CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-998

MEDICAL REVIEW(S)

MEDICAL OFFICER REVIEW
ANTI-INFLAMMATORY, ANALGESIC AND OPHTHALMIC DRUG
PRODUCTS DIVISION—HFD-550

NDA #:	**20,998**
SUBMISSION DATE:	July 8, 1998
REVIEWER:	Mordechai Averbuch, MD
PRODUCT:	**CELEBREX® (Celecoxib)**
REVIEW DATE:	October 22, 1998
SPONSOR:	G.D. Searle & Co. 4901 Searle Parkway Skokie, Illinois 60077 Phone (847) 982-7000
PHARMACOLOGICAL CATEGORY:	COX 2 Selective Inhibitor, Anti-inflammatory
PROPOSED INDICATIONS:	1) Acute or chronic use in the treatment of the signs and symptoms of osteoarthritis and rheumatoid arthritis. 2) Management of pain.
DOSAGE FORM & ROUTE:	Oral capsules, 100mg and 200mg
CSO:	V. Lutwak

ATTENTION:

This review is for the section of this NDA submitted to support the indication of the management of pain only. Studies supporting the indication of acute or chronic use in the treatment of the signs and symptoms of osteoarthritis and rheumatoid arthritis, as well as other clinical studied conducted to support the safety profile of celecoxib, are being reviewed by other medical reviewers.

RESUME:

Six clinical trials have been conducted to support the management of pain indication.
Four single dose, post third molar extraction studies, three of them are considered to be pivotal.
Two multiple dose, 3-5 day, post general and orthopedic surgery studies, one of them is considered to be pivotal.
In three OA studies pain was measured at bedtime on days one through seven and the sponsor is claiming this data to support the treatment of acute pain indication.

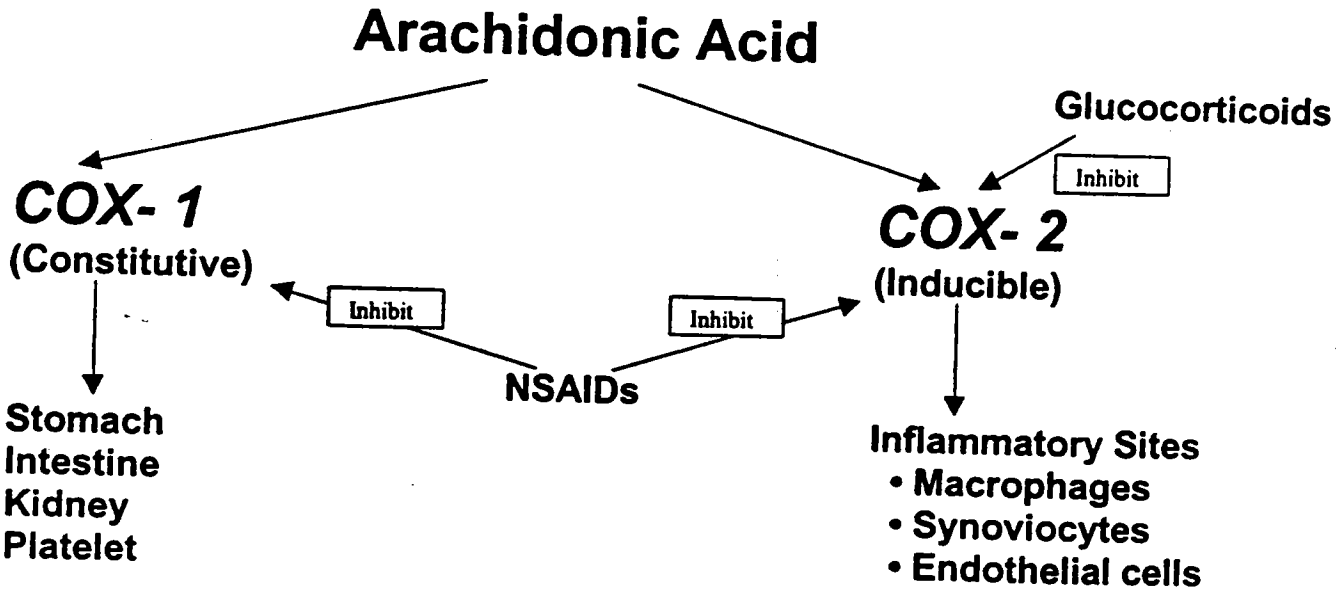
Table of Contents

Listing of Tables

INTRODUCTION:

Currently, the class of agents most commonly used for anti-inflammatory and analgesic conditions is the nonsteroidal anti-inflammatory drugs (NSAIDs). Although the mechanism by which NSAIDs achieve their effect is not completely understood, they are known to inhibit the activity of the enzyme cyclooxygenase (COX), which mediates conversion of arachidonic acid to the prostaglandins that serve as key components of inflammatory processes. However, prostaglandins are also needed to maintain normal gastrointestinal and platelet function, as well as renal function under physiologically stressed conditions. Thus, the anti-inflammatory and analgesic benefits of NSAID therapy are tempered by an increased risk of gastrointestinal ulceration and ulcer complications (such as bleeding, perforation, and gastric outlet obstruction), hemorrhagic diathesis, and nephrotoxicity. Recently, two distinct isoforms of COX were identified and designated COX-1 and COX-2. COX-1 is constitutively expressed in most tissues throughout the body, including the gastrointestinal tract, kidney, and platelets. COX-2, a cytokine-inducible enzyme, is normally found in very low amounts in healthy tissue (except the brain and kidney) but is prominently expressed in inflamed tissues. It is particularly noteworthy that COX-2 is not expressed in platelets or the gut. Studies of recombinant enzymes in vitro and in cell lines have demonstrated that as a class, NSAIDs nonselectively inhibit the activity of both COX-1 and COX-2 (figure).

Figure: Roles of COX-1 and COX-2 in Physiologic and Pathophysiologic Functions.



These findings gave rise to the hypothesis that the gastrointestinal, platelet, and renal toxicity of NSAIDs results from inhibition of COX-1, while their therapeutic benefit is a function of inhibition of COX-2. Evidence supporting this hypothesis has been provided by studies showing that:

- COX-2 expression is up-regulated by inflammatory mediators such as cytokines and bacterial endotoxin;
- up-regulation of COX-2 expression is blocked by anti-inflammatory glucocorticoids, which do not alter COX-1 expression; and
- in animals, selective inhibition of COX-2 is anti-inflammatory and analgesic, but cause less gastroduodenal toxicity.

In contrast, NSAIDs, which nonselectively inhibit both COX-1 and COX-2, cause pronounced gastrointestinal toxicity and interfere with platelet function at therapeutic doses.

Celecoxib is a novel compound that selectively inhibits cyclooxygenase 2 and is being developed as an oral anti-inflammatory and analgesic agent seeking the indications of: the treatment of the signs and symptoms of osteoarthritis (OA) and rheumatoid arthritis (RA), and for the management of pain.

INTEGRATED SUMMARY OF MEDICAL REVIEW

Summary of Clinical Studies Conducted in Patients with Postsurgical Pain

Six studies were conducted in patients with postsurgical pain, four in the dental pain model (025, 027, 070, 005) and two in the post orthopedic/general surgery model (028, 029,). Four of these studies are considered to be pivotal. However, only three of these studies (025, 027, and 070, all dental pain studies) provide substantial evidence of efficacy.

Studies 028 and 029 were multiple dose post general/orthopedic surgical pain studies. During the course of these trials, interim analyses (not included in the protocol) were conducted by an independent Data Monitoring Committee (DMC). 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". The DMC recommended that Study 028 be continued. They recommended that Study 029 be terminated because the active comparator (Darvocet-N) did not separate statistically from placebo; placebo response was unexpectedly high. Study 029 was terminated, at which time approximately 70% of the patients had been enrolled. Therefore the study results are not discussed in detail in this summary. However, the data is presented in the individual study review.

A seventh study (Study 080) enrolled only one patient when a decision was made to discontinue the study. The reason given was that the comparator selected (naproxen) was not considered to be suitable for that pain model, and is not included in the ISE.

A summary of these studies is provided in tables 1 and 2.

Summary of Clinical Studies Conducted in Patients with Postsurgical Pain:

Table 1: Post Oral Surgery - Single Dose

Protocol No. Report No. Short Title	Study Design	Treatment Regimen(s)	Results (Efficacy)
P: N49-96-02-025 R: N49-97-16-025 Dose-ranging Analgesic Efficacy in Postsurgical Dental Pain	Randomized, Double-Blind, Placebo-Controlled, Active Controlled, Parallel Group (single dose) ≥ 2 third molars	**Celecoxib** 25 mg (N=50), 50 mg (N=50), or 200 mg (N=50) **Ibuprofen** 400 mg (N=50) **Placebo** (N=50) Total N=250	Celecox.> Placebo Ibuprofen > Celecox
P: N49-97-02-027 R: N49-97-06-027 Analgesic Efficacy in Postsurgical Dental Pain	Randomized, Double-Blind, Placebo-Controlled, Active Controlled, Parallel Group (single dose) ≥ 2 third molars	**Celecoxib** 100 mg (N=55) or 200 mg (N=56) **Naproxen Sodium** 550 mg(N=54) **Placebo** (N=55) Total N=220	Celecox.> Placebo Naproxen > Celecox
P: N49-97-02-070 R: N49-97-06-070 Dose-response and Analgesic Efficacy in Postsurgical Dental Pain	Randomized, Double-Blind, Placebo-Controlled, Active Controlled, Parallel Group (single dose) ≥ 1 third molars	**Celecoxib** 50 mg (N=35), 100 mg (N=50), 200 mg (N=50), or 400 mg (N=35) **Naproxen Sodium** 550 mg (N=35) **Placebo** (N=50) Total N=225	Celecox.> Placebo Naproxen > Celecox
P: N49-95-02-005 R: N49-97-16-005 Analgesic Efficacy in Postsurgical Dental Pain	Randomized, *Single-Blind*, Placebo-Controlled, Active Controlled, Parallel Group (single dose) > 1 third molars	**Celecoxib** 100 mg (N=50) or 400 mg (N=50) **Aspirin** 650 mg (N=50) **Placebo** (N=50) Total N=200	Celecox.> Placebo Aspirin = Celecox.

