Study Number: N49-96-02-027

Study Dates: 4 March 1997 – 25 July 1997

Title of Study: A double-blind, randomized, active and placebo controlled, single dose comparison of the analgesic activity of celecoxib 25 mg, 50 mg, and 200 mg, ibuprofen 400 mg and placebo in a post surgical dental pain model.

Investigator and Location:

Objectives:
The primary objectives of this study were:
To compare the analgesic activity of celecoxib 100 mg and celecoxib 200 mg versus placebo in patients with moderate to severe pain in a postsurgical dental pain model.

The secondary objectives of this study were:

1. to compare the analgesic activity of a single dose of naproxen sodium (Anaprox® 550 mg) versus placebo in patients with moderate to severe pain in a postsurgical dental pain model; and
2. to assess the safety of celecoxib 100 mg and celecoxib 200 mg in patients with moderate to severe pain in a postsurgical dental pain model; and
3. to correlate plasma levels of celecoxib 100 mg and 200 mg with analgesic activity 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 CELECOXIB 100 mg, CELECOXIB 200 mg, naproxen sodium 550 mg, 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 0.25, 0.50, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, and 24 hours after the administration of study medication (table 1). Patients returned for posttreatment evaluations five to nine days after the administration of study medication.

Table 1 - Schedule of Observations and Procedures

	Pre-treatment	Baseline	Treatment																			Post-treatment
	-14 to 0 days	0 hr	15 mins	30 mins	45 mins	1 hours	1.5 hours	2 hours	3 hours	4 hours	5 hours	6 hours	7 hours	8 hours	9 hours	10 hours	11 hours	12 hours	24 hours			5-9 days
Medical History	x																					
Physical Examination	x																					x
Vital Signs	x	x																				x
Clinical Laboratory Testing	x																			x		
Pregnancy Test[a]	x																					
Blood Samples (PK)		x	x	x	x	x	x	x	x	x	x	x	x	x				x	x			
Pain Assessments[b]		x[c]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x			
Start Stopwatches for Perceptible & 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 will have a negative urine pregnancy test within 24 hours prior to receiving study drug.
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 hr) 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. Been females of childbearing potential, must have been using adequate contraception, not been lactating, and have 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 two or more impacted third molar teeth requiring bone removal, one of which must have been mandibular, and been experiencing moderate to severe postsurgical dental pain;
5. Had a Baseline pain intensity ≥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 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 who was scheduled to receive an 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 x the upper limit of the reference range;
9. Previously admitted to this study.

Treatments Administered:

1. Celecoxib 100 mg and 200 mg capsules each identical in size and color;
2. Placebo capsules each identical in size and appearance to celecoxib 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 the encapsulated Anaprox®.

Blinding:

For each patient, each dose of study medication was packaged in two bottles: Bottle A contained one capsule and Bottle B contained two capsules. For patients taking either celecoxib or naproxen sodium, one bottle contained the active drug and one bottle contained placebo. For patients randomized to receive placebo, both bottles contained placebo. 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 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 one hour following study drug administration; however, no foods or nutrient liquids were permitted during this one-hour time period. Ice packs were not allowed for the first hour following dosing. If used afterward, ice packs were removed 15 minutes before 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:
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 (tables 2 & 3)

Two hundred and twenty (220) patients were enrolled in this study at one site and were randomized to receive one of four treatments as follows: 55 patients received celecoxib 100 mg, 56 patients received celecoxib 200 mg, 54 patients received naproxen sodium 550 mg, and 55 patients received placebo. No patient received rescue medication during the first hour assessment period. Therefore all patients constituted the ITT Cohort. Eighty one patients completed the twenty four hour assessment period without taking rescue medication and completed the scheduled 24.0 hour assessments. One hundred and thirty eight (138) patients took rescue medication during the 24 hour assessment period and one patient (0314) who did not take rescue medication was discharged for personal reasons from the site before completing the 24 hour assessment period but returned for the posttreatment examination termination visit.

The treatment groups were comparable for race and gender. Across treatment groups the mean age ranged from 21.8 to 23.8. This difference between groups was not statistically significant (p=0.154). Across treatment groups, 44% to 46% of the patients were male (p=0.998) and 62% to 70% were Caucasian (p=0.204). With the exception of mean

diastolic blood pressures (p=0.043) which ranged from 74.0 mmHg to 79.1 mmHg across treatment groups all treatment groups were comparable (p≥0.089) with respect to height , weight, and vital signs at Baseline.

Table 2
Baseline Demographic Characteristics

	Placebo (N= 55)	Celecoxib 100mg (N= 55)	Celecoxib 200mg (N= 56)	Naproxen Na 550mg (N= 54)	p- VALUE
AGE (years)					0.154 (a)
N	55	55	56	54	
MEAN	21.8	23.3	23.8	23.7	
STD DEV	3.00	5.28	5.83	6.07	
MEDIAN	21.0	22.0	22.0	22.5	
RANGE	18- 32	18- 50	18- 45	18- 52	
<30	54(98%)	51(93%)	47(84%)	50(93%)	
30- 39	1(2%)	3(5%)	6(11%)	2(4%)	
40- 49	0(0%)	0(0%)	3(5%)	1(2%)	
50- 59	0(0%)	1(2%)	0(0%)	1(2%)	
60- 69	0(0%)	0(0%)	0(0%)	0(0%)	
70- 79	0(0%)	0(0%)	0(0%)	0(0%)	
>= 80	0(0%)	0(0%)	0(0%)	0(0%)	
RACE/ ETHNIC ORIGIN					0.204 (b)
ASIAN	0(0%)	1(2%)	0(0%)	1(2%)	
BLACK	5(9%)	3(5%)	3(5%)	1(2%)	
CAUCASIAN	36(65%)	34(62%)	39(70%)	35(65%)	
HISPANIC	11(20%)	17(31%)	14(25%)	17(31%)	
OTHER	3(5%)	0(0%)	0(0%)	0(0%)	
TOTAL	55(100%)	55(100%)	56(100%)	54(100%)	
GENDER					0.998 (b)
FEMALE	30(55%)	30(55%)	30(54%)	30(56%)	
MALE	25(45%)	25(45%)	26(46%)	24(44%)	
TOTAL	55(100%)	55(100%)	56(100%)	54(100%)	

