CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-932

MEDICAL REVIEW(S)

HFD170/McNeal

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CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHETIC, CRITICAL CARE & ADDICTION DRUG PRODUCTS

REVIEW AND EVALUATION OF CLINICAL DATA
Application Information

NDA #: 20-932

Sponsor: Roxane Laboratories

Clock Date: Received 12/31/97

Drug Name

Generic Name: Oxycodone Hydrochloride Sustained Release

Trade Name: Roxicodone SR

Drug Categorization

Pharmacological Class: Opioid Analgesic

Proposed Indication: Moderate to Severe Pain

NDA Classification: 3

Dosage Forms: 10 mg and 30 mg Tablets

Route: Oral

Reviewer Information

Clinical Reviewer: Monte L. Scheinbaum PhD, MD

Completion Date: July 15, 1998

Monte L. Scheinbaum 7/15/98

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1.0 Background

Oxycodone is a well known, morphine-like, semisynthetic opioid analgesic. It has been in clinical use as the hydrochloride salt since 1917. It is a pure opioid agonist with no ceiling effects as seen with partial antagonists. The sponsor currently markets it as an oral solution and as immediate-release tablets for management of pain. A controlled-release formulation of oxycodone hydrochloride (Roxycodone SR) has been developed by the sponsor for the treatment of chronic pain and studied under IND This NDA presents data intended to support approval for marketing of 10 and 30 mg tablets of this formulation.

2.0 Material Reviewed

NDA Hard Copy of Clinical Data: 43 Volumes

Volume	Contents
1.1	Draft labeling, summaries of efficacy and safety, risk/benefit
1.32	Population PK/PD Analysis from Studies 961/962, 1252 and 963
1.34-1.43	Study CBI-961/962 (10 volumes)
1.44-1.53	Study CBI-1252 (10 volumes)
1.54-1.64	Study CBI-963 (11 volumes)
1.65	Published Clinical Pharmacology Studies
1.66	Published Efficacy Studies
1.67-1.68	Published Safety Studies
1.69-1.70	Integrated Summary of Efficacy
1.71-1.74	Integrated Summary of Safety

Electronic Data mounted by EDR
Case Report Forms from discontinued patients; 3 from Phase I studies, 21 from CBI-961/962, 8 from CBI-1252, 42 from CBI-963, 33 from CBI-964.
Other Electronic Data: 7 diskettes with MS Word Text;
CDROM with 123 SAS files

3.0 Chemistry

3.1 Drug Substance Quality

Oxycodone hydrochloride is a white, odorless, crystalline powder derived from the opium alkaloid, thebaine. Oxycodone hydrochloride is soluble in water and slightly soluble in alcohol (octanol water partition coefficient 0.7). The chemical name is 4,5-epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one hydrochloride (MW = 351.83.)

3.2 How supplied

Roxicodone SR is supplied as white to off white 10 mg tablets embossed with 10 on one side and 54319 on the reverse side or as yellow 30 mg tablets embossed with 30 on one side and 54319 on the reverse side. Each strength comes in either bottles of 100 or as 25 tablets per card (4 cards per shipper.) A DEA order form is required. It should be dispensed in tight, light-resistant containers, protected from moisture and stored at 15-30°C.

4.0 Animal Pharmacology

Oxycodone is an opioid agonist with pharmacological properties similar to morphine. It has both analgesic and antitussive activity. Oxycodone binds to mu opioid receptors in rats with weak affinity. Its metabolites, noroxycodone and morphine, are active opioid analgesics, and may be responsible for much of its activity. Oxycodone had three to six times the antinociceptive effect of morphine sulfate in rodent analgesic model testing. Oxycodone is a more potent antitussive agent than codeine. Oxycodone was more potent than morphine in causing CNS depressant effects in rats. In mice, oxycodone and morphine increased spontaneous motor activity, caused Straub tail response, increased palpebral opening, decreased food intake, caused delayed hyperthermia, and inhibited gastrointestinal motility. Oxycodone suppressed abstinence in a dose-related manner in dogs. It can cause a morphine type of drug dependence. Tolerance can develop, and it has abuse potential. Carcinogenicity, mutagenicity and effect on fertility studies have not been carried out.

5.0 Proposed indication, Strengths, Route of Administration, and Directions for Use

5.1 Proposed Indication: Moderate to Severe Pain

5.2 Dosage Form: Controlled-Release Tablet

5.3 Strengths: 10 mg and 30 mg

5.4 Route of Administration: Oral

5.5 Proposed Directions for Use: Roxicodone SR tablets are to be swallowed whole. They are not to be broken, chewed or crushed, since this could lead to the rapid release and absorption of a potentially toxic dose of oxycodone. Roxicodone SR is intended for the management of moderate to severe pain in patients who require treatment with an oral opioid analgesic for more than a few days. It should be administered every 12 hours at the lowest dosage that will achieve adequate analgesia and be tolerated. The dose must be individually adjusted according to severity of pain, patient response, patient size, prior analgesic usage, patient's medical condition and side effects.

6.0 Description of Clinical Data Sources

There were 396 patients (190 received the drug at least 30 days) and 193 healthy subjects who were administered the oxycodone SR formulation in 14 completed studies. There were 11 pharmacokinetic studies among these (Table 1.) The two pivotal studies are CBI-961/962 (cancer pain) and CBI-1252 (chronic pain). CBI-963 is an open-label safety study. There is also an ongoing compassionate-use trial, CBI-964. These efficacy and safety studies are summarized in Table 2. Also included in the submission were 48 published articles relating to the clinical pharmacology, efficacy and safety of the drug substance, oxycodone. References to these are listed in Section 6.1.

Table 1 Pharmacokinetic Studies

Human Pharmacokinetic Studies					
		Number of Subjects/Patients			
Study No.	Title	Oxycodone SR Tablets	Oxycodone IR Tablets	Oxycodone IR Solution	All Treatments
Pilot/Background Studies					
315-01	Bioequivalency Study of Dosage Forms of Oxycodone (Single-Dose, Four-Way Crossover) in Normal Males	28		28	28
315-05	A Single-Dose, Two-Way Crossover Study to Compare the Relative Bioavailability of Oxycodone HCl 5 mg Immediate-Release Tablets With Oxycodone HCl Oral Solution 5 mg/5 ml		26	26	26
XIR0296	A Randomized, Open-Label, Crossover Study Comparing the Bioequivalence of Oxycodone Formulations of 3x5 mg Tablets, 1x15 mg Tablet, and 0.75 ml of a 20 mg/ml Oral Solution in Normal Volunteers	--	26	26	27
XIR0196	A Single-Dose, Randomized, Double-Blind, Three-Way Crossover Study Comparing the Dose Proportionality of 5 mg, 15 mg, and 30 mg Doses of Oxycodone Administered Orally to Healthy Volunteers Under Fasting Conditions	--	28	--	28
Bioavailability/Bioequivalence					
315-03	A Single-Dose, Three-Way Crossover Study to Compare the Relative Bioavailability of Two Formulations of Sustained-Release Oxycodone HCl (10 mg) to Immediate-Release Oxycodone HCl (10 mg)	30		29	30
315-08	A Single-Dose, Two-Way Crossover Study to Compare the Relative Bioavailability of Oxycodone HCl 30 mg Sustained-Release Tablets With Oxycodone HCl 10 mg Sustained-Release Tablets	26			26
Steady-State Pharmacokinetics					
315-04	A Bioequivalence Study to Compare Two Formulations of Sustained-Release Oxycodone HCl Tablets (10 mg) to Immediate-Release Oxycodone HCl Oral Solution (Multiple-Dose, Three-Way Crossover)	30		30	30
315-09	A Bioavailability Study to Compare A Sustained-Release Oxycodone HCl 10-mg Tablet Formulation to an Immediate-Release Oxycodone HCl Oral Solution	25		26	26
Food Effects					
315-10	A Single-Dose, Four-Way Crossover, Food Effect Study of the 10-mg Formulation of Oxycodone Sustained-Release Tablets and Oxycodone Immediate-Release Oral Solution in Healthy Volunteers	14		14	14
315-11	A Single-Dose, Four-Way Crossover, Time to Food Effect Study of 10 mg Oxycodone Sustained-Release Tablets in Healthy Volunteers	24			24
Dose Proportionality					
315-12	An Open-Label, Single-Dose, Randomized, Four-Way Crossover, Dose-Proportionality Study of Oxycodone Sustained-Release Tablets in Healthy Volunteers	15			15
Total		**193**	**80**	**179**	**275**

Table 2 Efficacy and Safety Studies

Design Features of the Phase III Clinical Studies				
Study No.	**Title**	**Trial Design**	**No. of Patients[a/b]**	**Evaluation Criteria**
Controlled Clinical Studies				
CBI-961/962	Randomized, Double-Blind, Double-Dummy, Active-Controlled, Multi-Site Crossover Investigation Comparing the Efficacy of Oxycodone SR (Roxicodone 10 mg or 30 mg Tablets) Administered Every Twelve Hours to Oxycodone IR (Roxicodone® 5 mg Tablets) Administered Every Six Hours in Patients With Chronic Cancer Pain	Randomized, Double-Blind, Double-Dummy, Active-Controlled, Multi-Site, Crossover	69/49	Efficacy: VAS score measuring pain intensity, doses of rescue medication taken for breakthrough pain, global VAS scores measuring overall effectiveness of pain control, correlation of pain intensity VAS and plasma oxycodone concentration Safety: Adverse experiences, laboratory values, vital signs
CBI-1252	Randomized, Double-Blind, Double-Dummy, Active-Controlled, Multi-Site Crossover Investigation Comparing the Efficacy of Oxycodone SR (Roxicodone 10 mg or 30 mg Tablets) Administered Every Twelve Hours to Oxycodone IR (Roxicodone® 5 mg Tablets) Administered Every Six Hours in Patients With Chronic Pain	Randomized, Double-Blind, Double-Dummy, Active-Controlled, Multi-Site, Crossover	114/86	Efficacy: VAS score measuring pain intensity, doses of rescue medication taken for breakthrough pain, global VAS scores measuring overall effectiveness of pain control, correlation of pain intensity VAS and plasma oxycodone concentration Safety: Adverse experiences, laboratory values, vital signs
Uncontrolled Clinical Study				
CBI-963	A Thirty-Day, Open-Label, Multi-Center Observational Study Assessing the Safety of Oxycodone Sustained Release (Roxicodone SR 10 mg or 30 mg) Tablets Administered Every Twelve Hours (q12 Hours) in Patients Experiencing Chronic Pain	Open-Label, Multi-center	292/233	Efficacy: Global VAS scores measuring overall effectiveness of pain control, doses of rescue medication taken for breakthrough pain, correlation of pain intensity VAS and plasma oxycodone concentration Safety: Adverse experiences, laboratory values, vital signs
Ongoing Compassionate-Use Study				
CBI-964		Open-Label, Multi-center	–/232	Safety monitored by adverse experiences

a/b = Number of patients in stabilization period/number of patients in treatment period.
Data Source: Individual clinical trial reports.

