These results are supplied for informational purposes only.
Prescribing decisions should be made based on the approved package insert

See Drug Details page of this website for approved drug label.

Proprietary Drug Name	**INN**	Therapeutic area and FDA approved indications
Celebrex	Celecoxib	Relief of signs and symptoms of osteoarthritis Relief of signs and symptoms of rheumatoid arthritis in adults Management of acute pain in adults Treatment of primary dysmenorrhea Reduce the number of adenomatous colorectal polyps in familial adenomatous polyposis as an adjunct to usual care

Name of Sponsor/Company: Pfizer Inc.

Title of Study: Protocol Number N49-97-02-071

A Multicenter, Double-Blind, Parallel Group Study Comparing the Incidence of Gastrodudenal Ulcer Associated With SC-58635(celecoxib) 200 mg BID With That of Diclofenac 75 mg BID and Iboprofen 800 mg TID, Taken for 12 Weeks in Patients With Osteoarthritis or Rheumatoid Arthritis

Study centre(s): 121 Investigators in the United States; 115 of whom enrolled at least one patient

Publication (reference, if applicable): See attached bibliography

Studied period: 21 Jul 1997 - 12 Jan 1998 **Phase of development:** Not stated

Objectives: The primary objective of this study was to compare the cumulative (up to 12 weeks) incidence of gastroduodenal ulcers associated with SC-58635 200 mg BID with that of diclofenac 75 mg BID and ibuprofen 800 mg TID in patients with OA or RA.

Secondary Objectives: The secondary objectives of this study were to:

- Compare the short-term safety and tolerability of SC-58635 200 mg BID with that of diclofenac 75 mg BID and ibuprofen 800 mg TID in patients with OA or RA
- Evaluate the effect of Helicobacter pylori (*H. pylori*) status on the development of gastroduodenal ulcers
- Compare the effect of SC-58635 versus diclofenac and ibuprofen on Quality of Life (QOL)
- Compare the arthritis efficacy of SC-58635 200 mg BID with that of diclofenac 75 mg BID and ibuprofen 800 mg TID in patients with OA or RA.

Methodology: This was a randomized, double-blind, multicenter, parallel group comparison of the cumulative incidence of gastroduodenal ulcers in OA or RA patients receiving SC-58635 with those receiving diclofenac or ibuprofen. The study consisted of 12 weeks of treatment with visits occurring at Screening/Baseline, and 4, 8, and 12 weeks after the first dose of study medication. Endoscopies were performed Pretreatment and 4, 8, and 12 weeks after the first dose of study medication. Patients who met the inclusion criteria (see below) were randomly assigned to receive SC-58635 200 mg BID, diclofenac 75 mg BID, or ibuprofen 800 mg TID for 12 weeks.

Number of patients (planned and analyzed): A total of 1099 patients were randomized to receive treatment for up to 12 weeks as follows: SC-58635 200 mg BID, 366 patients; diclofenac 75 mg BID, 387 patients; ibuprofen 800 mg TID, 346 patients.

Diagnosis and main criteria for inclusion: Patients were eligible to participate in the study if they had a documented clinical diagnosis of OA or RA with a Functional Capacity Classification of I-III and required chronic nonsteroidal anti-inflammatory drugs (NSAIDs). At the time of study enrollment, patients underwent an endoscopy to ensure they did not have an esophageal, gastric, pyloric channel, or duodenal ulcer.

Duration of treatment: 12 weeks

Test product, dose and mode of administration: Capsules containing 200 mg of SC-58635 and matching placebo

Reference therapy, dose and mode of administration: Tablets containing 75 mg of diclofenac and tablets containing 800 mg of ibuprofen and matching placebo

Criteria for evaluation: The incidence of upper gastrointestinal (UGI) ulcers was assessed by UGI endoscopies performed at the Week 4, 8, and 12 (or Early Termination) follow-up visits. Serologic testing for Helicobacter pylori (*H. pylori*) antibodies was performed at Screening using the FlexSure® HP test. Biopsies were obtained at the Week 12 (or Early Termination) Visit to perform the CLOtest® and for histological examination. The gastroduodenal, gastric and duodenal ulcer rates, and gastric and duodenal scores were compared between treatment groups. Arthritis Assessments were performed at Baseline and at the Weeks 4, 8, and 12 (or Early Termination) follow-up visits. Arthritis efficacy was based on Patient's Global Assessment of Arthritic Condition, Physician's Global Assessment of Arthritic Condition, Incidence of Withdrawal Due to Lack of Arthritis Efficacy, and Time to Withdrawal Due to Lack of Arthritis Efficacy. Quality of life was assessed using the SF-36 Health Survey. Overall safety and tolerability was assessed by comparing physical examinations, clinical laboratory tests, and the incidence of adverse events between treatment groups.

Statistical methods: Patient Population Analyzed - Arthritis Efficacy Analysis: All arthritis efficacy analyses were performed on the ITT Cohort only. The ITT Cohort for the arthritis efficacy analysis included all patients who were randomized to treatment and had taken at least one dose of study medication.

Endoscopy Analyses: Pyloric channel ulcers were grouped with gastric ulcers. For Gastric and Duodenal scores, the following analyses were performed on ITT Cohort. The cumulative ulcer rate was based on survival analysis techniques. Time to ulcer was first analyzed by grouped survival techniques and second by log-rank tests. The time intervals under consideration were 0-35 days, 0-63 days, and 0-91 days. Cumulative ulcer rates based on grouped survival analysis and Kaplan-Meier methods were calculated at the end of the above intervals.

