RESULTS:

Disposition of Patients

A total of 200 patients, 50 per treatment group, were enrolled into this study. The treatment groups were comparable in terms of age, race, gender, height, and weight (Tables 4 and 5, $p \geq 0.286$). Patients ranged in age from 18 to 60 years, approximately 70-84% were Caucasian, and 50-64% were female.

Summary of Dental Surgery

No statistically significant differences were observed among the four treatment groups for any of the variables. Across all treatment groups, on average, two molars with either partial or complete bony impaction were extracted and study medication was initiated approximately 2.5 hours following surgery. The p-value for surgical trauma rating was approaching the 0.05 significance level with 42% patients in the celecoxib 400 mg group and 20% in the placebo group having a severe surgical trauma rating.

Baseline pain intensity, both in categorical rating and visual analog scale, indicated no differences between treatment groups. Only patients with moderate or severe baseline pain intensity were enrolled into the study.

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

PID Scores (LOCF)
Mean PID scores over time are presented in table 2. All three active treatments had statistically significantly greater PID scores compared to placebo at 45 minutes postdosing and throughout the remaining eight-hour observation period.

Among active treatments overall, mean PID scores were numerically greater for aspirin than for both celecoxib doses within the first hour postdose, whereas, between two and eight hours postdose, scores were numerically greater for both celecoxib doses than for aspirin. The only statistically significant difference between the active treatment groups was at 45 minutes postdosing when the mean PID categorical score was greater in the aspirin group as compared to the celecoxib 400 mg group. No other statistically significant differences were noted between the three active treatments.

PR Scores (LOCF)
Mean PR scores over time are presented in table 3. Compared to placebo, PR scores were statistically significantly greater for both doses of celecoxib from 45 minutes to eight hours postdose and for aspirin from 30 minutes to eight hours postdose.

Statistically significant differences between active treatment groups were noted at various timepoints between 30 minutes and four hours. Statistically significant differences favoring celecoxib 100 mg versus aspirin were noted at three and four hours postdose. Statistically significant differences favoring aspirin versus celecoxib 400 mg were noted at 30 and 45 minutes and at one hour postdose and favoring aspirin versus celecoxib 100

mg at 45 minutes postdose. No statistically significant differences were noted between the two dosing levels of celecoxib.

PRID Scores (LOCF)
Mean PRID scores over time are presented in table 4. Compared to placebo, PRID scores were statistically significantly greater from 45 minutes postdosing for both dosing levels of celecoxib through eight hours and 30 minutes postdosing for aspirin through eight hours.

Statistically significant differences between active treatment groups were noted at various timepoints between 30 minutes and four hours postdose. Statistically significant differences favoring celecoxib 100 mg versus aspirin were noted at 45 minutes and at three and four hours postdosing. Statistically significant differences favoring aspirin versus celecoxib 400 mg were noted at 30 and 45 minutes and at one hour postdosing, and favoring aspirin versus celecoxib 100 mg at 45 minutes postdose. No statistically significant differences were noted between the two dosing levels of celecoxib.

Table 2: Pain Intensity Difference (LOCF)

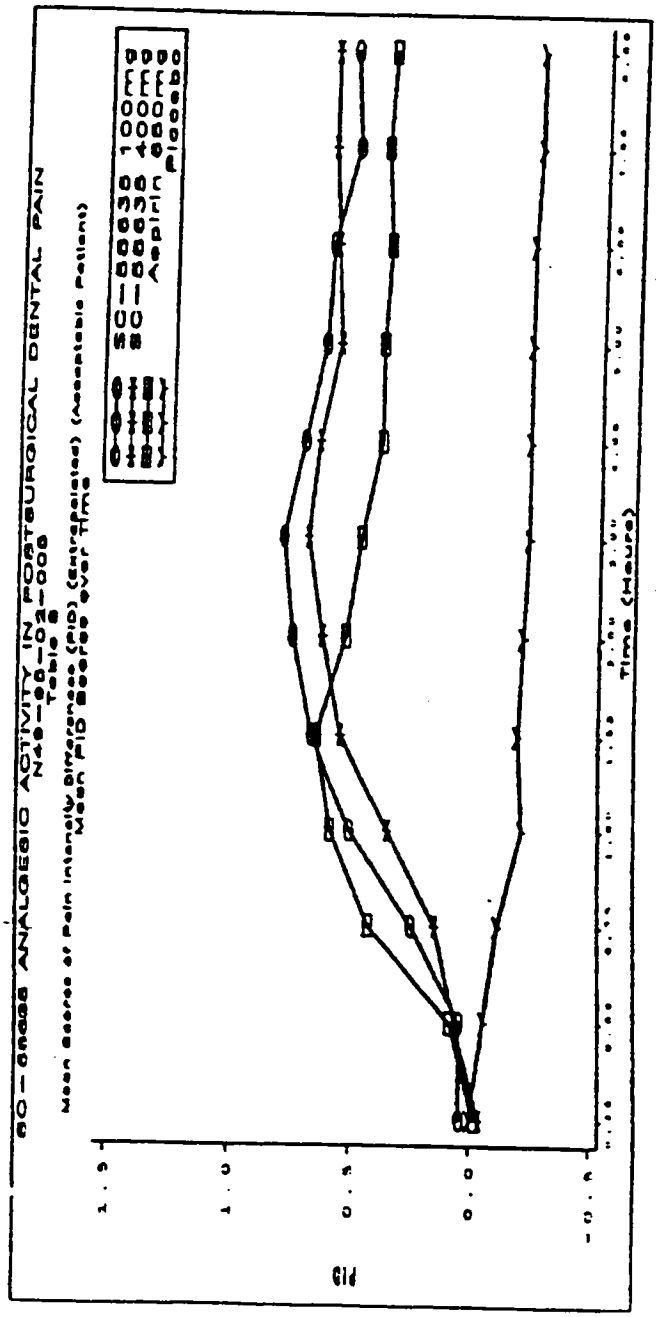
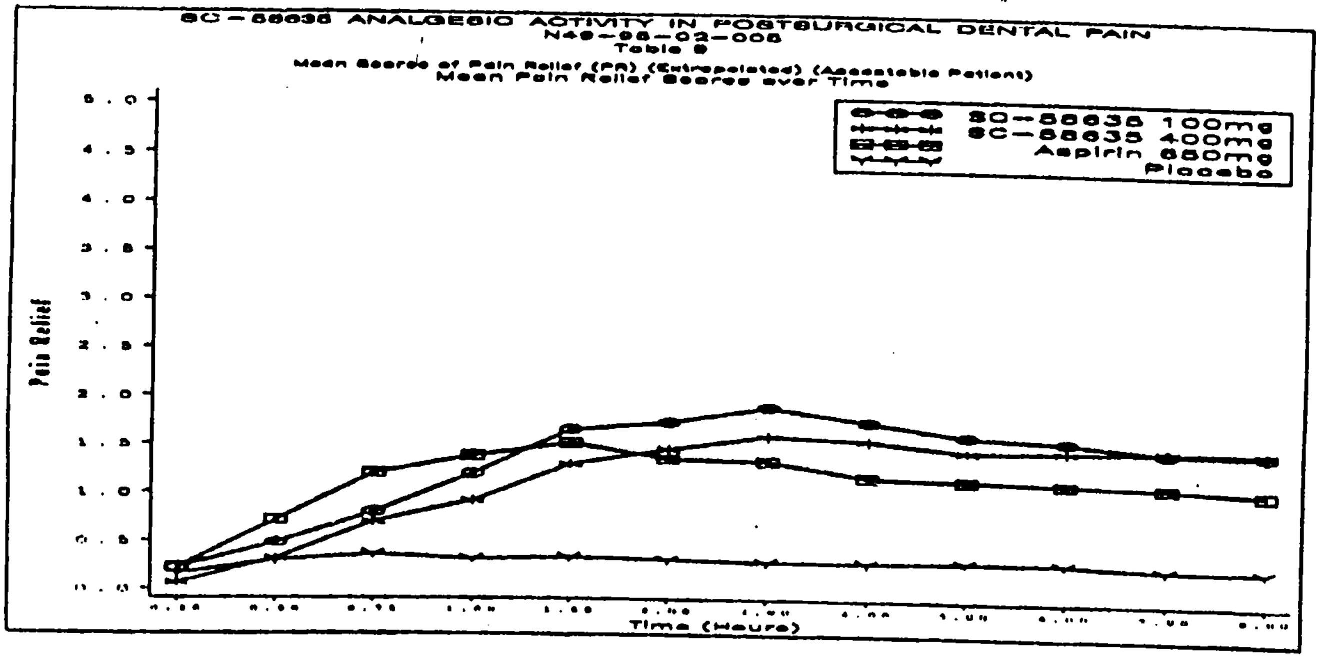


