Time to Rescue Medication

Median times to rescue medication for the double-blind, post-oral surgery studies (Studies 025, 027, and 070) are presented in table 10. Celecoxib at doses of 50 mg SD, 100 mg SD, 200 mg SD, and 400 mg SD was associated with a statistically significantly longer duration of analgesic effect compared with placebo. The median time to rescue medication was longer with increasing doses of celecoxib; however, no statistically significant differences were present between the 100 mg SD, 200 mg SD, and 400 mg SD groups. Celecoxib at a dose of 25 mg SD did not separate from placebo. The 50 mg SD, although superior to placebo, had a median time to rescue medication under 2 hours.

Table 10: Median Time to Rescue Medication for Individual and Pooled Studies 025, 027, and 070 by Study and Treatment Group (hour:minutes)

Treatment Group	Study 025	Study 027	Study 070	Pooled
Placebo	1:17	1:20	1:06	1:15
Celecoxib 25 mg SD	1:32	—	—	—
Celecoxib 50 mg SD	1:48*	—	1:41*	1.51*
Celecoxib 100 mg SD	—	4:17*	2:36*	3:48*
Celecoxib 200 mg SD	3:05*	10:02*	4:15*	6:03*
Celecoxib 400 mg SD	—	—	8:13*	—

* Indicates statistical significance compared to placebo by log-rank test.

The results from the post-orthopedic surgery study (Study 028) supported the observation that the time to remedication or rescue medication is about 4 to 5 hours after a single dose of 100 mg or 200 mg of celecoxib. However, in this study, the time to rescue/remedication was longer for placebo (3 hours, 33 minutes) than seen in the post-oral surgery studies.

Time to Onset of Perceptible Pain Relief

Table 11 presents the Median Times to Onset of Perceptible Pain Relief for Studies 025, 027, and 070. All doses of celecoxib were numerically superior to placebo. Statistically significant differences were observed for celecoxib 50 mg SD (Study 025) and for 200 mg SD (Studies 025 and 027).

Table 12: Median Times to Onset of Perceptible Pain Relief for Studies 025, 027, 070 by Study and Treatment Group (hour:minutes)

Dose Levels	Study 025	Study 027	Study 070
Placebo	>24:00	00:58	>24:00
Celecoxib 25 mg SD	00:53	–	–
Celecoxib 50 mg SD	1:05*	–	00:42
Celecoxib 100 mg SD	–	00:45	00:39
Celecoxib 200 mg SD	00:38*	00:30*	00:44
Celecoxib 400 mg SD	–	–	00:43

* Indicates statistical significance compared to placebo by log-rank test.

Time to Onset of Perceptible Pain Relief was not measured in the post-orthopedic surgery study (Study 028) or the post-general surgery study (Study 029).

Pain Intensity Difference-VAS

Pain Intensity Difference-Visual Analog Scale (PID-VAS) was determined by asking the patients to rate their pain on a scale of 0 to 100 mm with 0 representing no pain and 100 representing worst pain.

In the double-blind post-oral surgery studies, celecoxib at doses of 100 mg (Studies 027 and 070), 200 mg (Studies 025, 027 and 070), and 400 mg (Study 070) showed statistically significantly greater improvement compared to placebo beginning by 1 hour postdose and continuing through 7-8 hours postdose.

The BOCF analysis for the single dose response in the post-orthopedic surgery study (#028) showed that celecoxib at doses of 100 mg SD and 200 mg SD was associated with numerically but not statistically significant greater mean PID-VAS scores compared with placebo from 1.5-8 hours postdose.

The mean PID-VAS scores after multiple dosing in the post-orthopedic surgery study (#028) showed that again, celecoxib 100 mg BID PRN or 200 mg BID PRN were numerically but not statistically significant superior to placebo beginning at about 1.5 hour and continuing through the entire 24 hour observation period. Using the BOCF method of imputation, celecoxib 200 mg BID PRN was significantly different from placebo at 7, 8 and 12 hours after the first dose of study medication. These findings however, cannot support the claim for the management of pain.

Sum of Pain Intensity and Pain Relief, Sum of Pain Relief, and Sum of Pain Intensity Difference for First 3, 6, 8, and 12 Hours

Sum of Pain Intensity and Pain Relief (SPRID) was calculated as the sum of the PRID scores for 3, 6, 8, and 12 hours for Studies 025, 027, 070, 028 (single and multiple dose).

Sum of Pain Relief (TOTPAR) was calculated as the sum of the PR scores for 3, 6, 8, and 12 hours for Studies 025, 027, 070, 028 (single and multiple dose).

Sum of Pain Intensity Difference (Categorical and VAS) (SPID and SPID (VAS)) were calculated as the sum of the Pain Intensity Difference Scores for 3, 6, 8, and 12 hours for Studies 025, 027, 070, 028 (single dose and multiple dose).

In Studies 025, 027, and 070, celecoxib at doses of 100 mg SD, 200 mg SD, and 400 mg SD showed statistically significantly greater improvement compared to placebo at 3, 6, 8 and 12 hours (BOCF analyses). The exception was in Study 027; the mean SPID score at 12 hours for the 100 mg SD was numerically but not statistically different from placebo.

In the post-orthopedic surgery study (Study 028), after a single dose of celecoxib 100 mg and 200 mg, mean SPRID, SPID and TOTPAR scores were numerically but not statistically significant greater than placebo at 3, 6, 8, and 12 hours. At 8 and 12 hours the mean SPRID and TOTPAR scores associated with celecoxib 200 mg were statistically greater than the corresponding measures associated with placebo.

In the multiple dose BOCF analyses, the mean SPRID, TOTPAR and SPID scores were numerically greater with celecoxib 100 mg BID PRN and 200 mg BID PRN compared to placebo but again, the differences did not reach significance. (According to LOCF analyses, celecoxib 200 mg BID PRN was statistically superior to placebo at 6, 8 and 12 hours for SPRID and TOTPAR).

Proportion of Patients and Time First Experienced at Least 50% Pain Relief

Following oral surgery (studies 025, 027, 070), the percentage of patients experiencing at least 50% pain relief during the study observation period was statistically significantly greater with celecoxib at doses of 50 mg SD, 100 mg SD, 200 mg SD, and 400 mg SD compared to placebo (table 12).

Table 13: Number (%) Patients Experiencing at Least 50% Pain Relief for Individual and Pooled Studies 025, 027, and 070 by Study and Treatment Group

Dose Levels	Study 025	Study 027	Study 070	Pooled
Placebo	9 (18%)	13 (24%)	7 (14%)	29 (19%)
Celecoxib 25 mg SD	21 (42%)	–	–	–
Celecoxib 50 mg SD	23 (46%)*	–	17 (49%)*	40 (47%)*
Celecoxib 100 mg SD	–	29 (53%)*	27 (54%)*	56 (53%)*
Celecoxib 200 mg SD	27 (54%)*	40 (71%)*	28 (56%)*	95 (61%)*
Celecoxib 400 mg SD	–	–	21 (60%)*	–

* Indicates statistical significance on Time to 50% Pain Relief compared to placebo using log-rank test.

In the post-orthopedic surgery study (Study 028) the percentage of patients who experienced at least 50% pain relief during the first 24 hours was determined. The analysis included patients who had received one or more doses of study medication. Over the 24 hours, 57%, 55% and 59% of the patients who received celecoxib 200 mg BID PRN, celecoxib 100 mg BID PRN and placebo, respectively, experienced at least 50% pain relief. It should be noted that the placebo response was much greater in the 028 trial than in other studies for all measures of analgesia efficacy.

Proportion of Patients and Time First Experienced 100% Pain Relief

One hundred percent pain relief was defined as a PR score of 4 (complete pain relief) and a PI (categorical) score of 0 (no pain).

Following oral surgery (studies 025, 027, 070), the percentage of patients experiencing 100% pain relief during the study observation period was statistically significantly greater with celecoxib at doses of 50 mg SD, 100 mg SD, 200 mg SD, and 400 mg SD compared to placebo (table 13).

