Study Number: N49-97-02-070

Study Dates: 17 April 1997 – 1 July 1997

Title of Study: A Double-Blind, Placebo-Controlled, Single-Dose Comparison of the Analgesic Activity of celecoxib 50 mg, celecoxib 100 mg, celecoxib 200 mg, celecoxib 400 mg, Naproxen Sodium 550 mg and Placebo in a Postsurgical Dental Pain Model.

Investigator and Location:

Objectives:

Primary Objective
The primary objective of this study was to compare the analgesic activity of four different celecoxib doses (50 mg, 100 mg, 200 mg and 400 mg) versus placebo in patients with moderate to severe pain in a postsurgical dental pain model.

Secondary Objectives
The secondary objectives of this study were:

1. to compare the analgesic activity of a single dose of naproxen sodium 550 mg versus placebo in patients with moderate to severe pain in a postsurgical dental pain model;
2. to correlate plasma concentrations of celecoxib (50 mg, 100 mg, 200 mg and 400 mg) doses with analgesic activity in patients with moderate to severe pain in a postsurgical dental pain model;
3. to characterize the dose response profile of celecoxib; and
4. to assess the safety of celecoxib doses (50 mg, 100 mg, 200 mg and 400 mg) in patients with moderate to severe pain in a postsurgical dental pain model.

Study Description
This was a single-center, single-dose, randomized, double-blind, placebo-controlled, parallel group study designed to evaluate the safety and efficacy of single, orally administered doses of celecoxib50 mg, celecoxib 100 mg, celecoxib 200 mg and celecoxib 400 mg, naproxen sodium 550 mg (Anaprox®), and placebo in patients with moderate to severe postsurgical dental pain. The study consisted of a Baseline pain assessment prior to dosing with study drug and a 24 hour follow-up period with pain assessments at 15, 30, and 45 minutes postdose, and at 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, and 24 hours after administration of study drug. Patients returned for posttreatment evaluations five to nine days after the administration of study medication.

Schedule of Observations and Procedures

	Pre Treat-ment	Base-line	Treatment																	Post Treat-ment
	Days -14	Hr	Minutes			Hours														
	to 0	0	15	30	45	1	1.5	2	3	4	5	6	7	8	9	10	11	12	24	5-9 Days
Medical History	X																			
Physical Exam	X																			
Vital Signs	X	X																		X
Clinical Lab Tests	X																			X
Pregnancy Test (a)	X																		X	
Blood Samples (Pk)		X	X	X	X	X	X	X	X	X	X	X	X	X				X	X	
Pain Assessment (b)		X(c)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Start stopwatches for Perceptible and Meaningful Pain Relief (d)		X																		
Study Drug		X(e)																		
Global Evaluation																			X(f)	
Symptoms/Meds		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Collect Diary Cards																				X

(a) Female subjects of childbearing potential must have had a negative urine pregnancy test within 24 hours prior to receiving study drug (not collected on CRF).
(b) Pain intensity, pain relief, pain at least half gone, Visual Analog Scale.
(c) Pain intensity only (Categorical and Visual Analog Scale).
(d) Stopwatches were used to determine exact time to perceptible and meaningful pain relief.
(e) Study drug was administered immediately after Baseline (0 hour) pain assessment.
(f) Global evaluation was completed at the last hourly observation or just prior to rescue analgesia, if less than 24 hours.

Eligibility:

To qualify for study participation, candidates must have:

1. Been 18 years of age or older;
2. If a female of childbearing potential, must have been using adequate contraception, not been lactating, and had a negative urine pregnancy test within 24 hours prior to receiving study medication;
3. Been in good health as determined by the Investigator on the basis of medical history and physical examination;

4. Had surgical extraction of one or more impacted third molar teeth requiring bone removal, one of which was mandibular, and had been experiencing moderate to severe postsurgical dental pain;
5. Had a Baseline pain intensity of ≥50 mm on a Visual Analog Scale (VAS) of 100 mm; and
6. Provided written informed consent prior to admission to this study.

Exclusions:

1. A history of uncontrolled chronic disease that, in the opinion of the Investigator, would contraindicate study participation;
2. A history of a gastrointestinal ulcer within the past six months or were currently experiencing significant gastrointestinal complaints as determined by the Investigator;
3. Use of analgesics or other agents during the six hours preceding surgery that could have confounded the analgesic responses (a longer interval may have been necessary if the confounding drug was long-acting or a sustained release formulation). Specifically excluded were tricyclic antidepressants, narcotic analgesics, antihistamines, tranquilizers, hypnotics, sedatives, NSAIDs, or corticosteroids. Presurgical medications such as xylocaine with epinephrine, Brevital® (methohexital sodium), fentanyl, Demerol® (meperidine) and diazepam were exempt from this exclusion. Demerol® required a three-hour washout prior to the dose of study medication;
4. A history of known analgesic or narcotic use or known substance abuse;
5. An unwillingness to abstain from alcohol for at least six hours prior to and 24 hours after dosing with study medication;
6. Received any investigational medication within 30 days prior to the first dose of study medication or were scheduled to receive any investigational drug other than celecoxib during the course of this study;
7. A known hypersensitivity to analgesics, NSAIDs, cyclooxygenase inhibitors, lactose, or sulfonamides;
8. Any laboratory abnormality that, in the opinion of the Investigator, would contraindicate study participation, including AST or ALT >1.5 times the upper limit of the reference range;
9. Been previously admitted to this study.

Treatments Administered:

1. Celecoxib 50 mg, 100 mg and 200 mg capsules each identical in size and color;
2. Placebo capsules each identical in size and appearance to the celecoxib 50 mg, 100 mg, and 200 mg capsules;
3. Encapsulated Anaprox® (naproxen sodium) 275 mg tablets; and
4. Placebo capsules each identical in size and appearance to encapsulated Anaprox® (naproxen sodium).

Blinding:
For each patient, each dose was packaged in two bottles: Bottles A and B each contained two capsules. For patients taking celecoxib 50 mg, 100 mg, or 200 mg, Bottle A contained one active drug capsule and one matching placebo capsule and Bottle B contained two placebo capsules matching naproxen sodium. For patients taking celecoxib 400 mg, Bottle A contained two celecoxib 200 mg capsules and Bottle B contained two matching naproxen sodium placebo capsules. For patients taking naproxen sodium 550 mg, Bottle A contained two placebo capsules matching celecoxib and Bottle B contained two naproxen sodium 275 mg capsules. Patients randomized to receive placebo received placebo in both bottles. The labels on Bottles A and B provided instructions for use as follows: "Take entire contents of each individual dose bottle."

Efficacy Assessment:
Patients were provided with two stopwatches and a patient diary booklet in which to record pain assessments, concurrent medications, and all adverse signs and symptoms experienced after consumption of the study medication. Immediately before taking the dose of study medication, the patient rated his or her pain intensity on the VAS and recorded it in the patient diary. A blood sample was also obtained for the pharmacokinetic (PK) analysis.

The Treatment Period was defined as the 24 hour period immediately following the administration of study medication. Patients received the single dose of study medication, and were allowed water during the first hour following study drug administration; however, no foods or nutrient liquids were permitted for two hours following study drug administration. Ice packs were not allowed for the first hour after dosing. If used afterward, ice packs were removed 15 minutes prior to successive pain assessments. Patients remained in the research unit for the 24 hour Treatment Period and underwent the following assessments at 15, 30, 45 minutes and 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, and 24 hours postdose:

1. Pain Intensity (none = 0, severe = 3)
2. Pain Relief (none = 0, complete = 4)
3. Pain at Least Half Gone
4. Pain Intensity (VAS)
5. Time to Perceptible and Meaningful Pain Relief (by two stopwatches)
6. Patient's Global Evaluation (poor = 1, excellent = 5)
7. Time to Rescue Medication

RESULTS:

Disposition of Patients

Two hundred and fifty five (255) patients were enrolled in this study at one site and were randomized to receive one of five treatments as follows: 35 patients received celecoxib 50 mg, 50 patients received celecoxib 100 mg, 50 patients received celecoxib 200 mg, 35 patients received celecoxib 400 mg, 35 patients received naproxen sodium 550 mg, and 50 patients received placebo. These patients constituted the ITT Cohort. Forty nine patients completed the twenty four hour assessment period without taking rescue medication and completed the scheduled 24.0 hour assessments. Two hundred and six patients took rescue medication during the 24 hour assessment period. One celecoxib 50 mg patient, who took rescue medication, withdrew from the study due to an adverse event.