Table 3: Pain Relief (LOCF)

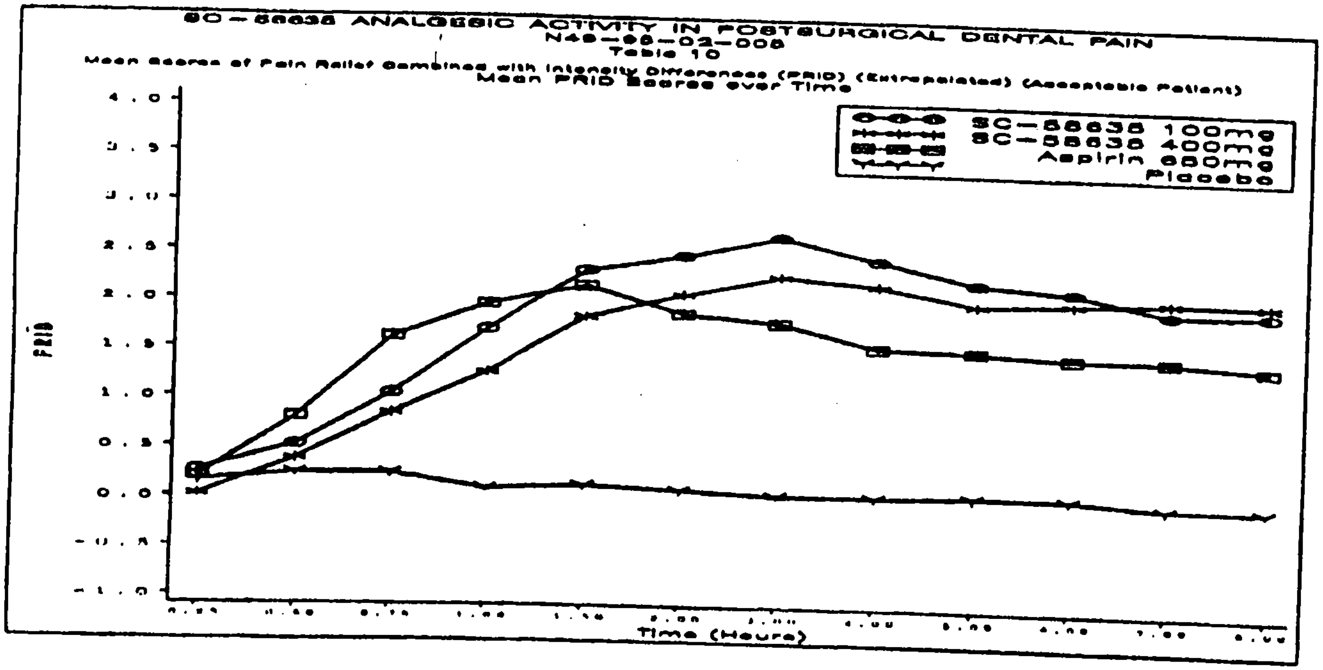


TREATMENT	0.25	0.50	0.75	1.00	1.50	2.00	3.00	4.00	5.00	6.00	7.00	8.00
SC-58635 100mg												
MEAN	0.06	0.32	0.10	0.92	1.30	1.46	1.60	1.56	1.46	1.48	1.50	1.50
STD DEV	(0.24)	(0.55)	(0.76)	(0.94)	(1.20)	(1.39)	(1.55)	(1.59)	(1.56)	(1.50)	(1.50)	(1.50)
SAMPLE SIZE (a)	50 A(c)	50 B	50 B	50 B	38 A	31 A	29 AB	26 AB	24 A	23 A	22 A	22 A
SC-58635 100mg												
MEAN	0.22	0.48	0.80	1.20	1.66	1.74	1.90	1.76	1.62	1.58	1.48	1.48
STD DEV	(0.46)	(0.58)	(0.76)	(1.07)	(1.33)	(1.45)	(1.57)	(1.57)	(1.54)	(1.57)	(1.50)	(1.50)
SAMPLE SIZE (a)	50 A	50 AB	50 B	50 AB	36 A	35 A	31 A	30 A	25 A	23 A	21 A	20 A
Aspirin 650mg												
MEAN	0.22	0.72	1.20	1.38	1.52	1.36	1.34	1.18	1.16	1.14	1.12	1.08
STD DEV	(0.42)	(0.78)	(1.03)	(1.07)	(1.11)	(1.22)	(1.30)	(1.26)	(1.27)	(1.26)	(1.32)	(1.28)
SAMPLE SIZE (a)	50 A	50 A	50 A	50 A	43 A	38 A	26 B	21 B	18 A	15 A	15 A	14 A
Placebo												
MEAN	0.16	0.30	0.36	0.32	0.34	0.32	0.30	0.30	0.32	0.32	0.28	0.24
STD DEV	(0.37)	(0.54)	(0.60)	(0.65)	(0.77)	(0.71)	(0.76)	(0.76)	(0.82)	(0.82)	(0.73)	(0.71)
SAMPLE SIZE (a)	50 A	50 B	50 C	50 C	20 B	12 B	6 C	5 C	5 B	4 B	4 B	2 B
TREATMENT P-VALUE (b)	0.123	0.002	< 0.001	< 0.001	< 0.001	< 0.001	0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
RMS ERROR (b)	0.383	0.614	0.807	0.943	1.166	1.235	1.337	1.335	1.324	1.343	1.335	1.315

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

NOTE: All information except sample size is based on interpolated/extrapolated data.