Table 2: Post General and Orthopedic Surgery

Protocol No. Report No. Short Title	Study Design (Duration of Treatment)	Treatment Regimen(s)	Results (Efficacy)
P: N49-96-02-028 R: N49-98-06-028 Multiple-dose Analgesic Efficacy after Orthopedic Surgery	Randomized, Double-Blind, Placebo-Controlled, Active Controlled, Parallel Group (5 days)	**Celecoxib** 100 mg PRN up to BID or 200 mg PRN up to BID **Darvocet-N®** 100 mg PRN up to QID **Placebo**	No superiority of neither drug over placebo **Interim analysis performed**
P: N49-96-02-029 R: N49-98-06-029 Multiple-dose Analgesic Efficacy after General (but not Orthopedic) Surgery	Randomized, Double-Blind, Placebo-Controlled, Active Controlled, Parallel Group (5 days)	**Celecoxib** 100 mg PRN up to BID or 200 mg PRN up to BID **Darvocet-N®** 100 mg PRN up to QID or **Placebo**	N/A **Terminated after interim analysis**
P: N49-97-02-080* R: N49-98-06-080 Multiple-dose Analgesic Efficacy after Orthopedic Surgery	Randomized, Double-Blind, Placebo-Controlled, Active-Controlled, Parallel Group (5 days)	**Celecoxib** 200 mg PRN up to BID **Naproxen** 500 PRN up to BID or Placebo	N/A **Stoped after enrolment of the first patient**

* Only one patient (naproxen 500 mg BID PRN group) was enrolled before this study was terminated. This study is not discussed in this ISE.

Studies Population and Design

Study Population and Design - Post-Oral Surgery
(Studies # 025, 027 and 070)

In order to be entered into the post-oral surgery pain studies, patients had to have undergone surgical extraction of one or more impacted third molar(s) requiring bone removal, one of which must have been mandibular, and been experiencing moderate to severe postsurgical pain, and rated their Baseline pain intensity ≥50 mm on a Visual Analog Scale (VAS) of 100 mm.

Studies 025, 027 and 070 were double blind, randomized, placebo-controlled, single-dose studies that contained an active control. These studies were comprised of a Pretreatment Visit, Surgical Procedure, a Baseline Visit, a 24-hour Treatment Period, and a Posttreatment Period. In these studies, the Pretreatment Visit occurred within 14 days prior to the administration of study medication. Each patient provided a medical history, underwent a limited physical examination, and had clinical laboratory tests performed. At the Surgical Procedure, the molar(s) was extracted and a surgical trauma rating was made by the oral surgeon. At the Baseline assessment, only patients experiencing moderate to severe pain within six hours of the completion of surgery were enrolled into the study.

The Treatment Period was the 24-hour period immediately following the administration of a single dose of study medication. Patients remained in the research unit for the 24-hour Treatment Period and underwent the scheduled 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 postdose. Assessments included Pain Intensity (Categorical Scale), Pain Relief, Pain at Least Half Gone, Pain Intensity (VAS), Patient's Global Evaluation, and patients were provided two stopwatches with which to separately record Time to Perceptible and Meaningful Pain Relief. The use of potentially confounding medications in the postsurgical period was restricted as specified in the protocol. Patients were allowed to take rescue medication at any time in the study, if needed. Prior to taking the rescue medication the patients completed a final pain assessment and were then dropped from the study. For those patients who did not take rescue medication, the final pain assessments and end-of-study safety assessments were performed in the Posttreatment Period.

The design of Study 005 differed from Studies 025, 027, and 070 in that it was single blind, the study duration was 8 hours and stopwatches were not used. This study was not considered to be pivotal.

Study Population and Design - Post-Orthopedic and General Surgery Studies
(Studies # 028 & 029)

In order to be entered into either a post-orthopedic or post-general surgery study, patients had to have undergone an orthopedic procedure requiring open manipulation of bone with periosteal elevation (Study # 028) or a general surgical procedure (Study # 029) that was

expected to require administration of analgesics for management of pain for 3-5 days. Patients were to have received administration of the first dose of study medication within 54 hours after the end of anesthesia. The Baseline pain intensity (Categorical) must have been moderate to severe. Studies 028 and 029 were double-blind, randomized, placebo-controlled, multiple dose studies which contained an active control. Patients were allowed to receive analgesic medications such as Patient Controlled Analgesia (PCA) in the postsurgical period prior to first dose of study medication. If they were administered PCA during the postsurgical period, they must have tolerated and received pain relief from an oral analgesic medication prior to receiving study medication.

The post-general and orthopedic surgery studies were comprised of a Pretreatment Period which included the Screening Visit, Surgery, and the Baseline assessment. The Screening Visit occurred up to 14 days prior to surgery. Each patient gave a medical history, underwent a physical examination, and had clinical laboratory tests performed.

The Baseline assessment occurred within 54 hours after the end of anesthesia. The clinical laboratory tests performed at Screening were repeated. Immediately prior to study drug administration, each patient was asked to record the severity of his or her starting pain and only patients indicating moderate or severe pain were enrolled in the study.

The Treatment Period was defined as up to a five-day period after the first dose of study medication. Day 1 was defined as the 24-hour period beginning with the date and time of the first dose of study medication. Patients received the second dose of study medication not less than four hours after the first dose of study medication. Subsequent doses of study medication were administered as needed, no closer than two hours apart, and could not exceed four doses in 24 hours. In the celecoxib groups, only the first two doses were active, doses 3 and 4 were matching placebo. In contrast, all four doses of Darvocet-N 50 (2 tablets) were active. Patients received study medication and remained in the study for up to a maximum of 5 days. Patients underwent the following assessments at 0.25, 0.50, 0.75, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 18, and 24 hours postdose: Pain Intensity (Categorical Scale), Pain Relief, Pain at Least Half Gone, Pain Intensity (VAS), and were provided with a stopwatch to record Meaningful Pain Relief. In addition, the APS Pain Measure was completed by each patient every 24 hours after the first dose of study medication.

Final pain assessments were performed at the last hourly observation; just prior to rescue analgesia or just prior to hospital discharge.

Patient Disposition and Characteristics in Postsurgical Patients

A total of 1347 patients with postsurgical pain were enrolled into clinical studies with celecoxib. In the four post-oral surgery studies (Studies 025, 027, 070, 005), patients were randomized to receive one of nine treatments: celecoxib 25 mg single-dose (SD), celecoxib 50 mg SD, celecoxib 100 mg SD, celecoxib 200 mg SD, celecoxib 400 mg SD, naproxen sodium 550 mg SD, ibuprofen 400 mg SD, ASA 650 mg SD, or placebo (table 3).

Table 3: Number of Patients Listed by Study and Treatment Group – Dental Pain Studies (ITT Cohort: Studies 025, 027, 070, 005)

Study Number	Number of Postsurgical Patients by Treatment Group									
		Celecoxib					Naproxen Sodium	Ibuprofen	Aspirin	
	Placebo	25 mg SD	50 mg SD	100 mg SD	200 mg SD	400 mg SD	550 mg SD	400 mg SD	650 mg SD	Total
025	50	50	50	–	50	–	–	50	–	250
027	55	–	–	55	56	–	54	–	–	220
070	50	–	35	50	50	35	35	–	–	255
005	50	–	–	50	–	50	–	–	50	200
Total # of Patients	205	50	85	155	156	85	89	50	50	925

In the post-general and post-orthopedic surgery studies (Studies 028, 029), patients were randomized to receive one of four treatments: celecoxib 100 mg BID PRN, celecoxib 200 mg BID PRN, Darvocet-N 100 mg QID PRN or placebo (table 4).

Table 4: Number of Patients Listed by Study and Treatment Group (ITT Cohort: Studies 028, 029)

Study Number	Placebo	Celecoxib		Darvocet-N 100 mg QID PRN	Total
		100 mg BID PRN	200 mg BID PRN		
028	60	68	62	65	255
029	40	45	42	40	167
Total # Patients	100	113	104	105	422

Of the 925 randomized patients from the post-oral surgery studies, 225 (24%) completed the study and did not require additional analgesic medications during the study. Table 5 presents a summary of all patients, by treatment group, who completed each study. The reasons for study termination, grouped by treatment, for all randomized patients are also summarized in this table.

