The protocol was identical to that of study #129.

d. Results

Figure33 shows the disposition of patients by treatment sequence and study cycle. Figure 34 shows the disposition of patients by treatment sequence and study medication. There were few study protocol violations including 33 for "study medication not received in all treatment cycles." There were significant differences among groups with respect to age (p=.043), weight (p=.028), temperature (p=.028), and resting heart rate (p=.034) at baseline.

Comment: These differences were unlikely to contribute significantly to this study.

The efficacy analyses were performed on the Intent-to-Treat (ITT) population, defined as patients who took study medication in all three treatment periods, and did not require rescue medication in any of the cycles prior to one hour, and did not have two consecutive pain assessments interpolated by the same two values within the first two hours. There were 121 patients in this cohort. Of the 154 patients randomized to the study, 33 did not receive study medication in all three treatment periods (cycles) and were not included in the efficacy analyses.

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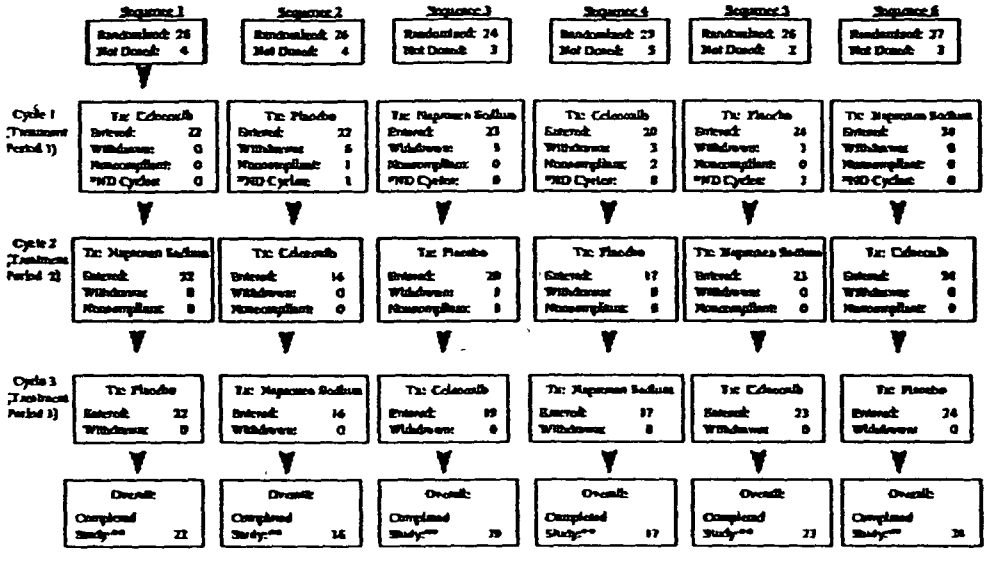
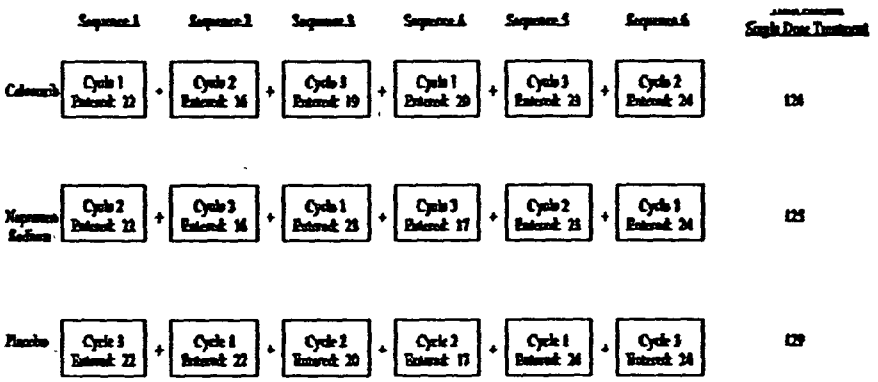
Figure 33: Patient disposition by treatment sequence and study cycle



Source: Tables T1 and T2.3.

Figure 34; Patient disposition by treatment sequence and study medication



Source: Tables T2.1 and T2.3.

2 Efficacy endpoints outcome

Analysis of primary efficacy measures:

Analyses of both SPID (8) and TOTPAR (8) based on the LOCF approach were higher in the celecoxib treatment period than in the placebo treatment period (see Figures 35 and 36) and these differences were significant. Naproxen was superior to placebo and celecoxib.

Figure 35: SPID 8 results

Treatment Group	Placebo (N=121)	Celecoxib (N=121)	Naproxen Sodium (N=121)
SPID(8)	6.41 (C)	9.60 (B)	11.71 (A)

Treatments with same letter are not significantly different from each other.
Source: Table T7.1.

Figure 36: TOTPAR 8 results

Treatment Group	Placebo (N=121)	Celecoxib (N=121)	Naproxen Sodium (N=121)
TOTPAR(8)	12.98 (C)	17.98 (B)	21.27 (A)

Treatments with same letter are not significantly different from each other.
Source: Table T8.1.

Analyses of secondary efficacy measures:

The following endpoints were significantly different between celecoxib and placebo, favoring celecoxib: time to rescue medication (Figure 37);

Figure 37: Median time to rescue

Treatment Group	Placebo (N=121)	Celecoxib (N=121)	Naproxen Sodium (N=121)
Patients Who Took Rescue Medication N (%)	49 (40%)	30 (25%)	16 (13%)
Median Time to Rescue Medication (hr:min) +*	>12:00(C)	>12:00(B)	>12:00(A)

+ Kaplan-Meier estimate
* Cox regression stratified by patient applied as in Fisher's protected LSD. Treatments with the same letter are not significantly different from each other.
Source: Table T14.

PRID (1-12 hours); peak PID (1.41 for placebo versus 1.75 for celecoxib versus 2.04 for naproxen); SPID (12) (10.01 for placebo versus 14.66 for celecoxib versus 18.10 for naproxen); peak PR (2.52 for placebo versus 3.15 for celecoxib versus 3.55 for naproxen); TOTPAR (12) (20.10 for placebo versus 27.62 for celecoxib versus 32.62 for naproxen); SPRID (8) and SPRID (12); patient's global assessment. However, time to onset of analgesia and time to onset of perceptible or meaningful pain relief for celecoxib were not significantly different from placebo (Figure 38).

Figure 38: Median time to onset of analgesia

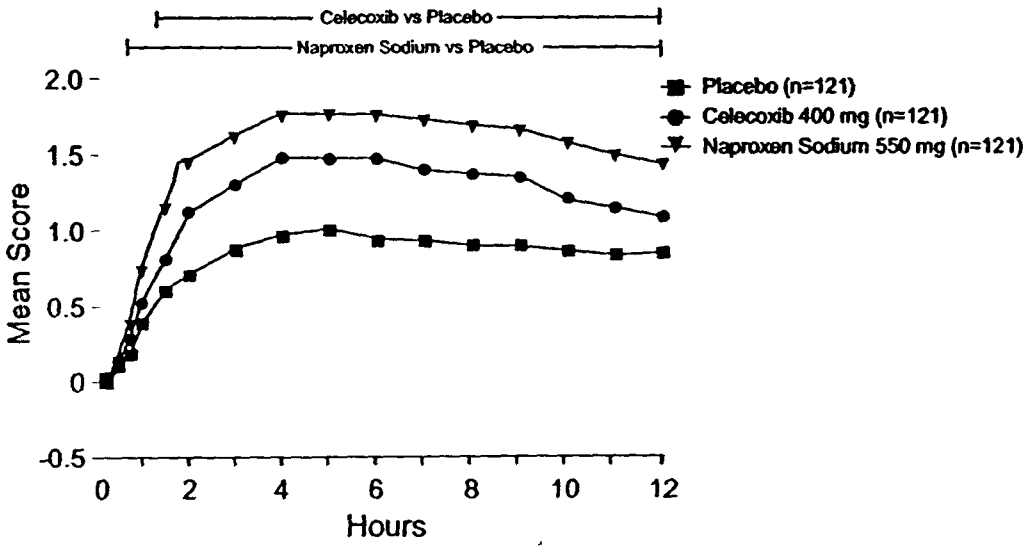
Treatment Group	Placebo (N=121)	Celecoxib (N=121)	Naproxen Sodium (N=121)
Patients Who Experienced Analgesia N (%)	83 (69%)	99 (82%)	109 (90%)
Median Time to Onset of Analgesia (hr:min) +*	01:27(B)	00:53(AB)	00:50(A)

+ Kaplan-Meier estimate
* Cox regression stratified by patient applied as in Fisher's protected least significant difference (LSD). Treatments with the same letter are not significantly different from each other.
Source: Table T13.

The mean PID score in the celecoxib treatment period was significantly different from the mean score during the placebo treatment period at 1.5 hours, and remained significant through the last assessment time point at 12 hours (Figure

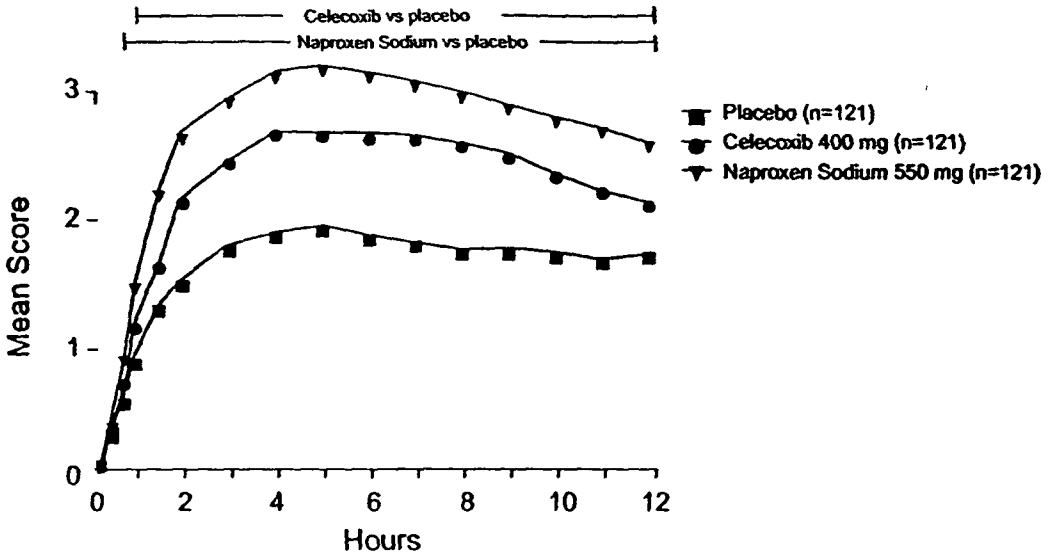
39). The mean PID score during the naproxen sodium treatment period was significantly different from the mean score during the placebo treatment period starting at 0.75 hour through the last assessment time point at 12 hours.

Figure 39: Mean PID scores



The mean PR score (figure 40) in the celecoxib treatment period was significantly different from the effect of placebo at 1 hour, and remained significant through the last assessment time point at 12 hours. The mean PR score during the naproxen sodium treatment period was significantly different from the mean scores during the placebo treatment period starting at 0.75 hour through the last assessment time point at 12 hours.

Figure 40: Mean PR scores



Fifty-four percent of patients during the celecoxib treatment period, 70% of patients during the naproxen sodium treatment period compared to 49% of patients during the placebo treatment period, required only one dose of study medication in the first 24 hours of the treatment period. A second dose of study medication was sufficient to allow another 15%, 11% and 9% of patients in the celecoxib, naproxen sodium and placebo treatment periods, respectively, to complete the first 24 hours of each treatment period. After the first day of dosing in each period, the majority of patients did not require additional study medication. During the multiple dose assessment period the number of patients remedicating declined rapidly and the secondary measures of efficacy including mean daily maximum pain intensity, mean patient global evaluation and pain intensity before day 2 dose 1, were not significantly different between the groups.

Re-analysis of efficacy data

A re-analysis of the data using the same approach as described in study 129 was provided by the sponsor (Figure 41).

Figure 41: Re-analysis of SPID and TOTPAR

Treatment	SPID8	SPID12	TOTPAR8	TOTPAR12
Naproxen	12.11 (6.01) A	18.54 (9.35) A	20.84 (7.59)	31.64 (11.77) A
Celecoxib	9.16 (6.16) A	13.09 (9.76) B	18.79 (8.86)	27.44 (13.29) A
Placebo	6.70 (6.14) B	10.25 (10.36) B	13.71 (9.63)	20.83 (15.27) B
Rx p value	<.001	.001	<.001	<.001

For celecoxib SPID8, but not SPID12 was significantly different compared to placebo. For celecoxib, both TOTPAR8 and 12 were significantly different from placebo. SPRID8 and 12 (not shown) was significantly different compared to placebo. However, for celecoxib PID separated from placebo between hours 4-8 only. For PR the separation occurred at hours 3-9, and for PRID hours 4-8. Time to onset of analgesia for celecoxib or naproxen was no different from placebo. However, for time to rescue medication naproxen was significantly superior to placebo but celecoxib was not.

For the analysis using the conservative imputation method results are similar to the sponsors original analysis.

e. Reviewers comments, conclusions, and summary for studies 129 and 130

The results of study 130 are consistent with those of study 129 and demonstrate that a single dose of celecoxib is efficacious in the treatment of patients with moderate to severe pain associated with primary dysmenorrhea. A statistical evaluation of the multiple dose portion of both studies was not possible because the number of patients remedicating on days 2-3 declined rapidly.

Both studies met their primary endpoints of SPID (8) and TOTPAR (8). SPID and TOTPAR by themselves would not be sufficient for demonstrating efficacy for an acute analgesic. However, in addition, secondary analyses demonstrated a statistically significant effect of celecoxib over placebo for such measures as PID (starting at 1.5 hours and continuing out to 12 hours); PR (1.5 to 12 hours); PRID (1.5 to 12 hours) for study 129. For study 130, celecoxib was significantly superior to placebo for PID (1.5-12 hours), PR (1-12 hours), and PRID (1-12 hours). The time to onset of analgesia while statistically different from placebo in study 129, was not different in study 130, although it was within an hour. However, the onset of perceptible pain relief and meaningful pain relief was no different from placebo in either study. The reason for this is not clear but may be related to the mild pain at baseline in this model. Time to rescue medication was significantly different favoring celecoxib over placebo. Furthermore naproxen was statistically superior to celecoxib for most measures.

Of concern is that the trial design allowed for the evaluation of about 120 patients per arm. In general the Analgesic Guidance recommends treatment arms for single dose effect contain no more than 50-60 patients per arm for these types of pain studies. Large trials may identify statistically significant but clinically irrelevant differences compared to placebo. To address this and other concerns the Division requested that the sponsor re-analyze the data using 2 methods described under study 129. Using the method of conservative imputation and examining the ITT population (took at least one dose of study medication), the re-analysis confirms the sponsors' original analytical approach. For the re-analysis of cycle 1 patients only, the results for study 129 confirm the sponsors' original analysis. However, study 130 fails at the primary endpoint SPID 12. In addition, the time specific efficacy measures such as PID do not demonstrate statistical superiority of celecoxib over placebo until hour 4 or after hour 8. For PR the times are hours 3-9; for PRID hours 4-8 etc.

In conclusion: 1) celecoxib was superior to placebo for time specific measures of efficacy starting at 1-1.5 hours and continuing up to 12 hours; 2) celecoxib was superior to placebo for duration of effect as measured by median time to rescue medication; 3) time to onset of perceptible pain relief showed to no difference between placebo and celecoxib in these studies; 4) in general, the positive comparator naproxen was superior to celecoxib. These results were corroborated by additional sensitivity analyses; 5) this is not a good model for assessment of multidose efficacy

3. Indication - management of acute pain

a. Trial N49-98-02-082

Single dose double blind placebo controlled comparison of the analgesic activity of celecoxib 200 mg, hydrocodone 10 mg/acetaminophen 1000mg and placebo in post-orthopedic surgical patients.

1.Objectives and rationale

The primary objective of this study was to compare the analgesic activity of celecoxib 200 mg versus placebo in patients with moderate to severe pain following orthopedic surgery. The secondary objective was to compare the analgesic activity of hydrocodone 10 mg/acetaminophen 1000 mg versus placebo in patients with moderate to severe pain following orthopedic surgery.

2. Design

The trial was a multicenter single dose double blind randomized placebo controlled parallel group study. Patients who were experiencing moderate to severe post-orthopedic surgery pain and met the inclusion and exclusion criteria were admitted to the study and were randomly assigned to receive a single dose of

celecoxib 200 mg, hydrocodone 10 mg/acetaminophen 1000 mg, or placebo. Patients must have received their first dose of study medication within 54 hours after the end of anesthesia. Pain was assessed by each patient at Baseline (0 hour), and at 0.25, 0.50, 0.75, 1.0, 1.5, 2.0, 3.0, 4.0, 5.0, 6.0, 7.0, and 8.0 hours post dose, or until rescue medication was administered, using self-rating scales. If the patient required rescue medication during the study, the patient was dropped from the study and no further pain assessments were conducted after rescue. The duration of the treatment period was up to 8 hours after administration of study medication.

3. Protocol

a. Population and procedures

Patients who were experiencing moderate to severe post-operative pain and who met the inclusion and exclusion criteria were admitted to the study. Pain was assessed by each patient at baseline and multiple time points using self rating scales. To qualify for the study candidates must have met the following inclusion criteria:

1. Been male or female of legal age of consent or older;
2. If the patient was female, she had been using adequate contraception, not been lactating, and had a negative serum pregnancy test within 14 days prior to surgery and had a negative pregnancy test (urine or serum) at Baseline (prior to administration of study medication);
3. Been in satisfactory health as determined by the Investigator on the basis of medical history and physical examination;
4. Undergone an orthopedic surgery procedure, such as a total or partial hip replacement or total or partial knee replacement or shoulder reconstruction.
5. Been administered the first dose of study medication within 54 hours after the end of anesthesia;
6. If the patient had received a parenteral analgesic, including patient controlled analgesia (PCA), subsequent to arrival in the recovery room, the patient must have tolerated and derived some pain relief from at least one oral dose of hydrocodone 10 mg/acetaminophen 1000 mg prior to receiving the first dose of study medication;

Comment: the reason for this is unclear, although relief from oral hydrocodone suggests that the patient was under medicated with use of PCA and there was potential for improvement with the use of study medication.

7. If the patient had used medication, such as tricyclic anti-depressants, anti-histamines, tranquilizers, neuroleptics, anti-emetics and parenteral analgesics subsequent to the end of anesthesia, the patient must have waited a minimum of three hours prior to receiving the first dose of study medication;

Comment: the washout for tricyclics is probably inadequate. However, baseline pain intensity was similar for all treatment groups.

8. Had a Baseline Pain Intensity 45 mm as measured on a Visual Analog scale.
9. Agreed to remain at facility allowing completion of protocol mandated pain assessments and safety evaluations through 8 hours after administration of the study medication;
10. Provided written informed consent prior to undergoing any procedures for this study.

Figure 42: Summary of protocol and evaluations

	Pretreatment Period (Up to 14 Days Prior to the First Dose of Study Medication			TREATMENT PERIOD												
				Hours												
	Screening	Surgery	Base-line [a]	0	.25	.50	.75	1	1.5	2	3	4	5	6	7	8	Post-Txt [b]
Medical history	x																
Physical examination	x																x
Vital signs [c]	x		x													x	x
Clinical laboratory assessments	x		x														x
Pregnancy test [d]	x		x														
Pain assessments [e]				x [f]	x	x	x	x	x	x		x		x	x	x	
Study drug				x [g]													
Global evaluation [h]																	x
Symptoms/ Medications			x	x	x	x	x	x	x	x		x		x		x	

a. Prior to administration of study medication.
b. After completion of the Treatment Period or administration of rescue medication.
c. Vital signs collected at Baseline (0 hour) and 8 hours after the first dose of study medication.
d Female patients of childbearing potential must have had a negative serum pregnancy test prior to surgery (not collected on CRF) and a negative pregnancy test (urine or serum) prior to first dose of study medication.
e. Pain intensity (Categorical and Visual Analog Scale (VAS)), pain relief, pain at least half gone, perceptible pain relief, and meaningful pain relief will also be recorded.
f. Pain intensity only (Categorical and VAS).
g. Study medication administered within 54 hours after the end of anesthesia.
h. The Patient Global Evaluation was completed at the end of the Treatment Period or just prior to the use of rescue medication.