Table 14: **Number (%) Patients Experiencing 100% Pain Relief for Individual and Pooled Studies 025, 027, 070 by Study and Treatment Group**

Dose Levels	Study 025	Study 027	Study 070	Pooled
Placebo	3 (6%)	9 (16%)	2 (4%)	14 (9%)
Celecoxib 25 mg SD	2 (4%)	–	–	—
Celecoxib 50 mg SD	7 (14%)*	–	4 (11%)*	11 (13%)*
Celecoxib 100 mg SD	–	15 (27%)*	14 (28%)*	29 (28%)*
Celecoxib 200 mg SD	14 (28%)*	21 (38%)*	11 (22%)*	46 (29%)*
Celecoxib 400 mg SD	–	–	12 (34%)*	—

* Indicates statistical significance on Time to First Experience 100% Pain Relief compared to placebo using log-rank test.

The proportion of patients experiencing 100% pain relief was not determined in the post-orthopedic surgery studies.

Summary of Clinical Studies Conducted in Patients with OA

Seven placebo-controlled studies were conducted in patients with OA. In four of them pain was first measured a week after initial dosing and therefore these studies cannot provide evidence to support the treatment of acute pain. In the other three OA studies (020, 021, 054) pain was first measured at bedtime of day one and continuing once daily through bedtime of day seven. Thus, these three OA studies may provide supportive evidence for the treatment of acute pain but can hardly provide any definitive evidence of efficacy to support such an indication. Neither time to onset of analgesia nor dosing interval information can be derived from such data.

Study Population and Design - OA Studies

In order to be entered into the OA studies, patients must have been diagnosed according to the ACR criteria as having OA of the knee or hip and have been in a flare state at the Baseline Visit.

Measures of Analgesic Efficacy in OA Studies

The American Pain Society (APS) Pain Scale (table 14) was used in the above mentioned three OA studies. The APS Pain Measure consists of five questions that assess pain experienced by the patient over the previous 24 hours.

Table 15: APS Pain Scale

	Question	Scale
1.	Have you experienced any pain in the past 24 hours?	yes/ no
2.	How much pain are you having right now?	0- 10
3.	Indicate the worst pain you have had in the past 24 hours.	0- 10
4.	Indicate the average level of pain you have had in the past 24 hours	0- 10
5.	Indicate how pain has interfered with you in:	
	• General Activity	0- 10
	• Mood	0- 10
	• Walking Ability	0- 10
	• Relations with other People	0- 10
	• Sleep	0- 10
	• Normal Work, Including Housework	0- 10
	• Enjoyment of Life	0- 10

APS Pain Measure Results

Table 15 shows the results of the APS measure at bedtime of day 1 in the three OA studies (020, 021, 054) for celecoxib in doses of 100mg and 200mg. In the hip OA study #054 celecoxib was statistically significantly better than the placebo in four APS questions and was not different than placebo in one question. In OA study #021 celecoxib was statistically significantly better than the placebo in one question but was not different than placebo in the other four. In study knee OA study #020 celecoxib was not statistically different than placebo in all 5 APS questions.

Table 16: OA Studies - APS Scores at Bedtime of Day I Compared to Placebo

	any pain in past 24h	pain now	worst pain in past 24h	average pain in past 24h	pain interfere in life-total
Hip OA (Study 054)	x	✔	✔	✔	✔
Knee OA (Study 021)	x	x	x	✔	x
Knee OA (Study 020)	x	x	x	x	x

✔ denotes statistically significantly better than placebo
x denotes not statistically significantly better than placebo

In general, at bedtime on day 2 through day 7 celecoxib was statistically better than placebo in most of the APS questions in all three studies.

Summary and Conclusions – All Pain Studies

For the "general purpose" management of acute pain the usual requirement is (replicated) evidence of efficacy in at least two different type of pain models. Replicated evidence of efficacy in single-dose studies when patients will not need more than one or few doses (e.g., dental pain) and replicated evidence of efficacy in multiple doses over several days studies in patients requiring short-term therapy (e.g., post surgery).

During the development program of celecoxib, six studies were conducted to support the management of pain indication in accordance with the above requirements. Four single dose studies in the dental pain model (025, 027, 070, 005) and two multiple dose studies in the post orthopedic/general surgery model (028, 029,).

Of the four dental pain studies, three are considered to be pivotal (study 005 had a single blind design). In these studies, celecoxib at doses of 100 mg SD (Studies 027 and 070), 200 mg SD (Studies 025, 027 and 070), and 400 mg SD (Study 070) showed statistically significantly greater improvement in pain compared to placebo beginning at 45 minutes to 1 hour postdose and continuing through 7 to 8 hours postdose for the time specific efficacy measures. Time to Rescue Medication was statistically significant longer compared to placebo with celecoxib doses of 50 mg, 100 mg, 200 mg and 400 mg. Shorter Time to Perceptible Pain Relief compared to placebo was statistically significant for only the 200 mg dose (Studies 025 and 027). It is important to note that the NSAID comparators (ibuprofen 400mg and naproxen sodium 550mg) demonstrated a more rapid onset of analgesia and a statistically significantly greater peak response than celecoxib at all doses studied (25 mg, 50 mg , 100 mg, 200 mg, and 400 mg) beginning at 30 to 45 minutes postdose and continuing trough 3 to 5 hours postdose for the time specific efficacy measures.

In the two multiple dose post general/orthopedic surgical pain studies interim analyses (not included in the protocol) were conducted. The reason given was that: "the enrollment had been slower than expected and the dropout rate had been higher than expected, raising concerns that the model was not behaving as anticipated". Study 029 (post general surgery) was terminated followin the interim analysis because neither celecoxib nor the comparator (Darvocet-N) separated statistically from placebo. In the multiple dose post-orthopedic surgery trial (028) the only statistically significant differences favoring celecoxib over the placebo were at a dose of 200 mg for the pain relief plus pain intensity difference (PRID) measurement, at 6, 7, and 9 hours when using BOCF technique and some scattered and inconsistant finding of a significant efficacy for the other time specific efficacy measures. Therefore, no substantial evidence has been demonstrated in the multiple dose post general/orthopedic surgical pain studies to support the management of pain indication.

Other acute pain assessments have been attempted in three OA studies which pain was first measured at bedtime beginning on the first study day and continuing for 7 days. Pain was measured at bedtime and we actually have no information available in regard to the time elapsed between ingesting the drug and the pain measuring. These three OA

studies demonstrate some positive efficacy results of a multiple-dose administration of celecoxib over a week period. These results can be regarded as supportive but still inconclusive evidence of efficacy.

A key issue here is whether a new molecular entity can gain a management of acute pain indication based only on evidence from single dose studies in one type of a pain model. Although the results of the osteoarthritis studies lend some general support to idea that celecoxib can have an analgesic effect, the evidence of its utility for acute analgesia is weak. Celecoxib "won" in three pivotal, single dose dental pain studies, but it appeared to be less effective than ibuprofen or naproxen sodium, and it failed in showing statistically significant efficacy in the treatment of pain in two multiple dose, 3-5 day post operative trials.

No outstanding safety issues have been demonstrated during the clinical trials conducted to investigate the treatment of pain. However, short-term studies are not expected to be a significant source for detecting adverse events of investigational new drugs.

Recommendations

1. This drug is recommended not approval for the treatment of acute pain at this time.
2. If an additional multiple dose, 3-5 day study shows a statistically significant efficacy in the treatment of acute pain, the results of the currently submitted studies might serve as a supportive evidence.
3. If and when this drug is approved for the treatment of acute pain it is recommended that the labeling will reflect its efficacy relative to other NSAID's (ibuprofen and naroxen sodium) tested in this submission.

