs of 'abdominal pain' were reported in four subjects, as outlined in the table below.

Table. Summary of Non-Fatal Serious Adverse Events of Abdominal 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	EN3202-015-037-016/ EN3202-020	64/F/C	Abdominal pain	Oxymorphone ER/ 80	22MAY00/ 04JUN00	Severe/ Unlikely/ ./ Resolved w/o sequelae	Patient took study medication for OA until May 21, 2000. On [redacted] she developed abdominal pain with nausea and vomiting, requiring hospitalization. Upper GI and endoscopy were reported as negative. Viral gastroenteritis was diagnosed. Study medication was resumed on June 6.
ISS	EN3202-016-007-002/ EN3202-016	45/M/C	Abdominal pain	Oxymorphone ER/ 10	18APR01/ 19APR01	Severe/ Probably/ 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 all symptoms resolved. No specific diagnosis was made. The investigator attributed the chest pain and increased CPK as possibly related to study drug. The abdominal pain was judged as probably related to study drug.
Update	EN3202-019-071-002/ EN3202-021	36/F/B	Abdominal pain	Oxymorphone ER/ 80	08APR02/ 14APR02	Severe/ Unlikely /Study drug dose changed/ Resolved w/o sequelae	Right upper quadrant abdominal pain was attributed to colon cancer metastatic to the liver.
Update	EN3202-019-071-002/ EN3202-021	36/F/B	Abdominal pain	Oxymorphone ER/ 160	23JUN02/ 02JUL02	Severe/ Unlikely/ Study drug dose changed/ Resolved w/o sequelae	Right upper quadrant abdominal pain treated with an increase in study medication. Though not mentioned in the narrative, the pain may have been due to colon cancer metastatic to the liver (see episode above)
Update	EN3202-019-071-002/ EN3202-021	36/F/B	Abdominal pain	Oxymorphone ER/ 200	11JUL02/ 11JUL02	Severe/ Unlikely/ None/ Continuing	Right upper quadrant abdominal pain was associated with right chest wall pain, and these were attributed to colon cancer metastatic to the liver.
Update	EN3202-019-071-003/ EN3202-021	46/F/B	Abdominal pain	Oxymorphone ER/ 80	06JUN02/ 10JUN02	Severe/ Unlikely/ None/ Resolved w/o sequelae	This episode of abdominal pain was associated with diarrhea, nausea, vomiting, a low-grade fever, and chills. Symptoms improved with Kao-pectate, Levaquin, and intravenous fluids.
Update	EN3202-019-071-003/ EN3202-021	46/F/B	Abdominal pain	Oxymorphone ER/ .	15OCT02/ 04NOV02	Moderate/ Unlikely/	This episode of upper abdominal pain was attributed

Table. Summary of Non-Fatal Serious Adverse Events of Abdominal 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
						None/ Resolved w/o sequelae	to metastatic renal cell carcinoma. It was associated with nausea and vomiting that 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 suggests that serious cases of abdominal pain were often related to complications of the underlying disease.

Serious AEs of 'osteoarthritis aggravated' were reported in four subjects, as outlined in the table below.

Table. Summary of Non-Fatal Serious Adverse Events of Osteoarthritis Aggravated

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	EN3202-015-020-012/ EN3202-020	50/M/C	Worsening of osteoarthritis	Oxymorphone ER/ 80	26SEP00/ 09OCT00	Severe/ Unlikely/ Study drug discontinued/ Resolved w/o sequelae	Patient had been taking oxymorphone ER 20-40 mg po bid from January 7, 2000 through October 23, 2000. He required right knee arthroplasty on [redacted] because of inability to bear weight. Oxymorphone ER was continued during his hospital stay. However, additional pain medication was required, resulting in mental status deterioration. IV analgesics were stopped, and his mental status improved. He was discharged on [redacted], and study drug was stopped on October 23.
ISS	EN3202-015-021-012/ EN3202-020	52/M/C	Worsening osteoarthritis of left knee	Oxymorphone ER/ 120 (post-treatment)	29NOV00/ 04DEC00	Severe/ Unlikely/ ./ Resolved w/o sequelae	Degenerative osteoarthritis required hospitalization for a right total knee arthroplasty
ISS	EN3202-015-071-006/ EN3202-020	60/F/C	Worsening of osteoarthritis of bilateral hips	Oxymorphone ER/ 40	22JAN01/ 05FEB01	Severe/ Unlikely/ ./ Resolved w/o sequelae	The patient required hospitalization of a right hip replacement due to worsening of arthritis. The event was judged to be unlikely related to study drug.
ISS	EN3202-015-075-015/ EN3202-020	54/F/C	Worsening of osteoarthritis of left hip	Oxymorphone ER/ 40	27SEP00/ 06OCT00	Moderate/ Unlikely/ ./ Resolved w/o sequelae	The patient required hospitalization of a left total hip replacement due to worsening of arthritis. The event was judged to be unlikely related to study drug. Study drug was resumed after the surgery.
ISS	EN3202-015-075-015/ EN3202-020	54/F/C	Total right hip replacement for o.a. worsening	Oxymorphone ER/ 40	23MAY01/ 28MAY01	Moderate/ Unlikely/ ./ Unknown	The patient was hospitalized on [redacted] for a hybrid right hip replacement, an event judged by the investigator to be unlikely related to the study drug.

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 suggests that these cases of 'osteoarthritis aggravated' were due to progression of underlying osteoarthritis.

In addition to these serious AEs, a wide variety of non-fatal serious AEs occurring in a three or fewer oxymorphone ER-treated subjects were reported.

In the Blood and Lymphatic System, among oxymorphone ER-treated subjects there were two cases of 'anemia NOS', and one case each of 'iron-deficiency anemia', 'leucocytosis NOS', and 'lymphadenopathy'. Among placebo-treated subjects, there was one case each of 'anemia NOS aggravated' and 'leucocytosis NOS'. For each of these serious AEs, the investigator judged the relationship of the event to the study drug as unlikely. Review of the narratives suggests that study drug was not causally related to these serious AEs.

In the Cardiac Disorders System, among oxymorphone ER-treated a variety of cardiac-related serious AEs occurred. The table below summarizes the number of individual serious AE events by Preferred Term and Treatment Group.

Table. Summary of Number of Subjects With Non-Fatal Serious Adverse Events in the Cardiac Disorders System in Phase 2/3 Trials

	Oxymorphone		Oxycodone			
Preferred Term	ER	IR	ER	IR	Morphine ER	Placebo
Arrhythmia NOS	1	0	0	0	0	0
Atrial fibrillation	3	0	0	0	0	1
Atrial fibrillation aggravated	0	0	0	0	0	1
Cardiac arrest	0	0	0	0	0	1
Cardiac failure congestive	1	0	0	0	0	0
Cardio-respiratory arrest	1	0	0	0	0	0
Cardiogenic shock	0	1	0	0	0	0
Coronary artery occlusion	1	0	0	0	0	0
Myocardial infarction	2	3	0	1	0	0
Oedema lower limb	1	0	0	0	0	0
Supraventricular tachycardia	1	0	0	0	0	0
Tachycardia NOS	0	0	1	0	0	1

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

Review of the above table is notable for the fact that most of the cardiac serious AEs occurred in oxymorphone ER-treated patients. Of all of these events, only one (supraventricular tachycardia in oxymorphone ER-treated Subject EN3202-012-011-023) was judged to be probably related to study drug. The event occurred in the post-operative setting (post-arthroplasty) at a time when the subject was receiving PCA oxymorphone and oxymorphone ER, and was also experienced hypotension and a decline in mental status, which improved upon administration of Narcan. All of the remaining serious AEs in the Cardiac Disorders System were judged by the investigator to be unlikely related to study drug. Of note, though not apparent from the table above, 12 of the 21 non-fatal serious AEs in this category occurred in the three trials in the post-operative setting (EN3202-012, EN3203-004, and EN3203-005). Review of the narratives indicates that, except for the case of supraventricular tachycardia in Subject EN3202-012-011-023, which the investigator judged as probably related to study drug, there is no clear evidence that study drug was a causative factor. Of 184 placebo-treated subject in acute post-operative studies, 4 had a serious cardiac AE (4/184=2.17%), while of 334 oxymorphone-treated subjects in this subset of studies, four had a cardiac-related serious AE (4/334=1.20%). Of note, three of 66 oxymorphone ER-treated subjects in the acute post-operative setting experienced a cardiac-related serious AE (3/66=4.55%). An additional 7 serious cardiac AEs occurred during the open-label extension studies. Review of the narratives in these

cases suggests no causative role for the study drug. Of note, one case of non-fatal cardio-respiratory arrest occurred in a patient who apparently aspirated food, and was resuscitated by family members and paramedics, although she apparently sustained nervous system damage as a result of this event.

In the Gastrointestinal Disorders System, among oxymorphone ER-treated subjects there were a variety of gastrointestinal-related serious AEs. The table below summarizes the number of individual serious AE events by Preferred Term and Treatment Group.

Table. Summary of Number of Subjects With Non-Fatal Serious Adverse Events in the Gastrointestinal Disorders System in Phase 2/3 Trials

	Oxymorphone		Oxycodone			
Preferred Term	ER	IR	ER	IR	Morphine ER	Placebo
Abdominal pain NOS	7	0	0	0	0	0
Appendicitis	1	0	0	0	0	0
Ascites	1	0	0	0	1	0
Colitis ischaemic	1	0	0	0	0	0
Constipation	1	0	0	0	0	0
Diarrhoea NOS	2	0	0	0	0	0
Duodenal ulcer	0	0	1	0	0	0
Faecal impaction	0	0	1	0	0	0
Faeces discoloured	0	0	1	0	0	0
Gastritis NOS	1	0	0	0	0	0
Gastrointestinal haemorrhage NOS	1	0	0	0	0	0
Ileus	0	2	0	1	0	0
Nausea	6	0	1	0	0	0
Pancreatitis NOS	2	0	0	0	0	0
Peritonitis	1	0	0	0	0	0
Rectal bleeding	1	0	0	0	1	0
Sore throat NOS	1	0	0	0	0	0
Vomiting NOS	8	0	1	0	0	0

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

The most common serious AEs in the Gastrointestinal Disorder System were abdominal pain, nausea, and vomiting. These have been previously discussed above.

Most of the serious AEs in this category were judged by the investigator to be unlikely related to study drug. Notable exceptions to this pattern include one case of ileus in an oxymorphone IR- treated subject (EN3202-004-003-002), who developed an ileus three days after surgery (either total hip or knee replacement), and one day after study drug was discontinued. This event was judged to be possibly related to study drug. One oxymorphone ER subject (EN3202-019-064-006) developed constipation that was judged to be probably related to study drug. One oxycodone ER-treated subject (EN3202-015-003-020) developed a case of fecal impaction, judged to be possibly related to study drug. Each of these two cases resolved without sequelae. One oxymorphone ER-treated subject (EN3202-015-014-001) developed gastritis, which was complicated by diabetic gastroparesis and a gastric ulcer. The investigator judged this event to be possibly related to study drug. Study drug was discontinued. One oxymorphone ER-treated subject (EN3202-025-033-009) developed pancreatitis 2.5 hours after taking the first dose of study drug, after he presented with abdominal pain, sweats, and vomiting. He was felt to have a low-grade pancreatitis after an extensive cardiac evaluation was negative. Two amylase levels were both normal (70 and 43, normal range 30-110 U/L). Lipase was elevated (393, normal range 23-300 U/L). He was kept NPO, and his symptoms resolved and the lipase returned to normal. This event was judged by the investigator to be probably related to study drug.

In the General Disorders and Administration Site Conditions System, the most common non-fatal serious AEs in oxymorphone ER-treated subjects were 'chest pain NEC' and 'drug interaction NOS', each of which has been previously summarized above. Of note, the overall most frequent serious AE in this category was 'concomitant disease progression', since nearly all of these cases resulted in death, they have been previously reviewed and are not considered further in this section. Among other serious AEs in this category, one case of lethargy (Subject EN3202-012-011-023) on oxymorphone ER 20 mg, developed after taking the first dose after a right knee arthroplasty. This event was judged to be probably related to study drug, and study drug was discontinued. Other non-fatal serious AEs in this category in oxymorphone-treated subjects included three or fewer cases each of fatigue, impaired healing, injection site infection, localized edema, mental status changes, pain exacerbated, pain NOS, pyrexia, and weakness. All these events were judged by the investigator to be unlikely related to study drug.

In the Hepatobiliary Disorders System, one oxymorphone ER-treated subject developed cholelithiasis and one oxycodone ER-treated subject developed hepatic failure. Each of these events resolved, and both were judged to be unlikely related to study.

In the Infections and Infestations System, of the 28 non-fatal serious AEs reported, 16 occurred in oxymorphone ER-treated subjects in open-label extension studies. These include cases of bronchitis (n=1), cellulitis (n=2), cellulitis gangrenous (n=1), viral gastroenteritis (n=1), pneumonia (n=3), sepsis (n=1), staphylococcal infection (n=1), tuberculosis (n=1), urinary tract infection (n=2), and wound infection (n=1). With the exception of a case of cellulitis gangrenous, each of these serious AEs in the open-label extension trials was judged by the investigator to be unlikely related to study drug. This subject (EN3202-016-006-025) had diabetes and known peripheral vascular disease, which the investigator judged to be unlikely related to the study drug. The most common non-fatal serious AE in this category was pneumonia which occurred in three oxymorphone ER-treated subjects (one subject EN3202-015-037-012 had two episodes of pneumonia), and in one subject in each of the oxymorphone IR, oxycodone ER, oxycodone IR, and placebo groups. All events of pneumonia were judged to be unlikely related to study drug.

In the Injury and Poisoning System, serious AEs fell into two broad categories – overdoses and traumatic injuries.

Four cases of overdoses were reported. One subject, EN3202-015-037-012, had an event described as "accidental tricyclic depressant overdose". This subject had been on amitriptyline 100 mg qhs and Mellaril 100 mg qhs for approximately 18 years. She was found to have a tricyclic antidepressant level of 739 (normal 0-20). The narrative notes that she may have accidentally doubled her dose. The antidepressant was discontinued, and mental status improved (see Sponsor information provided on September 8, 2003). In addition, three other subjects had adverse events of 'overdose NOS'. Subject EN3202-016 received a 120 mg dose of oxycodone ER on the evening of the first day of titration and an additional dose on the morning of the second day. He reportedly developed "symptoms of severe opioid overdose" on the first day of titration. On the second day of titration, he developed a decreased respiratory rate with confusion, bradycardia, diminished breath sounds, weakness, pallor, and clammy skin. The subject discontinued study medication, and the symptoms resolved. A Data Correction Form in the CRFs notes that "Due to conversion error, the patient overdosed on study medication on 3/14/01 and 3/15/01" but this comment is not further explained. Subject EN3202-016-021-002 was titrated on OxyContin, and was then randomized to a blinded treatment of placebo. After her fourth day of blinded treatment, she was lost to follow-up. Dosing records were not available, and study drug was not returned. On the 33rd day after her final study visit, she had a "severe drug overdose" with mild somnolence and mild respiratory depression, which apparently resolved the following day. The nature of the overdose (e.g., the drug involved) is not known. Subject EN3202-019-067-017 had a "narcotic overdose". The narrative notes that the subject had been taking oxymorphone ER with oxymorphone IR rescue medication for pain control. Upon admission to a hospital for pneumonia, oxycodone ER and morphine sulfate were added. Respiratory depression and somnolence developed, for which he required naloxone.

Subject EN3202-015-018-004 took oxymorphone ER 20 mg po bid from March 7, 2000 through April 14, 2000 in Study EN3202-020. On [redacted] he took his morning dose of the study drug between 7:00 and 8:00 am, and reported to the clinic for his visit at 8:30 am and left at about 9:15 am. While driving home,

he was involved in a motor vehicle accident, resulting in a subdural hematoma that required evacuation via a right frontotemporal craniotomy, a rib fracture, and a left pleural effusion. Of note, drowsiness had been reported a day after starting study medication on March 8, with a resolution date of April 18. Somnolence was also reported on April 18. The narrative notes that the somnolence may have contributed to the motor vehicle accident, which was judged by the investigator to be possibly related to study drug, which was then discontinued. Other events in this category were judged by the investigators to be unlikely related to study medication.

In the Investigations System, a variety of clinical laboratory, electrocardiogram, and vital sign abnormalities are presented. These will be discussed in the section of the safety review dealing with those topics.

In the Metabolism and Nutrition Disorders System, the most frequent non-fatal serious AE was dehydration, which has already been summarized above. Other events in this category included one case of hyperkalemia in the setting of renal failure in an oxycodone ER-treated subject, one case of hypoglycemia in an oxymorphone ER-treated diabetic subject on insulin, and two cases of hypokalemia, one in the setting of vomiting. Each of these events was judged by the investigator to be unlikely related to study medication.

In the Musculoskeletal, Connective Tissue and Bone Disorders System, the most frequent non-fatal serious AE was 'osteoarthritis aggravated' which has previously been discussed above. Subject EN3202-016-010-008 was receiving oxymorphone ER and developed a severe, acute exacerbation of back pain on the tenth day of treatment. The investigator attributed this event as possibly related to study medication, but the rationale for doing so is not apparent in the narratives or in the CRFs. Many of the events in this category were related to underlying conditions (e.g., osteoarthritis, back pain, or cancer pain) and were judged the investigators to be unlikely related to study medication. Review of the narratives supports this conclusion.

In the Neoplasms Benign and Malignant (Including Cysts and Polyps) System, seven of nine non-fatal serious adverse events were either recurrences or metastatic manifestations of underlying cancer. All were judged by the investigator to be unlikely related to the study drug. One case each of a benign laryngeal neoplasm and of uterine fibroids were also judged by the investigator to be unlikely related to the study drug. Apart from one case of bone metastases in a morphine ER-treated subject, all other cases in this category were in oxymorphone ER-treated subjects.

In the Nervous System Disorders System, there were a variety of serious AEs, some of which were judged to be possibly or probably related to study drug.

Two cases of CNS depression, both in oxymorphone ER-treated subjects, were judged to be probably related to study drug and required study drug discontinuation. One of these cases occurred in the post-operative setting after a single 20 mg dose of oxymorphone ER (Subject EN3202-102-018-002), while the other (Subject EN3202-025-035-008) occurred after three doses of oxymorphone ER 20 mg. In both cases, improvement was noted after Narcan administration. Two cases of unresponsiveness (verbatim term, coded term = coma) in oxymorphone IR-treated subjects were also judged to be probably related to study drug and required study drug discontinuation. In one subject (EN3203-004-032-001), the unresponsiveness occurred about one hour after a single oral dose of oxymorphone IR 30 mg in the post-operative setting. The subject required repeated doses of Narcan, and the unresponsiveness resolved. The second subject received a single oral dose of oxymorphone 10 mg on the first post-operative day, and became sleepy about one hour later, and responsiveness to only strong or painful verbal stimuli about three hours later. There were also "unusual tremors and flexing of the upper extremities" associated with this decreased level of consciousness. The decreased level of consciousness improved notably with Narcan.

A similar case (Subject EN3203-004-021-011, verbatim term = not arousable [obtunded], coded term = depressed level of consciousness) occurred in an oxymorphone IR-treated subject who received two doses of oxymorphone IR 20 mg in the post-operative setting (at 11:30 a.m. and at 3:30 p.m.). About 9-10 hours later (at about 1:00 am), the subject was diaphoretic, nonresponsive, lethargic, pale, and hypotensive (94/49). The non-responsiveness responded to Narcan. Within two days, the patient's symptoms had completely resolved. Study drug was discontinued. Another subject (En3202-017-014-006) with metastatic

mesothelioma developed a depressed level of consciousness (described as "unarousable") that required hospitalization and that resolved after study drug was discontinued. The dose of study drug was 100-140 mg po bid oxymorphone with oxymorphone IR 10 mg po q3hours prn. The exact dosage leading up to this event was not specified.

Serious AEs coded to the preferred term 'Somnolence' occurred in four subjects. Subject EN3202-012-011-004 was treated with a single oral dose of oxymorphone ER, along with oxymorphone PCA in the post-operative setting. She became disoriented, confused, and sedated, for which she was given Narcan, which reversed the sedation. Subject EN3203-004-030-022 developed somnolence after a total of three doses of oxymorphone IR 20 mg in the post-operative setting. The somnolence was treated with Narcan. Subject EN3202-015-018-014 developed somnolence while being treated for chronic pain. In the investigator's opinion, this somnolence may have contributed to a motor vehicle accident (see description of this adverse event in the Injury and Poisoning System).

One serious AE coded to the preferred term 'Sedation' occurred in Subject EN3202-012-018-002, who was given a single oral dose of oxymorphone ER as well as oxymorphone PCA as rescue in the post-operative setting. He developed sedation and oxygen desaturation. He was given Narcan, and his sedation and oxygen desaturation improved. This event was judged to be probably related to study drug.

Review of the above serious AEs coded to the preferred terms 'Central nervous system depression', Coma NEC', 'Depressed level of consciousness', 'Sedation', and 'Somnolence' reveals 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 related to opiate use. Review of the narratives suggests that these events are related to the study drug.

Most other serious AEs in the Nervous Systems Disorders System were judged by the investigator to be unrelated to study drug. The preferred terms used to describe these events, each of which occurred in three or fewer oxymorphone ER-treated subjects include 'Ataxia', 'Cerebrovascular accident', 'Dizziness (exc vertigo)', 'Gait abnormal NOS', 'Headache NOS', 'Hepatic encephalopathy', 'Hypoxic encephalopathy', 'Intracranial tumor hemorrhage', 'Loss of consciousness NEC', 'Muscle contractions involuntary', 'Spinal Stenosis NOS', 'Syncope', 'Tremor NEC' and 'Vasovagal attack'.

Serious AEs in the Psychiatric Disorders System included a variety events related to level of arousal and content of consciousness. One subject (EN3202-012-019-018) developed three serious AEs in this category, including 'Aggression', 'Agitation', and 'Confusion' after a single 20 mg dose of oxymorphone ER in the post-operative setting. She required Ativan for the agitation, which was thought to further depress her mental state. Study medication was discontinued, and the events were judged to be probably related to study drug.

Serious AEs in the Renal and Urinary Disorders System included one case of bilateral hydronephrosis, one subject with renal calculi, one subject with ureteral calculi, and four subjects with urinary retention. Each of the se subjects was on oxymorphone ER, and each of these events was judged to be unlikely related to study drug, with the exception of one case of urinary retention, which was judged to be possibly related to study drug. Three cases of acute renal failure were reported, one in each of three treatment groups (placebo, oxymorphone IR, and oxycodone IR). Each was judged to be unlikely related to study drug.

Serious AEs in the Reproductive System and Breast Disorders System included one case each of systole, pelvic pain, pelvic peritoneal adhesions, rectocele, and vaginal prolapse. Each event occurred in oxymorphone ER-treated subjects and each was judged to be unlikely related to study drug.

In the Respiratory, Thoracic and Mediastinal Disorders System, a variety of serious adverse events occurred. Dyspnea has already been reviewed above. Events in oxymorphone ER-treated subjects that were judged to be unlikely related to study drug treatment included atelectasis (n=1), bronchospasm (n=1), chronic obstructive pulmonary disease exacerbation (n=2), cough (n=1), dyspnea exacerbated (n=1), foreign body aspiration (n=1), pharyngeal hemorrhage (n=1), respiratory distress (n=1), respiratory failure (n=1), an wheezing (n=1). Three serious AEs in oxymorphone ER-treated subjects were judged probably

related to study drug (one case each of respiratory acidosis in Subjects EN3202-012-018-002 and respiratory depression and respiratory failure in Subject EN3202-019-067-017). These events in these two subjects required discontinuation of study drug. One event of pleural effusion in an oxymorphone ER-treated subject was judged to be possibly related to study drug.

Events in oxymorphone IR-treated subjects that were judged to be unlikely related to study drug treatment included adult respiratory distress syndrome and pneumothorax in a single subject. Four events were judged to possibly related to study drug: dyspnea, respiratory distress and hypoxia Subject (EN3203-004-007-005), and hypoventilation (subject EN3203-004-030-022). These four events resulted in study drug discontinuation.

One morphine ER-treated subjects experienced exacerbations of asthma, chronic obstructive pulmonary disease, and hypoxia, all of which were judged unlikely related to study drug. One case each of chest tightness and dyspnea and two cases of hypoxia were reported in four subjects treated with oxycodone ER. Each of these events was judged to be unlikely related to study drug. One case each of pleurisy and respiratory distress were reported in tow placebo-treated subjects.

In the Skin and Subcutaneous Tissue Disorders System, there were two serious AEs. One case of a foot ulcer, judged to unlikely related to study drug, occurred in an oxymorphone ER-treated subjects. One case of increased sweating occurred in an oxymorphone IR-treated subject. This case was judged to be possibly related to study drug, and the study drug was discontinued n response to this event.

In the Surgical and Medical Procedures category, there were four events, each judged to be unlikely related to study drug. These events included one event each of epidural anesthesia, knee arthroplasty, and operation, each in oxymorphone ER-treated subjects. There was also one event of post-operative hemorrhage in a placebo-treated subject.

In the Vascular Disorders System, one event of hypotension was judged to be probably related to study drug (oxymorphone ER). This event occurred in the post-operative setting, and the study drug was discontinued. Other event in oxymorphone ER-treated subjects, all of which were judged to be unlikely related to study drug, included arterial thrombosis (n=1), hypotension (n=2), pulmonary embolism (n=2), transient ischemic attack (n=2), venous obstruction (n=1), and deep limb venous thrombosis (n=4). In oxymorphone IR-treated subjects, one event of hypotension was judged to be possibly related to study drug and resulted in study drug discontinuation. Three other events of deep limb venous thrombosis in oxymorphone IR-treated subjects were each judged to be unlikely related to study drug. Two events of pulmonary embolism in oxycodone-treated subjects (one ER and one IR) were each judged to be unlikely related to study drug. Three events in placebo-treated subjects (ischemic foot, postural hypotension, and deep limb venous thrombosis) were each judged to be unlikely related to study drug.