Candidates were not eligible for admission if they had any of the following:

1. scheduled surgical procedure, along with the orthopedic procedure, that was expected to produce a greater degree of surgical trauma than the orthopedic procedure alone;
2. Any cognitive impairment that would, in the Investigator's opinion, preclude study participation or compliance with protocol mandated procedures;
3. Dysphagia, difficulty swallowing capsules, or inability to tolerate oral medication;
4. A diagnosis of having or having been treated for esophageal, gastric, pyloric channel, or duodenal ulceration within 30 days prior to receiving the first dose of study medication;
5. A history of uncontrolled chronic disease that, in the opinion of the Investigator,
would contraindicate study participation or confound interpretation of results;
6. Had or had been treated for (i.e., surgery, chemotherapy, radiation therapy, etc.) and/or had been in remission for any cancer other than basal cell carcinoma for less than two years prior to screening;

7. Any laboratory abnormality at screening that, in the opinion of the Investigator, would contraindicate study participation, including AST, ALT, blood urea nitrogen (BUN), or creatinine ³1.5 times the upper limit of the reference range;
8. Lactose intolerance that required significant dietary modification or treatment with enzyme supplementation;
9. A history of hypersensitivity to any NSAID, cyclooxygenase inhibitor, sulfonamide, opiate, or analgesic that has a cross sensitivity to the medication used in this study;
10. History of known alcohol, analgesic, or narcotic abuse within the two years prior to screening;
11. Receipt of agents during the first 8 hours following administration of study medication that could confound assessment of analgesic activity. Such medications included tricyclic anti-depressants, tranquilizers, anti-histamines, neuroleptics and anti-emetics;
12. Unwillingness to abstain from the routine use of NSAIDs and analgesics during this study, except aspirin <325 mg per day used for cardiovascular prophylaxis;
13. Received any investigational medication within the 30 days prior to the first dose of study medication or was scheduled to receive any investigational drug other than celecoxib during the course of this study;
14. An unwillingness to abstain from alcohol from the time of surgery through 24 hours after the completion of participation in the study;
15. Previous admission to this study.

Each patient was assigned two bottles with either celecoxib and placebo, hydrocodone and placebo, or placebo in both. Study medication was administered on site. Rescue medication was permitted at any time. Any patient requiring rescue medication completed a pain assessment just prior to the taking the rescue medication. The protocol and evaluations are summarized in Figure 42.

b.Endpoints

The primary measures of efficacy were: PID (categorical) PR, PRID, time to rescue medication, and time to onset of perceptible pain relief. The secondary measures of efficacy were: PID (VAS), PPID, PPR, SPID 4,6,8; TOTPAR 4, 6, 8; SPRID 4, 6, 8; time first experienced 50% pain relief; time to onset of meaningful pain relief; patients global evaluation. Other measures of efficacy were time to onset of analgesia; SPID 3;TOTPAR 3; SPRID 3.

Comment: The primary measures of efficacy are preferred by the Division.

c. Statistical consideration

All analyses were based on the intent to treat cohort. Isolated missing values were imputed using LOCF and BOCF. PID PR, PRID, TOTPAR etc were analyzed using ANOVA with treatment, center, and patient's pain intensity at baseline as

factors. Time to onset of meaningful pain relief etc. were analyzed using survival analysis methods. The proportion of patients with 50% pain relief was analyzed by pairwise Fisher's Exact test.

Safety analyses were examined with scatter diagrams, shift tables, and a display of descriptive statistics with paired t-test applied to mean changes from Baseline.

There were seven protocol violations including 2 in the placebo group, 2 in the celecoxib treated group, and 3 in the hydrocodone group.

4. Results

The ITT cohort consisted of 200 patients. The treatment groups were comparable for age, race, gender and with respect to height, weight, vital signs. Baseline pain intensity was comparable across treatment groups.

Efficacy endpoint outcomes

For all of the analyses discussed below, the LOCF approach is discussed. Mean PID scores for celecoxib treatment were numerically greater than placebo at .5 and 1 through 8 hours, and statistically significant at the 3 through 5 hour assessment (see Figure 43). For hydrocodone the differences from placebo were significant at the 2 through 5 hour assessment.
Figure 43 shows PID scores for hours 0-3; accompanying table provides PID values at each time point and statistical comparison with placebo.

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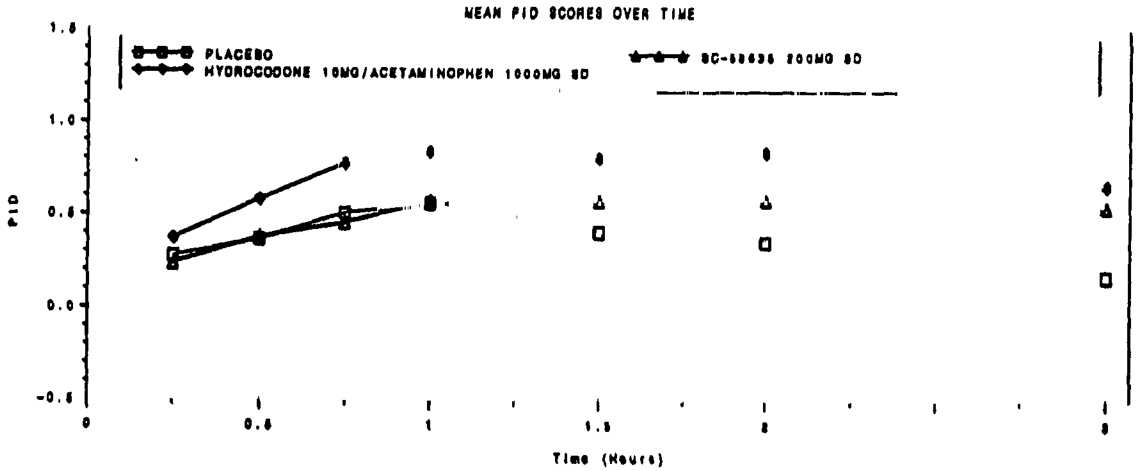
Figure 43: Plot of PID scores for hours 0-3

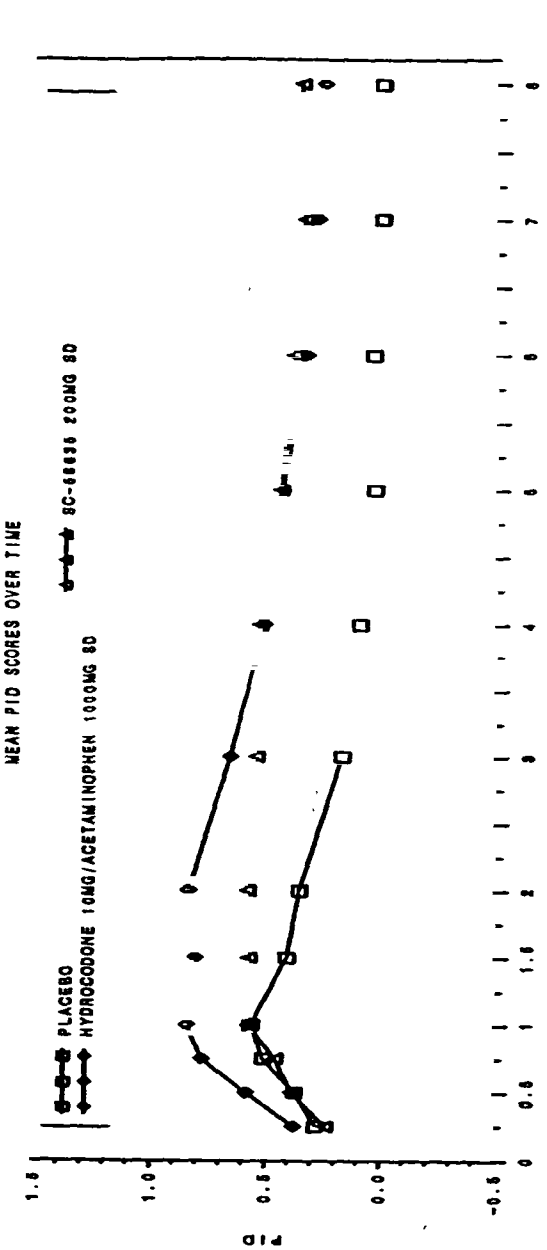


ASSESSMENT TIME POINTS (IN HOURS)

TREATMENT	0.25	0.50	0.75	1.00	1.50	2.00	3.00
HYDROCODONE 10MG/ ACETAMINOPHEN 1000MG SD	0.37 (0.60) 67(a) A(e)	0.58 (0.74) 67 A	0.76 (0.78) 67 A	0.84 (0.79) 67 A	0.81 (0.88) 50 A	0.84 (0.86) 46 A	0.65 (0.93) 42 A
SC-58635 200MG SD	0.24 (0.48) 66 A	0.38 (0.73) 66 A	0.48 (0.82) 66 B	0.57 (0.88) 67 A	0.57 (0.85) 50 A	0.56 (1.07) 42 AB	0.54 (1.08) 36 A
PLACEBO	0.28 (0.48) 66 A	0.37 (0.63) 66 A	0.51 (0.84) 65 AB	0.56 (0.88) 66 A	0.41 (0.86) 46 A	0.35 (1.04) 36 B	0.17 (0.84) 27 B
TREATMENT p-VALUE (b)	0.270	0.187	0.028	0.112	0.085	0.030	0.018
TRT*BASELINE p-VALUE (c)	0.594	0.563	0.162	0.864	0.458	0.416	0.304
TRT*CENTER p-VALUE (c)	0.718	0.632	0.617	0.710	0.771	0.026	0.630
GENDER p-VALUE (d)	0.548	0.207	0.760	0.894	0.653	0.805	0.254
BASELINE p-VALUE (b)	< 0.001	< 0.001	< 0.001	< 0.001	0.008	0.001	< 0.001
CENTER p-VALUE (b)	0.007	0.293	0.081	0.888	0.701	0.495	0.122
SURGERY TYPE p-VALUE (d)	0.654	0.956	0.969	0.144	0.073	0.156	0.088
RMS ERROR (b)	0.496	0.681	0.707	0.810	0.913	0.966	0.937

(a) Sample size is not extrapolated.
(b) Model: PID = mu + Ti + Pi(0)j + center + error.
(c) Model: PID = mu + Ti + Pi(0)j + interaction term + center + error.
(d) Model: PID = mu + Ti + Pi(0)j + effect term + center + error.
(e) Based on model (b) LSmeans. Treatments with the same letter are not significantly different from each other.

Figure 44: Plot of PID scores for hours 0-8



ASSESSMENT TIME POINTS (IN HOURS)

TREATMENT	4.00	6.00	6.00	7.00	8.00
HYDROCODONE 10MG/ ACETAMINOPHEN 1000MG BD	0.81 (0.88) 30(a) A(a)	0.43 (0.80) 30 A	0.33 (0.77) 23 A	0.25 (0.78) 16 A	0.25 (0.78) 17 A
SC-68636 200MG BD	0.89 (1.07) 26 A	0.44 (1.03) 26 A	0.38 (1.01) 26 A	0.34 (0.98) 20 A	0.36 (1.00) 18 A
PLACEBO	0.00 (0.00) 21 B	0.03 (0.82) 10 B	0.04 (0.82) 11 A	0.00 (0.92) 11 A	0.00 (0.92) 8 A

TREATMENT P-VALUE (b)	0.028	0.022	0.088	0.104	0.103
TRT*BASELINE P-VALUE (c)	0.420	0.662	0.835	0.880	0.878
TRT*CENTER P-VALUE (c)	0.842	0.880	0.838	0.823	0.729
GENDER P-VALUE (d)	0.282	0.338	0.197	0.097	0.119
BASELINE P-VALUE (b)	0.001	0.004	0.001	0.001	< 0.001
CENTER P-VALUE (b)	0.266	0.870	0.709	0.841	0.800
SURGERY TYPE P-VALUE (d)	0.181	0.284	0.111	0.198	0.181
RMS ERROR (b)	0.826	0.808	0.887	0.884	0.887

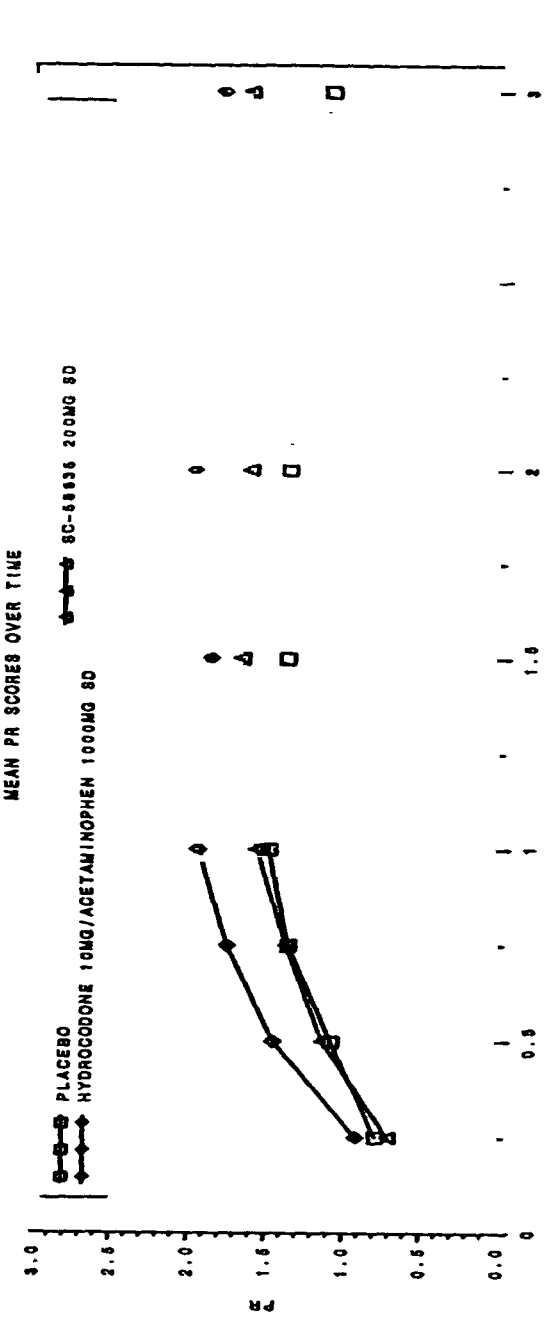
(a) Sample size in cell estimated.
(b) Model: PID = mu + TI + PI(TO) + interaction term + center + error. (c) Model: PID = mu + TI + PI(TO)| + center + error.
(d) Based on model (b) Lsmeans. Treatments with the same center + error.
letter are not significantly different from each other.

Mean PR scores for celecoxib treatment were numerically greater than placebo at the .5 through 8 hour assessment and statistically significant from 3 through 6

hours (see Figure 44). For hydrocodone the differences from placebo were significant at the 3 through 6 hour assessment.

Figure 45 provides PR scores for hours 0-3, and accompanying table provides PR values and statistical comparisons with placebo.

Figure 45: Plot of PR scores for hours 0-3



TREATMENT	0.25	0.50	0.75	1.00	1.50	2.00	3.00
	ASSESSMENT TIME POINTS (IN HOURS)						
HYDROCODONE 10MG/ ACETAMINOPHEN 1000MG BD	0.81 (0.98) 87(c) A(e)	1.45 (1.18) 87 A	1.78 (1.21) 87 A	1.94 (1.31) 87 A	1.86 (1.36) 80 A	1.87 (1.41) 48 A	1.79 (1.48) 42 A
SC-88035 200MG BD	0.71 (0.86) 88 A	1.13 (1.21) 88 A	1.57 (1.20) 88 A	1.88 (1.30) 87 A	1.66 (1.43) 80 A	1.62 (1.31) 42 A	1.62 (1.53) 36 A
PLACEBO	0.78 (0.84) 86 A	1.08 (1.06) 86 A	1.35 (1.16) 86 A	1.48 (1.34) 86 A	1.37 (1.40) 46 A	1.36 (1.48) 26 A	1.09 (1.33) 27 B
TREATMENT p-VALUE (b)	0.358	0.131	0.088	0.088	0.188	0.056	0.018
TRT*CENTER p-VALUE (c)	0.871	0.888	0.488	0.697	0.700	0.852	0.656
GENDER p-VALUE (d)	0.418	0.346	0.388	0.627	0.661	0.382	0.320
CENTER p-VALUE (d)	0.008	0.066	0.438	0.529	0.316	0.276	0.040
SURGERY TYPE p-VALUE (d)	0.189	0.809	0.610	0.512	0.405	0.489	0.264
RMS ERROR (b)	0.867	1.157	1.191	1.310	1.393	1.460	1.406

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

Figure 46: Plot of PR scores for hours 0-8

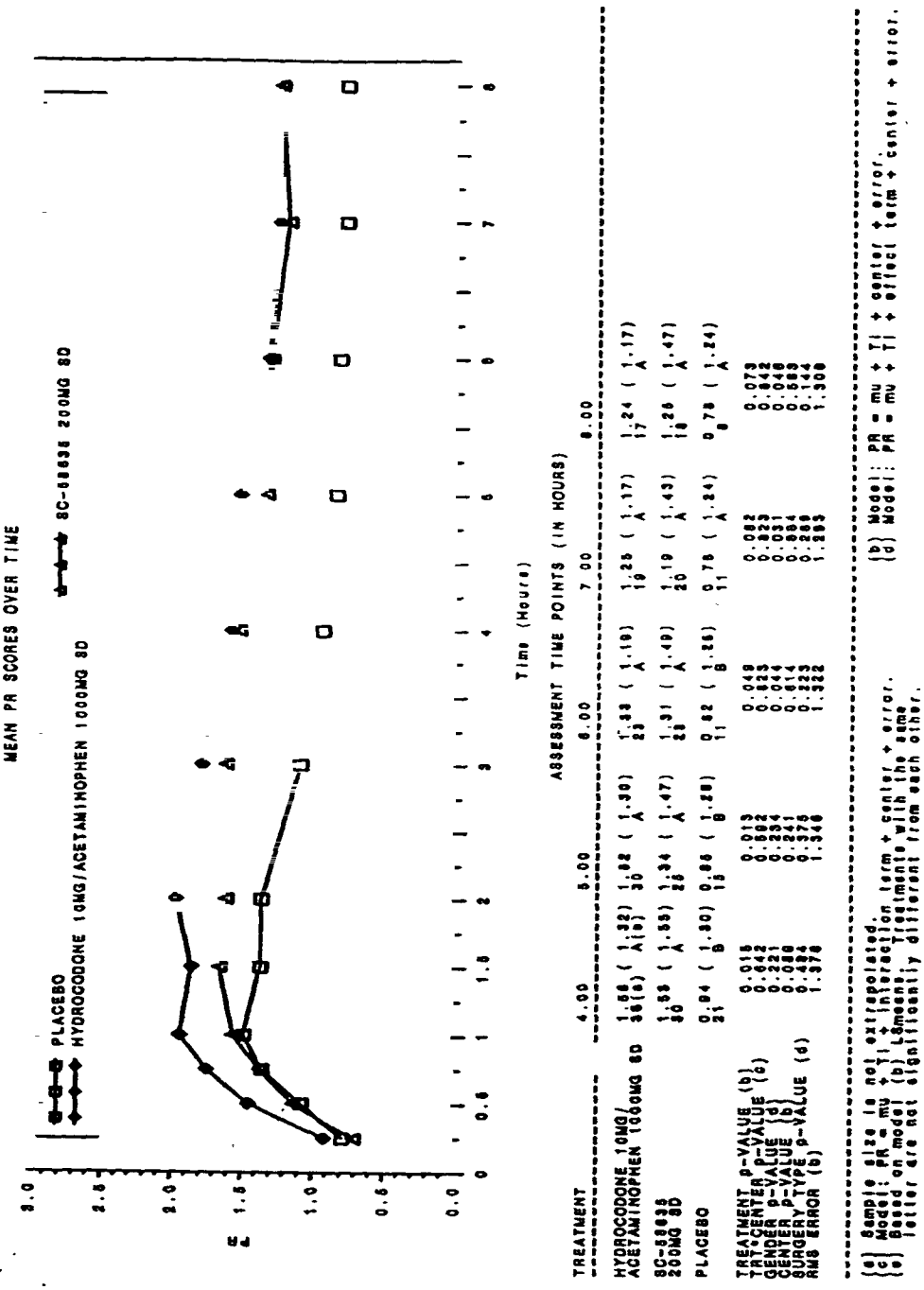


Figure 46 provides PR scores for hours 0-8 and table provides PR scores for hours 4-8.