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

Table 5
Additional Baseline Characteristics

	Placebo (N= 55)	Celecoxib 100MG SD (N= 55)	Celecoxib 200MG SD (N= 56)	Naproxen Na 550MG SD (N= 54)	p- VALUE (a)
HEIGHT (cm)					0.628
N	55	55	56	54	
MEAN	171.79	171.24	172.89	170.51	
STD DEV	11.948	8.500	9.418	8.905	
MEDIAN	170.20	170.20	175.30	170.20	
RANGE					
WEIGHT (kg)					0.516
N	55	55	56	54	
MEAN	76.78	76.16	79.55	73.23	
STD DEV	21.222	19.825	26.117	20.113	
MEDIAN	71.70	74.40	73.25	69.65	
RANGE					

(a) One- Way Analysis of Variance.

Summary of Dental Surgery

The treatment groups were comparable ($p \geq 0.332$) for surgical trauma rating, degree of impaction, pain intensity (Categorical) and number of molars extracted. A greater percentage of patients in the celecoxib 100 mg treatment group had severe pain intensity at Baseline(38%) as compared to the other treatment groups (24% to 27%), however this was not a statistically significant difference.

All treatment groups were comparable with respect to time from surgery until taking study medication and Baseline pain intensity as measured on the VAS ($p \geq 0.061$). The mean pain intensity across treatment groups was between 61.2 to 65.9 (0 to 100 scale) and the mean time until study medication across treatment groups was between 3:00 to 3:10 hours after surgery. The Baseline pain intensity (VAS) was greater in the celecoxib 100 mg treatment group as compared to the other treatment groups, however this was not a statistically significant difference.

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.

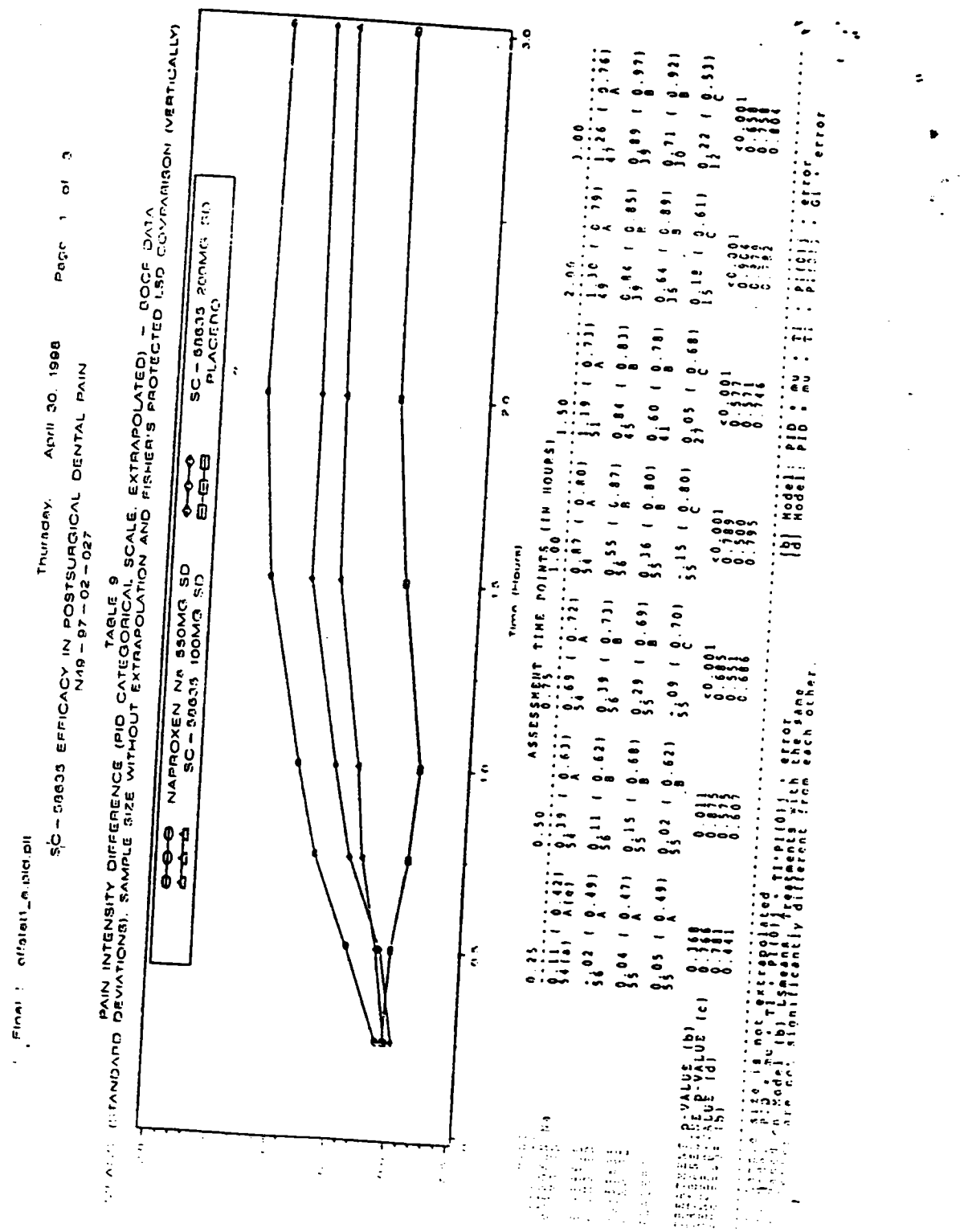
The mean PID values for the celecoxib 100 mg and 200 mg treatment groups were numerically greater than placebo at the pain assessments from 0.5 hour through 24.0 hours post dose. These differences from placebo were statistically significant at all assessment times from 0.75 hour through 24.0 hours postdose for the celecoxib 200 mg treatment group and through 6 hours for the 100 mg treatment group. Within the celecoxib treatment groups, the mean PID scores for the celecoxib 200 mg group were numerically greater than the mean scores for the celecoxib 100 mg group at the 0.75 through 24.0 hour assessment times. These differences were statistically significant at the 5.0 hour and 7.0 through 24.0 hour assessment times. The mean PID scores for the celecoxib 100 mg group were numerically greater than the mean scores for the CELECOXIB 200 mg group at the 0.25 hour and 0.5 hour assessment times, but these differences were not statistically significant.