The treatment groups were comparable ($p \geq 0.462$) for age, race, and gender (table 1). For all treatment groups, the age range was 18 to 47 years ($p=0.462$). Across treatment groups, 37% to 40% of the patients were male ($p=1.000$) and 51% to 66% were Caucasian ($p=0.960$). All treatment groups were comparable ($p \geq 0.318$) with respect to height, weight (table 2), and vital signs at Baseline.

Table 1
Baseline Demographic Characteristics

	Placebo (N= 50)	Celecoxib 50mg (N= 35)	Celecoxib 100mg (N= 50)	Celecoxib 200mg (N= 50)	Celecoxib 400mg (N= 35)	Naproxen Na 550mg (N= 35)	p- VALUE
AGE (years)							0.462 (a)
N	50	35	50	50	35	35	
MEAN	24.2	22.0	23.8	23.6	24.2	23.1	
STD DEV	5.03	3.93	6.00	5.11	5.97	4.98	
MEDIAN	23.0	21.0	22.0	23.0	22.0	22.0	
RANGE	19 - 43	18 - 33	18 - 47	18 - 47	18 - 41	18 - 44	
<30	42 (84%)	33 (94%)	43 (86%)	45 (90%)	29 (83%)	33 (94%)	
30- 39	7 (14%)	2 (6%)	6 (12%)	4 (8%)	5 14%)	1 (3%)	
40- 49	1 (2%)	0 (0%)	1 (2%)	1 (2%)	1 (3%)	1 (3%)	
50- 59	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
60- 69	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
70- 79		0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
>= 80	0(0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
RACE/ ETHNIC ORIGIN							0.960 (b)
ASIAN	2 (4%)	1 (3%)	2 (4%)	1 (2%)	0 (0%)	2 (6%)	
BLACK	3 (6%)	4 (11%)	6 (12%)	5 (10%)	3 (9%)	3 (9%)	
CAUCASIAN	32 (64%)	18 (51%)	28 (56%)	27 (54%)	23 (66%)	22 (63%)	
HISPANIC	13 (26%)	12 (34%)	14 (28%)	16 (32%)	8 (23%)	8 (23%)	
OTHER	0 (0%)	0 (0%)	0 (0%)	1 (2%)	1 (3%)	0 (0%)	
TOTAL	50 (100%)	35 (100%)	50 (00%)	50 (100%)	35 (100%)	35 (100%)	
GENDER							1.000 (b)
FEMALE	30 (60%)	22 (63%)	30 (60%)	30 (60%)	21 (60%)	21 (60%)	
MALE	20 (40%)	13 (37%)	20 (40%)	20 (40%)	14 (40%)	14 (40%)	
TOTAL	50 (100%)	35 (100%)	50 (100%)	50 (100%)	35 (100%)	35 (100%)	

(a) One- Way Analysis of Variance.
(b) Pearson Chi- Square.

Table 2
Additional Baseline Characteristics

	Placebo (N= 50)	Celecoxib 50mg (N= 35)	Celecoxib 100mg (N= 50)	Celecoxib 200mg (N= 50)	Celecoxib 400mg (N= 35)	Naproxen Na 550mg (N= 35)	p- VALUE (a)
HEIGHT (cm)							0.719
N	50	35	50	50	35	35	
MEAN	170.38	170.83	168.33	170.58	168.37	170.43	
STD DEV	10.667	8.008	9.517	9.369	11.348	9.811	
MEDIAN	170.20	170.20	168.90	170.20	167.60	170.20	
RANGE							
WEIGHT (kg)							0.795
N	50	35	50	50	35	35	
MEAN	75.72	71.22	70.44	73.40	72.39	72.44	
STD DEV	24.739	15.382	17.464	15.677	17.981	16.964	
MEDIAN	70.00	65.90	67.95	71.15	67.30	70.50	
RANGE							

(a) One- Way Analysis of Variance.

Summary of Dental Surgery

The treatment groups were comparable ($p \geq 0.072$) for surgical trauma rating, degree of impaction, and number of molars extracted. There was a slightly greater percentage of patients in the celecoxib 100 mg, celecoxib 200 mg, and placebo treatment groups with severe pain intensity (52%, 58% and 44%, respectively) than in the celecoxib 50 mg, 400 mg and naproxen sodium 550 mg treatment groups (29%, 40% and 23%, respectively). This difference was statistically significant ($p=0.010$), however, it was not considered clinically relevant for purposes of this study.

All treatment groups were comparable with respect to time from surgery until taking study medication ($p=0.115$). The mean time until study medication was 2:26 to 2:56. The mean Baseline pain intensity across treatment groups was 61.3 to 68.3 (0 to 100 scale). The difference in Baseline pain intensity was statistically significantly different across all treatment groups ($p=0.022$), however, these differences were not considered clinically relevant for purposes of this study.

Analysis of Primary Efficacy Measures (as defined in the protocol)

Mean Pain Intensity Difference Scores Over Time

Table 9 (the three following pages) presents the mean PID scores (categorical scale) at all assessment times during the 24 hour Treatment Period. The PID scores were calculated by subtracting the pain intensity at a specific assessment time from the Baseline pain intensity. Imputing pain intensity data has been done using baseline observation carried forward (BOCF) method.

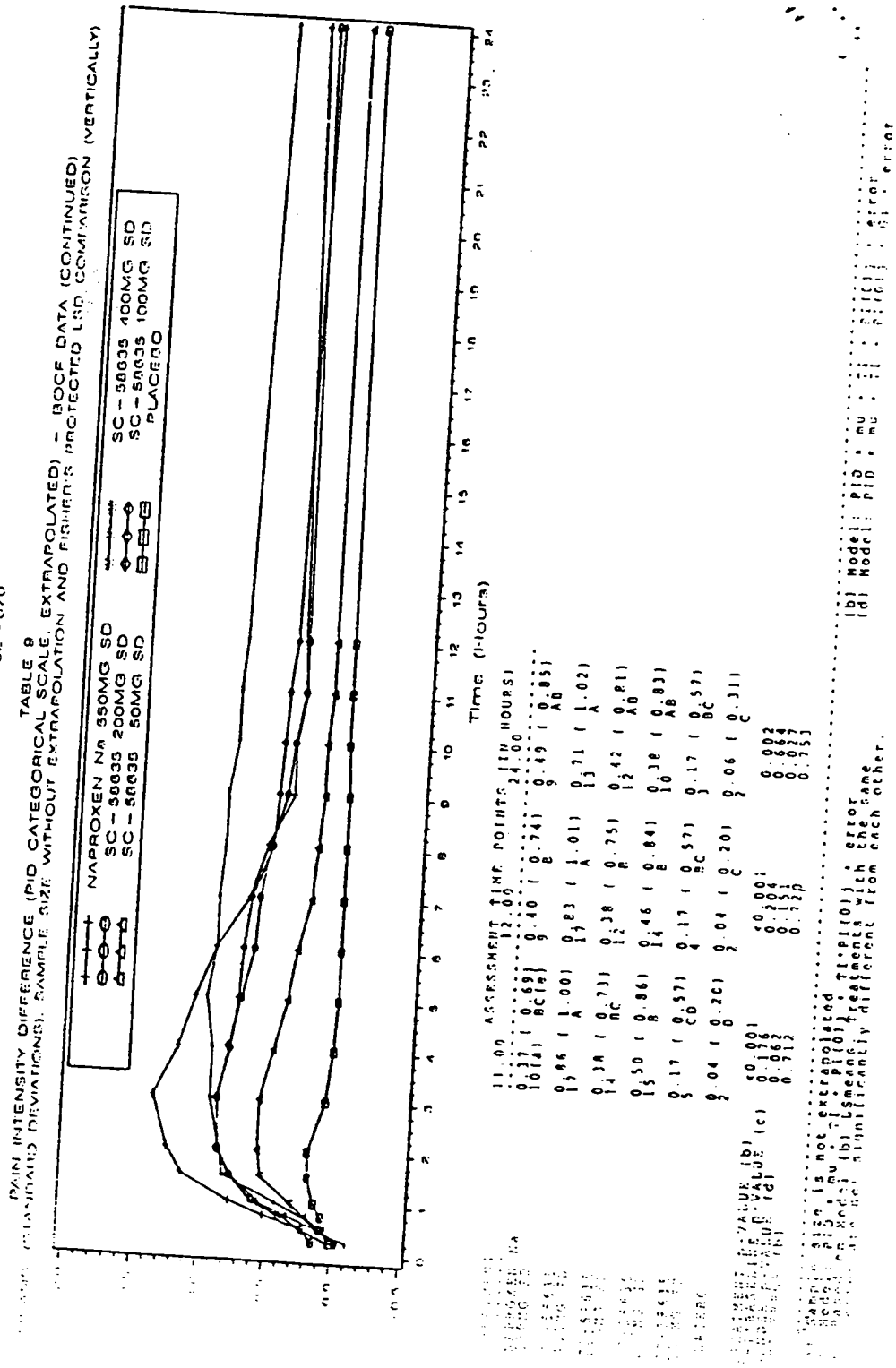
The mean PID values for the celecoxib 400 mg, 200 mg and 100 mg treatment groups were numerically greater than placebo at 0.5 hour through the 24.0 hour postdose and these differences from placebo were statistically significant at all assessment times from 1.0 hour through 24 hours postdose for the 200 and 100 mg groups and from 1.5 hour through 24.0 hours postdose for the 400 mg dose. The mean PID values for the celecoxib 50 mg group were numerically greater than placebo at the 0.75 hour through 24.0 hours postdose and this difference was statistically significant at the 1.5 through 5.0 hour assessments. Within the celecoxib treatment groups, the mean PID scores for the celecoxib 400 mg, 200 mg, and 100 mg were numerically greater than the mean scores for the celecoxib 50 mg group at the 0.50 through the 24.0 hour assessment times. The celecoxib 200 mg mean PID scores were numerically greater than the mean scores for the celecoxib 100 mg group at the 0.25 through the 24.0 hour assessment times except for the 3.0, 5.0, 6.0, 7.0, 9.0, 10.0, 11.0, and 12.0 hour assessment time. Mean PID scores for the celecoxib 400 mg group were numerically superior to the celecoxib 200 mg at the 3 hour through the remainder of the 24 hour assessment period but only at the 1.5 hour assessment during the first 2 hours. These differences between the celecoxib 200 mg and 400 mg groups were statistically significant at the 8 hour through 12 hours postdose.