Study Number: N49-96-02-025

Study Dates: 9 July 1996 – 7 November 1996

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:

1. To compare the analgesic activity of three different celecoxib doses (25 mg, 50 mg and 200 mg) versus placebo in patients with moderate to severe pain in a postsurgical dental pain model; ibuprofen 400 mg was used as a positive control; and
2. To assess the safety of three different celecoxib doses (25 mg, 50 mg, and 200 mg) 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 ibuprofen 400 mg versus placebo in patients with moderate to severe pain in a postsurgical dental pain model; and
2. To correlate plasma levels of 25 mg, 50 mg, and 200 mg celecoxib doses 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, double-blind, placebo-controlled, randomized, parallel-group comparison study to evaluate the safety and analgesic effectiveness of single, orally administered doses of celecoxib (25 mg, 50 mg, and 200 mg), ibuprofen 400 mg (Motrin IB®), 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
	Days -14 to 0	Hour 0	Hours																	5-9 days
			.25	.50	.75	1	1.5	2	3	4	5	6	7	8	9	10	11	12	24	
Medical History	x																			
Physical Exam	x																			x
Vital signs	x	x																		x
Clinical Lab Tests	x																		x	
Pregnancy Test (a)	x																			
Pain Assessment (b)		x(c)	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
PK Blood Samples		x	x	x	x	x	x	x	x	x	x	x	x	x				x	x	
Stopwatch for Perceptible and Meaningful Pain Relief (d)		x																		
Study Drug		x(e)																	x(f)	
Global Evaluation																				x
Collect Diary Cards																				

(a) Female subjects of childbearing potential had 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) Stopwatch was 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 medication 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 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 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 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 confound 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®, fentanyl, Demerol® (meperidine) and diazepam were exempt from this exclusion. Demerol® required a three-hour washout;
4. A history of chronic analgesic or tranquilizer use or known substance abuse within the last 90 days;
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 an investigational drug other than SC-58635 during the course of this study;
7. A known hypersensitivity to analgesics, 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 the upper limit of the reference range;
9. A history or current presence of nasal polyps, bronchospasm, or angioedema induced by NSAIDs; or
10. Previously admitted to this study.

Treatments Administered:

1. Celecoxib 25mg, 50 mg, and 200 mg capsules each identical in size and color;
2. Placebo capsules each identical in size and appearance to SC-58635 25 mg, 50 mg, and 200 mg capsules;
3. Encapsulated Motrin IB® (ibuprofen) 200 mg capsules;
4. Placebo capsules each identical in size and appearance to Motrin IB®.

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 ibuprofen, 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 first two hours following study drug administration; however, no foods or nutrient liquids were permitted during this time period. 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 0.25, 0.50, 0.75, 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)

RESULTS:

Disposition of Patients

Two hundred fifty (250) patients were enrolled in this study and were randomized to receive one of five treatments: 50 patients received celecoxib 25 mg, 50 patients received celecoxib 50 mg, 50 patients received celecoxib 200 mg, 50 patients received ibuprofen 400 mg, and 50 patients received placebo. These 250 patients constituted the ITT Cohort. Thirty six patients completed the 24 hour assessment period without taking rescue medication and completed the scheduled 24.0 hour assessments. Two hundred and fourteen patients took rescue medication during the 24 hour assessment period.

Baseline demographic characteristics are presented in Tables 3 and 4.
The treatment groups were comparable ($p \geq 0.182$) for age, race and gender. For all patients, the age range was 18 to 50 years ($p=0.269$). Across treatment groups, 20% to 42% of the patients were male ($p=0.182$) and 54% to 68% were Caucasian ($p=0.266$). All treatment groups were comparable ($p \geq 0.098$) with respect to height, weight, and vital signs at baseline.

TABLE 3
BASELINE DEMOGRAPHIC CHARACTERISTICS

	Placebo (N= 50)	Celecoxib 25mg (N= 50)	Celecoxib 50mg (N= 50)	Celecoxib 200mg (N= 50)	Ibuprofen 400mg (N= 50)	
AGE (years)						p- VALUE
N	50	50	50	50	50	0.269 (a)
MEAN	23.5	23.3	25.3	23.3	24.3	
STD DEV	4.80	5.72	6.04	4.88	5.48	
MEDIAN	22.0	22.0	24.0	22.0	24.0	
RANGE	18- 38	18- 46	18- 45	18- 46	18- 50	
<30	44(88%)	45 (90%)	42 (84%)	47 (94%)	45 (90%)	
30- 39	6 (12%)	4 (8%)	5 (10%)	2 (4%)	4 (8%)	
40- 49	0 (0%)	1 (2%)	3 (6%)	1 (2%)	0 (0%)	
50- 59	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (2%)	
60- 69	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%)	
RACE/ ETHNIC ORIGIN						0.266 (b)
ASIAN	0 (0%)	0 (0%)	3 (6%)	4 (8%)	2 (4%)	
BLACK	4 (8%)	3 (6%)	5 (10%)	2 (4%)	1 (2%)	
CAUCASIAN	27 (54%)	32 (64%)	34 (68%)	27 (54%)	32 (64%)	
HISPANIC	18 (36%)	14 (28%)	8 (16%)	17 (34%)	15 (30%)	
OTHER	1 (2%)	1 (2%)	0 (0%)	0 (0%)	0 (0%)	
TOTAL	50 (100%)	50 (100%)	50 (100%)	50 (100%)	50 (100%)	
GENDER						0.182 (b)
FEMALE	29 (58%)	32 (64%)	31 (62%)	33 (66%)	40 (80%)	
MALE	21 (42%)	18 (36%)	19 (38%)	17 (34%)	10 (20%)	
TOTAL	50 (100%)	50 (100%)	50 (100%)	50 (100%)	50 (100%)	

(a) One- Way Analysis of Variance

TABLE 4
ADDITIONAL BASELINE VARIABLES

	Placebo (N= 50)	Celecoxib 25mg (N= 50)	Celecoxib 50mg (N= 50)	Celecoxib 200mg (N= 50)	Ibuprofen 400mg (N= 50)	p- VALUE (a)
HEIGHT (cm)						0.448
N	50	50	50	50	50	
MEAN	168.96	169.68	170.68	168.78	167.19	
STD DEV	9.403	9.649	8.911	9.337	9.777	
MEDIAN	170.20	168.90	170.20	167.60	167.00	
RANGE						
WEIGHT (kg)						0.739
N	50	50	50	50	50	
MEAN	71.22	68.07	71.94	69.64	68.60	
STD DEV	16.579	16.234	17.693	17.610	15.112	
MEDIAN	66.85	65.00	66.80	66.35	65.00	
RANGE						

(a) One-way Analysis of Variance

Summary of Dental Surgery

The degree of impaction and Baseline pain intensity were comparable ($p \geq 0.217$) across all treatment groups. The celecoxib 200 mg group and the ibuprofen 400 mg group had a numerically greater number of patients with severe surgical trauma (50%-54%) than the other groups (30%). This difference between groups was statistically significant ($p=0.015$). However, since the Baseline pain intensity values were numerically similar and did not differ statistically across all groups, this difference in surgical trauma was not considered clinically relevant. All treatment groups were comparable with respect to number of molars extracted ($p=0.927$, categorical and $p=0.756$, continuous).

All treatment groups were comparable with respect to time from surgery until taking study medication and Baseline pain intensity on the VAS ($p \geq 0.281$). Mean pain intensity across treatment groups was 59.8 to 63.6 (0 to 100 scale) and mean time until taking study medication was 2:27 to 2:38 hours after surgery.

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 200 mg, 50 mg, and 25 mg treatment groups were numerically better than placebo at all assessment times from the 0.5 hour through 24.0 hours postdose (except for the 25 mg treatment arm, up to 4 hours). However, these differences from placebo were statistically significant for the celecoxib 200 mg treatment group at the 1.0 hour through 9.0 hour assessments, for the celecoxib 50 mg treatment group at the 0.75 hour through 9.0 hour postdose assessments, and for the celecoxib 25 mg treatment group at the 1.0, 1.5 and 2.0 hour assessments.