Table 5: Reasons for Study Termination (ITT Cohort: Studies 025, 027, 070, 005)

Study	Number of Postsurgical (Dental) Patients by Treatment Group							
		Celecoxib					Naproxen Sodium	Ibuprofen
	Placebo	25 mg SD	50 mg SD	100 mg SD	200 mg SD	400 mg SD	550 mg SD	400 mg SD
Study 025								
Total Completed [a]	4 (8%)	4 (8%)	7 (14%)	—	13 (26%)	—	—	8 (16%)
Total Withdrawn	46 (92%)	46 (92%)	43 (86%)	—	37 (74%)	—	—	42 (84%)
Treatment Failure/ Rescue Medication	46 (92%)	46 (92%)	43 (86%)	—	37 (74%)	—	—	42 (84%)
Adverse Event	0 (0%)	0 (0%)	0 (0%)	—	0 (0%)	—	—	0 (0%)
Study 027								
Total Completed [a]	9 (16%)	—	—	17 (31%)	27 (48%)	—	28 (52%)	—
Total Withdrawn	46 (84%)	—	—	38 (69%)	29 (52%)	—	26 (48%)[b]	—
Treatment Failure/ Rescue Medication	46 (84%)	—	—	38 (69%)	29 (52%)	—	25 (46%)	—
Adverse Event	0 (0%)	—	—	0 (0%)	0 (0%)	—	0 (0%)	—
Study 070								
Total Completed [a]	2 (4%)	—	3 (9%)	10 (20%)	12 (24%)	13 (37%)	9 (26%)	—
Total Withdrawn	48 (96%)	—	32 (91%)	40 (80%)	38 (76%)	22 (63%)	26 (74%)	—
Treatment Failure/ Rescue Medication	48 (96%)	—	31 (89%)	40 (80%)	38 (76%)	22 (63%)	26 (74%)	—
Adverse Event	0 (0%)	—	1 (3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	—
							Aspirin 650 mg SD	
Study 005	(N=50)	—	—	(N=50)	—	(N=50)	(N=50)	
Total Completed[a]	3 (6%)	—	—	20 (40%)	—	22 (44%)	14 (28%)	
Total Withdrawn	47 (94%)	—	—	30 (60%)	—	28 (56%)	36 (72%)	
Lost to Follow-up	2 (4%)	—	—	—	—	1 (2%)	1 (2%)	
Treatment Failure/ Rescue Medication	45 (90%)	—	—	30 (60%)	—	27 (54%)	35 (70%)	
Adverse Event	0 (0%)	—	—	0 (0%)	—	0 (0%)	0 (0%)	

Derived from Individual Study Reports

a) Completed patient was defined as having completed evaluations through 8 hours (Study 005) or 24 hours (Studies 025, 027 and 070) without taking rescue medication.

b) One patient was discharged before the 24 hour assessment.

Table 6 presents a summary of the 422 randomized patients from the post-general and post-orthopedic surgery studies by treatment group and by completion status. The high withdrawal rates were partially related to limited length of hospital stay mandated by managed care practice.

Table 6: Reasons for Study Termination (ITT Cohort: Studies 028, and 029)

Study	Number of Postsurgical Patients by Treatment Group			
	Placebo	Celecoxib		Darvocet-N
		100 mg BID PRN	200 mg BID PRN	100 mg QID PRN
Study 028	(N=60)	(N=68)	(N=62)	(N=65)
Total Completed [a]	1 (2%)	1 (1%)	0 (0%)	1 (2%)
Total Withdrawn	59 (98%)	67 (99%)	62 (100%)	64 (98%)
Pre-Existing Violation	2 (3%)	3 (4%)	0 (0%)	0 (0%)
Protocol Noncompliance	3 (5%)	16 (24%)	10 (16%)	19 (29%)
Treatment Failure/ Rescue Medication	51 (85%)	47 (69%)	43 (69%)	44 (68%)
Adverse Event	3 (5%)	1 (1%)	9 (15%)	1 (2%)
Study 029	(N=40)	(N=45)	(N=42)	(N=40)
Total Completed [a]	1 (3%)	1 (2%)	0 (0%)	0 (0%)
Total Withdrawn	39 (98%)	44 (98%)	42 (100%)	40 (100%)
Pre-Existing Violation	2 (5%)	0 (0%)	2 (5%)	0 (0%)
Protocol Noncompliance	5 (13%)	13 (29%)	9 (21%)	13 (33%)
Treatment Failure/ Rescue Medication	27 (68%)	29 (64%)	28 (67%)	22 (55%)
Adverse Event	5 (13%)	2 (4%)	3 (7%)	5 (13%)

Derived from Individual Study Reports

a) Completed patient was defined as having completed evaluations through 5 days without taking rescue medication.

Table 7 shows a descriptive summary of the pooled Baseline demographic characteristics for all patients enrolled in the three pivotal 24-hour post-oral surgery studies (Studies 025, 027, 070).

Table 7: Pooled Baseline Demographic Characteristics for Oral Surgery Pain Patients by Treatment Group (All Randomized Patients: Studies 025, 027, and 070)

Baseline Demographic Characteristic	Number of Postsurgical Patients by Treatment Group							
	Placebo (N=155)	Celecoxib					Naproxen Sodium	Ibuprofen
		25 mg SD (N=50)	50 mg SD (N=85)	100 mg SD (N=105)	200 mg SD (N=156)	400 mg SD (N=35)	550 mg SD (N=89)	400 mg SD (N=50)
Age (years)								
Mean (Std Dev)	23.1 (4.43)	23.3 (5.72)	24.0 (5.50)	23.6 (5.61)	23.6 (5.28)	24.2 (5.97)	23.4 (5.64)	24.3 (5.48)
Range	18-43	18-46	18-45	18-50	18-47	18-41	18-52	18-50
Race/Ethnic Origin								
Asian N (%)	2 (1%)	0 (0%)	4 (5%)	3 (3%)	5 (3%)	0 (0%)	3 (3%)	2 (4%)
Black N (%)	12 (8%)	3 (6%)	9 (11%)	9 (9%)	10 (6%)	3 (9%)	4 (4%)	1 (2%)
Caucasian N (%)	95 (61%)	32 (64%)	52 (61%)	62 (59%)	93 (60%)	23 (66%)	57 (64%)	32 (64%)
Hispanic N (%)	42 (27%)	14 (28%)	20 (24%)	31 (30%)	47 (30%)	8 (23%)	25 (28%)	15 (30%)
Other N (%)	4 (3%)	1 (2%)	0 (0%)	0 (0%)	1 (<1%)	1 (3%)	0 (0%)	0 (0%)
Gender								
Male N (%)	66 (43%)	18 (36%)	32 (38%)	45 (43%)	63 (40%)	14 (40%)	38 (43%)	10 (20%)
Female N (%)	89 (57%)	32 (64%)	53 (62%)	60 (57%)	93 (60%)	21 (60%)	51 (57%)	40 (80%)

Within these studies, there were no clinically significant differences between any of the treatment groups with regard to age, race or gender with the exception of a higher proportion of females in the ibuprofen group (Study 025).

Baseline demographics for the post-general and post-orthopedic surgery studies (Studies 028, 029) are presented in Tables 8 & 9. There were no meaningful differences across treatment groups in age, race or gender.

Table 8: Baseline Demographics Characteristics for Post-Orthopedic Surgery Patients by Treatment Group (All Randomized Patients: Study 028)

Baseline Demographic Characteristic	Number of Postsurgical Patients by Treatment Group			
	Placebo (N=60)	Celecoxib 100 mg BID PRN (N=68)	Celecoxib 200 mg BID PRN (N=62)	Darvocet-N 100 mg QID PRN (N=65)
Age (years)				
Mean (Std Dev)	52.2 (16.52)	55.7 (16.35)	59.0 (16.10)	56.4 (15.73)
Range	23-87	19-82	21-86	27-84
Race/Ethnic Origin				
Asian N (%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Black N (%)	7 (12%)	3 (4%)	1 (2%)	5 (8%)
Caucasian N (%)	51 (85%)	60 (88%)	59 (95%)	54 (83%)
Hispanic N (%)	2 (3%)	3 (4%)	2 (3%)	3 (5%)
Other N (%)	0 (0%)	2 (3%)	0 (0%)	3 (5%)
Gender				
Male N (%)	30 (50%)	37 (54%)	34 (55%)	36 (55%)
Female N (%)	30 (50%)	31 (46%)	28 (45%)	29 (45%)

Derived from Individual Study Report

Table 9: Baseline Demographics Characteristics for Post-General Surgical Patients by Treatment Group (All Randomized Patients: Study 029)

Baseline Demographic Characteristic	Number of Postsurgical Patients by Treatment Group			
	Placebo (N=40)	Celecoxib 100 mg BID PRN (N=45)	Celecoxib 200 mg BID PRN (N=42)	Darvocet-N 100 mg QID PRN (N=40)
Age (years)				
Mean (Std Dev)	44.6 (13.25)	44.4 (14.13)	48.0 (11.96)	41.5 (13.94)
Range	19-74	21-82	24-77	20-75
Race/Ethnic Origin				
Asian N (%)	0 (0%)	0 (0%)	0 (0%)	1 (3%)
Black N (%)	4 (10%)	1 (2%)	3 (7%)	4 10%)
Caucasian N (%)	28 (70%)	40 (89%)	29 (69%)	30 (75%)
Hispanic N (%)	3 (8%)	4 (9%)	9 (21%)	3 (8%)
Other N (%)	5 (13%)	0 (0%)	1 (2%)	2 (5%)
Gender				
Male N (%)	4 (10%)	6 (13%)	7 (17%)	5 (13%)
Female N (%)	36 (90%)	39 (87%)	35 (83%)	35 (88%)

Derived from Individual Study Report

Methods of Data Analysis

Endpoints for Analysis of Postsurgical Studies (Single Dose Analysis)
In general, the analysis of efficacy data for each study followed the FDA's "Presentation of Efficacy Results of Single-Dose Analgesics for Studies Using Acute Pain Models" dated January 1997. Efficacy measures for the post-oral surgery analgesia studies which were used in this ISE are:

Primary Efficacy Measures:

- Time-Specific Pain Intensity Difference (PID) (Categorical)
- Time-Specific Pain Relief (PR)
- Time-Specific Sum of PID on categorical scale and PR (PRID)
- Time to Onset of Perceptible Pain Relief
- Time to Rescue Medication

Secondary Efficacy Measures:

- Time-Specific Pain Intensity Difference (VAS)
- Summed Pain Intensity Difference, (SPID), for the sum of the PID scores through the first 3, 6, 8, 10 and 12 hours, respectively
- Total Pain Relief (TOTPAR) for the sum of the PR scores through the first 3, 6, 8, 10 and 12 hours, respectively
- Summed PRID scores (SPRID) for the sum of the PRID scores through the first 3, 6, 8, 10 and 12 hours, respectively
- Time to First Experienced 50% Pain Relief;
- Proportion of patients who experienced 50% pain relief;
- Proportion of patients who experienced 100% pain relief defined as complete pain relief (PR=4) and pain intensity (categorical) rating of none (PI=0).