The mean PID scores for the naproxen sodium 550 mg group were numerically greater than the placebo and celecoxib 50 mg groups at all postdose assessment times and these differences were statistically significant at the 0.75 hour through 24.0 hour assessment times compared to placebo and at the 0.75 through 8.0 hour assessment times compared to the celecoxib 50 mg group. The mean PID scores for the naproxen sodium 550 mg group were numerically greater than the PID scores for the celecoxib 100 mg at the 0.25 through the 8.0 hour assessment times and these differences were statistically significant at the 0.75 through 5.0 hour assessment times. The mean PID scores for the naproxen sodium 550 mg group were numerically greater than the mean PID scores for the celecoxib 400 mg and 200 mg at the 0.5 to 5.0 hour assessment times and these differences were statistically significantly different at the 0.75 through 3.0 hour assessment times for the 400 mg group and through the 5.0 hour assessment times for the 200 mg group. The mean PID scores for both celecoxib 400 mg and 200 mg were numerically greater than naproxen sodium 550 mg group at the 9.0 through 24.0 hour assessments, but these differences were not statistically significant.

Analysis of the PID data by using the worst observation carried forward (WOCF) method demonstrated the similar results.

Table 9 – Pain Intensity Difference
Page 1 of 3

Table 9 – Pain Intensity Difference
Page 2 of 3


SC – 50035 EFFICACY IN POSTSURGICAL DENTAL PAIN
NAB – 97 – 02 – 070
TABLE 8
PAIN INTENSITY DIFFERENCE (PID CATEGORICAL SCALE, EXTRAPOLATED) – BOCF DATA (CONTINUED)
(MEAN AND STANDARD DEVIATIONS), SAMPLE SIZE WITHOUT EXTRAPOLATION AND FISHER'S PROTECTED LSD COMPARISON (VERTICALLY)
NAPROXEN Na 550MG SD
SC – 50035 200MG SD
SC – 50035 50MG SD
SC – 50035 400MG SD
SC – 50035 100MG SD
PLACEBO
Time (Hours)
ASSESSMENT TIME POINTS (IN HOURS)
12.00
24.00
P-VALUE (b)
P-VALUE (c)
P-VALUE (d)
(b) Model: PID = mu + TI + P(TI)
(c) Model: PID = mu + TI + P(TI)(J) + error
(d) Model: PID = mu + TI + P(TI)(J) + error

Mean Pain Relief Scores Over Time

Table 10 (the three following pages) presents the mean PR scores for all assessment times during the 24 hour Treatment Period. Imputing pain intensity data has been done using baseline observation carried forward (BOCF) method.

The mean PR scores for the celecoxib 400 mg, 200 mg, 100 mg and 50 mg dose groups were numerically greater than the mean scores for placebo at the 0.5 hour through 24.0 hour assessment times and these differences were statistically significant at the 1.0 to 5.0 hour assessments for the celecoxib 50 mg dose group and at the 1.0 through 24.0 hour assessment times for the celecoxib 400 mg, 200 mg and 100 mg dose groups. Within the celecoxib treatment groups, the mean PR scores for the celecoxib 400 mg, 200 mg, and 100 mg dose groups were all numerically greater than the mean scores for celecoxib 50 mg at the 1.0 through 24.0 hour assessment times. These differences were statistically significant for the celecoxib 200 mg dose at the 7.0 and 8.0 hour assessment and for the celecoxib 400 mg at the 4.0 to 24.0 hour assessment times. The mean PR scores for the celecoxib 400 mg was numerically greater than the 200 mg and 100 mg at the 1.5 through 24.0 assessment times and these differences were statistically significant at the 8.0 hour through 12.0 hour assessment times.

The mean PR scores for the naproxen sodium 550 mg treatment group were numerically greater than placebo at the 0.5 through 24.0 hour assessment times during the Treatment Period and this difference was statistically significant from the 0.75 through 24.0 hour assessments. The mean PR scores for the naproxen sodium 550 mg group were numerically greater than the mean scores for celecoxib 200 mg, 100 mg, and 50 mg dose groups from the 0.5 hour through 24.0 hour assessments and these mean scores were statistically significant from the 0.75 through 6.0 and 5.0 hour assessments for the 200 mg and 100 mg dose groups respectively. The mean PR scores for the naproxen sodium 550 mg group were numerically greater than the mean scores for the celecoxib 400 mg dose group from the 0.5 hour through 6.0 hour assessment times and these mean scores were statistically significant from the 0.75 through 3 hour assessments. At the 7.0 through 24.0 hour assessment times the mean PR scores for the celecoxib 400 mg group were numerically greater than naproxen sodium 550 mg group and these differences were statistically significant at the 9.0, 10.0, 11.0 and 12.0 hour assessments.

Analysis of the PR data by using the worst observation carried forward (WOCF) method demonstrated the same results.

SC – 50635 EFFICACY IN POSTSURGICAL DENTAL PAIN
N49 – 97 – 02 – 070
Thursday April 30, 1998
TABLE 10
PAIN RELIEF (PR EXTRAPOLATED) – BOCF DATA
SIZE WITHOUT EXTRAPOLATION AND FISHER'S PROTECTED LSD COMPARISON (VERTICALLY)
NAPROXEN Na 550MG BD
SC – 50635 200MG BD
SC – 50635 50MG BD
SC – 50635 400MG BD
SC – 50635 100MG BD
PLACEBO
Time (Hours)
ASSESSMENT TIME POINTS (IN HOURS)
(b) Model: PR = MU + TI + error
Based on Model (b) LSmeans
Letter are not significantly different from each other