Table 4: Pain Intensity and Pain Relief (LOCF)



TREATMENT	0.25	0.50	0.75	1.00	1.50	2.00	3.00	4.00	5.00	6.00	7.00	8.00
SC-58635 400mg												
MEAN	0.02	0.38	0.84	1.26	1.84	2.08	2.28	2.20	2.02	2.06	2.10	2.10
STD DEV	(0.39)	(0.97)	(1.28)	(1.55)	(2.12)	(2.21)	(2.56)	(2.61)	(2.50)	(2.58)	(2.58)	(2.58)
SAMPLE SIZE (a)	50 A(d)	50 B	50 B	50 B	38 A	31 A	29 AB	26 AB	24 A	23 A	22 A	22 A
SC-58635 100mg												
MEAN	0.26	0.52	1.04	1.70	2.32	2.48	2.68	2.46	2.24	2.18	1.98	2.00
STD DEV	(0.66)	(0.79)	(1.23)	(1.81)	(2.18)	(2.38)	(2.57)	(2.58)	(2.45)	(2.53)	(2.39)	(2.42)
SAMPLE SIZE (a)	50 A	50 AB	50 B	50 AB	36 A	35 A	31 A	30 A	25 A	23 A	21 A	20 A
Aspirin 653mg												
MEAN	0.20	0.80	1.62	1.96	2.16	1.88	1.80	1.56	1.54	1.50	1.50	1.44
STD DEV	(0.67)	(1.25)	(1.55)	(1.60)	(1.78)	(1.94)	(2.07)	(1.97)	(2.02)	(2.01)	(2.15)	(2.04)
SAMPLE SIZE (a)	50 A	50 A	50 A	50 A	43 A	38 A	28 B	21 B	18 A	15 A	15 A	14 A
Placebo												
MEAN	0.16	0.22	0.24	0.10	0.14	0.10	0.06	0.08	0.08	0.08	0.02	0.02
STD DEV	(0.47)	(0.85)	(1.36)	(1.18)	(1.34)	(1.30)	(1.43)	(1.42)	(1.47)	(1.47)	(1.36)	(1.36)
SAMPLE SIZE (a)	50 A	50 B	50 C	50 C	20 B	12 B	6 C	5 C	5 B	4 B	4 B	3 B
TREATMENT P-VALUE (b)	0.239	0.033	< 0.001	< 0.001	< 0.001	< 0.001	0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
TRT*BASELINE P-VALUE (c)	0.185	0.659	0.090	0.276	0.209	0.518	0.303	0.668	0.565	0.516	0.635	0.526
RMS ERROR (b)	0.605	0.979	1.295	1.554	1.881	2.007	2.201	2.191	2.141	2.176	2.156	2.140

Assessment Time Points (in Hours)

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

NOTE: All information except sample size is based on interpolated/extrapolated data.

Time to Onset of Pain Relief

The time to onset of pain relief was calculated as 30 minutes divided by the mean PRID score at 30 minutes

The onset of pain relief was estimated to occur, overall, at approximately 1.3 hours for celecoxib 400 mg, one hour for celecoxib 100 mg, 0.6 hour for aspirin 650 mg and two hours for placebo. The onset of pain relief occurred significantly earlier for aspirin 650 mg compared to celecoxib 400 mg and placebo, however, the difference between aspirin and celecoxib 100 mg was not statistically significant. The onset of pain relief between the two dosing levels of celecoxib was not statistically different.

Time to Remedication with Rescue Analgesic

The need for patients to remedicate with a rescue analgesic medication occurred at approximately four hours for celecoxib 400 mg, five hours for celecoxib 100 mg, three hours for aspirin and one hour for placebo. All three active treatments provided a statistically significantly greater duration of relief compared to placebo as measured by time to remedication. At the last observation time, the number of patients remaining in the study was 44%, 40%, 28% and 6% for celecoxib 400 mg, celecoxib 100 mg, aspirin, and placebo, respectively.

Analysis of Secondary Efficacy Measures

Overall, a similar performance pattern was observed across all the variables: the mean scores of sum of pain intensity differences (SPID), total pain relief (TOTPAR), peak pain intensity difference (PPID), peak pain relief (PPR), and patient's global evaluation. All three active treatments had significantly better scores compared to placebo, and no statistically significant differences were observed among the three active treatments.

Safety Results

Twelve (24%) placebo patients, 13 (26%) celecoxib 100 mg patients, 15 (30%) celecoxib 400 mg patients and 17 (34%) aspirin 650 mg patients experienced adverse events. Events reported by more than 5% of the patients in a given treatment group were: nausea (8%) and vomiting (6%) for placebo; somnolence (8%) for celecoxib 100 mg; somnolence (8%), headache (6%) and nausea (6%) for celecoxib 400 mg; and nausea (14%), vomiting (10%), dizziness (10%), somnolence (6%) and headache (6%) for aspirin 650 mg. No patients were withdrawn from the study due to adverse events.

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

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

Discussion and Overall Conclusions for Study # 005

In this study, single doses of both dosing levels of celecoxib, 100 mg and 400 mg, provided significant pain relief and reduction in pain intensity compared to placebo following molar extraction surgery. Using categorical scales, both dosing levels of celecoxib provided significant relief within 45 minutes of dosing.

The positive control used in this study, aspirin 650 mg, also provided significant pain relief compared to placebo. Pain relief with aspirin occurred within 30 minutes of dosing and a reduction in pain intensity was observed within 45 minutes of dosing. Over time, the analgesic effects of aspirin tended to have an earlier onset, peaked at approximately 1.5 hours, and then decreased thereafter.

No major safety issues have been demonstrated.

Remedication, Time to Meaningful Pain Relief, Patient's Global Evaluation, PPID, PPR, SPID, TOTPAR, SPRID, and Number of Doses and Time Between Two Consecutive Doses of Study Medication at Day 1 through Day 5. In the single dose analysis (BOCF), mean PID (Categorical) scores and mean PRID scores for all three active treatment groups were generally numerically, but not statistically significant, greater than placebo from 1.0 hour through 24 hours. The mean PR scores were generally numerically, but not statistically significant, greater than placebo from 0.75 hour through 24 hours. All three active treatment groups showed numerically longer median times to rescue medication (celecoxib 100 mg BID PRN, 04:07 hr; celecoxib 200 mg BID PRN, 05:05 hr; Darvocet-N 100 QID PRN, 11:16 hr) than placebo (03:53 hr). All three active treatment groups showed numerically longer times to rescue medication or remedication (celecoxib 100 mg BID PRN, 04:01 hr; celecoxib 200 mg BID PRN, 03:56 hr; Darvocet-N 100 QID PRN, 04:02 hr) compared to placebo (03:48 hr). All three active treatment groups showed numerically shorter median times to meaningful pain relief than placebo. In the Patient's Global Evaluation, 23% of the patients in the placebo treatment group had a global evaluation of very good or excellent as compared to 32% in the celecoxib 100 mg BID PRN treatment group, 30% in the celecoxib 200 mg BID PRN treatment group, and 28% in the Darvocet-N 100 mg QID PRN treatment group. Similar results were seen in PPID, PPR, SPID, TOTPAR, and SPRID. However, no statistically significant differences were present between any of the active treatment groups compared to placebo in any of the above efficacy variables. The results of the single dose analyses (LOCF) were similar to the results utilizing the BOCF methods for the efficacy measures described above.

Safety was assessed by the incidence of treatment-emergent adverse events, and changes from Baseline in clinical laboratory tests, vital signs, and physical examination.

Adverse events were reported by a total of 80 patients: 17 (43%) patients in the placebo group; 20 (44%) patients in the celecoxib 100 mg BID PRN group; 21 (50%) patients in the celecoxib 200 mg BID PRN group; and 22 (55%) patients in the Darvocet-N 100 mg QID PRN group. The adverse events with the highest incidence (i.e., ≥5% in any group including placebo) were dizziness, vomiting, flatulence, nausea, arthralgia, dyspepsia, fever, headache, hot flushes, somnolence, and rigors.