The mean PID scores for the naproxen sodium 550 mg group were numerically greater than the placebo group at all postdose assessment times and this difference was statistically significant at the 0.5 hour through 24.0 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 100 mg and 200 mg groups at all assessment times with the exception of the 10.0, 12.0 and 24.0 hour assessments for the celecoxib 200 mg group. There was a statistically significant difference in the mean PID scores favoring the naproxen sodium 550 mg group as compared to the celecoxib 200 mg group at the 0.5

hour through 3.0 hour postdose assessments and as compared to the celecoxib100 mg group at the 0.5 hour through 24.0 hour postdose assessment times.

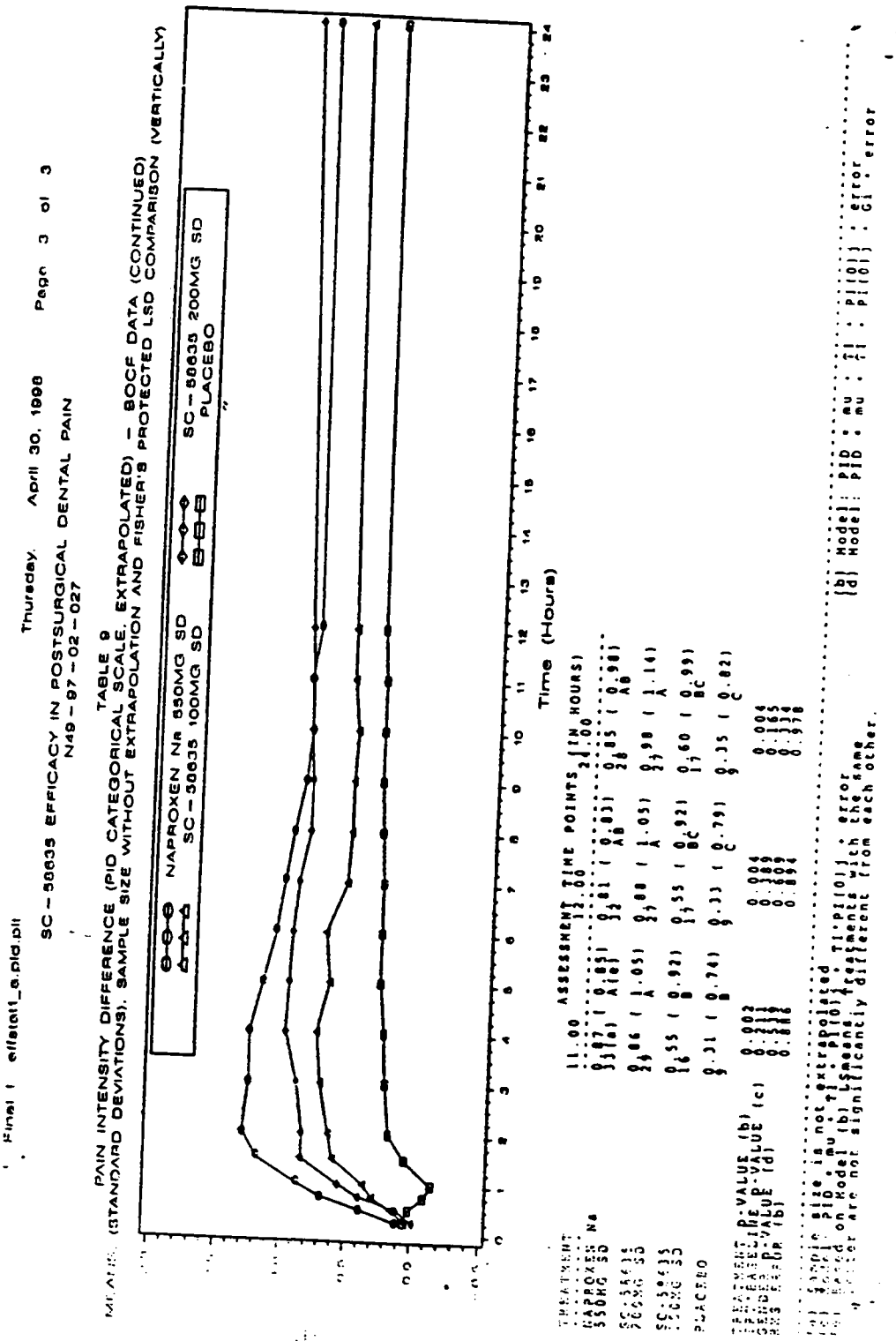
Analysis of the PID data by using the worst observation carried forward (WOCF) method demonstrated the same results.