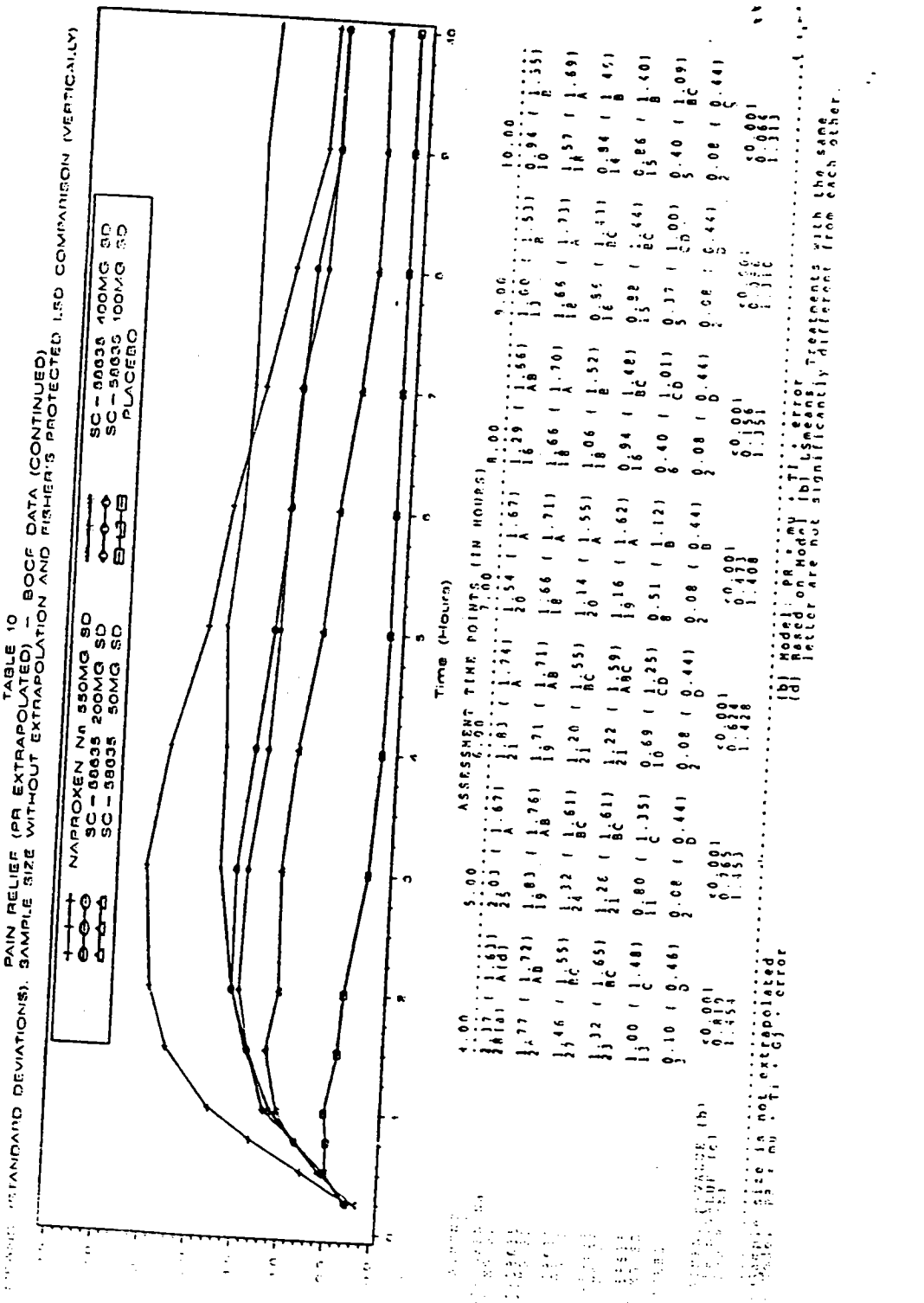

SC – 58635 EFFICACY IN POSTSURGICAL DENTAL PAIN
N49 – 97 – 02 – 070
TABLE 10
PAIN RELIEF (PR EXTRAPOLATED) – BOCF DATA (CONTINUED)
SAMPLE SIZE WITHOUT EXTRAPOLATION AND FISHER'S PROTECTED LSD COMPARISON (VERTICALLY)
NAPROXEN Na 550MG SD
SC – 58635 200MG SD
SC – 58635 50MG SD
SC – 58635 400MG SD
SC – 58635 100MG SD
PLACEBO
Time (Hours)

Table 10 – Pain Relief
Page 3 of 3

Mean Pain Intensity Difference and Pain Relief (PRID, Categorical Scale)

Table 11 (the three following pages) presents the mean PRID (categorical) scores for all assessment times during the 24 hour Treatment Period. PRID scores are a sum of PID and PR scores and range from a maximum score of 7 (best possible score) to a minimum score of -1 (worse possible score). Positive values indicate a lessening of the patients' pain while a negative value indicates a worsening. Imputing PRID data has been done using baseline observation carried forward (BOCF) method.

The mean PRID scores for the celecoxib 400 mg, 200 mg, 100 mg and 50 mg dose groups were numerically greater than the mean scores for placebo at the 0.5 hour through 24.0 hour assessment times and these differences were statistically significant at the 1.5 through 5.0 hour assessments for the celecoxib 50 mg dose and at the 1.0 through 24.0 hour assessment times for the celecoxib 100 mg, 200 mg and 400 mg dose levels. Within the celecoxib treatment groups, the mean PRID scores for the celecoxib 400 mg, 200 mg, and 100 mg dose groups were numerically greater than the mean scores for celecoxib 50 mg dose at the 1.0 through 24.0 hour assessment times and these differences were statistically significant for the celecoxib 400 mg dose group at the 4.0 through 24.0 hour assessments. The mean PRID scores for the celecoxib 400 mg were numerically greater than the 200 mg and 100 mg at the 3.0 through 24.0 assessment times. These differences were statistically significant compared to the celecoxib 100 mg dose at 8.0, 9.0, 10.0, 11.0 and 12.0 hour postdose and compared to the celecoxib 200 mg dose at 9.0, 10.0, 11.0, and 12.0 hours postdose.

The mean PRID scores for the naproxen sodium 550 mg treatment group were numerically greater than placebo at the 0.5 through 24.0 hour assessment times during the Treatment Period and this difference was statistically significant at the 0.75 through 24.0 hour assessments. The mean PRID scores for the naproxen sodium 550 mg group were numerically greater than the mean scores for celecoxib 200 mg, 100 mg, and 50 mg dose groups from the 0.5 hour through 9.0 hour assessments and these differences were statistically significant from the 0.75 through 5.0 hour assessments. The mean PRID scores for naproxen sodium 550 mg were numerically greater than the mean scores for the celecoxib 400 mg dose group from the 0.25 through 6.0 hour assessment times and these differences were statistically significant from the 0.75 through the 3.0 hour assessment times. The mean PRID scores for the celecoxib 400 mg dose were numerically greater than the mean scores for the naproxen sodium 550 mg group at the 7.0 through 24.0 hour assessment times.

Analysis of the PRID data by using the worst observation carried forward (WOCF) method demonstrated the similar results.

Table 11 – Pain Intensity Difference and Pain Relief (PRID)