Additional secondary efficacy variables were collected in the individual studies. These variables include maximum pain intensity (categorical scale), maximum pain relief, and APS pain measure (for Study 028) and Patients Global Evaluation (for Studies 005 and 028). These variables were analyzed in the individual study reports.

Patient Population Analyzed - Postsurgical Studies
Analyses in this ISE were based on the ITT Cohort. The ITT Cohort was defined as all randomized patients who took the dose of study drug with the following exceptions: patients who required rescue medication prior to the one-hour assessment were excluded from the efficacy analysis. In addition, if two consecutive scheduled pain assessments in the first two hours were missed, and therefore obtained by interpolation from the same two observed data points for any patient, that patient was excluded from the analyses.

Timepoints Analyzed

Patient's pain was assessed at Baseline and at 0.25, 0.50, 0.75, 1.0, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, and 24 hours postdose (the exception was Study 005 which only went through 8 hours postdose). Time-specific pain measurements were analyzed at all these timepoints.

Missing Values

For each individual study, the results reported in the clinical reports were analyzed using both the LOCF (last observation carried forward) and BOCF (baseline observation carried forward) approaches for imputing pain intensity and pain relief data after the patient took rescue medication.

Presentation of Data

Several tables employ the "ABC" method of designating statistical significance. The following example will serve to demonstrate the interpretation of this method.

If:

Treatment 1	A
Treatment 2	AB
Treatment 3	BC
Treatment 4	C

One would conclude that treatment 1 is significantly different from treatments 3 and 4 but not treatment 2, and that treatments 2 and 3 are not significantly different from each other, but 2 is significantly different from 4.

Comparison of Celecoxib to Placebo in Postsurgical Studies

Pain Intensity Difference and Pain Relief (PRID); Pain Relief (PR) and Pain Intensity Difference (PID, Categorical)

Mean Pain Intensity Difference and Pain Relief (PRID) Scores were calculated as the sum of the Pain Relief (PR) Score and Pain Intensity Difference (PID) Score. The best possible score was 7 (complete pain relief [PR=4] and change from severe pain at Baseline to no pain [PID=3]. The worst possible score was -1 (no pain relief [PR=0] and change from moderate pain at Baseline to severe pain [PID=-1]).

Mean Pain Relief (PR) scores were reported on a scale of 0 to 4 with 0 indicating no pain relief and 4 indicating complete pain relief.

Mean PID (Categorical) Scores were calculated by subtracting the pain intensity at a specific assessment time from the Baseline pain intensity. Scores could range from -1 (worst possible score) to 3 (best possible score).

Text Tables 83-87 present the mean PRID scores (BOCF method of imputation) for Studies 025, 027, 070, and 028. The mean PR and PID scores (BOCF), are present in the individual study reports.

In the double-blind post-oral surgery studies, celecoxib at doses 200 mg SD (Studies 025, 027 and 070), and 400 mg SD (Study 070) showed statistically significantly greater improvement compared to placebo beginning by 1.0 hour postdose and continuing through 8.0 hours postdose for the PRID (tables 83-85). In Studies 025 and 027 differences from placebo were seen by 0.75 hours postdose. Celecoxib at a dose of 100 mg SD (Studies 027 and 070), showed similar results except in Study 027 where the 100 mg dose separated statistically from placebo only up to 7 hours postdose. Analogous results were observed for the PID and PR for all three doses. Celecoxib in doses of 25 mg and 50 mg was subtherapeutic.

Ibuprofen 400 mg and naproxen sodium 550 mg validated the dental pain studies by showing statistically significant superiority over placebo in all pain measurements beginning at 0.75 hour postdose and continuing through 9 hours (8 hours in PR scores) for the ibuprofen and 24 hours for the naproxen sodium. Also, these active controls showed consistent, statistically significant superiority in all pain measurements over celecoxib. This significantly better efficacy began at 0.75 hour postdose (0.5 hour for naproxen in study # 027) and continued through 3 to 4 hours for all of the proposed therapeutic doses of celecoxib.

The post-orthopedic surgery study (Study 028) failed to detect statistically significant treatment differences between celecoxib and placebo (tables 86-87). In this study for single dose responses based on the BOCF analyses, celecoxib at doses of 100 mg SD and 200 mg SD was associated with numerically greater mean PRID (Text Table 86), PR and PID scores compared with placebo from 1.5-8 hours postdose, however, these differences were not statistically significant.

For the multiple dose analysis, again, efficacy scores with celecoxib 100 mg BID PRN or 200 mg BID PRN were numerically but not statistically significant superior to placebo, beginning at about 1 hour and continuing through the entire 24 hour postdose period. Using the BOCF method of imputation, celecoxib 200 mg BID PRN was significantly different from placebo at only a few and inconsistent timepoints for all of the measures of efficacy.

Darvocet-N which was used as an active control in this study did not separate from placebo as well suggesting that this pain model may not be appropriate for the tested medications and requires the highest degree of analgesia (i.e., opiates).

Table 11: Pain Intensity Difference and Pain Relief (PRID, Categorical Scale, Extrapolated) - BOCF - Study 025

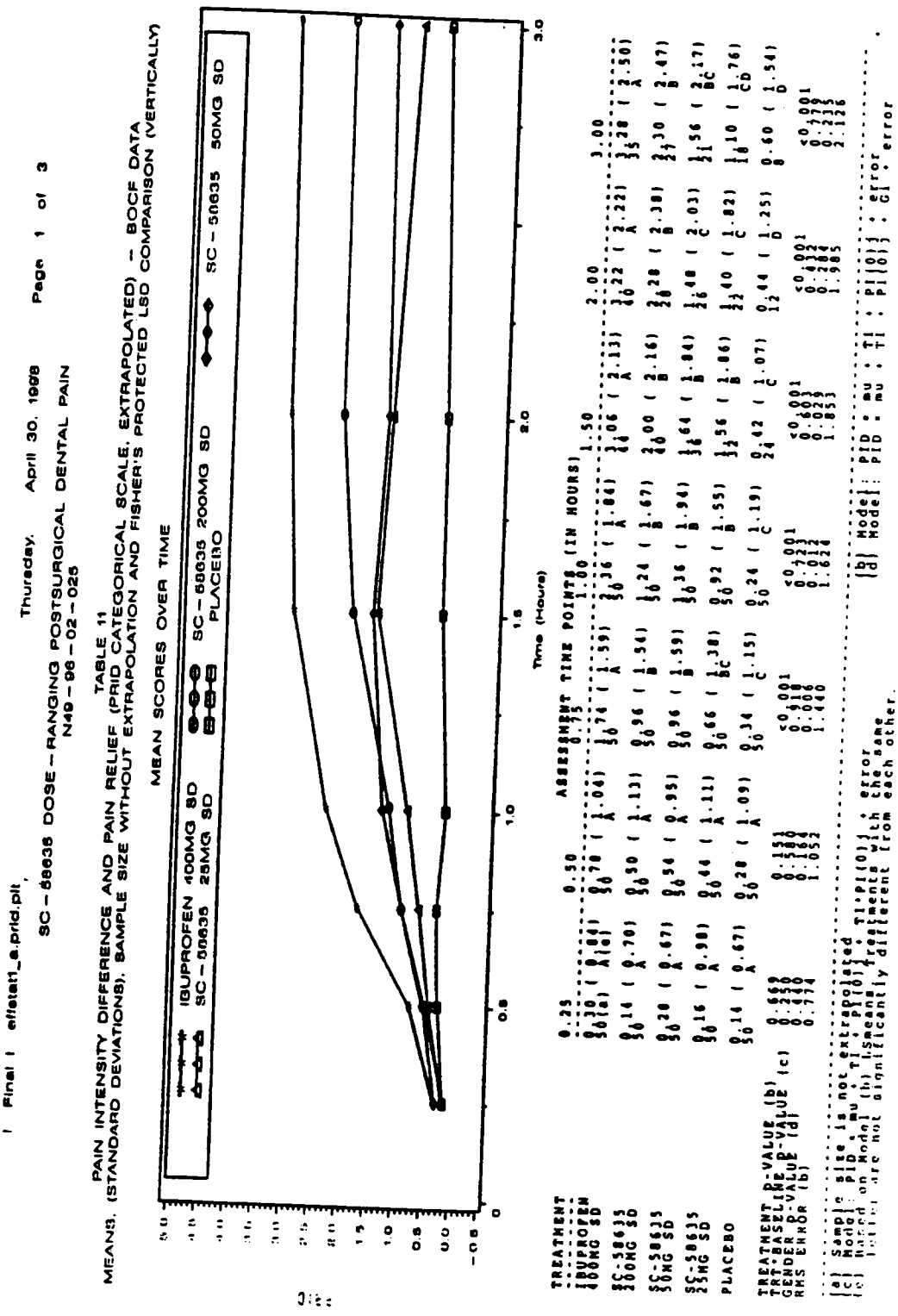


Table 11: Pain Intensity Difference and Pain Relief (PRID, Categorical Scale, Extrapolated) - BOCF - Study 025