Within celecoxib treatment groups, the mean PID scores for the celecoxib 200 mg group were numerically better than mean scores for the celecoxib 25 mg treatment group at the 0.75 through 24.0 hour assessment times and numerically greater than mean scores for the celecoxib 50 mg treatment group at the 1.5 hour through 24.0 hour postdose assessments. The mean PID scores for the celecoxib 50 mg treatment group were numerically better than mean scores for the celecoxib 25 mg group at the 0.25 through 24.0 hour assessment times. The mean PID scores for the celecoxib 50 mg treatment group were numerically better than the scores for the celecoxib 200 mg treatment group at the 0.25, 0.5, 0.75 and 1.0 hour postdose assessments. The mean PID scores for the 200 mg group were statistically significantly better than the 25 mg group mean PID scores at the 2.0 hour through 9.0 hour postdose assessments. The mean PID scores for the celecoxib 50 mg group were statistically significantly better than the scores for the 25 mg group at the 1.0 hour postdose assessment.

The mean PID scores for the ibuprofen 400 mg group were numerically better than the placebo group at all postdose assessment times and this difference was statistically significant at the 0.75 hour through 8.0 hour assessments. The mean PID scores for the ibuprofen 400 mg group were generally numerically better than the scores for all celecoxib groups. The mean PID scores for the ibuprofen 400 mg group were statistically significantly better than the celecoxib 200 mg group at the 0.75 hour through 4.0 hour postdose assessments, the celecoxib 50mg group at the 0.75 hour through 7.0 hour postdose assessments and the celecoxib 25 mg group at the 0.75 hour through 8 hour postdose assessments. The celecoxib 200 mg group had numerically better scores than the ibuprofen 400 mg group at the 8.0 through 24.0 hour postdose assessments but these differences were not statistically significant.

There was a statistically significant gender effect from 0.5 hour through 1.5 hours; however, further analysis showed that gender by treatment interaction was not significant, therefore treatment comparisons are valid.

Table 9 – Pain Intensity Difference
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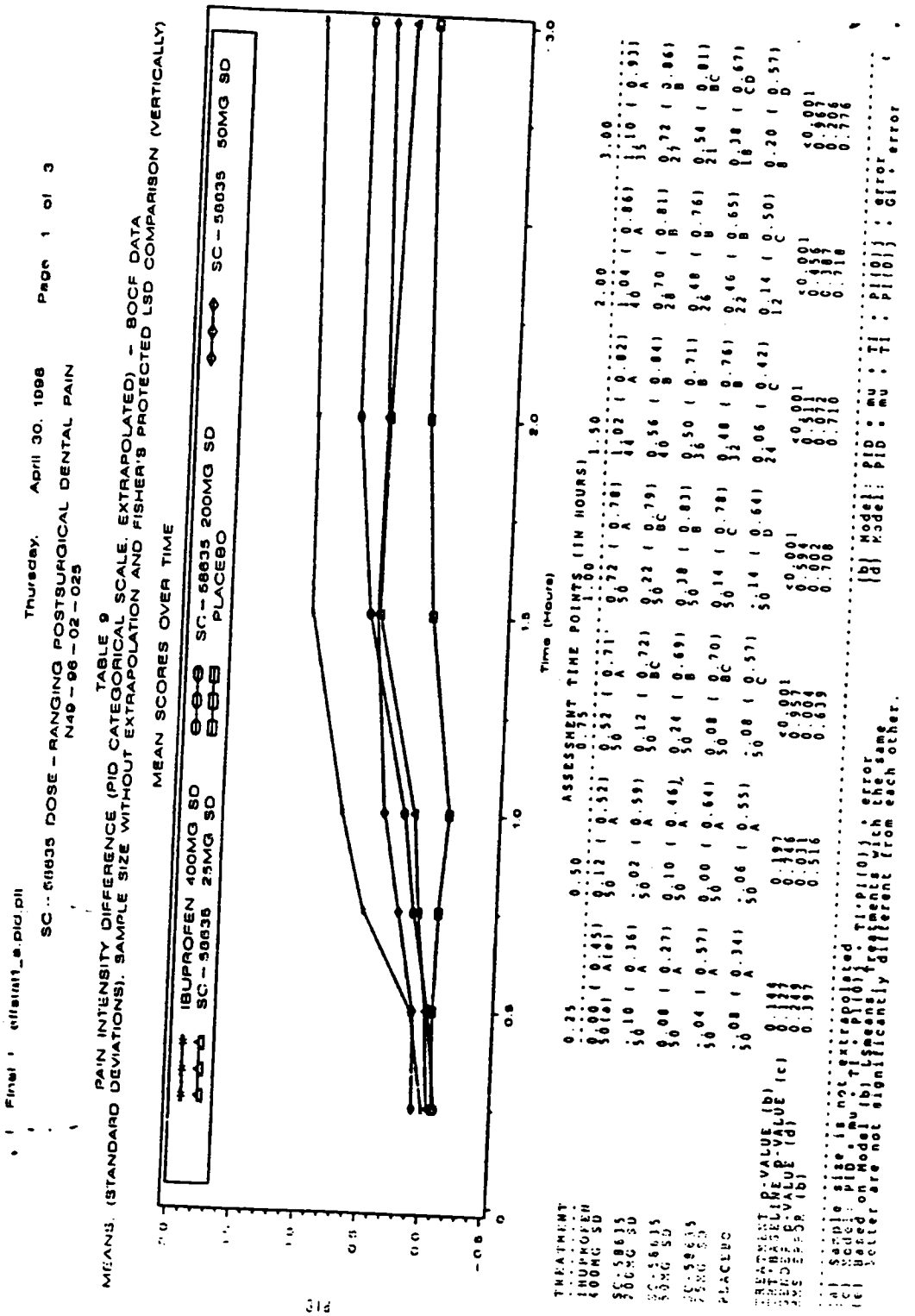

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SC-58635 DOSE-RANGING POSTSURGICAL DENTAL PAIN
N49-96-02-025
TABLE 9
PAIN INTENSITY DIFFERENCE (PID CATEGORICAL SCALE, EXTRAPOLATED) - BOCF DATA (CONTINUED)
MEANS, (STANDARD DEVIATIONS), SAMPLE SIZE WITHOUT EXTRAPOLATION AND FISHER'S PROTECTED LSD COMPARISON (VERTICALLY)
MEAN SCORES OVER TIME
IBUPROFEN 400MG SD
SC-58635 25MG SD
SC-58635 200MG SD
PLACEBO
SC-58635 50MG SD
Time (Hours)
ASSESSMENT TIME POINTS (IN HOURS)
TREATMENT
TREATMENT P-VALUE (b)
TRT*BASELINE P-VALUE (c)
GENDER P-VALUE (d)
RMS ERROR (b)
(a) Sample size is not extrapolated
(b) Model: PID = mu + TI + P1(01) + error
(c) Based on Model (b) LSmeans treatments with the same
letter are not significantly different from each other.
(d) Model: PID = mu + TI + P1(01) + GI + error

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SC-58635 DOSE-RANGING POSTSURGICAL DENTAL PAIN
N49-96-02-025
TABLE 9
PAIN INTENSITY DIFFERENCE (PID CATEGORICAL SCALE, EXTRAPOLATED) - BOCF DATA (CONTINUED)
MEANS, (STANDARD DEVIATIONS), SAMPLE SIZE WITHOUT EXTRAPOLATION AND FISHER'S PROTECTED LSD COMPARISON (VERTICALLY)
MEAN SCORES OVER TIME
IBUPROFEN 400MG SD
SC-58635 25MG SD
SC-58635 200MG SD
PLACEBO
SC-58635 50MG SD
PID
Time (Hours)
11.00 ASSESSMENT TIME POINTS 24.00 (IN HOURS)
TREATMENT
IBUPROFEN 400MG SD
SC-58635 200MG SD
SC-58635 50MG SD
SC-58635 25MG SD
PLACEBO
TREATMENT P-VALUE (b)
PRE-BASELINE P-VALUE (c)
GENDER P-VALUE (d)
RMS ERROR (b)
(a) Sample size is not extrapolated
(c) Model: PID = mu + TI + PI(0) + error
Letter are not significantly different from each other.
(b) Model: PID = mu + TI + PI(0) + GI + 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 all dose levels of celecoxib were numerically better than the mean scores for placebo at the 0.5 through 12.0 hour assessment times. This difference was statistically significant for the celecoxib 200 mg treatment group for the 0.75 hour through 9.0 hour assessments; for the celecoxib 50 mg treatment group for the 1.0 hour through 4.0 hour assessments; and for the celecoxib 25 mg treatment group at the 1.0, 1.5 and 2.0 hour assessments.