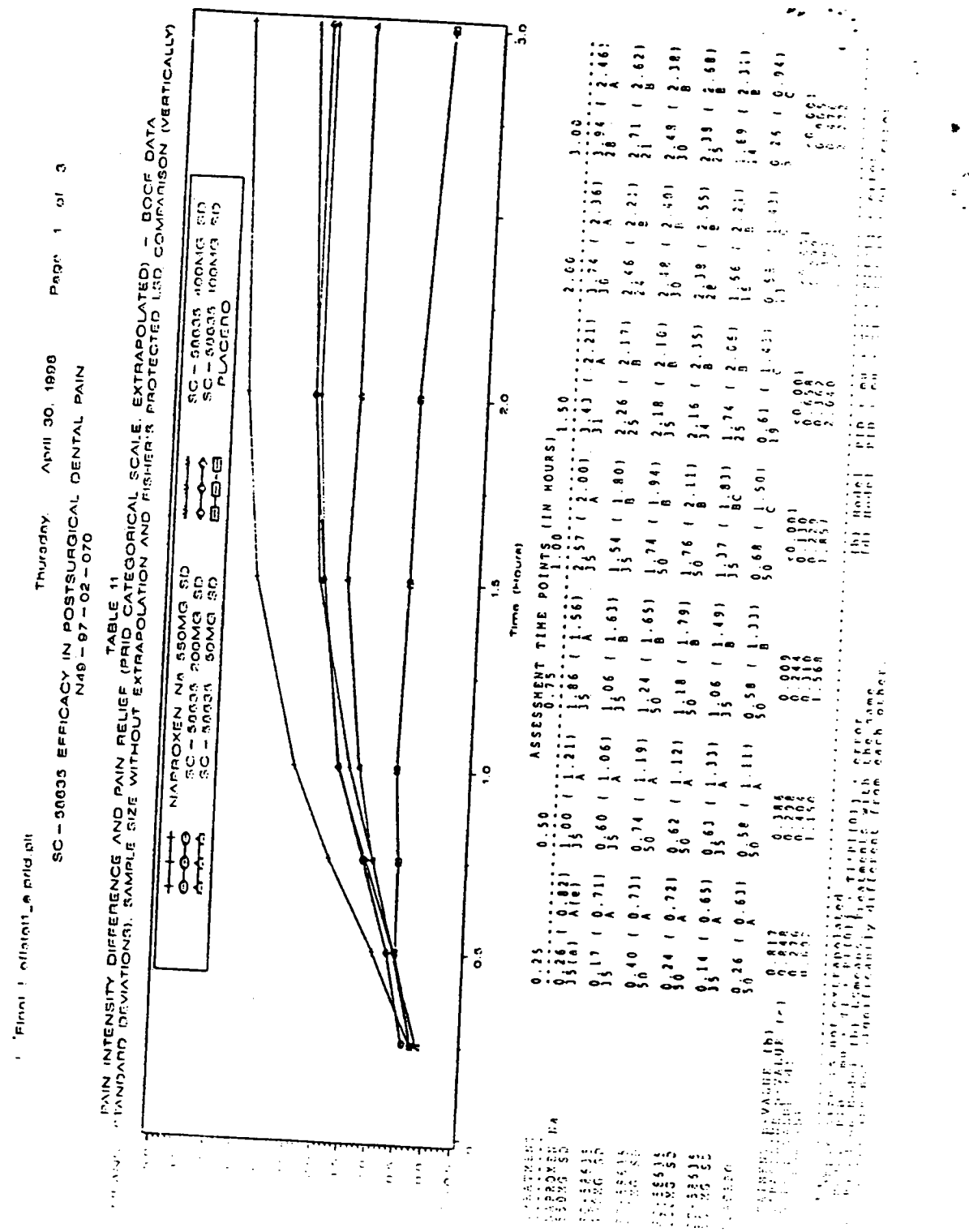


Table 11 – Pain Intensity Difference and Pain Relief (PRID)

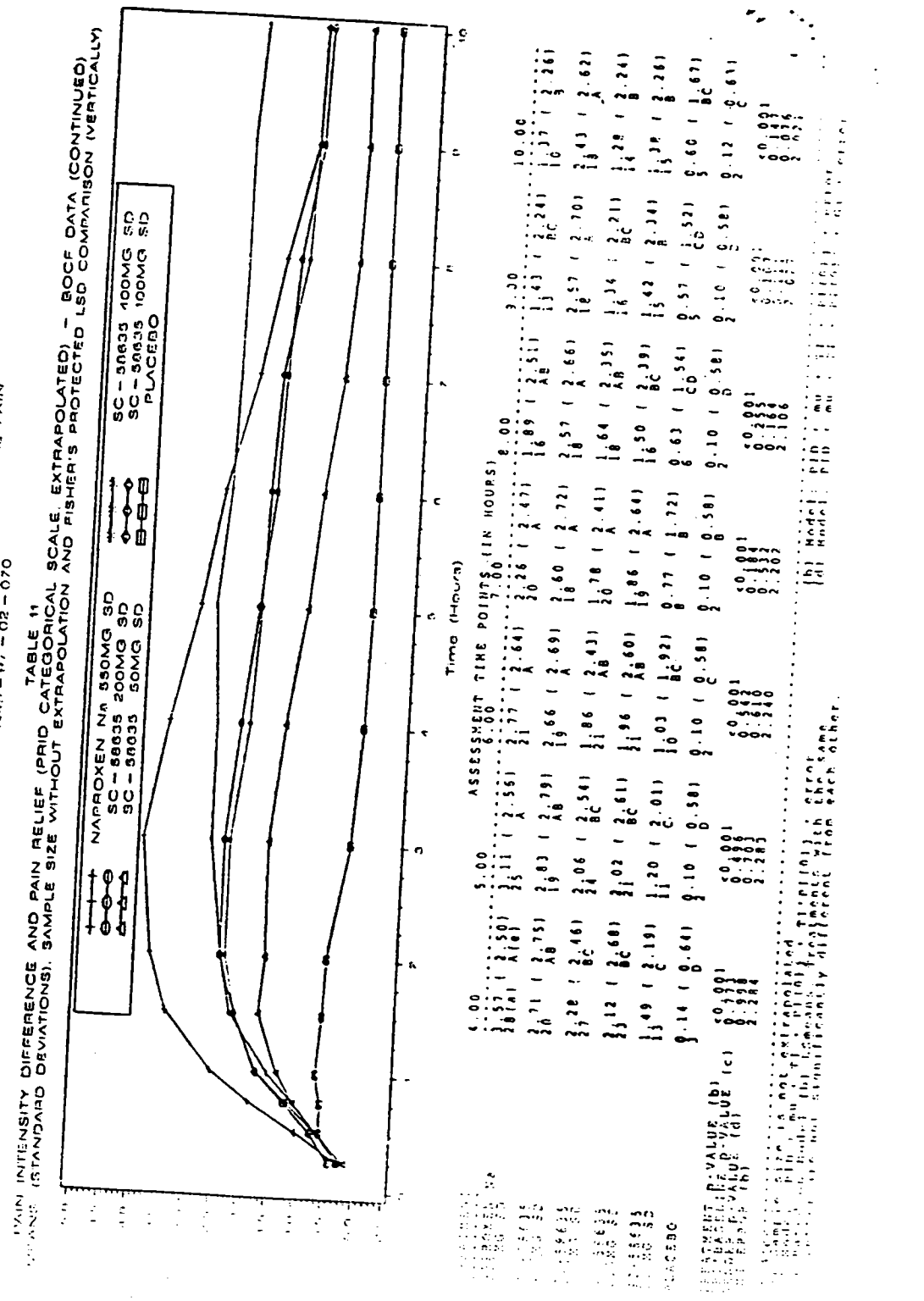
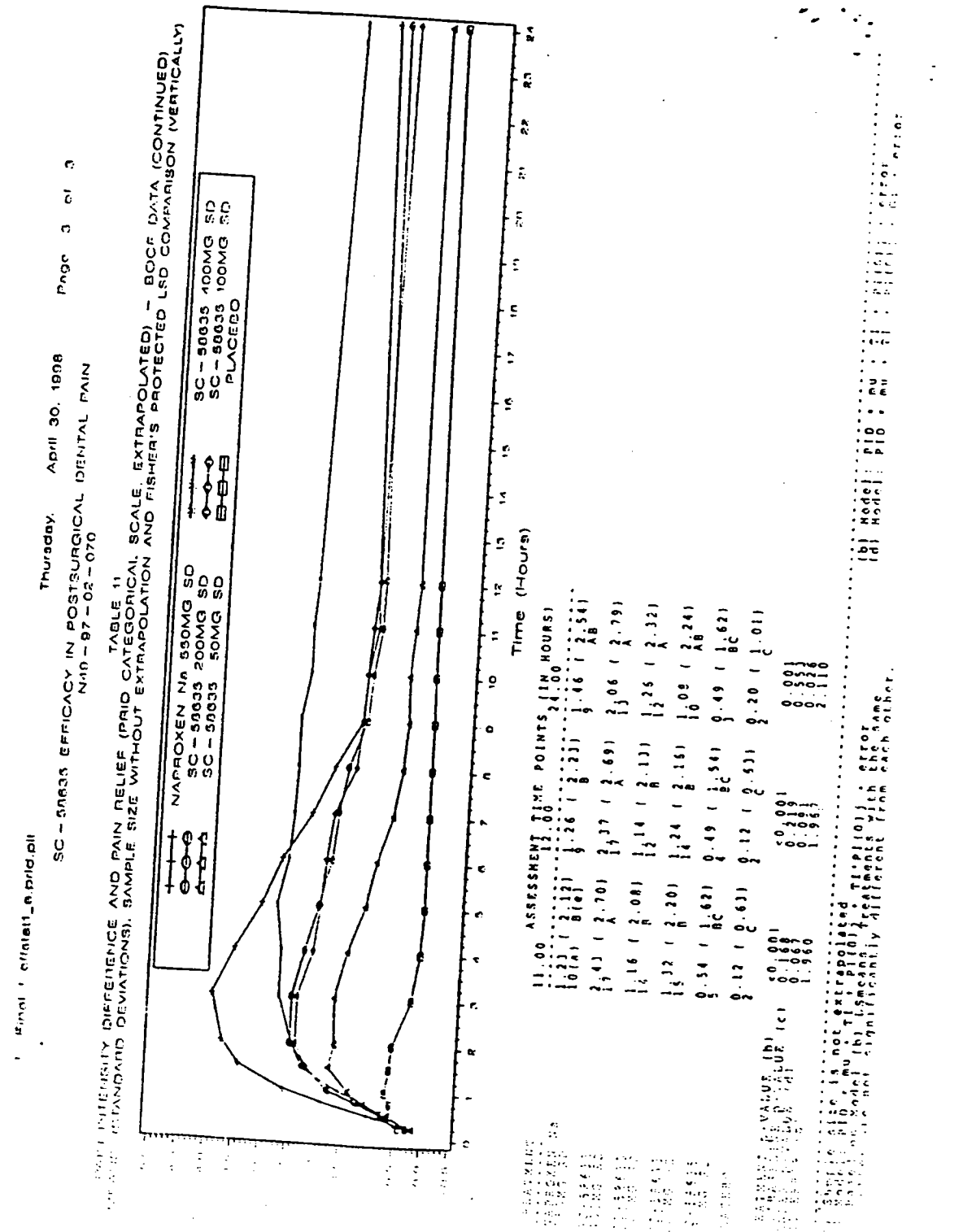