Table 9 – Pain Intensity Difference



SC-58635 EFFICACY IN POSTSURGICAL DENTAL PAIN
N49-97-02-027
Thursday, April 30, 1998
TABLE 9
PAIN INTENSITY DIFFERENCE (PID CATEGORICAL SCALE, EXTRAPOLATED) - BOCF DATA (CONTINUED)
(STANDARD DEVIATIONS), SAMPLE SIZE WITHOUT EXTRAPOLATION AND FISHER'S PROTECTED LSD COMPARISON (VERTICALLY)
NAPROXEN Na 550MG SD
SC-58635 100MG SD
SC-58635 200MG SD
PLACEBO
Time (Hours)
ASSESSMENT TIME POINTS (IN HOURS)
P-VALUE (b)
P-VALUE (c)
P-VALUE (d)
(a) Model: PID = RU : TI : PI(RU) : error
(b) Model: PID = RU : TI : PI(RU) : error
(b) LSmeans treatments with the same
significantly different from each other.

Table 9 – Pain Intensity Difference



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 200 mg and 100 mg dose groups were numerically greater than the mean scores for placebo at the 0.5 hour through 24.0 hour assessment times. These differences from placebo were statistically significant for the celecoxib 200 mg group at the 0.75 hour through 24.0 hour assessments and for the 100 mg group at the 0.75 hour through 7 hours. Within the celecoxib treatment groups the mean PR scores for the 200 mg group were numerically greater than the mean scores for the 100 mg group at all postdose assessment times and this difference was statistically significant at the 5.0 hour through 24.0 hour assessment times.

The mean PR scores for the naproxen sodium 550 mg treatment group were numerically greater than placebo at all assessment times during the 24 hour Treatment Period and this difference was statistically significant at the 0.5 hour through 24.0 hour assessments. The mean PR scores for the naproxen sodium 550 mg group were numerically greater than the mean scores for the celecoxib 200 mg and 100 mg groups at all assessment times during the 24 hour Treatment Period. These differences were statistically significant favoring the naproxen sodium treatment group at the 0.5 hour through 4.0 hour assessments as compared to the celecoxib 200 mg group and at the 0.5 through 24.0 hour assessment times as compared to the celecoxib 100 mg group.

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

Table 10 – Pain Relief

Table 10 – Pain Relief

Thursday, April 30, 1998
SC-58635 EFFICACY IN POSTSURGICAL DENTAL PAIN
N49-07-02-027
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 100MG SD
SC-58635 200MG SD
PLACEBO
Time (Hours)
ASSESSMENT TIME POINTS (IN HOURS)
(b) Model: PR = BL + TI + error
(d) Based on Model (b) LSmeans, treatments with the same letter are not significantly different from each other.

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

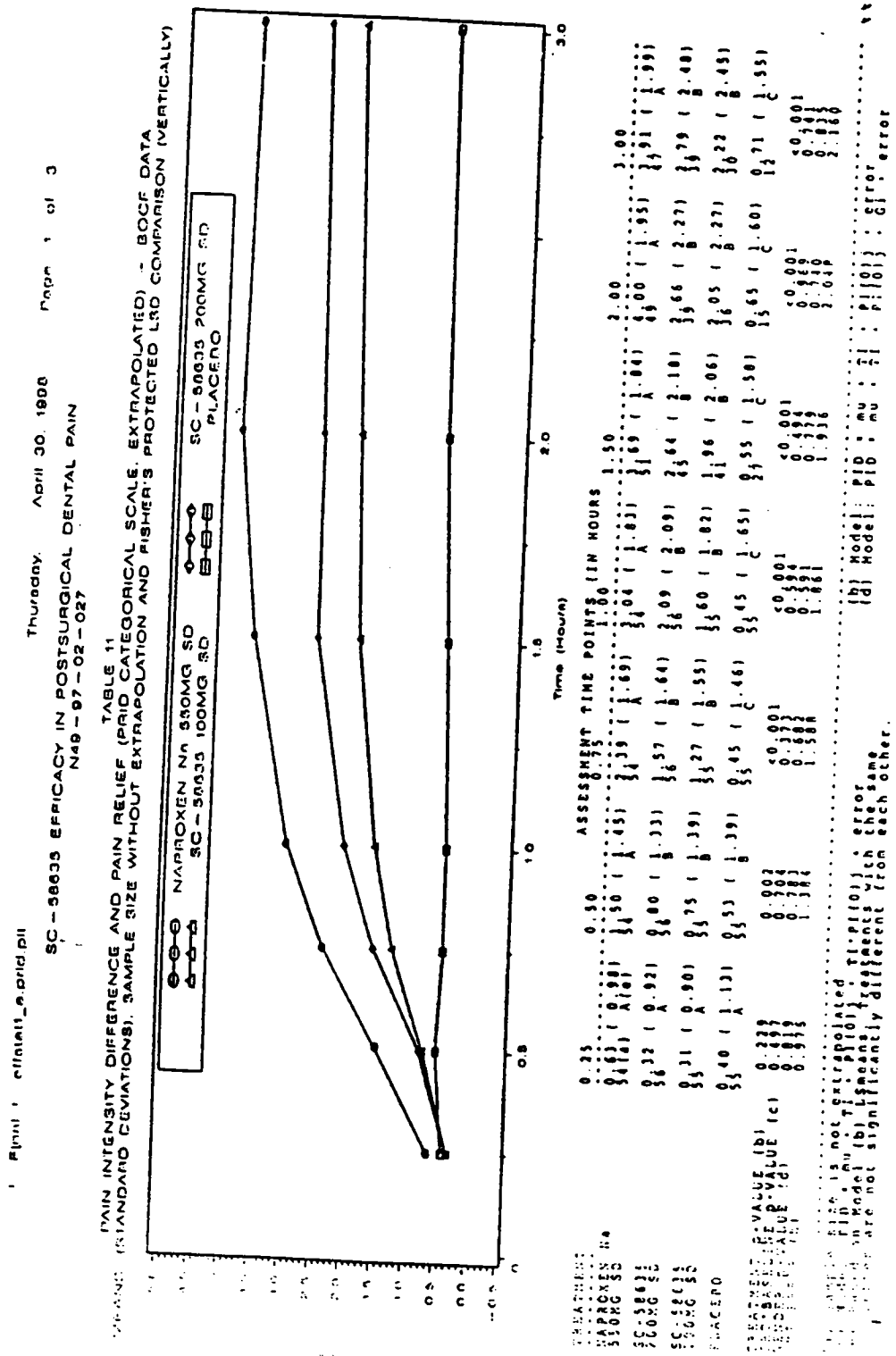
Table 11 (the three following pages) presents the mean PRID (categorical) scores for all assessment times during the 24 hour Treatment Period. PRID scores are a sum of PID and PR scores and range from a maximum score of 7 (best possible score) to a minimum score of -1 (worse possible score). Positive 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 both the celecoxib 100 mg and 200 mg treatment groups were numerically greater than placebo at all assessment times after the 0.25 hour assessment. These differences from placebo were statistically significant at all assessment times from 0.75 hour through 24.0 hours postdose for the celecoxib 200 mg treatment group and through 7 hours for the 100 mg treatment group. Within the celecoxib treatment groups, the mean PRID scores for the 200 mg dose group were numerically greater than the mean scores for the 100 mg group at all assessment times during the 24 hour Treatment Period. This difference was statistically significant at the 5.0 hours, and at 7.0 hour through 24.0 hour postdose assessment times.