6.1 References

1. Cooper SA, Precheur H, Rauch D, Rosenheck A, Ladov M, Engel J. Evaluation of oxycodone and acetaminophen in treatment of postoperative dental pain. Oral Surg 1980; 50:496-501.

2. Johnson GH, Van Wagoner JD, Brown J, Cooper SA. Bromfenac sodium, acetaminophen/oxycodone, ibuprofen, and placebo for relief of postoperative pain. Clin Ther 1997; 19:507-19.

3. Reines HD, Adams D, Hawkes T, Reynolds JC, Brown J, Bynum L, et al. Evaluation of oral ketorolac, oxycodone plus acetaminophen, and placebo for pain relief after orthopedic surgery. Curr Ther Res 1994; 55:615-24.

4. Sunshine A, Olson NZ, Zighelboim I, De Castro A. Ketoprofen, acetaminophen plus oxycodone, and acetaminophen in the relief of postoperative pain. Clin Pharmacol Ther 1993; 54:546-55.

5. Young RES. A comparison of analgesic effectiveness of oral butorphanol/acetaminophen, oxycodone/acetaminophen and placebo in hospitalized postsurgical patients. J Med 1979; 10:417-28.

6. Morrison JD, Loan WB, Dundee JW. Controlled comparison of the efficacy of fourteen preparations in the relief of postoperative pain. Br Med J 1971;3:287-90.

7. Sunshine A, Olson NZ, Colon A, Rivera J, Kaiko RF, Fitzmartin RD, et al. Analgesic efficacy of controlled-release oxycodone in postoperative pain. J Clin Pharmacol 1996;36:595-603.

8. Jonsson PE, Erichsen C, Holmin T, Petersson BA. Double-blind evaluation of intravenous indomethacin and oxycone-papaverine in the treatment of acute biliary pain. Acta Chir Scand 1985; 151:561-4.

9. Jonsson PE, Olsson AM, Petersson BA, Johansson K. Intravenous indomethacin and oxycone-papaverine in the treatment of acute renal colic. A double-blind study. Br J Urol 1987; 59:396-400.

10. Kortilla K, Pentti OM, Auvinen J. Comparison of IM lysine acetylsalicylate and oxycodone in the treatment of pain after operation. Br J Anaesth 1980; 52:613-7.

11. Laitinen J, Nuutinen L, Kiiskila EL, Freudenthal Y, Ranta P, Karvonen J. Comparison of intravenous diclofenac, indomethacin and oxycodone as post-operative analgesics in patients undergoing knee surgery. Eur J Anaesthesiol 1992; 9:29-34.

12. Nuutinen LS, Wuolijoki E, Pentikainen IT. Diclofenac and oxycodone in treatment of postoperative pain: a double-blind trial. Acta Anaesthesiol Scand 1986; 30:620-4.

13. Persson NH, Bergqvist D, Melander A, Zederfelt B. Comparison of a narcotic (oxicone) and a non-narcotic anti-inflammatory analgesic (indoprofen) in the treatment of renal colic. Acta Chir Scand 1985; 151:105-8.

14. Takki S, Tammisto T. A comparison of pethidine, piritramide and oxycodone in patients with pain following cholecystectomy. Anaesthesist 1973; 22:162-6.

15. Tammisto T, Tigerstedt I, Korttila K. Comparison of lysine acetylsalicylate and oxycodone in postoperative pain following upper abdominal surgery. Ann Chir Gynaecol 1980; 69:287-92.

16. Tigerstedt I, Leander P, Tammisto T. Postoperative analgesics for superficial surgery. Comparison of four analgesics. Acta Anaesth Scand 1981; 25:543-7.

17. Backlund M. Lindgren L, Kajimoto Y, Rosenberg PH. Comparison of epidural morphine and oxycodone for pain after abdominal surgery. J Clin Anesth 1997; 9:30-5.

18. Kalso E, Poyhia R, Onnela P, Linko K, Tigerstedt I, Tammisto T. Intravenous morphine and oxycodone for pain after abdominal surgery. Acta Anaesthesiol Scand 1991; 35:642-6.

19. Mattila MAK, Ahlstrom-Bengs E, Pekkola P. Intravenous indomethacin or oxycodone in prevention of post-operative pain. Br Med J 1983; 287:1026.

20. Tigerstedt I, Tammisto T, Leander P. Comparison of the analgesic dose-effect relationships of nefopam and oxycodone in postoperative pain. Acta Anaesth Scand 1979; 23:555-60.

21. Moertel CG, Ahmann DL, Taylor WF, Schwartau N. Relief of pain by oral medications. A controlled evaluation of analgesic combinations. JAMA 1974; 229:55-9.

22. Stambaugh JE. Analgesic equivalence of Tylox® and Percodan®: double-blind crossover study of patients with pain from malignancy. Curr Ther Res 1980; 27:302-8.

23. Stambaugh JE, Tejada F, Trudnowski RJ. Double-blind comparisons of zomepirac and oxycodone with APC in cancer pain. J Clin Pharmacol 1980; April:261-70.

24. Kalso E, Vainio A, Mattila MJ, Rosenberg PH, Seppala T. Morphine and oxycodone in the management of cancer pain: Plasma levels determined by chemical and radioreceptor assays. Pharmacol Toxicol 1990; 67:322-8.

25. Kalso E, Vainio A. Morphine and oxycodone hydrochloride in the management of cancer pain. Clin Pharmacol Ther 1990; 47:639-46.

26. Sandyk R. Tourette syndrome: successful treatment with clonidine and oxycodone. J Neurol 1986; 233:178-9.

27. Trzepacz PT, Violette EJ, Sateia MJ. Response to opioids in three patients with restless legs syndrome. Am J Psychiatry 1984; 141:993-4.

28. Walters AS, Wagner ML, Hening WA, Grasing K, Mills R, Chokroverty S, Kavey N. Successful treatment of the idiopathic restless legs syndrome in a randomized double-blind trial of oxycodone versus placebo. Sleep 1993; 16:327-32.

29. Bruera E, Belzile M, Pituskin E, Fainsinger R, Harsanyi Z, Babul N. Double-blind evaluation of the clinical efficacy and safety of controlled-release (CR) oxycodone and CR morphine in severe cancer pain. 16th Annual Scientific Meeting, American Pain Society 1997, New Orleans, LA. Abstract #672.

30. Hagen NA, Babul N. Comparative clinical efficacy and safety of a novel controlled-release oxycodone formulation and controlled-release hydromorphone in the treatment of cancer pain. Cancer 1997; 79:1428-37.

31. Jones M, Smith S, Fleishmann R, Hale M, Wild J, Salzman R, et al. Treatment of chronic low back pain (LBP) with around-the-clock CR oxycodone administration: A PK/PD model. 14th Annual Scientific Meeting, American Pain Society 1995, Los Angeles, CA. Abstract #95883.

32. Jones M, Smith S, Roth S, Burch F, Fleischmann R, Dietz F, et al. The effect of controlled-release (CR) oxycodone on pain intensity and activities in patients with pain secondary to osteoarthritis. 14th Annual Scientific Meeting, American Pain Society 1995, Los Angeles, CA. Abstract #95884.

33. De Conno F, Ripamonti C, Sbanotto A, Barletta L, Zecca E, Martini C, Ventafridda V. A clinical study on the use of codeine, oxycodone, dextropropoxyphene, buprenorphine, and pentazocine in cancer pain. J Pain Symptom Manage 1991; 6:423-7.

34. Glare PA, Walsh TD. Dose-ranging study of oxycodone for chronic pain in advanced cancer. J Clin Oncol 1993; 11:973-8.

35. Maruta T, Swanson DW. Problems with the use of oxycodone compound in patients with chronic pain. Pain 1981; 11:389-96.

36. Poyhia R, Vainio A, Kalso E. A review of oxycodone's clinical pharmacokinetics and pharmacodynamics. J Pain Symptom Manage 1993; 8:63-7.

7.0 Human Pharmacokinetics

7.1 Absorption

Oral oxycodone is 60 to 87% bioavailable relative to a parenteral dose due to presystemic and/or first-pass metabolism. There was 100% bioavailability for the sustained-release (SR) tablets relative to the immediate-release (IR) tablet formulation or solution. There was dose proportionality from 10 to 100 mg for the SR tablets with respect to absorption (but not peak concentrations). There is a food effect resulting in increased rate of absorption without affecting extent of absorption.

7.2 Distribution

The volume of distribution for intravenous-administered oxycodone was 2.6 L/kg. There is 45% binding to plasma protein. Distribution includes skeletal muscle, liver, intestinal tract, lungs, spleen, brain and breast milk.

7.3 Pharmacokinetics

Peak plasma concentrations were observed at 4-6 hours (1.3-1.5 hours for IR). The apparent elimination half-life was 7-12 hours (compared to 4 hours for IR). Steady State is achieved in 48 hours.

7.4 Metabolism

Metabolism is extensive, mostly to noroxycodone, oxymorphone (the latter by CYP2D6) and to glucuronides. Noroxycodone, the principal metabolite, is a weak analgesic.

7.5 Elimination

Excretion is mainly by the kidney. Hence hepatic or renal impairment will be associated with increased plasma drug concentrations. Elderly patients (>65 years) have slightly reduced clearances, resulting in 25% increased plasma levels. Gender and race effects appear to be absent.

8.0 Efficacy Findings

8.1 Overview of Efficacy

Two double-blind, controlled pivotal trials were carried out to demonstrate efficacy of the sustained-release tablets as compared to the immediate release formulation of oxycodone. Two trials with the same crossover design were begun in patients with cancer pain, CBI-961 and CBI-962, but due to slow patient enrollment for both protocols, the sponsor merged the two individual protocols into one multicenter study CBI-961/962. This change was submitted for review in May 1996 (Serial No. 028) and implemented via a protocol amendment in November 1996 (Serial No. 034). The second pivotal trial, CBI-1252, involved patients with chronic pain (cancer or non-cancer), but with a different sample size and a change in the entry Visual Analog Scale (VAS) score from ≤ 50 mm to < 70 mm. Both the CBI-961/962 and CBI-1252 studies were multicenter crossover trials with one-week legs, comparing pain scores and escape medication usage. Immediate-release oxycodone 5 mg tablets were used as escape medication. Plasma levels of oxycodone were obtained from some patients in both studies to develop data for examining pharmacodynamic/pharmacokinetic relationships.