1.5.4 Adverse Events Leading to Study Drug Discontinuation

1.5.4.1 Adverse Events Leading to Study Drug Discontinuation in Phase 1 Studies

In the original ISS, two oxymorphone ER-treated subjects and one oxymorphone IR-treated subject discontinued due to adverse events. In the two oxymorphone ER-treated subjects, adverse events leading to study drug discontinuation included one case each of nausea, pain in limb, and vomiting. In one oxymorphone IR-treated subject, a back injury required discontinuation of study drug. The ISS also reports a case of another subject in Study EN3203-001 who withdrew after a single dose of oxymorphone IR when a urinary tract infection developed.

The 120-Day Safety Update presents an additional five subjects who discontinued due to an adverse event. In Study EN3202-026, two subjects discontinued due to an adverse event. One subject (034) discontinued due to headache, nausea, dizziness and hypoglycemia, while the other (038) discontinued due to a toothache and right cheek swelling. In Study EN3202-027, three subjects discontinued due to an adverse event. Adverse Events leading to discontinuation included headache, dizziness, and vomiting (Subject 018),

hypertension (Subject 033), and fainting, combativeness, altered mental status, and signs and symptoms of withdrawal (Subject 077).

Subject 077, a 47-year-old man with no health problems noted at screening, received oxymorphone ER 10 mg twice daily (0800 and 2000) on October 23, 25, and 25. On October 26, he received oxymorphone ER 20 mg twice daily (0800 and 2000), and he received a 20 mg dose at 0800 on October 27. On October 22, (Study Day –1) he experienced weakness, associated with a fingerstick glucose value of 49 mg/dL that was attributed to tolbutamide 500 mg, which was also administered to subjects in this study. On October 24, (Study Day 2), he experienced weakness and dizziness. The weakness was judged to be probably related to study drug, and the dizziness was judged to be possibly related to study drug. Both of these adverse events resolved later that day without sequelae and without treatment. On October 27, the subject experienced fainting, combativeness, altered mental status, and signs and symptoms of withdrawal. The latter three adverse events were of moderate intensity, while the fainting was of mild intensity. He was treated with normal saline for the fainting, and with two doses of Versed for the combativeness. He received Narcan for "reversal of narcotic" (according to the CRF, though the narrative notes that the Narcan was administered for "reversal of narcotic withdrawal"). All adverse events resolved without sequelae. The investigator judged the fainting to be probably related to study drug, while the combativeness, altered mental status, and signs and symptoms of withdrawal were judged to be unrelated to study drug. The reason for these judged relationships is not explained in the narrative, nor are alternative explanations of these adverse events given.

1.5.4.2 Adverse Events Leading to Study Drug Discontinuation in Phase 2/3 Studies

Adverse events leading to study drug discontinuation occurred frequently in the clinical development program. The table below summarizes the number and percentage of subjects who discontinued study drug due to an adverse event by treatment group in selected clinical trial subsets. The Sponsor notes in the ISS (Section 6.11) that "within each subset, subjects are categorized according by treatment according to the last treatment received in the first trial in the subgroup in which they participated".

Table. Number and Percentage of Subject With Adverse Events Leading to Study Drug Discontinuation in the Clinical Development Program

	Oxymorphone				Oxycodone			
	ER			IR	ER	IR	Morphine ER	Placebo
Study Subset	ISS*	120-Update*	Overall*	Overall*	Overall*	Overall*	Overall*	Overall*
Phase 2/3 ER Trials								
Number Treated	818	235	1078	5	276	0	35	350
Number (%) Discontinued Due to Any Adverse Event	264 (32.3%)	24 (10.2%)	386 (35.8%)	2 (40.0%)	65 (23.6%)	0 (0.0%)	11 (31.4%)	20 (5.7%)
All IR Phase 2/3 Trials								
Number Treated	0	---	---	334	0	195	0	95
Number (%) Discontinued Due to Any Adverse Event	0 (0.0%)	---	---	34 (10.2%)	0 (0.0%)	7 (3.6%)	0 (0.0%)	7 (7.4%)
All Acute Post-operative Trials								
Number Treated	66	---	---	334	0	195	0	156
Number (%) Discontinued Due to Any Adverse Event	8 (12.1%)	---	---	34 (10.2%)	0 (0.00%)	7 (3.6%)	0 (0.0%)	7 (4.5%)
All Cancer Pain Trials								
Number Treated	100	---	---	5	32	0	35	0
Number (%) Discontinued Due to Any Adverse Event	3 (3.0%)	---	---	2 (40.0%)	4 (12.5%)	0 (0.0%)	11 (31.4%)	0 (0.0%)
All Chronic Non-Malignant Pain Trials								
Number Treated	652	---	---	0	244	0	0	289
Number (%) Discontinued Due to Any Adverse Event	253 (38.8%)	---	---	0 (0.00%)	61(25.0%)	0 (0.00%)	0 (0.00%)	20 (6.9%)

*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.

Source: Appendix 3.140 in ISS and Appendix 1, Table 10 in 120-Day Safety Update

Review of the above table is notable for the 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%.

The following table presents the frequency of adverse events leading to study drug discontinuation occurring in four or more oxymorphone ER-treated subjects in the original ISS.

Table. Frequency of Adverse Events Leading to Study Drug Discontinuation Occurring in Four or More Oxymorphone ER-Treated Subjects in All Clinical Trials in the Original ISS

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

Source: Appendix 3.140 in the ISS

Review of the above table is notable for the fact that these adverse events, as described by the MedDRA preferred terms, 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 in the above table 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 table below presents the frequency of adverse events leading to study drug discontinuation in four or more oxymorphone ER-treated subjects in the ISS, the 120-Day Safety Update, and the overall Phase 2/3 clinical development program.

Table. Incidence of Adverse Experiences Causing Discontinuation of Study Drug By Preferred Term in Four or More Oxymorphone ER-treated Subjects in the Overall Phase 2/3 Oxymorphone ER Trials

	Oxymorphone ER		
MedDRA Preferred Term	ISS	120-Day Update	Overall
Number of subjects N (c)	818	235	1078
Any Adverse Experience (d)	264 (32.27)	24 (10.21)	386 (35.81)
Nausea	124 (15.16)	3 (1.28)	155 (14.38)
Dizziness (exc vertigo)	77 (9.41)	1 (0.43)	92 (8.53)
Vomiting NOS	65 (7.95)	2 (0.85)	85 (7.88)
Constipation	28 (3.42)	0 (0)	43 (3.99)
Somnolence	35 (4.28)	0 (0)	43 (3.99)
Pruritus NOS	31 (3.79)	2 (0.85)	39 (3.62)
Headache NOS	24 (2.93)	0 (0)	26 (2.41)
Sweating increased	20 (2.44)	0 (0)	26 (2.41)
Sedation	19 (2.32)	0 (0)	23 (2.13)
Fatigue	12 (1.47)	1 (0.43)	16 (1.48)
Confusion	10 (1.22)	1 (0.43)	13 (1.21)
Dry mouth	12 (1.47)	0 (0)	13 (1.21)
Diarrhoea NOS	7 (0.86)	1 (0.43)	11 (1.02)
Abdominal pain NOS	10 (1.22)	0 (0)	10 (0.93)
Concomitant disease progression	0 (0)	5 (2.13)	9 (0.83)
Insomnia NEC	8 (0.98)	1 (0.43)	9 (0.83)
Lethargy	7 (0.86)	1 (0.43)	8 (0.74)
Weakness	6 (0.73)	0 (0)	8 (0.74)
Disorientation	5 (0.61)	0 (0)	7 (0.65)
Appetite decreased NOS	3 (0.37)	2 (0.85)	6 (0.56)
Dyspnoea NOS	4 (0.49)	1 (0.43)	6 (0.56)
Rigors	4 (0.49)	1 (0.43)	6 (0.56)
Anxiety NEC	3 (0.37)	0 (0)	5 (0.46)
Depression NEC	1 (0.12)	1 (0.43)	5 (0.46)
Euphoric mood	5 (0.61)	0 (0)	5 (0.46)
Feeling jittery	3 (0.37)	0 (0)	5 (0.46)
Nervousness	3 (0.37)	0 (0)	5 (0.46)
Tremor NEC	4 (0.49)	0 (0)	5 (0.46)
Urinary retention	4 (0.49)	0 (0)	5 (0.46)
Vision blurred	4 (0.49)	0 (0)	5 (0.46)
Anxiety aggravated	1 (0.12)	0 (0)	4 (0.37)
Arthralgia	3 (0.37)	0 (0)	4 (0.37)
Back pain aggravated	2 (0.24)	1 (0.43)	4 (0.37)
Chest pain NEC	3 (0.37)	0 (0)	4 (0.37)
Dermatitis NOS	3 (0.37)	0 (0)	4 (0.37)
Drug interaction NOS	4 (0.49)	0 (0)	4 (0.37)
Hallucination NOS	4 (0.49)	0 (0)	4 (0.37)
Oedema lower limb	3 (0.37)	0 (0)	4 (0.37)
Pain exacerbated	3 (0.37)	1 (0.43)	4 (0.37)
Pain NOS	1 (0.12)	2 (0.85)	4 (0.37)

Source: Appendix 1, Table 10 in the 120-Day Safety update

Review of the above table confirms the same general pattern of adverse events as was seen in the 'All Clinical Trials' data from the ISS. Many of the adverse events leading to study drug discontinuation were serious adverse events, which have already been reviewed in detail above.

The spectrum of adverse events leading to study drug discontinuation was generally similar in the other sponsor-defined study subsets, with the possible exception of the acute-post-operative pain trials. The table below summarizes the frequency of all adverse events leading to study drug discontinuation in any oxymorphone ER-treated subject in the acute post-operative pain trials.

Table. Frequency of Adverse Events Leading to Study Drug Discontinuation Occurring in One or More Oxymorphone ER-Treated Subjects in Acute Post-Operative Pain Clinical Trials in the Original ISS

	Oxymorphone			Oxycodone			
MedDRA Preferred Term	ER/IR	ER	IR	ER	IR	Morphine ER	Placebo
Number of Subjects	400	66	334	0	195	0	156
Number (%) Discontinued Due to Any Adverse Event	42 (10.5%)	8 (12.1%)	34 (10.2%)	0 (0.00%)	7 (3.59%)	0 (0.00%)	7 (4.49%)
Confusion	7 (1.75%)	4 (6.06%)	3 (0.90%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Drug interaction NOS	4 (1.00%)	4 (6.06%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Lethargy	3 (0.75%)	2 (3.03%)	1 (0.30%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Sedation	6 (1.50%)	2 (3.03%)	4 (1.20%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Aggression	1 (0.25%)	1 (1.52%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Agitation	2 (0.50%)	1 (1.52%)	1 (0.30%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Central nervous system depression NOS	1 (0.25%)	1 (1.52%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Depressed level of consciousness	2 (0.50%)	1 (1.52%)	1 (0.30%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Electrocardiogram ST segment abnormal	1 (0.25%)	1 (1.52%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Hypotension NOS	2 (0.50%)	1 (1.52%)	1 (0.30%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Oxygen saturation decreased	1 (0.25%)	1 (1.52%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Respiratory acidosis	1 (0.25%)	1 (1.52%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Respiratory rate decreased	1 (0.25%)	1 (1.52%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Somnolence	6 (1.50%)	1 (1.52%)	5 (1.50%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Supraventricular tachycardia	1 (0.25%)	1 (1.52%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Vomiting NOS	7 (1.75%)	1 (1.52%)	6 (1.80%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (1.92%)

Source: Appendix 3.140 in the ISS

While the small number of subjects treated with oxymorphone ER in acute post-operative pain trials (N=66) and the even smaller number of oxymorphone ER-treated subjects who discontinued study medication due to an adverse event (n=8) require caution in the interpretation of the data in the table above, 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. These have been reviewed in the section on serious AEs above. 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 confustion 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.

Review of the narratives and other safety data submitted in the NDA reveals that some subjects required treatment for adverse events that led to study drug discontinued, especially nausea and vomiting, which required treatment with anti-emetics.

1.5.5 Adverse Events Leading to Study Drug Interruption or Dose Change

1.5.5.1 Adverse Events Leading to Study Drug Interruption or Dose Change in Phase 1 Studies

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

1.5.5.2 Adverse Events Leading to Study Drug Interruption or Dose Change in Phase 2/3 Studies

Adverse events leading to study drug interruption or dose changes occurred relatively infrequently in the Phase 2/3 studies.

The table below summarizes the frequencies of adverse events leading to study drug interruption in the Phase 2/3 studies that occurred in at least two oxymorphone ER-treated subjects.

Table. Frequency of Adverse Events Leading to Study Drug Interruption Occurring in Two or More Oxymorphone ER-Treated Subjects in Phase 2/3 Clinical Trials in the Original ISS

	Oxymorphone			Oxycodone			
MedDRA Preferred Term	ER/IR	ER	IR	ER	IR	Morphine ER	Placebo
Number of Subjects	1398	1057	368	382	195	69	473
Any Cause	32 (2.29%)	30 (2.84%)	3 (0.82%)	4 (1.05%)	1 (0.51%)	1 (1.45%)	1 (0.21%)
Nausea	6 (0.43%)	6 (0.57%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.21%)
Vomiting NOS	6 (0.43%)	5 (0.47%)	1 (0.27%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.21%)
Sedation	4 (0.29%)	4 (0.38%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Anxiety aggravated	3 (0.21%)	3 (0.28%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Dizziness (exc vertigo)	4 (0.29%)	3 (0.28%)	1 (0.27%)	1 (0.26%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Pruritus NOS	3 (0.21%)	3 (0.28%)	0 (0.00%)	1 (0.26%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Sweating increased	3 (0.21%)	3 (0.28%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Constipation	2 (0.14%)	2 (0.19%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Irritability	2 (0.14%)	2 (0.19%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Somnolence	2 (0.14%)	2 (0.19%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

Source: Appendix 3.141 in the ISS

Review of the above table is notable for the fact that the frequency of study drug interruptions was low (2.84% in the oxymorphone ER-treated group, and lower in all other treatment groups). Adverse events leading to study drug interruption were those that commonly occur in opioid-treated patients. Of note, there were three cases of "anxiety aggravated" that required oxymorphone ER interruption. Two of these subjects (EN3202-016-010-003 and EN3202-019-062-003) each had a prior history of anxiety. A third subject (EN3202-016-019-002) had no history of anxiety documented in his medical history from his first study (EN3202-016).

The table below summarizes the frequencies of adverse events leading to study drug dose changes in the Phase 2/3 studies that occurred in at least one oxymorphone ER-treated subject.

Table. Frequency of Adverse Events Leading to Study Drug Dose Changes Occurring in One or More Oxymorphone ER-Treated Subject in Phase 2/3 Clinical Trials in the Original ISS

	Oxymorphone			Oxycodone			
MedDRA Preferred Term	ER/IR	ER	IR	ER	IR	Morphine ER	Placebo
Number of Subjects	1398	1057	368	382	195	69	473
Any cause	9 (0.64%)	8 (0.76%)	3 (0.82%)	5 (1.31%)	0 (0.00%)	3 (4.35%)	1 (0.21%)
Sedation	2 (0.14%)	2 (0.19%)	2 (0.54%)	0 (0.00%)	0 (0.00%)	2 (2.90%)	0 (0.00%)
Abdominal pain upper	1 (0.07%)	1 (0.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Back pain aggravated	1 (0.07%)	1 (0.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Clamminess	1 (0.07%)	1 (0.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Disorientation	1 (0.07%)	1 (0.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Dizziness (exc vertigo)	2 (0.14%)	1 (0.09%)	2 (0.54%)	1 (0.26%)	0 (0.00%)	2 (2.90%)	0 (0.00%)
Headache NOS	1 (0.07%)	1 (0.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Irritability	1 (0.07%)	1 (0.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Nausea	1 (0.07%)	1 (0.09%)	0 (0.00%)	2 (0.52%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Restlessness	1 (0.07%)	1 (0.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Vomiting NOS	1 (0.07%)	1 (0.09%)	0 (0.00%)	1 (0.26%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

Source: Appendix 3.142 in the ISS

Review of the above table is notable for the fact that the frequency of study drug dose changes was low (0.76% in the oxymorphone ER-treated group). Adverse events leading to study drug dose changes were generally those that commonly occur in opioid-treated patients.

1.5.6 All Adverse Experiences

1.5.6.1 Approach to Review of All Adverse Experiences

The Sponsor's summary tables include only those adverse events that were treatment-emergent, defined as "adverse events with onset dates on or after the treatment start date and within 7 days after the treatment stop date, or adverse events with onset dates prior to the start of treatment that increased in severity after the start of treatment" (see Section 2.3.3.1 of the ISS). Serious adverse events could have occurred up to 30 days after the treatment was stopped. Adverse events were attributed to the treatment the subject was receiving at the time of onset of the event (or at the time of increased severity of the event), or to the last treatment received if the adverse event onset date was after treatment had stopped. In crossover trials, an adverse event was counted as occurring during both treatments under two conditions – first, if it started and stopped during one treatment, and started again during another treatment, and second, if it started on the day that a subject crossed over from one treatment to another.

The Sponsor has analyzed adverse events for all of the trials, and for the eight subsets listed in Section 1.2.3 above (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, and all Phase 1 trials). Because data in some subsets overlaps with data from other subsets, the information obtained from each of the subsets differs slightly. For the purposes of this review of all adverse events, the subsets will be reviewed in the following way:

Trial Subset	Role of Subset in Clinical Safety Review
All Trials	Because of the heterogeneity of trials, including differences across trials in subject selection, doses received, and duration of treatment, this group will not be used for cross-treatment comparisons. Rather, it will be used to highlight certain selected, less common adverse events.
All Phase 2/3 trials	This subset will not be reviewed in detail, because of the same limitations noted in the All Trials group. All information contributing to this subset is covered by other, smaller subsets.
Oxymorphone ER Phase 2/3 trials	This subset will be used to present the frequency of adverse events in all subjects taking oxymorphone ER. However, because of the heterogeneous patient populations (cancer pain, osteoarthritis, and low back pain) as well as differences in study design (some studies are placebo-controlled, some are active-controlled, and some are open-label extensions), these frequency rates will not be analyzed in detail.
Oxymorphone IR Phase 2/3 trials	This subset will be used to examine the adverse event profile of oxymorphone IR in the post-operative phase.
Acute post-operative pain trials	This subset, per se, will not be used, since it combines placebo-controlled data from studies of both oxymorphone IR and oxymorphone ER. Rather, controlled data from oxymorphone ER will be compared to controlled data from oxymorphone IR in the acute post-operative setting.
Chronic non-malignant pain trials	This subset will be used to evaluate the adverse event profile of oxymorphone ER in placebo-controlled trials in this clinical setting.
Cancer pain trials	This subset will be used to present the frequency of adverse events in this clinical setting. However, there are no placebo-controlled trials in this subset.
Open-label extension trials	This subset will be used to present the frequency of adverse events in subjects with long-term exposure. However, there are no placebo-controlled trials in this subset.
All Phase 1 trials	This subset will be used to evaluate the adverse event profile of oxymorphone in the Phase 1 setting.

1.5.6.2 Adverse Events in Phase 1 Trials

The table below, based on Table 3.128 in the ISS, present all adverse events occurring in 1% or more of oxymorphone (ER or IR) treated subject in the Phase 1 clinical development program (except for studies EN3202-026 and EN3202-027). 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, headache, 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, and discontinuations due to adverse events were infrequent.

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

	Oxymorphone		
	ER/IR	ER	IR
Number of Subjects	366	275	197
Any Adverse Experience	133 (36.3%)	112 (40.7%)	60(30.5%)
Dizziness (exc vertigo)	53 (14.5%)	39 (14.2%)	35 (17.8%)
Headache NOS	46 (12.6%)	35 (12.7%)	14 (7.1%)
Nausea	42 (11.5%)	32 (11.6%)	19 (9.6%)
Fatigue	34 (9.3%)	28 (10.2%)	17 (8.6%)
Vomiting NOS	24 (6.6%)	16 (5.8%)	12 (6.1%)
Constipation	11 (3.0%)	11 (4.0%)	0 (0.0%)
Euphoric mood	12 (3.3%)	11 (4.0%)	4 (2.0%)
Pruritus NOS	11 (3.0%)	9 (3.3%)	5 (2.5%)
Feeling of relaxation	8 (2.2%)	8 (2.9%)	0 (0.0%)
Somnolence	7 (1.9%)	7 (2.5%)	0 (0.0%)
Abdominal pain NOS	5 (1.4%)	5 (1.8%)	0 (0.0%)
Arthralgia	5 (1.4%)	5 (1.8%)	0 (0.0%)
Feeling hot	5 (1.4%)	5 (1.8%)	1 (0.5%)
Vision blurred	4 (1.1%)	4 (1.5%)	0 (0.0%)
Back pain	3 (0.8%)	3 (1.1%)	0 (0.0%)
Dry mouth	6 (1.6%)	3 (1.1%)	4 (2.0%)
Palpitations	4 (1.1%)	3 (1.1%)	1 (0.5%)
Rigors	3 (0.8%)	3 (1.1%)	0 (0.0%)
Sweating increased	3 (0.8%)	3 (1.1%)	0 (0.0%)
Chest pain NEC	3 (0.8%)	2 (0.7%)	1 (0.5%)
Dermatitis NOS	3 (0.8%)	2 (0.7%)	1 (0.5%)
Dyspepsia	2 (0.5%)	2 (0.7%)	0 (0.0%)
Feeling jittery	2 (0.5%)	2 (0.7%)	0 (0.0%)
Hiccups	2 (0.5%)	2 (0.7%)	0 (0.0%)
Hypertension NOS	2 (0.5%)	2 (0.7%)	0 (0.0%)
Muscle cramps	2 (0.5%)	2 (0.7%)	0 (0.0%)
Pain in limb	2 (0.5%)	2 (0.7%)	0 (0.0%)
Paraesthesia NEC	4 (1.1%)	2 (0.7%)	2 (1.0%)

Source: Appendix 3.128 in the ISS

1.5.6.3 Adverse Events in All Phase 2/3 Trials

The table below, based on Table 3.15 in the ISS, present all adverse events occurring in 5% or more of oxymorphone ER-treated subjects in the Phase 2/3 clinical development program in the original ISS (additional open-label extension study data from the 120-Day Safety Update are not included). Adverse events were relatively common in the Phase 2/3 studies, occurring in 88.5% of oxymorphone ER-treated subjects, 71.2% of oxymorphone IR-treated subjects, 78.5% of oxycodone ER-treated subjects, 64.6% of oxycodone IR-treated subjects, 76.8% of morphine ER-treated subjects, and 59.6% of placebo-treated subjects. Eleven adverse events occurred in 5.0% or more of oxymorphone ER-treated subjects, and most were adverse events typically associated with opioid treatment (dizziness, nausea, fatigue, vomiting, constipation, euphoric mood, and pruritus). In general, frequencies of common adverse events were higher in oxymorphone ER-treated subjects compared to other treatment groups. Because of the longer duration of exposure to oxymorphone ER (the only treatment to be administered in open-label extension studies), and the wide range of clinical conditions for which this treatment was administered (e.g., acute post-operative pain, chronic non-malignant pain, and cancer pain), comparison to other treatment groups, especially the placebo group (administered only in controlled acute post-operative studies and controlled chronic non-malignant pain studies) is not appropriate. Such comparison will be analyzed more fully in other clinical trial subsets below.

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

	Oxymorphone			Oxycodone			
	ER/IR	ER	IR	ER	IR	Morphine ER	Placebo
Number of Subjects N	1398	1057	368	382	195	69	473
Any Adverse Experience	1178 (84.3%)	935 (88.5%)	262 (71.2%)	300 (78.5%)	126 (64.6%)	53 (76.8%)	282 (59.6%)
Nausea	515 (36.8%)	458 (43.3%)	63 (17.1%)	128 (33.5%)	38 (19.5%)	26 (37.7%)	71 (15.0%)
Constipation	415 (29.7%)	396 (37.5%)	25 (6.8%)	143 (37.4%)	14 (7.2%)	23 (33.3%)	64 (13.5%)
Dizziness (exc vertigo)	279 (20.0%)	249 (23.6%)	34 (9.2%)	85 (22.3%)	10 (5.1%)	17 (24.6%)	37 (7.8%)
Pruritus NOS	268 (19.2%)	242 (22.9%)	30 (8.2%)	79 (20.7%)	12 (6.2%)	16 (23.2%)	46 (9.7%)
Vomiting NOS	258 (18.5%)	232 (21.9%)	28 (7.6%)	53 (13.9%)	13 (6.7%)	13 (18.8%)	28 (5.9%)
Somnolence	226 (16.2%)	177 (16.7%)	49 (13.3%)	39 (10.2%)	27 (13.8%)	3 (4.3%)	19 (4.0%)
Sweating increased	173 (12.4%)	166 (15.7%)	14 (3.8%)	71 (18.6%)	5 (2.6%)	13 (18.8%)	39 (8.2%)
Sedation	167 (11.9%)	160 (15.1%)	15 (4.1%)	76 (19.9%)	1 (0.5%)	16 (23.2%)	38 (8.0%)
Headache NOS	131 (9.4%)	120 (11.4%)	11 (3.0%)	44 (11.5%)	8 (4.1%)	3 (4.3%)	27 (5.7%)
Dry mouth	84 (6.0%)	76 (7.2%)	8 (2.2%)	26 (6.8%)	1 (0.5%)	0 (0.0%)	1 (0.2%)
Diarrhoea NOS	62 (4.4%)	61 (5.8%)	1 (0.3%)	15 (3.9%)	0 (0.0%)	3 (4.3%)	18 (3.8%)

Source: Appendix 3.15 in the ISS

1.5.6.4 Adverse Events in All Phase 2/3 Oxymorphone ER Trials

The table below, based on Table 3.29 in the ISS, presents all adverse events occurring in 5% or more of oxymorphone ER-treated subjects in the Phase 2/3 oxymorphone ER clinical development program in the original ISS (additional open-label extension study data from the 120-Day Safety Update are not included). Data in this subgroup of trials comprises data from the controlled trials in cancer pain, the placebo-controlled trials in chronic non-malignant pain, the single placebo-controlled trial in acute post-operative pain, and the open-label extension studies. Because each of these groups will be considered in more detail in the section below, data from this large subset of trials will not be reviewed in detail. Brief review of this table, however, indicates that the pattern of adverse events in this subgroup is similar to the pattern of adverse events in all Phase 2/3 clinical trials. This similarity is expected, since a large portion of the data from all Phase 2/3 trials is derived from the Phase 2/3 ER trials.