The mean PRID scores for the naproxen sodium 550 mg treatment group were numerically greater than placebo at all assessment times during the 24 hour Treatment Period and this difference was statistically significant at the 0.5 hour through 24.0 hour assessment times. The mean PRID scores for the naproxen sodium 550 mg group were numerically greater than the mean scores for the celecoxib 100 mg and 200 mg groups at all assessment times during the 24 hour Treatment Period with the exception of the 24.0 hour assessment for the celecoxib 200 mg group. This difference was statistically significant at the 0.5 hour through 4.0 hour assessment times compared to the celecoxib 200 mg group and at the 0.5 hour through 12.0 hour assessment times compared to the celecoxib 100 mg group.

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

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



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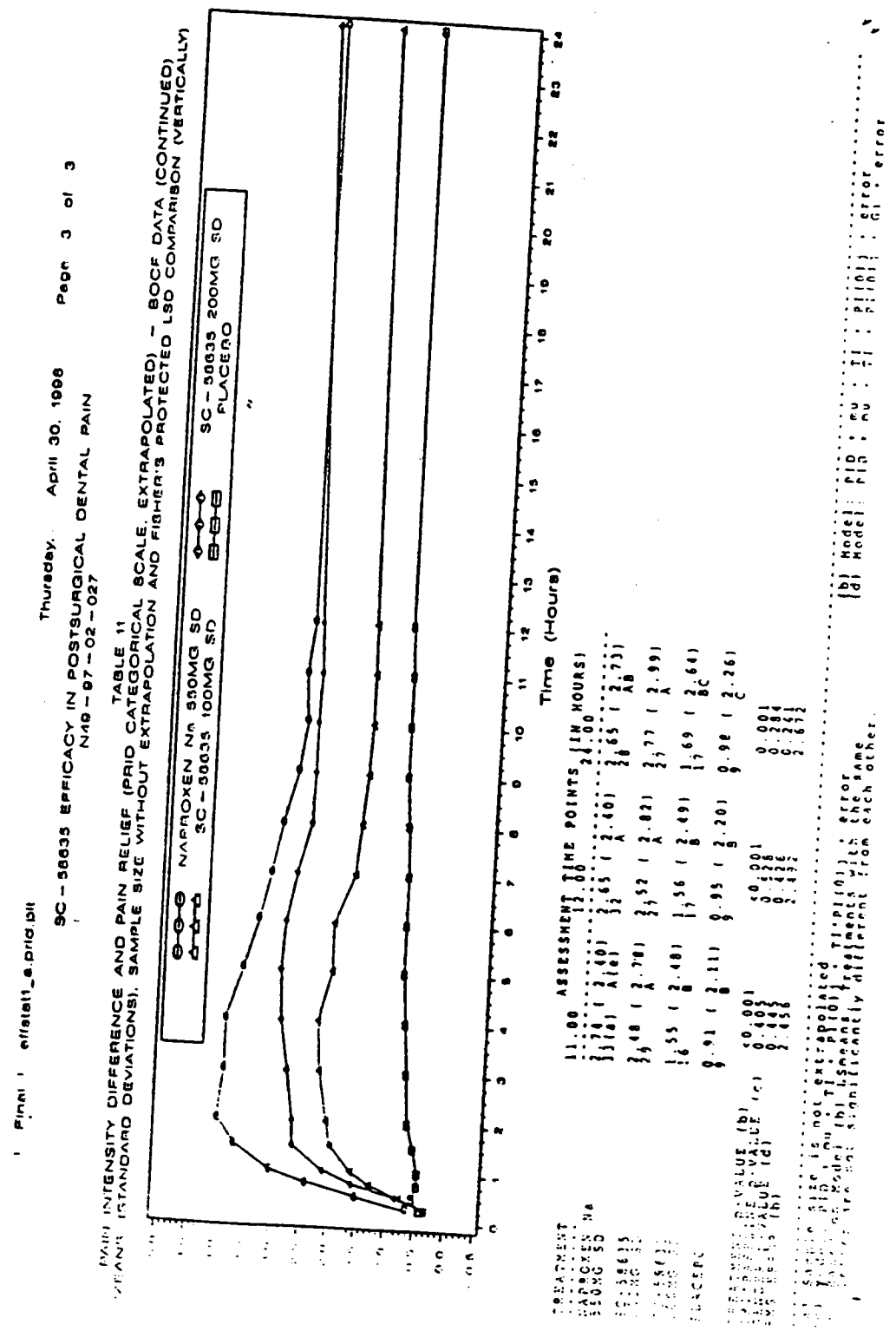
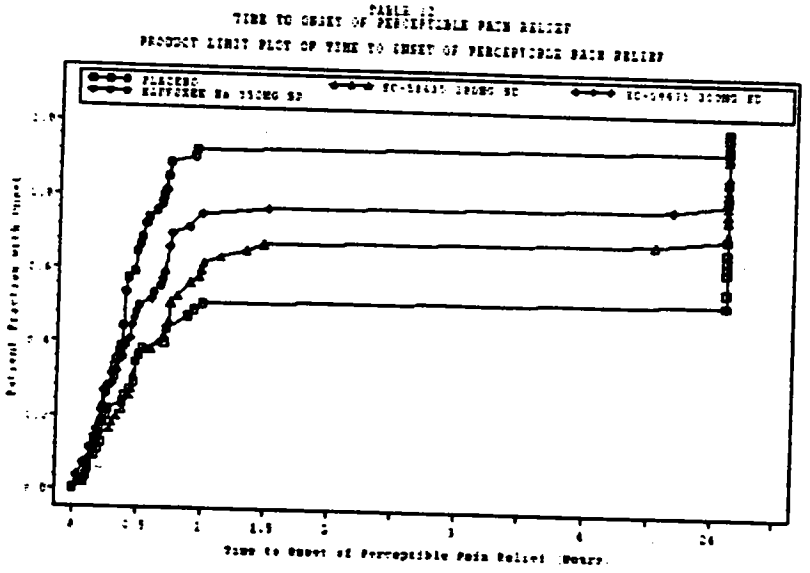