Table 11 – Pain Intensity Difference and Pain Relief (PRID)



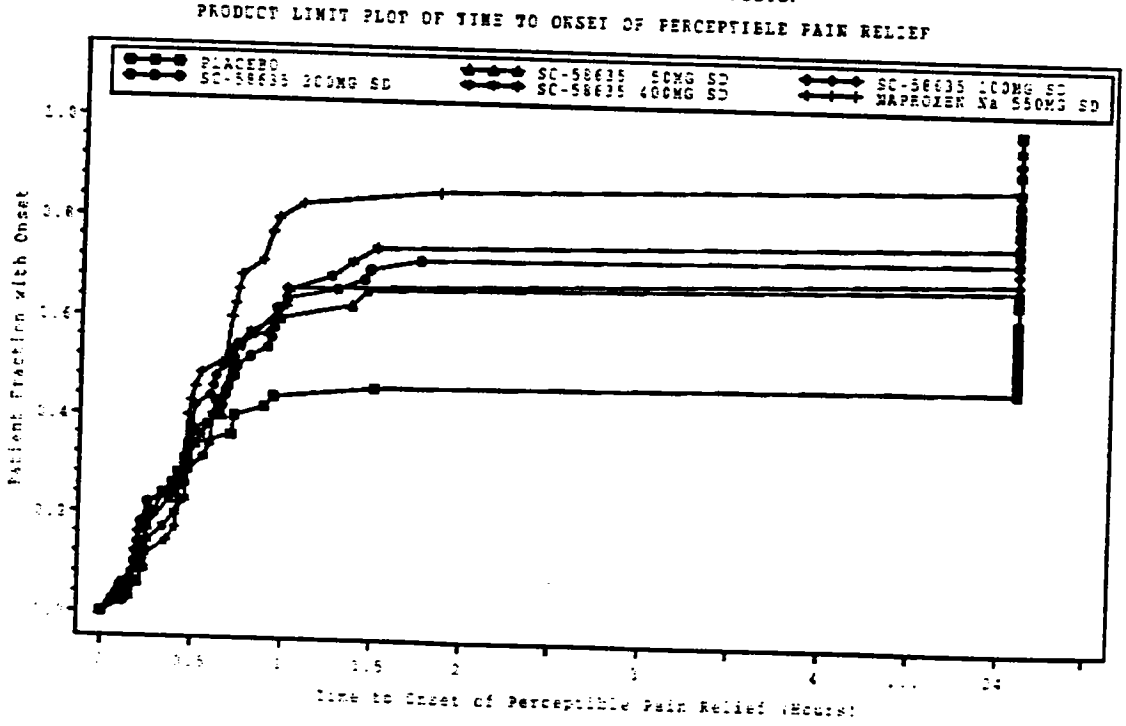
Time to Onset of Perceptible Pain Relief

Table 12 presents the median times to Onset of Perceptible Pain Relief for all treatment groups and a product limit plot of the individual times to Perceptible Pain Relief for all treatment groups. Twenty-three (46%) patients in the placebo group, 23 (66%) patients in the celecoxib 50 mg treatment group, 33 (66%) patients in the celecoxib 100 mg treatment group, 36 (72%) patients in the celecoxib 200 mg treatment group, 26 (74%) patients in the celecoxib 400 mg treatment group and 30 (86%) patients in the naproxen sodium 500 mg treatment group experienced perceptible pain relief. The difference across treatment groups in the number of patients who experienced perceptible pain relief was statistically significant (p=0.005).

The median times to onset of perceptible pain relief celecoxib 400 mg (43 min), 200 mg (44 min), 100 mg (39 min), and 50 mg (42 min) were markedly shorter than the median time for placebo (>24 hours). The differences between treatment groups in the distribution of patients over time who experienced perceptible pain relief were not statistically significant based on the log rank test.

The median time to onset of perceptible pain relief in the naproxen sodium 550 mg group (36 min) was comparable to the median times for the celecoxib 400 mg, 200 mg, 100 mg, and 50 mg treatment groups and markedly shorter than the median time for placebo. None of these differences in the distribution of patients over time who experienced perceptible pain relief between treatment groups were statistically significant.

TABLE 12
TIME TO ONSET OF PERCEPTIBLE PAIN RELIEF
PRODUCT LIMIT PLOT OF TIME TO ONSET OF PERCEPTIBLE PAIN RELIEF



Time to Rescue Medication

Table 13 presents the median times to administration of rescue medication for all treatment groups and a product limit plot of the individual times for each treatment group.

Forty eight (96%) patients in the placebo group took rescue medication as compared with 31 (91%) patients in the celecoxib 50 mg treatment group, 40 (80%) patients in the 100 mg treatment group, 38 (76%) patients in the 200 mg treatment group, and 22 (63%) patients in the 400 mg treatment group. Twenty six (74%) patients in the naproxen sodium 550 mg treatment group took rescue medication. The difference across treatment groups in the number of patients who took rescue medication was statistically significant (p=0.002).

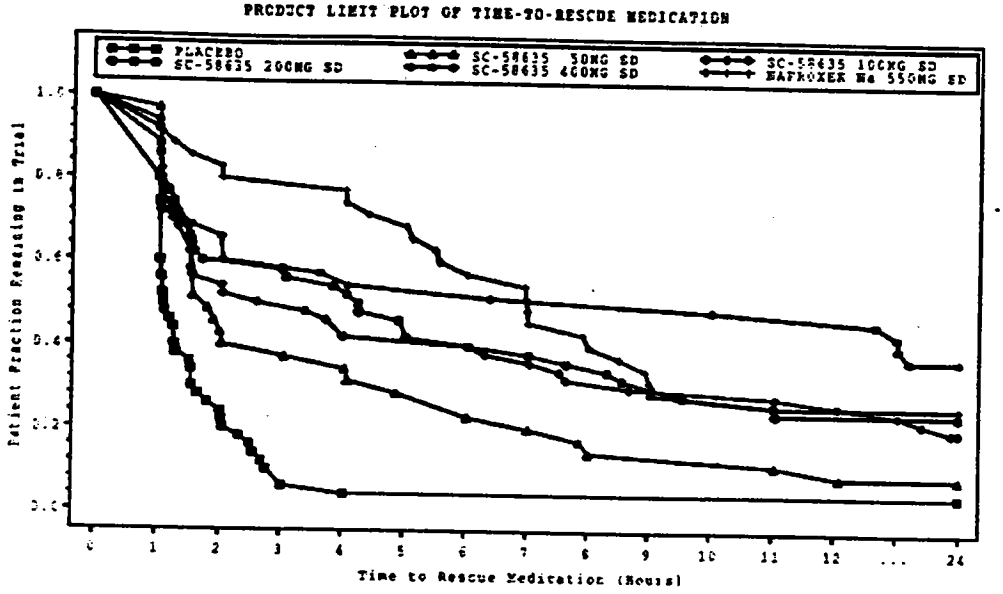
All celecoxib treatment groups had longer median times to administration of rescue medication than placebo and these differences were statistically significant for all SC-58635 dose levels. While the median times to rescue medication increased with increasing dose levels of celecoxib, the only statistically significant difference in median time to rescue medication was for the celecoxib 400 mg treatment group (8 hours and 13 minutes) compared to the median time to rescue medication for the celecoxib 50 mg group (1 hour and 41 minutes).