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

	Oxymorphone			Oxycodone			
	ER/IR	ER	IR	ER	IR	Morphine ER	Placebo
Number of Subjects N	1064	1057	34	382	0	69	350
Any Adverse Experience	941 (88.4%)	935 (88.5%)	25 (73.5%)	300 (78.5%)	0 (0.0%)	53 (76.8%)	225 (64.3%)
Nausea	460 (43.2%)	458 (43.3%)	8 (23.5%)	128 (33.5%)	0 (0.0%)	26 (37.7%)	63 (18.0%)
Constipation	398 (37.4%)	396 (37.5%)	8 (23.5%)	143 (37.4%)	0 (0.0%)	23 (33.3%)	63 (18.0%)
Dizziness (exc vertigo)	251 (23.6%)	249 (23.6%)	6 (17.6%)	85 (22.3%)	0 (0.0%)	17 (24.6%)	35 (10.0%)
Pruritus NOS	242 (22.7%)	242 (22.9%)	4 (11.8%)	79 (20.7%)	0 (0.0%)	16 (23.2%)	42 (12.0%)
Vomiting NOS	232 (21.8%)	232 (21.9%)	2 (5.9%)	53 (13.9%)	0 (0.0%)	13 (18.8%)	23 (6.6%)
Somnolence	177 (16.6%)	177 (16.7%)	0 (0.0%)	39 (10.2%)	0 (0.0%)	3 (4.3%)	14 (4.0%)
Sweating increased	168 (15.8%)	166 (15.7%)	9 (26.5%)	71 (18.6%)	0 (0.0%)	13 (18.8%)	37 (10.6%)
Sedation	161 (15.1%)	160 (15.1%)	9 (26.5%)	76 (19.9%)	0 (0.0%)	16 (23.2%)	37 (10.6%)
Headache NOS	121 (11.4%)	120 (11.4%)	1 (2.9%)	44 (11.5%)	0 (0.0%)	3 (4.3%)	26 (7.4%)
Dry mouth	76 (7.1%)	76 (7.2%)	0 (0.0%)	26 (6.8%)	0 (0.0%)	0 (0.0%)	1 (0.3%)
Diarrhoea NOS	62 (5.8%)	61 (5.8%)	1 (2.9%)	15 (3.9%)	0 (0.0%)	3 (4.3%)	18 (5.1%)

Source: Appendix 3.29 in the ISS

The table below presents the data on all adverse events occurring in 3.0% or more of oxymorphone ER-treated subjects in the Phase 2/3 oxymorphone ER clinical development program form the 120-Day Safety Update.

Table. Incidence Rates of Treatment-Emergent Adverse Events Occurring 3% or More of Subjects in Phase 2/3 ER Trials

	ISS Total	120-Day Safety Update	Overall
Number of Subjects	1057	235	1089
Any Adverse Experience (b)	935 (88.5)	175 (74.5)	976 (89.6)
Nausea	458 (43.3)	36 (15.3)	500 (45.9)
Constipation	396 (37.5)	30 (12.8)	434 (39.9)
Dizziness (exc vertigo)	249 (23.6)	23 (9.8)	280 (25.7)
Pruritus NOS	242 (22.9)	13 (5.5)	264 (24.2)
Vomiting NOS	232 (21.9)	23 (9.8)	256 (23.5)
Sweating increased	166 (15.7)	35 (14.9)	199 (18.3)
Sedation	160 (15.1)	26 (11.1)	188 (17.3)
Somnolence	177 (16.7)	2 (0.9)	179 (16.4)
Headache NOS	120 (11.4)	10 (4.3)	129 (11.8)
Dry mouth	76 (7.2)	5 (2.1)	81 (7.4)
Diarrhoea NOS	61 (5.8)	6 (2.6)	68 (6.2)
Insomnia NEC	48 (4.5)	11 (4.7)	62 (5.7)
Fatigue	47 (4.4)	12 (5.1)	60 (5.5)
Appetite decreased NOS	45 (4.3)	8 (3.4)	54 (5.0)
Pyrexia	45 (4.3)	6 (2.6)	51 (4.7)
Arthralgia	30 (2.8)	10 (4.3)	42 (3.9)
Oedema lower limb	27 (2.6)	10 (4.3)	40 (3.7)
Abdominal pain NOS	32 (3.0)	5 (2.1)	38 (3.5)
Influenza	20 (1.9)	16 (6.8)	37 (3.4)
Dyspnoea NOS	26 (2.5)	5 (2.1)	33 (3.0)

Source: Appendix 1, Table 14 in the 120-Day Safety Update

Review of this table indicates that the pattern of adverse events in the original ISS is similar to the pattern of ISS in the 120-Day Safety Update.

1.5.6.5 Adverse Events in All Phase 2/3 Oxymorphone IR Trials

The table below, based on Table 3.43 in the ISS, present all adverse events occurring in 2% or more of oxymorphone IR-treated subjects in the Phase 2/3 clinical development program for oxymorphone IR in the original ISS. This subset of trials consisted of two placebo-controlled studies for acute post-operative pain. As such, data from these trials represent short-term exposure to study drug (generally one or a few doses).

Adverse events were relatively common in the Phase 2/3 oxymorphone IR studies, occurring 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 in this subset of studies was pyrexia, which occurred in 21.9% of oxymorphone IR-treated subject, 15.9% of oxycodone IR-treated subjects, and 15.4% of placebo-treated subjects. The Sponsor notes in the ISS (See Section 6.2.4 of 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. For all adverse events except hypoxia, the adverse event frequency was higher in the oxymorphone IR-treated group that 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 (ie,

oxymorphone IR versus oxycodone IR) differences was large, though there were notable between-group differences in dizziness, hypotension, and tachycardia.

Table. 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	334	195	123
Any Adverse Experience	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%)
Anaemia 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

1.5.6.6 Adverse Events in All Acute Post-operative Pain Trials

The acute-post-operative trials comprised the two trials that used oxymorphone IR and a single trial that used oxymorphone ER. The adverse events from the two studies using oxymorphone IR have been reviewed above. This section of the review will focus therefore on adverse events in Study EN3202-012, the single study in which oxymorphone ER was studied in acute post-operative pain.

Review of the table below, which lists the frequency of adverse events occurring in two or more oxymorphone ER-treated subjects in Study EN3202-012, is notable for the observation that most of the adverse events are typical of those seen in opioid-treated subjects. Other adverse events are typical of the 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 oxymorphone ER-treated subjects, a pattern that is opposite to what was noted in the placebo-controlled studies of oxymorphone IR in the post-operative setting.

Four subjects had an adverse event coded to the term "drug interaction NOS". These events have been reviewed above. The table below, derived form Appendix 16.2.2, Table 5.21 in the EN3202-012 study report, notes that "drug interaction NOS' occurred in 3 of 65 oxymorphone ER-treated subjects, while Appendix 3.43 in the ISS notes that serious adverse events with this preferred term occurred in 4 of 66 oxymorphone ER-treated subjects in that study. The reason for this discrepancy is not clear. 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. The Sponsor notes in Section 6.2.5 of the ISS that these events, described by the investigator as a "drug interaction", were likely the results of the additive effects of oxymorphone via two different routes of administration.

The adverse events lethargy, sedation, and somnolence occurred in four, four, and three subjects, respectively. (See Sponsor Table 5.2.1 in Appendix 16.2.2 in the EN3202-012 study report. Of note, Appendix 3.57 reports that four subjects, not three, experienced somnolence. The reason for this discrepancy is not clear). Review of the ISS dataset (filename iss_aes.xpt) indicates that a total of 12 oxymorphone ER-treated subjects experienced lethargy, sedation, or somnolence. There was no overlap of subjects who experienced these events. Of these 12 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.

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

Preferred Term	Oxymorphone ER N=65	Placebo N=61
At least one adverse event	52 (80.0%)	48 (78.7%)
Nausea	19 (29.2%)	12 (19.7%)
Pyrexia	14 (21.5%)	18 (29.5%)
Dizziness (exc vertigo)	8 (12.3%)	3 (4.9%)
Pruritus NOS	8 (12.3%)	8 (13.1%)
Confusion	3 (4.6%)	3 (4.9%)
Drug interaction NOS	3 (4.6%)	0 (0.0%)
Insomnia NEC	4 (6.2%)	1 (1.6%)
Lethargy	4 (6.2%)	0 (0.0%)
Sedation	4 (6.2%)	3 (4.9%)
Somnolence	3 (4.6%)	4 (6.6%)
Hypotension NOS	3 (4.6%)	1 (1.6%)
Vomiting NOS	3 (4.6%)	6 (9.8%)
Dry mouth	2 (3.1%)	0 (0.0%)
Haemoglobin decreased	2 (3.1%)	0 (0.0%)
Headache NOS	2 (3.1%)	2 (3.3%)

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

1.5.6.7 Adverse Events in Chronic Non-malignant Pain Trials

The table below, based on Table 3.67 in the ISS, presents all adverse events occurring in 2% or more of oxymorphone ER-treated subjects in the Phase 2/3 chronic non-malignant pain trials. Data in this subgroup of trials comprises data from the placebo-controlled trials in chronic non-malignant pain. Review of this table indicates that 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, 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) in 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.

Table. Adverse Events Occurring in 3% or More of Oxymorphone ER-Treated Subjects in Chronic Non-malignant Pain Clinical Trials

	Oxymorphone ER	Oxycodone ER	Placebo
Number of Subjects N	684	286	289
Any Adverse Experience	588 (86.0%)	231 (80.8%)	177 (61.2%)
Nausea	301 (44.0%)	105 (36.7%)	51 (17.6%)
Constipation	226 (33.0%)	121 (42.3%)	59 (20.4%)
Dizziness (exc vertigo)	168 (24.6%)	68 (23.8%)	32 (11.1%)
Vomiting NOS	152 (22.2%)	38 (13.3%)	17 (5.9%)
Pruritus NOS	147 (21.5%)	63 (22.0%)	34 (11.8%)
Somnolence	123 (18.0%)	35 (12.2%)	10 (3.5%)
Sweating increased	90 (13.2%)	56 (19.6%)	36 (12.5%)
Headache NOS	87 (12.7%)	42 (14.7%)	24 (8.3%)
Sedation	70 (10.2%)	53 (18.5%)	35 (12.1%)
Dry mouth	59 (8.6%)	24 (8.4%)	1 (0.3%)
Diarrhoea NOS	32 (4.7%)	13 (4.5%)	18 (6.2%)
Appetite decreased NOS	31 (4.5%)	5 (1.7%)	1 (0.3%)
Fatigue	31 (4.5%)	4 (1.4%)	4 (1.4%)
Insomnia NEC	24 (3.5%)	9 (3.1%)	7 (2.4%)
Abdominal pain NOS	20 (2.9%)	8 (2.8%)	4 (1.4%)
Pyrexia	16 (2.3%)	6 (2.1%)	0 (0.0%)
Rigors	16 (2.3%)	8 (2.8%)	0 (0.0%)
Oedema lower limb	14 (2.0%)	6 (2.1%)	2 (0.7%)

Source: Appendix 3.67 in the ISS

Overall, the adverse event profile in this subset of trials is typical of that seen with opioid analgesics.

1.5.6.8 Adverse Events in Cancer Pain Trials

The table below, based on Table 3.81 in the ISS, presents all adverse events occurring in 2% or more of oxymorphone ER-treated subjects in the Phase 2/3 oxymorphone ER cancer pain clinical trials. Data in this subgroup of trials comprises 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. Each of these studies was amended to change the titration medication from oxymorphone IR to morphine ER (Study EN3202-018) or oxycodone ER (Study EN3202-019).

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, 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.

Table. Adverse Events Occurring in 2% or More of Oxymorphone ER-Treated Subjects in Cancer Pain Clinical Trials

	Oxymorphone				
	ER/IR	ER	IR	Oxycodone ER	Morphine ER
Number of Subjects	145	138	34	96	69
Any Adverse Experience	107 (73.8%)	100 (72.5%)	25 (73.5%)	69 (71.9%)	53 (76.8%)
Constipation	45 (31.0%)	42 (30.4%)	8 (23.5%)	22 (22.9%)	23 (33.3%)
Nausea	34 (23.4%)	31 (22.5%)	8 (23.5%)	23 (24.0%)	26 (37.7%)
Sedation	32 (22.1%)	31 (22.5%)	9 (26.5%)	23 (24.0%)	16 (23.2%)
Pruritus NOS	25 (17.2%)	25 (18.1%)	4 (11.8%)	16 (16.7%)	16 (23.2%)
Dizziness (exc vertigo)	24 (16.6%)	22 (15.9%)	6 (17.6%)	17 (17.7%)	17 (24.6%)
Sweating increased	26 (17.9%)	22 (15.9%)	9 (26.5%)	15 (15.6%)	13 (18.8%)
Vomiting NOS	16 (11.0%)	15 (10.9%)	2 (5.9%)	15 (15.6%)	13 (18.8%)
Somnolence	5 (3.4%)	5 (3.6%)	0 (0.0%)	4 (4.2%)	3 (4.3%)
Insomnia NEC	4 (2.8%)	4 (2.9%)	0 (0.0%)	2 (2.1%)	1 (1.4%)
Pain in limb	4 (2.8%)	4 (2.9%)	0 (0.0%)	0 (0.0%)	2 (2.9%)
Concomitant disease progression	5 (3.4%)	3 (2.2%)	2 (5.9%)	4 (4.2%)	2 (2.9%)
Confusion	3 (2.1%)	3 (2.2%)	0 (0.0%)	4 (4.2%)	0 (0.0%)
Dysphoria	3 (2.1%)	3 (2.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Gait abnormal NOS	3 (2.1%)	3 (2.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Pyrexia	4 (2.8%)	3 (2.2%)	1(2.9%)	2 (2.1%)	6 (8.7%)

Source: Appendix 3.81 in the ISS

1.5.6.9 Adverse Events in Open-label Extension Trials

The table below, based on an updated version of Appendix 3.95 I the ISS (submitted by the Sponsor on September 30, 2003 at the Agency's request), presents all adverse events occurring in 5% or more of oxymorphone ER-treated subjects in the open-label extension studies, based on the overall population of subjects treated in these studies. This clinical trial subset is different from the other subsets in several ways, including: 1) all data were obtained in an open-label fashion, 2) all subjects received oxymorphone ER, and 3) the duration of treatment was generally much longer than that in the controlled trials, with a broad range of durations of treatment. Subjects in this subset, as in the Phase 2/3 ER subset, had pain due either to cancer or to non-malignant chronic pain. However, the data for the open-label extension studies are not further subdivided into these two categories. It should also be noted that subjects could use oxymorphone IR as rescue medication. While the amount of oxymorphone IR rescue medication that was dispensed and returned was recorded, actual use of rescue medication was not recorded. Thus, the relative contributions of oxymorphone ER and oxymorphone IR (rescue medication) to the development of any individual adverse events can not be ascertained from the data.

As in the other clinical trial subsets, the most common adverse events (those occurring in over 10% of oxymorphone ER-treated subjects) were those typically associated opioid analgesic therapy. In addition, some of the adverse events listed in the table below are typical of those expected in a population of individuals followed for several months (eg, upper respiratory tract infection, urinary tract infection, etc.).

Table. Incidence of All Treatment-Emergent Adverse Experiences [N (%)] by Treatment Group and Preferred Term (MedDRA) in Descending Frequency Subset: Open-Label Extension Trials

MedDRA Preferred Term	Oxymorphone ER
Number of Subject N	460
Any Adverse Event	426 (92.6%)
Constipation	249 (54.1%)
Nausea	202 (43.9%)
Sedation	134 (29.1%)
Sweating increased	120 (26.1%)
Pruritus NOS	119 (25.9%)
Dizziness (exc vertigo)	108 (23.5%)
Vomiting NOS	103 (22.4%)
Somnolence	54 (11.7%)
Headache NOS	44 (9.6%)
Diarrhoea NOS	39 (8.5%)
Arthralgia	33 (7.2%)
Insomnia NEC	31 (6.7%)
Fatigue	27 (5.9%)
Influenza	26 (5.7%)
Upper respiratory tract infection NOS	26 (5.7%)
Urinary tract infection NOS	25 (5.4%)
Oedema lower limb	24 (5.2%)
Concomitant disease progression	23 (5.0%)
Sinusitis NOS	23 (5.0%)

Source: Updated Appendix 3.95 in Sponsor Submission of September30, 2003

1.5.7 Severity of Adverse Experiences

The Sponsor has analyzed the severity of adverse experiences for all clinical trials, as well as for the eight Sponsor-defined subsets of clinical trials. Because many of these clinical trial subsets overlap with other subsets, and because the inferences that can be made from each of the subsets vary, the review of the severity of adverse events will focus on six clinical trial subsets: 1) Phase 1 studies, 2) Phase 2/3 oxymorphone IR studies, 3) acute post-operative pain studies, 4) chronic non-malignant pain studies, 5) cancer pain studies, and 6) open-label extension studies. In addition, the review of adverse event severity will focus on adverse events judged to be severe.

1.5.7.1 Severity of Adverse Experiences in Phase 1 Clinical Trials

Among the 366 subjects in the Phase 1 clinical development program, there were two adverse events that were reported as severe. One case of dizziness in a subject on oxymorphone IR and one case of back pain in a subject on oxymorphone ER. All other adverse events were reported to be mild or moderate in severity (see Appendix 1.130 in the ISS).

1.5.7.2 Severity of Adverse Experiences in Phase 2/3 Oxymorphone IR Clinical Trials

Among the 334 oxymorphone IR-treated subjects in Phase 2/3 clinical trials (ie, two clinical trials in the acute post-operative setting), the most frequently reported severe adverse event was somnolence, which was reported in 5 (1.5%) oxymorphone IR-treated subjects (see Appendix 3.47 in ISS). Other severe adverse events in this clinical trial subset affecting level of arousal or content of consciousness in oxymorphone IR-treated subjects included confusion (n=2), sedation (n=1), coma (n=1), depressed level of

consciousness (n=1), disorientation (n=1), and feeling abnormal (n=1). None of these events was reported in severe form for any placebo-treated subjects or in any oxycodone IR-treated subjects. There was one severe case of 'sedation aggravated' in one oxycodone IR-treated subject. Of these 12 events, which occurred in 12 separate oxymorphone IR-treated subjects, six resulted in study drug discontinuation. Each of the six events resulting in study drug discontinuation was judged by the investigator to be possibly or probably related to study drug. Of the remaining six events that did not result in study drug discontinuation, none was judged by the investigator to be possibly or probably related to study drug.

Other adverse events rated as severe in oxymorphone IR-treated subjects included vomiting (n=2), hypotension (n=1), ileus (n=3), myocardial infarction (n=2), deep limb venous thrombosis (n=3), cardiogenic shock (n=1), hypotension aggravated (n=1), pneumonia (n=1), radius fracture (n=1), acute renal failure (n=1), tendon rupture (n=1), wound infection (n=1), and prolonged coagulation time (n=1). Many of these events were also reported as serious adverse events, and have thus been reviewed above. Of note, ileus occurred in 3/334 (0.9%) oxymorphone IR-treated subjects and in 2/195 (1.0%) oxycodone IR-treated subjects. However, all cases of ileus in the oxymorphone IR-treated subjects were rated as severe, while both cases of ileus in oxycodone IR-treated subjects were rated as mild.

1.5.7.3 Severity of Adverse Experiences in All Acute Post-Operative Clinical Trials

The acute-post-operative trials comprised the two trials that used oxymorphone IR and a single trial that used oxymorphone ER. The severe adverse events from the two studies using oxymorphone IR have been reviewed above. This section of the review will focus therefore on severe adverse events in Study EN3202-012, the single study in which oxymorphone ER was studied in acute post-operative pain.

Among the 66 oxymorphone ER-treated subjects in study EN3202-012, the most frequently reported severe adverse events were drug interaction, sedation, and somnolence, each of which was reported in 2 (3.0%) oxymorphone ER-treated subjects (see Appendix 3.61 in ISS). The two cases of drug interaction, which involved subjects receiving oxymorphone ER after having received oxymorphone via a PCA pump, have been previously discussed. Severe adverse events in this clinical trial affecting level of arousal or content of consciousness in oxymorphone ER-treated subjects included confusion central nervous system depression (n=1), confusion (n=1), lethargy (n=1), sedation (n=2), and somnolence (n=2). None of these events was reported in severe form for any placebo-treated subjects. These seven events occurred in five subjects, three of whom required discontinuation of study drug because of the adverse event. All seven events were judged by the investigator to be probably related to study drug.

Other adverse events rated as severe in oxymorphone ER-treated subjects included respiratory acidosis (n=1), supraventricular tachycardia (n=1), urinary tract infection (n=1), vasovagal attack (n=1) and an abnormal ST segment (n=1). Apart from one case of vasovagal attack and one case of an abnormal ST segment, each of these events was also reported as a serious adverse event.

1.5.7.4 Severity of Adverse Experiences in Chronic Non-malignant Pain Clinical Trials

The table below, based on Appendix 3.71 in the ISS, presents the severity of the nine adverse events that occurred in severe form in 1.0% or more of oxymorphone ER-treated subjects in the chronic non-malignant pain clinical trials. Review of this table reveals that these nine adverse events are typical of those seen in a population of opioid-treated patients. Second, the frequency of the severe form of the nine adverse events is higher in the two treated groups (ie, oxymorphone ER and oxycodone ER) than in the placebo group. Third, the frequency of severe adverse events is generally similar between the oxymorphone ER and oxycodone ER treatment groups for these nine adverse events. Fourth, for each of the adverse events, there are more mild and moderate events than there are severe events.

Table. Severe Adverse Events Occurring in 1.0% or More of Oxymorphone ER-Treated Subjects in Chronic Non-Malignant Pain Clinical Trials

MedDRA Preferred Term	Treatment Group	Number Treated	Number (%) Reporting Events			
			Mild	Moderate	Severe	Missing
Nausea	Oxymorphone ER	684	114 (16.7%)	125 (18.3%)	62 (9.1%)	0 (0.0%)
	Oxycodone ER	286	48 (16.8%)	32 (11.2%)	25 (8.7%)	0 (0.0%)
	Placebo	289	32 (11.1%)	14 (4.8%)	5 (1.7%)	0 (0.0%)
Constipation	Oxymorphone ER	684	122 (17.8%)	80 (11.7%)	24 (3.5%)	0 (0.0%)
	Oxycodone ER	286	60 (21.0%)	45 (15.7%)	16 (5.6%)	0 (0.0%)
	Placebo	289	34 (11.8%)	20 (6.9%)	5 (1.7%)	0 (0.0%)
Dizziness (exc vertigo)	Oxymorphone ER	684	76 (11.1%)	72 (10.5%)	20 (2.9%)	0 (0.0%)
	Oxycodone ER	286	40 (14.0%)	20 (7.0%)	8 (2.8%)	0 (0.0%)
	Placebo	289	26 (9.0%)	6 (2.1%)	0 (0.0%)	0 (0.0%)
Vomiting NOS	Oxymorphone ER	684	49 (7.2%)	73 (10.7%)	30 (4.4%)	0 (0.0%)
	Oxycodone ER	286	17 (5.9%)	10 (3.5%)	11 (3.8%)	0 (0.0%)
	Placebo	289	9 (3.1%)	2 (0.7%)	6 (2.1%)	0 (0.0%)
Pruritus NOS	Oxymorphone ER	684	93 (13.6%)	39 (5.7%)	15 (2.2%)	0 (0.0%)
	Oxycodone ER	286	36 (12.6%)	18 (6.3%)	9 (3.1%)	0 (0.0%)
	Placebo	289	25 (8.7%)	6 (2.1%)	3 (1.0%)	0 (0.0%)
Somnolence	Oxymorphone ER	684	46 (6.7%)	54 (7.9%)	23 (3.4%)	0 (0.0%)
	Oxycodone ER	286	21 (7.3%)	10 (3.5%)	4 (1.4%)	0 (0.0%)
	Placebo	289	9 (3.1%)	1 (0.3%)	0 (0.0%)	0 (0.0%)
Sweating increased	Oxymorphone ER	684	41 (6.0%)	39 (5.7%)	10 (1.5%)	0 (0.0%)
	Oxycodone ER	286	30 (10.5%)	18 (6.3%)	8 (2.8%)	0 (0.0%)
	Placebo	289	21 (7.3%)	12 (4.2%)	3 (1.0%)	0 (0.0%)
Headache NOS	Oxymorphone ER	684	38 (5.6%)	39 (5.7%)	10 (1.5%)	0 (0.0%)
	Oxycodone ER	286	21 (7.3%)	16 (5.6%)	5 (1.7%)	0 (0.0%)
	Placebo	289	13 (4.5%)	11 (3.8%)	0 (0.0%)	0 (0.0%)
Sedation	Oxymorphone ER	684	36 (5.3%)	23 (3.4%)	11 (1.6%)	0 (0.0%)
	Oxycodone ER	286	25 (8.7%)	21 (7.3%)	7 (2.4%)	0 (0.0%)
	Placebo	289	23 (8.0%)	12 (4.2%)	0 (0.0%)	0 (0.0%)

Source: Appendix 3.71 in the ISS

Other severe adverse events occurring in 2 or more oxymorphone ER-treated subjects include dry mouth (n=2), diarrhea (n=3), decreased appetite (n=3), fatigue (n=4), insomnia (n=3), abdominal pain (n=5), weakness (n=6), dyspepsia (n=2), blurred vision (n=2), nervousness (n=2), restlessness (n=2), anxiety (n=2), arthralgia (n=2), feeling jittery (n=2), confusion (n=2) tremor (n=2), back pain aggravated (n=4),pain exacerbated (n=2), and urinary retention (n=2).

1.5.7.5 Severity of Adverse Experiences in Cancer Pain Clinical Trials

The table below, based on Appendix 3.85 in the ISS, presents the severity of the six adverse events that occurred in severe form in 1.0% or more of oxymorphone ER-treated subjects in the cancer pain clinical trials. Review of this table reveals that these six adverse events are typical of those seen in a population of opioid-treated patients. Second, the frequency of severe adverse events is generally similar among the treatment groups for these six adverse events. Given the relatively small numbers of subjects in each of the treatment groups, differences in percentages must be interpreted cautiously. Fourth, for each of the adverse events, there are more mild and moderate events than there are severe events in the oxymorphone treatment groups.