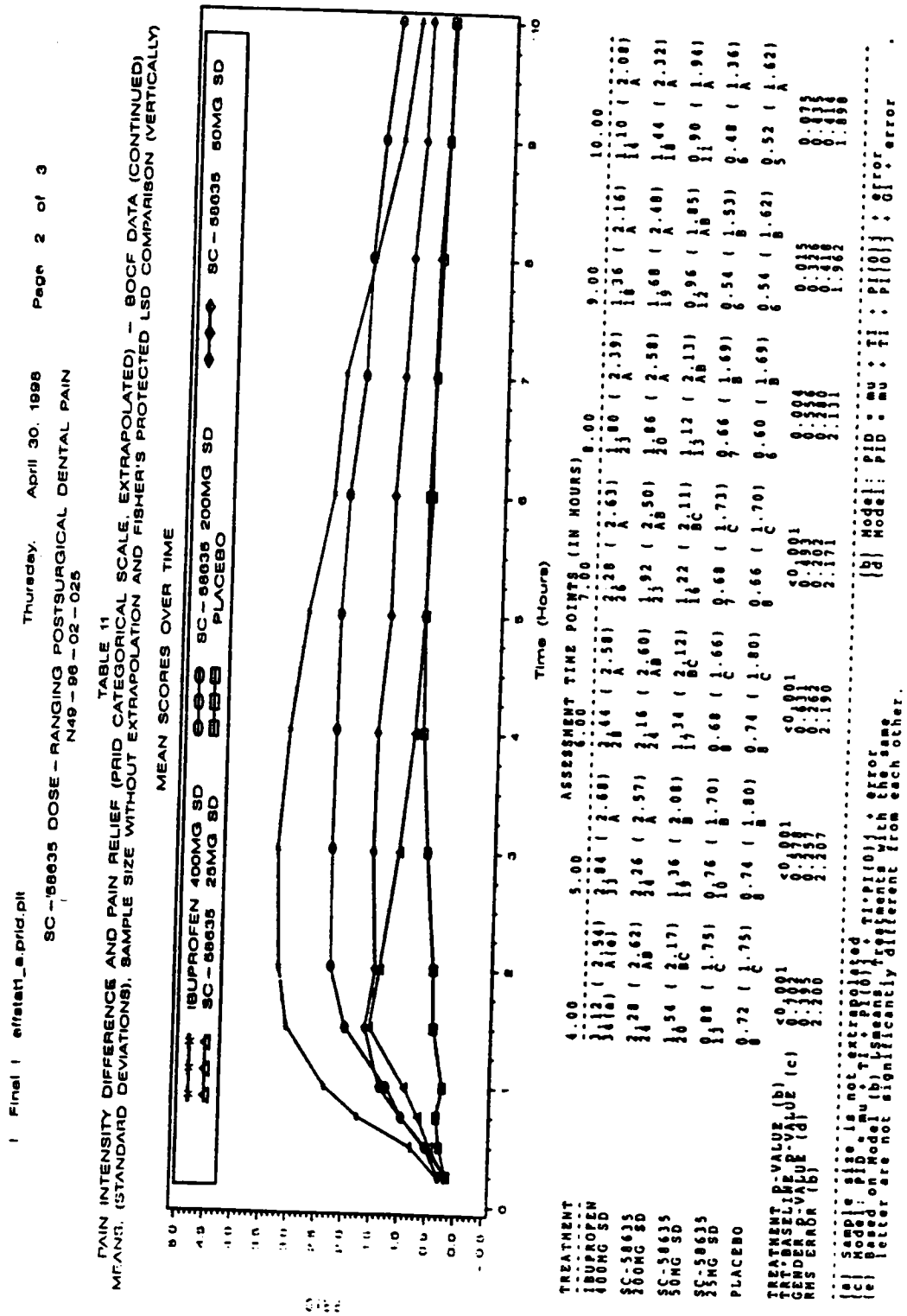


Table 11: Pain Intensity Difference and Pain Relief (PRID, Categorical Scale, Extrapolated) - BOCF - Study 025

Table 11: Pain Intensity Difference and Pain Relief (PRID, Categorical Scale, Extrapolated) - BOCF - Study 027

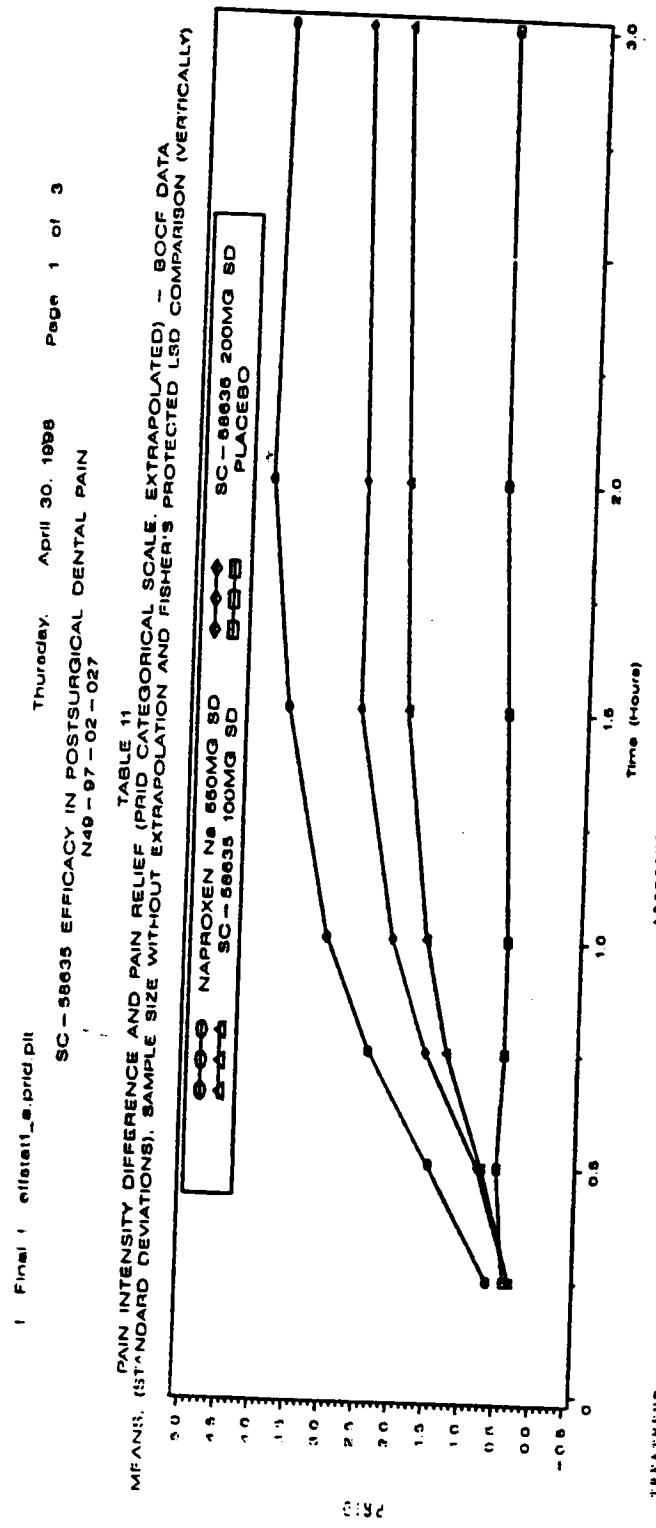


Table 11: Pain Intensity Difference and Pain Relief (PRID, Categorical Scale, Extrapolated) - BOCF - Study 027