Mean PRID for the celecoxib treatment was numerically greater than placebo for the .5 and 1 through 8 hour assessment and statistically significant compared to

placebo at the 3 through 5 hour assessment. For hydrocodone the differences from placebo were significant at the 2 through 5 hour assessment.

Figures 47 and 48 and accompanying tables (following page) provides PRID scores for hours 0-8.

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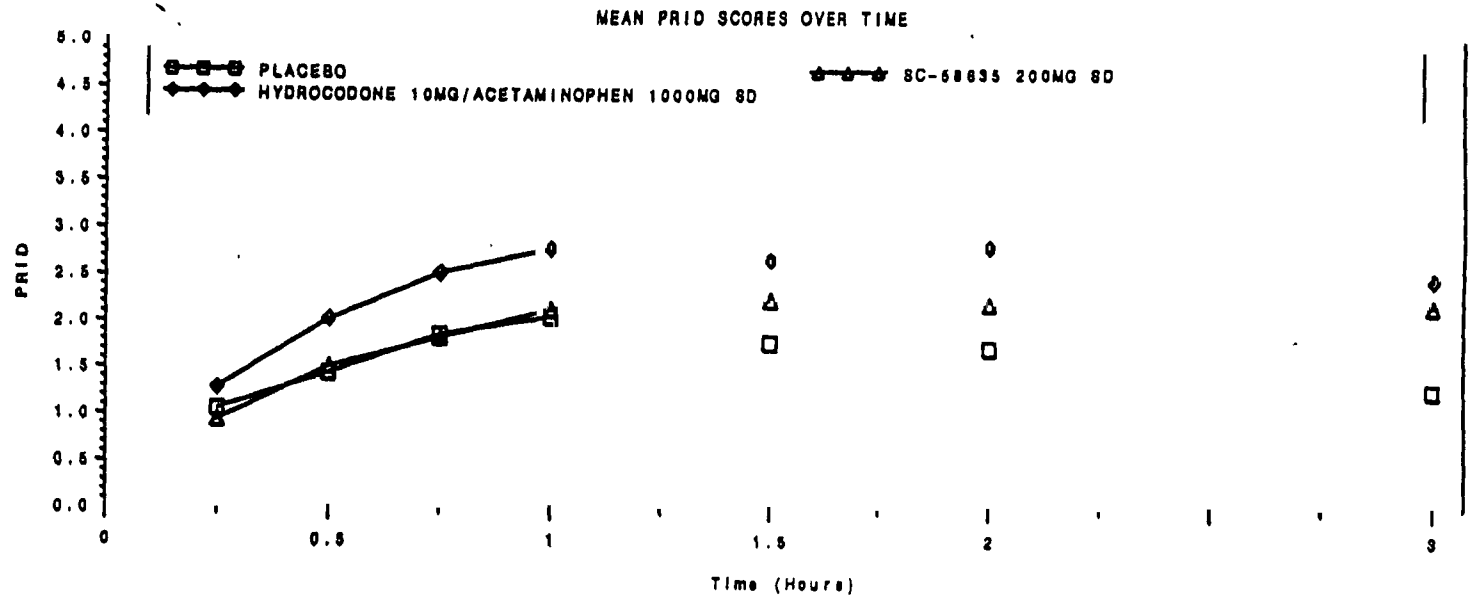


ASSESSMENT TIME POINTS (IN HOURS)

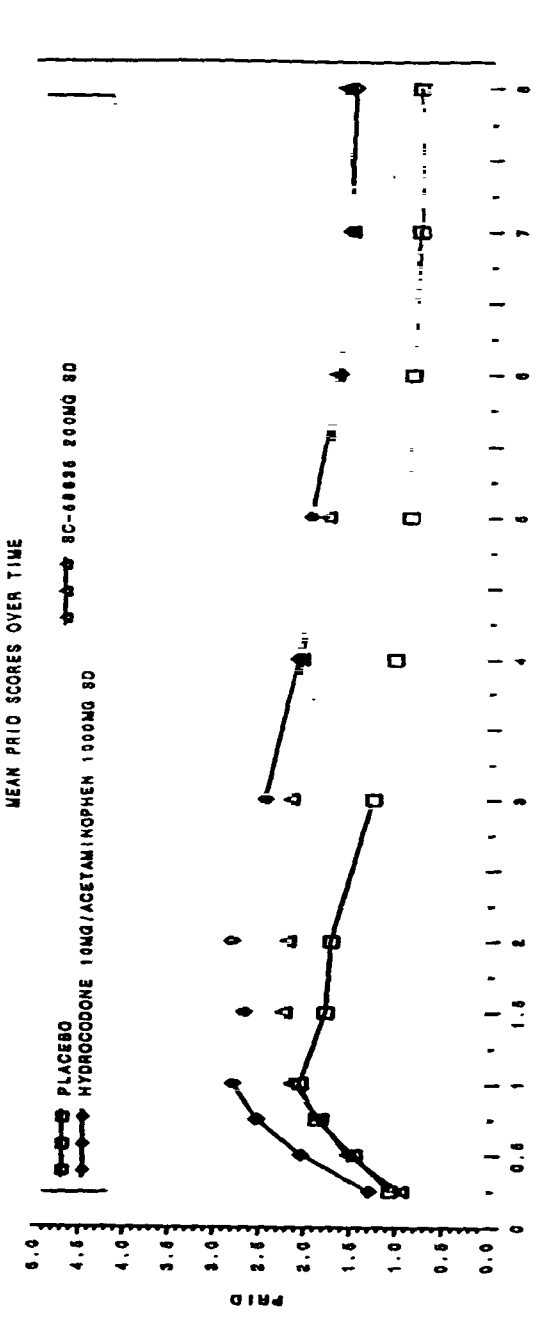
TREATMENT	0.25	0.50	0.75	1.00	1.50	2.00	3.00
HYDROCODONE 10MG/ ACETAMINOPHEN 1000MG SD	1.28 (1.41) 67 (a) A (e)	2.03 (1.79) 67 A	2.52 (1.86) 67 A	2.79 (1.99) 67 A	2.66 (2.12) 60 A	2.61 (2.27) 48 A	2.45 (2.24) 42 A
SC-58635 200MG SD	0.94 (1.26) 68 A	1.51 (1.66) 68 A	1.82 (1.92) 68 A	2.13 (2.11) 67 A	2.24 (2.36) 50 A	2.19 (2.52) 42 AB	2.19 (2.52) 35 A
PLACEBO	1.06 (1.18) 65 A	1.45 (1.61) 65 A	1.66 (1.69) 65 A	2.05 (2.12) 65 A	1.77 (2.25) 46 A	1.72 (2.42) 36 B	1.26 (2.20) 27 B

TREATMENT p-VALUE (b)	0.276	0.129	0.051	0.093	0.090	0.041	0.013
TRT*BASELINE p-VALUE (c)	0.624	0.114	0.197	0.568	0.283	0.365	0.345
TRT*CENTER p-VALUE (c)	0.873	0.554	0.475	0.892	0.750	0.704	0.732
GENDER p-VALUE (d)	0.409	0.244	0.854	0.640	0.604	0.525	0.278
BASELINE p-VALUE (b)	0.027	0.002	0.009	0.020	0.304	0.162	0.189
CENTER p-VALUE (b)	0.003	0.141	0.634	0.630	0.460	0.347	0.061
SURGERY TYPE p-VALUE (d)	0.328	0.955	0.610	0.226	0.218	0.316	0.167
RMS ERROR (b)	1.236	1.699	1.811	2.049	2.234	2.387	2.279

(a) Sample size is not extrapolated.
(b) Model: PRID = mu + TI + PI(Q)| + center + error.
(c) Model: PRID = mu + TI + PI(Q)| + interaction term + center + error.
(d) Model: PRID = mu + TI + PI(Q)| + effect term + center + error.
(e) Based on model (b) LSmeans. Treatments with the same letter are not significantly different from each other.

Figure 47: Plot of PRID scores for hours 0-3

Figure 48: Plot of PRID scores for hours 0-8



ASSESSMENT TIME POINTS (IN HOURS)

TREATMENT	4.00	5.00	6.00	7.00	8.00
HYDROCODONE 10MG/ ACETAMINOPHEN 1000MG BD	2.08 (2.07) 36(6) A(B)	1.98 (2.00) 30 A	1.88 (1.84) 23 A	1.64 (1.88) 19 A	1.49 (1.88) 17 A
SC-66835 200MG BD	2.00 (2.08) 30 A	1.70 (2.43) 25 A	1.60 (2.43) 23 A	1.53 (2.34) 20 A	1.00 (2.41) 16 A
PLACEBO	1.08 (2.14) 21 B	0.88 (2.10) 15 B	0.68 (2.06) 11 A	0.78 (2.07) 11 A	0.78 (2.07) 8 A

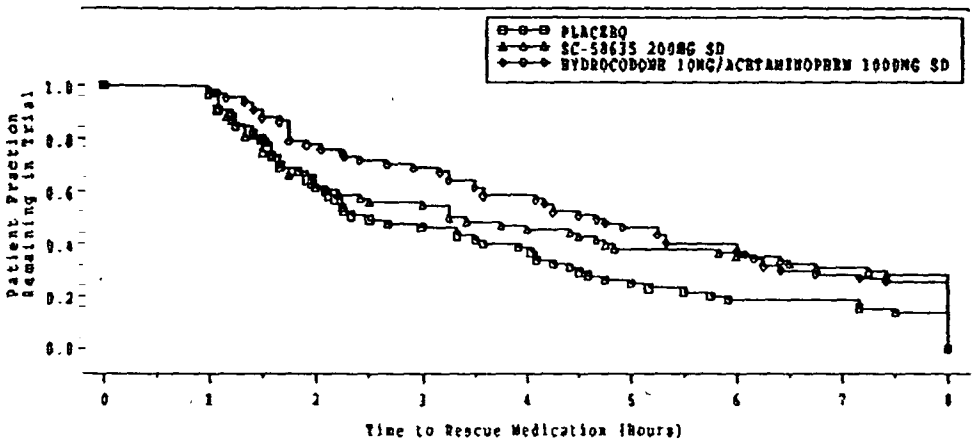
TREATMENT P-VALUE (b)	0.015	0.015	0.054	0.088	0.079
TRT*BASELINE P-VALUE (c)	0.201	0.686	0.771	0.868	0.801
TRT*CENTER P-VALUE (c)	0.787	0.789	0.808	0.849	0.810
GENDER P-VALUE (b)	0.220	0.207	0.058	0.044	0.081
BASELINE P-VALUE (b)	0.208	0.286	0.187	0.108	0.078
CENTER P-VALUE (b)	0.198	0.377	0.664	0.800	0.731
SURGERY TYPE P-VALUE (c)	0.339	0.312	0.102	0.826	0.134
RMS ERROR (d)	2.243	2.186	2.141	2.106	2.124

(a) Sample size is not extrapolated.
(b) Model: PRID = mu + TI + PI(0)] + interaction term + center + error. (d) Model: PRID = mu + TI + PI(0)] + center + error.
(c) Based on model (b) LSmeans. Treatments with the same letter are not significantly different from each other.

For the preceding endpoints, even the positive comparator did not separate from placebo for the first 2-3 hours.

Rescue medication was taken by 56 (86%) placebo, 49 (72%) celecoxib, and 50 (75%) hydrocodone group. The median time to rescue was longer for celecoxib than placebo but this was not significant. The rescue time for hydrocodone was longer than placebo and this was significant (figure 49).

Figure 49: Time to rescue medication



TREATMENT	N	PATIENTS WHO TOOK RESCUE MEDICATION N (%)	MEDIAN TIME IN H : MIN (a,b)	95%-CI IN H : MIN (c)
HYDROCODONE 10MG/ACETAMINOPHEN 1000MG SD	67	50(75%)	04:35(A)	03:38 TO 06:08
SC-58635 200MG SD	68	49(72%)	03:15(AB)	02:08 TO 05:58
PLACEBO	65	56(86%)	02:25(B)	02:04 TO 04:02

(a) Kaplan-Meier estimate (see Miller, Survival Analysis, page 75).
(b) Logrank test applied as in Fisher's Protected LSD. Treatments with the same letter are not significantly different from each other.
(c) Method of Simon & Lee, Cancer Treat Rep, 1982.

For time to onset of perceptible pain relief there were no differences between any of the groups.

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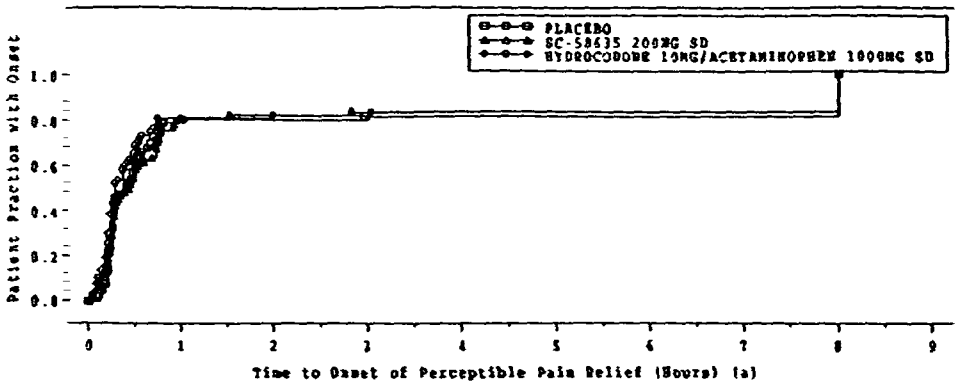
Figure 50: Time to onset of perceptible pain relief



TREATMENT	N	PATIENTS WHO ACHIEVED PERCEPTIBLE PAIN RELIEF N (%)	MEDIAN TIME IN H : MIN (b,c)	95%-CI IN H : MIN (d)
HYDROCODONE 10MG/ACETAMINOPHEN 1000MG SD	67	56 (84%)	00:17 A)	00:14 TO 00:26
SC-58635 200MG SD	68	58 (85%)	00:26 A)	00:16 TO 00:41
PLACEBO	65	53 (82%)	00:23 A)	00:16 TO 00:32

TNT FOR PATIENTS WHO TOOK RESCUE MEDICATION BEFORE REACHING PAIN RELIEF, the time to pain relief is assigned an event time of 0.1 + 0.005((time rescue medication taken - time study drug taken).
(b) Kaplan-Meier estimate (see Miller, Survival Analysis, page 75).
(c) Logrank test applied as in Fisher's Protected LSD. Treatments with the same letter are not significantly different from each other.
(d) Method of Simon & Lee, Cancer Treat Rep, 1982.

Analysis of secondary efficacy measures:

For PID (VAS), celecoxib treatment was significantly different from placebo at the 5 hour assessment only, while for hydrocodone differences were significant at 2, 3, and 5 hours.

PPID (categorical) and PPR for celecoxib and hydrocodone were not significantly different from placebo. For PPID (VAS) only hydrocodone was significantly different from placebo. For patient global assessment there were no significant differences between groups.

The following parameters showed significant differences between celecoxib and placebo: SPID 8 (categorical); SPRID 8.

The following did not show any significant differences between celecoxib and placebo: SPID 4, 6, 8 (VAS); TOTPAR 3, 4, 6, 8; time first experienced at least 50% pain relief; percent of patients experiencing at least 50% pain relief; time to meaningful pain relief; time to onset of analgesia.

Reviewers comments

There is evidence of efficacy of celecoxib for some primary endpoints. Specifically, for the time specific measures of efficacy, celecoxib differs from placebo starting at 2-3 hours continuing only until 5-6 hours post dose. Time to rescue medication was not significantly different from placebo. Time to onset of perceptible pain relief was also not different from placebo.

Therefore, the sponsor has not demonstrated the efficacy of celecoxib in this model of acute pain. It is likely that this is a poor model for demonstrating efficacy of celecoxib because of the initial severity of pain in the post-operative setting.

5. Indication - Acute pain

a. Trial N49-98-02-083

Single dose double blind placebo controlled comparison of the analgesic activity of celecoxib 200 mg, hydrocodone 10mg/acetominophen 1000 mg and placebo in post-general surgical patients.

b. Objectives and rationale

The primary objective of this study was to compare the analgesic activity of celecoxib 200 mg versus placebo in patients with moderate to severe pain following hysterectomy (with or without bilateral salpingo-oophorectomy). The secondary objective was to compare the analgesic activity of hydrocodone/acetaminophen versus placebo in patients with moderate to severe pain following hysterectomy.

b. Design

This was a multi-center single dose double blind randomized placebo controlled parallel group comparison similar to study 082.

Figure 51: Treatment protocol and evaluation

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	Pretreatment Period (Up to 14 Days Prior to the First Dose of Study Medication			TREATMENT PERIOD													
				Hours													
	Screening	Surgery	Base-line [a]	0	.25	.50	.75	1	1.5	2	3	4	5	6	7	8	Post-Txt [b]
Medical history	x																
Physical examination	x																x
Vital signs [c]	x		x													x	x
Clinical laboratory assessments	x		x														x
Pregnancy test [d]	x		x														
Pain assessments [e]				x [f]	x	x	x	x	x	x	x	x	x	x	x	x	
Study drug				x [g]													
Global evaluation [h]																	x
Symptoms/ Medications			x	x	x	x	x	x	x	x	x	x	x	x	x	x	

a. Prior to administration of study medication.
b. After completion of the Treatment Period or administration of rescue medication.
c. Vital signs collected at Baseline (0 hour) and 8 hours after the first dose of study medication.
d. Female patients of childbearing potential must have had a negative serum pregnancy test prior to surgery (not collected on CRF) and a negative pregnancy test (urine or serum) prior to first dose of study medication.
e. Pain intensity (Categorical and VAS), pain relief, pain at least half gone, perceptible pain relief, and meaningful pain relief.
f. Pain intensity only (Categorical and VAS).
g. Study drug administered within 54 hours after the end of anesthesia.
h. The Patient Global Evaluation was completed at the end of the Treatment Period or just prior to rescue analgesia.

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c. Protocol

1 Population

Patients who were experiencing moderate to severe post-operative pain and met all inclusion and exclusion criteria were admitted into the study. Patients with moderate to severe pain after general surgical procedures were enrolled and randomized.

To qualify for study participation, candidates must have:
1. Been male or female of legal age of consent or older;
2. If the patient was female, she had been using adequate contraception, not been lactating, and had a negative serum pregnancy test within 14 days prior to surgery and had a negative pregnancy test (urine or serum) at Baseline (prior to administration of study medication) unless the surgical procedure was a hysterectomy, which would obviate the possibility of a Baseline pregnancy;
3. Been in satisfactory health as determined by the Investigator on the basis of medical history and physical examination;
4. Undergone a non-orthopedic surgical procedure such as hysterectomy with or without salpingo-oophorectomy;
5. Been administered study medication within 54 hours after the end of anesthesia;
6. If, subsequent to arrival in the recovery room, the patient had received a parenteral analgesic, including patient controlled analgesia (PCA), the patient must have tolerated and derived some pain relief from at least one oral dose of hydrocodone 10 mg/acetaminophen 1000 mg prior to receiving the first dose of study drug;
7. Waited a minimum of three hours prior to receiving the first dose of study medication if the patient had used tricyclic antidepressants, antihistamines, tranquilizers, neuroleptics, anti-emetics, or parenteral analgesics subsequent to the end of anesthesia;
8. Had a Baseline Pain Intensity $^{3}45$ mm measured on a Visual Analog scale (VAS);
9. Agreed to remain at the study facility through completion of the protocol mandated pain assessments and safety evaluations for 8 hours after administration of the study medication;
10. Provided written informed consent prior to admission to the study.