Table. Severe Adverse Events Occurring in 1.0% or More of Oxymorphone ER-Treated Subjects in Cancer Pain Clinical Trials

MedDRA Preferred Term	Treatment Group	Number Treated	Number (%) Reporting Events			
			Mild	Moderate	Severe	Missing
Constipation	Oxymorphone ER/IR[d]	145	16 (11.0%)	20 (13.8%)	9 (6.2%)	0 (0.0%)
	Oxymorphone ER	138	16 (11.6%)	18 (13.0%)	8 (5.8%)	0 (0.0%)
	Oxymorphone IR	34	3 (8.8%)	4 (11.8%)	1 (2.9%)	0 (0.0%)
	Oxycodone ER	96	7 (7.3%)	10 (10.4%)	5 (5.2%)	0 (0.0%)
	Morphine ER	69	13 (18.8%)	5 (7.2%)	5 (7.2%)	0 (0.0%)
Nausea	Oxymorphone ER/IR[d]	145	22 (15.2%)	9 (6.2%)	3 (2.1%)	0 (0.0%)
	Oxymorphone ER	138	21 (15.2%)	7 (5.1%)	3 (2.2%)	0 (0.0%)
	Oxymorphone IR	34	6 (17.6%)	2 (5.9%)	0 (0.0%)	0 (0.0%)
	Oxycodone ER	96	9 (9.4%)	10 (10.4%)	4 (4.2%)	0 (0.0%)
	Morphine ER	69	9 (13.0%)	10 (14.5%)	6 (8.7%)	1 (1.4%)
Sedation	Oxymorphone ER/IR[d]	145	20 (13.8%)	10 (6.9%)	2 (1.4%)	0 (0.0%)
	Oxymorphone ER	138	19 (13.8%)	10 (7.2%)	2 (1.4%)	0 (0.0%)
	Oxymorphone IR	34	5 (14.7%)	3 (8.8%)	1 (2.9%)	0 (0.0%)
	Oxycodone ER	96	14 (14.6%)	7 (7.3%)	2 (2.1%)	0 (0.0%)
	Morphine ER	69	11 (15.9%)	3 (4.3%)	2 (2.9%)	0 (0.0%)
Pruritus NOS	Oxymorphone ER/IR[d]	145	22 (15.2%)	2 (1.4%)	1 (0.7%)	0 (0.0%)
	Oxymorphone ER	138	23 (16.7%)	2 (1.4%)	0 (0.0%)	0 (0.0%)
	Oxymorphone IR	34	3 (8.8%)	0 (0.0%)	1 (2.9%)	0 (0.0%)
	Oxycodone ER	96	14 (14.6%)	2 (2.1%)	0 (0.0%)	0 (0.0%)
	Morphine ER	69	9 (13.0%)	5 (7.2%)	2 (2.9%)	0 (0.0%)
Dizziness (exc vertigo)	Oxymorphone ER/IR[d]	145	15 (10.3%)	7 (4.8%)	2 (1.4%)	0 (0.0%)
	Oxymorphone ER	138	15 (10.9%)	5 (3.6%)	2 (1.4%)	0 (0.0%)
	Oxymorphone IR	34	2 (5.9%)	4 (11.8%)	0 (0.0%)	0 (0.0%)
	Oxycodone ER	96	14 (14.6%)	3 (3.1%)	0 (0.0%)	0 (0.0%)
	Morphine ER	69	10 (14.5%)	6 (8.7%)	1 (1.4%)	0 (0.0%)
Vomiting NOS	Oxymorphone ER/IR[d]	145	7 (4.8%)	6 (4.1%)	3 (2.1%)	0 (0.0%)
	Oxymorphone ER	138	7 (5.1%)	5 (3.6%)	3 (2.2%)	0 (0.0%)
	Oxymorphone IR	34	1 (2.9%)	1 (2.9%)	0 (0.0%)	0 (0.0%)
	Oxycodone ER	96	3 (3.1%)	7 (7.3%)	5 (5.2%)	0 (0.0%)
	Morphine ER	69	5 (7.2%)	3 (4.3%)	5 (7.2%)	0 (0.0%)

Source: Appendix 3.85 in the ISS

1.5.7.6 Severity of Adverse Experiences in Open-Label Extension Clinical Trials

The table below, based on Appendix 3.99 in the ISS, presents the severity of the ten adverse events that occurred in severe form in 1.0% or more of oxymorphone ER-treated subjects in the open-label extension clinical trials. Review of this table reveals that these ten adverse events are typical of those seen in a population of opioid-treated patients. For each of the adverse events except concomitant disease progression, there are more mild and moderate events than there are severe events oxymorphone treatment groups.

Table. Severe Adverse Events Occurring in 1.0% or More of Oxymorphone ER-Treated Subjects in Open-label Extension Clinical Trials in the ISS

MedDRA	Number (%) Reporting Events (n=376)			
Preferred Term	Mild	Moderate	Severe	Missing
Constipation	104 (27.7%)	58 (15.4%)	23 (6.1%)	0 (0.0%)
Nausea	60 (16.0%)	60 (16.0%)	30 (8.0%)	0 (0.0%)
Sedation	49 (13.0%)	35 (9.3%)	7 (1.9%)	0 (0.0%)
Sweating increased	39 (10.4%)	31 (8.2%)	7 (1.9%)	0 (0.0%)
Vomiting NOS	19 (5.1%)	37 (9.8%)	18 (4.8%)	0 (0.0%)
Somnolence	31 (8.2%)	13 (3.5%)	8 (2.1%)	0 (0.0%)
Diarrhoea NOS	9 (2.4%)	16 (4.3%)	6 (1.6%)	0 (0.0%)
Concomitant disease progression	0 (0.0%)	2 (0.5%)	12 (3.2%)	0 (0.0%)
Abdominal pain NOS	2 (0.5%)	6 (1.6%)	4 (1.1%)	0 (0.0%)
Back pain	6 (1.6%)	2 (0.5%)	4 (1.1%)	0 (0.0%)

Source: Appendix 3.99 in the ISS

Review of data from the 120-Day Safety Update (see Appendix 1, Table 6 in the 120-Day Safety Update) reveals the same general pattern of adverse event severity.

1.5.8 Treatment-Related Adverse Experiences

The relationship of adverse events to study drug treatment was judged by the investigator and recorded on the CRFs. Treatment-related adverse events were those who relationship to study drug treatment, as determined by the investigator, was possible or probable.

The table below, based on Appendix 3.4 of the ISS, presents the frequency of the 19 treatment-related adverse events occurring in 1.0% or more of oxymorphone (ER or IR)-treated subjects. Review of this table reveals that these nineteen adverse events are typical of opioid-related adverse events.

Table. Treatment-Related Adverse Events Occurring in 1.0% or More of Oxymorphone (ER or IR)-treated Subjects in All Clinical Trials

	Oxymorphone			Oxycodone			
	ER/IR	ER	IR	ER	IR	Morphine ER	Placebo
Number of SubjectsTreated	1764	1332	565	382	195	69	473
Any Adverse Experience	1102 (62.50%)	923 (69.30%)	235 (41.60%)	258 (67.50%)	83 (42.60%)	41 (59.40%)	182 (38.50%)
Nausea	503 (28.50%)	452 (33.90%)	66 (11.70%)	122 (31.90%)	24 (12.30%)	21 (30.40%)	66 (14.00%)
Constipation	418 (23.70%)	401 (30.10%)	23 (4.10%)	143 (37.40%)	10 (5.10%)	23 (33.30%)	62 (13.10%)
Dizziness (exc vertigo)	315 (17.90%)	277 (20.80%)	63 (11.20%)	79 (20.70%)	7 (3.60%)	16 (23.20%)	36 (7.60%)
Pruritus NOS	260 (14.70%)	240 (18.00%)	27 (4.80%)	78 (20.40%)	9 (4.60%)	15 (21.70%)	38 (8.00%)
Vomiting NOS	249 (14.10%)	225 (16.90%)	30 (5.30%)	48 (12.60%)	5 (2.60%)	11 (15.90%)	24 (5.10%)
Somnolence	224 (12.70%)	178 (13.40%)	46 (8.10%)	37 (9.70%)	25 (12.80%)	3 (4.30%)	16 (3.40%)
Sweating increased	168 (9.50%)	161 (12.10%)	14 (2.50%)	68 (17.80%)	3 (1.50%)	13 (18.80%)	38 (8.00%)
Sedation	166 (9.40%)	159 (11.90%)	15 (2.70%)	75 (19.60%)	1 (0.50%)	16 (23.20%)	36 (7.60%)
Headache NOS	121 (6.90%)	104 (7.80%)	19 (3.40%)	32 (8.40%)	3 (1.50%)	1 (1.40%)	15 (3.20%)
Dry mouth	83 (4.70%)	73 (5.50%)	11 (1.90%)	21 (5.50%)	1 (0.50%)	0 (0.00%)	1 (0.20%)
Fatigue	72 (4.10%)	65 (4.90%)	18 (3.20%)	5 (1.30%)	1 (0.50%)	1 (1.40%)	3 (0.60%)
Appetite decreased NOS	40 (2.30%)	38 (2.90%)	2 (0.40%)	4 (1.00%)	0 (0.00%)	0 (0.00%)	1 (0.20%)
Diarrhoea NOS	26 (1.50%)	25 (1.90%)	1 (0.20%)	6 (1.60%)	0 (0.00%)	0 (0.00%)	8 (1.70%)
Euphoric mood	28 (1.60%)	24 (1.80%)	7 (1.20%)	1 (0.30%)	4 (2.10%)	0 (0.00%)	1 (0.20%)
Insomnia NEC	24 (1.40%)	24 (1.80%)	0 (0.00%)	8 (2.10%)	0 (0.00%)	0 (0.00%)	4 (0.80%)
Abdominal pain NOS	25 (1.40%)	23 (1.70%)	2 (0.40%)	4 (1.00%)	0 (0.00%)	1 (1.40%)	4 (0.80%)
Weakness	17 (1.00%)	16 (1.20%)	1 (0.20%)	6 (1.60%)	0 (0.00%)	1 (1.40%)	4 (0.80%)
Confusion	25 (1.40%)	13 (1.00%)	12 (2.10%)	5 (1.30%)	3 (1.50%)	0 (0.00%)	4 (0.80%)
Rigors	13 (0.70%)	13 (1.00%)	0 (0.00%)	2 (0.50%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

Source: Appendix 3.4 in the ISS

The relationship of adverse events to study drug treatment will not be further explored for the eight other clinical trial subsets.

The Sponsor has noted in Section 6.5 of the ISS that "the patterns of occurrence of severe treatment-related, treatment-emergent AEs were similar to patterns of occurrence of severe treatment-emergent AEs." Because severe adverse events were reviewed in detail above, the subset of severe adverse events that were judged to be treatment-related will not be further reviewed here.

1.5.9 Clinical Review of Selected Adverse Events in Phase 2/3 Clinical Trials

There were several adverse events in the adverse events frequency tables that require some comment.

Ten events of 'Palpitations' occurred in eight subjects who received oxymorphone ER and in one subject who received oxymorphone IR. All of these events were judged to be non-serious. One event was rated as severe, three were rated as moderate, and six were rated as mild. One mild event was rated as unlikely related to study drug, six events were rated as possibly related to study drug, and three events were rated as probably related to study drug. In four subjects, study drug was discontinued due to this adverse event. The duration of these events ranged from one to four days. There were no events in for this preferred term in any other treatment groups.

Eleven events of 'Vertigo NEC occurred in nine subjects who received oxymorphone ER. All of these events were judged to be non-serious. Two events were rated as severe, six were rated as moderate, and three were rated as mild. Five events (one severe, three moderate, and one mild) in five subjects were judged to be probably related to study drug, and required discontinuation in four subjects (the mild event did not result in study drug discontinuation. One mild event was rated as probably related to study drug. The remaining five events were judged to be unlikely related to study medication. These events did not result in study drug discontinuation. There were no events for this preferred term in any other treatment group.

Three events of 'Pancreatitis' in occurred in three subjects who received oxymorphone ER. All of these events were judged to be serious. One event, associated with multiple other medical problems in subject with cancer, resulted in death (Subject EN3202-017-008-006). Two other events, one rated as mild and one rated as severe, both resulted in study drug discontinuation. The severe event was judged to be unlikely related to study drug, while the mild event was judged to be probably related to study drug. There were no events for this preferred term in any other treatment group.

Ten events of Drug Withdrawal' occurred in nine subjects who received oxymorphone ER. None of the events was a serious adverse event. No events required study drug discontinuation. With the exception of one event in one subject (EN3202-016-004-004) that was judged to be unlikely related to study drug, all the other events were judged to be possibly (n=2) or probably (n=7) related to study drug. Drug withdrawal was also reported for one subject who received placebo and for two subjects who received oxycodone ER.

Nineteen oxymorphone ER-treated subjects experienced 23 events of 'Fall'. None was a serious adverse event. Two events were judged to be possibly related to study drug, and the remainder were judged to be unlikely related to study drug. No action was taken with regard to study drug for these events. No events were rated as severe. The remainder were either moderate or mild in severity. Two oxycodone ER-treated subjects each had one episode of 'Fall', neither of which was a serious adverse event. Falls are not unexpected occurrences in a population with joint disease (ie, osteoarthritis) or advanced medical illness (ie, cancer). In the three placebo-controlled studies in chronic non-malignant pain, the incidence of 'Fall' was similar in the oxymorphone ER and oxycodone ER treatment groups (0.9% and 0.7%, respectively). The incidence in the placebo group in that subset of studies was 0%.

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 (ie, 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 (ie, 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. The table below summarizes these findings.

Table. Frequency of Any Alteration in Mental Status in All Clinical Trials, All Post-Op Trials, and All Chronic Non-Malignant Pain Trials

Clinical Trial Subset	Oxymorphone			Oxycodone			
Preferred Term	ER/IR	ER	IR	ER	IR	Morphine ER	Placebo
All Clinical Trials							
Number of Subjects Exposed	1764	1332	565	382	195	69	473
Any alteration in mental status	469 (26.6%)	391 (29.4%)	86 (15.6%)	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	13 (0.7%)	12 (0.9%)	1 (0.2%)	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 level of consciousness	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%)
Central nervous system depression NOS	2 (0.1%)	2 (0.2%)	0 (0.0%)	1 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Loss of consciousness 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 abnormal 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%)
All Acute Post-Op Trials							
Number of Subjects Exposed	400	66	334	0	195	0	184
Any alteration in mental status	91 (22.8%)	15 (22.7%)	76 (22.8%)	0 (. %)	35 (17.9%)	0 (. %)	18 (9.8%)
Confusion	19 (4.8%)	4 (6.1%)	15 (4.5%)	0 (. %)	5 (2.6%)	0 (. %)	5 (2.7%)
Lethargy	8 (2.0%)	4 (6.1%)	4 (1.2%)	0 (. %)	0 (0.0%)	0 (. %)	0 (0.0%)
Sedation	10 (2.5%)	4 (6.1%)	6 (1.8%)	0 (. %)	1 (0.5%)	0 (. %)	3 (1.6%)
Somnolence	53 (13.3%)	4 (6.1%)	49 (14.7%)	0 (. %)	27 (13.8%)	0 (. %)	9 (4.9%)
Central nervous system depression NOS	1 (0.3%)	1 (1.5%)	0 (0.0%)	0 (. %)	0 (0.0%)	0 (. %)	0 (0.0%)
Depressed level of consciousness	5 (1.3%)	1 (1.5%)	4 (1.2%)	0 (. %)	1 (0.5%)	0 (. %)	0 (0.0%)
Disorientation	4 (1.0%)	1 (1.5%)	3 (0.9%)	0 (. %)	1 (0.5%)	0 (. %)	1 (0.5%)
Coma NEC	4 (1.0%)	0 (0.0%)	4 (1.2%)	0 (. %)	0 (0.0%)	0 (. %)	0 (0.0%)
Delirium	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (. %)	1 (0.5%)	0 (. %)	0 (0.0%)
Mental status changes	3 (0.8%)	0 (0.0%)	3 (0.9%)	0 (. %)	0 (0.0%)	0 (. %)	0 (0.0%)
Sedation aggravated	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (. %)	1 (0.5%)	0 (. %)	1 (0.5%)
All Chronic Non-malignant Pain Trials							
Number of Subjects Exposed	684	684	0	286	0	0	289
Any alteration in mental status	211 (30.8%)	211 (30.8%)	0 (. %)	93 (32.5%)	0 (. %)	0 (. %)	45 (15.6%)
Somnolence	123 (18.0%)	123 (18.0%)	0 (. %)	35 (12.2%)	0 (. %)	0 (. %)	10 (3.5%)
Sedation	70 (10.2%)	70 (10.2%)	0 (. %)	53 (18.5%)	0 (. %)	0 (. %)	35 (12.1%)
Confusion	7 (1.0%)	7 (1.0%)	0 (. %)	2 (0.7%)	0 (. %)	0 (. %)	0 (0.0%)
Disorientation	7 (1.0%)	7 (1.0%)	0 (. %)	2 (0.7%)	0 (. %)	0 (. %)	0 (0.0%)
Lethargy	7 (1.0%)	7 (1.0%)	0 (. %)	1 (0.3%)	0 (. %)	0 (. %)	0 (0.0%)
Disturbance in attention NEC	6 (0.9%)	6 (0.9%)	0 (. %)	2 (0.7%)	0 (. %)	0 (. %)	0 (0.0%)
Mental impairment NOS	2 (0.3%)	2 (0.3%)	0 (. %)	1 (0.3%)	0 (. %)	0 (. %)	0 (0.0%)
Central nervous system depression NOS	1 (0.1%)	1 (0.1%)	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%)
Mental status changes	1 (0.1%)	1 (0.1%)	0 (. %)	0 (0.0%)	0 (. %)	0 (. %)	0 (0.0%)

Source: Appendices 3.1, 3.57, and 3.67 in the ISS and Sponsor information submitted on September 30, 2003

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 (ie 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 are 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. While somnolence accounted for a large number of the events in the oxycodone IR group, the range of reported preferred terms was broader for the two oxymorphone groups. Of note, four subjects in the oxymorphone IR group were reported as having 'coma NEC'. Three of these cases occurred in study EN3203-004 (Subjects EN3203-004-028-007, EN3203-004-028-014, and EN3203-004-032-001) and one occurred in Study EN3203-005 (Subject EN3203-005-302-022). For each of the four subjects, the investigator verbatim term for the adverse events was 'unresponsiveness'. For two subjects, the event was not listed as a serious adverse event (Subjects EN3203-004-028-007 and EN3203-004-028-014), while for the other two it was. For one subject, the event was judged to be unlikely related to study drug (Subject EN3203-004-028-014), while for the other three the event was judged to be likely related to study drug. Each of the four subjects required naloxone for treatment of the event.

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'. These events are summarized in the table below.

Selected Respiratory System Adverse Events

Subject ID/ Protocol	Age/ Gender/ Race	Treatment/ Dose (mg)	Preferred Term	Investigator Term	Serious AE	AE Onset Date/ AE End Date	Severity/ Relationship/ Action Taken/ Outcome
EN3202-012-018-002/ EN3202-012	65/M/C	Oxymorphone ER/ 20	Respiratory acidosis	Respiratory acidosis	Yes	06JUL00/ 06JUL00	Severe/ Probably/ Study drug discontinued/ Unknown
EN3202-016-006-030/ EN3202-021	47/M/C	Oxymorphone ER/ 220	Hypoventilation	Intermittent shallow respiration	No	09OCT01/ 31OCT01	Mild/ Probably/ None/ Resolved w/o sequelae
EN3202-016-021-002/ EN3202-016	53/F/C	Post-treatment	Respiratory distress	Respiratory distress	Yes	08JUN01/ 09JUN01	Mild/ Unlikely/ None/ Resolved w/o sequelae
EN3202-017-008-001/ EN3202-020	67/M/C	Oxymorphone ER/ 280	Respiratory distress	Respiratory distress	Yes	14MAR01/ 30MAR01	Moderate/ Unlikely/ ./ Resolved w/o sequelae
EN3202-017-008-001/ EN3202-020	67/M/C	Oxymorphone ER/ 200	Respiratory failure (exc neonatal)	Resp. Insufficiency	No	11JUL00/ 05JUL01	Moderate/ Unlikely/ ./ Continuing

Selected Respiratory System Adverse Events							
Subject ID/ Protocol	Age/ Gender/ Race	Treatment/ Dose (mg)	Preferred Term	Investigator Term	Serious AE	AE Onset Date/ AE End Date	Severity/ Relationship/ Action Taken/ Outcome
EN3202-017-008-001/ EN3202-020	67/M/C	Oxymorphone ER/ 280	Respiratory failure (exc neonatal)	Respiratory failure	Yes	14MAR01/ 30MAR01	Moderate/ Unlikely/ ./ Unknown
EN3202-017-008-003/ EN3202-020	50/F/C	Oxymorphone ER/171	Respiratory distress	Inc. Resp. Distress	No	11NOV00/ 06DEC00	Severe/ Unlikely/ ./ Continuing
EN3202-017-008-003/ EN3202-020	50/F/C	Oxymorphone ER/171	Respiratory failure (exc neonatal)	Resp. Insufficiency sob	No	23SEP00/ 11NOV00	Mild/ Unlikely/ ./ Continuing
EN3202-019-067-017/ EN3202-021	62/M/C	Oxymorphone ER/ 40	Respiratory depression	Resp depression	Yes	20FEB02/ 01MAR02	Severe/ Probably/ Study drug discontinued/ Resolved w/o sequelae
EN3202-019-067-017/ EN3202-021	62/M/C	Oxymorphone ER/ 40	Respiratory failure (exc neonatal)	Resp failure	Yes	20FEB02/ 01MAR02	Severe/ Probably/ Study drug discontinued/ Resolved w/o sequelae
EN3203-004-007-005/ EN3203-004	75/M/C	Oxymorphone IR/ 40	Respiratory distress	Respiratory distress	Yes	13APR01/ 13APR01	Moderate/ Possibly/ Study drug discontinued/ Resolved w/o sequelae
EN3203-004-014-038/ EN3203-004	55/F/C	Oxymorphone IR/ 60	Respiratory depression	Respiratory depression	No	15JAN02/ 15JAN02	Moderate/ Unlikely/ Study drug discontinued/ Resolved w/o sequelae
EN3203-004-028-014/ EN3203-004	72/M/O	Oxymorphone IR/ 30	Respiratory depression	Respiratory depression	No	23FEB02/ 23FEB02	Mild/ Unlikely/ None/ Resolved w/o sequelae
EN3203-004-030-012/ EN3203-004	70/F/C	Oxymorphone IR/ 20	Respiratory depression	Respiratory depression	No	26FEB02/ 27FEB02	Moderate/ Probably/ Study drug discontinued/ Resolved w/o sequelae
EN3203-004-030-013/ EN3203-004	54/F/C	Oxymorphone IR/120	Respiratory depression	Respiratory depression	No	27FEB02/ 28FEB02	Mild/ Probably/ Study drug discontinued/ Resolved w/o sequelae
EN3203-004-030-022/ EN3203-004	72/M/C	Oxymorphone IR/ 20	Hypoventilation	Hypoventilation	Yes	06MAR02/ 07MAR02	Moderate/ Possibly/ Study drug discontinued Resolved w/o sequelae
Source: Appendix 10.3 in the ISS							

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'.

Review of the other cases, which occurred in the studies for chronic non-malignant pain or cancer pain, reveals the following:

Subject EN3202-016-006-030 had intermittent shallow respiration (preferred term – hypoventilation), which was not rated as serious and required no action with regard to the study drug.

Subject EN3202-016-021-002 had a drug overdose 33 days after her last study visit, accompanied by mild somnolence and mild respiratory distress. These events resolved the following day. The drugs involved were not identified. Her last study visit occurred four days after she began double-blind treatment with oxycodone ER, and was subsequently lost to follow-up.

Subject EN3202-017-008-001, a 68-yearold man with metastatic lung carcinoma, had one episode of respiratory distress and respiratory failure that was attributed to post-obstructive pneumonia. A second episode of respiratory distress and respiratory failure was attributed to disease progression. Each of these events was judged to be unlikely related to study medication.

Subject EN3202-017-008-003, a 53-year-old woman with metastatic breast carcinoma, experienced one episode of respiratory failure associated with a malignant pleural effusion. She later experienced an episode of respiratory distress associated with a recurrent pleural effusion. Each of these events was judged to be unrelated to study drug.

Subject EN3202-019-067-017, a 62-year-old man with metastatic prostate cancer, had a "narcotic overdose". The narrative notes that the subject had been taking oxymorphone ER with oxymorphone IR rescue medication for pain control. Upon admission to a hospital for pneumonia, oxycodone ER and morphine sulfate were added. Respiratory depression and somnolence developed, for which he required naloxone. The respiratory failure was attributed to the study medication and to the other narcotics. Study medication was discontinued.

Review of these selected respiratory cases is notable for the fact that in the setting of chronic pain, these respiratory events were usually in the setting of, and attributed to, the chronic underlying disease, usually progression of cancer. In one subject, respiratory depression was due to receiving three opioid analgesics simultaneously. Because many of these cases occurred in the open-label extension studies, comparisons with other treatments or placebo can not be made. These selected respiratory event in the acute post-operative setting, however, are notably different from those in the chronic pain setting. First, most of the events in the post-operative setting appear 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 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. At the Agency's request, the Sponsor has prepared a table of all adverse events in all subjects in the oxymorphone clinical development program who received naloxone. Using data from the adverse event dataset and the concomitant medication dataset, the Sponsor identified, when possible, the adverse event(s) that required treatment with naloxone in each subject. The table below summarizes these events.