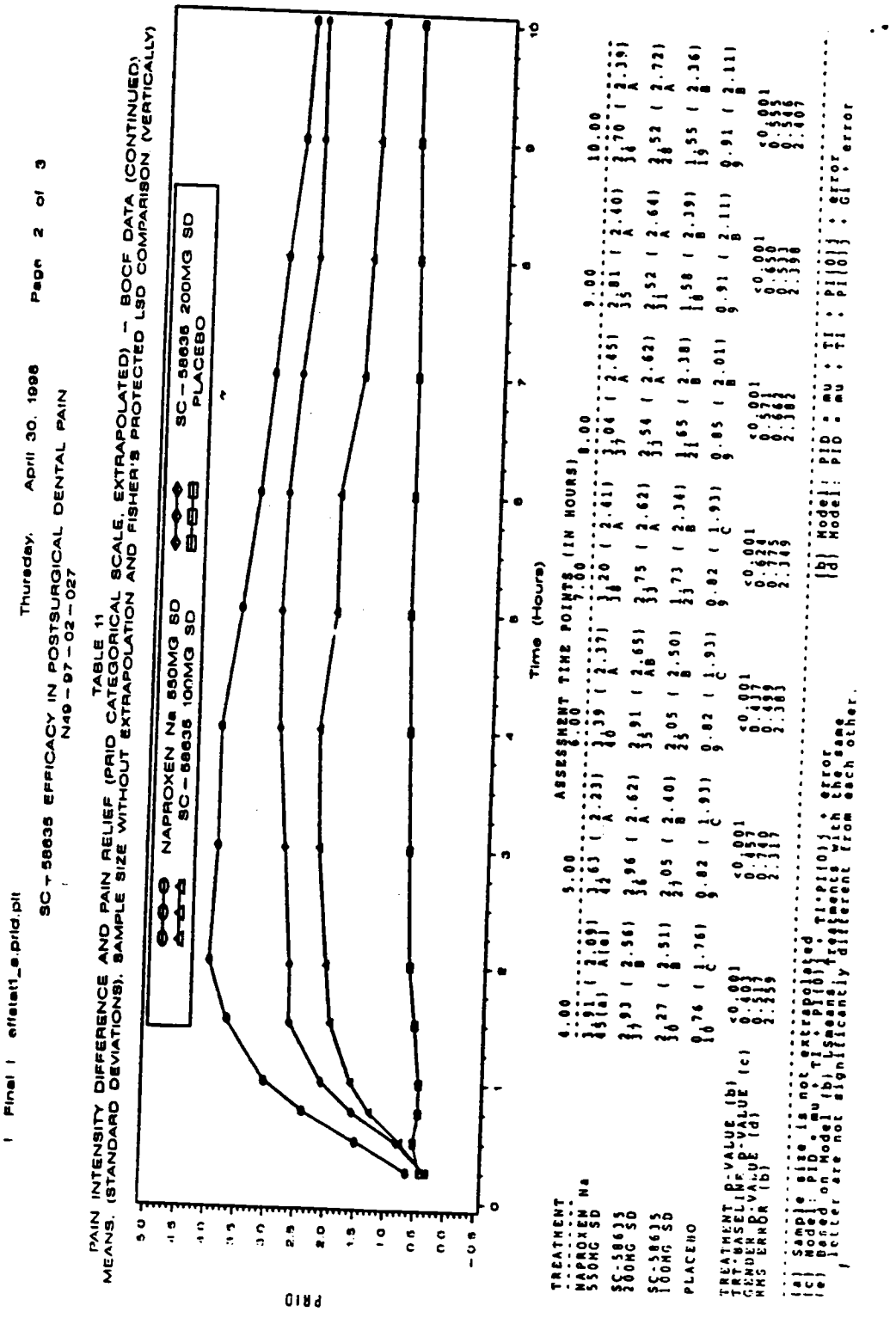


Table 11: Pain Intensity Difference and Pain Relief (PRID, Categorical Scale, Extrapolated) - BOCF - Study 027

Page 3 of 3

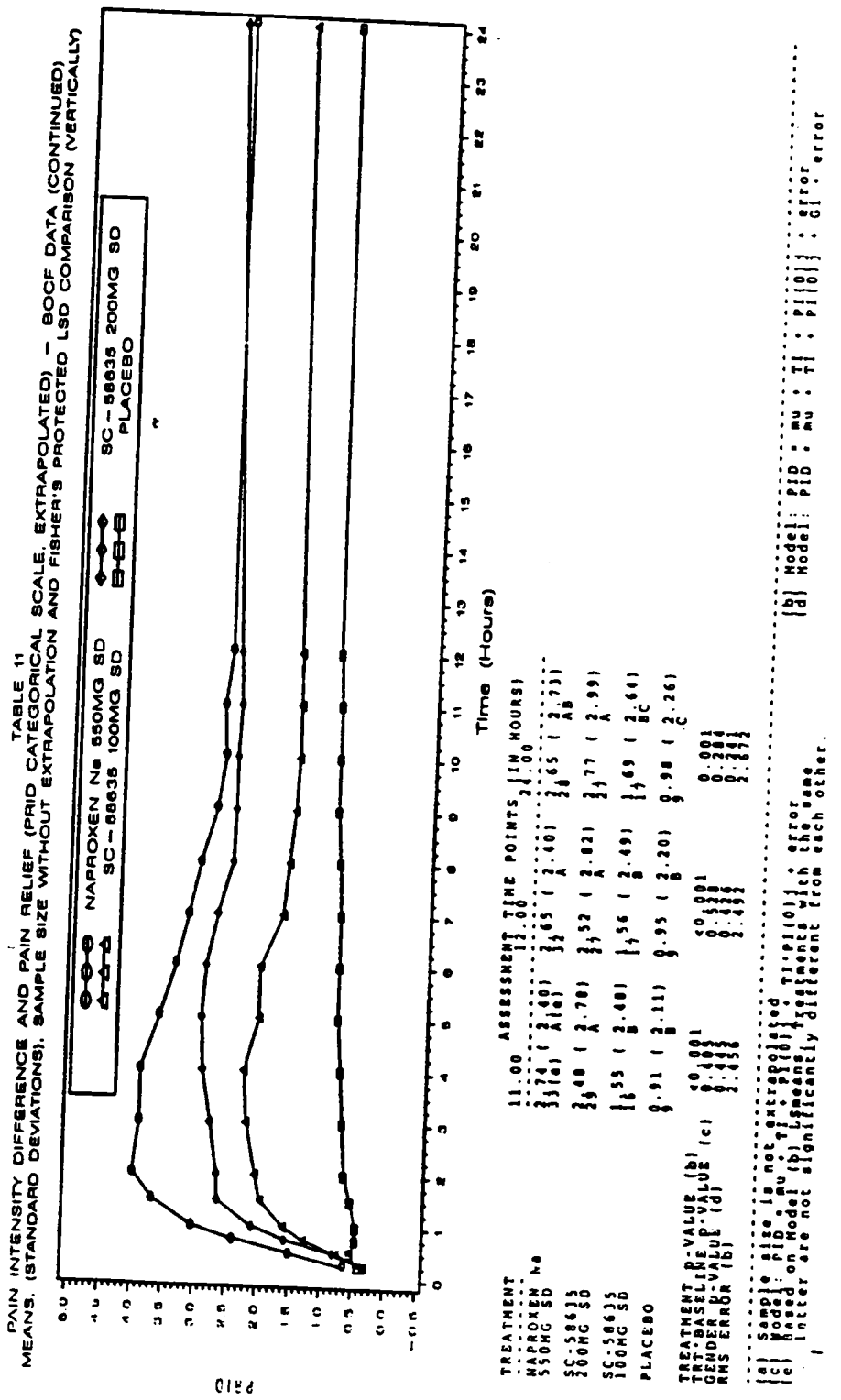
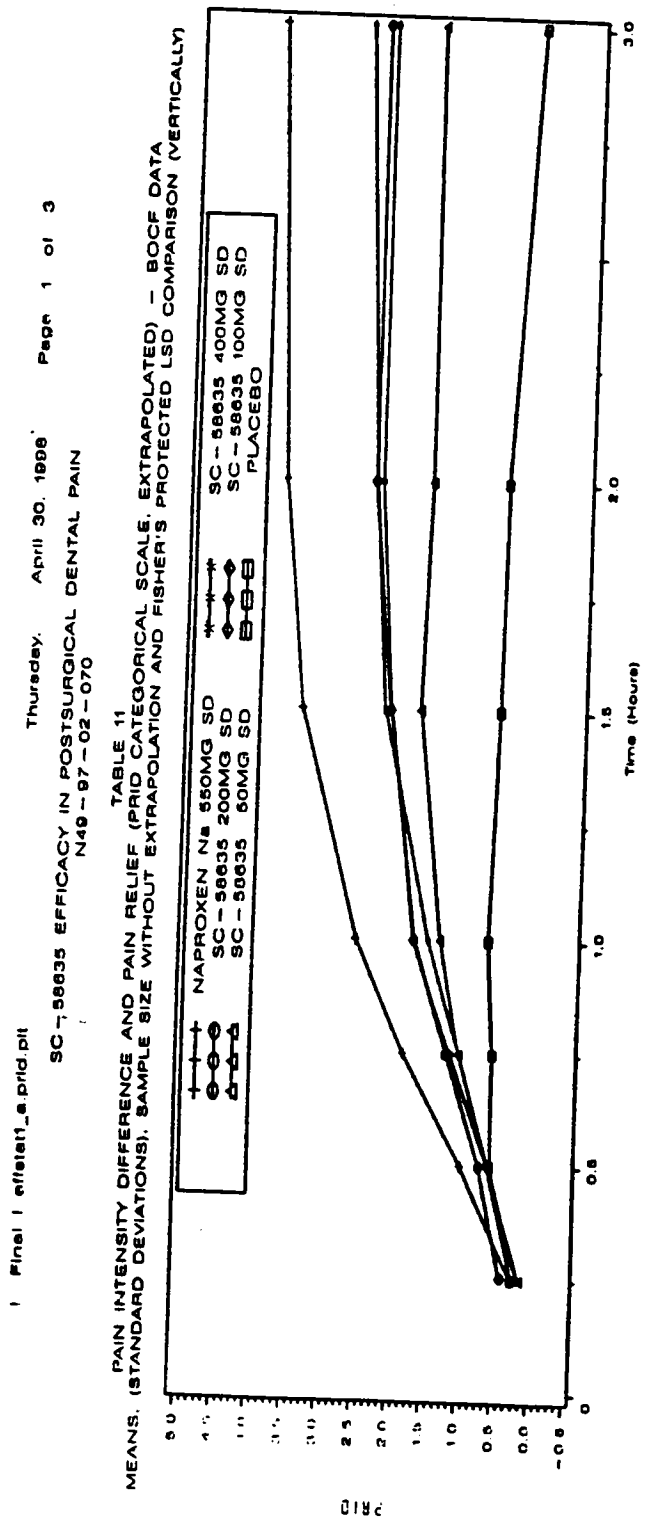


Table 11: Pain Intensity Difference and Pain Relief (PRID, Categorical Scale, Extrapolated) - BOCF - Study 070