Candidates were not eligible if they had any of the following:
1. Any other surgical procedure, along with the non-orthopedic procedure, that was expected to produce a greater degree of surgical trauma than the non-orthopedic surgical procedure alone;
2. Any cognitive impairment that would, in the Investigator's opinion, preclude study participation or compliance with protocol mandated procedures;
3. Dysphagia, difficulty swallowing capsules, or inability to tolerate oral medication;

4. A diagnosis of having or having been treated for esophageal, gastric, pyloric channel, or duodenal ulceration within the 30 days prior to receiving the study medication;
5. A history of any uncontrolled chronic disease that, in the opinion of the Investigator, would contraindicate study participation or confound interpretation of results;
6. Been treated for any cancer (i.e., surgery, chemotherapy, radiation therapy, etc.) and/or been in remission for any cancer other than basal cell carcinoma for less than two years prior to Screening;
7. Any laboratory abnormality at Screening that, in the opinion of the Investigator, would have contraindicated study participation, including AST, ALT, blood urea nitrogen (BUN), or creatinine ^{3}1.5 times the upper limit of the reference range;
8. Lactose intolerance that required significant dietary modification or treatment with enzyme supplementation;
9. A history of hypersensitivity to any NSAID, cyclooxygenase inhibitor, sulfonamides, opiates, or any analgesic that has a cross sensitivity to the medications used in this study;
10. A history of known alcohol, analgesic, or narcotic substance abuse within the two years prior to screening;
11. Receipt of agents during the first 8 hours following administration of study drug that could confound assessment of analgesic activity (i.e., tricyclic antidepressants, tranquilizers, antihistamines, neuroleptics, and anti-emetics);
12. Unwillingness to abstain from the routine use of NSAIDs and analgesics during this study, except aspirin <325 mg per day used for cardiovascular prophylaxis;
13. Received any investigational medication within the 30 days prior to administration of study medication or was scheduled to receive any investigational drug (other than celecoxib) during the course of the study;
14. Unwillingness to abstain from alcohol from the time of surgery through 24 hours after the completion of participation in the study;
15. Previously admitted to this study.

2 Endpoints

Same as study 082.

3 Statistical considerations

Same as study 082.

d. Results

1. Patient disposition

One hundred and ninety eight patients were enrolled at 7 centers and 2 dropped out; therefore the ITT cohort consisted of 196 patients. Baseline demographics were similar for all groups including age, race, height, weight, and vital signs. All patients were female. There was no difference in baseline pain intensity for the groups.

2. Efficacy endpoints outcomes

Analysis of primary endpoints:

The mean PID (categorical) scores for celecoxib using the LOCF approach were significantly different compared to placebo at the 3 through 8 hour assessments, while for hydrocodone the differences were significant at the 2 through 8 hour assessments (see Figures 52 and 53).

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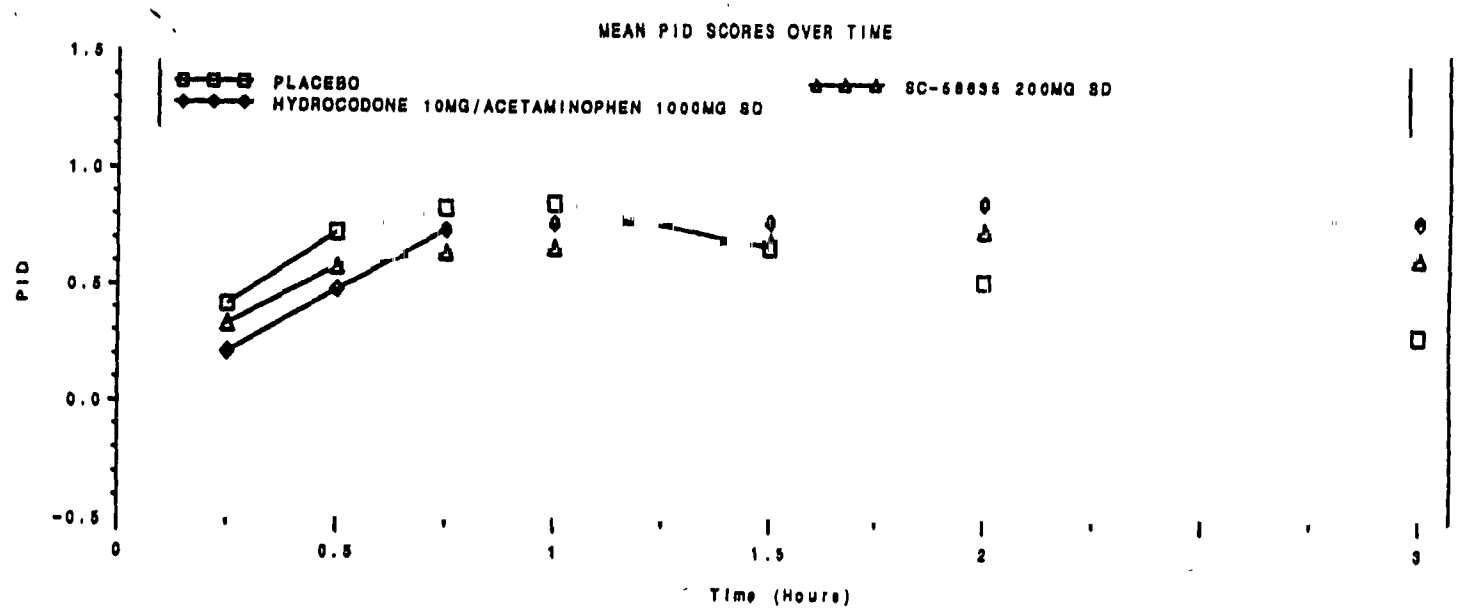


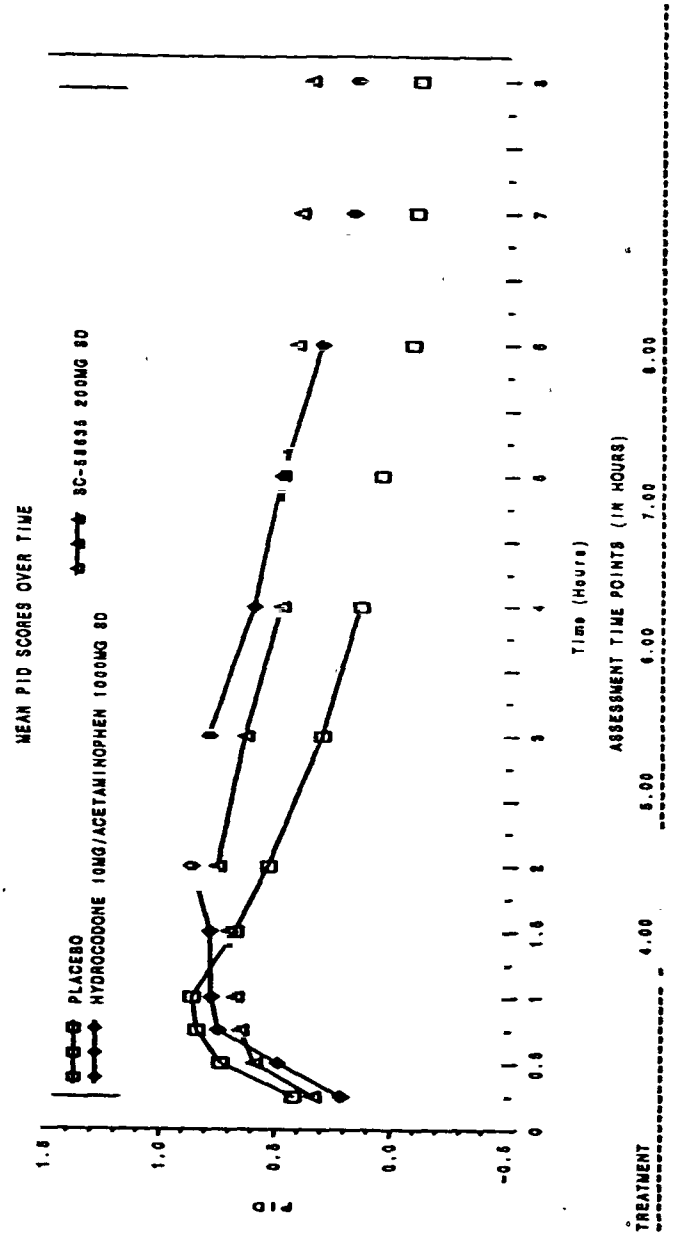
ASSESSMENT TIME POINTS (IN HOURS)

TREATMENT	0.25	0.50	0.75	1.00	1.50	2.00	3.00
HYDROCODONE 10MG/ ACETAMINOPHEN 1000MG SD	0.21 (0.51) 64(a) A(e)	0.45 (0.71) 64 A	0.74 (0.75) 64 A	0.77 (0.78) 64 A	0.78 (0.83) 55 A	0.86 (0.93) 45 A	0.79 (0.92) 44 A
SC-58635 200MG SD	0.33 (0.59) 65 A	0.56 (0.77) 65 A	0.65 (0.84) 65 A	0.67 (0.92) 65 A	0.70 (0.91) 44 A	0.75 (0.95) 39 AB	0.63 (1.02) 36 A
PLACEBO	0.42 (0.66) 67 A	0.73 (0.73) 67 A	0.84 (0.77) 67 A	0.66 (0.85) 67 A	0.67 (0.89) 52 A	0.53 (0.89) 42 B	0.30 (0.82) 30 B
TREATMENT p-VALUE (b)	0.301	0.252	0.204	0.238	0.384	0.043	0.002
TRT*BASELINE p-VALUE (c)	0.748	0.838	0.793	0.938	0.997	0.527	0.741
TRT*CENTER p-VALUE (c)	0.636	0.367	0.736	0.887	0.575	0.333	0.543
BASELINE p-VALUE (b)	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
CENTER p-VALUE (b)	0.064	0.012	0.032	0.012	0.036	0.205	0.563
SURGERY TYPE p-VALUE (d)	0.659	0.566	0.089	0.152	0.152	0.122	0.178
RMS ERROR (b)	0.639	0.666	0.729	0.769	0.828	0.894	0.901

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

Figure 52 :Plot of PID scores for hours 0-3

Figure 53:Plot of PID scores for hours 0-8



TREATMENT	4.00	5.00	6.00	7.00	8.00
	ASSESSMENT TIME POINTS (IN HOURS)				
HYDROCODONE 10MG/ ACETAMINOPHEN 1000MG BD	0.58 (0.82) 87(a) A(e)	0.49 (0.82) 20 A	0.30 (0.83) 22 A	0.17 (0.78) 13 A	0.15 (0.76) 11 A
SC-58635 200MG BD	0.40 (0.87) 27 A	0.48 (0.82) 25 A	0.42 (0.86) 17 A	0.40 (0.83) 16 A	0.35 (0.82) 16 A
PLACEBO	0.15 (0.76) 16 B	0.04 (0.71) 12 B	-0.09 (0.87) 8 B	-0.10 (0.86) 6 B	-0.12 (0.86) 4 B
TREATMENT P-VALUE (b)	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
TRT*BASELINE P-VALUE (c)	0.380	0.856	0.151	0.144	0.149
TRT*CENTER P-VALUE (b)	0.536	0.616	0.600	0.738	0.787
BASELINE P-VALUE (b)	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
CENTER P-VALUE (b)	< 0.018	< 0.001	< 0.001	< 0.004	< 0.003
SURGERY TYPE P-VALUE (d)	0.246	0.127	0.069	0.086	0.102
RMS ERROR (b)	0.801	0.778	0.748	0.689	0.678

(a) Sample size is not adjusted.
(b) Model: PID = mu + Ti + Pi(0)] + interaction term + center + error.
(c) Based on model (b) + Tm*Pm(0)] + Treatments with the same letter are not significantly different from each other.
(d) Model: PID = mu + Ti + Pi(0)] + center + surgery + center + error.

Mean PR scores for celecoxib treatment were significantly different from placebo at the 3 through 8 hour assessment, while for hydrocodone the differences were significant at the 1.5 through 8 hour assessment (see Figures 54 and 55).

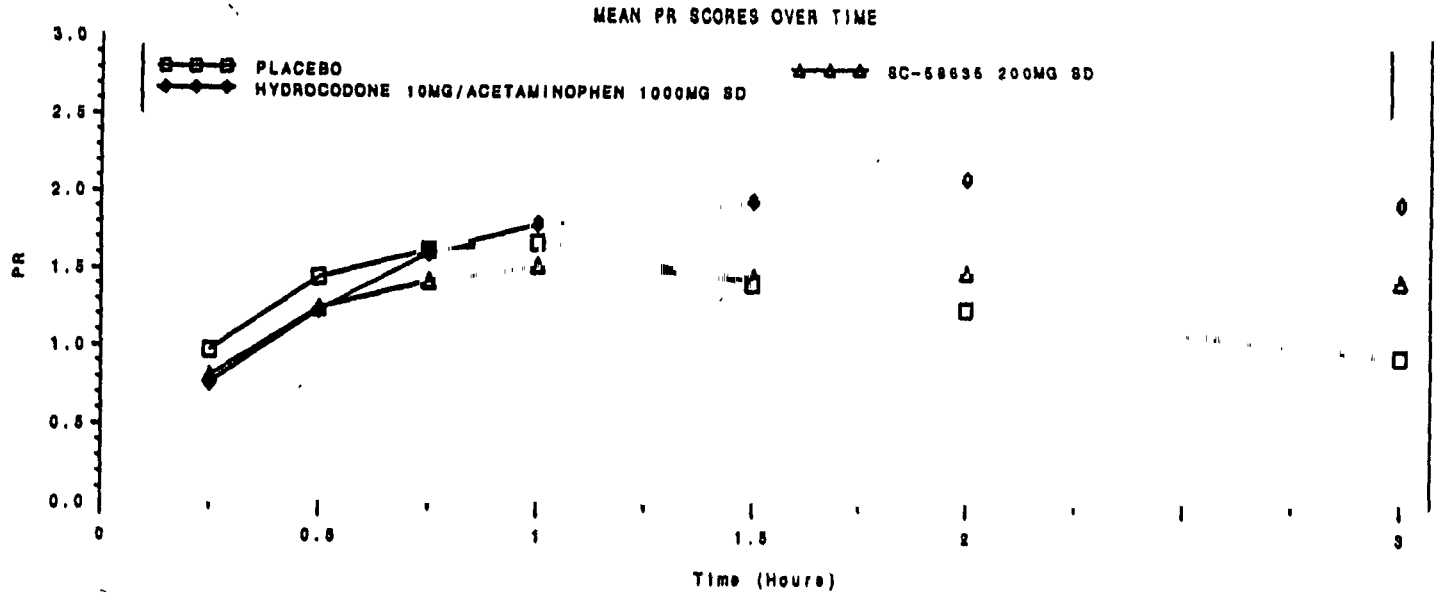


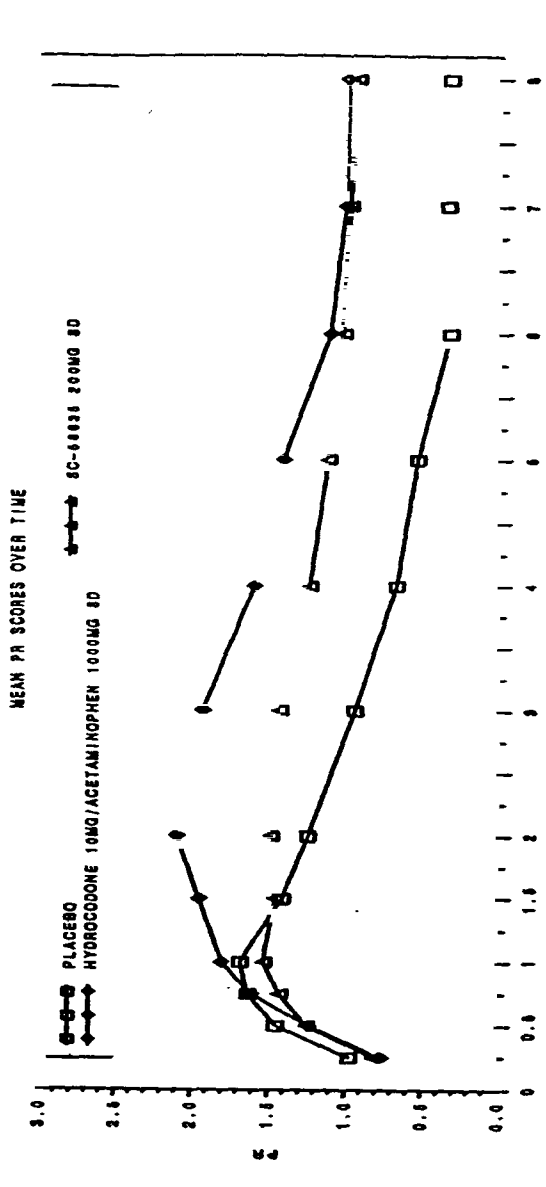
Figure 54 :Plot of PR scores for hours 0-3

ASSESSMENT TIME POINTS (IN HOURS)

TREATMENT	0.25	0.50	0.75	1.00	1.50	2.00	3.00
HYDROCODONE 10MG/ ACETAMINOPHEN 1000MG SD	0.76 (0.89) 64(a) A(e)	1.23 (1.03) 64 A	1.61 (1.19) 64 A	1.60 (1.19) 64 A	1.95 (1.25) 56 A	2.09 (1.42) 45 A	1.93 (1.39) 44 A
SC-58635 200MG SD	0.61 (0.92) 65 A	1.25 (1.08) 65 A	1.43 (1.14) 65 A	1.53 (1.23) 65 A	1.46 (1.26) 44 B	1.49 (1.37) 39 B	1.43 (1.60) 38 B
PLACEBO	0.67 (1.03) 67 A	1.45 (1.17) 67 A	1.63 (1.22) 67 A	1.66 (1.25) 67 A	1.41 (1.32) 52 B	1.25 (1.31) 42 B	0.94 (1.20) 30 C
TREATMENT p-VALUE (b)	0.395	0.462	0.465	0.385	0.022	0.001	< 0.001
TRT*CENTER p-VALUE (c)	0.320	0.568	0.811	0.860	0.505	0.394	0.609
CENTER p-VALUE (b)	0.001	< 0.001	0.001	0.010	0.024	0.122	0.693
SURGERY TYPE p-VALUE (d)	0.245	0.445	0.075	0.342	0.050	0.090	0.139
RMS ERROR (b)	0.907	1.040	1.136	1.180	1.249	1.354	1.376

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

Figure 55:Plot of PR scores for hours 0-8

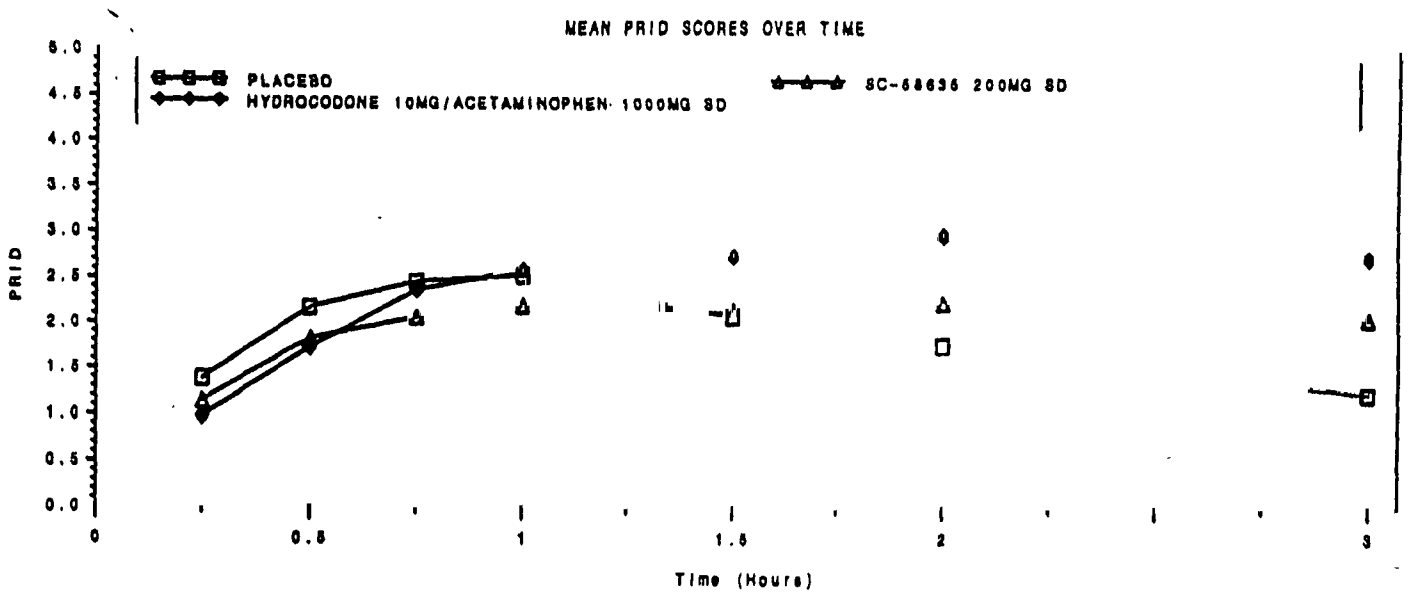


ASSESSMENT TIME POINTS (IN HOURS)

TREATMENT	4.00	5.00	6.00	7.00	8.00
HYDROCODONE 10MG/ ACETAMINOPHEN 1000MG BD	1.60 (1.87) 67(a) A(c)	1.41 (1.33) 25 A	1.11 (1.20) 22 A	1.01 (1.17) 15 A	1.00 (1.14) 11 A
SC-66036 200MG BD	1.24 (1.66) 27 A	1.12 (1.30) 23 A	1.03 (1.30) 17 A	0.88 (1.02) 16 A	0.84 (1.01) 16 A
PLACEBO	0.87 (1.00) 10 B	0.84 (0.84) 10 B	0.83 (0.84) 8 B	0.84 (0.88) 8 B	0.83 (0.84) 6 B
TREATMENT p-VALUE (b)	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
TRT*CENTER p-VALUE (b)	0.610	0.354	0.188	0.332	0.351
CENTER p-VALUE (b)	0.074	0.004	0.002	0.008	0.006
SURGERY TYPE p-VALUE (d)	0.231	0.256	0.188	0.063	0.147
RMS ERROR (b)	1.348	1.184	1.108	1.048	1.038

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

Mean PRID (categorical) for celecoxib was statistically different from placebo at the 3 through 8 hour assessment, while for hydrocodone the differences were significant at the 2 through 8 hour assessments (see Figures 56 and 57).