Listing of Subjects Who Received Naloxone Treatment

Protocol	Subject ID	Study Treatment/Dose(mg)	Preferred Term	AE Verbatim Name
EN3202-012	EN3202-012-011-004	Oxymorphone ER/60	Confusion	Confusion
			Drug Interaction NOS	Drug interaction
			Somnolence	Somnolence
	EN3202-012-011-023	Oxymorphone ER/20	Lethargy	Lethargy
	EN3202-012-018-002	Oxymorphone ER/20	Central nervous system depression NOS	CNS depression
	EN3202-012-019-023	Oxymorphone ER/20	Sedation	Over sedation
EN3202-017	EN3202-017-010-002	Oxycodone ER/160	Lethargy	Lethargy
	EN3202-017-011-003	Oxycodone ER/200	Central nervous system depression NOS	Narcotic depression
EN3202-020	EN3202-017-016-010	Oxymorphone ER/40	Sedation	Extreme sedation
EN3202-025	EN3202-025-035-008	Oxymorphone ER/40	Central nervous system depression NOS	CNS depression
EN3203-004	EN3203-004-013-080	Oxymorphone IR/40	Lethargy	Lethargic
	EN3203-004-014-017*	Placebo/0	Received naloxone prior to study medication for 'apnea'	
	EN3203-004-014-030	Oxymorphone IR/90	Hypoxia	Hypoxia
	EN3203-004-014-038	Oxymorphone IR/60	Respiratory Depression	Respiratory depression
			Somnolence	Somnolence
	EN3203-004-015-030	Oxymorphone IR/30	Sedation	Sedation
	EN3203-004-019-008	Oxymorphone IR/30	Confusion	Confusion
			Aggression	Combative
			Agitation	Agitation
			Depressed level of consciousness	Decreased level of consciousness
			Lethargy	Lethargy
	EN3203-004-021-011	Oxymorphone IR/60	Depressed level of consciousness	Not arousable (Obtunded)
	EN3203-004-022-003*	Oxymorphone IR/60	No AE - Received naloxone prior to study medication for 'itching'	
	EN3203-004-027-007*	Oxymorphone IR/10	No AE - Received naloxone prior to study medication for 'post-op somnolence'	
	EN3203-004-028-007	Oxymorphone IR/30	Coma NEC	Unresponsiveness
			Somnolence	Drowsiness
	EN3203-004-028-014	Oxymorphone IR/30	Coma NEC	Unresponsiveness
			Respiratory Depression	Respiratory depression
	EN3203-004-029-022*	Oxymorphone IR/30	No AE - Received naloxone prior to study medication for 'reversal of sedative effects'	
	EN3203-004-030-012	Oxymorphone IR/20	Respiratory depression	Respiratory depression
	EN3203-004-030-022	Oxymorphone IR/20	Somnolence	Somnolence
	EN3203-004-032-001	Oxymorphone IR/30	Coma NEC	Unresponsiveness
EN3203-005	EN3203-005-105-099	Oxycodone IR/30	Sedation aggravated	Increased sedation
	EN3203-005-201-020*	Oxycodone IR/30	No AE - Received naloxone prior to study medication for 'anesthesia'	
	EN3203-005-301-117	Oxymorphone IR/20	No AE listed corresponding to reason for naloxone, which is listed as 'respiratory stimulus' in the concomitant medication dataset	
	EN3203-005-302-022	Oxymorphone IR/20	Coma NEC	Unresponsiveness

*Received naloxone prior to receiving study medication

Source: Sponsor table in information sent to Agency on September 30, 2003, and reviewer's analysis of concomitant medication dataset (iss_meds.xpt)

Review of the above table is notable for the fact that 5 of the 27 subjects who received naloxone did so before receiving any study medication. In addition, 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 complete table of adverse events in these subjects that the Sponsor has prepared (see submission of September 30, 2003) is notable for the observation that many subjects had multiple, simultaneous adverse events, any one of which, if sufficiently severe, could have required naloxone treatment. The adverse events in the above table are based on the reason for the concomitant medication that the investigator provided on the concomitant medication CRF. 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 EN3203-004 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.

1.5.10 Adverse Events Over Time

The Sponsor has explored the time course of adverse events by examining the duration of adverse events (section 6.6.1 if the ISS), the time to onset of opioid-related adverse events (Section 6.6.2 of the ISS), and the occurrence of late-onset adverse events (Section 14 if the ISS).

The Sponsor notes that the time course of adverse events in the Phase 1 trials and in the Phase 2 acute post-operative pain trials were not assessed due to the short duration of treatment in those studies.

1.5.10.1 Duration of Adverse Events

The analysis of duration of adverse events does not include adverse events obtained from adverse event checklists.

The table below, based on Table 33 in the ISS and on Appendix 3.37 in the ISS, presents the median duration and range of durations for treatment-emergent adverse events occurring in more that 5% of subjects treated with oxymorphone ER in the Phase 2/3 oxymorphone ER trials. Review of this table indicates that the adverse events with the longest median duration in oxymorphone ER-treated subjects were constipation (median duration 12.0 days), somnolence (median duration 11.0 days), and dry mouth (median duration 10.5 days). The corresponding median durations for these three adverse events in oxycodone ER-treated subjects was 18.0, 15.0, and 13.5 days, respectively. All other adverse events had a median duration of 6.0 days or less in oxymorphone ER-treated subjects. The wide range of durations indicates that some events were persistent. The differences in the upper end of the duration ranges between the oxymorphone ER treatment group and the other treatment group is a reflection of the fact that that oxymorphone ER treatment group includes data from the open-label extension studies, while data for the other treatment groups come exclusively from controlled clinical trials.

Table. Median Duration (Days) of Treatment-Emergent Adverse Events Occurring in 5% or more Oxymorphone ER Subjects by Treatment – Phase 2/3 Oxymorphone ER Trials

	Median (Range) Duration (in days) of Adverse Events [a] [b] [c]					
	Oxymorphone					
MedDRA Preferred Term	ER/IR	ER	IR	Oxycodone ER	Morphine ER	Placebo
Number of Subjects [e]	1064	1057	34	382	69	350
Nausea	3.0(1-589)	3.0(1-589)	0.0(0-0)	4.0(1- 33)	3.0(1- 16)	2.0(1- 28)
Constipation	12.0(1-679)	12.0(1-679)	0.0(0-0)	18.0(1- 42)	21.0(21- 21)	3.5(1- 30)
Vomiting NOS	2.0(1- 45)	2.0(1- 45)	0.0(0-0)	2.0(1- 8)	4.0(1-7)	1.0(1- 5)
Somnolence	11.0(1-665)	11.0(1-665)	0.0(0-0)	15.0(2- 32)	9.0(5-9)	4.5(1- 27)
Dizziness (exc vertigo)	3.0(1-374)	3.0(1-374)	8.0(8-8)	3.0(1- 28)	7.0(3-7)	3.0(1- 16)
Pruritus NOS	6.0(1-629)	6.0(1-629)	0.0(0-0)	7.5(2- 33)	5.5(5-6)	1.0(1- 15)
Headache NOS	2.0(1-573)	2.0(1-573)	11.0(11- 11)	3.0(1- 28)	1.0(1-1)	2.5(1- 24)
Dry mouth	10.5(1-295)	10.5(1-295)	0.0(0-0)	13.5(1- 45)	0.0(0-0)	22.0(22- 22)
Diarrhoea NOS	4.0(1-394)	4.0(1-394)	4.0(4-4)	2.0(1- 13)	5.0(1- 23)	2.0(1- 7)
Sweating increased	3.0(1-426)	3.0(1-426)	0.0(0-0)	1.0(1- 10)	0.0(0-0)	2.0(1- 22)
Sedation	4.0(1- 49)	4.0(1- 49)	0.0(0-0)	2.0(1- 14)	0.0(0-0)	1.0(1- 1)

[a] Longest duration is used for subjects that have more than one occurrence
[b] Duration is reported for the treatment the subject was on at the onset of the AE and is the total duration of the AE
[c] Duration could not be determined for AEs obtained from the opioid symptom checklist and are not included
[d] Either or both Oxymorphone formulations
[e] Number of subjects at risk

Source: Sponsor Table 33 in the ISS

The table below, based in Appendix 3.75 in the ISS, presents the median duration and range of durations for treatment-emergent adverse events occurring in more that 5% of subjects treated with oxymorphone ER in the chronic non-malignant pain clinical trials. Review of this table indicates that the adverse events with the longest median duration in oxymorphone ER-treated subjects were constipation (median duration 9.0 days), somnolence (median duration 9.0 days), and dry mouth (median duration 10.0 days). The corresponding median durations for these three adverse events in oxycodone ER-treated subjects were 18.0, 15.0, and 14.5 days, respectively. In the placebo group, the median duration of constipation was notably shorter than in the other two groups (4.0 days), while the median duration for somnolence (11.5 days) and dry mouth (22.0 days) were longer than the median durations in the oxymorphone ER-treated groups. All other adverse events had a median duration of 6.0 days or less in oxymorphone ER-treated subjects. The wide range of durations indicates that some events were persistent, and is similar between the oxymorphone ER treatment group and the oxycodone ER treatment group.

Table. Median Duration (Days) of Treatment-Emergent Adverse Events Occurring in 5% or more Oxymorphone ER Subjects by Treatment – Chronic Non-malignant Pain Trials

MedDRA Preferred Term	Median (range) Duration (in days) of Adverse Events [a] [b] [c] Oxymorphone ER	Oxycodone ER	Placebo
Number of Subjects [d]	684	286	289
Nausea	3.0(1- 49)	4.5(1- 33)	5.0(1- 28)
Constipation	9.0(1- 34)	18.0(1- 42)	4.0(1- 30)
Dizziness (exc vertigo)	3.0(1- 48)	3.0(1- 28)	6.0(1- 16)
Vomiting NOS	2.0(1- 27)	1.0(1- 8)	1.0(1- 5)
Somnolence	9.0(1- 41)	15.0(2- 32)	11.5(2- 27)
Pruritus NOS	5.0(1- 34)	7.5(2- 33)	2.5(1- 15)
Headache NOS	2.0(1- 22)	3.5(1- 28)	3.0(1- 24)
Dry mouth	10.0(1- 34)	14.5(1- 45)	22.0(22- 22)
Sweating increased	3.0(1- 21)	1.0(1- 4)	2.5(1- 22)
Sedation	5.5(2- 49)	0.0(0- 0)	0.0(0- 0)

[a] Longest duration is used for subjects that have more than one occurrence
[b] Duration is reported for the treatment the subject was on at the onset of the AE and is the total duration of the AE
[c] Duration could not be determined for AEs obtained from the opioid symptom checklist and are not included (EN3202-016)
[d] Number of subjects at risk

Source: Appendix 3.75 in the ISS

1.5.10.2 Time to Onset of Opioid-related Adverse Events

The time to onset of treatment-emergent adverse events was evaluated in the two-placebo-controlled studies in subjects with chronic non-malignant pain (EN3202-015 and EN3202-025). In these two studies, subjects participated in a 2-7 day washout period, during which all analgesic treatment was prohibited. Subjects who were then randomized to the highest doses of oxymorphone ER (ie, 40 or 50 mg) received 1-2 weeks of double-blind treatment at a lower dose (20 mg) before receiving the assigned dose randomized treatment for an additional 1 to 2 weeks. Kaplan-Meier analysis was used to estimate the cumulative proportion of subjects with treatment emergent adverse events. The focus of the analysis was on the time – to-onset of opioid-related adverse events (ie, constipation, dizziness, sedation, nausea, vomiting, sweating increased, and pruritus). The table below summarizes the cumulative proportion experiencing an given adverse event at each of eight time points.

Table. Cumulative proportion [a] of subjects experiencing selected adverse events (first occurrence) over time in oxymorphone ER-treated subjects in studies EN3202-015 and EN3202-025

Preferred Term	Study Day 1	3	5	7	14	21	28	>28
Nausea	0.18	0.39	0.42	0.43	0.47	0.51	0.54	0.57
Constipation	0.03	0.18	0.23	0.26	0.33	0.34	0.35	0.36
Dizziness	0.1	0.21	0.22	0.22	0.25	0.28	0.29	
Vomiting NOS	0.08	0.20	0.21	0.22	0.25	0.26	0.29	0.32
Somnolence	0.05	0.18	0.20	0.20	0.24	0.27	0.27	0.29
Pruritus	0.06	0.15	0.18	0.18	0.20	0.21		

[a] Kaplan-Meier product limit estimate

Source: Appendix 3.112 in the ISS

Review of the above table indicates that these relatively common opioid-related adverse events occurred early in the course of treatment, with little rise in the cumulative frequency after 14 days of treatment. Data

for the placebo and oxycodone ER-treated subjects is not shown in the table above, though the data in Appendix 3.112 of the ISS indicates that the same temporal pattern occurs in these two treatment groups.

1.5.10.3 Late-onset Adverse Events

The Sponsor defined late-onset adverse events as "adverse events for which the day of onset of the first occurrence was after 28 days of treatment" (see Section 14 of the ISS).

The table below, based on Appendix 9.5 of the ISS, presents the incidence rates of late-onset adverse events occurring in 5% or more or oxymorphone ER-treated subjects in the Phase 2/3 clinical trials.

Incidence Rate of Late-onset Adverse Events Occurring in 5% or More of Oxymorphone ER-treated subjects in the Phase 2/3 Clinical Trails in the ISS

	One or More Occurrences	
MedDRA Preferred Term	Oxymorphone ER	
Number of Subjects N[a]	417	
Any Adverse Experience[b]	315	(75.5%)
Nausea	75	(18.0%)
Vomiting NOS	58	(13.9%)
Constipation	57	(13.7%)
Pruritus NOS	38	(9.1%)
Diarrhoea NOS	36	(8.6%)
Somnolence	34	(8.2%)
Dizziness (exc vertigo)	32	(7.7%)
Sedation	25	(6.0%)
Headache NOS	25	(6.0%)
Sweating increased	23	(5.5%)

[a] Total number of subjects at risk
[b] Total number of subjects with adverse experiences (one or more)

Source: Appendix 9.5 in the ISS

Review of the above table indicates that the incidence of any individual late-onset adverse event is lower than those observed in the time-to-onset analyses, which focused on the first 28 days of treatment. The Sponsor concludes that these data demonstrate that "opioid-acclimated subjects are less likely to develop new AEs".

1.5.11 Analysis of Dose-Response Relationships

To evaluate potential dose-response relationships between study medication and adverse events, the Sponsor performed an incident-dose analysis. In the incident-dose analysis, the number of subjects "at risk" in a dose group was the total number of subjects who had received that dose of study medication, excluding subjects who had the first occurrence of the adverse event at a lower dose of the same study medication. The incidence was then determine by the calculating the proportion of "at-risk" subjects whose first occurrence of the adverse event was at that dose.

The table below, based on Appendix 5.1 in the ISS, presents the incidence rates for the most frequently occurring adverse events by incident daily oxymorphone ER daily dose for subjects in the Phase 2/3 oxymorphone ER trials.

Table. Incidence of Treatment-Emergent Adverse Experiences by Dose (mg/day) and Preferred Term (MedDRA) at First Occurrence In Descending Frequency (events occurring in >= 5% of Oxymorphone ER-treated subjects) Subset: All ER Phase 2/3 Trials

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

[a] Total number of subjects at risk

Source: Appendix 5.1 in the ISS

Review of this table indicates that the incidence of adverse events at the 10-29 mg/day dose level was higher than the incidence at doses less than or equal to 10 mg/day for most adverse events. At dose levels of >29-50 mg/day, the incidence of some adverse events was higher than at the 10-29 mg/day dose levels. As dose levels increased to >50-70 mg/day and to >70-90 mg/day, the incidence of adverse events was somewhat lower than at the >29-50 mg/day dose level. At the >90 mg/day dose level, the incidence many adverse events was somewhat higher than the incidence at the two dose levels immediately below the >90 mg/day dose level. For three adverse events (constipation, sedation, and sweating increased), the highest incidence was at the >90 mg/day level. For six adverse events (nausea, dizziness, pruritus, vomiting, somnolence, and headache), the highest incidence was at the 29-50 mg/day level. For dry mouth the highest incidence was at the 10-29 mg/day dose level, while for diarrhea the highest incidence was at the >70-90 mg/day dose level.

The dose-response pattern was generally similar in the chronic-non-malignant pain trials, though more adverse events had their highest incidence at the >90 mg/day dose level (see Appendix 5.7 in the ISS). Constipation, sweating increased, headache, and sedation each had the highest incidence at the >90 mg/day dose level. Nausea, dizziness, pruritus, and somnolence each had their highest incidence at the 29-50 mg/day dose level. The incidence of vomiting was equally high at the 29-50 mg/day and >90 mg/day dose levels. The incidence of dry moth was highest at the 10-29 mg/day dose level.

Incident dose analyses in the cancer pain subset of trial was notable for the higher incidence of adverse events at dose levels below 50 mg/day compared to dose level higher than 50 mg/day (see Appendix 5.13 in the ISS).

The Sponsor has also prepared analyses of dose response by modal daily dose and by maximum daily dose. These analyses will not be considered any further here.

The table below, based on Appendix 5.19 in the ISS, presents the incidence rates for the most frequently occurring adverse events by incident daily oxymorphone IR daily dose for subjects in the Phase 2/3 oxymorphone ER trials.

Table. Incidence of Treatment-Emergent Adverse Experiences by Dose (mg/day) and Preferred Term (MedDRA) at First Occurrence In Descending Frequency (events occurring in >= 5% of Oxymorphone IR-treated subjects)

	Oxymorphone IR Dose					
MedDRA Preferred Term	<=10 mg	>10-29 mg	>29-50 mg	>50-70 mg	>70-90 mg	>90 mg
PYREXIA [a]	93	108	90	48	38	25
	16 (17.2%)	13 (12.0%)	17 (18.9%)	10 (20.8%)	9 (23.7%)	8 (32.0%)
NAUSEA [a]	93	108	93	52	39	29
	10 (10.8%)	12 (11.1%)	13 (14.0%)	9 (17.3%)	8 (20.5%)	3 (10.3%)
SOMNOLENCE [a]	93	108	91	50	41	31
	10 (10.8%)	18 (16.7%)	9 (9.9%)	7 (14.0%)	3 (7.3%)	2 (6.5%)
DIZZINESS (EXC VERTIGO) [a]	93	108	93	51	41	31
	5 (5.4%)	12 (11.1%)	3 (3.2%)	5 (9.8%)	2 (4.9%)	1 (3.2%)
PRURITUS NOS [a]	93	108	92	51	41	30
	2 (2.2%)	7 (6.5%)	7 (7.6%)	3 (5.9%)	3 (7.3%)	4 (13.3%)
VOMITING NOS [a]	93	108	93	52	40	29
	6 (6.5%)	3 (2.8%)	8 (8.6%)	4 (7.7%)	5 (12.5%)	0 (0.0%)
CONSTIPATION [a]	93	108	92	52	40	29
	6 (6.5%)	2 (1.9%)	2 (2.2%)	4 (7.7%)	3 (7.5%)	0 (0.0%)

[a] Total number of subjects at risk

Source: Table 5.19 in the ISS

Compared to the data from the Phase 2/3 oxymorphone ER studies, the data from the oxymorphone IR studies demonstrate relatively little dose-response with regard to the frequent adverse events, especially in light of the small number of subjects in these studies.

The above data do not suggest a linear dose-response relationship between oxymorphone dose and the incidence of frequent adverse events. In the oxymorphone ER trials, there may be more of a bimodal pattern of adverse events, relative to dose, with increasing incidence through dose levels up to 50 mg/day, followed by decreasing incidences at doses between 50-90 mg/day, followed again by increasing incidences at doses above 90 mg/day. This pattern may be true for some adverse events and not others. There may be other confounding factors, such as duration of treatment at each dose level, that may influence these rates. Data on duration of treatment at these dose levels was not analyzed.

The Sponsor did not analyze the relationship of adverse events to drug concentration . The Sponsor did note, however, that there was no association between plasma concentration and age, gender, or race after accounting for dose (see Section 10.2 of the ISS).

1.5.12 Adverse Events in Opioid Naïve and Opioid Experienced Subjects

The Sponsor has compared the incidence rates of adverse events occurring in 5% or more oxymorphone ER-treated subjects in Studies EN3202-015 and EN3202-025 between opioid naïve subjects and opioid experienced subjects. These data are summarized in the table below.

Incidence of All Treatment-Emergent Adverse Experiences [N(%)] by Opioid Experience, Treatment Group, and Preferred Term (MedDRA) in Descending Frequency (Events Occurring in >= 5% of Oxymorphone ER-treated subjects) Subset: EN3202-015 and EN3202-025

	Number (%) of Subjects Reporting	
	Opioid Naïve	Opioid Experienced
Number of Subjects [a]		
Oxymorphone ER	309	209
Oxycodone ER	67	58
Placebo	126	89
Any Adverse Experience		
Oxymorphone ER	228 (73.8%)	146 (69.9%)
Oxycodone ER	50 (74.6%)	37 (63.8%)
Placebo	31 (24.6%)	21 (23.6%)
Nausea		
Oxymorphone ER	155 (50.2%)	99 (47.4%)
Oxycodone ER	33 (49.3%)	21 (36.2%)
Placebo	11 (8.7%)	10 (11.2%)
Constipation		
Oxymorphone ER	93 (30.1%)	56 (26.8%)
Oxycodone ER	31 (46.3%)	14 (24.1%)
Placebo	13 (10.3%)	5 (5.6%)
Dizziness (EXC vertigo)		
Oxymorphone ER	90 (29.1%)	45 (21.5%)
Oxycodone ER	20 (29.9%)	12 (20.7%)
Placebo	6 (4.8%)	4 (4.5%)
Vomiting NOS		
Oxymorphone ER	83 (26.9%)	49 (23.4%)
Oxycodone ER	6 (9.0%)	7 (12.1%)
Placebo	2 (1.6%)	2 (2.2%)
Pruritus NOS		
Oxymorphone ER	62 (20.1%)	37 (17.7%)
Oxycodone ER	5 (7.5%)	5 (8.6%)
Placebo	2 (1.6%)	2 (2.2%)
Sweating increased		
Oxymorphone ER	26 (8.4%)	17 (8.1%)
Oxycodone ER	5 (7.5%)	3 (5.2%)
Placebo	1 (0.8%)	3 (3.4%)

[a] Total number of subjects at risk

Source: Appendix 3.105 in the ISS

Review of the above table suggests that each of these adverse events was more common in oxymorphone ER and oxycodone ER-treated subjects than in placebo-treated subjects, regardless of prior opioid experience. In general, 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. However, for all adverse events in the table above except dizziness, the between-group differences among oxymorphone ER-treated subjects were less than 4%. Dizziness occurred in 29.1% of opioid naïve oxymorphone ER-treated subjects, compared to 21.5% of opioid experienced oxymorphone ER-treated subjects.

1.5.13 Elicited Adverse Events

Three clinical studies of oxymorphone ER (EN3202-016, EN3202-018, and EN3202-019) used a checklist to assess the occurrence and severity of opioid-related symptoms, including constipation, dizziness, sedation, nausea, vomiting, sweating and pruritus. In these studies, this checklist was used instead of recording the events on the adverse event CRF page, unless the event was serious. Serious adverse events were also recorded on the adverse event CRF page. Adverse events collected on the checklist were pooled with the spontaneously reported adverse events for calculation of incidence rates and for analyses of intensity, relationship to treatment, and prevalence.

Across these three clinical trials, the most common elicited adverse events among oxymorphone ER-treated subjects were constipation (49.6%), sedation (37.9%), nausea (30.8%), and pruritus (30.0%). Because these data have been incorporated into the pooled adverse event data for this ISS, they will not be considered here any further. Section 6.8 of the ISS has full details of these analyses.

1.6 Clinical Evaluations

1.6.1 Clinical Laboratory Tests

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

1.6.1.1 Clinical Chemistry Results

Clinical chemistry tests included the tests listed in the table below.

Clinical Chemistry Tests		
Sodium	Alanine aminotransferase (ALT)	Creatine kinase
Potassium	Aspartate aminotransferase (AST)	CK BB isoenzyme
Chloride	Alkaline phosphatase	CK MB isoenzyme
Carbon dioxide	Gamma-glutamyl transferase	CK MM isoenzyme
Calcium	Lactate dehydrogenase	
Phosphorus	Total bilirubin	
Uric acid	Total protein	
Blood urea nitrogen	Albumin	
Creatinine	Cholesterol	
Glucose	Triglycerides	

Not all tests were performed in all studies. Some tests, such as the creatine kinase BB, MB, and MM isoenzymes were performed on only a few subjects.

The Sponsor provided the normal ranges for all clinical chemistry tests used in each of the trials. In addition, the Sponsor defined limits for clinically significantly abnormal lab values. The Sponsor presented clinical chemistry results in three ways: 1) mean and median changes from baseline were calculated for each lab test for six clinical trial subsets: Phase 2/3 ER studies, chronic non-malignant pain studies, cancer pain studies, Phase 2/3 IR studies, and Phase 1 studies, 2) shift tables were prepared for each lab test for each of the six clinical trial subsets, and 3) a listing of clinically significant abnormal labs was presented.

Review of the definitions of the clinically significant abnormal lab values (see Appendix 4.1.B in the ISS) is notable for the definition of a clinically significantly abnormal creatinine, which is defined as a creatinine level greater than three times the upper limit of normal. This definition appears too restrictive, as it will miss many creatinine values between 2.0 mg/dL and 4.0 mg/dL, assuming an upper limit of normal of 1.3 mg/dL (as was used in Study EN3202-001).

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.

For oxymorphone ER-treated subjects in the Phase 2/3 ER studies, the mean and median changes in each clinical chemistry test were calculated based on the subject's dose at the endpoint, with the endpoint doses grouped into six ranges (<=10 mg/day, >10-29, >29-50, >50-70, >70-90, and >90) (see Appendix 4.32 in the ISS). Review of these data 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.

The Sponsor calculated the proportion of subjects in each treatment group with at least one abnormal lab value for each clinical chemistry test (see Appendix 4.33 in the ISS). In general, the incidence of treatment-emergent abnormal lab values was similar among the treatment groups, but varied among the tests themselves. Among oxymorphone ER-treated subjects, the incidence of treatment-emergent abnormal lab values was below 5% for alkaline phosphatase, chloride, carbon dioxide, creatinine, and uric acid. The incidence of treatment-emergent abnormal lab values was between 5% and 10% for blood urea nitrogen, calcium, gamma-glutamyl transferase, lactate dehydrogenase, alanine aminotransferase (SGPT), sodium, and total protein. The incidence of treatment-emergent abnormal lab values was above 10% for albumin, cholesterol, creatine kinase, glucose, phosphorus, SGOT, total bilirubin, and triglycerides. The Sponsor notes that there were two chemistry tests for which the incidence rates in the oxymorphone ER group were greater than 1% and at least two time the percentage among placebo-treated subjects: chloride (2.7% in the oxymorphone ER group and 0.9% in the placebo group) and ALT (9.8% in the oxymorphone ER group and 2.6% in the placebo group).