8.2 Adequate and Well-Controlled Trials Pertinent to Efficacy Claims

8.21 Study CBI-961/962

8.211 Investigators/Location

Although 19 investigational sites were planned, 23 sites were initiated, and only 15 sites enrolled patients. Investigators for these 15 sites are as follows:

Leslie J. Bricker, M.D., Henry Ford Hospital, Detroit, MI
Daniel B. Carr, M.D., New England Medical Center #298, Boston, MA
Thomas H. Cartwright, M.D., Ocala, FL
Troy Guthrie, M.D., University of Florida, Jacksonville, FL
Robert Kerr, M.D., Southwest Regional Cancer Center, Austin, TX
Alan Lipton, M.D., Milton S. Hershey Medical Center, Hershey, PA
Timothy T. McLaughlin, Sr., M.D., Clinical Research of West Florida, Inc., Clearwater, FL
Manuel Modiano, M.D./Pat Plezia, Pharm.D., Arizona Clinical Research Center, Inc., Tucson, AZ
Joanne Mortimer, M.D., Barnard Cancer Center, St. Louis, MO
George A. Pyke, M.D., Altamonte Springs, FL
Mark Rubin, M.D., Medical Studies Florida, Ft. Myers, FL
Charles Scarantino, M.D., Rex Cancer Center, Raleigh, NC
Katherine Tkaczuk, M.D., University of Maryland, Baltimore, MD
Jeffrey Weisberg, M.D., Comprehensive Cancer Research Group, Inc., North Miami Beach, FL
Michael Zimmer, M.D., Doctor's Clinic Research, Vero Beach, FL

8.212 Plan

8.2121 Objective

The primary aim of this study was to assess the ability of oxycodone SR tablets administered every 12 hours (q 12 hours) versus oxycodone IR tablets administered every 6 hours (q 6 hours) to control pain in patients with chronic pain of cancer origin. Secondary objectives were to compare population pharmacokinetics and safety for the two formulations.

8.2122 Population

Patients with chronic pain of cancer origin were eligible for entry if :

a) male or female 18 years of age or older (if female and of child-bearing potential, the patient was to be practicing suitable means of birth control. b) pain intensity VAS assessment score ≤ 50 mm (0 = no pain, 100 = worst pain possible) for pain over the 24 hours prior to being randomized,
c) currently being treated adequately for chronic pain of cancer origin associated with a TDD of at least 20 mg of oral oxycodone.
d) life expectancy was at least 8 weeks.
e) able to ingest and tolerate oral medications (without emesis).
f) required no more than two breakthrough doses of analgesic during the 24 hours prior to being randomized.

Patients were excluded from entry into the double-blind treatment period if:

a) pregnant or lactating.
b) had surgery in the month prior to stabilization or were scheduled for surgery at any time during the stabilization period or at any time during the trial.
c) had a history of allergic, anaphylactic, hypersensitivity, idiosyncratic, or other adverse reaction to opioids or opioid-like medications, as determined by the investigator.
d) had a physical or mental disorder that would have prohibited completion of study measures.
e) had a condition that would have interfered with the absorption, distribution, metabolism, or excretion of study medications.
f) were scheduled to receive a course of radiation therapy within 14 days prior to the screening, at any time during the trial.
g) were judged to have a history of noncompliance with prescribed therapy (medications) or believed to be unable to keep records (diaries) or scheduled clinic appointments.
h) had any clinically significant medical condition that would, in the investigator's opinion, compromise patient safety, or preclude treatment with oxycodone.
I) had received any investigational drug within 30 days prior to screening.

8.2123 Design

This was a randomized, double-blind, double-dummy, active-controlled, multi-center two-period crossover (one-week legs) investigation comparing the efficacy of oxycodone SR administered q 12 hours to oxycodone IR administered q 6 hours in patients with chronic pain of cancer origin.

8.21231 Stabilization Period (Days -7 to -2)

After completing screening, patients were sent home with either open-label oxycodone IR q 6 hours or open-label oxycodone SR q 12 hours. The investigator determined the total daily dose (TDD) of these medications based upon the previous medication regimen and standard conversions to oxycodone equivalence. Rescue doses of oxycodone IR (supplied as 5-mg tablets) were used for breakthrough pain. Assessment of pain control and dose adjustment of oxycodone was carried out by telephone calls to patients. When patients required no more than two doses of rescue medication in a 24-hour period, and pain intensity was rated ≤ 5 on a verbal scale of 0 to 10 in the same 24-hour period, they were asked to come to the clinic to complete a VAS assessment for pain intensity over the prior 24-hour dosing period. If patients marked ≤ 50 mm pain intensity on the VAS over the prior 24-hour dosing period, and they continued to meet all other criteria, they were randomized to one of two double-blind treatment sequences.

8.21232 Double-Blind Treatment Period (2-weeks)

The oxycodone dose for the double-blind period was calculated by dividing the final TDD of stabilization medication (including scheduled and rescue doses) by 2, rounding up to the nearest multiple of 10, and then dividing the quantity into either two or four equal doses. Patients were randomized to one of two double-blind crossover treatment sequences (IR/SR or SR/IR). The individual treatments consisted of either SR (oxycodone SR administered q 12 hours with IR placebo administered q 6 hours) or IR (oxycodone IR administered q 6 hours with SR placebo administered q 12 hours.) After 7 days of the first treatment (either oxycodone IR/SR placebo or oxycodone SR/IR placebo), patients were crossed over to the alternate treatment for another 7 days. In the event of an intervening weekend or if a patient had difficulty in scheduling a visit, an additional 2 days was permitted for each period. During each of the double-blind treatments, patients took study medication in combination with placebo (double-dummy) four times per day regardless of treatment. Oxycodone IR (supplied as 5-mg tablets) was used as rescue medication for breakthrough pain during both legs of the crossover.

8.2124 Assessments

Patients completed each day VAS (100-mm) assessment measuring pain intensity "right now", immediately prior to their 6:00 am, 12:00 noon, and 6:00 pm doses. The primary efficacy variables were the VAS scores as recorded on Day 6 of each 7-day double-blind treatment, were the primary efficacy variables for this study. VAS scores on the other study days, the last measurement after each Study Day 3 (presumed steady-state value) and at each of three scheduled visits were secondary efficacy variables. The latter VAS assessments measured pain intensity over the prior 12-hour (at Visits 3 and 4) and prior 24-hour (at Visit 2), "right now" scores (at Visits 2, 3, and 4) and 7-day global VAS assessments (at the end of each double-blind treatment).

Adverse experience (AE) reporting, review of patient diaries documenting AE's and daily intake of medication, including rescue medication (oxycodone IR), and drug accountability were carried out at each visit. Collection for clinical laboratory safety evaluations were done at screening and the final visit.

Blood samples for population pharmacokinetic analysis were drawn from a subset of patients after the stabilization period and at the end of each 7-day double-blind treatment. The time that samples were drawn was determined utilizing a random block design. Analyses of these blood samples were used in a population pharmacokinetic model to correlate VAS assessment scores and plasma concentration of oxycodone, as well as a comparison of the plasma concentrations following dosing with each formulation (SR and IR).

8.2125 Analysis Plan

Analysis of variance models (ANOVA) were used to test comparability of treatment sequences at baseline for the overall stabilized doses of oxycodone and the VAS assessment scores at baseline (end of the stabilization period) and following double-blind treatments. A calculated sample size of 34 patients for this cross-over study, 17 in each of the two treatment sequences, provided 90% power to ensure that the average difference in VAS pain relief between formulations was no more than 8 mm based on a 100-mm scale. An "intent-to-treat" analysis of efficacy was performed, including all patients who were randomized, received at least one dose of double-blind study drug and recorded at least one VAS score or used rescue medication. Treatment comparisons for mean VAS scores were carried out for the 6:00 am, 12:00 noon, and 6:00 pm time points and for overall (i.e., the average of all available scores). The ratio of mean VAS assessment scores obtained for each of the two formulations (i.e., SR/IR) and the 95% confidence interval of the difference were also calculated. The global VAS assessment scores for overall drug effectiveness were analyzed using an ANOVA model similar to the one for mean VAS scores. The numbers and percentages of patients who required rescue medication for breakthrough pain on each study day, on Days 1 through 3, on Days 4 through 6, and overall were displayed for each formulation (IR and SR). For these intervals, the number and percentage of patients who required rescue medication on both formulations, on either formulation, and did not require any rescue medication were compared using McNemar's test to assess statistical significance. For each formulation, the average total daily dose of rescue medication on each study day and overall (i.e., total dose of rescue medication taken during each double-blind treatment divided by the total number of days on treatment) was displayed. The mean overall dose of rescue medication, the standardized number of days that rescue medication was taken and the average number of doses of rescue medication taken per day during each double-blind treatment were compared between treatments using the same ANOVA model as for VAS assessment scores. An integrated assessment of VAS scores and rescue medication consumption ("summated percent difference") was also carried out using ANOVA to compare formulations. All "intent-to-treat" patients were included in these analyses and in the safety analysis.

8.213 Study Conduct/Outcome

8.2131 Patient Disposition

A total of 69 patients entered, and 50 of these patients (72.5%) completed the stabilization period. Forty-nine of these 50 patients were randomized to receive one of two treatment sequences during the double-blind treatment period: 24 patients received SR/IR and 25 patients received the IR/SR sequence. One patient withdrew consent prior to randomization. There were 47 of the 49 (95.9%) randomized patients who actually took study medication during this phase of the study. Two of the patients who were randomized to the SR/IR treatment sequence did not complete the study medication page of the patient diary and therefore did not provide any dosing information. There were thirty-seven (78.7%) patients who completed this phase of the study; five patients withdrew due to AE's, three withdrew due to inadequate therapeutic response, and two withdrew consent (Table 3). Table 4 lists patient disposition by investigator. The number of days to stabilization for patients in each double-blind treatment sequence is presented in Table 5.