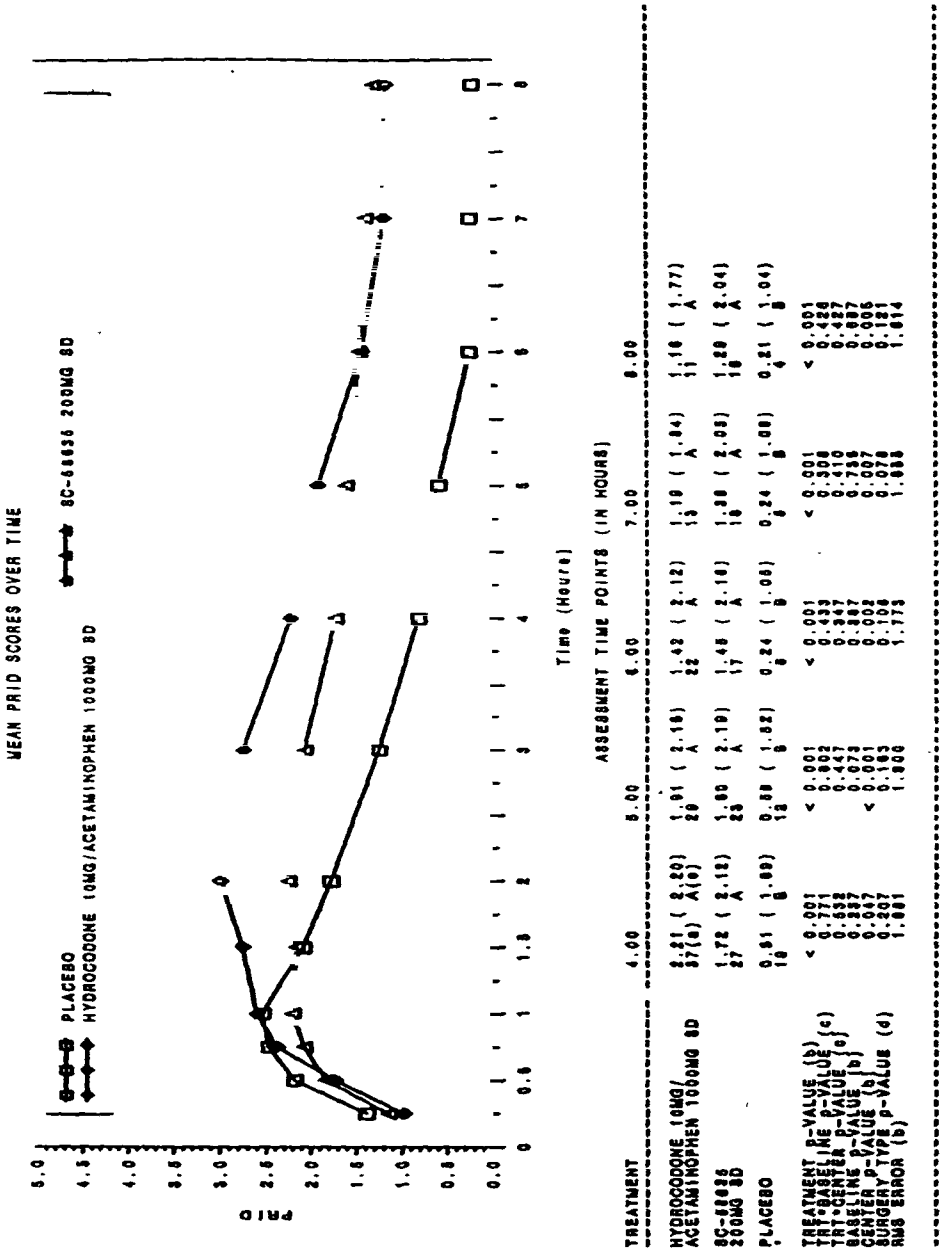
ASSESSMENT TIME POINTS (IN HOURS)

TREATMENT	0.25	0.50	0.75	1.00	1.50	2.00	3.00
HYDROCODONE 10MG/ ACETAMINOPHEN 1000MG SD	0.98 (1.33) 64(a) A(e)	1.73 (1.66) 64 A	2.38 (1.67) 64 A	2.59 (1.67) 64 A	2.75 (1.98) 56 A	2.98 (2.26) 46 A	2.74 (2.22) 44 A
SC-58635 200MG SD	1.14 (1.38) 65 A	1.83 (1.66) 65 A	2.07 (1.65) 65 A	2.20 (2.03) 65 A	2.16 (2.06) 44 A	2.24 (2.22) 39 B	2.06 (2.43) 36 A
PLACEBO	1.39 (1.82) 67 A	2.18 (1.81) 67 A	2.48 (1.90) 67 A	2.54 (2.00) 67 A	2.08 (2.11) 52 A	1.77 (2.12) 48 B	1.24 (1.91) 30 B
TREATMENT p-VALUE (b)	0.367	0.358	0.271	0.281	0.068	0.005	< 0.001
TRT*BASELINE p-VALUE (c)	0.854	0.690	0.609	0.750	0.960	0.909	0.998
TRT*CENTER p-VALUE (c)	0.294	0.524	0.907	0.923	0.975	0.471	0.614
BASELINE p-VALUE (b)	< 0.001	0.008	0.015	0.042	0.179	0.015	0.569
CENTER p-VALUE (b)	0.003	< 0.001	0.001	0.004	0.017	0.119	0.889
SURGERY TYPE p-VALUE (d)	0.668	0.361	0.044	0.186	0.068	0.085	0.141
RMS ERROR (b)	1.363	1.601	1.782	1.898	2.001	2.180	2.211

(a) Sample size is not extrapolated.
(b) Model: PRID = mu + TI + PI(O)] + center + error.
(c) Model: PRID = mu + TI + PI(O)] + interaction term + center + error.
(d) Model: PRID = mu + TI + PI(O)] + surgery + center + error.
(e) Based on model (b) LSmeans. Treatments with the same letter are not significantly different from each other.

Figure 56 :Plot of PRID scores for hours 0-3

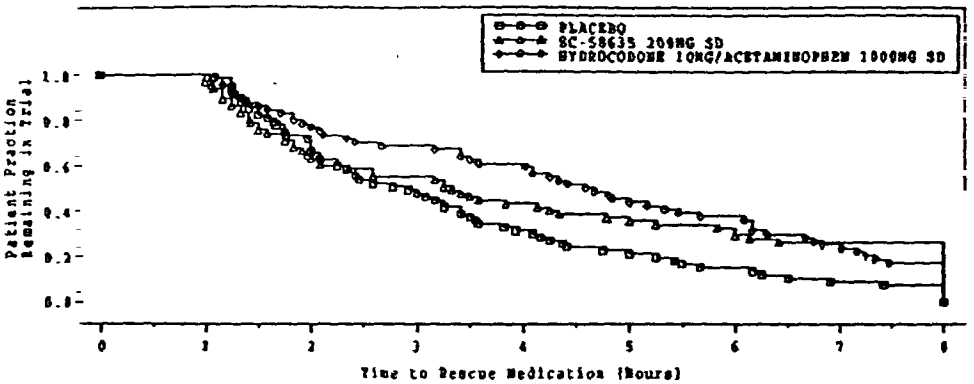
Figure 57: Plot of PRID scores for hours 0-8



In general, the positive comparator separated from placebo only starting at 1.5-2 hours, while celecoxib did not separate from placebo until 3 hours post dose.

The time to rescue medication in the celecoxib group was significantly different from placebo, and likewise for hydrocodone (see Figure 58).

Figure 58: Time to rescue medication

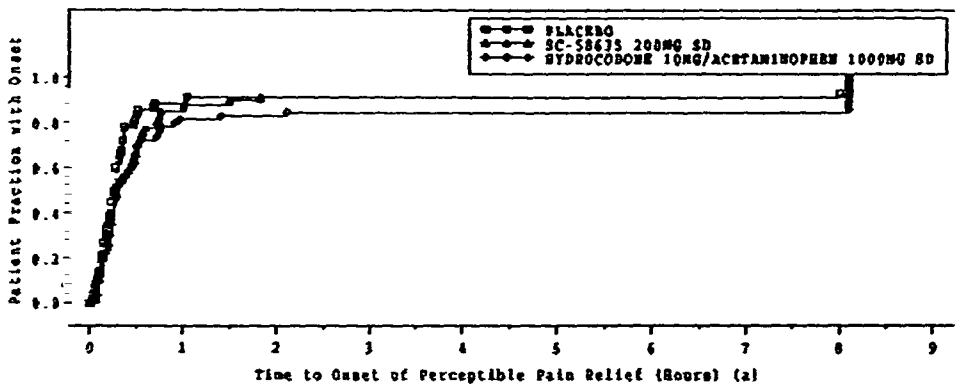


TREATMENT	N	PATIENTS WHO TOOK RESCUE MEDICATION N (%)	MEDIAN TIME IN H : MIN (a,b)	95%-CI IN H : MIN (c)
HYDROCODONE 10MG/ACETAMINOPHEN 1000MG SD	64	51(80%)	04:39[A]	03:35 TO 06:05
SC-58635 200MG SD	65	48(74%)	03:18[A]	02:05 TO 04:47
PLACEBO	67	62(93%)	02:51[B]	02:15 TO 03:38

(a) Kaplan-Meier estimate (see Miller, Survival Analysis, page 75).
(b) Logrank test applied as in Fisher's Protected LSD. Treatments with the same letter are not significantly different from each other.
(c) Method of Simon & Lee, Cancer Treat Rep, 1982.

Time to onset of perceptible pain relief was not significantly different for the celecoxib treatment; however the differences for hydrocodone were also not significant (see Figure 59).

Figure 59: Time to onset of perceptible pain relief



TREATMENT	N	PATIENTS WHO ACHIEVED PERCEPTIBLE PAIN RELIEF N (%)	MEDIAN TIME IN H : MIN (b,c)	95%-CI IN H : MIN (d)
HYDROCODONE 10MG/ACETAMINOPHEN 1000MG SD	64	52(81%)	00:18[A]	00:15 TO 00:28
SC-58635 200MG SD	65	59(91%)	00:16[A]	00:12 TO 00:25
PLACEBO	67	61(91%)	00:15[A]	00:13 TO 00:18

(a) For patients who took rescue medication before reaching pain relief, the time to pain relief is assigned an event time of 0.1 + 0.005* (time rescue medication taken - time study drug taken).
(b) Kaplan-Meier estimate (see Miller, Survival Analysis, page 75).
(c) Logrank test applied as in Fisher's Protected LSD. Treatments with the same letter are not significantly different from each other.
(d) Method of Simon & Lee, Cancer Treat Rep, 1982.

Analysis of secondary efficacy measures:

The following secondary measures demonstrated differences that were statistically different comparing celecoxib and placebo, favoring celecoxib: PID (VAS) at 4 through 8 hours; SPID (categorical) at 6 and 8 hours; SPID (VAS) at 8 hours only; TOTPAR at 6 and 8 hours; SPRID at 6 and 8 hours; percent of patients experiencing at least 50% pain relief at 6 through 8 hours.

The following secondary measures for celecoxib did not show statistically significant differences from placebo: PPID (categorical); PPID (VAS); PPR; time first experienced 50% pain relief; time to meaningful pain relief; time to onset of analgesia.

e. Reviewer's comments

This study demonstrates that for some of the primary efficacy measures celecoxib is superior to placebo in regards to analgesic efficacy. Specifically, celecoxib was superior to placebo for time to remedication. However, it was not superior to placebo for time to onset of perceptible pain relief. In addition, for the time specific measures of efficacy celecoxib differed from placebo starting at 3 hours post dose and continued up to 8 hours. Hydrocodone differed from placebo starting at 1.5-2 hours post dose through 8 hours. However, time to onset of perceptible pain relief was also not significantly different comparing hydrocodone to placebo.

Therefore, for this model of pain the data do not support the conclusion that celecoxib is superior to placebo. Celecoxib appears to provide marginal analgesia at later time points after dosing, but did not appear efficacious at early time points of treatment as a significant effect was not seen until 3 hours post dose.

4. Indication-management of acute pain

a. Trial N49-99-06-085

Randomized double blind placebo controlled single dose and active controlled multiple dose assessment of the analgesic activity of celecoxib 200 mg in post-orthopedic surgical patients.

b. Objectives and rationale

The primary objectives of this study were to compare the analgesic efficacy of single dose of celecoxib 200 mg versus placebo during the first 8 hours after study medication in patients with moderate to severe pain following orthopedic

surgery and to evaluate the safety of celecoxib 200 mg. The secondary objectives of this study were to evaluate the analgesic efficacy and dosing regimen for celecoxib 200 mg during the repeated dosing phase and to compare the analgesic efficacy of a single dose of hydrocodone 10 mg/acetaminophen 1000mg versus placebo in patients with moderate to severe pain following orthopedic surgery.

c. Design

This trial was a multi-center double blind randomized active and placebo controlled single dose and active controlled multiple dose parallel group comparison of the safety and efficacy of celecoxib 200 mg, hydrocodone 10 mg/acetaminophen 1000mg, orally administered to patients with moderate to severe post-orthopedic surgical pain.
Patients who met the inclusion criteria were randomly assigned to receive either celecoxib 200 mg, hydrocodone 10 mg/acetaminophen 1000 mg, or placebo. The duration of the study was up to 5 days. The study was divided into two assessment periods, the SDAP and the MDAP. The duration of the SDAP was 8.0 hours after the first dose of study medication. The duration of the MDAP was up to 5 days

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Figure 60: Protocol and evaluations for single and multiple dose periods

	Pretreatment Period (Up to 14 Days Prior to the First Dose of Study Medication)			SINGLE-DOSE ASSESSMENT PERIOD												
				Hours												
	Screening	Surgery	Base-line [a]	0	25	.50	.75	1	1.5	2	3	4	5	6	7	8
Medical history	x															
Physical Examination	x															
Vital signs	x		x													x
Clinical Laboratory Tests	x		x													
Pregnancy Test [b]	x		x													
Pain Assessments [c]				x [d]	x	x	x	x	x	x	x	x	x	x	x	x
Study drug [e]				x												
Diary cards			x	x	x	x	x	x	x	x	x	x	x	x	x	x
Symptoms/ Medication			x	x	x	x	x	x	x	x	x	x	x	x	x	x

a) Prior to administration of study medication.
b) Female patients of childbearing potential must have had a negative serum pregnancy test prior to surgery (not collected on CRF) and a negative pregnancy test (urine or serum) prior to first dose of study medication.
c) Pain intensity (Categorical and VAS), Pain Relief, Pain at Least Half Gone, Perceptible Pain Relief, and Meaningful Pain Relief On Day 1, Hour 0, only Pain Intensity (Categorical and VAS) was recorded
d) Pain Intensity only (Categorical and VAS).
e) The first dose of study medication was administered within 24 hours after the end of anesthesia and patients randomized to receive placebo as first dose received either SC-58635 200 mg or hydrocodone 10 mg/acetaminophen 1000 mg during the MDAP.

	MULTIPLE-DOSE ASSESSMENT PERIOD					POSTTREATMENT [f]
	Day 1	Day 2	Day 3	Day 4	Day 5	
Physical Examination						x
Vital Signs						x
Clinical Laboratory Testing						x
Pregnancy Test [g]						x
Pain Assessments [h]	x	x	x	x	x	
Study Drug	x	x	x	x	x	
Global Evaluation [i]	x	x	x	x	x	
APS Pain Measure [j]					x	
Symptoms/Medication	x	x	x	x	x	
Diary Cards	x	x	x	x	x	

f) Posttreatment evaluations were carried out at the end of the study or at termination in either the SDAP or the MDAP (within 72 hours after completion of the MDAP or administration of rescue medication).
g) Pregnancy test performed at Posttreatment on outpatients only (not collected on CRF).
h) Pain Intensity only (Categorical) was assessed prior to every dose of study medication and, if used, prior to rescue medication. Maximum Pain Intensity and Maximum Pain Relief were assessed at bedtime.
i) A Patient's Overall Global Evaluation was completed at bedtime on each of the treatment days and at the end of the Treatment Period.
j) APS Pain Measure was completed at the end of the MDAP.

following the first dose of study medication. Patients who took one dose of rescue medication during the SDAP were continued into the MDAP along with patients who took no rescue medication. Patients who required a second dose of rescue medication during the SDAP were discontinued from the study. In the MDAP, any patient who had been randomized to placebo during the SDAP and who continued into the MDAP, was blindly pre-assigned to receive either celecoxib 200 mg TID PRN or hydrocodone 10 mg/acetaminophen 1000 mg TID PRN; no patients received placebo during this period. Remedication with study medication was permitted no less than 8 hours after the first dose of study medication and every 8 hours thereafter, up to three doses per day, as needed. Patients who required rescue medication during the MDAP were discontinued from the study whereas patients who remedicated with study medication remained in the study.

d. Protocol

1. Population and procedures

To qualify for the study candidates must meet the following inclusion criteria:
1. Been male or female of legal age of consent.
2. For women of childbearing potential, confirmed use of adequate contraception, not been lactating, and had a negative serum pregnancy test within 14 days prior to surgery and a negative pregnancy test (serum or urine) at Baseline prior to receiving the first dose of study medication.
3. Been in satisfactory health as determined by the Investigator on the basis of medical history and physical examination.
4. Undergone uncomplicated orthopedic surgery for:
a. bunionectomy;
b. anterior cruciate ligament repair;
c. open reduction and internal fixation of long bone fractures;
d. laminectomy;
e. osteotomy for acquired or congenital malformations; or
f. other orthopedic procedure requiring open manipulation of bone with periosteal elevation.
5. Received the first dose of study medication within 24 hours after the end of anesthesia.
6. If the patient had used an analgesic or other agent subsequent to the end of anesthesia that could confound the analgesic response, the patient had to wait a minimum of three hours prior to receiving the first dose of study medication. Such medications included tricyclic antidepressants, tranquilizers, neuroleptics, neuroleptic anti-emetics (i.e. compazine, Phenergan, etc.), and analgesics.
7. Had a Baseline Pain Intensity >45 mm as measured on a Visual Analog scale (VAS).
8. Been able to remain at a facility allowing completion of protocol mandated pain assessments under the supervision of the site personnel through 8 hours after the first dose of study medication.
9. Provided written informed consent prior to admission to this study.