The Sponsor calculated the proportion of subjects in each treatment group with at least one clinically significant abnormal lab value for each clinical chemistry test (see Appendix 4.34 in the ISS). In general, the incidence of treatment-emergent clinically significant abnormal lab values was similar among the treatment groups, but varied among the tests themselves. 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%). The Sponsor noted that the incidence of treatment-emergent clinically significant abnormal lab values similar in the placebo group and in the oxymorphone ER group for all clinical chemistry tests except albumin. The incidence of a clinically significant abnormal albumin values was 9.1% in the placebo group and 4.6% in the oxymorphone ER group.

Review of the above analyses for the chronic non-malignant pain trials and the cancer pain trials subsets provided little additional insight.

The Sponsor has presented shift tables for selected clinical chemistry laboratory tests: albumin, alkaline phosphatase, AST, ALT and total bilirubin.. These shift tables have been presented only for oxymorphone-treated subjects. The post-baseline values used in the shift tables were the values that represented the maximum absolute change from baseline. For albumin, only shift to lower values were of interest, for the other tests, only shifts to higher values were of interest.

For albumin, 88.1% of subjects in all Phase 2/3 ER studies with normal results at baseline had post-baseline results that remained in the normal range (see Appendix 4.42). 9.5% of subjects had a shift from normal to abnormally low, and 1.4% of subjects had a shift from normal to clinically significantly abnormal. For the 72 subjects with an abnormally low baseline albumin level, 42 (58.4%) remained abnormally low or returned to the normal range. Thirty subjects (41.7%) developed clinically significantly abnormal albumin levels (see Appendix 4.42 in the ISS). Shift tables for albumin in the chronic non-malignant pain studies and in the cancer pain studies reveal a lower incidence of shifts to the clinically significantly abnormal range, compared to all Phase 2/3 studies. Review of the listing of clinically significantly abnormal albumin values among oxymorphone ER-treated subjects indicates that many of these occurred in the acute post-operative stetting (Study EN3202-012), where clinically significantly low albumin values occurred in all treatment groups.

Shift in alkaline phosphatase were rare (see Appendix 4.45). Among oxymorphone ER-treated subjects in the Phase 2/3 ER studies, 37 subjects (4.3%) shifted from a normal value at baseline to an abnormally high value post-baseline. One subject who had a clinically significantly high value at baseline had a persistently clinically significantly high value post-baseline. Apart from this subject, no oxymorphone ER-treated subject in the Phase 2/3 ER program had a clinically significantly high alkaline phosphatase value. There were no clinically significantly abnormal values of LDH among oxymorphone ER-treated subjects in the Phase 2/3 ER program (see Appendix 4.66).

In the Phase 2/3 ER studies, there were no clinically significantly abnormal values of blood urea nitrogen among oxymorphone ER-treated subjects (see Appendix 4.48). There was one shift among oxymorphone ER-treated subjects in the Phase 2/3 ER trials of creatinine from abnormally high (1.4 mg/dL) at baseline to clinically significantly high post-baseline (3.6 mg/dL) (Subject EN3202-017-011-005 in Study EN3202-020) (see Appendix 4.60).

Among oxymorphone ER-treated subjects in the Phase 2/3 clinical trial shifts in glucose levels were mainly to abnormally high levels (see Appendix 4.63). Of 719 oxymorphone ER-treated subjects with normal glucose levels at baseline, 31 (4.3%) developed clinically significantly high levels post-baseline. The shift rates were similar in the subsets of chronic non-malignant pain trials and cancer pain trials.

Among oxymorphone ER-treated subjects in the Phase 2/3 ER studies, there was only one oxymorphone ER-treated subject who had a normal baseline calcium level and a clinically significantly high post-baseline calcium level (see Appendix 4.51). Subject EN3202-016-024-003 had a clinically significantly high calcium level at the end of placebo treatment in Study EN3202-016, which was recorded as the screening value in study EN3202-021. Among 853 oxymorphone ER-treated subjects in the phase 2/3 studies with abnormal calcium level at baseline, 8 (0.9%) developed a clinically significantly low post-baseline values. Most of the clinically significantly low values of calcium were in the 7.4-8.0 mg/dL range. Two subjects had post baselines values below 7.0 mg/dL. These were Subject EN3202-017-013-001 (treated with morphine ER) and Subject EN3202-019-067-001 (treated with oxycodone ER). Shifts in phosphorus were more common (see Appendix 4.69). Of 903 oxymorphone ER-treated subjects who had normal baseline phosphorus levels, 74 (8.2%) developed clinically significantly low post-baseline levels. As noted below, while these abnormalities occurred in all clinical trial groups, they were specially frequent in the acute post-operative setting.

Clinically significantly abnormal values of potassium included both high and low levels. Among 908 oxymorphone ER-treated subjects in the Phase 2/3 trials with normal baseline potassium levels, 7 (0.8%) developed clinically significantly low levels, while 8 (0.9%) developed clinically significantly high levels. Clinically significantly abnormal levels of sodium were rare. Of 856 oxymorphone ER-treated subjects in

the Phase 2/3 studies, 2 (0.2%) developed clinically significantly low values post-baseline, while none developed clinically significantly high values post-baseline.

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 (ie, 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 trial, 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. Data for these four subjects is presented in the table below:

Table. Subjects with Treatment Emergent, Clinically Significantly Abnormal Elevations of Both AST and ALT.

Subject ID	Protocol	Treatment	Study Day	Lab Test	On Study	Baseline	Comments
EN3202-012-019-006	EN3202-012	Oxymorphone ER	2	ALT	177	16	No follow-up values available. Adverse events describing increased AST and increased ALT judged these events to be moderate in severity, possibly related to study drug, and outcome unknown. Investigator notes that this may be possibly due to study drug.
				AST	173	20	
EN-3202-012-022-010	EN3202-012	Oxymorphone ER	2	ALT	264	12	No follow-up labs available. Investigator notes that this may be due to the surgical procedure (left knee arthroplasty), but provides no further rationale for this opinion.
				AST	438	14	
EN3203-004-021-006	EN3203-004	Oxymorphone IR	1	ALT	229	16	No follow-up labs available
				AST	236	20	
EN3203-004-021-011	EN3203-004	Oxymorphone IR	2	ALT	142	26	No follow-up labs available
				AST	156	31	
EN3202-016-012-003	EN3202-021	Oxymorphone ER	97	ALT	220	19	Subject discontinued due to adverse event "Increased liver enzymes", judged by investigator to be moderate in intensity and unlikely related to study drug. GGT was also elevated (180 U/L normal range: 10-61). No further detail are avialable
				AST	236	14	

Source: Appendix 10.11 in the ISS

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 two other oxymorphone IR-treated subjects (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.

Clinically significant abnormalities of albumin, calcium, and phosphorus occurred predominantly in the acute post-operative trials, where they occurred in all treatment groups. Hypoalbuminemia, ranging mostly from 2.6-2.9 g/dL, was the principal clinically significant abnormality of albumin in this setting. Similarly, hypocalcemia, ranging generally form 7.4-7.9 mg/dL, was the most common clinically significant abnormality of calcium in the acute post-operative setting. Hypophosphatemia was the most common clinically significant abnormality of phosphorus in the acute post-operative setting, with most values ranging from 1.7-2.3 mg/dL.

Clinically significant abnormalities of glucose occurred in nearly all trial settings and in all treatment groups, with the vast majority of these abnormalities being hyperglycemia, with most values in the 160-300 mg/dL range. Hypoglycemia occurred only rarely.

Clinically significant abnormalities of cholesterol occurred in all treatment groups, and generally involved cholesterol level sin the 300-350 mg/dL range. Clinically significant abnormalities of triglycerides occurred infrequently, and involved triglyceride levels in the 550-1,000 mg/dL range, in subjects in many 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.

Clinically significant abnormalities of potassium were infrequent, but occurred in all treatment groups in all trials settings, and involved both hypokalemia and hyperkalemia. Clinically significant abnormalities of sodium were also infrequently, and mainly involved hyponatremia, usually in the 125-120 mEq/L range. These abnormalities occurred in all treatment groups.

The rates of clinically significantly abnormal lab values in the Phase 1 trials were low. The most common clinically significantly abnormal lab values in this setting were glucose (8/251 [3.2%] in oxymorphone ER-treated subjects and 2/181 [1.1%] in oxymorphone IR-treated subjects). Phosphorus (5/251 [2.0%] in oxymorphone ER-treated subjects and 3/180 [1.7%] in oxymorphone IR-treated subjects), and uric acid (1/55 [1.8%] in oxymorphone ER-treated subjects) (see Appendix 4.41).

In the Phase 2/3 oxymorphone IR trials, clinical chemistry data were collected only in Study EN3203-004. Review of the mean and median lab values at baseline and post-treatment indicate that the observed changes were consistent with the acute post-operative setting, and that they were similar across all treatment groups.

1.6.1.2 Clinical Hematology Results

Clinical hematology tests included the tests listed in the table below.

Clinical Hematology Tests		
Hemoglobin	White blood Cells	Platelets
Hematocrit	Bands	Prothrombin time
Red blood cells	Neutrophils	
RBC morphology	Lymphocytes	
	Eosinophils	
	Basophils	
	Monocytes	
	Atypical lymphocytes	

Not all tests were performed in all studies. Some tests, such as the atypical lymphocytes, bands, and prothrombin time were performed on only a few subjects.

The Sponsor provided the normal ranges for all clinical hematology tests used in each of the trials. In addition, the Sponsor defined limits for clinically significantly abnormal lab values for selected hematology tests (hemoglobin, hematocrit, white blood cell count, absolute neutrophil count, absolute lymphocyte count, and platelet count). The Sponsor presented clinical hematology results in three ways: 1) mean and median changes from baseline were calculated for each lab test for six clinical trial subsets: Phase 2/3 ER studies, chronic non-malignant pain studies, cancer pain studies, Phase 2/3 IR studies, and Phase 1 studies, 2) shift tables were prepared for each lab test for selected clinical trial subsets, and 3) a listing of clinically significant abnormal labs was presented.

Review of the definitions of the clinically significant abnormal lab values (see Appendix 4.1.B in the ISS) indicates that the chose limits appears appropriate, although there are only lower limits for each of the hematology tests.

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).

For oxymorphone ER-treated subjects in the Phase 2/3 ER studies, the mean and median changes in each clinical hematology test were calculated based on the subject's dose at the endpoint, with the endpoint doses grouped into six ranges (<=10 mg/day, >10-29, >29-50, >50-70, >70-90, and >90) (see Appendix 4.3 in the ISS). Review of these data 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.

The Sponsor calculated the proportion of subjects in each treatment group with at least one abnormal lab value for each clinical hematology test (see Appendix 4.4 in the ISS). In general, the incidence of treatment-emergent abnormal lab values was similar among the treatment groups, but varied among the tests themselves. Among oxymorphone ER-treated subjects, the incidence of treatment-emergent abnormal lab values was below 10% for lymphocytes, monocytes, and platelets. The incidence of treatment-emergent abnormal lab values was between 10% and 15% for eosinophils, hemoglobin, hematocrit, red blood cells, and white blood cells. The incidence of treatment-emergent abnormal lab values was above 15% for basophils, and neutrophils. For each of the hematology tests, the rates of abnormal lab values was similar among the oxymorphone ER, oxycodone ER, morphine ER, and placebo groups. Rates in the

oxymorphone IR groups were more variable, in part due to the small number (n=23) of subjects in that treatment group in the Phase 2/3 ER studies.

The Sponsor calculated the proportion of subjects in each treatment group with at least one clinically significant abnormal lab value for each clinical hematology test (see Appendix 4.5 in the ISS). In general, the incidence of treatment-emergent clinically significant abnormal lab values was similar among the oxymorphone ER, oxycodone ER, and placebo treatment groups, but varied among the tests themselves. (The relatively small number of oxycodone IR and morphine ER-treated subjects resulted in wider variations in the percentages of clinically significant abnormalities.) 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 significantly abnormal post-baseline value was 7.0%, while the corresponding percentage in the placebo group was 2.9%.

Review of the above analyses for the chronic non-malignant pain trials and the cancer pain trials subsets indicates that the incidence of treatment-emergent abnormal hematology lab values and treatment-emergent clinically significant hematology lab values are generally higher in the cancer pain clinical trial than in the chronic non-malignant pain clinical trials. Within each trial subset, however, the incidence rates for each lab test were generally similar among the oxymorphone ER, oxycodone ER (cancer pain only trials), and placebo groups.

Shift tables for hemoglobin among oxymorphone ER-treated subjects in all Phase 2/3 ER studies indicate that of 788 subjects with normal hemoglobin at baseline, 7 (0.9%) developed a clinically significantly low hemoglobin post-baseline (see Appendix 4.13). Review of individual clinically significant hemoglobin values indicates that such abnormalities were frequent among all treatment groups in the acute post-operative trials. In most cases, the values were above 8.7 g/dL. Among the Phase 2/3 trials, the majority of clinically significant abnormalities were in cancer pain subjects, both in the controlled cancer pain trials and in the open-label extension. This pattern is seen not only for the oxymorphone ER-treated group, but also for the oxycodone ER and morphine ER-treated groups.

Shift tables for lymphocytes indicate that clinically significant abnormal values for lymphocytes were much more frequent among cancer pain subjects than among chronic non-malignant pain subjects. For example, of 561 subjects with chronic non-malignant pain with normal lymphocyte counts at baseline, 22 (3.9%) developed clinically significantly low post-baseline abnormalities. Among89 cancer pain subjects with normal lymphocytes at baseline, 16 (18.0%) developed clinically significantly low post-baseline lymphocyte values. Review of the individual clinically significant lymphocyte lab values indicates that such abnormalities were observed frequently in the acute post-operative pain studies in all treatment groups. In each treatment group in the acute post-operative pain trials, the majority of clinically significant abnormal lymphocyte values were above 0.700 (x10^3/mm^3). In the chronic non-malignant pain trials and the Phase 1 trials, the majority of clinically significant abnormal lymphocytes were above 0.750 (x10^3/mm^3). In the cancer pain trials, the majority of clinically significant abnormal lymphocyte values were above 0.500 (x10^3/mm^3), with a wide range of values.

Shift tables for neutrophils indicate that clinically significant abnormal values for neutrophils were much more frequent among cancer pain subjects than among chronic non-malignant pain subjects. For example, of 548 subjects with chronic non-malignant pain with normal neutrophil counts at baseline, 2 (0.4%) developed clinically significantly low post-baseline abnormalities. Among 91 cancer pain subjects with normal neutrophils at baseline, 3 (3.3%) developed clinically significantly low post-baseline neutrophil values. Review of the individual clinically significantly abnormal neutrophil values indicates that in the chronic non-malignant pain trials and the Phase 1 trials, the majority of clinically significant abnormal neutrophils were above 0.750 (x10^3/mm^3). In the cancer pain trials, the majority of clinically significant abnormal neutrophil values were above 0.500 (x10^3/mm^3), with a wide range of values.

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. The table below summarizes these values:

Table. Selected Cases of Treatment-Emergent Neutropenia

		Baseline		On Treatment	
Subject ID	Treatment	WBC*	Absolute Neutrophil Count*	WBC*	Absolute Neutrophil Count*
EN3202-005-001-002	Oxymorphone ER	4.9	1.676	4.4	1.258
EN3202-009-001-001	Oxymorphone ER	6.4	3.590	5.4	1.242
EN3202-009-001-010	Oxymorphone ER	6.0	3.396	4.0	0.784
EN3202-009-001-019	Oxymorphone IR	5.5	2.888	3.4	0.755
EN3202-009-001-022	Oxymorphone ER	7.7	4.374	6.7	0.817
EN3202-009-001-026	Oxymorphone ER	7.3	4.73	2.9	0.316
EN3202-009-001-028	Oxymorphone ER	7.1	3.649	1.6	0.112

* X10^3/mm^3

Source: Appendices 10.10 and 10.11 in the ISS

Review of the above table indicates that in some cases the clinically significantly abnormal low neutrophil count was associated with a depressed total WBC count. In all cases, the neutrophil count was normal at baseline. In other cases, there the neutrophil count was significantly low, even in the presence of a normal total WBC count. 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 (ie, ER for 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 (see Appendix 3.10 in the EN3202-009 study report). 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 (see Section 4.4.3 of the Study EN3202-009 clinical study report).

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.

Shift tables for white blood cells indicate that clinically significant abnormal values for white blood cells were much more frequent among cancer pain subjects than among chronic non-malignant pain subjects (see Appendices 4.29 and 4.30). For example, of 548 subjects with chronic non-malignant pain with normal white blood cell counts at baseline, 1 (0.2%) developed clinically significantly low post-baseline abnormalities. Among 87 cancer pain subjects with normal white blood cells at baseline, 7 (8.0%) developed clinically significantly low post-baseline white blood cell values. Review of the individual clinically significant white blood cell lab values indicates in the chronic non-malignant pain trials and the Phase 1 trials, there were three clinically significant abnormal white blood cells values, two of which are noted in the discussion of neutropenia n Phase 1 studies above. In the chronic non-malignant pain studies, a single oxymorphone ER-treated subject had a treatment emergent white blood cell value of 2.800 (x10^3/mm^3). On Day 15 in Study EN3202-015, which decreased to 2.67 (x10^3/mm^3) on Day 50 in Study EN3202-020. In the cancer pain trials, the majority of clinically significant abnormal white blood cell values were above 1.500 (x10^3/mm^3), with a wide range of values in al treatment groups.

Shift tables for platelets indicate that treatment-emergent clinically significant abnormal values for platelets were much more frequent among cancer pain subjects than among chronic non-malignant pain subjects (see Appendices 4.25, 4.26, and 4.27). For example, of 548 subjects with chronic non-malignant pain with normal platelet counts at baseline, none developed clinically significantly low post-baseline abnormalities. Among 103 cancer pain subjects with normal platelets at baseline, 2 (1.9%) developed clinically significantly low post-baseline platelet values. Review of the individual clinically significant platelet lab values indicates in the cancer pain trials, the majority of clinically significant abnormal platelet values were between 40 and 74 (x10^3/mm^3).

In the Phase 2/3 oxymorphone IR trials, clinical chemistry data were collected only in Study EN3203-004. Review of the mean and median lab values at baseline and post-treatment indicate that the observed changes were consistent with the acute post-operative setting, and that they were similar across all treatment groups.

In the Phase 2/3 oxymorphone IR trials, clinical hematology data were collected only in Study EN3203-004. Review of the mean and median lab values at baseline and post-treatment indicate that the observed changes were consistent with the acute post-operative setting, and that they were similar across all treatment groups.

1.6.1.3 Clinical Urinalysis Results

The Sponsor has not defined normal ranges for urinalysis results, not have clinically significant abnormal ranges been defined. A review of the dataset iss_urin.xpt indicates that not treatment-emergent clinically significant abnormal urinalysis results have been obtained. In addition, it appears that 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 (ie, one subject). Other adverse events based on abnormal urinalysis results occurred in less than 1.0% of oxymorphone ER-treated subjects.

The Sponsor also notes that there were no adverse vents associated with abnormal urinalysis results for any subjects in the Phase 1 trials.

1.6.2 Vital Signs

The Sponsor defined clinically vital sign abnormalities for systolic blood pressure, diastolic blood pressure, heart rate, respiratory rate, temperature, and body weight.

The Sponsor presented vital sign results in three ways: 1) mean and median changes from baseline were calculated for each vital sign the clinical trial subsets, 2)the incidence of clinically significant vital sign values was calculated for each vital sign, and 3) a listing of clinically significant abnormal labs was presented.

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%).

Review of the above analyses for other clinical trial subsets is notable for the following observations:

1) In the oxymorphone ER Phase 2/3 studies, the incidence of clinically significant vital sign abnormalities for oxymorphone IR-treated subjects was 0.0% for all vital signs (see Appendix 8.5 in the ISS). Only 25 oxymorphone IR-treated subjects were studied in this subset.
2) In the Phase 2/3 IR studies, the incidence of clinically significant vital sign abnormalities was higher than in the Phase 2/3 ER studies: systolic blood pressure (3.6%), diastolic blood pressure (3.9%), heart rate (2.7%), respiration (0.3%), and temperature (1.2%) (see Paeendix 8.7 in the ISS). In this subjects, the incidence rates among oxymorphone IR-treated subjects were similar to those in oxycodone IR-treated subjects, and minimally higher than those n placebo-treated subjects.
3) 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%) (see Appendix 8.9 in the ISS).

For oxymorphone ER-treated subjects in the Phase 2/3 ER studies, the mean and median changes in each vital sign were calculated based on the subject's dose at the endpoint, with the endpoint doses grouped into six ranges (<=10 mg/day, >10-29, >29-50, >50-70, >70-90, and >90) (see Appendix 8.13 in the ISS). Review of these data 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. Similar analyses from other clinical trial subsets confirm this observation. Some weight gain over time was noted, though this was only for the oxymorphone ER-treated group, since only this group received long-term treatment.

Analyses of mean and median change from baseline over time do not suggest that the mean or median values of vital signs change over time. The incidence of clinically significant vital sign abnormalities also does not increase with time (see Appendices 8.18-8.29). Some weight gain over time was noted, though this was only for the oxymorphone ER-treated group, since only this group received long-term treatment.

Review of the individual clinically significant vitals sign abnormalities reveals that most clinically significant abnormalities of systolic blood pressure were elevations of systolic blood pressure, mainly in the 180-220 mmHg range. Occasional drops in systolic blood pressure, mainly in the 80-90 mmHg range, were also noted.

Review of the individual clinically significant vitals sign abnormalities reveals that clinically significant abnormalities of diastolic blood pressure were both elevations of diastolic blood pressure, mainly in the 105-120 mmHg range, as well as decreases in diastolic blood pressure, mainly in the 35-50 mmHg range.

Review of the individual clinically significant vitals sign abnormalities reveals that most clinically significant abnormalities of pulse rate were elevations of systolic blood pressure, mainly in the 120-135/min range. Occasional decreases in pulse rate, mainly in the 40-50/in range, were also noted.

Review of the individual clinically significant vitals sign abnormalities reveals that most clinically significant abnormalities of respiratory rate were decreases in respiratory rate, mainly in the 8-9/min range. Many of these values were recorded in the Phase 1 studies.

Review of the individual clinically significant vitals sign abnormalities reveals that all clinically significant abnormalities of body temperature pressure were elevations of body temperature, mainly in the 102.3-103.0 °F range.

Review of the individual clinically significant vitals sign abnormalities reveals that clinically significant abnormalities of body weight were both increases and decreases, occurring over a wide range of body weights. Some of the values noted, however, are clinically impractical. For example, one subjects (EN3202-012-010-004) increased from 220 lbs. to 349 lbs. vver two days. Similarly, Subject EN3202-012-0111-007 decreased from 229 lbs. to 104 lbs. over two days, while subject EN3202-012-011-019 decreased from 263 lbs. to 120 lbs. over 2 days (see Appendix 10.12).

Of note, given the respiratory abnormalities noted as serious adverse events in the acute post-operative pain studies, it is surprising that there are not more abnormalities of respiratory rate noted in the data presented in this section.

1.6.3 Electrocardiograms

There was limited recording of electrocardiograms (ECGs) during the clinical development program. 12-lead ECGs were obtained in three Phase 1 studies (EN3202-001, EN3202-002, and EN3202-003) and in three Phase 2/3 studies (EN3202-015, EN3202-020, and EN3202-025).

1.6.3.1 Electrocardiograms in Phase 1 Studies

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. The protocols for each of these three studies specified these collection time points, but did not further specify any planned analyses of the ECG data. Data collected included standard quantitative ECG data (heart rate and PR, QRS, QT, and QTc intervals), an investigator rating of the ECG (normal, abnormal – not clinically significant, and abnormal – clinically significant), and investigator comments on the ECG. The study reports for Studies EN3202-001 and EN3202-002 contain shift tables comparing the pre-dose investigator rating of the ECG to the post-dose rating. These study reports also contain by-subject listings of the quantitative ECG data and the investigator comments. No analyses of the quantitative data are presented. The study report for Study EN3202-003 contains no ECG data of any kind. None of the ECG data from the Phase 1 studies are mentioned in the ISS.

The shift tables for Studies EN3202-001 and EN3202-002 indicate that all ECGs were rated as normal both before and after treatment for all formulations of oxymorphone administered. (Both studies used two different formulations of oxymorphone ER and one formulation of oxymorphone oral solution). Review of the data in the database (filename iss_ecgs.xpt) also indicates that all ECGs in Study EN3203-003 were rated as normal both before and after treatment.

At the request of the Agency, the Sponsor analyzed pre-dose to post-dose changes in heart rate and PR, QRS, QT, and QTc intervals for each of the three studies separately, as well as for the three studies pooled together. If a subject participated in more than one period for a given dosage form (ie, two formulations of oxymorphone ER tablets), pre-dose data were averaged and post-dose data were averaged for this analysis. The data from the pooled analysis are presented below.