At all assessment times during the 24 hour Treatment Period, the mean PR scores were numerically better with increasing doses of celecoxib. The mean PR scores for the celecoxib 200 mg treatment group were statistically significantly better than the mean PR scores for the 50 mg treatment group at the 2.0, 3.0, 5.0, and 6.0 hour assessments and the 25 mg treatment group at the 2.0 hour through 9 hour assessments. The difference between the mean PR scores for the celecoxib 50 mg and 25 mg treatment groups were not statistically significant at any assessment time during the 24 hour Treatment Period.

The mean PR scores for the ibuprofen 400 mg treatment group were numerically better than placebo at all assessment times during the 24 hour Treatment Period and this difference was statistically significant at the 0.75 hour through 9 hour assessments. With the exception of the celecoxib 200 mg treatment group which had numerically, but not statistically significant, better mean PR scores at the 8.0 hour through 24.0 hour assessments, the mean PR scores for the ibuprofen 400 mg treatment group were numerically better than the scores for all celecoxib treatment groups at all assessment times. This difference was statistically significant at the 0.75 through 3.0 hour assessments compared to all celecoxib dose levels and at the 4.0 hour through 7.0 hour assessments compared to the celecoxib 50 mg and 25 mg treatment groups. The difference between ibuprofen 400 mg treatment group and the celecoxib 25 mg treatment group continued to be statistically significantly different at the 9.0 hour assessment.

There was a statistically significant difference in gender effect at the 0.75 and 1.5 hour assessments, but further analysis did not indicate any effect of gender on the treatment comparisons.

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SC-58635 DOSE-RANGING POSTSURGICAL DENTAL PAIN
N40-00-02-025

TABLE 10
PAIN RELIEF (PR EXTRAPOLATED) - - GOCF DATA
SAMPLE SIZE WITHOUT EXTRAPOLATION AND FISHER'S PROTECTED LSD COMPARISON (VERTICALLY)

MEAN SCORES OVER TIME

IBUPROFEN 400MG SD
SC-58635 25MG SD
SC-58635 200MG SD
PLACEBO
SC-58635 50MG SD

Time (Hours)

MEANS (STANDARD DEVIATIONS), SAMPLE SIZE WITHOUT EXTRAPOLATION AND FISHER'S PROTECTED LSD COMPARISON (VERTICALLY)

TREATMENT	ASSESSMENT TIME POINTS (IN HOURS)								
	0.25	0.50	0.75	1.00	1.50	2.00	3.00		
IBUPROFEN 400MG SD	0.30 (0.51) A	0.66 (0.83) A	1.22 (1.00) A	1.64 (1.16) A	2.04 (1.38) A	2.18 (1.45) A	2.18 (1.62) A		
SC-58635 25MG SD	0.24 (0.48) A	0.52 (0.65) A	0.84 (0.91) B	1.02 (0.98) B	1.44 (1.22) B	1.58 (1.60) B	1.58 (1.65) B		
SC-58635 200MG SD	0.20 (0.45) A	0.44 (0.61) A	0.72 (0.99) BC	0.98 (1.19) B	1.14 (1.20) B	1.00 (1.32) C	1.02 (1.39) C		
SC-58635 50MG SD	0.20 (0.49) A	0.44 (0.58) A	0.58 (0.78) BC	0.78 (0.86) B	1.00 (1.18) B	0.94 (1.22) C	0.72 (1.14) CD		
PLACEBO	0.22 (0.46) A	0.34 (0.66) A	0.42 (0.70) C	0.38 (0.67) C	0.36 (0.72) C	0.30 (0.79) D	0.40 (0.99) D		
TREATMENT P-VALUE (a)	0.836	0.133	<0.001	<0.001	<0.001	<0.001	<0.001		
ERROR P-VALUE (b)	0.439	0.625	0.018	0.067	0.020	0.226	0.225		
			0.885	0.989	1.194	1.309	1.386		

(a) Sample size is not extrapolated
(b) Model: PR = mu + TI + error
(c) Based on Model (b) LSmeans Treatments with the same letter are not significantly different from each other.

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SC-58635 DOSE-RANGING POSTSURGICAL DENTAL PAIN
N49-98-02-025
TABLE 10
PAIN RELIEF (PR EXTRAPOLATED) - - BOCF DATA (CONTINUED)
MEANS, (STANDARD DEVIATIONS), SAMPLE SIZE WITHOUT EXTRAPOLATION AND FISHER'S PROTECTED LSD COMPARISON (VERTICALLY)
MEAN SCORES OVER TIME
IBUPROFEN 400MG SD
SC-58635 25MG SD
SC-58635 200MG SD
PLACEBO
SC-58635 50MG SD
Time (Hours)
TREATMENT
IBUPROFEN 400MG SD
SC-58635 200MG SD
SC-58635 50MG SD
SC-58635 25MG SD
PLACEBO
TREATMENT P-VALUE (b)
GENDER P-VALUE (d)
RMS ERROR (b)
(a) Sample size is not extrapolated
(b) Model: PR = AU + TI + GJ + error
(d) Model: PR = AU + TI + error
Based on Model (b) LS-means.
Letter are not significantly different from each other.

Table 10 – Pain Relief
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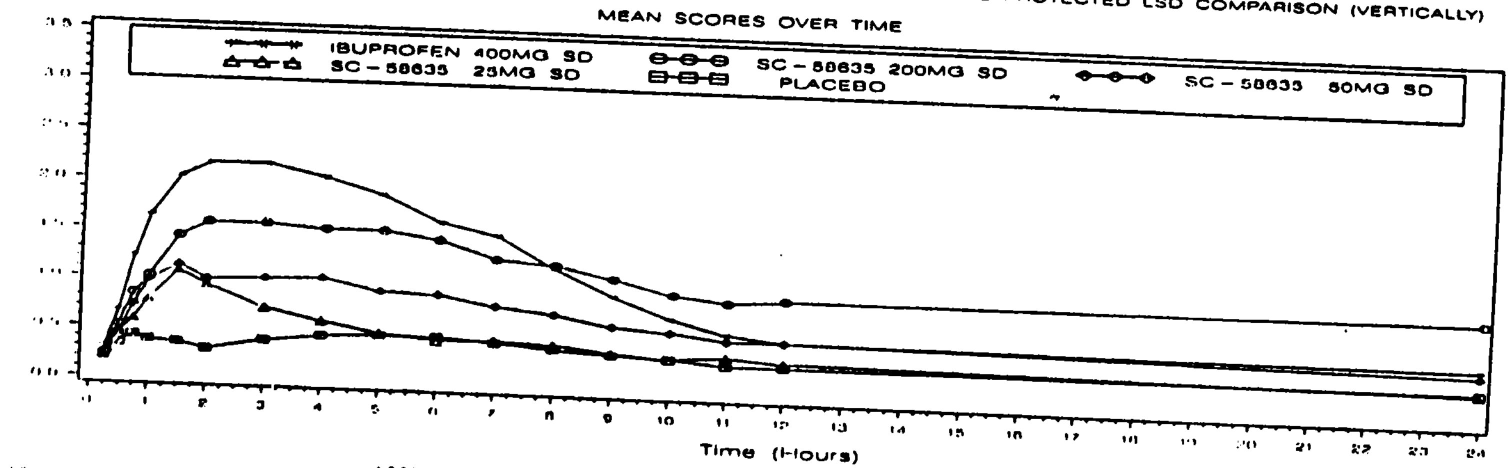
SC – 58635 DOSE – RANGING POSTSURGICAL DENTAL PAIN
N49 – 96 – 02 – 025