Table 3 Disposition of Patients

	IR	*SR*	*Total**
Enrolled in Stabilization Period			69
Completed Stabilization Period			50
Randomized to Double-Blind			49
Took Double-Blind Medication	43	44	47
Evaluable for Safety and Efficacy	43	44	47
Completed Double-Blind			37
Discontinued Double-Blind	5	5	10
Adverse experiences	3	2	5
Inadequate therapeutic response	1	2	3
Withdrew consent	1	1	2

* Received either treatment

Table 4 Patient Disposition by Investigator

	Number (%) of Patients Screened N = 74	Number (%) Enrolled in Stabilization Period N = 69		Patients Randomized to DB Rx Period[a] No (%) N = 49		Total Patients Completing StudyN = 37
Investigator (No.)		Oxycodone IR	Oxycodone SR	SR/IR	IR/SR	
Brotherton (46)	0	0	0	0	0	0
Bricker (04)	3	3	0	1	0	1
Carr (08)	2	2	0	1	1	2
Cartwright (40)	1	1	0	0	1	1
Galandiuk (12)	0	0	0	0	0	0
Guthrie (06)	11	11	0	5	5	8
Kerr (02)	18	16	0	5	4	9
Larijani (43)	0	0	0	0	0	0
Lipton (10)	3	2	0	0	1	1
Litton (44)	0	0	0	0	0	0
McLaughlin (15)	5	1	3	1	1	1
Mortimer (07)	3	3	0	0	1	0
Ndubisi (47)	0	0	0	0	0	0
Plezia (09)	11	10	0	4	3	5
Pyke (41)	3	0	3	1	1	1
Rubin (42)	2	2	0	1	1	1
Scarantino (13)	1	1	0	0	1	1
Simmonds (01)	0	0	0	0	0	0
Tkaczuk (03)	6	6	0	3	3	4
Weisberg (14)	1	1	0	0	1	0
Whaley (45)	0	0	0	0	0	0
Zimmer (11)	4	4	0	2	1	2
Total	74	63	6	24	25	37

Table 5 Number of Days to Stabilization by Treatment Sequence
Patients Who Entered Double-Blind Treatment

Number of Days	SR/IR n (%)	IR/SR n (%)	Total n (%)
3	1 (4.2)	1 (4.0)	2 (4.1)
4	4 (16.7)	4 (16.0)	8 (16.3)
5	1 (4.2)	2 (8.0)	3 (6.1)
6	3 (12.5)	3 (12.0)	6 (12.2)
7	6 (25.0)	8 (32.0)	14 (28.6)
8	2 (8.3)	4 (16.0)	6 (12.2)
9	4 (16.7)	2 (8.0)	6 (12.2)
> 9	3 (12.5)	1 (4.0)	4 (8.2)
Total Pts. Randomized	24 (100.0)	25 (100.0)	49 (100.0)

8.2132 Demographics/Group Comparability

Demographic information is listed in Table 6. The patient population of the double-blind treatment period ranged in age from years, with a mean age of 57.6 years. Patients were predominantly female (59.2%) and white (73.5%). All patients had cancer, with most patients suffering from chronic pain as a result of lung (12/49; 24.5%) or breast cancer (10/49; 20.4%) (Table 7). All patients had taken other opioid medication prior to this study, although one patient had stopped taking opioids 3 months prior to study entry. The most common opioids used prior to study entry were oxycodone (32/49; 65.3%), morphine (12/49 (24.5%), and hydrocodone (11/49 (22.4%). Percocet was the most common (17/49; 34.7%) oxycodone-containing medication taken. Other oxycodone-containing medications used prior to study entry include pure oxycodone (10/49; 20.4%), Tylox (7/49; 14.3%), Roxicet (5/49; 10.2%), and acetaminophen with oxycodone (1/49; 2.0%). The mean VAS score for the patients at the end of stabilization was 23.7 mm (range, mm) and the stabilized dose of oxycodone was 94.8 mg (range, mg).

Table 6 Demographics

Characteristics	Overall (N = 49)	SR/IR (N = 24)	IR/SR (N = 25)	p-value
Age (yrs)				0.347
N	49	24	25	
Mean (S.D.)	57.6 (13.68)	59.1 (14.21)	56.2 (13.27)	
Range				
Gender [N (%)]				0.243
Male	20 (40.8%)	8 (33.3%)	12 (48.0%)	
Female	29 (59.2%)	16 (66.7%)	13 (52.0%)	
Race [N (%)]				0.147
White	36 (73.5%)	17 (70.8%)	19 (76.0%)	
Black	10 (20.4%)	6 (25.0%)	4 (16.0%)	
Hispanic	2 (4.1%)	1 (4.2%)	1 (4.0%)	
Other	1 (2.0%)	0 (0.0%)	1 (4.0%)	
Height (in)				0.635
N	45	22	23	
Mean (S.D.)	66.23 (4.024)	65.80 (3.844)	66.64 (4.233)	
Range				
Weight (lbs)				0.183
N	45	22	23	
Mean (S.D.)	167.56 (54.541)	175.50 (63.405)	159.96 (44.591)	
Range				
Primary Pain Treatment Site [N (%)]				–
Back	14 (28.6%)	9 (37.5%)	5 (20.0%)	
Chest	10 (20.4%)	3 (12.5%)	7 (28.0%)	
Abdomen	9 (18.4%)	4 (16.7%)	5 (20.0%)	
Pelvis	8 (16.3%)	4 (16.7%)	4 (16.0%)	
Leg	3 (6.1%)	2 (8.3%)	1 (4.0%)	
Body as a Whole	2 (4.1%)	1 (4.2%)	1 (4.0%)	
Neck	2 (4.1%)	0 (0.0%)	2 (8.0%)	
Shoulder	1 (2.0%)	1 (4.2%)	0 (0.0%)	
Total Daily Oxycodone Dose (mg) (Screening)				0.974
N	49	24	25	
Mean (S.D.)	70.3 (66.31)	68.7 (61.35)	71.8 (71.98)	
Range				
Stabilized Total Daily Oxycodone Dose (mg)				0.666
N	49	24	25	
Mean (S.D.)	94.8 (84.69)	100.2 (84.76)	89.6 (86.05)	
Range				
Number (%) of Patients Stabilized on				0.607
Oxycodone SR	4 (8.2%)	2 (8.3%)	2 (8.0%)	
Oxycodone IR	45 (91.8%)	22 (91.7%)	23 (92.0%)	
Baseline VAS Assessment (mm)[e]				0.853
N	47	23	24	
Mean (S.D.)	23.7 (18.82)	23.2 (17.16)	24.3 (20.64)	
Range				

Table 7 Summary of Primary Cancer Sites at Baseline

Location	Overall n (%)	SR/IR n (%)	IR/SR n (%)
Lung	12 (24.5)	7 (29.2)	5 (20.0)
Breast	10 (20.4)	4 (16.7)	6 (24.0)
Other	6 (12.2)	3 (12.5)	3 (12.0)
Colon/Intestine	3 (6.1)	3 (12.5)	0
Head & Neck	3 (6.1)	0	3 (12.0)
Prostate	2 (4.1)	0	2 (8.0)
Stomach	2 (4.1)	1 (4.2)	1 (4.0)
Kidney	2 (4.1)	0	2 (8.0)
Cervical	2 (4.1)	1 (4.2)	1 (4.0)
Lymphoma	2 (4.1)	1 (4.2)	1 (4.0)
Ovary	1 (2.0)	1 (4.2)	0
Bladder	1 (2.0)	1 (4.2)	0
Pancreas	1 (2.0)	1 (4.2)	0
Leukemia	1 (2.0)	1 (4.2)	0
Unknown	1 (2.0)	0	1 (4.0)
Total No. of Patients	49 (100.0)	24 (100.0)	25 (100.0)

8.2133 Dosing Information

The investigators had the option of altering the patients' stabilized dose at the beginning of the double-blind treatment period. The recorded total daily dose (TDD, in mg) of double-blind oxycodone and rescue medication taken by the 47 patients who took study drug during the double-blind treatment period is presented in Table 8. Overall compliance was said to be approximately 94% for both formulations. Patients took from 40.9% to 118.6% of the prescribed number of tablets while receiving the SR formulation and from 28.6% to 121.4% of the prescribed number of tablets while receiving the IR formulation. Sixty-three patients began stabilization on oxycodone IR; forty-five of these (71.4%) successfully completed the conversion from prior opioid therapy to oxycodone IR and entered double-blind treatment. The most common reasons patients receiving IR did not complete the stabilization process were adverse experiences (14.3%, 9/63) or withdrawal of consent (11.1%, 7/63). There were large variations in percent dose change (-33.3 % to 200.0%) from the time of conversion to oxycodone IR until a stabilized dose was achieved. The least change were in patients who received oxycodone (as monotherapy or in combination with aspirin or acetaminophen) prior to entering the study. Six patients stabilized on oxycodone SR; four patients (66.7%) completed the conversion process and entered double-blind treatment; one patient withdrew consent and the other withdrew for adverse experiences prior to achieving stabilization. There were large variations among the patients in the percent dose change associated with achieving a stabilized SR dose (range;

%.)

Table 8 Total Daily Dose (mg) of Oxycodone

		Oxycodone SR (N=44)	Oxycodone IR (N=43)
Recorded Double-Blind Study Med	Mean (S.E.)	108.2 (16.26)	107.4 (16.63)
	Median	60.0	60.0
	Range		
Recorded Rescue Medication	Mean (S.E.)	15.8 (5.52)	16.3 (5.76)
	Median	5.0	3.6
	Range		

8.2134 Concomitant Medication

Concomitant opioid medications were not permitted during this study. Six patients (12.2%) deviated from this requirement but were permitted to continue in the study. One patient took Tylox on Day 4 and another took Percocet on Day 1 of the double-blind period; the others took disallowed opioid medication during the stabilization period. The majority of patients (46/49; 93.9%) who entered the double-blind treatment period took their first dose of some form of non-opioid medication prior to study entry, i.e., prior to the stabilization period. Certain types of medications such as antihypertensives, laxatives, and non-narcotic, non-opioid analgesics were permitted during treatment at stable scheduled doses. The most common medications used were dexamethasone (11/49; 22.4%), prochlorperazine (11/49; 22.4%), and granisetron (9/49; 18.4%). Non-opioid analgesics taken during the study included acetaminophen (4/49; 8.2%), ibuprofen (3/49; 6.1%), oxaprozin (3/49; 6.1%), aspirin (acetylsalicylic acid: 1/49; 2.0%), and naproxen (1/49; 2.0%). Three patients took NSAIDs (i.e., ibuprofen) as rescue medication at some time during the course of the study (Plezia/7, Tkaczuk/1, and Tkaczuk/5). The rescue medications were single doses taken on different study days and different time points for each patient; therefore, the use of NSAIDs was expected to minimally affect the VAS scores.

8.214 Efficacy Results

8.2141 VAS Scores on Day 6

The primary efficacy variable for this study was the VAS scores for pain intensity at 6:00 am, 12:00 noon, 6:00 pm, and overall (average of available measurements) on the sixth day of each double-blind treatment. The mean Day 6 VAS assessment scores, the mean differences of the two formulations in VAS assessment score and the 95% confidence intervals are summarized for the intent-to-treat population by oxycodone formulation in Table 9. The ratios of mean VAS assessment scores and the corresponding 95% confidence interval are also summarized at each time point on Day 6 in Table 9. There were no significant differences between treatments for the overall day 6 means and at the 6 am and 12 noon time points. There was a significant difference (p=0.049) favoring SR (22.94 vs. 26.00 mm) at 6 pm. Results are shown graphically in Figure 1. There were no statistically significant differences in Day 6 mean VAS assessment scores between the two formulations for the analyses of gender, age, and race subgroups, with the exception of the 6:00 pm time points for male patients (SR, 27.15 [N=13]; IR, 25.40 [N=15]; p=0.023) and white patients (SR, 22.74 [N=27]; IR, 27.43 [N=28]; p=0.010). No statistical differences between formulations were observed when changes of Day 6 VAS pain intensity scores from baseline were examined (Table 10).