GI-related adverse events were reported by 45 patients: 8 (20%) placebo patients, 12 (27%) celecoxib 100 mg BID PRN patients, 10 (24%) celecoxib 200 mg BID PRN patients, and 15 (38%) Darvocet-N 100 mg QID PRN patients. The majority of all reported GI adverse events were mild to moderate in severity. The most commonly reported adverse events in the GI system (≥5% in any group) were nausea, vomiting, flatulence, and dyspepsia.

Adverse events with the highest incidence (i.e., ≥ 5% in any group):

Adverse Event	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)
Dizziness	0 (0%)	1 (2%)	4 (10%)	1 (3%)
Vomiting	5 (13%)	3 (7%)	4 (10%)	6 (15%)
Flatulence	1 (3%)	3 (7%)	3 (7%)	4 (10%)
Nausea	4 (10%)	8 (18%)	3 (7%)	10 (25%)
Arthralgia	0 (0%)	0 (0%)	2 (5%)	0 (0%)
Dyspepsia	1 (3%)	3 (7%)	2 (5%)	0 (0%)
Fever	6 (15%)	2 (4%)	2 (5%)	1 (3%)
Headache	4 (10%)	2 (4%)	2 (5%)	2 (5%)
Hot Flushes	0 (0%)	0 (0%)	2 (5%)	1 (3%)
Somnolence	1 (3%)	1 (2%)	2 (5%)	2 (5%)
Rigors	3 (8%)	0 (0%)	0 (0%)	1 (3%)

A total of 15 patients withdrew from the study due to an adverse event: five (13%) placebo patients, two (4%) celecoxib 100 mg BID PRN patients, three (7%) celecoxib 200 mg BID PRN patients, and five (13%) Darvocet-N 100 mg QID PRN patients. Serious adverse events, due to prolonged hospitalization or rehospitalization, were reported for three patients: one (3%) placebo patient, one (2%) celecoxib 200 mg BID PRN patient, and one (3%) Darvocet-N 100 mg QID PRN patient. These three events are not considered to be related to study drug (two cases of wound infection andd one case of Crohn's disease). There were no deaths during the study. There were no consistent alterations in mean laboratory test values; however, there were individual patients who had abnormal laboratory test results. None of these findings is considered medically significant.

CONCLUSIONS

It is concluded that, in this study:

This pain model failed to detect statistically significant treatment differences between the active treatment arms and the placebo. This might have been caused by the unexpectedly large placebo response and the early assessment of smaller number of patients.

The safety profile of celecoxib as appears in this study is an acceptable risk.

Study Number: N49-97-02-080
Study Dates: 15 December 1997 - 5 January 1998

Title of Study: A Multiple Dose, Double-Blind, Placebo-Controlled Comparison of the Analgesic Activity of celecoxib 200 mg, Naproxen 500 mg and Placebo in Post-Orthopedic Surgical Patients

Investigator and Location:

Summary

One patient receiving naproxen 500 mg BID PRN was enrolled in this study for a total of five days. No adverse experiences were reported.

This study was discontinued and the reason given: "...because the comparator selected was not considered to be suitable for this pain model in order to differentiate the active treatments from placebo in terms of treating patients who have undergone orthopedic surgery."

M. Averbuch 12/23/97
M. Averbuch, MD

Orig. NDA # 20,998
HFD-550/Div File
HFD-550/CSO/Lutwak
HFD-550/Chem/
HFD-550/Pharm/Yang
HFD-550/MO/Averbuch/Hyde
HFD-850/Sta/Patrician/Lin

JEH 12-23-97
John E. Hyde, PhD, MD

Celebrex Capsules
(Celecoxib)

NDA 20-998

Medical Officer Review

Submission Date:	June 29, 1998
Received Date:	June 30, 1998
Review Date:	July 8, 1998
Drug Name:	Celebrex™
Generic Name:	celecoxib
Applicant:	G.D. Searle & Co. 4901 Searle Parkway Skokie, IL 60077
Pharmacologic category:	COX-2 inhibitor
Proposed Indication:	Management of: • pain • rheumatoid arthritis • osteoarthritis
Dosage forms and route:	Oral capsule, 100 and 200 mg
Submission type:	Original NDA

Orig NDA # 20-998
HFD-550/Div File
HFD-550/PM/Lutwak
HFD-550/Pharm/Yang
HFD-550/Chem/Bhavnagri
HFD-550/Biopharm/Bashaw
HFD-550/Statistics/Lin
HFD-550/MO/Witter

(James Witter, M.D., Ph.D. Medical Officer)

JEH 12-29-98

Celecoxib
NDA # 20-998

Table of Contents

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Celecoxib
NDA 20-998

Listing of NDA Review Tables

Listing of NDA Review Tables
(continued)

Celecoxib
NDA 20-998

Listing of Appendix Tables/Figures:

Reviewer's comment: My apologies to the reader that there are so many appendix tables/figures but this seems unavoidable due to the sheer volume of studies included in this NDA and limitations of the computer software. The reader will note that the tables/figures will not necessarily be referenced in this review in consecutive order.

Listing of Appendix Tables/Figures:
(continued)

Celecoxib Executive Summary

Significant Issues

- If approved, celecoxib would be the first so-called "COX-2 selective" agent approved in the U.S. In fact, as noted below, it is suggested that celecoxib be called a "specific" COX-2 inhibitor. The biological and clinical implications of this designation are, at present, not fully characterized.

- Although the single-dose, dental pain trials have established that celecoxib is efficacious compared to placebo, the other postsurgical pain trials did not confirm the analgesic properties of the proposed doses.

- Because serum bicarbonates were not measured, the NDA database cannot exclude an adverse effect of celecoxib on acid-base balance.

- Celecoxib is efficacious in the treatment of the signs and symptoms of osteoarthritis and rheumatoid arthritis at the proposed doses.

Highlights

- Endoscopic data with celecoxib have found that it is associated with significantly fewer endoscopically-defined ulcers as compared to studies with ibuprofen and naproxen. However, celecoxib was associated with fewer ulcers in only one of two such endoscopic studies with diclofenac. However, these ulceration rates are not equivalent to placebo.

- The overall safety profile of celecoxib suggests at this time that it is generally more comparable to NSAIDs (ibuprofen, diclofenac, naproxen) than to placebo.

- Randomized and open-label trials, to date, suggest the rate for clinically relevant upper gastrointestinal events is less with celecoxib than that of traditional NSAIDs.

- If approved, celecoxib would be the first compound with properties similar to currently understood NSAIDs to successfully employ the Western Ontario and McMaster Universities (WOMAC) Osteoarthritis Index as well as the American College of Rheumatology (ACR-20) Responder Index for rheumatoid arthritis in a New Drug Application.

BACKGROUND AND OVERVIEW:

Celecoxib (Cx) is the USAN name for 4-[5-(methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide which is a diarylsubstituted pyrazole compound. The trade name for this same compound is ***Celebrex*** while the code name is ***SC-58635.*** Cx was originally developed as a "selective" prostaglandin G/H synthase-2 (i.e. ***COX-2***) inhibitor. However, during the development of this compound, Cx is now presented as a "specific" COX-2 inhibitor (SCI). According to current thinking, such "SCI inhibitors" at therapeutic doses would inhibit COX-2 and would be maximally effective in treating inflammation and pain, but would not inhibit COX-1 activity involved in normal physiologic function (see below). Many regard this compound as a new class of anti-inflammatory and analgesic agents. In fact, the WHO has recently changed the ATC classification of Cx to "COX-2 specific inhibitors".