Time to Onset of Perceptible Pain Relief

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 eight (51%) patients in the placebo group, 38 (69%) patients in the celecoxib 100 mg treatment group, 44 (79%) patients in the celecoxib 200 mg treatment group and 50 (93%) patients in the naproxen sodium treatment group experienced perceptible pain relief. The difference across treatment groups in the number of patients who experienced perceptible pain relief was statistically significant ($p<0.001$).

The median times to onset of perceptible pain relief for both the celecoxib 100 mg group (45 min) and the celecoxib 200 mg group (30 min) were shorter than the median time for placebo (58 min). The differences between the celecoxib 200 mg group and the placebo group in the distribution of patients over time who experienced perceptible pain relief were statistically significant based on the log rank test. These differences were not statistically significant between the celecoxib 100 and 200 mg groups.

The median time to onset of perceptible pain relief in the naproxen sodium 550 mg group (24 min) and the differences in the distribution of patients over time who experienced perceptible pain relief were statistically significant based on the log rank test as compared to the celecoxib and placebo groups.



Time to Rescue Medication

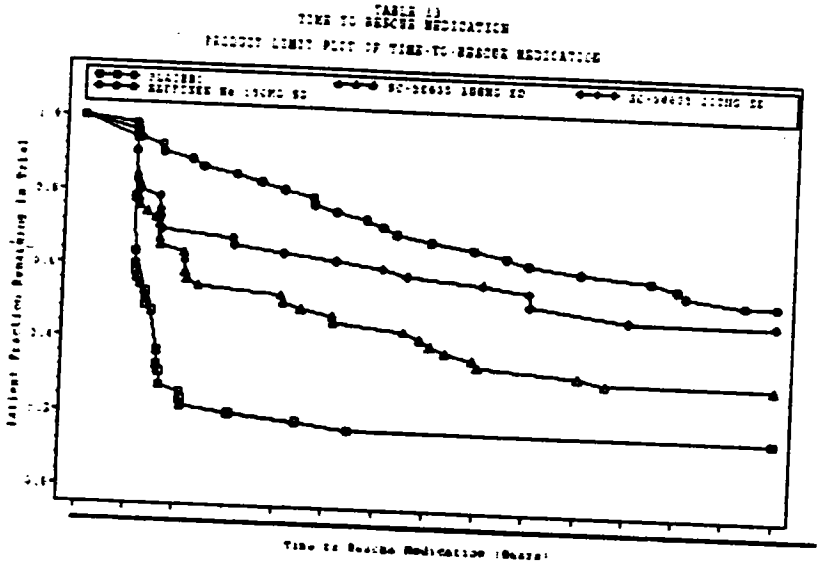
Table 13 presents the median times to administration of rescue medication for all treatment groups and a product limit plot of the individual times for each treatment group.

Forty-six (84%) patients in the placebo group took rescue medication as compared with 38 (69%) patients in the celecoxib 100 mg treatment group and 29 (52%) patients in the celecoxib 200 mg group. Twenty five (46%) 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 ($p<0.001$).