Figure 1: Mean VAS Score (mm) on Day 6

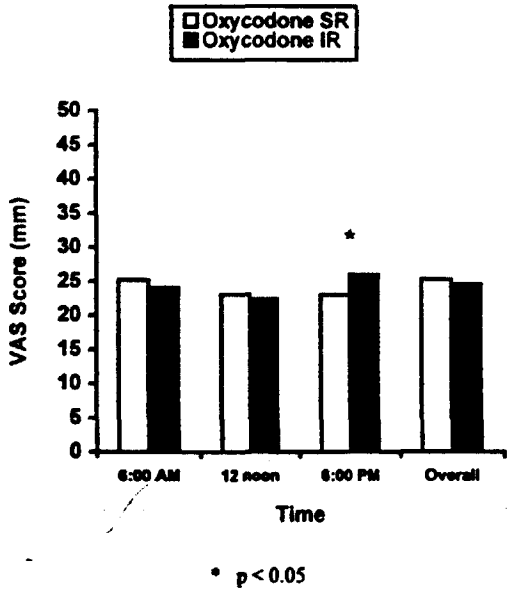


Table 9 Mean Day 6 VAS Assessment Score (mm)

(Intent-to-Treat Population)

		Formulation		Least Squares Mean Difference			Mean Ratio[c]	
Time point		Oxycodone SR	Oxycodone IR	SR-IR	95% Confidence Interval[d]	p-value[e]	SR/IR	95% Confidence Interval[d]
6:00 am	N	39	38					
	Mean	25.15	24.05	0.478	(-4.99, 5.95)	0.865	1.019	(0.80, 1.23)
	S.E.	3.401	3.663	2.792	-			
12:00 noon	N	36	37					
	Mean	23.00	22.35	-1.086	(-5.55, 3.38)	0.637	0.955	(0.77, 1.14)
	S.E.	3.266	3.332	2.278				
6:00 pm	N	36	37					
	Mean	22.94	26.00	-5.343	(-10.44, -0.24)	0.049	0.808	(0.62, 0.99)
	S.E.	3.477	3.688	2.602				
Overall[f]	N	39	38					
	Mean	25.25	24.55	-1.326	(-5.51, 2.85)	0.539	0.950	(0.79, 1.11)
	S.E.	3.302	3.007	2.132				

[a] VAS = Visual Analog Scale for pain intensity on a scale of 0 (no pain) to 100 (worst possible pain).

[b] Refers to Day 6 of the indicated double-blind treatment.

[c] Includes patients whose VAS assessment scores were obtained during both double-blind treatments.

[d] Although expressed using a comma per statistical convention, this interval is interpreted as the range between these two values.

[e] P-value based on comparison between oxycodone SR and oxycodone IR.

[f] Overall = Sum of the scores at all three time points divided by the number of time points with non-missing data.

Data Source: End-of-Text Tables 8.1 and 9.1; Patient Data Listing 11.

Table 10 Mean Change From Baseline for VAS Score (mm) on Day 6

(Least Square Means, Intent to Treat Population)	Time Point	SR	IR	SR-IR	95% Confidence Interval[d]	p-value[e]
N	6:00 am	38	37			
Mean Change		0.89	1.62	-0.634	(-8.34, 7.07)	0.873
S.E.		2.439	2.548	3.929		
N	12:00 noon	34	34			
Mean Change		-0.21	-1.12	2.893	(-5.62, 11.41)	0.512
S.E.		2.512	2.832	4.344		
N	6:00 pm	31	27			
Mean Change		3.81	4.74	1.227	(-8.18, 10.64)	0.801
S.E.		2.813	2.562	4.801		
N	Overall[f]	38	37			
Mean Change		1.57	0.74	0.982	(-5.39, 7.36)	0.765
S.E.		2.011	2.137	3.253		-

8.2142 VAS Assessment Scores for Days 1 through 5

Mean VAS assessment scores, differences between the two formulations' VAS assessment scores, and the 95% confidence intervals for Days 1 through 5 are summarized by oxycodone formulation in Table 11. Ratios of mean VAS assessment scores and the corresponding 95% confidence interval are also presented for the intent-to-treat population. Mean VAS scores are depicted graphically in Figure 2. For Day 1, the IR formulation was associated with 4.7 to 6.8 mm less VAS pain intensity; these differences were statistically significant at 6 am, 12 noon and overall. Except for 12 noon on Day 5, in which there was significantly less pain intensity with IR, there were no other significant differences in VAS pain intensity scores for Days 1 to 5. Changes from baseline for Days 1 to 5 VAS pain intensity scores showed no significant differences between treatments except for overall Day 5 changes in score; the SR exhibited a small increase in pain of 1.23 mm (S.E. = 2.034), while IR had 3.55 mm ((S.E. = 2.269) less pain (p=0.047).

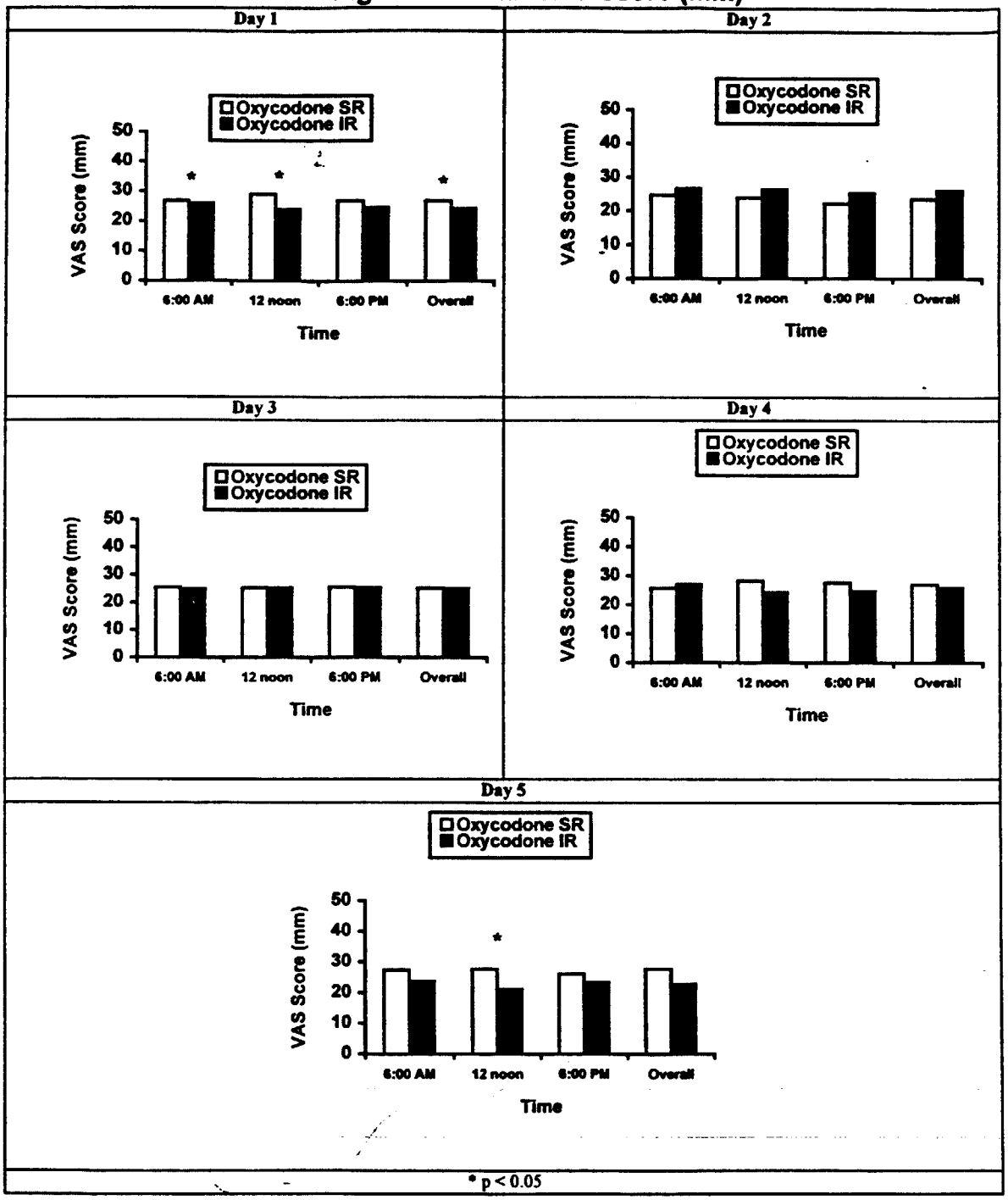
8.2143 VAS Assessment Scores at Endpoint

There were no differences between treatments for mean VAS scores at endpoint (Figure 3). Endpoint is defined as the last day on which a VAS score was recorded on Day 4 or later.