TABLE 10
PAIN RELIEF (PR EXTRAPOLATED) – – BOCF DATA (CONTINUED)
MEANS, (STANDARD DEVIATIONS), SAMPLE SIZE WITHOUT EXTRAPOLATION AND FISHER'S PROTECTED LSD COMPARISON (VERTICALLY)



TREATMENT	ASSESSMENT TIME POINTS (IN HOURS) 11.00	12.00	24.00
IBUPROFEN 400MG SD	0.60 (1.29) 10(a) A(d)	0.54 (1.16) 10 A	0.52 (1.22) 9 AB
SC-58635 400MG SD	0.92 (1.58) 15 A	0.96 (1.60) 14 A	0.98 (1.70) 13 A
SC-58635 [illegible] SD	0.54 (1.22) 9 A	0.54 (1.22) 9 A	0.46 (1.18) 9 B
SC-58635 [illegible] SD	0.38 (1.07) 6 A	0.36 (1.04) 6 A	0.28 (0.97) 4 B
PLACEBO	0.30 (1.04) 4 A	0.30 (1.04) 4 A	0.30 (1.04) 4 B
TREATMENT P-VALUE (b)	0.122	0.065	0.038
GENDER P-VALUE (d)	0.448	0.360	0.750
MS ERROR (b)	1.253	1.230	1.246

(a) Sample size is not extrapolated
(c) [illegible]: PR = mu + TI + G) + error
(b) Model: PR = mu + 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 all the celecoxib treatment groups were numerically better than placebo at all assessment times after the 0.25 hour assessment. This difference was statistically significant for the celecoxib 200 mg treatment group at the 0.75 hour through 24.0 hour assessments and for the celecoxib 50 mg treatment group at the 0.75 hour through 10.0 hour assessments. The celecoxib 25 mg treatment group had statistically significantly better mean PRID scores than placebo at 1.0, 1.5 and 2.0 hour postdose assessments.

At all assessment times during the 24 hour Treatment Period, the mean PRID scores were numerically better with increasing doses of celecoxib. The mean PRID scores for the celecoxib 200 mg treatment group were not statistically significantly better than the mean PRID scores for the 50 mg treatment group at all times and the 25 mg treatment group at the 2.0 hour through 8 hour assessments. The difference between the mean PRID scores for the celecoxib 50 mg and 25 mg treatment groups were not statistically significant at any assessment time during the 24 hour Treatment Period.

The mean PRID scores for the ibuprofen 400 mg treatment group were numerically better than placebo at all assessment times during the 24 hour Treatment Period. This difference was statistically significant compared to the placebo at the 0.75 hour through 24.0 hour assessments. The mean PRID scores for the ibuprofen 400 mg treatment group were statistically significantly better than the mean scores for the celecoxib 200 mg treatment group at the 0.75 hour through 4.0 hour assessments, the celecoxib 50 mg treatment group at the 0.75 hour through 7.0 hour assessments, and the celecoxib 25 mg treatment group at the 0.75 hour through 10.0 hour assessments.

There was a statistically significant gender effect at the 0.75, 1.0 and 1.5 hour assessments, but further analysis did not indicate any effect of gender on the treatment comparisons.

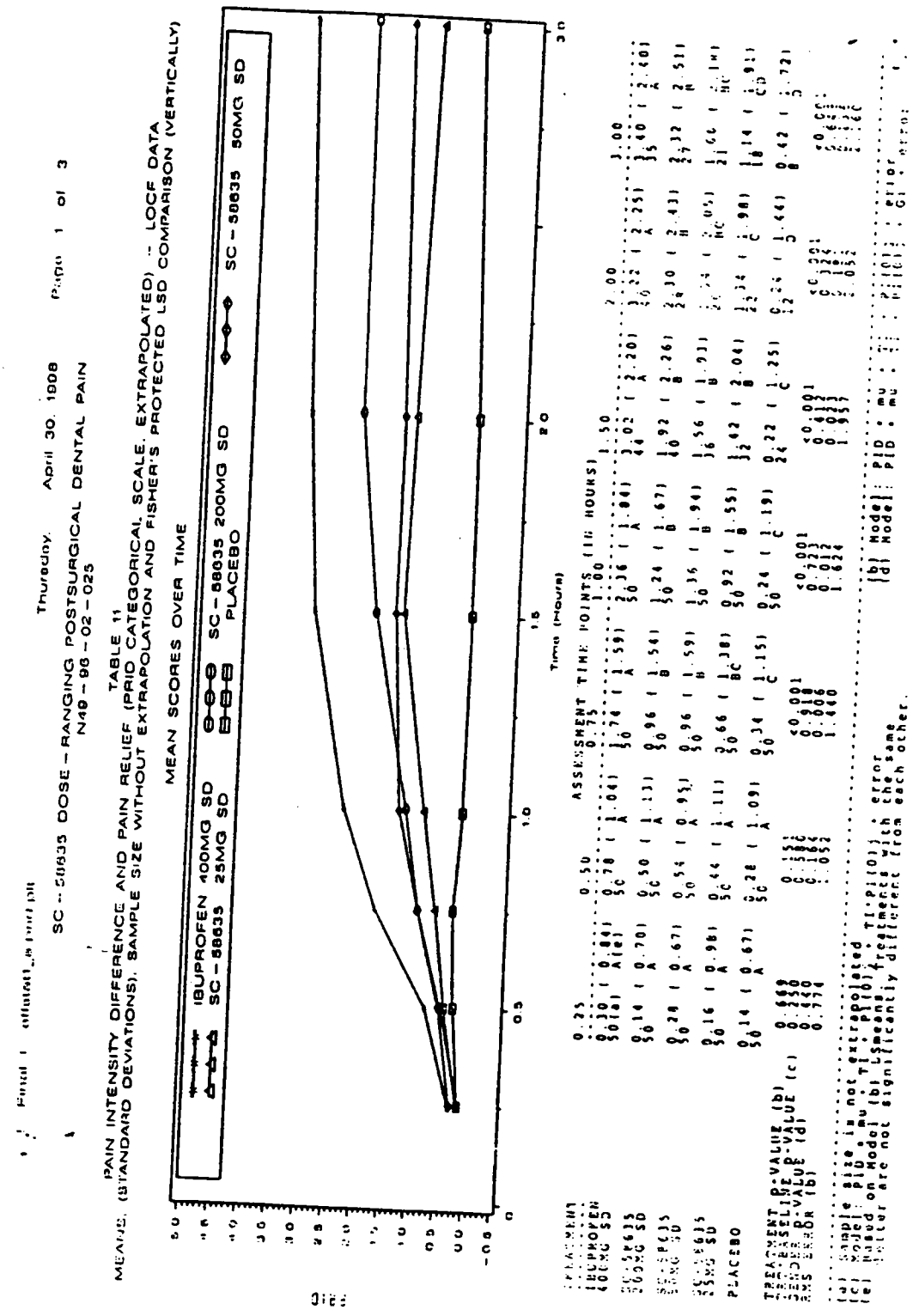

SC - 58635 DOSE - RANGING POSTSURGICAL DENTAL PAIN
N49 - 96 - 02 - 025
TABLE 11
PAIN INTENSITY DIFFERENCE AND PAIN RELIEF (PRID CATEGORICAL SCALE, EXTRAPOLATED) - LOCF DATA
MEANS, (STANDARD DEVIATIONS), SAMPLE SIZE WITHOUT EXTRAPOLATION AND FISHER'S PROTECTED LSD COMPARISON (VERTICALLY)
MEAN SCORES OVER TIME
IBUPROFEN 400MG SD
SC - 58635 25MG SD
SC - 58635 200MG SD
PLACEBO
SC - 58635 50MG SD
Time (Hours)
ASSESSMENT TIME POINTS (IN HOURS)
TREATMENT
IBUPROFEN 400MG SD
SC-58635 25MG SD
SC-58635 50MG SD
PLACEBO
TREATMENT P-VALUE (b)
PAIRWISE P-VALUE (c)
TIME P-VALUE (d)
(a) Sample size is not extrapolated
(c) Based on Model (b) Least squares means
(e) Letter are not significantly different from each other.