Candidates were not eligible for admission if they had any of the following:
1. Undergone a total hip or total knee replacement.
2. Were scheduled to undergo any other surgical procedure, along with the orthopedic procedure, that was expected to produce a greater degree of surgical trauma than the orthopedic procedure alone.
3. Any cognitive impairment that would, in the Investigator's opinion, preclude study participation or compliance with protocol mandated procedures.
4. Dysphagia, difficulty swallowing capsules, or was unable to tolerate oral medication.
5. Been diagnosed as having or had treatment initiated for esophageal, gastric, pyloric channel, or duodenal ulceration within the 30 days prior to receiving the first dose of study medication.
6. A history of uncontrolled chronic disease that, in the opinion of the Investigator, would have contraindicated study participation or confounded interpretation of results.
7. Were being or had been treated for cancer (i.e., surgery, chemotherapy, radiation therapy, etc.) and/or had been in remission for any cancer other than basal cell carcinoma for less than two years prior to screening.
8. Had any laboratory abnormality at screening that, in the opinion of the Investigator, would contraindicate study participation, including aspartate transaminase (AST), alanine transaminase (ALT), blood urea nitrogen (BUN), or creatinine >1.5 times the upper limit of the reference range.
9. Were lactose intolerant and required significant dietary modification or treatment with enzyme supplementation.
10. Had a history of hypersensitivity to any NSAID, COX inhibitor, sulfonamides, opiates or any analgesic that has a cross sensitivity to the medications used in this study.
11. Had a history of known alcohol, analgesic, or narcotic substance abuse within the two years prior to screening.
12. Had long acting (greater than six hours) local anesthetics such as Marcaine injected into the index joint space at the time of arthroscopy.
13. Been treated with patient controlled analgesia (PCA) or NSAIDs subsequent to the end of anesthesia.
14. Would have received agents during the first 8 hours following the first dose of study medication that could confound assessment of analgesic efficacy. Such medications included tricyclic antidepressants, neuroleptics, tranquilizers, and neuroleptic anti-emetics.
15. Were unwilling to abstain from the routine use of NSAIDs and analgesics during this study other than specified in Sections 4.4 and 4.5 of the protocol. Aspirin <325 mg per day used for cardiovascular prophylaxis was exempt from this exclusion.
16. Received any investigational medication within the 30 days prior to the first dose of study medication or was scheduled to receive any investigational medication other than celecoxib during the course of this study.
17. Were unwilling to abstain from alcohol from the time of surgery through 24 hours after the completion of participation in this study.

18. Were previously admitted to this study.
19. The patient took corticosteroids (oral, IV, IM) or changed the dose regimen of corticosteroids (oral, IV, IM) within four weeks before receiving the first dose of study medication (doses of up to and including 10 mg prednisone or equivalent/day were allowed if begun >4 weeks prior to receiving the first dose of study medication).

Patients were randomized to receive 4 bottles of study medication with either celecoxib and placebo or hydrocodone and placebo or placebo only for the single dose assessment period (SDAP). Patients randomized to the placebo during SDAP and who continued into the MDAP were blindly pre-assigned to receive either celecoxib or hydrocodone.

Endpoints

The primary measures of efficacy for the SDAP were: PID (categorical), PR, PRID, time to rescue medication, and time to onset of perceptible pain relief. The secondary measures of efficacy were PID (VAS), PPID, PPR, SPID 4,6,8, TOTPAR 4,6,8, SPRID 4,6,8, time first experienced at least 50% pain relief, proportion of patients who experienced at least 50% pain relief, time to onset of meaningful pain relief. Other measures of efficacy for the SDAP were: time to onset of analgesia, SPID 3, TOTPAR 3, SPRID 3.

Efficacy measurements for the MDAP included: the number of patients who dropped out due to treatment failure/rescue medication; number of doses of study medication taken; duration between two consecutive doses; maximum pain intensity in the past 24 hours; maximum pain relief in the past 24 hours; APS pain measure; patient's global assessment; pain intensity before each dose of study medication.

Statistical considerations

A sample size of 60 patients per treatment group was chosen to detect a difference of at least .50 in the PID score with at least 80% power and an alpha level of .05.

There were eight protocol violations including 4 in the placebo group, 3 in the celecoxib group, and one in the hydrocodone group, but no patient was withdrawn.

Results

Patient disposition

All 198 randomized patients received a single dose of either celecoxib, hydrocodone, or placebo. 176 patients entered the MDAP and 31 withdrew. In the

SDAP there were 42 (61%) treatment failures in the placebo group, 29 (43%) in the celecoxib group, and 29 (47%) in the hydrocodone group. In the MDAP there were 5 (5%) patients terminated from the study for treatment failure in the celecoxib group and 18 (21%) in the hydrocodone group.

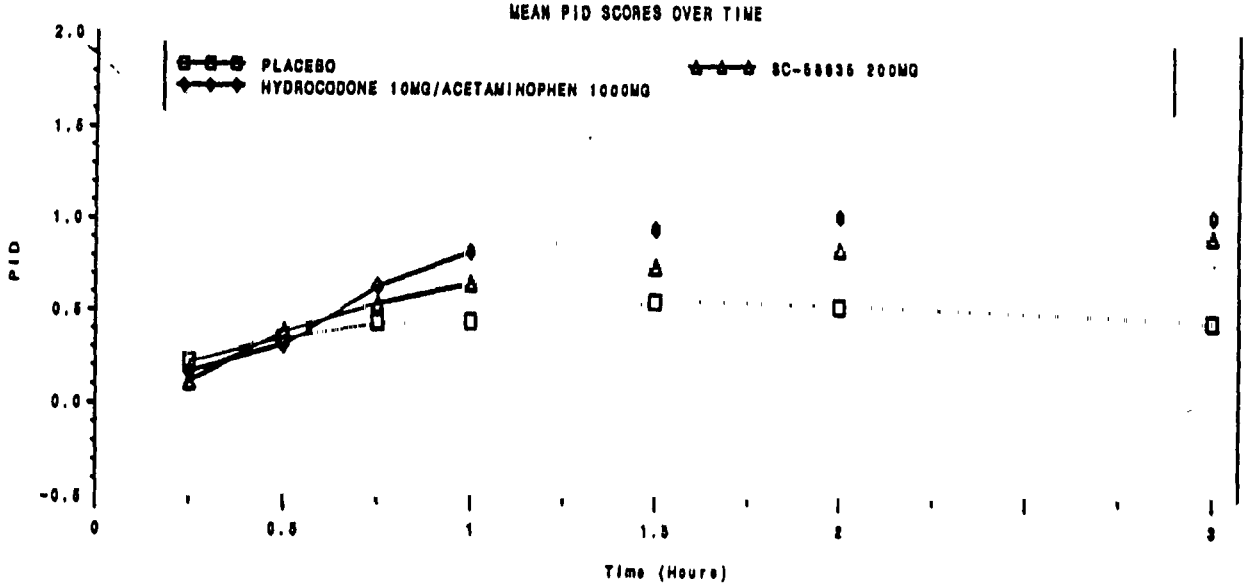
In terms of baseline demographics, for the SDAP, the treatments were comparable for race, gender. There was a statistically significant difference for age across treatment groups (p=.03). For the MDAP baseline demographics were comparable for race and gender but was again different for age. All groups were comparable for height, weight, vital signs. The type of surgical procedure was comparable across treatment groups. The baseline pain intensity was also comparable across treatment groups.

Results

Analysis of primary efficacy measures:

For the SDAP:

Differences in mean PID (categorical) scores for celecoxib were statistically significant compared to placebo at the 2 through 8 hour assessments. For hydrocodone differences were significant compared to placebo at the 1 through 7 hour assessment (see Figures 61 and 62).



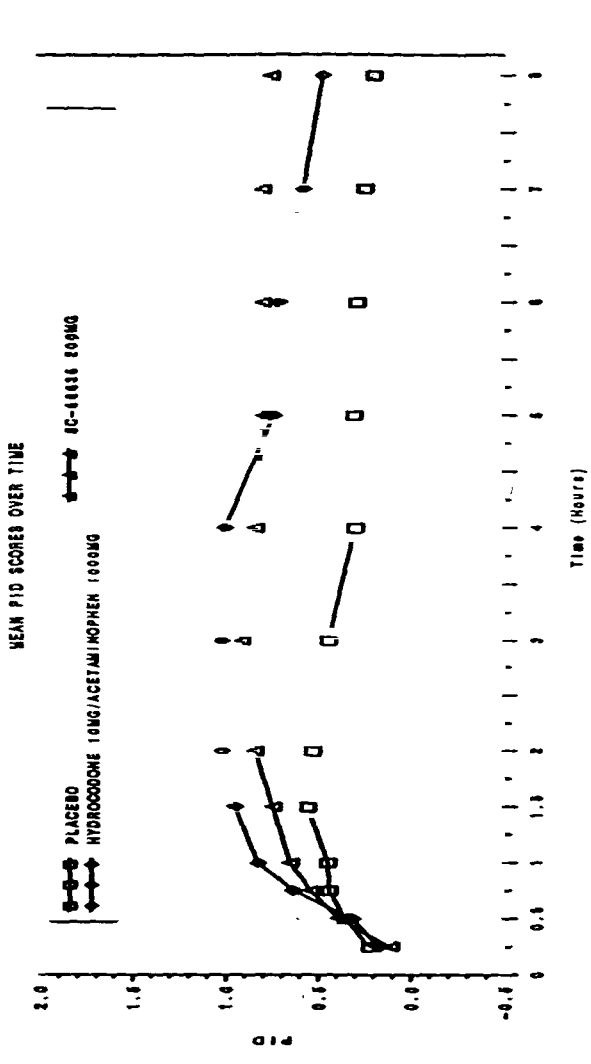
ASSESSMENT TIME POINTS (IN HOURS)

TREATMENT	0.25	0.50	0.75	1.00	1.50	2.00	3.00
HYDROCODONE 10MG/ ACETAMINOPHEN 1000MG	0.17 (0.38) 80(a) A(e)	0.32 (0.59) 80 A	0.63 (0.84) 80 A	0.83 (0.88) 80 A	0.86 (0.78) 56 A	1.02 (0.81) 52 A	1.02 (0.98) 47 A
SC-58635 200MG	0.11 (0.44) 84 A	0.38 (0.81) 84 A	0.54 (0.78) 84 A	0.86 (0.83) 84 AB	0.75 (0.82) 58 AB	0.84 (0.81) 50 A	0.91 (0.98) 45 A
PLACEBO	0.22 (0.48) 68 A	0.35 (0.66) 68 A	0.44 (0.72) 68 A	0.45 (0.72) 67 B	0.66 (0.82) 53 B	0.53 (0.88) 43 B	0.44 (0.84) 35 B
TREATMENT p-VALUE (b)	0.182	0.818	0.211	0.009	0.018	0.005	< 0.001
TRT*BASELINE p-VALUE (c)	0.786	0.767	0.793	0.888	0.745	0.934	0.868
TRT*CENTER p-VALUE (c)	0.003	0.277	0.112	0.059	0.106	0.470	0.321
GENDER p-VALUE (d)	0.009	0.684	0.254	0.725	0.704	0.838	0.568
BASELINE p-VALUE (b)	0.105	0.051	0.027	0.051	0.084	0.033	0.013
CENTER p-VALUE (b)	< 0.001	0.103	0.005	0.040	0.412	0.288	0.091
SURGERY TYPE p-VALUE (d)	0.884	0.927	0.301	0.056	0.093	0.131	0.428
RMS ERROR (b)	0.411	0.562	0.569	0.716	0.804	0.811	0.891

(a) Sample size is not extrapolated.
(b) Model: PID = mu + TI + PI(O)| + center + error.
(c) Model: PID = mu + TI + PI(O)| + interaction term + center + error.
(d) Model: PID = mu + TI + PI(O)| + effect term + center + error.
(e) Based on model (b) LSmeans. Treatments with the same letter are not significantly different from each other.

Figure 61 :Plot of PID scores for hours 0-3

Figure 62:Plot of PID scores for hours 0-8



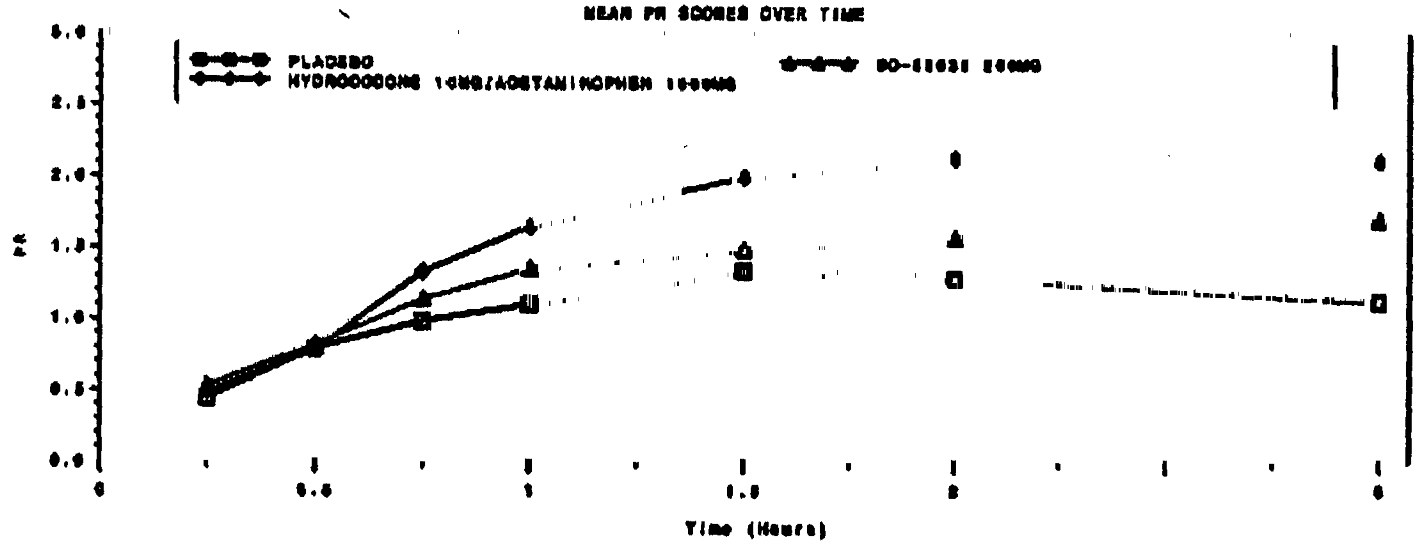
ASSESSMENT TIME POINTS (IN HOURS)

TREATMENT	4.00	5.00	6.00	7.00	8.00
HYDROCODONE 10MG/ ACETAMINOPHEN 1000MG	1.06 (0.09) 44(b) A(c)	0.74 (0.09) 38 A	0.71 (0.09) 38 A	0.88 (0.09) 34 A	0.47 (0.09) 36 AB
SC-58635 200MG	0.84 (0.09) 37 A	0.78 (0.09) 35 A	0.79 (0.09) 35 A	0.79 (1.02) 35 A	0.79 (1.09) 35 A
PLACEBO	0.30 (0.09) 33 B	0.30 (0.09) 33 B	0.26 (0.09) 33 B	0.24 (0.09) 34 B	0.19 (0.09) 33 B

TREATMENT p-VALUE (b)	< 0.001	0.004	0.004	0.004	0.004
TRT*BASELINE p-VALUE (e)	0.810	0.774	0.200	0.800	0.810
TRT*CENTER p-VALUE (e)	0.815	0.074	0.200	0.800	0.478
GENDER p-VALUE (d)	0.074	0.081	0.814	0.800	0.800
BASELINE p-VALUE (b)	0.012	0.001	0.003	< 0.001	< 0.001
CENTER p-VALUE (b)	0.826	0.815	0.881	0.386	0.444
SURGERY TYPE p-VALUE (d)	0.348	0.488	0.848	0.646	0.750
RMS ERROR (b)	0.870	0.888	0.882	0.888	0.870

(a) Sample size is not extrapolated.
(b) Model: PID = mu + TI + PI(O)] + interaction term + center + error.
(c) Based on model (b) Lsmeans. Treatments with the same letter are not significantly different from each other.
(d) Model: PID = mu + TI + PI(O)] + center + error.

Differences in mean PR scores for celecoxib were significant compared to placebo at the 3 through 8 hour assessment. For hydrocodone these differences were significant at the 1 through 8 hour assessment (see Figures 63 and 64).



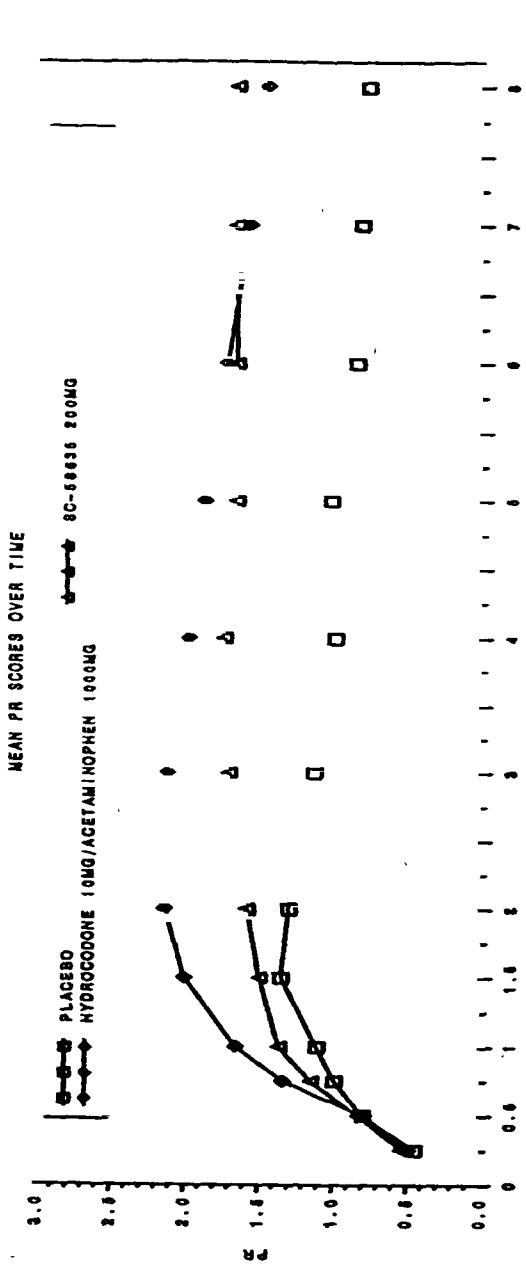
ASSESSMENT TIME POINTS (IN HOURS)

TREATMENT	0.25	0.50	0.75	1.00	1.50	2.00	3.00
HYDROCODONE 10MG/ ACETAMINOPHEN 1000MG	0.45 (0.77) 60(a) A(c)	0.78 (0.67) 60 A	1.33 (1.00) 60 A	1.65 (1.13) 60 A	2.00 (1.16) 55 A	2.13 (1.18) 52 A	2.12 (1.40) 47 A
SC-[illegible] 200MG	0.53 (0.81) 64 A	0.82 (0.88) 64 A	1.14 (1.13) 64 A	1.36 (1.21) 64 AB	1.45 (1.28) 58 B	1.60 (1.51) 56 B	1.70 (1.48) 45 A
PLACEBO	0.44 (0.74) 66 A	0.79 (0.94) 66 A	0.99 (1.06) 66 A	1.10 (1.10) 61 B	1.33 (1.35) 53 B	1.29 (1.38) 43 B	1.10 (1.37) 36 B
TREATMENT p-VALUE (b)	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	< [illegible]
TRT-CENTER p-VALUE (c)	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
GENDER p-VALUE (d)	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
CENTER p-VALUE (b)	< [illegible]	< [illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
SURGERY TYPE p-VALUE (d)	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
RMS ERROR (b)	0.748	0.861	1.057	1.156	1.266	1.379	1.364

(a) Sample size is not extrapolated.
(b) Model: PR = mu + Ti + center + error.
(c) Model: PR = mu + Ti + interaction term + center + error.
(d) Model: PR = mu + Ti + effect term + center + error.
(e) Based on model (b) LSmeans. Treatments with the same letter are not significantly different from each other.