The median time to rescue medication for the celecoxib 400 mg dose was greater than the median time for naproxen sodium 550 mg (7.0 hours). The median time to administration of rescue medication for the naproxen sodium 550 mg treatment group was longer than that observed for the celecoxib 200 mg, 100 mg, 50 mg, and placebo treatment groups. The differences in time to rescue medication were statistically significant only as compared to the celecoxib 50 mg and placebo groups by log rank test. (see table).

TRAETMENT	Median Time to Remedication (H : MIN)
Naproxen sodium 550 mg	07:00
Celecoxib 400 mg	08:13
Celecoxib 200 mg	04:15
Celecoxib 100 mg	02:36
Celecoxib 50 mg	01:41
Placebo	01:06

TABLE 13
TIME TO RESCUE MEDICATION

PRODUCT LIMIT PLOT OF TIME-TO-RESCUE MEDICATION



Analysis of Secondary Efficacy Measures (as defined in the protocol)

Mean Pain Intensity Difference Scores Over Time - Visual Analog Scale

(Analysis done using LOCF method)
The mean PID(VAS) scores for the celecoxib 400 mg, 200 mg, 100 mg, and 50 mg treatment groups were numerically greater than placebo at the 0.75 hour through the 24.0 hour assessment times. This difference was statistically significant for all celecoxib treatment groups as compared to placebo at the 1.0 hour through 11.0 hour assessments. These differences remained statistically significant through the 24.0 assessments for the 400 mg, 200 mg, and 100 mg dose groups. Within the celecoxib treatment groups, the 400 mg, 200 mg, and 100 mg groups had numerically greater mean scores than the celecoxib 50 mg group at the 1.0 hour through 24 hour assessment times and these differences were statistically significant for the celecoxib 400 mg group at 5.0 through 24.0 hour assessment times. The differences between the mean PID(VAS) scores for the celecoxib 400 mg group and the mean scores for the celecoxib 100 mg and 200 mg groups were statistically significant at the 11.0 hour assessment.

The mean PID(VAS) scores for the naproxen sodium 550 mg treatment group were numerically greater than those for placebo at all postdose assessment times and this difference was statistically significant at the 0.75 hour through 24.0 hour assessments. The mean scores for naproxen sodium 550 mg group were numerically greater than the mean scores for all celecoxib treatment groups at the 0.25 to 6.0 hour assessment and

these differences were statistically significant at 0.75 through 3.0 hour assessment times. times. At the 7.0 hour through 24.0 hour assessments, the celecoxib 400 mg group had higher mean scores than the naproxen sodium 550 mg group.

Peak Pain Intensity Difference, Peak Pain Relief and Patient Global Evaluation
For PPID (Categorical and VAS), PPR, and Patient Global Evaluation, the celecoxib 400 mg, 200 mg, 100 mg and 50 mg treatment groups had numerically greater mean scores than placebo and these differences were statistically significant for all measures. For these measures, the celecoxib 400 mg, 200 mg, and 100 mg groups had numerically greater mean scores than the celecoxib 50 mg group. The celecoxib 400 mg group was statistically significantly different from the celecoxib 50 mg group for PPR. There were no other statistically significant differences for any of these.

The naproxen sodium 550 mg treatment group had numerically greater mean scores than placebo, celecoxib 200 mg, 100 mg, and 50 mg for these measures and the differences were statistically significant. The naproxen sodium 550 mg treatment group had numerically higher mean scores than celecoxib 400 mg treatment groups for these measures but the differences were not statistically significant.

Sum of Pain Intensity Difference for 6, 8, 10, 12, and 24 Hours (Categorical and Visual Analog Scale)
At all assessment times, all celecoxib treatment groups had numerically higher mean SPID (Categorical and VAS) scores than placebo and these differences were statistically significant at all assessment times except the celecoxib 50 mg for SPID (Categorical) at 24.0 hours. The celecoxib 400 mg and 200 mg groups had numerically higher mean SPID (Categorical) scores than celecoxib 100 mg and 50 mg at all assessment times but none of the differences were statistically significant. The celecoxib 400 mg, 200 mg, and 100 mg groups had numerically higher mean SPID(VAS) scores than celecoxib 50 mg but these differences were not statistically significant. The celecoxib 400 mg group had numerically higher mean SPID(VAS) scores than all other celecoxib treatment groups for all assessment times, however these differences were not statistically significant.

The mean SPID (Categorical and VAS) scores for the naproxen sodium 550 mg treatment group were numerically higher than the mean SPID (Categorical and VAS) scores for placebo at all assessment times and these differences were statistically significant at all assessment times. The mean SPID (Categorical) scores were higher in the naproxen sodium 550 mg group than in the celecoxib dose groups at the 6.0, 8.0, 10.0 and 12.0 hour assessments. These differences were statistically significant compared to the celecoxib 50 mg group at 6.0, 8.0, 10.0, 12.0 and 24.0 hours and as compared to the celecoxib 100 mg and 200 mg dose group at the 6.0, 8.0, and 10.0 hour assessments. The differences in mean SPID(VAS) scores were statistically significant as compared to celecoxib 400 mg treatment group at 6.0 hours and as compared to the celecoxib 200 mg, 100 mg, and 50 mg treatment groups at all assessment times.

Total Pain Relief for First 6, 8, 10, 12, and 24 Hours

At all assessment times, all celecoxib treatment groups had numerically higher mean TOTPAR scores than placebo and these differences were statistically significant at all assessment times except for celecoxib 50 mg compared to placebo at the 24.0 hour assessment time. The celecoxib 400 mg, 200 mg, and 100 mg groups had numerically higher mean TOTPAR scores than celecoxib 50 mg and the differences between celecoxib 400 mg and celecoxib 50 mg were statistically significant at the 6.0, 8.0, 10.0, 12.0, and 24.0 hour assessment times. The celecoxib 400 mg group had numerically higher mean TOTPAR scores than the celecoxib 200 mg and 100 mg treatment groups at all assessment times; however, these differences were not statistically significant.

The mean TOTPAR scores for the naproxen sodium 550 mg treatment group were numerically higher than the mean TOTPAR scores for placebo and all celecoxib treatment groups at all assessment times except for celecoxib 400 mg at the 12.0 and 24.0 hour assessment. These differences were statistically significant for naproxen sodium 550 mg as compared to the placebo and the celecoxib 50 mg treatment groups at all assessment times. The differences in mean TOTPAR scores were statistically significant at the 6.0 and 8.0 hour assessment for the naproxen sodium 550 mg group compared to the celecoxib 100 mg and 200 mg groups.

Summed Pain Relief Intensity Difference (SPRID) for First 6, 8, 10, 12, and 24 Hours

At all assessment times, all celecoxib treatment groups had numerically higher mean SPRID scores than placebo and these differences were statistically significant at all assessment times except for celecoxib 50 mg at the 24.0 hour assessment time. The celecoxib 400 mg, 200 mg, and 100 mg groups had numerically higher mean SPRID scores than the celecoxib50 mg group at all assessment times, and the differences between the celecoxib 400 mg and celecoxib 50 mg treatment groups were statistically significant at the 8.0, 10.0, 12.0, and 24.0 hour assessment times. The celecoxib 400 mg group had numerically higher mean SPRID scores than the celecoxib 200 mg and 100 mg treatment groups at all assessment times but these differences were not statistically significant.

The mean SPRID scores for the naproxen sodium 550 mg treatment group were numerically higher than the mean SPRID scores for the placebo and all celecoxib treatment groups at all assessment times except for the celecoxib 400 mg dose at the 24.0 hour assessment time. These differences were statistically significant for naproxen sodium 550 mg as compared to the placebo and celecoxib 50 mg treatment groups at all assessment times. The difference in mean SPRID scores for naproxen sodium 550 mg were statistically significant compared to the celecoxib 100 mg group at the 6.0, 8.0 and 10.0 hour assessments and compared to the celecoxib 200 mg group at the 6.0 and 8.0 hour assessment.