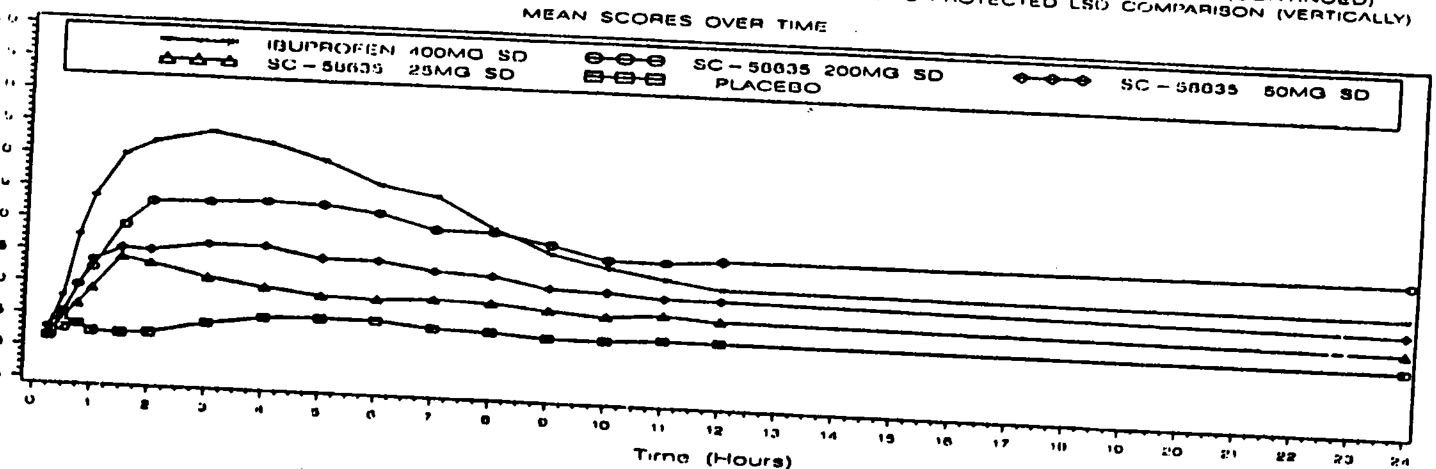
Table 11 - Pain Intensity Difference and Pain Relief (PRID)

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

SC - 58635 DOSE - RANGING POSTSURGICAL DENTAL PAIN
N49 - 96 - 02 - 025

TABLE 11
PAIN INTENSITY DIFFERENCE AND PAIN RELIEF (PRID CATEGORICAL SCALE, EXTRAPOLATED) - LOCF DATA (CONTINUED)
MEANS (STANDARD DEVIATIONS), SAMPLE SIZE WITHOUT EXTRAPOLATION AND FISHER'S PROTECTED LSD COMPARISON (VERTICALLY)

MEAN SCORES OVER TIME



TREATMENT	ASSESSMENT TIME POINTS (IN HOURS) 11.00	12.00	24.00
IBUPROFEN 400MG SD	1.40 (1.87) 10(a) AB(e)	1.28 (1.64) 1C AB	1.26 (1.75) 7 AB
SC-58635 200MG SD	1.66 (2.34) 15 A	1.72 (2.38) 14 A	1.78 (2.52) 13 A
SC-58635 50MG SD	1.10 (1.92) 9 ABC	1.10 (1.92) 9 ABC	1.00 (1.88) 7 BC
SC-58635 25MG SD	0.84 (1.72) 6 BC	0.78 (1.69) 6 BC	0.72 (1..31) 4 BC
PLACEBO	0.44 (1.90) 4 C	0.44 (1.90) 4 C	0.44 (1.90) 4 C
TREATMENT P-VALUE (b)	0.011	0.009	0.006
TRT*BASELINE P-VALUE (c)	0.626	0.512	0.421
GENDER P-VALUE (d)	0.159	0.122	0.269
RMS ERROR (b)	1.951	1.917	1.950

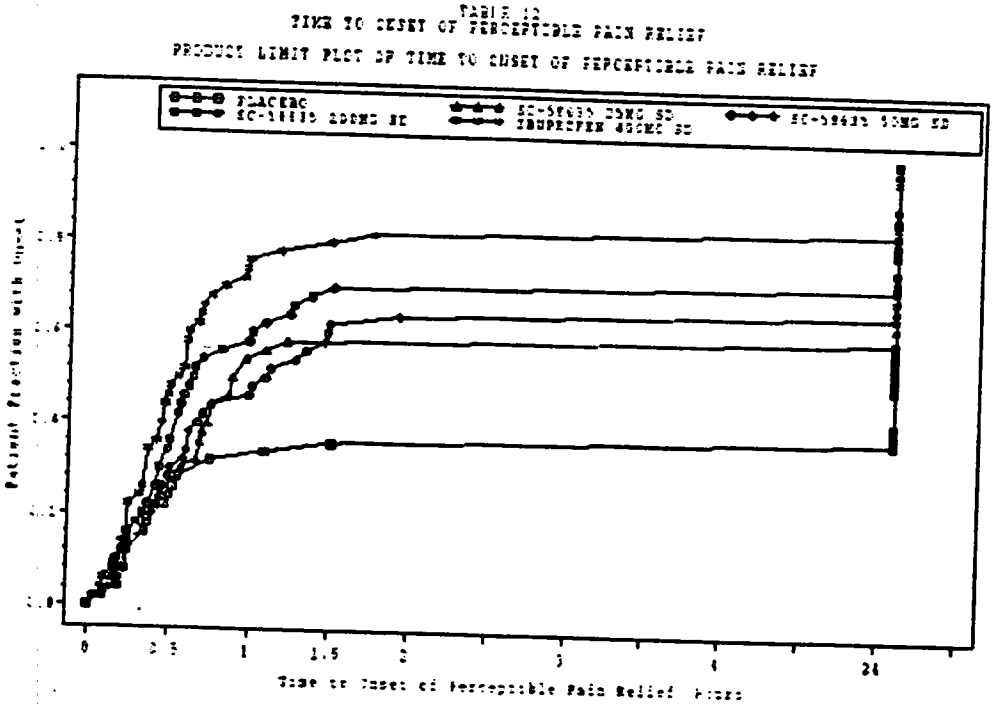
(a) Sample size is not extrapolated
(b) Model: PID = mu + TI + PI(0) + error
(c) Model: PID = mu + TI + PI(0) + TI*PI(0) + error
(d) Model: PID = mu + TI + PI(0) + GI + error
(e) Based on Model (b) LSmeans. Treatments with the same letter are not significantly different from each other.

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. Forty-one (82%) of the patients in the ibuprofen 400 mg treatment group, 35 (70%) of the patients in the celecoxib 200 mg treatment group, 32 (64%) of the patients in the celecoxib 50 mg treatment group, and 29 (58%) of the patients in the celecoxib 25 mg treatment group experienced Perceptible Pain Relief. Only 18 (36%) of the patients in the placebo treatment group reported experiencing 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 celecoxib 200 mg (38 minutes), 50 mg (1 hour and 5 minutes) and 25 mg (53 minutes) were shorter than the median time for placebo (>24 hours).

The median time to Onset of Perceptible Pain Relief was comparable for the ibuprofen 400 mg treatment group (33 minutes) and the celecoxib 200 mg treatment group and numerically shorter than the median time for the celecoxib 50 and 25 mg treatment groups. The differences between the ibuprofen 400 mg dose groups and the celecoxib 50 mg, celecoxib 25 mg, and placebo groups in the distribution of patients over time who experienced perceptible pain relief were statistically significant based on the log rank test.