TREATMENT	0.25	0.50	0.75	1.00	1.50	2.00	3.00
NAPROXEN Na 550MG SD	$_{550}^{0.18}$ (0.82) A(e)	$_{550}^{1.00}$ (1.21) A	$_{550}^{1.86}$ (1.56) A	$_{550}^{2.57}$ (2.00) A	$_{550}^{3.43}$ (2.21) A	$_{550}^{3.74}$ (2.36) A	$_{550}^{3.94}$ (2.46) A
SC-58635 400MG SD	$_{51}^{0.17}$ (0.71) A	$_{51}^{0.60}$ (1.06) A	$_{51}^{1.06}$ (1.63) B	$_{51}^{1.54}$ (1.80) B	$_{51}^{2.26}$ (2.17) B	$_{51}^{2.46}$ (2.21) B	$_{51}^{2.71}$ (2.62) B
SC-58635 200MG SD	$_{50}^{0.40}$ (0.73) A	$_{50}^{0.74}$ (1.19) A	$_{50}^{1.24}$ (1.65) B	$_{50}^{1.74}$ (1.94) B	$_{51}^{2.18}$ (2.10) B	$_{50}^{2.48}$ (2.40) B	$_{50}^{2.48}$ (2.38) B
SC-58635 100MG SD	$_{50}^{0.24}$ (0.72) A	$_{50}^{0.62}$ (1.12) A	$_{50}^{1.18}$ (1.79) B	$_{50}^{1.76}$ (2.11) B	$_{51}^{2.16}$ (2.35) B	$_{28}^{2.38}$ (2.55) B	$_{25}^{2.38}$ (2.68) B
SC-58635 50 MG SD	$_{51}^{0.14}$ (0.65) A	$_{51}^{0.63}$ (1.33) A	$_{51}^{1.06}$ (1.49) B	$_{51}^{1.77}$ (1.83) BC	$_{25}^{2.74}$ (2.06) B	$_{16}^{2.66}$ (2.21) B	$_{14}^{2.69}$ (2.31) B
PLACEBO	$_{50}^{0.26}$ (0.63) A	$_{50}^{0.58}$ (1.11) A	$_{50}^{0.58}$ (1.33) B	$_{50}^{0.68}$ (1.50) C	$_{19}^{0.61}$ (1.43) C	$_{13}^{0.58}$ (1.43) C	$_{5}^{0.26}$ (0.94) C

TREATMENT P-VALUE (b)	0.817	0.386	0.009	<0.001	<0.001	<0.001	<0.001
INT*BASELINE P-VALUE (c)	0.818	0.298	0.244	0.1330	0.658	0.299	0.905
GENDER P-VALUE (d)	0.419	0.404	0.310	0.229	0.362	0.382	0.876
MSE ERROR (b)	0.692	1.150	1.560	1.857	2.040	2.205	2.272

(a) Sample size is not extrapolated
(c) Model: PID = mu + TI + PID(0) + TI*PID(0) + error (b) Model: PID = mu + TI + PID(0) + error
(d) Model: PID = mu + TI + PID(0) + GI + error
Letter are not significantly different from each other.

Table 11: Pain Intensity Difference and Pain Relief (PRID, Categorical Scale, Extrapolated) - BOCF - Study 070

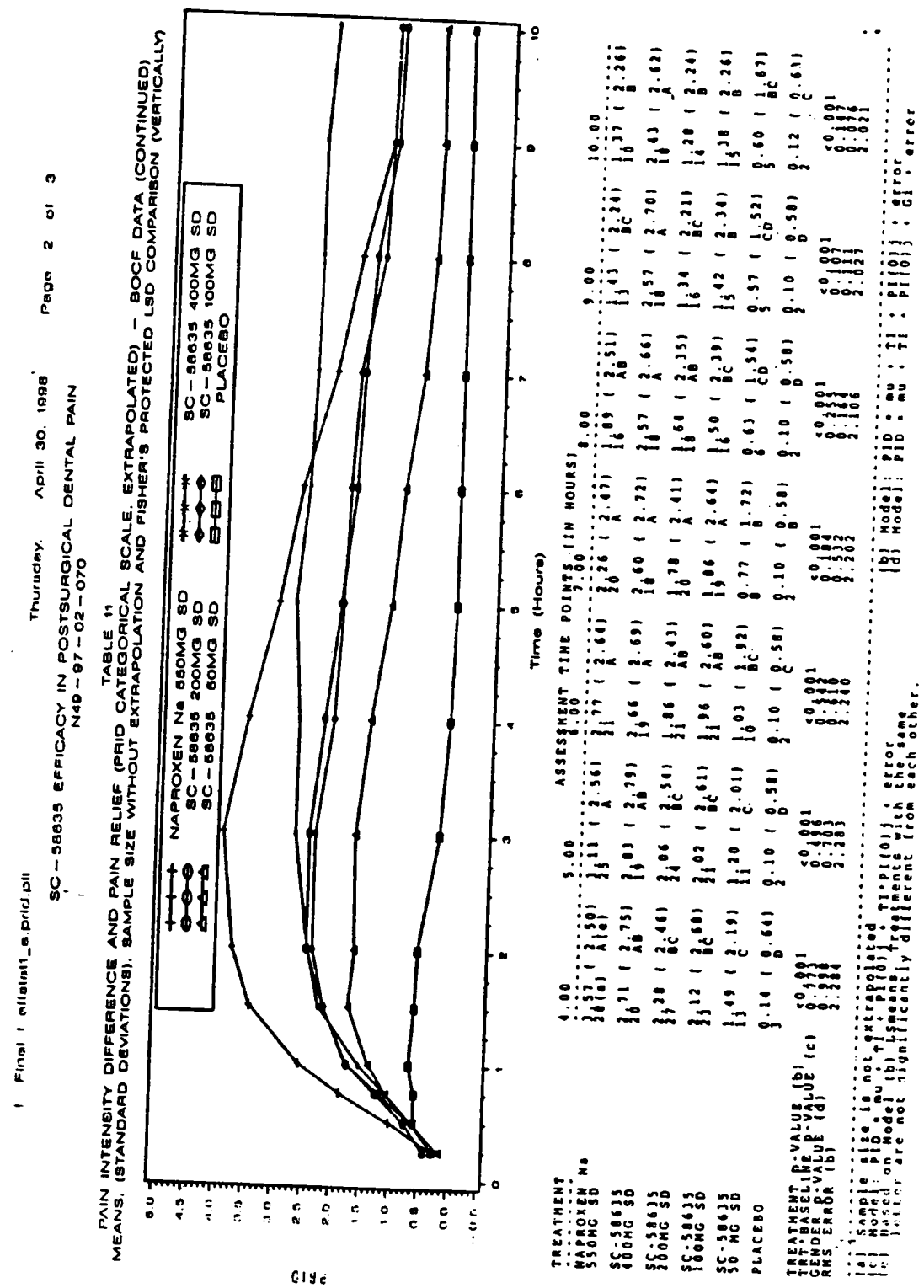
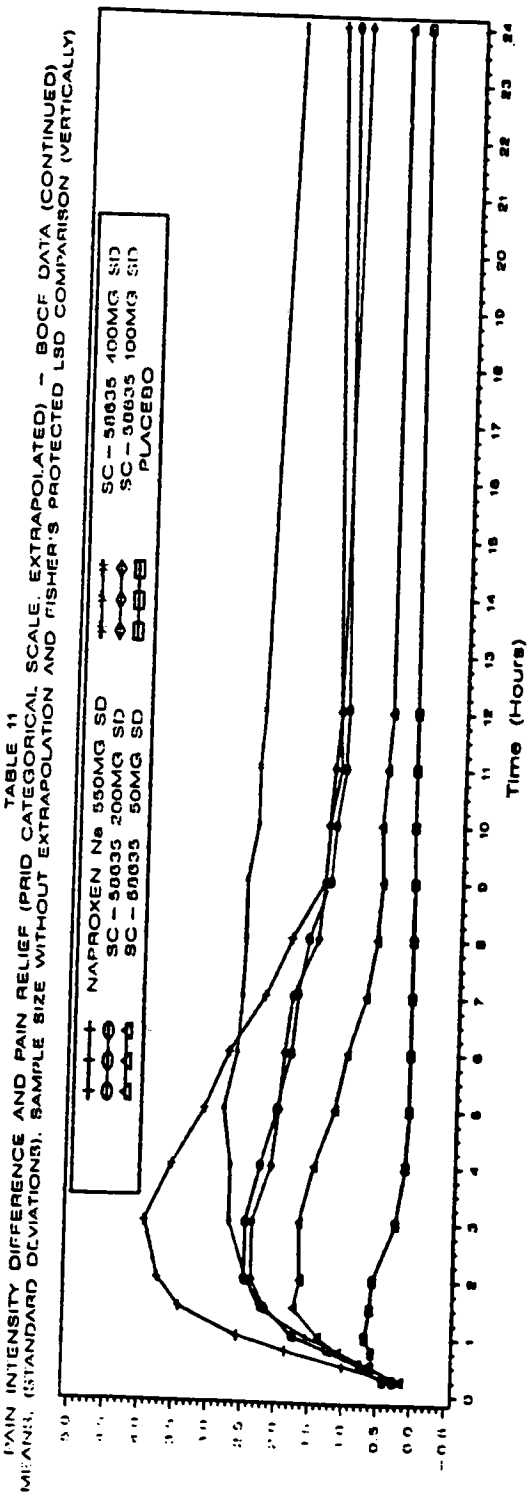


Table 11: Pain Intensity Difference and Pain Relief (PRID, Categorical Scale, Extrapolated) - BOCF - Study 070