Table 11 Mean VAS Assessment Score (mm) on Days 1 through 5

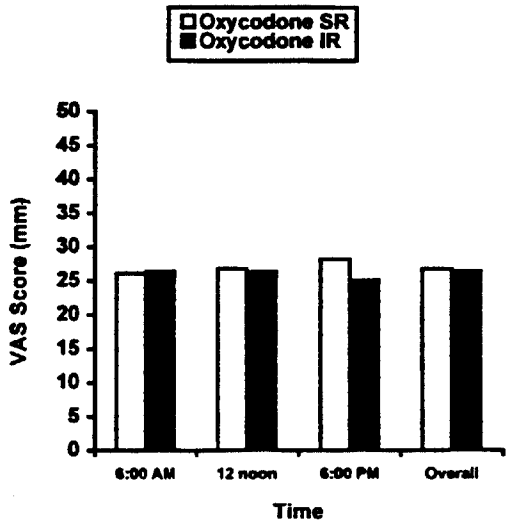
				Least Squares Mean Difference			Ratio of Means	
Time point		Oxycodone SR	Oxycodone IR	SR-IR	95% Confidence Interval	p-value	SR/IR	95% Confidence Interval
Day 1								
6:00 am	N	39	35					
	Mean (S.E.)	26.85 (3.218)	25.97 (3.369)	6.757 (3.039)	(0.80, 12.71)	0.035	1.285	(1.03, 1.54)
12:00 noon	N	44	38					
	Mean (S.E.)	29.07 (3.262)	23.89 (3.593)	6.600 (2.580)	(1.54, 11.66)	0.015	1.289	(1.07, 1.51)
6:00 pm	N	45	42					
	Mean (S.E.)	26.87 (3.318)	24.71 (3.072)	2.485 (2.840)	(-3.08, 8.05)	0.387	1.101	(0.88, 1.33)
Overall	N	45	43					
	Mean (S.E.)	28.26 (3.032)	24.28 (2.804)	4.734 (2.003)	(0.81, 8.66)	0.023	1.194	(1.03, 1.35)
Day 2								
6:00 am	N	44	41					
	Mean (S.E.)	24.59 (3.421)	26.59 (3.390)	-0.557 (3.284)	(-6.99, 5.88)	0.866	0.979	(0.73, 1.22)
12:00 noon	N	44	41					
	Mean (S.E.)	23.89 (3.309)	26.39 (3.622)	-3.164 (2.835)	(-8.72, 2.39)	0.272	0.886	(0.69, 1.09)
6:00 pm	N	44	41					
	Mean (S.E.)	22.23 (3.053)	25.29 (3.385)	-2.060 (2.486)	(-6.93, 2.81)	0.413	0.918	(0.72, 1.11)
Overall	N	44	41					
	Mean (S.E.)	23.57 (2.979)	26.09 (3.196)	-1.927 (2.264)	(-6.36, 2.51)	0.400	0.927	(0.76, 1.10)
Day 3								
6:00 am	N	44	41					
	Mean (S.E.)	25.50 (3.682)	24.78 (3.324)	2.582 (3.081)	(-3.46, 8.62)	0.407	1.108	(0.86, 1.36)
12:00 noon	N	45	41					
	Mean (S.E.)	25.31 (3.396)	25.17 (2.925)	0.576 (2.553)	(-4.43, 5.58)	0.823	1.023	(0.82, 1.22)
6:00 pm	N	42	40					
	Mean (S.E.)	25.52 (3.518)	25.28 (3.541)	1.616 (2.656)	(-3.59, 6.82)	0.547	1.068	(0.85, 1.29)
Overall	N	45	41					
	Mean (S.E.)	25.23 (3.197)	25.05 (2.929)	1.628 (2.217)	(-2.72, 5.97)	0.468	1.067	(0.89, 1.25)
Day 4								
6:00 am	N	43	39					
	Mean (S.E.)	25.65 (3.398)	26.97(3.737)	0.475(3.493)	(-6.37, 7.32)	0.893	1.018	(0.76, 1.28)
12:00 noon	N	42	38					
	Mean (S.E.)	28.17 (3.418)	24.29 (3.141)	3.256 (2.881)	(-2.39, 8.90)	0.266	1.132	(0.90, 1.36)
6:00 pm	N	42	38					
	Mean (S.E.)	27.57 (3.403)	24.58 (3.347)	1.925 (3.056)	(-4.06, 7.91)	0.533	1.076	(0.84, 1.31)
Overall	N	43	39					
	Mean (S.E.)	26.85 (3.191)	25.84 (3.088)	1.885 (2.792)	(-3.59, 7.36)	0.504	1.073	(0.86, 1.29)
Day 5								
6:00 am	N	42	39					
	Mean (S.E.)	27.38 (3.482)	23.69 (3.517)	4.003 (3.083)	(-2.04, 10.05)	0.203	1.168	(0.91, 1.42)
12:00 noon	N	40	38					
	Mean (S.E.)	27.63 (3.657)	21.11 (3.285)	7.102 (2.540)	(2.12, 12.08)	0.009	1.346	(1.10, 1.59)
6:00 pm	N	39	39					
	Mean (S.E.)	26.08 (3.486)	23.28 (3.280)	0.840 (2.827)	(-4.70, 6.38)	0.768	1.034	(0.81, 1.26)
Overall	N	42	39					
	Mean (S.E.)	27.62 (3.318)	22.68 (3.035)	4.229 (2.237)	(-0.16, 8.61)	0.067	1.181	(0.99, 1.37)

Figure 2 Mean VAS Score (mm)



* $p < 0.05$

Figure 3. Mean VAS Score at Endpoint



There were no statistically significant differences between formulations.
Entrance criteria at randomization was a VAS score ≤ 50 mm.
0 mm = No pain; 100 mm = Worst possible pain.

8.2144 Global VAS Assessment for Overall Effectiveness of Study Drug

There were no significant differences between treatments for mean global VAS assessment scores (Table 12). Table 13 displays the number and percentage of patients who recorded global VAS scores > 90 and 100 mm, between 70 and 90 mm, between 50 and 70, and less than 50 mm for each formulation. There were similar numbers of patients with global scores for excellent pain control (> 90 and 100 mm) and each of the other categories (>50 mm would be poor control).

Table 12 Mean Global VAS Assessment Score

Mean Global VAS Assessment Score[a] (mm) (Intent-To-Treat Population)					
	Oxycodone SR	Oxycodone IR	LS Mean Difference[b]	95% Confidence Interval[c]	p-value[d]
N	30	29			
Mean	60.73	60.00	-2.050	(-15.07, 10.97)	0.760
S.E.	5.560	5.242	6.643		

[a] Global VAS = Global Visual Analog Scale for overall effectiveness of drug in controlling pain intensity (0 = poor pain control, 100 = excellent pain control) over each 7-day double-blind treatment period.

[b] Difference = SR - IR.

[c] Although expressed using a comma per statistical convention, this interval is interpreted as the range between these two values.

[d] p-value based on comparison between oxycodone SR and oxycodone IR..

Table 13 Numbers of Patients in Defined Ranges of VAS Global Scores

Global VAS Score (range, mm)	(Intent-to-Treat) SR Treatment n (%)	IR Treatment n (%)
N	30	29
	7 (23.3%)	5 (17.2%)
	8 (26.7%)	9 (31.0%)
	3 (10.0%)	5 (17.2%)
	12 (40.0%)	10 (34.5%)

8.21345 Breakthrough Pain and Rescue Medication

The numbers and percentages of patients (intent-to-treat population) experiencing breakthrough pain were not significantly different for either formulation for Days 1-3, Days 4-6, and Days 1-6. The majority of patients (25/40, 63%) required at least one dose of rescue medication for Days 1-6 while on either formulation. The mean total daily doses of rescue medication are tabulated by study day in Table 14. The overall mean total daily doses of rescue medication were slightly higher for the IR formulation; however, this difference was not statistically significant (p=0.9453). Table 15 shows the average number of days and number of doses of rescue medication taken for each formulation by the intent-to-treat population. The results are very similar for the two treatments. Figures 4 and 5 provide graphic illustration of rescue medication use by percentages of patients and numbers of doses used.

Table 14 Mean Total Daily Dose of Rescue Medication

By Study Day and Overall Intent-To-Treat Population[a]						
Study Day[b]	Oxycodone SR			Oxycodone IR		
	N	Mean	S.D.	N	Mean	S.D.
1	44	19.09	43.338	43	14.88	38.102
2	44	13.30	32.564	42	16.43	38.782
3	44	17.73	38.040	40	16.38	40.573
4	42	20.48	50.531	39	16.03	40.036
5	42	14.88	37.636	38	18.42	41.819
6	39	13.33	38.871	37	21.08	47.407
7	34	15.88	42.932	35	22.71	53.031
8	18	20.00	64.420	12	21.67	47.832
9	11	8.64	16.747	3	0.00	0.000
Overall[c]	44	15.79	36.639	43	16.33	37.803

[a] Includes patients who did not take any rescue medication.

[b] Relative to the first day of the indicated double-blind treatment.

[c] For each patient, the TDD of rescue medication taken during treatment was divided by the number of days of therapy.

Table 15 Rescue Medication Days and Doses Taken

	Intent-To-Treat Population[a]	
	Oxycodone SR	Oxycodone IR
Standardized No. of Days[b]		
N	44	43
Mean	2.7	2.8
S.D.	2.025	2.468
Average No. of Doses[c]		
N	44	43
Mean	0.815	0.884
S.D.	1.022	1.198

a Includes patients who did not take rescue medication.

b For each patient, the number of days rescue medication was taken was divided by the number of days of therapy. Values were adjusted to assume 6 days of therapy for each formulation.

c For each patient, the total number of doses of rescue medication taken was divided by the number of days of therapy with the indicated double-blind treatment.

Figure 4: Rescue Medication Use for Breakthrough Pain

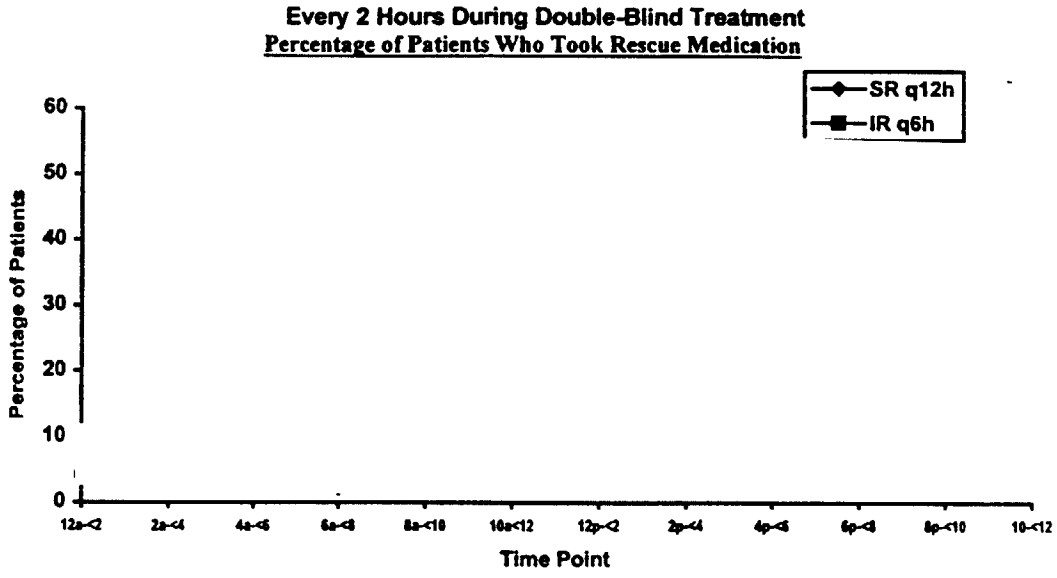
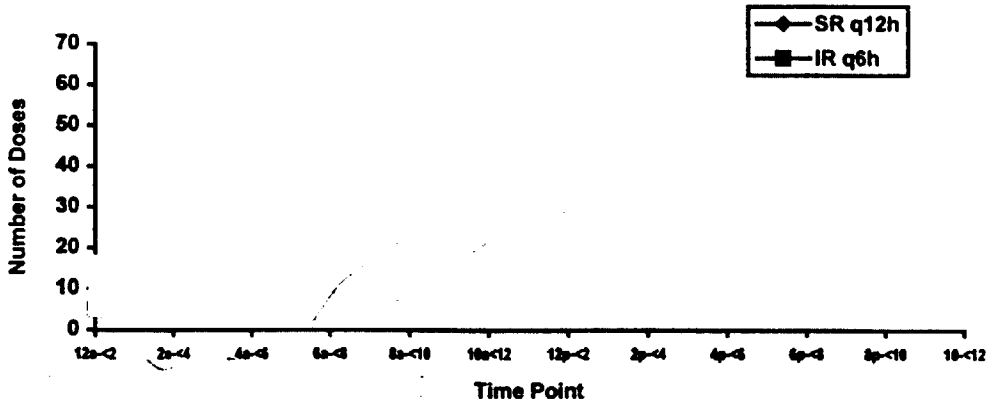