Table. Overall Summary of Quantitative ECG Data from Combined EN3202-001-, EN3202-002, and EN3202-003 Studies

Treatment	ECG Test	ECG Units	N	Pre-Dose Mean	Pre-Dose SD	Post-Dose Mean	Post-Dose SD	Change from Pre-Dose (%) Mean	Change from Pre-Dose (%) SD	Change from Pre-Dose (%) Min	Change from Pre-Dose (%) Max
OXYMORPHONE ER 20 MG	CORRECTED QT INTERVAL (MSEC)	MSEC	56	388.37	16.48	377.25	20.14	-2.81	4.51	-15.25	15.71
	HEART RATE (/MIN)	BPM	14	71.89	9.35	58.68	7.85	-17.94	9.30	-31.64	2.92
	PR INTERVAL (MSEC)	MSEC	56	151.52	19.13	151.57	18.83	0.21	5.54	-19.35	11.20
	QRS INTERVAL (MSEC)	MSEC	56	91.53	10.37	91.57	10.23	0.13	3.30	-6.29	11.33
	UNCORRECTED QT INTERVAL (MSEC)	MSEC	56	363.18	29.35	380.35	35.32	4.78	5.89	-6.39	28.79
	VENTRICULAR RATE (BPM)	BPM	42	69.37	10.98	60.98	11.29	-12.04	8.21	-29.93	3.65
OXYMORPHONE SOLUTION 10 MG	CORRECTED QT INTERVAL (MSEC)	MSEC	55	385.42	22.73	378.53	17.25	-1.54	6.01	-19.50	19.82
	HEART RATE (/MIN)	BPM	15	71.27	10.23	56.13	7.79	-20.99	6.05	-30.26	-10.61
	PR INTERVAL (MSEC)	MSEC	55	149.86	18.14	148.40	28.63	-0.91	15.71	-100.0	24.60
	QRS INTERVAL (MSEC)	MSEC	55	91.85	10.44	91.88	9.84	0.17	3.92	-10.23	11.90
	UNCORRECTED QT INTERVAL (MSEC)	MSEC	55	362.15	30.83	379.73	29.61	5.11	6.65	-9.28	19.24
	VENTRICULAR RATE (BPM)	BPM	40	68.24	8.98	62.73	11.22	-7.74	13.42	-35.14	19.08
Overall	CORRECTED QT INTERVAL (MSEC)	MSEC	58	387.72	17.33	378.78	15.11	-2.23	3.53	-11.91	8.96
	HEART RATE (/MIN)	BPM	15	71.51	8.63	57.67	7.42	-19.24	5.70	-27.95	-8.93
	PR INTERVAL (MSEC)	MSEC	58	150.76	17.73	150.58	19.96	-0.06	6.87	-37.11	14.93
	QRS INTERVAL (MSEC)	MSEC	58	91.80	10.15	91.82	9.76	0.12	3.11	-8.16	8.70
	UNCORRECTED QT INTERVAL (MSEC)	MSEC	58	362.57	28.96	379.05	31.52	4.65	5.40	-6.77	21.71
	VENTRICULAR RATE (BPM)	BPM	43	69.33	10.03	62.55	10.69	-9.73	8.51	-29.48	6.35

Note: If a patient participated in more than one period for a treatment the average value on the treatment was used in the summary. This summary includes studies EN3202-001, EN3202-002 and EN3202-003.

Source: Table 4 in Sponsor's Response to Teleconference with FDA Held September 12, 2003. Response submitted September 17, 2003

Review of the above table 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 above table indicates that there was a slight decline in the corrected QT interval (e.g., in the Overall group, the mean corrected QT interval decline from 387.72 msec at pre-dose to 378.78 msec at post dose. While the mean uncorrected QT interval from pre-dose to post-dose (ie, 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 subject data indicate that there were some subjects who had notably high QTc intervals post-dose(ie, for females, a QTc of 450 msec of higher and for males a QTc of 430 msec or higher). In addition, some subjects had an increase in QTc, from pre-dose to post-dose, of 30 msec or higher. These subjects are highlighted in the table below:

Table. ECG Measures for Phase 1 Subjects With Clinically Significant QTc Interval Abnormalities

			Heart Rate			PR Interval (msec)			QRS Interval (msec)			QT Interval (msec)			QTc Interval (msec)		
Subject ID	A/G/R#	Treatment^	Pre-Dose	Post-Dose	Change	Pre-Dose	Post-Dose	Change	Pre-Dose	Post-Dose	Change	Pre-Dose	Post-Dose	Change	Pre-Dose	Post-Dose	Change
EN3202-001-001-010	34/M/C	OM ER	87	65	-22	162	144	-18	96	95	-1	360	374	14	433*	389	-44
EN3202-001-001-011	23/M/C	OM ER	54	45	-9	125	139	14	98	92	-6	475	456	-19	450*	394	-56
EN3202-001-001-011	23/M/C	OM ORAL SOL	52	41	-11	132	135	3	98	98	0	474	430	-44	441*	355	-86
EN3202-002-001-001	22/M/C	OM ER	56	40	-16	144	149	5	103	108	5	386	584	198	372	476*	104*
EN3202-002-001-001	22/M/C	OM ER	56	41	-15	190	151	-39	111	96	-15	455	420	-35	439*	347	-92
EN3202-002-001-006	22/M/C	OM ER	66	55	-11	160	153	-7	95	96	1	342	513	171	358	491*	133*
EN3202-002-001-009	25/M/C	OM ER	82	77	-5	174	179	5	104	102	-2	405	370	-35	473*	419	-54
EN3202-002-001-009	25/M/C	OM ER	80	82	2	168	174	6	97	97	0	350	383	33	404	447*	43*
EN3202-003-001-002	19/M/C	OM ER	55	54	-1	153	175	22	81	83	2	400	435	35	382	412	30*
EN3202-003-001-005	24/M/C	OM ER	53	50	-3	145	145	0	102	97	-5	448	475	27	421	433*	12
EN3202-003-001-005	24/M/C	OM ORAL SOL	54	53	-1	145	125	-20	100	102	2	496	471	-25	470*	442*	-28
EN3202-003-001-006	36/M/C	OM ORAL SOL	71	75	4	127	144	17	83	82	-1	466	361	-105	506*	403	-103
EN3202-003-001-012	21/M/A	OM ORAL SOL	58	67	9	170	168	-2	90	92	2	334	372	38	328	393	65*
EN3202-003-001-020	33/M/C	OM ER	108	91	-17	144	154	10	102	104	2	323	345	22	433*	424	-9
EN3202-003-001-027	30/M/B	OM ORAL SOL	59	64	5	202	193	-9	94	90	-4	378	413	35	374	426	52*

#A/G/R=Age/Gender/Race
^OM ER=Oxymorphone ER tables, OM ORAL SOL=Oxymorphone Oral Solution
*Clinically significant QTc abnormality is a QTc interval >= 430 msec (males) or 450 msec (females) or a change from pre-dose of >=30 msec.

Source: Sponsor data in datafile iss_ecgs.xpt, as analyzed by FDA medical reviewer. See also Appendix 8.12 is EN3202-001 study reprot and Appendix 8.12 in EN3203-002 study report.

Review of these individual changes indicates several QTc abnormalities - either QTc values that were significantly prolonged (ie >= 430 msec for males or >=450 msec for females) or clinically significant increases in QTc from pre-dose to post-dose (ie, >=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 in the table above 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 studied 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.

1.6.3.2 Electrocardiograms in Phase 2/3 Studies

Electrocardiograms in the Phase 2/3 clinical development program were limited to three studies (EN3202-015, EN3202-020, and EN3202-025). The ECGs done in the Phase 2/3 studies do not have any quantitative data (ie, no intervals), just investigator comments and ratings (ie, normal, abnormal - not clinically significant, and abnormal - clinically significant). The Sponsor has prepared a shift table (see Appendix 8.30 in the ISS) of the ECG ratings. The majority of ECGs were either normal both at baseline and on-

treatment, or abnormal but not clinically significant both at baseline and on-treatment, as indicated in the table below.

Shift Table of ECG Data in Phase 2/3 Clinical Trials

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

CS = Clinically Significant

Source: Appendix 8.30 in the ISS

Two subjects in Study EN3202-020 (EN3202-017-011-005 and EN3202-017-015-003) had missing ECGs at screening and also had clinically significantly abnormal ECGs while on treatment with oxymorphone ER. The missing ECGs were assumed to be normal at baseline, and thus these two subjects represent the two cases of ECGs that went from normal at baseline to clinically significant abnormal while on treatment. The former subject's ECG revealed left ventricular systolic dysfunction, a depressed ejection fraction (30-35%), and sclerodegenerative changes of the aortic valve. The latter subject's ECG revealed biatrial enlargement, left ventricular hypertrophy, and repolarization abnormalities.

Three oxymorphone-treated subjects had ECGs that were rated as 'Abnormal – not clinically significant' at baseline to 'Clinically significant' on treatment (EN3202-015-041-001, EN3202-015-071-002, and EN3202-015-077-025). Review of the investigator comments on the pre- and post-treatment ECGs sheds little light on any new cardiac problems that could have occurred during the treatment interval. Review of the actual ECGs would be necessary for any conclusions to be made.

1.7 Adverse Experiences Not From Clinical Trials

Post-marketing adverse event data are available for intravenous (NDA 11-707, approved April 2, 1959) and suppository (NDA 11-738, approved May 31, 1960) formulations of oxymorphone. During the period 1964-2001, sales figures, provided by the Sponsor in the ISS, for the intravenous formulation were [redacted] 1-mg ampules, [redacted] 1.5-mg ampules, [redacted] 1-mg vials, and [redacted] 1.5-mg vials. During this same time period, [redacted] 5-mg suppositories were sold.

The Sponsor reports that there were few adverse events reported with either formulation. 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.

Dr. Martin Pollock of the Division of Drug Risk Evaluation in the Office of Drug Safety has also reviewed the post-marketing safety experience with the intravenous and suppository formulations of oxymorphone. Of 37 unique cases in the AERS database that involved use of oxymorphone, 17 were excluded, either 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, Dr. Pollock notes that none of the reports mentions oxymorphone being taken as a separate drug. Because oxymorphone is a metabolite of oxycodone, its presence could have resulted from exposure to oxycodone. In any event, these cases were excluded from Dr. Pollock's analysis.

Of the remaining 20 cases used in the analysis, there were two deaths. One death occurred in a pediatric patient (age unknown) being treated for advanced cerebral leukemia. This patient received one-half of a 5-mg suppository (ie, 2.5 mg) at 12:30 p.m. for severe headache and pain. She became drowsy and by 5:00 PM was in a coma. She died at 6:30 PM. Dr. Pollock notes that there was little other information, such as prior exposure to opioids and concomitant medication usage, to put this event in perspective. The physician

reporter, however, 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. She remained on this medication until her death 51 days after the oxymorphone was started. Daily doses were as high as 4.5 mg/day. Concomitant medications were unknown. No attribution of the cause of death is given.

Of the non-fatal serious cases, the two most serious cases involved the cardiac system (n=1) and the respiratory system (n=1). In the first case, a 70-year-old man was receiving oxymorphone via a PCA pump as well as oxymorphone ER in a clinical trial after a knee arthroplasty. She developed confusion, a decreased mental status, and atrial fibrillation. Diagnostic tests indicated that she did not sustain a myocardial infarction. She was treated with naloxone, digoxin, oxazepam, thiamine, and enoxaparin. Her symptoms resolved. (Note: It appears that this case was also reviewed as part of the clinical trial information in the adverse event sections above.) The second case involved a 4-year-old child who underwent a tonsillectomy and adenoidecotmy. The child (gender unknown) was treated with one-half of a 2-mg suppository. The child soon thereafter became apneic, requiring intubation and naloxone. Spontaneous respiration then returned. Dr. Pollock notes that oxymorphone suppositories are not labeled for pediatric use.

Dr. Pollock concludes his review by noting that the relatively small number of reports over the past three decades are not sufficient to determine any trends or identify any particular safety concerns.

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

1.8 Drug-Drug Interactions

The Sponsor did not perform any clinical trials designed explicitly to evaluate possible drug-drug interactions of oxymorphone with other drugs. The ISS (see Section 11.2) indicates that the Sponsor is currently conducting such studies.

The Sponsor notes in Section 11.1 in the ISS that in vitro data indicate that oxymorphone dose not inhibit the activity of CYP450 1A2, 2C9, 2C19, 2D6, or 2E1. Oxymorphone did inhibit nifedipine dehydrogenation mediated by CYP450 3A4 at high concentrations, but did not inhibit 3A4-mediated hydroxylation of midazolam or testosterone. The Sponsor concludes that since the inhibitory concentrations observed in vitro are about 10,000-fold higher than the expected concentration in clinical use, there should be no relevant level of risk of oxymorphone-mediated inhibition of CYP450 3A4 or any other isozymes tested.

The sponsor also notes that oxymorphone induced an increase in the activity of CYP 3A4 at 72 hours (a 3.3-fold increase) at concentrations about 300-1,000-fold higher than the concentrations expected in vivo. The Sponsor concludes that the clinical significance of these findings is uncertain.

To evaluate possible drug-drug interactions from the clinical trial data, the Sponsor identified adverse events with an incidence at least 1.25-fold higher among oxymorphone ER/IR subjects taking a concomitant medication in a particular ATC Level 1 class than among subjects not taking that type of medication for all oxymorphone ER/IR and placebo subjects in the Phase 2/3 trials. Four such adverse events were identified: somnolence, pyrexia, dry mouth, and headache. In general, the increased adverse event incidence rate noted among subjects taking a particular class of concomitant medication was present for both the oxymorphone-treated group and the placebo-treated group. For headache, the incidence among oxymorphone-treated subjects taking hormonal preparations (11.5%) was slightly higher than the rate in oxymorphone–treated subjects not taking that class of concomitant medication (8.8). In placebo-treated subjects, the rates among subjects taking the concomitant medication (1.7%) were lower than the rate among these placebo-treated subjects not taking the concomitant medication (6.3%). The significance of this findings is not clear. In any case, there is not definitive evidence for a clinically significant interaction between oxymorphone and the concomitant medication resulting in the observed adverse events.

1.9 Drug-Demographic Interactions

The Sponsor calculated the incidence of common (ie, occurring in 5% or more of oxymorphone ER-treated subjects in the Phase 2/3 ER trials) adverse events by age group (<65 years old, over age 65, and over age 74 years) for the Phase 2/3 ER trials (see Section 12.1.2.1 of the ISS). Two adverse events, dizziness and somnolence, had an increasing incidence with increasing age among oxymorphone ER-treated subjects. The incidence of dizziness was 21.2% in those less than age 65 years, 28.2% in those age 65 years and older, and 33.9% in those age 74 years and older. The incidence of somnolence was 14.8% in those less than age 65 years, 20.6% in those age 65 years and older, and 28.9% in those age 74 years and older. These patterns wee also noted in the chronic non-malignant pain trials.

In the oxymorphone IR Phase 2/3 studies, the incidence of dizziness was less strongly age related: 7.2% in those less than age 65 years, 9.5% in those age 65 years and older, and 10.4% in those age 74 years and older. Among oxymorphone IR-treated subjects, the incidence of pyrexia was slightly higher in the younger age group: 24.7 % in those less than age 65 years, 19.0% in those age 65 years and older, and 13.4%% in those age 74 years and older.

The Sponsor also calculated the incidence rates of these common adverse events by gender in the Phase 2/3 ER trials. Nausea, vomiting, and headache were notably more frequent 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. For all other frequently occurring adverse events the incidence rates were similar in males and females. In the chronic non-malignant pain studies, nausea and vomiting were again more common in females than in males. In cancer pain studies, constipation and vomiting were notably more frequent in females than in males.

In the oxymorphone IR studies, the incidence rate for pyrexia was higher in males (27.0%) than in females (18.1%) among oxymorphone IR-treated subjects. This pattern was also true among placebo subjects (males – 19% and females –13%). In this trial subset, the rate of nausea in oxymorphone IR-treated subjects was higher in females (21.2%) than in males (9.9%). This difference was not seen in placebo subjects (males – 6.87% and females – 6.3%).

To examine the effect of race on the development of adverse events in the Phase 2/3 ER trials, the Sponsor focused its analysis on differences between Caucasians (n=941 in oxymorphone ER group) and Blacks (n=90 in oxymorphone ER group). The number of Asians (n=1) and subjects classified as Other (n=25) was too small for meaningful analyses. 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.

1.10 Drug-Disease Interaction

The Sponsor notes that although adverse event rates were tabulated by indication (ie, acute post-operative pain studies, chronic non-malignant pain studies, and cancer pain studies), the differences across these trial groups in study design and duration of treatment confounds comparisons across indications and thus makes any attempt to study drug-disease interactions problematic.

To explore the effect of hepatic impairment on the development of adverse events in oxymorphone-treated subjects, the Sponsor analyzed adverse event data from Study EN3202-005, a pharmacokinetic study of oxymorphone ER in hepatically impaired individuals. That study demonstrated that the bioavailability of oxymorphone increased substantially in subjects with moderate and severe hepatic impairment, as defined by Child Pugh Class B and C, respectively. For common adverse events (ie, adverse events with incidence rates of 5% or greater in oxymorphone ER-treated subjects) in the Phase 2/3 studies, the Sponsor analyzed adverse event incidence rates for 1) subjects with serum albumin <= 3.0 g/dL, 2) subjects with total bilirubin > 3x the upper limit of normal, 3) subjects with either of the two previous abnormalities, and 4) normal subjects (ie, subjects without either of the two abnormalities). 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. Review of the incidence rates of common adverse events in these groups of subjects (see Appendix 3.107 in the ISS) indicates that there was no obvious association between the abnormalities in albumin and bilirubin and the development of common adverse events.

To explore the effect of renal impairment on the development of adverse events in oxymorphone-treated subjects, the Sponsor cited data from Study EN3202-010, a pharmacokinetic study of oxymorphone ER in renally impaired individuals. That study demonstrated that the bioavailability of oxymorphone increased by about 60% in subjects with moderate and severe renal impairment. For common adverse events (ie, adverse events with incidence rates of 5% or greater in oxymorphone ER-treated subjects) in the Phase 2/3 studies, the Sponsor analyzed adverse event incidence rates in this study for 1) subjects with baseline creatinine clearance rates between 51-80 ml/min, 2) subjects with baseline creatinine clearance rates between 30-50 ml/min, 3) subjects with baseline creatinine clearance <30 ml/min, and 4) normal subjects. Review of the incidence rates of common adverse events in these groups of subjects (see Appendix 3.110 in the ISS) indicates that there a slight increase in the rates of nausea, dizziness, vomiting, and dry mouth in subjects with mild renal impairment compared to subjects with normal renal function. Among placebo-treated subjects, the incidence rates for dizziness, vomiting, and dry mouth were similar in subjects with mild renal impairment and normal subjects, and the incidence rate for nausea was lower in subjects with mild renal impairment than in normal subjects. There is 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. Due to the small number of subjects, no meaningful evaluation could be made for subjects with moderate or severe renal impairment.

1.11 Withdrawal Effects

The Sponsor notes in Section 15 if the ISS that the "development of physical dependence is not unusual during chronic opioid therapy" and that "physical dependence results in withdrawal symptoms in patients who abruptly discontinue the drug...". In the oxymorphone clinical development program, the Sponsor notes that when "study treatments were discontinued (either at study completion or discontinuation), the investigator was instructed to use his/her clinical judgment in treating the subjects in such a way as to avoid any possible withdrawal effects...".

In the original ISS, there were six oxymorphone ER-treated subjects (0.3%, based on all studies) with an adverse event mapped to the MedDRA preferred term 'Drug withdrawal syndrome'. There were also two oxycodone ER-treated subjects (0.5%, based on all studies) who had adverse events mapped to the MedDRA preferred term 'drug withdrawal syndrome'. All subjects who experienced one of these adverse events were in the Phase 2/3 ER studies. In some cases, the Sponsor notes that these events occurred in Study EN3202-016, in which subjects were re-randomized to placebo treatment after stabilization on double-blind treatment with oxymorphone ER or oxycodone ER. All cases of drug withdrawal syndrome were rated as moderate or severe in intensity. None was judged to be a serious adverse event.

The Sponsor also notes that physical dependence was assessed in Study EN3202-015 using a Physical Dependence Survey. The Sponsor further notes that this instrument is not validated, and that interpretation of the results from this test would be uncertain. Three cases of withdrawal syndrome were reported in this study, all in subjects on the oxymorphone ER 40 mg dose. The withdrawal syndrome in these subjects was rated as moderate in intensity.

1.12 Drug Abuse and Overdose

In Section 16 of the ISS, the Sponsor notes that oxymorphone is a mu-agonist opioid, and thus has an abuse liability similar to morphine.

The Sponsor notes in Section 16 of the ISS that there was one case "overdose NOS" (MedDRA preferred term) in the clinical trials reported in the ISS. This subject (EN3202-025-029-040) was taking oxymorphone 10 mg bid at the time of the overdose. The subject took four 10-mg tablets one morning, rather than one. The subjects apparently realized this error and contacted the study site. The investigator asked the subject to come to the clinical for observation. No adverse events were noted. This event, however, was labeled an "overdose" but did not result in discontinuation of the study drug. An additional case of "overdose NOS" was reported in the ISS. This case, which was reviewed in the section on serious adverse events above, describes the development of respiratory depression and respiratory failure in an oxymorphone ER-treated subject with cancer pain who also was given morphine sulfate and OxyContin during a hospitalization for pneumonia. This event was attributed to the effects of morphine and oxycodone.

There was also a case of an "accidental overdose", in which an oxymorphone ER-treated subject overdosed on a tricyclic anti-depressant drug. This case was reviewed in the section on serious adverse events in this review.

The Sponsor further notes that four cases of "drug interaction", where were reviewed in the section on serious adverse events above, were also cases of drug overdose. Each involved the additive effects of oxymorphone administered by two different routes – both parenterally via a PCA pump and orally.

The Sponsor reports that it has reviewed the data for the 13 oxymorphone ER-treated subjects whose modal daily dose was 180 mg or greater. All these subjects were opioid-experienced. The Sponsor concludes that "there was no apparent dosing pattern to suggest than any of these subjects were abusing oxymorphone". This conclusion was based on a review of dosing patterns, though no further details are presented.

Further review of the safety data, however, suggests that serious effects of excessive opioid may be more prominent that the Sponsor has presented in this section of the ISS. Specifically, there were several cases of oxymorphone IR and oxymorphone ER-treated subjects who required naloxone for reversal of either opioid-related CNS effects or opioid-related respiratory effects. These cases have been reviewed in the section on adverse events above. Review of these cases indicated that naloxone use was more common in oxymorphone ER and oxymorphone IR-treated subjects than in placebo-treated subjects (who were receiving opioids via PCA) and oxycodone IR-treated subjects. Most of these cases were confined to the acute post-operative setting. The oxymorphone ER cases prompted protocol revision to eliminate the 60 mg dose from that study. In the case of oxymorphone IR, the optimal dose, with regard to safe use of the product, may not yet be known.

With regard to the abuse liability of the product it is important to note that there was documented drug diversion from two investigative sites in the oxymorphone clinical development program. These events have been summarized by Dr. Shaun Comfort in his review of the efficacy data. Dr. Comfort's summary of these events from his review is as follows:

> DSI conducted 'for cause' audits of Study Sites 023 (Dr. Barry Miskin, principal investigator) and 002 (Dr. J. Appelrouth, principal investigator). These sites were involved in cases of drug diversion detected and reported by the Sponsor (reported to all appropriate authorities and FDA notified June 28, 2002). Patients from Site 023 were enrolled in Studies EN3202-016 and 021, and patients from Site 002 were enrolled in Studies EN3202-015 and 020. The Sponsor terminated the safety extension study EN3202-021 but continued patients already enrolled in study EN3202-016. While the DSI audit considered the data from Site 023 acceptable for use in safety and efficacy analyses, the Sponsor and the Division excluded subjects from this site in the efficacy analyses.
>
> The Division of Scientific Investigations (DSI) found that the study coordinator from Site 002 (Principal Investigator - Dr. Appelrouth) enrolled herself in the Studies EN3202-015 and EN3202-020. The Sponsor terminated these studies at that site. Additionally, DSI found falsification of records at the site, failure of the PI to personally perform global

assessments, and many protocol violations. These deficiencies were felt to affect both safety and efficacy data obtained from these sites. The Sponsor and the Division excluded this site's data from the efficacy analyses. In conclusion, the Sponsor and the Agency excluded all subjects from Sites 002 and 023 in the efficacy analyses, presented in this review. Safety data from these sites were included in the Review of Safety.

Thus, the data collected in the clinical development program point to the potential for abuse and diversion of the product, as well as for the occurrence of the known effects of opioid overdose. The Sponsor has submitted a risk management plan for this product, which is currently being reviewed by the review team.

1.13 Review of Clinical Literature

The Sponsor has reviewed the clinical literature regarding oxymorphone by using the search terms 'human' and 'oxymorphone'. The principal findings of some of these studies are presented below, though the data on which they are based, and thus the conclusions drawn, are not reviewed in further detail.

- One report, which studied oxymorphone in 194 subjects, noted that one subject developed respiratory depression with a 1.5 mg intramuscular dose of oxymorphone (Beaver WT and Feise GA. A comparison of the analgesic effect of oxymorphone by rectal suppository and intramuscular injection in patients with post-operative pain. J. Clin Pharmacol 1977;17(5-6):276-291).

- One report calculated the relative potency of oral and intramuscular formulations of oxymorphone. The potency ratios were 1/6 for total effect and 1/13 for peak effect. The paper also concluded that at equianalgesic doses, the side of effects of the two oral and intramuscular formulations were qualitatively and quantitatively similar (Beaver WT, Wallenstein SL, Houde RW, Rogers A. Comparisons of the analgesic effects of oral and intramuscular oxymorphone and of intramuscular oxymorphone and morphine in patients with cancer. J Clin Pharmacol 1977;17(4):186-198).

- One report studied the sedative effect of five opioids (diamorphine, dihydromorphinone, dihydrocodeine, oxymorphone, and oxycodone) as pre-anesthetic agents in women. The authors concluded that diamorphine and dihydromorphinone produced the best sedation. They also concluded that dihydromorphinone and oxymorphone "were markedly more toxic than the others." The latter conclusion was based on the these two drugs caused a higher incidence of emetic effects and dizziness, taken together, than did the other drugs (Loan WB, Morrison JD, Dundee JW, Clarke RS, Hamilton RC, Brown SS. Studies of drugs given before anaesthesia XVII: the natural and semi-synthetic opiates. Brit J Anesthesiol 1969;41(1):57-63).

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/s/

Gerald DalPan
10/14/03 04:52:44 PM
MEDICAL OFFICER

You've already reviewed for entry into DFS.

Sharon Hertz
10/15/03 05:36:55 PM
MEDICAL OFFICER
I concur with this review. See Team Leader memo for integration of efficacy and safety.

1ST Cycle Review Clinical (RMP

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 Risk Management Plan

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

The Sponsor has submitted a Risk Management Plan in several parts. This review will summarize the main features of each part of the risk management plan, as well as the comments from other offices within CDER, which have consulted in the RMP.