The median time to rescue medication for both the celecoxib 200 mg treatment group (10 hours and 2 minutes) and the celecoxib 100 mg treatment group (4 hours and 17 minutes) were longer than the median time for the placebo group (1 hour and 20 minutes). The difference between the celecoxib and the placebo in the distribution of patients over time who used rescue medication were statistically significant based on the log rank test. These differences were not statistically significant between the celecoxib 100 and 200 mg groups.

The median time to administration of rescue medication observed for the naproxen sodium 550 mg treatment group (>24.0 hours) and the difference in distribution of patients over time who took rescue medication were statistically significant based on log rank test as compared to the placebo and celecoxib 100 mg treatment groups. These differences were not statistically significant between the celecoxib 200 mg and naproxen. (see table).

TRAETMENT	Median Time to Remedication (H : MIN)
Naproxen sodium 550 mg	> 24:00
Celecoxib 200 mg	10.02
Celecoxib 100 mg	04:17
Placebo	01:20



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 generally paralleled those of the categorical scale scores. Naproxen sodium 550 mg was statistically significant superior to celecoxib 200 mg through the first 4 hours, and to the 100 mg and the placebo groups through 24 hours. Within the celecoxib treatment groups, the celecoxib 200 mg group had numerically greater mean scores than the celecoxib 100 mg group at all assessment times during the 24 hour Treatment Period. This difference was statistically significant at the 5.0 hour and the 7.0 hour through 24.0 hour assessment times.

Peak Pain Intensity Difference, Peak Pain Relief and Patient Global Evaluation
The naproxen sodium 550 mg treatment group had numerically greater mean scores than placebo for these measures and the differences were statistically significant. The naproxen sodium 550 mg group had numerically higher mean scores than either of the celecoxib treatment groups for these measures. These differences were statistically significant for PPID(VAS) and PPR compared to mean scores for the celecoxib 200 mg group and for all measures compared to the mean scores for the celecoxib 100 mg group.

For PPID (Categorical and VAS), PPR, and Patient Global Evaluation, both the celecoxib 100 mg and 200 mg treatment groups had numerically greater mean scores than placebo and these differences were statistically significant for all measures. For these measures, the celecoxib 200 mg group had numerically greater mean scores than the celecoxib 100 mg group but this difference was statistically significant only for the Patient Global Evaluation mean scores.

Sum of Pain Intensity Difference for 6, 8, 10, 12, and 24 Hours (Categorical and Visual Analog Scale)
At all assessment times, both the celecoxib 100 mg and 200 mg treatment groups had numerically higher mean SPID (Categorical and VAS) scores than placebo and these differences were statistically significant at all assessment times. The celecoxib 200 mg group had numerically higher mean SPID (Categorical and VAS) scores than the celecoxib 100 mg group for all assessment times. These differences were statistically significant at the 8.0, 10.0, 12.0 and 24.0 hour assessment times for the SPID (Categorical) and at the 12.0 and 24.0 hour assessment times for SPID(VAS).

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 and the celecoxib treatment groups at all assessment times. These differences were statistically significant as compared to the placebo and the celecoxib 100 mg treatment groups at all assessment times and compared to the celecoxib 200 mg group for the SPID(VAS) at the 6.0 and 8.0 hour assessment.

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

At all assessment times, statistically significant differences in mean scores favoring both celecoxib treatment groups as compared to placebo were seen. The celecoxib 200 mg group had numerically higher mean TOTPAR scores than the celecoxib 100 mg group for all assessment times.

The mean TOTPAR scores for the naproxen sodium 550 mg treatment group were numerically higher than the mean TOTPAR scores for placebo and the celecoxib treatment groups at all assessment times. These differences were statistically significant as compared to the placebo and the celecoxib 100 mg treatment groups at all assessment times and compared to the celecoxib 200 mg group at the 6.0, 8.0 and 10.0 hour assessments.

Summed Pain Relief Intensity Difference (SPRID) for First 6.0, 8, 10, 12, and 24 Hours

At all assessment times, statistically significant differences in mean scores favoring both celecoxib treatment groups as compared to placebo were seen. The celecoxib 200 mg group had numerically higher mean SPRID scores than the celecoxib 100 mg group at all assessment times. These differences were statistically significant at the 10.0, 12.0, and 24.0 hour assessment times.

The mean SPRID scores for the naproxen sodium 550 mg treatment group were numerically higher than the mean SPRID scores for placebo and the celecoxib treatment groups at all assessment times. These differences were statistically significant compared to the placebo and the celecoxib100 mg treatment groups at all assessment times and compared to the celecoxib 200 mg group at the 6.0 and 8.0 hour assessments. The mean SPRID scores for the naproxen sodium 550 mg treatment group were not statistically significantly different from celecoxib 200 mg at the 10.0, 12.0, and 24.0 hour assessment times.

Time to Meaningful Pain Relief

Thirteen (24%) of the patients in the placebo group, 29 (53%) of the patients in the celecoxib 100 mg group, 40 (71%) of the patients in the celecoxib 200 mg group, and 48 (89%) 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 ($p<0.001$).

The median time to Meaningful Pain Relief for both the celecoxib 200 mg treatment group (1 hour 20 minutes) and the celecoxib 100 mg treatment group (2 hours and 47 minutes) were shorter than the median time to Meaningful Pain Relief for the placebo group (>24 hours). The differences between the celecoxib groups and placebo in the distribution of patients over time who experienced meaningful pain relief were statistically significant based on the log rank test. These differences were not statistically significant between the celecoxib 100 mg and 200 mg groups.

The median time to Meaningful Pain Relief observed for the naproxen sodium 550 mg treatment group (47 minutes) and the differences in the distribution of patients over time

who experienced meaningful pain relief were statistically significant based on the log rank test as compared to the celecoxib and placebo groups.