Time to Rescue Medication

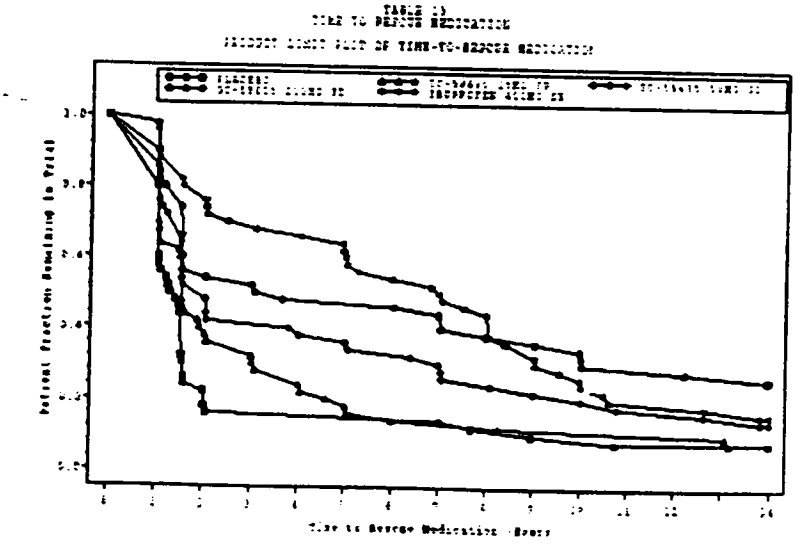
Table 13 presents the median times to administration of rescue medication for all treatment groups and a product limit plot of the individual times for each treatment group.

Thirty-seven (74%) patients in the celecoxib 200 mg treatment group took rescue medication as compared with 42 (84%) patients in the ibuprofen 400 mg treatment group, 43 (86%) patients in celecoxib 50 mg treatment group and 46 (92%) patients in the celecoxib 25 mg treatment group and the placebo treatment group.

The median times to rescue medication for the celecoxib 200 mg group (3 hours and 5 minutes); the celecoxib 50 mg group (1 hour and 48 minutes); the celecoxib 25 mg group (1 hour and 32 minutes) were longer than the median time to rescue medication for the placebo group (1 hour and 17 minutes). The differences between the celecoxib 200 mg and 50 mg groups as compared to placebo in the distribution of patients over time who took rescue medication was statistically significant based on the log rank test. Within the celecoxib treatment groups, these differences were statistically significant only for the celecoxib 200 mg group as compared to the celecoxib 25 mg group.

The median time to administration of rescue medication for the ibuprofen 400 mg treatment group (seven hours) was more than twice as long as for placebo or any celecoxib treatment group (see table).

TRAETMENT	Median Time to Remedication (H : MIN)
Ibuprofen 400 mg	7:00
Celecoxib 200 mg	3:05
Celecoxib 50 mg	1:48
Celecoxib 25 mg	1:32
Placebo	1:17



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

Mean Pain Intensity Difference Scores Over Time - Visual Analog Scale

The mean PID (VAS) scores generally paralleled those of the categorical scale scores. Ibuprofen 400 mg was statistically significant superior to celecoxib 200 mg through the first 4 hours, 50 mg through the first 8 hours, an 25 mg and the placebo through the first 9 hours. Celecoxib 200 mg was as effective as 50 mg and they were both superior to the 25 mg and the placebo.

Peak Pain Intensity Difference, Sum of Pain Intensity Difference, Peak Pain Relief, Sum of Pain Relief, Sum of Pain Relief Intensity Difference for First Six Hours, and Patient Global Evaluation

The ibuprofen 400 mg treatment group had numerically higher mean scores than placebo for all measures, and these differences were statistically significant for all measures. The ibuprofen 400 mg treatment group had numerically higher mean scores than the celecoxib treatment groups for all measures. With the exception of the PPR and TOTPAR for the celecoxib 200 mg treatment group, these differences in scores were statistically significant.

For all the measures, the celecoxib treatment groups had numerically greater mean scores than placebo and the scores increased with increasing dose levels of celecoxib. These differences were statistically significant for the celecoxib 200 mg treatment group for all measures and for the celecoxib 50 mg treatment group for all measures except Patient Global Evaluation as compared to placebo. For all measured values, the celecoxib 200 mg treatment group had numerically better scores than the celecoxib 50 mg and 25 mg treatment groups. The difference was not statistically significant when compared with the celecoxib 50 mg treatment group except for the 6.0 hour TOTPAR. This difference was statistically significant for all measured values except PPID (categorical) when compared with the celecoxib 25 mg treatment group.

Time to Meaningful Pain Relief

Thirty-seven (74%) of the patients in the ibuprofen 400 mg treatment group, 27 (54%) of the patients in the celecoxib 200 mg treatment group, 23 (46%) of the patients in the celecoxib 50 mg treatment group, and 21 (42%) of the patients in the celecoxib 25 mg treatment group experienced Meaningful Pain Relief. Nine (18%) of the patients in the placebo 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).

Median times to Meaningful Pain Relief were:

TRAETMENT	Median Time (H : MIN)
Ibuprofen 400 mg	1:01
Celecoxib 200 mg	1:55
Celecoxib 50 mg	> 24:00
Celecoxib 25 mg	> 24:00
Placebo	>24:00

The median Time to Meaningful Pain Relief for the ibuprofen 400 mg treatment group was numerically shorter than that for the celecoxib and placebo treatment groups. The differences between the ibuprofen 400 mg group and the celecoxib 200 mg, celecoxib 50 mg, celecoxib 25 mg, and placebo groups in the distribution of patients over time who experienced meaningful pain relief were statistically significant based on the log rank test.

Pain Half Gone

The celecoxib 200 mg treatment group had a statistically significant shorter median Time to 50% Pain Relief (2.0 hours) as compared with placebo (>24 hours) in the distribution of patients over time for the time first experienced 50% pain relief were based on the log rank test. However, the median Time to 50% Pain Relief for the ibuprofen 400 mg treatment group (one hour and one minute) was statistically significant shorter than the median times for placebo, and the SC-58635 200 mg, SC-58635 50 mg and SC-58635 25 mg treatment groups in the distribution of patients over time based on the log rank test.

The celecoxib 200 mg and 50 mg treatment groups had a statistically significant better percentages of patients experiencing at least 50% pain relief trough 8 and 3 hours respectively. The percentages of patients experiencing at least 50% pain relief in ibuprofen 400 mg and celecoxib 200 mg treatment groups did not differ statistically significantly at any time point, except at the one hour assessment (52% vs. 20%).

Safety Results

Overall, 110 (44%) of the 250 patients who completed the study reported one or more adverse events during the study. Adverse events were reported by 20 (40%) of the placebo patients; 23 (46%) of the patients receiving celecoxib 25 mg; 20 (40%) of the patients receiving celecoxib 50 mg; 24 (48%) of the patients receiving celecoxib 200 mg; and 23 (46%) of the patients receiving ibuprofen 400 mg. No patients withdrew from the study as a result of an adverse event.

The adverse events reported by the greatest number of patients (≥5%) in one or more of the celecoxib treatment groups were alveolar osteitis (dry socket), nausea, dizziness, tooth disorder, vomiting, and headache. 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 or clinically significant changes in vital signs either across treatment groups or within treatment groups ($p \geq 0.098$).

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

Discussion and Overall Conclusions for Study # 025

The results of this study demonstrate that, for all primary (PID, PR, PRID, Time to Perceptible Pain Relief, Time to Rescue Medication) and secondary (Time-Specific PID VAS, PPID, Peak Pain Relief, Time to Meaningful Pain Relief, Time to 50% Pain Relief, Percent of Patients Experiencing at Least 50% Pain Relief, Patient Global Evaluation, and the 6, 8,10, 12, and 24 hour SPID, TOTPAR, and SPRID) measures of efficacy, single oral doses of celecoxib at dose levels of 25 mg, 50 mg and 200 mg provided greater relief from moderate to severe postoperative dental pain than placebo. The celecoxib 200 mg dose level demonstrated significantly greater analgesic efficacy as compared to the celecoxib 50 mg, 25 mg and placebo treatments.
Ibuprofen 400 mg was statistically significant better in all scores compared to all dose groups of celecoxib.

No major safety issues have been demonstrated.