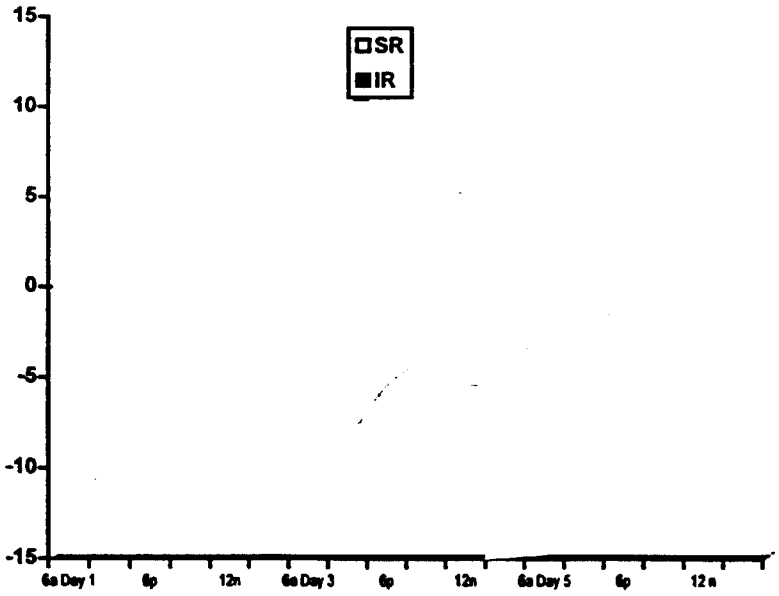
Figure 5 Number of Doses of Rescue Medication Taken



8.2146 Integrated Analysis of VAS Scores and Rescue Medication Use

At the request of the agency, the sponsor performed an integrated assessment of VAS scores and rescue medication consumption using analysis of variance (ANOVA) to compare treatment groups during both legs of the double-blind treatment period. All patients who took both formulations (SR and IR) were assigned a rank according to their VAS score. The mean rank of treated patients (SR and IR) was determined as (n+1)/2. (For example, if 42 patients received both SR and IR, and all have VAS scores at the time point being analyzed, then the mean rank is 43/2 or 21.5.) The percent difference of the VAS rank and the rank mean was calculated for each patient: [(pt. VAS rank - rank mean)/rank mean]. The same procedure was performed for rescue medication use rank. For each patient, the percent differences for the two ranks were added together as the "Summated Percent Difference". Means of this variable (summated percent difference) per formulation were compared using ANOVA. All "intent-to-treat" patients, including those that did not require rescue medication, were included in the analysis. For Days 1 through 6, the integrated assessment of VAS scores and rescue medication use over the 6 hours preceding each VAS score (summated percent difference) is summarized for the intent-to-treat population in Figure 6. Note that negative mean values for summated percent differences indicate lower VAS scores (better pain control) and less rescue medication use than the total rank mean. Except for one time point (12 noon on Day 5), that favored the IR formulation, there were no other significant differences between treatments.

Figure 6: Integrated Assessment of VAS Scores (mm) and Rescue Medication (Oxycodone IR) Use
(Summated Percent Differences on Days 1 Through 6)



*p<0.05

8.2147 Reviewer Comparison of Individual Patient Efficacy

The reviewer examined results for the 36 patients for which there was complete Day 6 (or Day 5 or 7- 9, if Day 6 data was unavailable) VAS pain intensity score and total daily dose (including escape medication) crossover data. One treatment was considered more effective if there was >10 mm less VAS pain or at least 10 mg less escape medication use on Day 6 (or its alternate) with no opposing exacerbation of the other parameter. Otherwise neither treatment was judged to be superior for the patient. On this basis, neither formulation demonstrated meaningfully better efficacy for 27 (75%) patients, four (11%) patients did slightly better on IR, and five (14%) patients did slightly better on SR.

8.215 Study Conclusions

The efficacy of the sustained release formulation given q12h appeared no different than that seen with oxycodone IR administered every 6 hours in this study of cancer patients with chronic pain. The primary efficacy variable , VAS pain intensity for the study (Day 6), and the secondary efficacy parameters (breakthrough pain; VAS scores; and an integrated analysis of VAS scores and breakthrough pain treatment for Days 1 through 6)) and the reviewer's comparison of individual patient results are all consistent with similar efficacy for both formulations in this trial.

8.22 Study CBI-1252

8.221 Investigators/Location

The principal investigators for the 13 sites that enrolled patients were:

David Beatty, M.D., South Bend, IN; Nancy Faller, D.O., Winston-Salem, NC:
Oscar Gluck, M.D., Phoenix, AZ; Sheldon Goldberg, M.D., Denver, CO:
Charles Huh, M.D., Lawrenceville, NJ; Nathaniel Katz, M.D., Boston, MA:
Gus Larijani, Pharm.D., Camden, NJ; Theodore Lefton, M.D., Melbourne, FL:
Mitchell Lowenstein, M.D./David Baras, M.D., Clearwater, FL:
Kenneth Niejadlik, M.D., Denver, CO; Richard Rauck, M.D., Winston-Salem, NC
Frederick Schaerf, M.D., Fort Meyers, FL;
Abbey Strauss, M.D., Boynton Beach,FL.

8.222 Plan

8.2221 Objective

The primary aim of this study was to compare the efficacy of oxycodone SR tablets administered every 12 hours (q 12 hours) versus oxycodone IR tablets administered every 6 hours (q 6 hours) for controlling chronic pain of cancer or non-malignant origin. Secondary objectives were to assess safety and population pharmacokinetics in this patient population.

8.2222 Population

Patients with chronic pain of pain intensity VAS assessment score < 70 mm (0 = no pain, 100 = worst pain possible), who were currently being treated with at least 20 mg daily of oral oxycodone, but required no more than two breakthrough doses of analgesic during the prior 24 hours, were eligible for randomization. Patients were 18 years of age or older, with life expectancy of at least 8 weeks. Patients were male or female, and nonpregnant, nonlactating and practicing suitable means of birth control, if female of child-bearing potential. Patients were not eligible for randomization if they had surgery in the month prior to stabilization or were scheduled for surgery at any time during the trial. Patients with a history of hypersensitivity to opioids, any clinically significant medical or mental disorder that would prohibit completion of study measures or compromise patient safety, were ineligible. Patients scheduled to receive a course of radiation therapy within 14 days prior to screening or at any time during the trial, received any investigational drug within 30 days prior to screening or participated in previous oxycodone SR studies, were excluded.

8.2223 Design

This was a multicenter, randomized, double-blind, double-dummy, active-controlled, two-period crossover trial, comparing the efficacy of oxycodone SR administered q 12 hours to oxycodone IR administered q 6 hours in patients with chronic pain of cancer or non-cancer origin.

8.22231 Stabilization Period (Days -7 to -2)

After completing the screening visit, eligible patients were sent home receiving open-label oxycodone SR q 12 hours; the Total Daily Dose (TDD) of this medication was determined by the investigator based upon the patient's previous medication regimen and standard conversions to oxycodone equivalence. Rescue doses of oxycodone IR (supplied as 5-mg tablets) were used for breakthrough pain. Telephone calls to patients were made to assess their pain control and adjust the dose of oxycodone to stabilize the patient. When patients required no more than two doses of rescue medication in a 24-hour period and pain intensity was rated < 7 on a verbal scale of 0 to 10 in the same 24-hour period, the patient was asked to come to the clinic to complete a VAS assessment measuring pain intensity over the prior 24-hour dosing period. If patients marked < 70 mm pain intensity on the VAS over the prior 24-hour dosing period, and they continued to meet all other criteria, they were randomized to one of two double-blind treatment sequences. The oxycodone dose for the Double-Blind Treatment Period was calculated by dividing the final TDD of stabilization medication (including scheduled and rescue doses) by 2, rounding up to the nearest multiple of 10, and then dividing the quantity into either two or four equal doses.

8.22232 Double-Blind Period

After 7 days of the first treatment (either oxycodone IR/SR placebo or oxycodone SR/IR placebo), patients were crossed over to the alternate treatment for another 7 days. During each of the double-blind treatments, patients took study medication in combination with placebo four times per day regardless of treatment. During each treatment, oxycodone IR (supplied as 5-mg tablets) was used as rescue medication for breakthrough pain.

8.2224 Assessments

Patients completed a VAS assessment measuring pain intensity "right now," immediately prior to their double-blind 6:00 am, 12:00 noon, and 6:00 pm doses. The scores recorded on Day 6 of each 7-day double-blind treatment, were the primary efficacy variables for the study. Scores on the other study days and the last measurement after Study Day 3 (i.e., endpoint after having achieved steady-state) of each double-blind treatment were secondary efficacy variables. Patients also completed VAS assessments at each of three scheduled visits measuring pain intensity "right now" and over the prior 12-hour (at Visits 3 and 4) or 24-hour (at Visit 2) period. Global VAS assessments measuring the level of pain control over the previous 7 days of treatment were completed at the end of each 7-day double-blind treatment. Visit activities also included review of patient diaries documenting AE's, daily intake of medication (including rescue medication), and drug accountability. Blood samples were collected for population pharmacokinetic analysis after the Stabilization Period and at the end of each 7-day double-blind treatment. Timing of when samples were to be drawn was determined utilizing a random block design.

8.2225 Analysis Plan

Analysis of variance models (ANOVA) were used to test comparability of treatment sequences at baseline for the overall stabilized doses of oxycodone and the VAS assessment scores at baseline (end of the stabilization period) and following double-blind treatments. An "intent-to-treat" analysis of efficacy was performed, including all patients who were randomized, received at least one dose of double-blind study drug and recorded at least one VAS score or used rescue medication. Treatment comparisons for mean VAS scores were carried out for the 6:00 am, 12:00 noon, and 6:00 pm time points and for overall (i.e., the average of all available scores). The ratio of mean VAS assessment scores obtained for each of the two formulations (i.e., SR/IR) and the 95% confidence interval of the difference were also calculated. The global VAS assessment scores for overall drug effectiveness were analyzed using an ANOVA model similar to the one for mean VAS scores. The numbers and percentages of patients who required rescue medication for breakthrough pain on each study day, on Days 1 through 3, on Days 4 through 6, and overall were displayed for each formulation (IR and SR). For these intervals, the number and percentage of patients who required rescue medication on both formulations, on either formulation, and did not require any rescue medication were compared using McNemar's test to assess statistical significance. For each formulation, the average total daily dose of rescue medication on each study day and overall (i.e., total dose of rescue medication taken during each double-blind treatment divided by the total number of days on treatment) was displayed. The mean overall dose of rescue medication and the standardized number of days that rescue medication was taken during each double-blind treatment and the average number of doses of rescue medication taken per day during each double-blind treatment were compared between treatments. The same ANOVA model as used for VAS assessment scores was employed. An integrated assessment of VAS scores and rescue medication consumption ("summated percent difference") was also carried out using ANOVA to compare formulations. All "intent-to-treat" patients were included in these analyses and in the safety analysis.