From studies dating back only to the late 1980's and early 1990's, it became clear that there must be another isoform of human cyclooxygenase (COX), the enzyme which catalyzes the rate-limiting step in converting arachidonic acid to prostaglandins (PG), thromboxanes, and leukotrienes. For example, early experiments with endotoxin-treated monocytes showed that the significant increase in PGE_2 was inhibited by dexamethasone, this corticosteroid is not known to alter the transcription of COX-1. Subsequently, the theory has evolved that COX-1 and COX-2 may subserve different roles in the body. Originally, COX-1 was postulated to be a constitutive form of COX involved in "house-keeping" functions, such as maintenance of the gastrointestinal (GI) tract mucosal integrity, normal platelet function, and renal function while COX-2 represented the inducible form of COX involved in inflammation and pain. Similarly, it was postulated early that COX-1 was present in all cells (and, most importantly, in platelets) while COX-2 was only distributed at sites of inflammation, such as arthritic joints; COX-2 was not present in platelets (since they lack the transcriptional machinery necessary to produce this inducible enzyme).

Currently, it is appreciated that the COX story is much more complicated, and potentially much more interesting. For example, it is now accepted that COX-2 can also be constitutively expressed in areas like the kidney and brain whereas previously these areas were felt to be devoid of any significant COX-2. The situation of whether COX-2 is present in the human GI tract has also rapidly evolved in the last few years. Early on, it was felt that COX-2 was not present in the human GI tract. It is now clear that this enzyme is not only present in the lower GI tract, it is a target for prophylactic therapy of colonic cancer. Similarly, COX-2 is also recognized to be increased in the upper GI tract in situations of ulcer healing or infection with Helicobacter pylori infection. Conversely, there is an understanding that COX-1 can also be inducible under certain experimental systems and COX-1 may be upregulated in situations when COX-2 is absent or blocked; animals models have been particularly illustrative in this regard. Finally, it is becoming evident that COX-2 may also play important roles in Alzheimer's disease, cardiovascular disease, angiogenesis, along with their already recognized important roles in inflammation, pain and pyrexia.

While on the surface, NDA 20-998 might appear to represent just another drug to review, in reality one could easily argue it represents a test to the various hypotheses of the proposed roles of COX-2 in human health and disease. While reviewing this NDA, the reader is therefore encouraged to constantly question whether we are testing a drug, a theory, or both with this compound? It will be of interest to see where this NDA positions itself in the future in terms of helping to address some of these very important biological and clinical questions.

A total of 51 trials were submitted to support NDA 20-998. As detailed in the Table 1 below, these 51 trials have been divided by the Sponsor into three basic types of studies (Phase 1, Arthritis, Postsurgical Analgesia):

Table 1. Studies Included in NDA 20-998

TYPE OF STUDY	NO. OF STUDIES	STUDY NUMBERS
Phase 1		
Single dose	9	001, 006, 009, 018, 019, 037, 044, 084, 088
Multiple dose	11	003, 004, 010, 014, 015, 026, 032, 033, 043, 065, 069
Drug Interaction	7	017, 038, 039, 040, 050, 051, 072
Hepatic Impairment	1	016
Renal Impairment	1	038
Arthritis		
OA		
Pivotal Efficacy	5	020, 021, 054, 060, 087
Supportive	3	042, 013, 047
RA		
Pivotal Efficacy	2	022, 023
Supportive	2	041, 012
OA/RA combined	2	062, 071
Long-term open label	1	024
Postsurgical Analgesia		
Dental pain		
Pivotal Efficacy	3	025, 027, 070
Supportive	1	005
Surgical Pain		
Pivotal Efficacy	1	028
Supportive	2	029, 080
Total	51	

Reviewer's comment: To facilitate review of the clinical aspect of this NDA, several different Divisions within CDER have been engaged as follows:

Mickey Averbuch, M.D.	***Pain trials***
Lawrence Goldkind, M.D.	***UGI safety***
Douglas Throckmorton, M.D.	***Renal Safety***
Lourdes Villalba, M.D.	***General Safety***
Lilia Talarico, M.D.	***Platelet Safety***

While these other reviews have addressed the safety and efficacy of Cx, the consultant reviews outside the Division have focused on platelet effect and function, along with the effects of Cx on the GI tract and kidneys. This review will attempt to integrate the highlights of all these critically important consultant reviews but the interested reader is referred to the original reviews for in-depth details.

Single-Dose Analgesia Trials

Reviewer's comment: For more details regarding the single-dose trials, the interested reader is referred to the complete review by M. Averbuch.

Prostaglandins are important mediators in the generation and amplification of pain. Prostaglandins decrease the sensory pain threshold and activate a cascade of inflammatory processes, resulting in hyperalgesia and local edema. In addition, prostaglandins may sensitize central nociceptors.

For the indication of "Management of Pain", single-dose studies are useful to help understand the early analgesic characteristics of any drug. The analgesic efficacy of Cx was evaluated in this regard with clinical trials employing the postsurgical (oral surgery) pain model. Three double-blind, and one single-blind, placebo-controlled studies were conducted in patients with the dental pain model as noted in the Table 2 below:

Table 2. Single-Dose Postsurgical Pain (Oral Surgery) Trials

Protocol No. Report No. Short Title	No. of Investigators Country(ies) Start Date	Study Design (Duration of Treatment)	Treatment Regimen(s)
P: N49-96-02-025 R: N49-97-16-025 Dose-ranging Analgesic Efficacy in Postsurgical Dental Pain	One Investigator U.S. 9 Jul 1996	Randomized, Double-Blind, Placebo-Controlled, Active Controlled, Parallel Group (single dose)	Celecoxib 25 mg, 50 mg, or 200 mg or Ibuprofen 400 mg or Placebo
P: N49-97-02-027 R: N49-97-06-027 Analgesic Efficacy in Postsurgical Dental Pain	One investigator U.S. 4 Mar 1997	Randomized, Double-Blind, Placebo-Controlled, Active Controlled, Parallel Group (single dose)	Celecoxib 100 mg or 200 mg or Naproxen Sodium 550 mg or Placebo
P: N49-97-02-070 R: N49-97-06-070 Dose-response and Analgesic Efficacy in Postsurgical Dental Pain	One investigator U.S. 17 Apr 1997	Randomized, Double-Blind, Placebo-Controlled, Active Controlled, Parallel Group (single dose)	Celecoxib 50 mg, 100 mg, 200 mg, or 400 mg or Naproxen Sodium 550 mg or Placebo
P: N49-95-02-005 R: N49-97-16-005 Analgesic Efficacy in Postsurgical Dental Pain	One investigator U.S. 23 Aug 1995	Randomized, Single-Blind, Placebo-Controlled, Active Controlled, Parallel Group (single dose)	Celecoxib 100 mg or 400 mg or Aspirin 650 mg or Placebo

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 these post-oral surgery analgesia studies included:

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 Patients Global Evaluation (Study 005).

In order to be entered into these dental 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. Subjects then must have been experiencing moderate to severe postsurgical pain; and rated their Baseline pain intensity ≥50 mm on a VAS of 100 mm.

The treatment period in theses studies 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 post-dose. Assessments included those noted above.

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

Reviewer's comment: Generally speaking in the dental pain studies, there was a dose-response with Cx and the analgesic efficacy tended to be more sustained than that seen with active controls. However, the active controls showed a more rapid onset and peak analgesic response.

Multiple-Dose Analgesia Trials

Reviewer's comment: For more details regarding the multiple-dose trials, the interested reader is referred to the complete review by M. Averbuch.