Figure 63 :Plot of PR scores for hours 0-3

Figure 64 :Plot of PR scores for hours 0-8



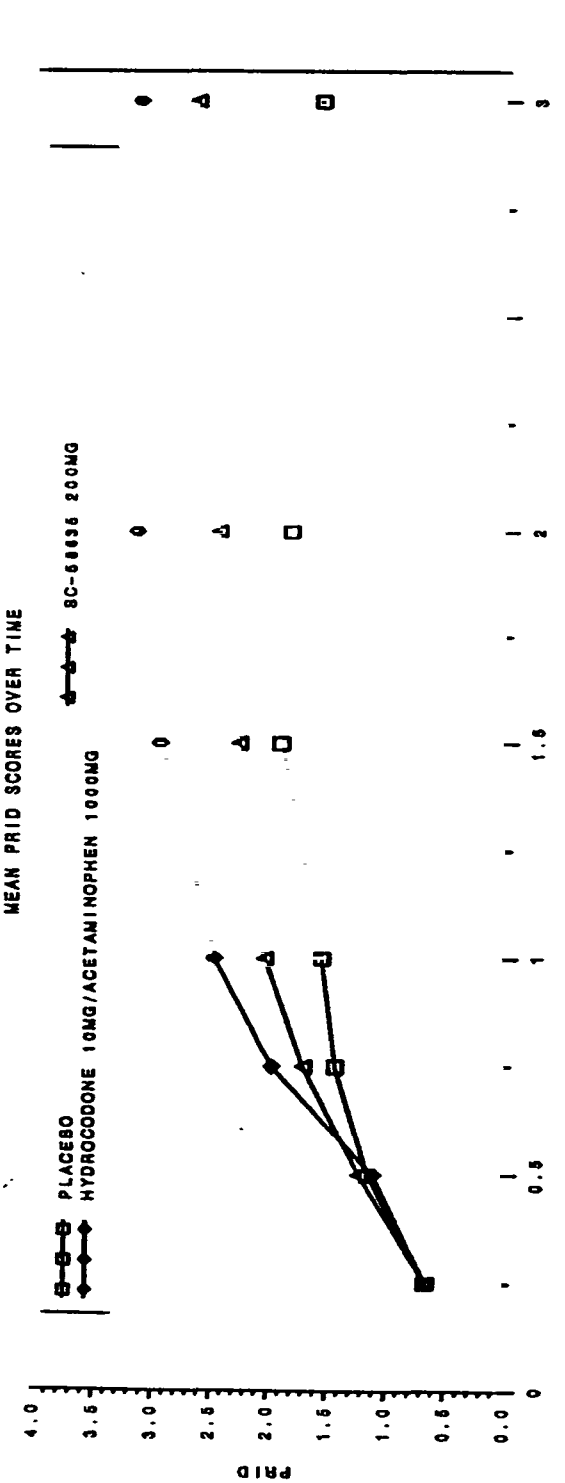
ASSESSMENT TIME POINTS (IN HOURS)

TREATMENT	4.00	5.00	6.00	7.00	8.00
HYDROCODONE 10MG/ ACETAMINOPHEN 1000MG	1.88 (1.37) 44(a) A(c)	1.87 (1.37) 38 A	1.72 (1.42) 36 A	1.67 (1.37) 34 A	1.46 (1.38) 30 A
SC-68836 200MG	1.74 (1.40) 37 A	1.66 (1.40) 37 A	1.58 (1.44) 36 A	1.68 (1.47) 35 A	1.60 (1.40) 35 A
PLACEBO	0.88 (1.18) 41 B	1.01 (1.33) 28 B	0.85 (1.06) 26 B	0.82 (1.06) 24 B	0.78 (1.04) 23 B
TREATMENT P-VALUE (b)	< 0.001	0.001	< 0.001	< 0.001	< 0.001
TRT*CENTER P-VALUE (c)	0.775	0.886	0.606	0.416	0.456
GENDER P-VALUE (d)	0.488	0.881	0.488	0.409	0.849
CENTER P-VALUE (b)	0.304	0.040	0.288	0.417	0.489
SURGERY TYPE P-VALUE (d)	0.171	0.154	0.260	0.244	0.455
RMS ERROR (b)	1.386	1.386	1.382	1.384	1.288

(a) Sample size is not extrapolated.
(b) Model: PR = mu + T1 + center + error.
(c) Based on model (b) + treatment with the same letter are not significantly different from each other.
(d) Model: PR = mu + T1 + effect term + center + error.

Differences in mean PRID for celecoxib were statistically significant compared to placebo at the 3 through 8 hour assessment. For hydrocodone the differences were significant at the 1 through 8 hour assessment (see Figures 65 and 66).

Figure 65: Plot of PRID scores for hours 0-3

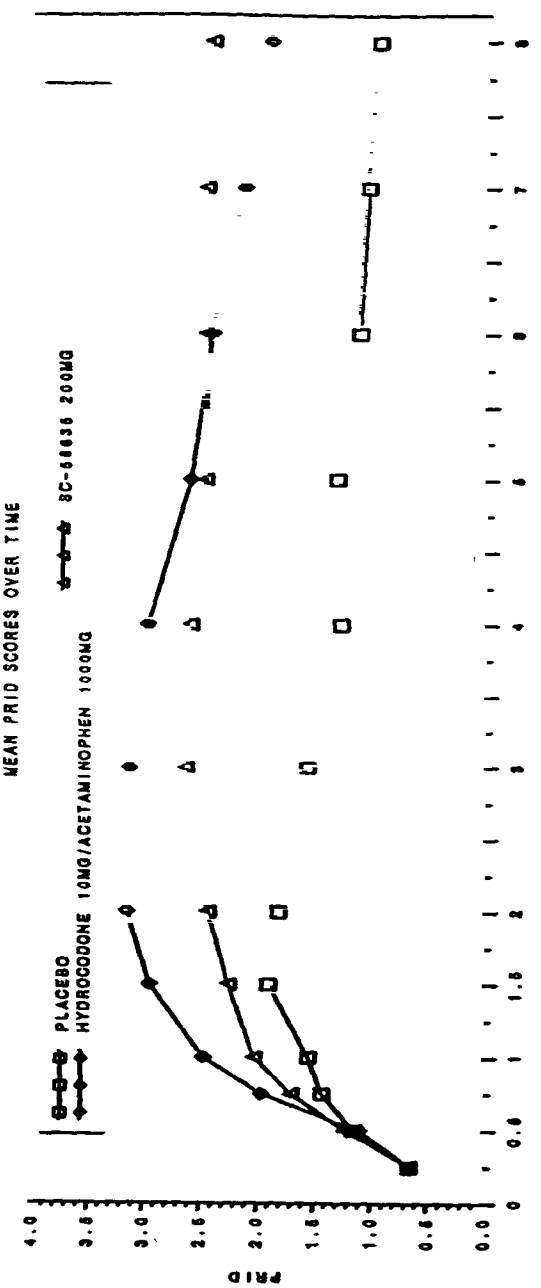


ASSESSMENT TIME POINTS (IN HOURS)

TREATMENT	0.25	0.50	0.75	1.00	1.50	2.00	3.00
HYDROCODONE 10MG/ ACETAMINOPHEN 1000MG	0.86 (1.04) 60(a) A(c)	1.10 (1.28) 60 A	1.07 (1.62) 60 A	2.48 (1.71) 60 A	2.86 (1.86) 58 A	3.15 (1.88) 58 A	3.13 (2.24) 47 A
SC-58035 200MG	0.66 (1.20) 64 A	1.22 (1.42) 64 A	1.70 (1.76) 64 A	2.03 (1.92) 64 AB	2.20 (1.98) 58 AB	2.44 (1.97) 50 AB	2.64 (2.33) 45 A
PLACEBO	0.66 (1.11) 58 A	1.18 (1.50) 58 A	1.48 (1.66) 58 A	1.55 (1.76) 57 B	1.91 (2.05) 55 B	1.82 (2.10) 48 B	1.87 (2.01) 38 B
TREATMENT P-VALUE (b)	0.958	0.805	0.167	0.018	0.013	0.001	0.001
TRT*BASELINE P-VALUE (c)	0.800	0.859	0.355	0.713	0.898	0.926	0.870
TRT*CENTER P-VALUE (c)	0.221	0.825	0.403	0.842	0.367	0.558	0.346
GENDER P-VALUE (d)	0.014	0.666	0.737	0.848	0.559	0.866	0.426
BASELINE P-VALUE (b)	0.582	0.666	0.470	0.400	0.516	0.946	0.124
CENTER P-VALUE (b)	0.001	0.001	0.008	0.074	0.316	0.207	0.240
SURGERY TYPE P-VALUE (d)	0.822	0.783	0.208	0.056	0.163	0.124	2.166
RMS ERROR (b)	1.047	1.307	1.575	1.787	1.958	1.988	

(a) Sample size is not extrapolated.
(b) Model: PRID = mu + TI + PI(O) + interaction term + center + error.
(c) Based on model (b) Lsmeans, treatments with the same letter are not significantly different from each other.
(d) Model: PRID = mu + TI + PI(O)] + center + error. + effect term +

Figure 66: Plot of PRID scores for hours 0-8



ASSESSMENT TIME POINTS (IN HOURS)

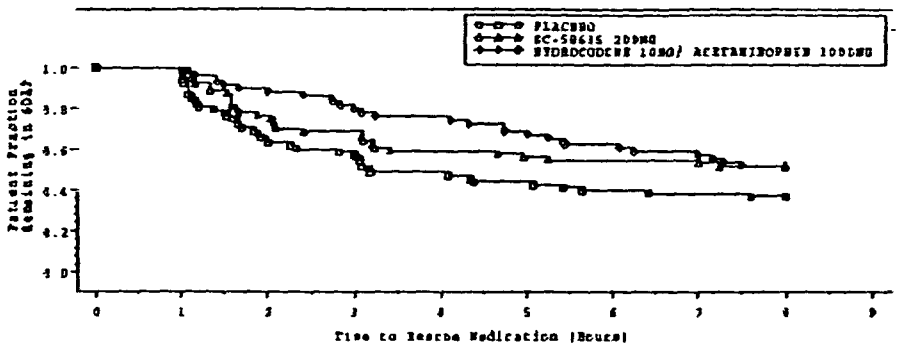
TREATMENT	4.00	5.00	7.00	8.00
HYDROCODONE 10MG/ ACETAMINOPHEN 1000MG	2.38 (2.18) 44(b) A(b)	2.61 (2.14) 38 A	2.49 (2.17) 38 A	2.14 (2.16) 34 A	1.82 (2.12) 30 A
SC-58036 200MG	2.06 (2.03) 37 A	2.48 (2.00) 37 A	2.49 (2.31) 35 A	2.48 (2.37) 35 A	2.43 (2.04) 33 A
PLACEBO	1.28 (1.87) 31 B	1.82 (1.95) 28 B	1.19 (1.78) 26 B	1.08 (1.72) 24 B	0.87 (1.71) 23 B

TREATMENT P-VALUE (b)	< 0.001	< 0.001	< 0.001	< 0.001
TRT*BASELINE P-VALUE (c)	0.478	0.648	0.381	0.288	0.291
TRT*CENTER P-VALUE (d)	0.788	0.948	0.371	0.467	0.437
GENDER P-VALUE (b)	0.832	0.862	0.469	0.711	0.804
BASELINE P-VALUE (b)	0.758	0.728	0.812	0.803	0.482
CENTER P-VALUE (b)	0.222	0.069	0.339	0.330	0.514
SURGERY TYPE P-VALUE (d)	0.283	0.286	0.288	0.404	0.720
RMS ERROR (b)	2.194	2.116	2.088	2.082	2.068

(a) Sample size is not extrapolated.
(b) Model: PRID = mu + Ti + P(i(j)) + interaction term + center + error.
(c) Based on model (b) LSmeans; treatments with the same letter are not significantly different from each other.
(d) Model: PRID = mu + Ti + P(i(j)) + effect term + center + error.

The difference in time to first rescue medication for celecoxib was significant compared to placebo but at the .1 level. For hydrocodone the difference was significant ($p<.05$) (figure 67).

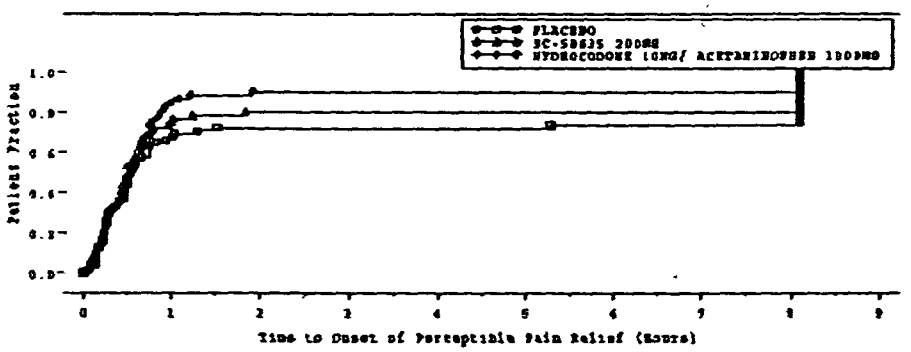
Figure 67: Time to rescue medication



TREATMENT	N	PATIENTS WHO TOOK RESCUE MEDICATION N (%)	MEDIAN TIME IN N : MIN (a,b)	95%-CI IN N : MIN (c)
HYDROCODONE 10MG/ ACETAMINOPHEN 1000MG	66	28 (42%)	>60:00(A)	05:27 TO >00:00
SC-58635 200MG	64	31 (48%)	>60:00(AB)	03:14 TO >00:00
PLACEBO	69	43 (63%)	03:10(B)	02:16 TO 07:36

(a) Kaplan-Meier estimate (see Miller, Survival Analysis, page 75)
(b) Logrank test applied as in Fisher's Protected LSD. Treatments with the same letter are not significantly different from each other.
(c) Method of Gibbons & Lee, Cancer Treat Rep, 1982.

Figure 68: Time to onset of perceptible pain relief



TREATMENT	N	PATIENTS WITH PERCEPTIBLE PR N (%)	MEDIAN TIME IN N : MIN (a,b)	95%-CI IN N : MIN (c)
HYDROCODONE 10MG/ ACETAMINOPHEN 1000MG	66	56 (85%)	00:33(A)	00:26 TO 00:40
SC-58635 200MG	64	51 (80%)	00:30(A)	00:25 TO 00:40
PLACEBO	69	50 (74%)	00:32(A)	00:30 TO 00:45

(a) Kaplan-Meier estimate (see Miller, Survival Analysis, page 75)
(b) Logrank test applied as in Fisher's Protected LSD. Treatments with the same letter are not significantly different from each other.
(c) Method of Gibbons & Lee, Cancer Treat Rep, 1982.

The difference in time to onset of perceptible pain relief for celecoxib and hydrocodone was not significantly different than placebo (Figure 68).

Analysis of secondary efficacy measures:

The differences in PID (VAS) were statistically different compared to placebo at the 2 through 8 hour assessments. For hydrocodone the differences were significant at the 1 through 8 hour assessments.

The PPID and PPR scores for celecoxib were significantly different compared to placebo. This was also true for hydrocodone.

The mean SPID (categorical) score differences for celecoxib and placebo were statistically significant at the 4, 6, 8 hour assessments. For hydrocodone this difference was significant at all time assessments. For SPID (VAS) the differences were significant at all time points for both celecoxib and hydrocodone.

The differences in mean TOTPAR scores for celecoxib were significantly different from placebo at the 4, 6, and 8 hour assessments. For hydrocodone these differences were significant at all time points. For SPRID 3,4,6,8 hours celecoxib was significantly different from placebo at the 4, 6, 8 hour assessments. For hydrocodone the differences were significant at all assessment periods.

The median time to onset of 50% pain relief in the celecoxib treated group was not significantly different than placebo. For hydrocodone the difference was significant.

The percent of patients experiencing 50% pain relief was significantly different for celecoxib versus placebo at the 4 through 8 hour assessments. For hydrocodone the differences were significantly different at the 1 through 8 hour assessments.

The time to onset of meaningful pain relief was significantly different comparing celecoxib to placebo ($p<05$). The difference was also significant for the hydrocodone group.

The median time to onset of analgesia was significantly different for celecoxib versus placebo ($p<.05$). The same was true for hydrocodone.

For the MDAP:

For maximum pain intensity, pain relief and patients global evaluation the numbers and proportions of patients in each category were numerically similar across treatment groups.

The number of patients who dropped out due to treatment failure/rescue medication on days 2-5 for celecoxib was significantly less than those who dropped out in the hydrocodone group.

The number of doses of study medication taken on days 2-5 showed no statistical difference between the two groups.

The time between two consecutive doses on days 2-5 showed no numerical differences.

The mean maximum pain intensity scores were statistically different at all assessment times for days 2-5.

The mean maximum pain relief scores were not statistically different between the two groups.

In response to the questions about pain using American Pain Society measures the responses for celecoxib were statistically different (better) than for hydrocodone.

The mean patient global evaluation scores for celecoxib treatment were greater than for hydrocodone. The differences between the two groups was statistically significant (p=.024).

e. Reviewer's comments:

For two of the primary endpoints, time to first rescue medication and time to onset of perceptible pain relief, celecoxib was not superior to placebo. For the other endpoints such as the time specific efficacy measures celecoxib was superior to placebo for time points after 3 hours while hydrocodone was significant from one hour on. Therefore in this study celecoxib showed only marginal efficacy compared to placebo for acute pain. For the multiple dose assessment period multiple endpoints were evaluated and no placebo control was used. A few of these endpoints showed a significant benefit of celecoxib over hydrocodone and the remainder were numerically similar to hydrocodone. This is supportive of the efficacy in the multiple dose period. For a more complete discussion see additional comments after study 086 and the discussion for the multiple dose period.

7. Trial 086

Double blind placebo controlled single dose and active controlled multiple dose assessment of the analgesic activity of celecoxib 200 mg in post orthopedic surgical patients.

The objective, rationale, design, protocol, endpoints, statistical consideration are all identical to protocol 085.