TREATMENT	11.00	ASSESSMENT TIME POINTS (IN HOURS) 24.00
NAPROXEN Na 550MG SD	1.23 (1.11) A (181)	1.26 (1.23) A 93	1.46 (1.54) A 88
SC-58635 400MG SD	1.43 (1.70) A 70	1.37 (1.69) A 69	1.06 (1.79) A 71
SC-58635 200MG SD	1.16 (1.08) B 76	1.14 (1.13) B 77	1.26 (1.32) A 77
SC-58635 100MG SD	1.32 (1.20) B 71	1.24 (1.16) B 71	1.08 (1.24) AB 71
SC-58635 50 MG SD	0.54 (1.62) BC 74	0.49 (1.54) BC 73	0.49 (1.62) BC 73
PLACEBO	0.12 (0.63) C 82	0.12 (0.63) C 82	0.20 (1.01) C 81

TREATMENT P-VALUE (b)	<0.001	<0.001
TRT-BASELINE P-VALUE (c)	0.1668	0.2119
GENDER P-VALUE (d)	0.6667	0.0911
RMS ERROR (b)	1.9560	1.9671

	0.001
	0.3555
	0.0226
	2.1110

(a) Sample size is not extrapolated
(b) Model: PID = mu + TI + P(I(1)) + error
(c) Based on Model (b) Means with the same letter are not significantly different from each other.
(d) Model: PID = mu + TI + P(I(1)) + error

Table 11: Pain Intensity Difference and Pain Relief (PRID, Categorical Scale, Extrapolated) - BOCF - Study 028 - Single Dose

Page 1 of 3

Table 11: Pain Intensity Difference and Pain Relief (PRID, Categorical Scale, Extrapolated) - BOCF - Study 028 - Single Dose

Page 2 of 3

Table 11: Pain Intensity Difference and Pain Relief (PRID, Categorical Scale, Extrapolated) - BOCF - Study 028 - Single Dose

Page 3 of 3

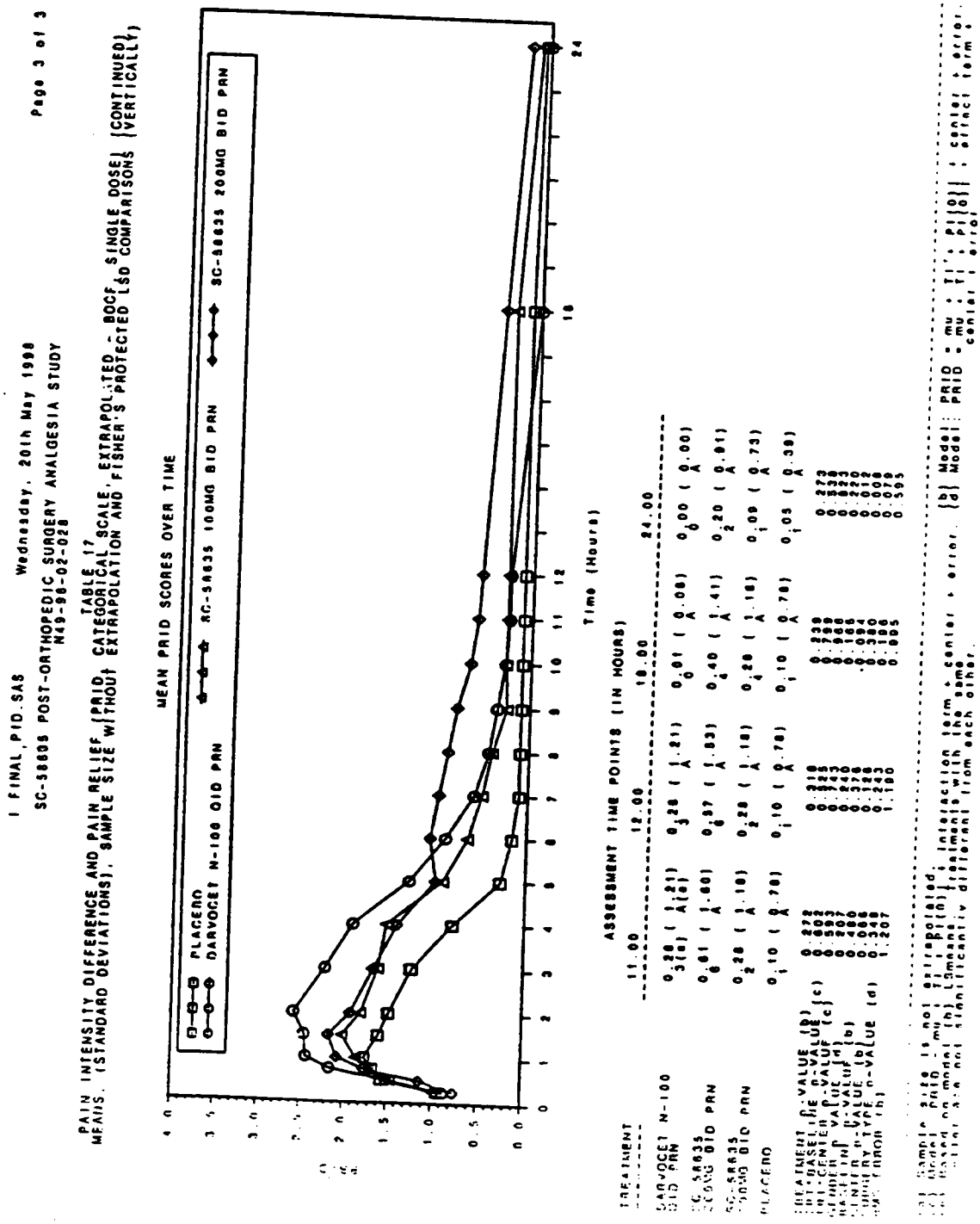


Table 11: Pain Intensity Difference and Pain Relief (PRID, Categorical Scale, Extrapolated) - BOCF - Study 028 - Multiple Dose

Page 1 of 3

I FINAL.PID.SAS Wednesday, 20th May 1998 Page 1 of 3
SC-58635 POST-ORTHOPEDIC SURGERY ANALGESIA STUDY
N49-96-02-028

TABLE 10
MEANS, (STANDARD DEVIATIONS), SAMPLE SIZE WITHOUT EXTRAPOLATION AND FISHER'S PROTECTED LSD COMPARISONS (VERTICALLY)
PAIN INTENSITY DIFFERENCE AND PAIN RELIEF (PRID, CATEGORICAL SCALE, EXTRAPOLATED - BOCF, MULTIPLE DOSE)

MEAN PRID SCORES OVER TIME

PLACEBO
DARVOCET N-100 QID PRN
SC-58635 100MG BID PRN
SC-58635 200MG BID PRN

Time (Hours)

TREATMENT	ASSESSMENT TIME POINTS (IN HOURS) 0.25	0.50	0.75	1.00	1.50	2.00	3.00
DARVOCET N-100 QID PRN	0.02 (1.20) 116 A(a)	0.30 (1.03) 81 A	0.58 (1.08) 80 A	0.93 (2.08) 81 A	2.45 (2.17) 83 A	2.58 (2.21) 77 A	2.32 (2.24) 74 A
SC-58635 200MG BID PRN	0.70 (1.08) 58 A	0.94 (1.00) 87 A	1.28 (1.01) 87 A	2.07 (2.07) 86 A	2.17 (2.08) 46 A	2.02 (1.95) 36 B	1.87 (2.04) 33 B
SC-58635 100MG BID PRN	0.88 (1.30) 86 A	0.46 (1.01) 84 A	1.20 (1.72) 84 A	1.85 (1.82) 85 A	2.01 (1.88) 56 A	1.81 (1.98) 48 B	1.82 (1.80) 36 B
PLACEBO	0.03 (1.27) 58 A	0.56 (1.07) 56 A	1.08 (1.85) 56 A	1.75 (1.77) 56 A	1.80 (1.77) 51 A	1.49 (1.84) 46 B	1.25 (1.88) 34 B
INTERMENT P-VALUE (a)	0.814	0.417	0.454	0.149	0.021	0.012	0.018
INT:BASELINE P-VALUE (c)	0.881	0.285	0.270	0.256	0.065	0.050	0.378
INT:CENTER P-VALUE (c)	0.881	0.881	0.803	0.826	0.675	0.280	0.178
GENDER P-VALUE (b)	0.901	0.803	0.703	0.312	0.468	0.280	0.162
BASELINE P-VALUE (b)	0.836	0.414	0.842	0.684	0.312	0.320	0.812
CENTER P-VALUE (b)	0.994	0.332	0.852	0.684	0.001	0.345	0.830
CURRENT TYPE P-VALUE (b)	0.994	0.804	0.988	0.893	< 0.000	0.006	0.008
RMSE ERROR (b)	1.226	1.801	1.765	1.800	1.890	1.814	1.823
						1.841	1.881

(a) Sample size is not extrapolated
(b) Model: mu = T|(0) + Interaction term + center + error. (c) Model: PRID = mu : T| : P|(0)|| : center : error
(c) Model: mu = T|(0) + LSmeans treatment with the same center + error. (d) Model: PRID = mu : T| : P|(0)|| : center : error
Error: are not significantly different from each other

Table 11: Pain Intensity Difference and Pain Relief (PRID, Categorical Scale, Extrapolated) - BOCF - Study 028 - Multiple Dose

Table 11: Pain Intensity Difference and Pain Relief (PRID, Categorical Scale, Extrapolated) - BOCF - Study 028 - Multiple Dose