For the indication of "Management of Pain", multiple-dose studies are useful to further understand the characteristics of any drug, especially the dosing regimen. The analgesic efficacy of Cx was evaluated in this regard with clinical trials employing the postsurgical pain (general surgery and orthopedic surgery) models as noted in Table 3.

Table 3. Multiple-Dose Postsurgical (General/Orthopedic) Pain

Protocol No. Report No. Short Title	No. Investigators Country(ies) Start Date	Design Study (Duration of Treatment)	Treatment Regimen(s)
P: N49-96-02-028 R: N49-98-06-028 Multiple-dose Analgesic Efficacy after Orthopedic Surgery	12 investigators U.S. 6 May 1997	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 or Darvocet-N 100 mg PRN up to QID or Placebo
P: N49-96-02-029 R: N49-98-06-029 Multiple-dose Analgesic Efficacy after General (but not Orthopedic) Surgery	13 Investigators U.S. and New Zealand 12 May 1997	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 or Darvocet-N 100 mg PRN up to QID or Placebo
P: N49-97-02-080* R: N49-98-06-080 Multiple-dose Analgesic Efficacy after Orthopedic Surgery	1 Investigator U.S. 15 Dec 1997	Randomized, Double-Blind, Placebo-Controlled, Active-Controlled, Parallel Group (5 days)	Celecoxib 200 mg PRN up to BID or naproxen 500 PRN up to BID or Placebo

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. 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 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 Cx 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 post-dose: 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.

As noted in Table 3, 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) because "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 but study 029 be terminated because the active comparator (Darvocet-N100) 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. Similarly, **study 080** had 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.

Study 028 failed to detect statistically significant treatment differences between Cx and placebo. In this study, for single-dose responses, (BOCF analyses), celecoxib at doses of 100 mg SD and 200 mg SD was associated with numerically greater mean PRID, PR and PID scores compared with placebo (from 1.5-8 hours post-dose); these differences were not statistically significant. For the multiple-dose analysis, efficacy scores with Cx 100 mg BID PRN or 200 mg BID PRN were again numerically but not statistically significant superior to placebo (from about 1 hour to the 24-hour post-dose period). Using the BOCF method of imputation, Cx 200 mg BID PRN was significantly different from placebo at only a few and inconsistent time-points for all of the measures of efficacy. Interestingly, Darvocet-N100 which was used as an active control in this study also did not statistically separate from placebo. This suggests that this pain model may not be appropriate for the tested medications and requires the highest degree of analgesia (i.e., opiates).

> ***Reviewer's comment: It should be noted that there are ongoing surgical pain studies that were only noted in the 120-Day Safety Update (i.e. no efficacy results given). These include both single-dose (Protocol 082, 083) and multiple-dose (Protocol 085 and 086) studies.***

Osteoarthritis Efficacy Trials

Ten studies were conducted to establish efficacy in OA. These trials consisted of both placebo-controlled and active-controlled trials with durations from 2 to 12 weeks. Also, a few of the trials (062, 071 and 042) employed "non-flare" designs and different entry criteria, as discussed below. Some basic characteristics of these OA trials are described in Table 4.

Table 4. Summary characteristics of Osteoarthritis trials

12-Week Pivotal Studies

Protocol No. Report No. Short Title	No. of Investigators Country(ies) Start Date	Study Design (Duration of Treatment)	Treatment Regimen(s)
P: N49-96-02-020 R: N49-98-06-020 Celecoxib Comparative Safety and Efficacy vs Naproxen in OA of the Knee	72 Investigators U.S. and Canada 5 Aug 1996	Randomized, Double-Blind, Placebo-Controlled, Active Controlled, Multicenter, Parallel (12 Weeks)	Celecoxib 50 mg BID, 100 mg BID, or 200 mg BID or Naproxen 500 mg BID or Placebo
P: N49-96-02-021 R: N49-98-06-021 Celecoxib Comparative Efficacy and UGI Safety vs Naproxen in OA of the Knee	80 Investigators U.S. and Canada 26 Aug 1996	Randomized, Double-Blind, Placebo-Controlled, Active Controlled, Multicenter, Parallel (12 Weeks)	Celecoxib 50 mg BID, 100 mg BID, or 200 mg BID or Naproxen 500 mg BID or Placebo
P: N49-96-02-054 R: N49-98-06-054 Celecoxib Comparative Safety and Efficacy vs Naproxen in OA of the Hip	125 Investigators U.S. and Canada 9 Jan 1997	Randomized, Double-Blind, Placebo-Controlled, Active Controlled, Multicenter, Parallel (12 Weeks)	Celecoxib 50 mg BID, 100 mg BID, or 200 mg BID or Naproxen 500 mg BID or Placebo

6-Week Pivotal Studies

Protocol No. Report No. Short Title	No. of Investigators Country(ies) Start Date	Study Design (Duration of Treatment)	Treatment Regimen(s)
P: N49-96-02-060 R: N49-98-06-060 QD vs BID Efficacy in OA of the Knee	51 Investigators United States 29 May 1997	Randomized, Double-Blind, Placebo-Controlled, Multicenter, Parallel (6 Weeks)	Celecoxib 100 mg BID or Celecoxib 200mg QD or Placebo
P: N49-98-02-087 R: N49-98-06-087 QD vs BID Efficacy in OA of the Knee	101 Investigators United States 26 Jan 1998	Randomized, Double-Blind, Placebo-Controlled, Multicenter, Parallel (6 Weeks)	Celecoxib 100 mg BID or Celecoxib 200mg QD or Placebo

Placebo-Controlled Supportive Studies

Protocol No. Report No. Short Title	No. of Investigators Country(ies) Start Date	Study Design (Duration of Treatment)	Treatment Regimen(s)
P: N49-96-02-047 R: N49-97-06-047 Dose-ranging Efficacy in OA	26 Investigators United States 9 Jan 1997	Randomized, Double-Blind, Placebo-Controlled, Multicenter, Parallel (4 Weeks)	Celecoxib 25 mg BID, 100 mg BID or 400 mg BID or Placebo
P: N49-96-02-013 R: N49-96-16-013 Pilot Efficacy in OA	26 Investigators United States 26 Jan 1996	Randomized, Double-Blind, Placebo-Controlled, Multicenter, Parallel (2 Weeks)	Celecoxib 40 mg BID, 100 mg BID or 200 mg BID or Placebo

Active-Controlled Supportive Studies

Protocol No. Report No. Short Title	No. of Investigators Country(ies) Start Date	Study Design (Duration of Treatment)	Treatment Regimen(s)
P: I49-96-02-042 R: I49-98-06-042 Ex-U.S. OA Trial	129 Investigators 20 countries in Australia, Europe and South Africa 2 Dec 1996	Randomized, Double-Blind, Active Controlled, Multicenter, Parallel (6 Weeks)	Celecoxib 100 mg BID or Diclofenac 50 mg BID
P: N49-97-02-062 R: N49-98-06-062 Comparative Incidence of UGI Ulcers: Celecoxib vs Naproxen in Patients with OA and RA	75 Investigators in United States 13 May 1997	Randomized, Double-Blind, Active Controlled, Multicenter, Parallel (12 Weeks)	Celecoxib 200 mg BID or Naproxen 500 mg BID
P: N49-97-02-071 R: N49-98-06-071 Comparative Incidence of UGI Ulcers: Celecoxib vs Diclofenac and Ibuprofen in Patients with OA and RA	121 Investigators in United Sates 21 Jul 1997	Randomized, Double-Blind, Active Controlled, Multicenter, Parallel (12 Weeks)	Celecoxib 200mg BID or Diclofenac 75 mg BID or Ibuprofen 800 mg TID

Reviewer's comment: Since all the placebo-controlled trials employed the same primary endpoints (as noted below), this review will focus primarily on two 12-week protocols (i.e. 020 and 054) to discuss the efficacy and dose-response characteristics of Cx; these trials are considered "pivotal" by the sponsor. In addition, two trials (i.e. 060 and 087) will also be reviewed since these studies explored the question of efficacy with different dosing regimens of Cx (i.e. BID vs. QD). The results of other protocols will be added and/or summarized as appropriate.