Time to Meaningful Pain Relief

Six (12%) of the patients in the placebo group, 17 (49%) of the patients in the celecoxib 50 mg group, 27 (54%) of the patients in the celecoxib 100 mg group, 27 (54%) of the patients in the celecoxib 200 mg group, 21 (60%) of the patients in the celecoxib 400 mg group, and 27 (77%) of the patients in the naproxen sodium 550 mg group experienced Meaningful Pain Relief. The difference across treatment groups in the number of patients who experienced Meaningful Pain Relief was statistically significant (p=0.001).

All the celecoxib groups had shorter median times to Meaningful Pain Relief than placebo. The median time to Meaningful Pain Relief for the celecoxib 400 mg treatment group (1 hour 45 minutes), the celecoxib 200 mg group (2 hours sixteen minutes), the celecoxib 100 mg group (1 hour 57 minutes), and for the celecoxib 50 mg group (8 hours 56 minutes) were statistically significant compared to the median time to Meaningful Pain Relief for the placebo group (>24 hours). There were no statistically significant differences in median time to Meaningful Pain Relief among the celecoxib dose groups.

The median time to Meaningful Pain Relief, for the naproxen sodium 550 mg treatment group (1 hour and 1 minute) was statistically significant as compared to the placebo, celecoxib 200 mg, 100 mg and 50 mg treatment groups.

Median times to Meaningful Pain Relief were:

TRAETMENT	Median Time (H : MIN)
Naproxen Na 550 mg	1:01
Celecoxib 400 mg	1:45
Celecoxib 200 mg	2:16
Celecoxib 100 mg	1:57
Celecoxib 50 mg	8:56
Placebo	>24:00

Pain Half Gone

All the celecoxib treatment groups had shorter median times for Time First Experienced at Least 50% Pain Relief than placebo. The median time to at least 50% pain relief for the celecoxib 400 mg treatment group (1 hour 45 minutes), for celecoxib 200 mg treatment group (2 hours), for celecoxib 100 mg treatment group (2 hours), and for celecoxib 50 mg treatment group (9 hours and 14 minutes) were statistically significant as compared to the median time to at least 50% pain relief for the placebo group (>24 hours). There were no statistically significant differences in median time to at least 50% pain relief among the celecoxib treatment groups.

The median time to at least 50% pain relief observed for the naproxen sodium 550 mg treatment group (1 hour and 4 minutes) was statistically significant as compared to median times to at least 50% pain relief for the placebo, celecoxib 200 mg, 100 mg and 50 mg treatment groups.

Percent of Patients Experiencing at Least 50% Pain Relief

The percentage of patients experiencing at least 50% pain relief in all the celecoxib treatment groups was higher than in placebo at the 0.75 hour through 24.0 hours postdose assessment times and these differences were statistically significant for all celecoxib treatment groups at the 1.50 hour through 7.0 hour postdose. From the 8.0 hour through 24.0 hour postdose, the celecoxib 400 mg, 200 mg and 100 mg dose groups were statistically significantly higher than placebo. The percentage of patients experiencing at least 50% pain relief in the celecoxib 400 mg, 200 mg, and 100 mg was numerically higher than observed in celecoxib 50 mg at the 1.0 hour through 24.0 hours postdose and only statistically significant at the 8.0 hour assessment time.

The percentage of patients experiencing at least 50% pain relief in the naproxen sodium 550 mg treatment group was numerically greater than placebo at the 0.25 hour through 24.0 hour assessment times and statistically significantly greater than placebo at the 0.75 hour through 24.0 hour assessment times. The percentage of patients experiencing at least 50% pain relief in the naproxen sodium 550 mg treatment group was numerically greater than celecoxib 400 mg treatment groups at the 0.25 hour through 5.0 hour assessment times and also numerically greater than celecoxib 200 mg and 100 mg at the 0.25 hour through 8.0 hour assessment times.

Time to Onset of Analgesia

The median times to onset of analgesia were 54 minutes for the celecoxib 400 mg treatment group; 1 hour for the celecoxib 200 mg treatment group; and 54 minutes for the celecoxib 100 mg treatment group and were all shorter than the median Time to Onset of Analgesia for the celecoxib 50 mg and placebo groups (>24 hours). The differences between the celecoxib groups and the placebo group in the distribution of patients over time who experienced onset to analgesia were statistically significant based on the log rank test. The difference between the celecoxib treatment groups were not statistically significant. The median time to onset of analgesia was 36 minutes for the naproxen sodium 550 mg group and the differences between the naproxen sodium 550 mg group and the celecoxib 200 mg, celecoxib 50 mg, and placebo groups in the distribution of patients over time who experienced onset of analgesia were statistically significant based on the log rank test.

Safety Results

Overall, 99 (39%) of the 255 patients receiving at least one dose of study drug reported one or more adverse events during the study. Adverse events were reported by 24 (48%) of the placebo patients; 20 (57%) of the patients receiving celecoxib 50 mg; 12 (24%) of the patients receiving celecoxib 100 mg; 18 (36%) of the patients receiving celecoxib 200 mg; 15 (43%) of the patients receiving celecoxib 400 mg; and 10 (29%) of the patients receiving naproxen sodium 550 mg (see table).

Incidence Of Adverse Events
Patients With At Least One Dose Of Study Medication

Summary (Number Of Patients)	PLACEBO (N= 50)	Celecoxib 50mg (N= 35)	Celecoxib 100mg (N= 50)	Celecoxib 200mg (N= 50)	Celecoxib 400mg (N= 35)	Naproxen Na 550mg
Patients With At Least One Adverse Event	24 (48%)	20 (57%)	12 (24%)	18 (36%)	15 (43%)	10 (29%)
Patients With No Adverse Events	26 (52%)	15 (43%)	38 (76%)	32 (64%)	20 (57%)	25 (71%)
Patients With No Adverse Event Information	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Patients Who Took At Least One Dose Of Study Medication	50 (100%)	35 (100%)	50 (100%)	50 (100%)	35 (100%)	
All Randomized Patients	50	35	50	50	35	35

The adverse events with the highest incidence (i.e. ≥5% reported in one or more of the celecoxib treatment groups) were alveolar osteitis, nausea, headache, oral hemorrhage, dizziness, somnolence and vomiting.

One celecoxib 50 mg patient withdrew from the study due to severe oral hemorrhage which was determined by the Investigator to be unrelated to study drug.

There were no serious adverse events reported during the study.

There were no deaths reported during the study.

There were no clinically relevant changes in vital signs or body weight from Baseline.

There were no clinically significant changes in clinical laboratory evaluation from baseline to past treatment.

Discussion and Overall Conclusions for Study # 070

The results of this study demonstrate that for all primary (PID[Categorical], PR, PRID, Time to perceptible PR, Time to Rescue Medication) and secondary (PID[VAS], PPID, PPR, Time to Meaningful PR, Time to 50% PR, Proportion of patients experiencing 50% PR , Patient Global Evaluation and the 6, 8, 10, 12, and 24 hour sums for SPID, TOTPAR, and SPRID) measures of efficacy, single oral doses of celecoxib 50 mg, 100 mg, 200 mg, and 400 mg produced a numerically greater improvement in mean scores than placebo at all postdose assessment times after 0.75 hours. This improvement was statistically significant for the celecoxib 100 mg, 200 mg, and 400 mg doses at 1.0 hour postdose through 24.0 hours postdose as compared to placebo. Statistically significant differences favoring the celecoxib treatment groups as compared to placebo were also seen with all summed measures. Celecoxib 50 mg was a submaximally effective therapeutic dose. In general, a positive dose response was present and the celecoxib 400 mg dose exhibited a numerically greater and longer analgesic efficacy than the celecoxib 50 mg, 100 mg and 200 mg dose levels and placebo.

Naproxen sodium 550 mg was statistically significant better in the primary end points of PID, PR, and PRID as early as 0.5 hour postdose and continuing through 3 to 4 hours postdose compared to celecoxib 400 mg and through 4 to 6 hours compared to celecoxib 200 mg. Naproxen sodium 550 mg was comparable to celecoxib in time to perceptible pain relief and time to rescue medication.

No major safety issues have been demonstrated.