Median times to Meaningful Pain Relief were:

TRAETMENT	Median Time (H : MIN)
Naproxen sodium 550 mg	0:47
Celecoxib 200 mg	1:20
Celecoxib 100 mg	2:47
Placebo	>24:00

Pain Half Gone

The median time to at least 50% pain relief for both the celecoxib 200 mg treatment group (1 hour and 20 minutes) and the celecoxib 100 mg treatment group (3 hours and 31 minutes) were shorter than the median time to 50% pain relief for the placebo group (>24 hours). The differences between the celecoxib groups and placebo in the distribution of patients over time who experienced at least 50% pain relief were statistically significant based on the log rank test. These differences were not statistically significant between the celecoxib 100 mg and 200 mg groups.

The median time to at least 50% pain relief for the naproxen sodium 550 mg treatment group (50 minutes) and the differences in the distribution of patients over time who experienced 50% pain relief were statistically significant based on the log rank test as compared to the celecoxib and placebo groups.

Percent of Patients Experiencing at Least 50% Pain Relief

The percentage of patients experiencing at least 50% pain relief in the celecoxib 100 mg and 200 mg treatment groups were numerically higher than in placebo at the 0.75 hour through 24.0 hour postdose assessment times. These differences were statistically significant for the celecoxib 200 mg group as compared to placebo at the 0.5 hour through 24.0 hour assessments. The increase in the percentage of patients experiencing at least 50% pain relief in the celecoxib 100 mg group was statistically significant as compared to placebo at the 1.0 hour through 6.0 hour postdose assessment times. There was a greater percentage of patients in the celecoxib 200 mg treatment group as compared to the celecoxib 100 mg treatment group who experienced at least 50% pain relief at the 0.5 hour through 24.0 hour assessment times. These differences were statistically significant at the 6.0 , 7.0, and 10.0 hour through 24.0 hour postdose assessment times.

The percentage of patients experiencing at least 50% pain relief in the naproxen sodium 550 mg treatment group was numerically and statistically significantly greater than placebo at the 0.5 hour through 24.0 hour assessment times. The percentage of patients experiencing at least 50% pain relief in the naproxen sodium 550 mg group were numerically greater than the percentage of patients experiencing at least 50% pain relief in the celecoxib 100 mg and 200 mg groups at all postdose assessment times. These

differences were statistically significant as compared to the celecoxib 200 mg group at the 1.0 hour through 4.0 hour assessments and as compared to the celecoxib 100 mg group at the 0.75 hour through 24.0 hour assessments.

Time to Onset of Analgesia

The median times to onset of analgesia were 36 minutes for the celecoxib 200 mg treatment group and 57 minutes for the celecoxib 100 mg treatment group and were shorter than the median time to onset of analgesia for the placebo group (>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 differences between the celecoxib treatment groups were also statistically significant. The median time to onset of analgesia was 24 minutes for the naproxen sodium 550 mg treatment group and the differences between the naproxen sodium group and the celecoxib 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, 105 (48%) of the 220 patients receiving at least one dose of study drug reported one or more adverse events during the study. Adverse events were reported by 27 (49%) of the placebo patients; 24 (44%) of the patients receiving SC-58635 100 mg; 29 (52%) of the patients receiving SC-58635 200 mg; and 25 (46%) of the patients receiving naproxen sodium 550 mg. No patient withdrew from the study as a result of an adverse event.

The adverse events with the highest incidence (i.e., reported by ≥5% of the patients in any SC-58635 treatment group) were alveolar osteitis (dry socket), headache, nausea, and vomiting. Of these, the number of patients reporting alveolar osteitis, nausea, dizziness, and vomiting in the celecoxib groups was similar to the ibuprofen group and greater than the placebo group. There were no adverse events causing withdrawal of patients from the study. There were no serious adverse events during the study.

There were no statistically significant differences from Baseline in mean changes in vital signs across treatment groups or within treatment groups ($p \geq 0.402$).

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

Discussion and Overall Conclusions for Study # 027

The results of this study demonstrate that, For all primary (PID (Categorical), PR, PRID, Time to Perceptible PR, Time to Rescue Medication) and secondary (Time-Specific PID(VAS); PPID; PPR; TOTPAR; SPRID and SPID for the first 6, 8, 10, 12 and 24

hours; Time to Meaningful Pain Relief; Time First Experienced 50% Pain Relief; Percentage of Patients Experiencing at Least 50% Pain Relief; Patient Global Evaluation) measures of efficacy, single oral doses of celecoxib at dose levels of 100 mg and 200 mg produced a numerically greater improvement in mean score than placebo at all postdose assessment times after 0.5 hours. With few exceptions, this improvement was also statistically significant as early as 0.75 hour postdose and continuing through 24.0 hours postdose for the celecoxib 200 mg dose group and through 4 to 5 hours for the 100 mg group as compared to placebo. The celecoxib 200 mg dose produced numerically greater improvement in all efficacy measures as compared to the celecoxib 100 mg dose at all assessment times past 0.75 hours postdose. In most efficacy measures, this improvement in mean scores was statistically significant at the 5.0 and 24.0 hour assessment times and most of the 8.0 hour, 10.0 hour and 12.0 hour summed measures as compared to scores for the celecoxib 100 mg dose. In general, a positive dose response was present and the celecoxib 200 mg dose exhibited greater and longer analgesic efficacy than the celecoxib 100 mg and placebo doses.

Naproxen sodium 550 mg was statistically significant better in all scores as early as 0.5 hour postdose and continuing through 3 to 4 hours postdose compared to celecoxib 200 mg and through 24 hours compared to celecoxib 100 mg.

No major safety issues have been demonstrated.