8.223 Study Conduct/Outcome

8.2231 Patient Disposition

A total of 114 patients entered and 87 of these patients (76.3%) completed the stabilization period; 86 of these 87 patients were randomized to receive one of two treatment sequences during the double-blind treatment period. Forty-two patients were randomized to receive SR/IR and 44 to the IR/SR sequence. One patient withdrew consent prior to randomization. There were 85 of the 86 (98.8%) randomized patients who actually took study medication during this phase of the study (one patient randomized to the IR/SR treatment sequence withdrew because of an adverse event prior to taking double-blind study medication). There were 82 patients who took IR and 82 who took SR. There were 78 (98.2%) patients who completed this phase of the study (took both IR and SR for each 7-day period). Three patients withdrew due to adverse events (two on SR, one on IR). One patient on SR withdrew due to protocol violation, one on IR was lost to follow-up, and two (one on each treatment) withdrew consent (Table 16). Table 17 lists patient disposition by investigator. The number of days to stabilization for patients in each double-blind treatment sequence is presented in Table 18. Adequate pain stabilization was achieved by 62.8% (54/86) of randomized patients by the end of the protocol-specified 2- to 7-day Stabilization period and by 91.9% (79/86) at the end of the 2- to 9-day (7 days plus the 2-day "grace period"). The remaining 8.1% (7/86) of the population took longer than 9 days to achieve stabilization; one patient took 18 days to achieve stabilization

Table 16 Patient Disposition

Treatment	IR	SR	*Total**
Enrolled in Stabilization Period		114	114
Completed Stabilization Period			87
Randomized to Double-Blind			86
Received Double-Blind Medication	82	82	85
Evaluable for Efficacy	82	82	85**
Completed Double-Blind	—	—	78
Discontinued Double-Blind	3	4	7
D/C for Adverse Experiences	1	2	3
D/C for Protocol Violation	0	1	1
D/C for Withdrawal of Consent	1	1	2
Lost to Follow-up	1	0	1

- * Received either treatment.
- ** 79 Patients received both treatments

Table 17 Patient Disposition By Investigator

	Number (%) of Patients Screened	Number (%) Enrolled in Stabilization Period	Number (%) of Patients Randomized to Double-Blind Treatment Period[a]		Total Patients Who Completed Study
Investigator (No.)	N = 124	N = 114	SR/IR (N = 42)	IR/SR (N = 44)	(N = 78)
Allen (50)	1 (0.8)	0	0	0	0
Beatty (51)	6 (4.8)	6 (5.3)	3 (7.1)	3 (6.8)	6 (7.7)
Faller (52)	6 (4.8)	4 (3.5)	1 (2.4)	2 (4.5)	3 (3.8)
Gluck (53)	12 (9.7)	12 (10.5)	5 (11.9)	4 (9.1)	8 (10.3)
Goldberg (54)	6 (4.8)	6 (5.3)	2 (4.8)	2 (4.5)	3 (3.8)
Huh (63)	6 (4.8)	6 (5.3)	2 (4.8)	2 (4.5)	4 (5.1)
Katz (55)	7 (5.6)	7 (6.1)	2 (4.8)	3 (6.8)	5 (6.4)
Larijani (58)	7 (5.6)	6 (5.3)	3 (7.1)	3 (6.8)	3 (3.8)
Lefton (61)	9 (7.3)	9 (7.9)	3 (7.1)	3 (6.8)	6 (7.7)
Lowenstein (56)	25 (20.2)	24 (21.1)	8 (19.0)	8 (18.2)	15 (19.2)
Niejadlik (60)	6 (4.8)	6 (5.3)	2 (4.8)	3 (6.8)	5 (6.4)
Rauck (57)	10 (8.1)	10 (8.8)	4 (9.5)	3 (6.8)	7 (9.0)
Schaerf (62)	8 (6.5)	7 (6.1)	2 (4.8)	3 (6.8)	4 (5.1)
Strauss (59)	15 (12.1)	11 (9.6)	5 (11.9)	5 (11.4)	9 (11.5)
Total	124 (100.0)	114 (100.0)	42 (100.0)	44 (100.0)	78 (100.0)

Table 18 Days to Stabilization

Number of Days	SR/IR n (%)	IR/SR n (%)	Overall n (%)
4	6 (14.3%)	1 (2.3%)	7 (8.1%)
5	3 (7.1%)	5 (11.4%)	8 (9.3%)
6	2 (4.8%)	6 (13.6%)	8 (9.3%)
7	13 (31.0%)	18 (40.9%)	31 (36.0%)
8	10 (23.8%)	10 (22.7%)	20 (23.3%)
9	4 (9.5%)	1 (2.3%)	5 (5.8%)
> 9	4 (9.5%)	3 (6.8%)	7 (8.1%)
Total Intent-to-Treat Pts. Randomized	42	44	86

8.2232 Demographics

The demographic and baseline characteristics of all patients who entered the Double-Blind Treatment Period are summarized in Table 19. There were no statistically significant differences between sequence groups in demographic and baseline characteristics. Only one patient had an etiology of pain categorized as "cancer"; the primary site of cancer was the lung. The mean VAS score for the 86 patients who were randomized to receive double-blind study medication was 41.1 mm (range, mm) and the stabilized dose of oxycodone was 65.9 mg (range, mg) at the end of stabilization.

Table 20: Demographic and Baseline Characteristics

Patients Who Entered the Double-Blind Treatment Period				
Characteristic	Overall	SR/IR[a]	IR/SR[a]	p-value[b]
Age (yrs)				
N	86	42	44	
Mean (S.D.)	48.4 (13.37)	49.0 (13.55)	47.8 (13.33)	0.617
Range	23-81	23-81	26-79	
Gender [N (%)]				
Male	38 (44.2%)	21 (50.0%)	17 (38.6%)	0.381
Female	48 (55.8%)	21 (50.0%)	27 (61.4%)	
Race [N (%)]				
White	83 (96.5%)	41 (97.6%)	42 (95.5%)	0.835
Black	2 (2.3%)	1 (2.4%)	1 (2.3%)	
Hispanic	1 (1.2%)	0 (0.0%)	1 (2.3%)	
Weight (lbs)				
N	86	42	44	
Mean (S.D.)	174.03 (37.778)	173.56 (38.227)	174.48 (37.780)	0.838
Range				
Primary Pain Treatment Site[c] [N (%)]				
Back	43 (50.0%)	21 (50.0%)	22 (50.0%)	
Leg	17 (19.8%)	7 (16.7%)	10 (22.7%)	
Neck	6 (7.0%)	4 (9.5%)	2 (4.5%)	
Abdomen	4 (4.7%)	3 (7.1%)	1 (2.3%)	
Pelvis	4 (4.7%)	1 (2.4%)	3 (6.8%)	
Entire Left Side	3 (3.5%)	2 (4.8%)	1 (2.3%)	
Body as a Whole	3 (3.5%)	0 (0.0%)	3 (6.8%)	
Arm	2 (2.3%)	2 (4.8%)	0 (0.0%)	
Shoulder	2 (2.3%)	1 (2.4%)	1 (2.3%)	
Head	1 (1.2%)	1 (2.4%)	0 (0.0%)	
Chest	1 (1.2%)	0 (0.0%)	1 (2.3%)	
Total Daily Dose (mg) of Oxycodone at Screening				
N	86	42	44	
Mean (S.D.)	55.9 (98.78)	51.7 (89.20)	59.9 (108.02)	0.779
Range				
Stabilized Total Daily Dose (mg) of Oxycodone				
N	86	42	44	
Mean (S.D.)	65.9 (98.79)	62.1 (91.47)	69.5 (106.25)	0.731
Range				
Baseline VAS Assessment (mm)[d]				
N	82	41	41	
Mean (S.D.)	41.1 (20.68)	41.7 (20.24)	40.4 (21.34)	0.783
Range				
Number (%) of Patients By Pain Etiology				
Cancer Pain	1 (1.2%)	0 (0.0%)	1 (2.3%)	
Non-cancer Pain	85 (98.8%)	42 (100.0%)	43 (97.7%)	

a SR/IR: Oxycodone SR/Oxycodone IR.
IR/SR: Oxycodone IR/Oxycodone SR.

b Comparisons between treatment sequences were carried out using a one-way analysis of variance (ANOVA) for continuous variables and chi-square tests for categorical variables.

c Pain at this site was treated with opioid medication.

d Refers to last VAS assessment completed at end of the Stabilization Period.

8.2233 Dosing Information

The investigators had the option of altering the patients' stabilized dose at the beginning of the double-blind treatment period. The mean and median total daily doses (TDD, in mg) of double-blind oxycodone and of rescue medication taken by patients who entered the double-blind treatment period are shown in Table 21. Table 22 shows mean and median data for study drug compliance during the double-blind treatment period. Overall compliance was calculated based on the total number of tablets to be taken and the total number of tablets taken (i.e., No. Dispensed - No. Returned).

Table 21: Total Daily Dose (mg) of Oxycodone
Patients Who Entered the Double-Blind Treatment Period

	Oxycodone SR (N=82)	Oxycodone IR (N=82)
Recorded Double-Blind Study Drug		
Mean (S.E.)	65.4 (11.09)	58.5 (8.92)
Median	40.0	40.0
Range		
Recorded Rescue Medication Use (Oxycodone IR)		
Mean (S.E.)	13.8 (1.60)	13.8 (1.47)
Median	9.4	9.3
Range		

Table 22: Compliance with Study Drug Administration
During the Double-Blind Treatment Period

Overall Compliance (%)	Oxycodone SR (N=82)	Oxycodone IR (N=82)
Mean (S.D.)	90.3 (9.66)	90.9 (6.93)
Median	90.3	90.7
Range		

8.2234 Previous and Concomitant Medication

All patients had previously used opioids. Oxycodone, hydrocodone and propoxyphene were the most common previously used opioid medications. Concomitant opioid medications were not permitted during this study. Three patients (3.5%) deviated from this requirement but were permitted to continue in the study. The three most common nonopioid medications used were amitriptyline (18/86; 20.9%), carisoprodol (14/86; 16.3%), and acetaminophen (13/86; 15.1%). Commonly used analgesics included acetylsalicylic acid: 9/86; 10.5%), ibuprofen (8/86; 9.3%), naproxen (3/86; 3.5%), and ketoprofen (2/86; 2.3%). Certain types of medications such as antihypertensives, laxatives, and non-narcotic, non-opioid analgesics were permitted during treatment at stable scheduled doses. Fourteen (16.3%) patients not at stable doses prior to the Stabilization Period did take nonopioid analgesics during the Double-Blind Period. Three patients took single doses of NSAIDs as rescue medication at different time points during the course of the study; this was not expected to seriously affect efficacy conclusions.