Results

1 Patient disposition/comparability

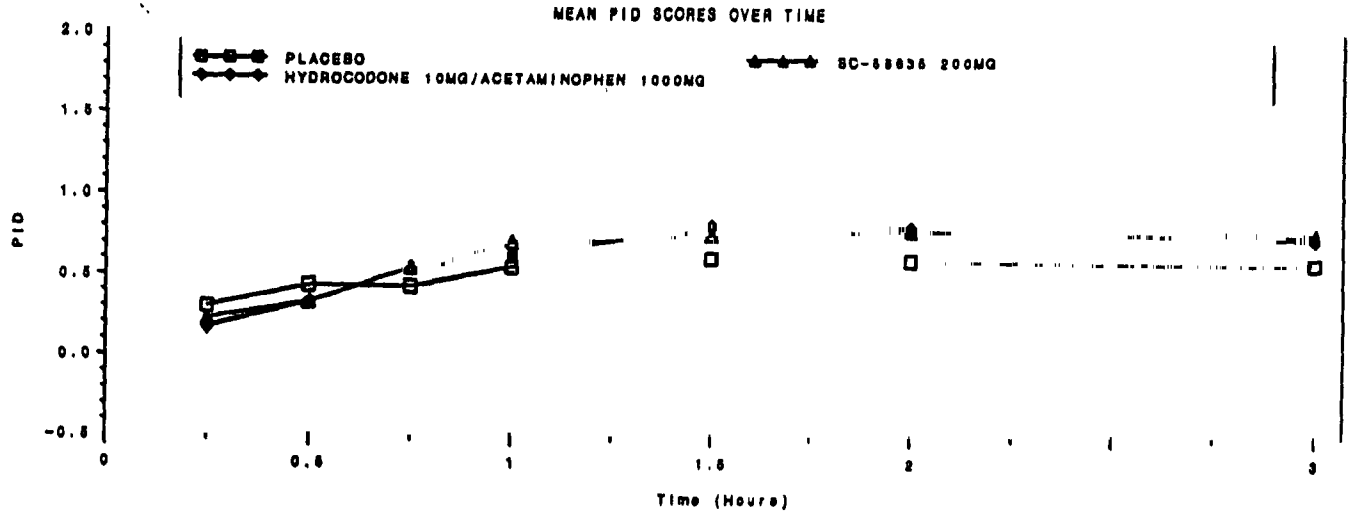
Two hundred twenty patients were enrolled and randomized to receive treatment; 74 received celecoxib, 74 received hydrocodone, and 72 patients received placebo. For the SDAP there were no statistically significant differences across the treatment groups in terms of age, race, gender. In the MDAP there were also no differences between the two treatment groups. Groups were also comparable for height, weight, and vital signs.

There were no differences between the treatment groups in terms of type of surgery for the SDAP and MDAP. However, baseline differences were observed in the baseline pain intensity measures (p=.027). There were more patients (30 (42%)) who reported severe pain at baseline in the placebo group compared to patients in the celecoxib treatment (23(31%)) and 16 (22%) in the hydrocodone treated group. For the MDAP, twice as many placebo patients with severe pain were blindly assigned to the celecoxib treated group as were assigned to the hydrocodone treated group. There was a statistically significant difference (p=.009) in the time from end of anesthesia to the first dose of study medication.

2 Efficacy outcomes

Primary efficacy measures (for the SDAP):

Mean PID (categorical) scores for celecoxib were statistically significant compared to placebo at the 4 through 8 hour assessments. For hydrocodone the differences were not statistically significant at any assessment time. Comparing celecoxib and hydrocodone the differences were significant only at 8 hours (Figures 69 and 70).



ASSESSMENT TIME POINTS (IN HOURS)

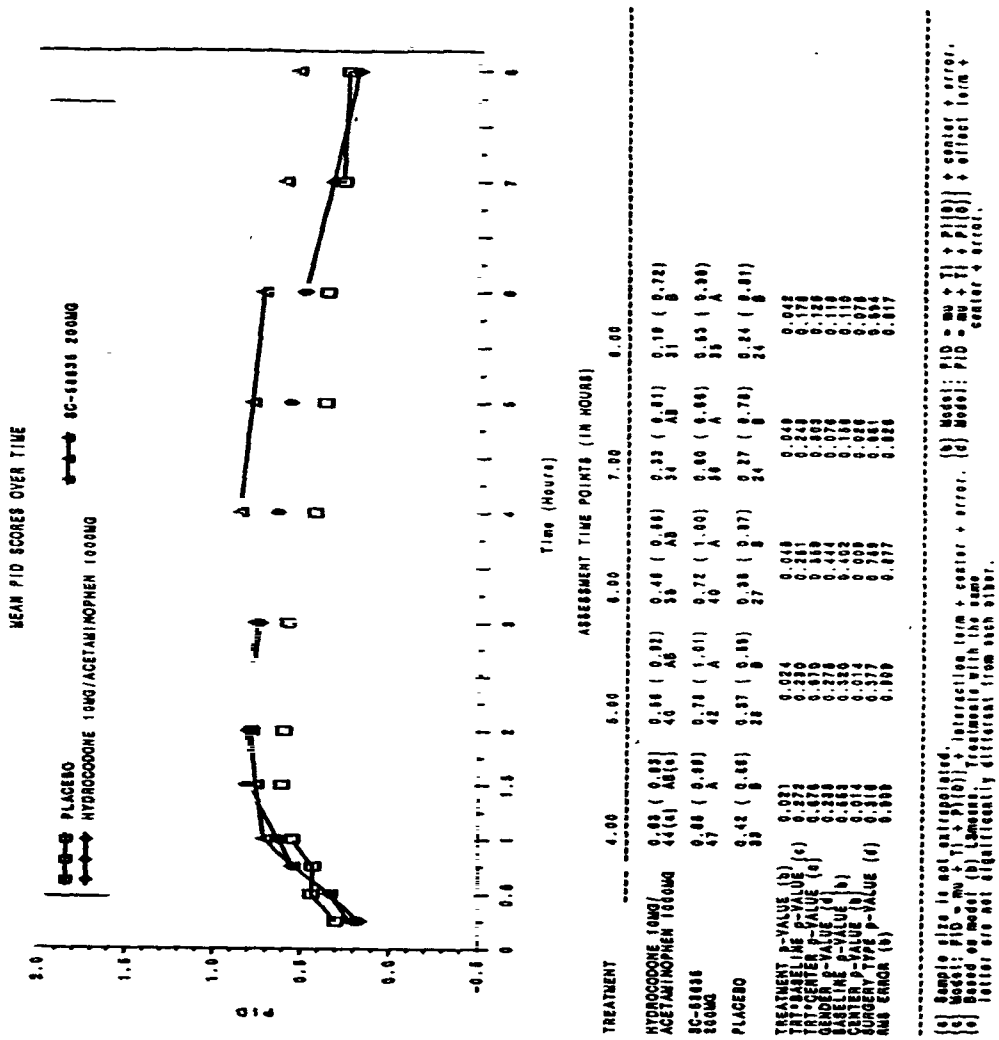
TREATMENT	0.25	0.50	0.75	1.00	1.50	2.00	3.00
HYDROCODONE 10MG/ ACETAMINOPHEN 1000MG	0.17 (0.46) 70(a) A(e)	0.33 (0.87) 70 A	0.64 (0.76) 68 A	0.63 (0.80) 69 A	0.61 (0.88) 68 A	0.66 (0.87) 68 A	0.73 (0.86) 49 A
SC-58635 200MG	0.22 (0.84) 71 A	0.33 (0.69) 70 A	0.64 (0.78) 69 A	0.71 (0.79) 69 A	0.78 (0.81) 80 A	0.78 (0.88) 81 A	0.78 (0.93) 80 A
PLACEBO	0.30 (0.62) 70 A	0.44 (0.86) 68 A	0.49 (0.73) 68 A	0.68 (0.73) 68 A	0.61 (0.84) 81 A	0.60 (0.87) 46 A	0.68 (0.95) 68 A

TREATMENT p-VALUE (b)	0.592	0.833	0.846	0.844	0.227	0.236	0.426
TRT*BASELINE p-VALUE (c)	0.801	0.446	0.642	0.504	0.360	0.401	0.402
TRT*CENTER p-VALUE (c)	0.169	0.869	0.818	0.653	0.884	0.844	0.708
GENDER p-VALUE (d)	0.869	0.609	0.470	0.171	0.656	0.239	0.263
BASELINE p-VALUE (b)	0.092	0.007	0.069	0.107	0.378	0.588	0.857
CENTER p-VALUE (b)	0.238	0.048	0.043	0.028	0.039	0.043	0.068
SURGERY TYPE p-VALUE (d)	0.998	0.978	0.766	0.918	0.181	0.561	0.623
RMS ERROR (b)	0.640	0.647	0.738	0.746	0.822	0.848	0.866

(a) Sample size is not extrapolated.
(b) Model: PID = mu + TI + PI(0)] + center + error.
(c) Model: PID = mu + TI + PI(0)] + interaction term + center + error.
(d) Model: PID = mu + TI + PI(0)] + effect term + center + error.
(e) Based on model (b) Lsmeans. Treatments with the same letter are not significantly different from each other.

Figure 69:Plot of PID scores for hours 0-3

Figure 70:Plot of PID scores for hours 0-8

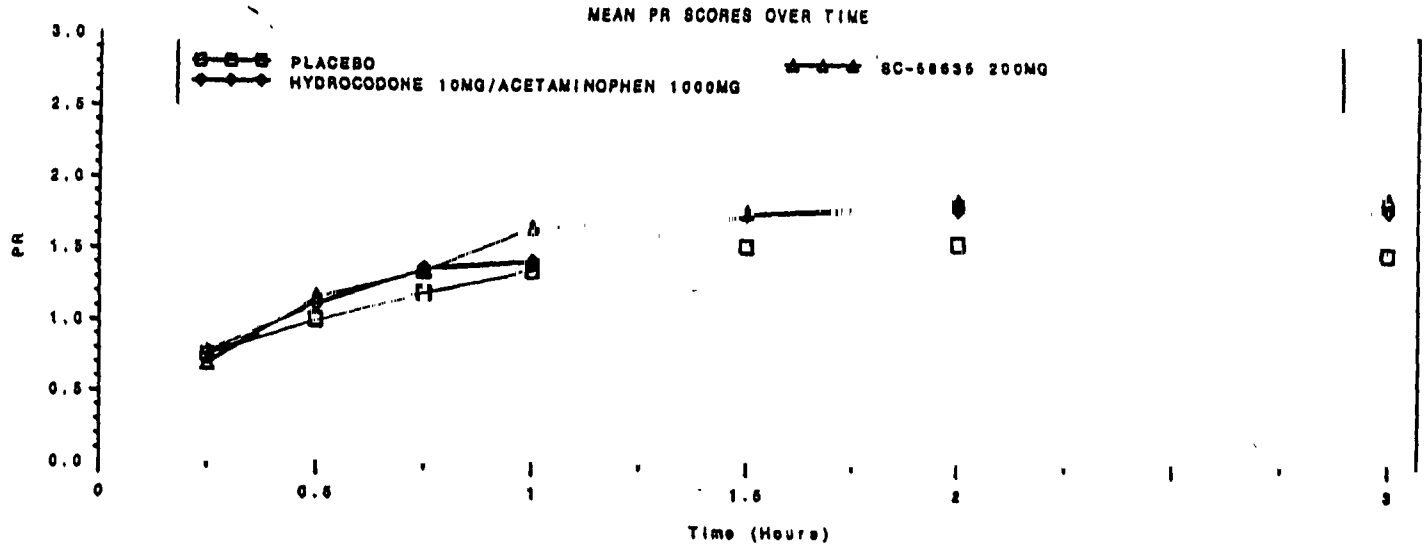


ASSESSMENT TIME POINTS (IN HOURS)

TREATMENT	4.00	5.00	6.00	7.00	8.00
HYDROCODONE 10MG/ ACETAMINOPHEN 1000MG	0.83 (0.82) 44(c) AB(c)	0.66 (0.82) 46 AB	0.46 (0.66) 56 AB	0.33 (0.61) 54 AB	0.19 (0.72) 51 B
BC-88836 200MG	0.88 (0.88) 47 A	0.78 (1.01) 42 A	0.72 (1.00) 40 A	0.60 (0.96) 36 A	0.63 (0.98) 35 A
PLACEBO	0.42 (0.66) 55 B	0.37 (0.86) 50 B	0.30 (0.87) 27 B	0.27 (0.78) 24 B	0.24 (0.81) 24 B
TREATMENT P-VALUE (b)	0.021	0.024	0.048	0.049	0.042
TRT*BASELINE P-VALUE (c)	0.372	0.230	0.261	0.240	0.178
TRT*CENTER P-VALUE (c)	0.476	0.870	0.869	0.803	0.128
GENDER P-VALUE (d)	0.388	0.278	0.444	0.078	0.116
BASELINE P-VALUE (b)	0.883	0.380	0.402	0.166	0.116
CENTER P-VALUE (b)	0.014	0.014	0.009	0.026	0.078
SURGERY TYPE P-VALUE (d)	0.310	0.377	0.749	0.861	0.994
RMS ERROR (b)	0.966	0.909	0.877	0.826	0.817

(a) Sample size is not extrapolated.
(b) Model: PID = MU + TI + PI(BI) + interaction term + center + error. (c) Model: PID = MU + TI + PI(BI) + center + error.
(d) Based on model (b) LSmeans. Treatments with the same letter are not significantly different from each other.

Mean PR scores (Figures 71 and 72) for the celecoxib group were significant compared to placebo at the 4, 5, and 7 hour assessment. For hydrocodone the differences were not significant at any assessment. Comparing celecoxib with hydrocodone the differences were not significant at all assessments.



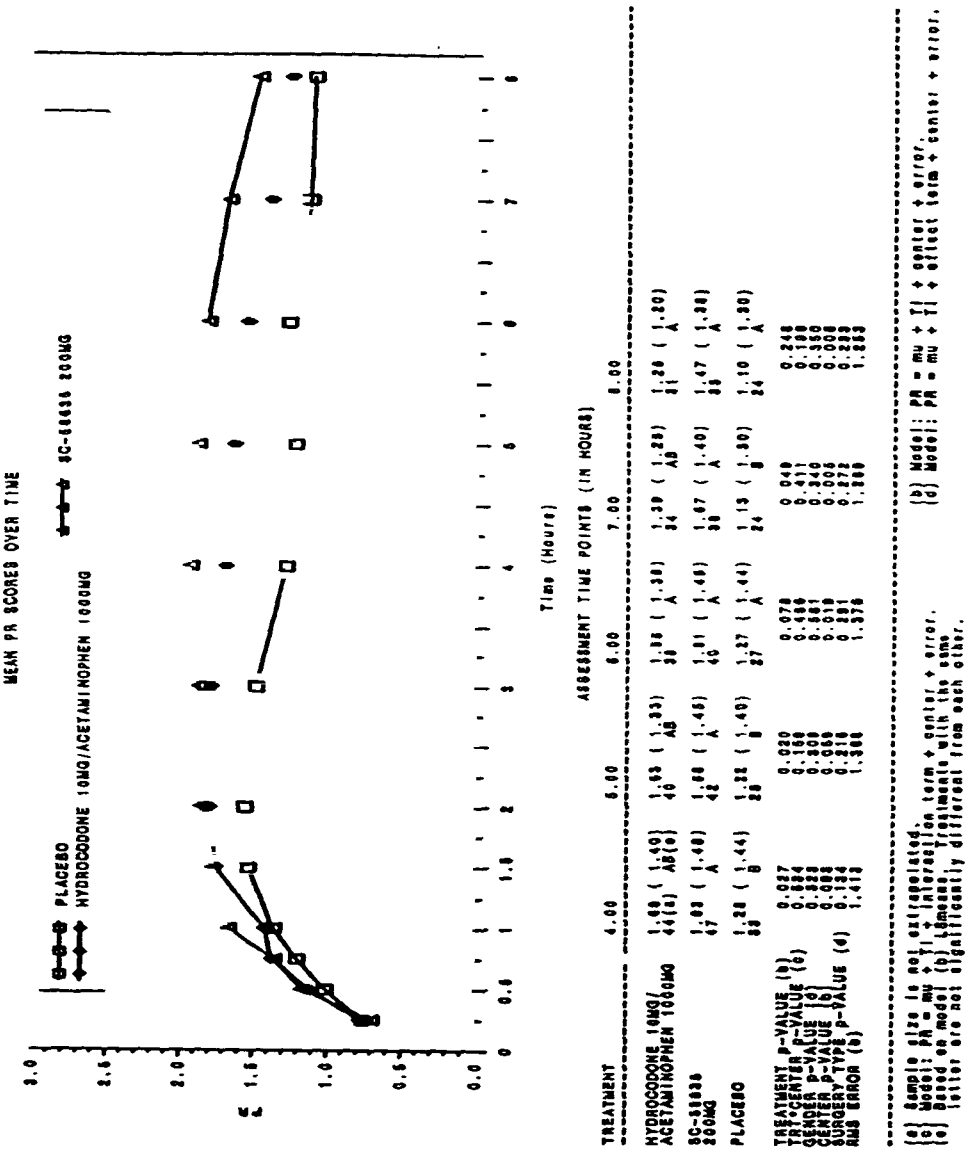
ASSESSMENT TIME POINTS (IN HOURS)

TREATMENT	0.25	0.50	0.75	1.00	1.50	2.00	3.00
HYDROCODONE 10MG/ ACETAMINOPHEN 1000MG	0.77 (0.84) 70(a) A(e)	1.11 (1.10) 70 A	1.37 (1.16) 66 A	1.42 (1.20) 69 A	1.75 (1.40) 66 A	1.79 (1.36) 58 A	1.76 (1.39) 49 A
SC-58635 200MG	0.69 (0.78) 71 A	1.17 (1.06) 70 A	1.36 (1.10) 69 A	1.66 (1.23) 69 A	1.77 (1.32) 60 A	1.85 (1.34) 51 A	1.87 (1.44) 50 A
PLACEBO	0.76 (0.87) 70 A	1.01 (1.06) 69 A	1.20 (1.14) 69 A	1.38 (1.17) 69 A	1.63 (1.31) 61 A	1.56 (1.55) 46 A	1.46 (1.44) 36 A
TREATMENT p-VALUE (b)	0.868	0.864	0.612	0.290	0.503	0.401	0.251
TRT*CENTER p-VALUE (c)	0.674	0.653	0.481	0.614	0.606	0.197	0.477
GENDER p-VALUE (d)	0.104	0.207	0.643	0.893	0.328	0.116	0.394
CENTER p-VALUE (b)	0.054	0.051	0.302	0.541	0.291	0.280	0.070
SURGERY TYPE p-VALUE (d)	0.505	0.469	0.340	0.378	0.150	0.021	0.120
RMS ERROR (b)	0.886	1.051	1.129	1.204	1.338	1.363	1.398

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

Figure 71:Plot of PR scores for hours 0-3

Figure 72 :Plot of PR scores for hours 0-8



ASSESSMENT TIME POINTS (IN HOURS)

TREATMENT	4.00	6.00	7.00	8.00
HYDROCODONE 10MG/ ACETAMINOPHEN 1000MG	1.40 (1.49) 44(a) AB(b)	1.65 (1.33) 46 AB	1.38 (1.38) 36 A	1.39 (1.28) 34 AB	1.28 (1.30) 31 A
SC-58635 200MG	1.68 (1.40) 47 A	1.68 (1.40) 48 A	1.81 (1.40) 46 A	1.67 (1.40) 38 A	1.47 (1.38) 35 A
PLACEBO	1.28 (1.44) 88 B	1.22 (1.40) 88 B	1.27 (1.44) 87 A	1.15 (1.30) 24 B	1.10 (1.30) 24 A
TREATMENT P-VALUE (b)	0.027	0.020	0.078	0.049	0.248
TRT*CENTER P-VALUE (b)	0.884	0.166	0.486	0.411	0.198
GENDER P-VALUE (c)	0.328	0.806	0.881	0.340	0.350
CENTER P-VALUE (c)	0.008	0.066	0.019	0.006	0.008
SURGERY-TYPE P-VALUE (c)	0.134	0.216	0.291	0.272	0.283
RMS ERROR (b)	1.413	1.366	1.376	1.366	1.283

(a) Sample size is not unstratified.
Model: PR = mu + TI + interaction term + center + error.
(b) Based on model (b) Lsmeans; Treatments with the same letter are not significantly different from each other.
(c) Model: PR = mu + TI + center + error.
(d) Model: PR = mu + TI + effect term + center + error.

Mean PRID (categorical) for celecoxib compared to placebo was significant at the 4 and 5 hour assessments (Figure 73). For hydrocodone the differences were not significant at any time point.