Study Characteristics:

As noted in table 4 above, studies 020 and 054 were double-blind, placebo-controlled, multicenter, parallel group comparisons of Cx versus placebo and naproxen in patients with OA of the knee (020) and hip (054). Protocol 054 was amended on November 4, 1996 (Amendment No. 5), to include only patients with OA of the knee; hip patients were not included in the efficacy analyses. The hip or knee joint studied was designated the **"Index Joint"**.

Table 5, list the numbers of patients with OA who were studied in ALL the protocols with the exclusion of the long-term, open-label trial.

Table 5. Number of Patients with OA Studied in All Protocols (excludes open-label)

Study	Treatment (mg/day)										Total
	Plc	Celecoxib						Naproxen	Diclofenac	Ibuprofen	
		50	80	100	200	400	800	1000	150	2400	
013	71	-	73	-	76	73	-	-	-	-	293
047	101	101	-	-	101	-	99	-	-	-	402
020	203	-	-	203	197	202	-	198	-	-	1003
054	217	-	-	216	207	213	-	207	-	-	1060
021	242	-	-	252	240	233	-	226	-	-	1193
060	231	-	-	-	453	-	-	-	-	-	684
087	243	-	-	-	472	-	-	-	-	-	715
062[1]	-	-	-	-	-	194 (270)	-	195 (267)	-	-	389 (537)
071[1]	-	-	-	-	-	272 (366)	-	-	285 (387)	255 (345)	812 (1098)
042	-	-	-	-	346	-	-	-	341	-	687
Total	1308	101	73	671	2092	1187	99	826	626	255	7238

1. Numbers in ( ) = total number of patients with OA studied in these protocols (i.e. remainder had RA)

As can be seen table 5, between protocols 020 and 054, a total of 2063 patients were enrolled and received at least one dose of study drug as follows:

- **placebo** 420
- **Cx 50 mg BID** 419
- **Cx 100 mg BID** 404
- **Cx 200 mg BID** 415
- **Naproxen 500 mg BID** 405

These studies consisted of Arthritis Assessments at pretreatment screening, at Baseline prior to dosing with study drug (i.e. after a flare, see below), and at treatment Week 2, Week 6 and Week 12 following the first dose of study drug (see ***Appendix Table A.1*** for details of Protocol 020 as an example of the schedule of observations and procedures).

The criteria for demonstrating **OA flare** depended on whether the patient was currently receiving NSAID/analgesic therapy for his/her OA (Category 1), or was not receiving NSAID/analgesic therapy, and had uncontrolled OA (Category 2). For patients receiving NSAID or analgesic therapy for OA (Category 1), an OA flare was demonstrated if both the Baseline Patient's Global Assessment of Arthritic Condition and the Baseline Physician's Global Assessment of Arthritic Condition were rated as "fair," "poor" or

"very poor" and a comparison of the Screening Visit Arthritis Assessments and the Baseline Visit Arthritis Assessments met at least three of the following four criteria:

1. **Patient's Assessment of Pain (100 mm VAS) at Baseline of at least 40.**
2. **An increase of two or more points in the Osteoarthritis Severity Index.**
3. **An increase of one or more grades in the Patient's Global.**
4. **An increase of one or more grades in the Physician's Global.**

Patients who did not demonstrate an OA flare within 14 days of discontinuing NSAID or analgesic treatment for OA were not eligible for enrollment.

For patients who were not receiving treatment for their OA and whose OA was not controlled (Category 2), an OA flare was demonstrated if they met at least three of the following four criteria during the Baseline Arthritis Assessments:

1. **Patient's Assessment of Pain at least 40 mm on VAS;**
2. **The Osteoarthritis Severity Index was ≥7.**
3. **The Patient's Global Assessment of Arthritic Condition was "poor" or "very poor".**
4. **The Physician's Global Assessment of Arthritic Condition was "poor" or "very poor."**

Patients satisfying this criteria were assigned a patient number and completed the Baseline Visit. Any patient not satisfying the arthritis flare criteria was not assigned a patient number and was considered a screen failure.

Patients who met the inclusion criteria (see below) were randomly assigned to receive Cx 50 mg BID, Cx 100 mg BID, Cx 200 mg BID, naproxen 500 mg BID, or placebo.

To qualify for inclusion in either trial (020 or 054), candidates must have:

1. **Been of legal age of consent or older;**
2. **For women of childbearing potential, confirmed use of adequate contraception since last menses and confirmed continued use of adequate contraception during the study, were not lactating, and had a negative serum pregnancy test within 14 days prior to the Baseline Arthritis Assessments;**
3. **Been diagnosed according to the American College of Rheumatology (ACR) criteria as having OA of the knee or hip;**
4. **Had a Functional Capacity Classification of I-III at the Baseline Visit;**
5. **Had OA in a flare state at the Baseline Visit; and**
6. **Provided written informed consent before undergoing any study procedure.**

Exclusion criteria included:

1. **Any inflammatory arthritis or gout (patients with fibrositis or fibromyalgia were not excluded) or any acute joint trauma at the knee with OA;**
2. **An anticipated need for any surgical or other invasive procedure (e.g., arthroscopy or lavage) that would have been performed on the knee with OA during the course of the study;**

3. **Received oral, intramuscular, intra-articular, or soft-tissue injections of corticosteroids within four weeks before the first dose of study medication;**
4. **Taken any NSAIDs or any analgesic within 48 hours before the Baseline Arthritis Assessments. (Patients taking ≤ 325 mg aspirin per day for non-arthritic reasons, if stable for at least 30 days before the first dose of study medication, were allowed to continue their aspirin regimen for the duration of the study. Patients must have discontinued piroxicam and/or oxaprozin at least four days before the Baseline Arthritis Assessments.);**
5. **An active malignancy of any type or history of a malignancy. (Patients who had a history of basal cell carcinoma that had been treated were eligible. Patients with a history of other malignancies that had been surgically removed and who had no evidence of recurrence for at least five years before study enrollment were also eligible.);**
6. **Diagnosed as having or had been treated for esophageal, gastric, pyloric channel, or duodenal ulceration within 30 days prior to the first dose of study medication;**
7. **Active GI disease (e.g., inflammatory bowel disease), a chronic or acute renal or hepatic disorder, or a significant coagulation defect;**
8. **Abnormal screening laboratory test values >1.5 x upper limits of normal (ULN) for either aspartate transaminase (AST, SGOT) or alanine transaminase (ALT, SGPT) or any other laboratory abnormalities considered by the Investigator to be clinically significant within 14 days before the Baseline Arthritis Assessments;**
9. **Known hypersensitivity to COX-2 inhibitors, sulfonamides, or NSAIDs;**
10. **Received any investigational medication within 30 days before the first dose of study medication or was scheduled to receive an investigational drug, other than study medications described in the protocol, during the course of this study; or**
11. **Previous admission to this study.**

Demographics:

There did not appear to be any remarkable differences in baseline demographics between treatment groups in the 12-week (***Appendix, Table A.2***) or 6-week (***Appendix, Table A.3***) protocols. These patients were mostly elderly, white females with OA involving the knee. However, it is interesting to note (as shown below) that the patients in the knee protocol (020) were generally heavier than those in the hip protocol (054).