1) The original Risk Management Plan submitted in the original NDA on December 19, 2002.
2) A protocol to test the Screening for Opiate Addiction Potential (SOAP) tool, submitted on August 5, 2003.
3) A Patient Package Insert (PPI) submitted on September 12, 2003.
4) A Post-Marketing Safety Surveillance Program for Oxymorphone, submitted on September 23, 2003.
5) A Standard Operating Procedure of the Endo Safety Review Board, submitted on September 23, 2003
6) Educational materials

The original Risk Management Plan (RMP) contained a summary of the clinical, pharmacological, pharmacokinetic and chemistry data that were pertinent to the abuse liability of oxymorphone. The clinical data included a discussion of the opioid-related adverse events and adverse events of withdrawal in the clinical development program.

The original RMP consisted of three principal components: 1) education, 2) the SOAP screening tool, and 3) a post-marketing safety surveillance program. Each of these components was briefly outlined, and none was explained in detail. In a consult to Division of Anesthetic, Critical Care, and Addiction Drug Products (HFD-170), the Office of Drug Safety (ODS) noted that the "sponsor has provided a limited description of their RMP." Specifically, the ODS consult noted that there were no specific goals, no objectives, and no evaluation plan. The ODS consult noted that the plans for post-marketing surveillance were useful, but not complete. Specifically, surveillance for abuse and diversion requires a multi-faceted approach. No plans for intervention were mentioned in the RMP.

The Agency held a teleconference with the Sponsor on August 6, 2003 to discuss the RMP. The Agency explained that more information about the educational programs was needed. In addition, more information about the surveillance programs was needed. Specifically, the Agency needed more information about the databases that will be utilized, and the frequency of data analysis and reporting to the Agency. The Sponsor noted during this teleconference that it was preparing a Patient Package Insert, and that it would also forward to the Agency information regarding the composition and function of a safety monitoring board. The Agency noted that the RMP should include details of proposed interventions if signals are detected through surveillance. The Sponsor noted that it had not fully explored their approach to intervention.

The Division of Medication Errors and Technical Support (DMETS) within ODS provided a consult on the RMP to HFD-170 on August 27, 2003. The DMETS consult noted that the RMP lacked a complete description of the goals, objectives, and components of the program. In addition, the educational materials were not available for review. Thus, a complete evaluation could not be performed. DMETS did note however, that the educational programs should be evaluated for effectiveness. DMETS also noted that educational materials should provide education on adherence and issues affecting adherence, and should stress that the management of pain involves a multi-disciplinary approach. Furthermore, DMETS recommended that all potential and actual medication errors be reported to FDA.

The Screening for Opioid Addiction Protocol (SOAP) protocol was submitted to the Agency on August 5, 2003. The SOAP tool is being designed to screen patients for risk of opioid abuse. The questionnaire is being developed by a contractor under the auspices of a NIDA/NIH grant. Development and validation of this tool is still in progress.

The Division of Surveillance, Research, and Communication Support (DSRCS) within ODS provided a consult on the Patient Package Insert (PPI) to HFD-170 on September 30, 2003. DSRCS recommended changes to the proposed PPI, including changes to simplify the language, remove unnecessary information, and make the PPI consistent with other PPIs.

DSRCS also provided a consult on the proposed educational materials to HFD-170 on October 3, 2003. This consult noted that the RMP did not have goals or objectives, and reiterated the prior ODS recommendation that the RMP have goal(s), objective(s), interventions, and evaluation for the entire RMP. The consult also noted that the target audience for the education materials is broad (healthcare providers from several different professions as well as patients and their families). The consults recommended that the Sponsor identify narrower target audiences to whom educational programs can be focused to change practice behavior with regard to abuse and misuse of opioids. Specific comments with regard tot he healthcare provider education included 1) focus not only on achieving knowledge and understanding, but also on addressing practice behaviors, 2) using local or community faculty in addition to the proposed nationally renowned faculty, and 3) an evaluation of how well the goals and objectives of the healthcare

provider education are being achieved. The consult also recommended that the Patient and Family Education Part of the RMP have goals, objectives, interventions, and evaluations built into it.

The Sponsor submitted more details of the post-marketing surveillance program on September 23, 2003. ODS (DDRE and DSRCS) provided a consult to HFD-170 on this proposed plan. The consult made several points. First, the nature of some of the post-marketing safety data, such as post-marketing clinical studies and post-marketing epidemiological studies, is not explained. Second, The Sponsor should provide education to practitioners that abuse, dependence, misuse and diversion are reportable events. Third, the safety review board is composed entirely of Endo employees. External members may reduce the chance of biased opinions. Fourth, the two databases that the Sponsor plans to use for monitoring trends, DAWN and TESS, each have limitations. The consult recommends expanding the number of databases used. Fifth, the consult notes that monitoring drug utilization and prescribing patters may be valuable. Sixth, the comparator products that will be used to analyze the surveillance data. Seventh, the definitions of abuse, dependence, misuse, and diversion have not been described. Eighth, the Sponsor has not inidcated if it will use only numerators, or if it will calculate rates. If rates are to be used, the Sponsor need to describe the denominators that will be used. Ninth, more detail on the timing and nature of interventions needs to be included.

The Controlled Substances Staff (CSS) submitted a consult to HFD-170, based on review of the RMP in the original NDA, on October 8, 2003. CSS noted that the RMP requires more detail. Specific issues include the need for definitions of abuse and misuse, a statement on the composition and function of the Safety Review Board, a statement of goals for the RMP, identification of interventions to be used, plan to monitor sales and prescription patterns tin order to identify an abnormal clusters, the need for a data collection and analysis plan, the need for an evaluation of the RMP, the need to reinforce the message that products containing a potent drug should be kept out of the reach of children, and the need for cases of abuse, misuse, and diversion to be reported to the Agency.

The Division of Drug Marketing, Advertisting, and Communications (DDMAC) has reviewed the proposed educational materials. DDMAC has made several detailed comments on specific slides and speaker notes used in the educational presentations. Many of these comments focus of the need to clearly specify only the approved indication and to note contraindications and warnings.

Draft Language for the Action Letter:

The following comments pertain to the proposed Risk Management Plan (RMP).

a) Clearly articulated goals, objectives, and plans for evaluating the effectiveness of the overall risk management have not been provided.

b) Clearly articulated goals, objectives, and plans for evaluating the effectiveness of the educational materials for professionals, patients and caregivers have not been provided.

c) Specific interventions in response to signals of abuse or misuse, and the threshold for initiating those interventions, have not been provided.

d) A plan for the frequency of data analysis and reporting to the Agency have not been provided.

e) Ensurance that the content of the educational materials for professionals focuses not only on achieving knowledge and understanding, but also on addressing practice behaviors, has not been provided.

f) Additional detail on the surveillance programs should be provided. Specifically, given the limitations of the two databases (DAWN and TESS) that you propose to use justify the use of only these two databases, or expand the number of proposed databases.

g) As drug utilization data could also be valuable in studying prescribing patterns and patterns of abuse and misuse, justification for omitting this data from the risk management program should be provided.

h) More detail on your planned post-marketing clinical and epidemiological studies should be provided.

i) Additional detail on the analytical methods in the surveillance program, i.e., whether rates of events will be used and the denominators used for such rates, should be provided.

j) Rationale for specified comparator products, including omission of some common opioid analgesics from the proposed comparators, that will be used to analyze the surveillance data should be provided.

k) The definitions of abuse, dependence, misuse, and diversion that will be used in the RMP should be provided.

l) A rationale for composing the Safety Review Board from exclusively Endo employees, given that an external review board may reduce the chance for bias in the analysis of safety data, should be provided.

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/s/

Gerald DalPan
10/15/03 04:55:29 PM
MEDICAL OFFICER

You've already reviewed for entry into DFS.

Sharon Hertz
10/15/03 05:38:46 PM
MEDICAL OFFICER
I concur with this review. See Team Leader Memo for integration of safety and efficacy.

1ST Cycle

NDA 21.610 CLINICAL REVIEW

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

MEDICAL OFFICER'S DRAFT REVIEW OF CLINICAL DATA

NDA # (serial):	**21,610**
Related IND(s):	**56,919 & 58,602**
Drug Name (generic):	**Numorphan ER (Oxymorphone HCL)**
Sponsor:	**Endo Pharmaceuticals, Inc.**
Indication:	**Moderate to severe pain in patients requiring continuous, around-the-clock opioid therapy for an extended period**
Type of Submission:	**NDA**
Date of Receipt (CDR):	**17DEC02**
Date of Review:	**15JAN03 to 17SEP03**
Material Reviewed:	**Electronic NDA Submission Documents**
Reviewer:	**Shaun M. Comfort, M.D.**
Team Leader:	**Sharon Hertz, M.D.**
Project Manager:	**Lisa Basham-Cruz**

EXECUTIVE SUMMARY AND CLINICAL REVIEW

Clinical Review for NDA 21-610

EXECUTIVE SUMMARY

1 RECOMMENDATIONS:

1.1 Recommendations on Approvability:

Based on the clinical information submitted, I recommend an approvable action be taken for this application, based upon the following conclusions:

1) The Sponsor has failed to demonstrate efficacy in two adequate- and well-controlled clinical trials.

1.2 Recommendations on Phase 4 Studies and Risk Management Steps:

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

1.3 Deficiencies and Recommended Corrective Action:

Conduct an adequate- and well-controlled trial demonstrating efficacy for oxymorphone extended-release tablets.

2 SUMMARY OF CLINICAL FINDINGS:

2.1 Brief Overview of Clinical Program

The Sponsor has submitted NDA 21-610 in support of oral oxymorphone hydrochloride extended- release (ER) 5, 10, 20, and 40 mg tablets. Oxymorphone is a semi-synthetic opioid analgesic proposed for treatment of moderate to severe pain where the use of an opioid is appropriate. Two trade names have been proposed at the time of this writing: Opana and ——— . In a review by the Division of Medication Errors and Technical Support of the Office of Drug Safety, the trade name Opana was not recommended because of concerns about possible errors due to the availability of tincture of opium. There were no objections to the tradename ——— .

Four pivotal studies examined single and multiple and single doses of oxymorphone ER in 1318 randomized patients with chronic low back pain, osteoarthritis pain, and post-operative pain. The following sections discuss the efficacy and safety findings.

2.2 Efficacy

Oxymorphone modified-release was evaluated in four adequate and well-controlled studies, submitted in support of efficacy for this product. Each study had a different design. Three were performed in chronic pain populations, and one (EN3202-012) was

conducted in a post-operative pain setting. Study duration ranged from one day to four weeks of multiple dosing.

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

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

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

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

imputed data reflecting treatment on the lower titration dose, OM 20 mg bid, used during Week 1. In summary, analysis of the data using BOCF imputation does not find any statistical support for the efficacy of the OM 10, 40, or 50 mg doses compared to placebo.

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

2.3 Safety

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

2.4 Dosing

The Sponsor proposes oxymorphone ER in 5, 10, 20, and 40 mg tablet strengths with a lowest starting dose of 5mg q12 hours (in opioid naïve subjects), with further dose titration based on the patient's response. However, the 5 mg IR and ER formulations were evaluated in PK studies only, therefore no conclusions regarding efficacy of 5 mg can be made. The lowest oxymorphone ER starting doses evaluated clinically were 10 mg ER q12 hours in opioid experienced subjects (Studies EN3202-016) and opioid naïve and experienced subjects (EN3202-025), and 20 mg ER q12 hours in opioid naïve and experienced subjects (Study EN3202-015).

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

- Dose Interval:
  The Sponsor proposes a q12 hour dosing interval, which was used in all four adequate and well-controlled studies. Based upon the efficacy and clinical pharmacology studies (half-life from 10-12 hours), the current dosing interval appears appropriate.

- Dosing Age Groups:
  PK studies evaluated ER and IR oxymorphone in subjects ranging from 18 to 81 years of age and clinical efficacy studies evaluated patients with ages ranging from 22 to 89. It is unlikely that the 18 to 22 age range will exhibit different efficacy responses to oxymorphone. Therefore, the proposed 18 to elderly age range is acceptable.

- Dosage Administration Adjustments:

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

caution in moderately impaired patients, and titrated cautiously in mildly impaired patients.

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

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

- Dose Conversion from Other Oral Opioids:
  The Sponsor estimated equianalgesic dose ratios based on results from four studies. The Sponsor approximate oxycodone ER to oxymorphone ER equianalgesic ratios of 1.2 – 2x and a morphine ER to oxymorphone ER ratio of 3x. The Sponsor recommends initially converting patients from oxycodone ER and morphine ER to total daily doses of oxymorphone ER in 2:1 and 3:1 ratios, respectively. These recommendations appears reasonable, based upon the information presented.

2.5 Special Populations

Gender Effects:
There were no gender effects when pharmacokinetic values were corrected for weight.

Age Effects:
Use in the elderly will require caution as patients over the age of 65 years exhibited a 40% increase in single-dose and steady-state serum concentrations.

Race and Ethnicity Effects:
There were too few non-Caucasian subjects for race or ethnicity effects to be evaluated.

Pediatrics:
The Sponsor is requesting a deferral for pediatric studies at this time. As the sponsor has failed to demonstrate adequate evidence of efficacy in adults, no further consideration is required concerning pediatric studies. Should the Sponsor provide adequate evidence of efficacy in adults and be granted approval to market oxymorphone ER, it would be acceptable to defer pediatric studies pending at least one year of use in adults to acquire additional safety information.

CLINICAL REVIEW

3 INTRODUCTION AND BACKGROUND

The Sponsor has submitted NDA 21-610 in support of oral oxymorphone hydrochloride Extended Release (ER) 5, 10, 20, and 40 mg tablets.

3.1 Proposed Indication:

The current indication proposed for this NDA is analgesia for relief of moderate to severe pain in patients requiring continuous, around-the-clock opioid therapy for an extended period of time.

3.2 Oxymorphone Regulatory History:

Immediate-release (IR) oxymorphone (Numorphan 2 and 5 mg tablets) was first approved by the Food and Drug Administration (FDA) (New Drug Application [NDA-11-737]) in 1959 and marketed in June of that year. Oral formulations were later voluntarily removed in 1979, for commercial reasons, per the Sponsor. Oxymorphone for parenteral administration was submitted under NDA 11-707 (1 mg/ml for intramuscular and subcutaneous routes). NDA 11-707 and NDA 11-738 (rectal administration of 2 and 5 mg suppository dosages) were approved for marketing by the Agency in 1959. Both products are still marketed in the US.

IND 58,602 was filed on 7/7/99 for reactivation of IR oxymorphone HCL tablets. IND 56,919 was filed on 9/10/98 to proceed with development of the modified-release product. As the development of both formulations proceeded simultaneously, the following development history applies to both products. All protocols having the EN3202 designation refer to the modified-release (called ER) oxymorphone product. All studies having an EN3203 designation involve the IR oxymorphone product.

3.2.1 Oxymorphone ER and IR Protocol Review History:

Specific events of interest regarding important clinical studies are discussed as follows:

- **Study EN3202-012** – Original protocol received (6/8/99), amended (11/1/99) and reviewed.

- **Pivotal Study EN3202-015** – Protocol received (4/20/99) and reviewed:
  1. Statistical reviewer noted that the use of LOCF may yield an artificially inflated difference in efficacy between the active and placebo groups.
  2. A single, unambiguous primary outcome was suggested.

- **Pivotal Study EN3202-016** – Protocol received (7/25/00).

- **Study EN3202-019** – Protocol received (7/10/00) and the review conclusions were that the study was:

1. Inadequately designed to demonstrate efficacy
2. Even in the event of statistically significant differences, the study would not be able to substantiate a claim of superiority to OxyContin, due to the method of dose assignment.

This information was communicated to the Sponsor in a letter dated 8/18/00.

- **Clarification of Trial Duration (12/7/01)** – The Division stated that the requirement for 3-month efficacy study duration was developed after the sponsor's NDA studies were planned, and for this reason were not applicable.

- **Study EN3202-025** – A Statistical analysis plan amendment was received (4/11/02) and that the review concluded that:
  1. A multiplicity adjustment should be made for the pair-wise comparisons of oxymorphone 10, 40, and 50 mg versus placebo.
  2. Use of last observation carried forward (LOCF) was concerning due to potential for biased results.

- **Draft Labeling for Hepatic Impairment (8/20/02)** – Sponsor proposal to contraindicate oxymorphone ER in patients with severe hepatic impairment reviewed and found acceptable.

- **Study EN3203-004** –Multiple issues regarding the design and analysis plan were noted, most importantly:

  1. The protocol can only assess efficacy of a single dose of study drug because there was no placebo-based comparison during the multiple-dose portion of the study.
  2. The use of "every 4-6 hour" dosing regimen may lead to considerable variability for medication taken.

- **NDA Submission** - 21-610 (Oxymorphone ER) and 21-611 (Oxymorphone IR) were submitted in electronic format to the agency on 12/17/02.

3.2.2 Sponsor-Division Meetings & Correspondence:

- **End of Phase II Meeting (5/11/00)**:
  1. Carcinogenic potential of OM must be studied but could be conducted as a Phase IV commitment
  2. The Division stated that the design of EN3202-015 appeared to be appropriate for demonstrating efficacy.
  3. A detailed EN3202-015 statistical analysis plan should be filed before unblinding.
  4. A target of 1000 single patient exposures with up to 100 patients exposed for 1 year, would be required.
  5. The Division stated that studies EN3202-015 and 016 are considered pivotal.

- **Type C Guidance Meeting (10/4/01)**:

2. The Division stated that a risk management plan (RMP) would be a necessary component of the NDA.

- **Pre-NDA Meeting (7/11/02)**::
1. The Division agreed that total and long-term safety exposure had been adequately addressed.
2. The Division stated that while pediatric studies could be deferred, they would not be waived. The IR formulation will require study in all age groups, but study of the ER formulation below age 2 will be waived.
3. The Division reminded the Sponsor concerning the use of LOCF and potential bias in the efficacy outcomes.
4. The Division stated that EN3202-015 and 016 appear to support the proposed indication.
5. The Division stated that the proposed pivotal studies did not appear to provide adequate support for the sponsor's dosing recommendations (BID for the ER formulation and QID for the IR formulation).
6. The potential clinical benefit of a 5 mg ER formulation for titration purposes was noted, but regulatory approval of such a dose may require efficacy data depending on the Sponsor's intended claim for this dose.

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

4.1 Chemistry

4.1.1 Drug, Drug Class, and Trade Name:

Oxymorphone hydrochloride extended release (ER) tablets, is a semi-synthetic oral opioid agonist derived from thebaine. Oxymorphone acts primarily at the mu opioid receptor site. The Sponsor is proposing four oxymorphone ER tablet strengths for approval: 5 mg, 10 mg, 20 mg, and 40 mg. Oxymorphone ER uses a proprietary extended-release technology (TIMERx-N®) to achieve its modified-release characteristics. Two trade names have been proposed: Opana and ——. No final name has been chosen at the time of this writing.

4.1.2 Clinically Relevant CMC Findings:

Please refer to the separate Chemistry Review.

4.2 Animal Pharmacology and Toxicology

Please refer to the separate Pharmacology and Toxicology Review.

4.3 Biopharmaceutics

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

Absorption

Following oral administration oxymorphone IR is with a mean absolute bioavailability of 10.8%. The extent of absorption (AUC) was comparable between IR and ER tablets. The rate of absorption (Cmax) was higher (approximately 35%) for IR tablets, compared with ER tablets. The significance of increased Cmax with IR tablets may not warrant dosage adjustment, per Biopharmaceutics. Summary oxymorphone ER PK parameters are shown in Table 3.1.1 below, from the Sponsor's draft label.

Table 3.1.1 Mean (±SD) Oxymorphone ER PK Parameters
(Source: Table 1, EN3202 Proposed Label, pg. 4, 4/15/03 Submission)

Regimen	Dosage	C_{max} (ng/mL)	AUC (ng·hr/mL)	$T_{½}$ (hr)
Single Dose	5 mg	0.27 ± 0.13	4.54 ± 2.04	11.30 ± 10.81
	10 mg	0.65 ± 0.29	8.94 ± 4.16	9.83 ± 5.68
	20 mg	1.21 ± 0.77	17.81 ± 7.22	9.89 ± 3.21
	40 mg	2.59 ± 1.65	37.90 ± 16.20	9.35 ± 2.94
Multiple Dose[a]	5 mg	0.70 ± 0.55	5.60 ± 3.87	NA
	10 mg	1.24 ± 0.56	9.77 ± 3.52	NA
	20 mg	2.54 ± 1.35	19.28 ± 8.32	NA
	40 mg	4.47 ± 1.91	36.98 ± 13.53	NA

NA = not applicable, [a] Results after 5 days of q12h dosing.

Food Effects:

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

Dose Linearity, Proportionality, and Steady-State PK

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

Metabolism

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

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

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

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

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

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

differences were observed when the PK results were normalized for body weight. In summary, caution should be used in dose titration of elderly patients.

Pharmacodynamics:
There is no exposure-response relationship information for IR tablets. The Sponsor stated that they did not observe any exposure-response relationship for ER tablets.

4.4 Biostatistics
Please refer to the separate Biostatistics Review.

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

5 DESCRIPTION OF CLINICAL DATA AND SOURCES:

5.1 Overall Data
This review was based on the data from the sponsor's four placebo-controlled studies submitted in support of efficacy of the ER oxymorphone formulation (EN3202-012, 015, 016, and 025). These studies are reviewed in detail in section 6.0. Supportive, active-controlled, and non-inferiority studies (EN3202-017, 018, and 019) are briefly discussed, but were not designed adequately to support a finding of efficacy.

Additional, supplementary information from the scientific literature was provided by the Sponsor. This material was not formally evaluated as part of this review.

5.2 Tables Listing the Clinical Trials:
The clinical development plan included trials evaluating both the extended-release (ER) and immediate-release (IR) formulations of oxymorphone. The Sponsor has used both extended release and controlled release terms throughout the application. The term extended release (ER) will be used by this Reviewer for the sake of consistency. As both development programs ran simultaneously, the following table lists all clinical studies performed, along with numbers of patients and basic design features. Note that all placebo-controlled pivotal trials are in bold type to distinguish them from clinical pharmacology, open-label, and active-controlled studies.

Table 4.2 Clinical Trials in the Oxymorphone ER and IR Development Program

Protocol No.	Development Plan		Study Type	Does Regimen and Formulation and Duration of Treatment	N
	ER	IR			
3202-001	Yes	Yes	Clinical pharmacology	OM ERa 20, OM ERb 20 OM 10 solution, Single dose crossover	15
3202-002	Yes		Clinical pharmacology	OM ERa 20, OM ERb 20 OM 10 solution, Single dose crossover	15
3202-003	Yes		Clinical pharmacology	OM ERa 20 tab, OM 10 solution, Single dose crossover	15
3202-004	Yes		Clinical pharmacology	NTX/OM ER 50/20 tabs OM ER 20 tabs, Single dose crossover	12
3202-005	Yes		Clinical pharmacology	NTX/OM ER 50/20 tabs, Single dose	24
3202-006	Yes		Clinical pharmacology	NTX/OM ER 50/20 tabs, Single/multiple dose	48
3202-007	Yes		Clinical pharmacology	Day 1 and 7 OM ER 5, 10, 20, and 40 tab (qd) Days 3 and 6 OM ER 5, 10, 20, and 40 tab (bid) Single/multiple dose crossover	24
3202-008	Yes		Clinical pharmacology	OM ER 40 tab, OM IR 10 x 4 tabs Single dose crossover	28
3202-009	Yes		Clinical pharmacology	Day I OM ER 20 x 1 tab (qd), OM IR 10 x 1 tab (qd) Day 3 through 8 OM ER 20 tab (bid), OM IR 10 tab (qid) Day 9 OM ER 20 x 1 tab (qd), OM IR 10 x 2 tab (qd), Single/multiple dose crossover	28
3202-010	Yes		Clinical pharmacology	OM ER 20 tab, Single dose	34
3202-011	Yes		Clinical pharmacology	OM ER 40 tab manufactured by Novartis; 2 doses OM ER 40 tab manufactured by IPC; 2 doses	24
3202-011A	Yes		Clinical pharmacology	OM ER 40 tab manufactured by Novartis; 2 doses OM ER 40 tab manufactured by IPC; 2 doses	6
3202-012	**Yes**	**Yes**	**Phase III, Acute post-operative pain, placebo-controlled**	**OM ER 20 tab, Placebo, Multiple dose**	127
3202-015	**Yes**	**Yes**	**Phase III, Osteoarthritis pain, placebo-controlled**	**Weeks 1-2** **OM ER 20 tab, OM ER 20 tab, OC .10 tab, Placebo** **Weeks 3-4** **OM ER 20 tab, OM ER 40 tab, OC .20 tab, Placebo, Multiple dose**	**489, 491 Rand**
3202-016	**Yes**		**Phase III, Lower back pain, placebo-controlled**	**10-14 day Titration Period** **OM ER 10-110, OC ER 20-220** **18-Day Double-Blind Treatment** **OM ER 10-110, OC ER 20-220, Placebo**	**329, 330 Rand**
3202-017	Yes		Cancer pain	OM ER 20-300 tab, MS C® 15-900 tab OC® 10-600 tab, Multiple dose crossover	86
3202-018	Yes		Cancer pain	Titration to optimal doses for each of the Trt Arms OM ER 10-100 tab, MS C® 30-300 tab 1 wk OL titration, 2 wks (1 wk/arm) crossover	36
3202-019	Yes		Cancer pain	Titration to optimal doses for each of the Trt Arms OM ER 10-110 tab, OC® 20-220 tab, Crossover	44
3202-020	Yes		Osteoarthritis and cancer pain	Completed studies 015 and 017 patients will start at dosage level from previous controlled-study; may be titrated up or down based on individual patient's pain relief and tolerability of side effects	197
3202-021	Yes		Osteoarthritis and cancer pain	Completed studies 016& 019. Optimal dose will be established during first week of dosing and may be titrated up or down based on individual patient's pain relief and tolerability of side effects	239 (164) *
3202-022	Yes		Cancer pain	Completed study 018 patients will start at dosage level from previous controlled-study; may be titrated up or down based on individual patient™s pain relief and tolerability of side effects	24 (15)*