Table 6. Weights of Patients in Osteoarthritis Trials

Protocol	Weight (kg)	Treatment				
		Placebo	Cx 50 BID	Cx 100 BID	Cx 200 BID	Naproxen 500 BID
020	mean	87.7	88.5	85.8	89.1	90.8
	range					
054	mean	82.8	83.9	83.1	83.2	83.8
	range					

Primary/Secondary Endpoints

In the OA studies, the **original** primary endpoints were:

- **Patient's Global Assessment of Arthritic Condition**
- **Patient's Assessment of Arthritis Pain - VAS**
- **Physician's Global Assessment of Arthritic Condition**

The per protocol secondary measures of arthritis efficacy were:

- **Functional Capacity Classification**
- **WOMAC OA Index**
- **Incidence of Withdrawal Due to Lack of Arthritis Efficacy**
- **Time to Withdrawal Due to Lack of Arthritis Efficacy**
- **Osteoarthritis Severity Index (OSI)**
- **APS Pain Measure**
- **Patient Assessment of Function**
- **SF-36 Health Survey.**

A modification of the primary and secondary efficacy variables occurred as a result of recommendations from the **Agency**. The principal change was the inclusion of the WOMAC Index for osteoarthritis as a primary measure of efficacy. Therefore, the **retrospectively defined primary OA efficacy endpoints included:**

- **Patient's Global Assessment of Arthritic Condition**
- **Patient's Assessment of Arthritis Pain (VAS):**
  - **"How much pain are you having because of OA in your index hip/knee"**
  - **0 mm = no pain, 100 mm = most severe pain**
- **Physician's Global Assessment of Arthritic Condition**
- **WOMAC OA Index**
  - **Composite plus subscores for pain, joint stiffness, and physical function**

The **Patient's Global Assessment** is based on the patient's response to the question, "Considering all the ways your arthritis affects you, how are you doing today?" The **Physician's Global Assessment** is based on the patient's disease signs at the time of the visit. The categorical (from grade 1-5, respectively) answers to these questions are:

•very good	**Asymptomatic and no limitation of normal activities**
•good	**Mild symptoms and no limitation of normal activities**
•fair	**Moderate symptoms and limitation of some normal activities**
•poor	**Severe symptoms and inability to carry out most normal activities**
•very poor	**Very severe symptoms with an inability to carry out all normal activities**

The Western Ontario and McMaster Universities (**WOMAC**) Osteoarthritis Index is a tri-dimensional, self-administered questionnaire that probes clinically important, patient-relevant outcomes in patients with OA of the hip and/or knee. The patient responded to 24 component items: 5 regarding pain, 2 regarding stiffness, and 17 regarding physical function (see ***Appendix, Table A.4***).

The **Osteoarthritis Severity Index (OSI)** of the knee (see ***Appendix Table A.5***) or hip (see ***Appendix Table A.6***) is based on the patient's responses to questions related to pain, walking distance, and activities of daily living. The Osteoarthritis Severity Index is the sum of scores of the eight inquiries and ranges from 0 to 24, with a lower score indicating a better condition.

The physician assessed the **Functional Capacity** of the patient according to Steinbrocker's criteria as noted below (IV patients not enrolled):

Class	Description
I	Complete functional capacity with ability to carry on all usual duties without handicaps
II	Functional capacity adequate to conduct normal activities despite handicap of discomfort or limited mobility of one or more joints
III	Functional capacity adequate to perform only few or none of the duties of usual occupation or of self care
IV	Largely or wholly incapacitated with patient bedridden or confined to wheelchair, permitting little or no self care

Quality of Life

Scores of eight domains (Physical Functioning, Role-Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role-Emotional, and Mental Health) for the **SF-36 Health Survey** were observed at Baseline, Week 2, and Week 12 (or Early Termination).

The **APS pain** measure consists of five questions:

1. **Have you experienced any pain in the past 24 hours? (yes or no)**
2. **How much pain are you having right now? (0-10)**
3. **Indicate the worst pain you have had in the past 24 hours. (0-10)**
4. **Indicate the average level of pain you have had in the past 24 hours. (0-10)**
5. **Indicate how pain has interfered with you in:**
    - **General Activity (0-10)**
    - **Mood (0-10)**
    - **Walking ability (0-10)**
    - **Relations with other people (0-10)**
    - **Sleep (0-10)**
    - **Normal work, including house work (0-10)**
    - **Enjoyment of life (0-10)**

Patient Populations Analyzed/Statistics:

Intent-to-Treat (ITT) Cohort

The ITT Cohort included all patients who had OA of the index joint (hip/knee), who were randomized to treatment and who had taken at least one dose of study medication. The Last Observation Carried Forward (LOCF) approach was used for either missing data or data that was obtained on days that fell outside the observation window (i.e. >19 days for Week 2, >49 days for Week 6, and >93 days for Week 12). The LOCF approach was employed in the ITT analyses only.

Evaluable Cohort

The Evaluable Cohort included each patient who satisfied the requirements for the ITT Cohort and met the following criteria:

1. **Was diagnosed by the ACR criteria for having OA of the knee/hip;**
2. **Had a Functional Capacity Classification of I-III at the Baseline Visit;**
3. **Had OA in a flare state at the Baseline Visit;**
4. **No inflammatory arthritis, gout or any acute joint trauma at the knee/hip;**
5. **No corticosteroids within four weeks of the first dose of study medication;**
6. **Did not take NSAIDs or any analgesic within 48 hours before any study visit;**
7. **Had baseline arthritis assessments within seven days before the first dose;**
8. **No surgical or other invasive procedure performed on the knee/hip during the study;**
9. **Did not take any NSAIDs (other than > 325 mg aspirin/day), oral or injectable corticosteroids, or analgesic (other than acetaminophen ≤ 2 g/day for non-arthritic reasons) during the study;**
10. **Was compliant with study medications as described below:**
    - **For the Week 2 Visit: took at least 70% of the doses prescribed from Day 1 through the Week 2 Visit; or**
    - **For the Week 6 Visit: took at least 70% of the doses prescribed from the Week 2 through the Week 6 Visit and took at least 50% of the doses prescribed from Day 1 through the Week 2 Visit; or**
    - **For the Week 12 Visit: took at least 70% of the doses prescribed from the Week 6 Visit through the Week 12 Visit and at least 50% of the doses prescribed from the Week 2 Visit through the Week 6 Visit and 50% of the doses prescribed from Day 1 through the Week 2 Visit.**
11. **Underwent the Arthritis Assessments for each visit according to the following schedule:**
    a. **14±5 days after the first dose of study medication for the Week 2 Visit;**
    b. **42±7 days after the first dose of study medication for the Week 6 Visit;**
    c. **84±9 days after the first dose of study medication for the Week 12 Visit; and**
    d. **≤2 days after the last dose of study medication for the Final Visit.**
12. **Had complete primary efficacy data available for each visit under consideration.**

Patients who did not have data for all primary efficacy variables at baseline were excluded from all analyses. Evaluability determinations were made prior to unblinding the data and no subsequent revisions were made.