Endoscopy scores were analyzed by CMH test stratified by Baseline score. The differential effect of H. pylori status as determined from both the FlexSure and, separately, the CLOtest and histology results, were examined by both ANCOVA (with treatment, center, and H. pylori status as factors and Baseline value as covariate) and CMH (stratified by Baseline and treatment). In addition, H. pylori status by treatment interaction was also examined by ANCOVA (with treatment, center, H. pylori status and H. pylori status by treatment interaction as factors and Baseline value as covariate). Similarly, the differential effect of H. pylori status within treatment group was also examined. The CLOtest and histology data are not available at the time of writing this report, but will be reported separately in an addendum.

For gastroduodenal ulcer rates, analyses were similar to those for gastric and duodenal ulcer rates, except that no gastroduodenal scores were calculated and analyzed. The analyses were performed on both the ITT and Evaluable Cohorts.

Arthritis Efficacy Analyses: The measures of arthritis efficacy were:

1. Patient's Global Assessment of Arthritic Condition;
2. Physician's Global Assessment of Arthritic Condition;
3. Incidence of Withdrawal Due to Lack of Arthritis Efficacy; and
4. Time to Withdrawal Due to Lack of Arthritis Efficacy.

Patient's and Physician's Global Assessments of Arthritic Condition were graded on the following scale: 1 very good; 2 good; 3 fair; 4 poor; and 5 very poor. For a one-grade change analysis, the patient was classified as improved if a reduction of at least one grade from Baseline was observed or as worsened if an increase of at least one grade from Baseline was observed. The changes were analyzed by the CMH test stratified by center. Improvement and worsening defined as two-grade changes from Baseline were similarly analyzed.

Mean values for Patient's and Physician's Global Assessments of Arthritic Condition were also analyzed. These analyses were carried out using ANCOVA with treatment and center as factors and Baseline value as covariate.

Incidence of Withdrawal Due to Lack of Arthritis Efficacy was analyzed by Fisher's exact test. Time to Withdrawal Due to Lack of Arthritis Efficacy was calculated as the difference between the date of last dose of study medication and the date of first dose of study medication plus one day.

Quality of Life Analysis: Scores of eight domains for the SF-36 Health Survey were calculated. Quality of life data was observed Pretreatment and at Week 12 (or Early Termination). Mean changes from Baseline for quality of life data observed at Week 12 or Early Termination were analyzed using ANCOVA with treatment and center as factors and corresponding Baseline score as covariate. The analyses were performed on the ITT Cohort only.

Safety Analyses: Every randomized patient who received at least one dose of study medication was included in the safety analyses.

An external committee of independent gastroenterologists (the "GI Events Committee") defined clinically significant GI events using pre-established criteria. If a GI-related adverse event met the pre-established criteria, the GI Events Committee designated the case as constituting a clinically significant GI event. Changes in weight and vital signs from Baseline to Final Visit were calculated and compared across treatment groups using two-way ANOVA with treatment group and center as factors. Clinical laboratory data were compared between Baseline and Week 4, Baseline and Week 12, and Baseline and Early Termination and examined.

Shifts in laboratory test values at Week 4, Week 12, and Early Termination were compared pairwise among the treatment groups in terms of the numbers of patients showing an increase, decrease, and no change from Baseline, with respect to the normal range, using the Chi square test. Mean changes from Baseline were compared among the treatment groups using one-way ANCOVA with pairwise treatment contrasts using treatment group as factor and Baseline as covariate. The percent of patients showing changes from Baseline in the following laboratory test values were compared between the three treatment groups.

Summary: Efficacy Results: The results of this study demonstrated that over 12 weeks, SC-58635 200 mg BID was associated with a statistically significantly lower incidence of gastroduodenal ulcers than ibuprofen 800 mg TID and a numerically (although not statistically significant) lower incidence of gastroduodenal ulcers than diclofenac 75 mg BID. Serial endoscopies at monthly intervals over 12 weeks revealed ulceration of the gastric or duodenal mucosa in 25 (9%) SC-58625 patients. In contrast, gastric or duodenal ulceration was observed in 36 (12%) diclofenac-treated patients and 78 (28%) ibuprofen-treated patients. The same treatment effect observed with the 0-Week12 gastroduodenal ulcer data was also seen in the 0-Week 4 and 0-Week 8 gastroduodenal ulcer data and in the gastric and duodenal ulcer data when considered separately. The only exception to this was for duodenal ulcers where SC-58635 was statistically significantly different from diclofenac as well as ibuprofen. In addition to ulcers, gastric erosions were observed in fewer SC-58635 200 mg BID patients than diclofenac 75 mg BID patients in the majority of intervals (2 of 3) and were observed in fewer SC-58635 200 mg BID patients than ibuprofen 800 mg TID patients at all timepoints. Duodenal erosions were observed in fewer SC-58635 200 mg BID patients than diclofenac 75 mg BID or ibuprofen 800 mg TID patients at all time intervals.

The gastrointestinal (GI) tolerability of SC-58635 was better than diclofenac and ibuprofen as measured by GI adverse events and rates of withdrawal due to GI adverse events. GI-related adverse events were reported by 381 patients: 110 (30%) patients in the SC-58635 200 mg BID treatment group; 140 (36%) patients in the diclofenac 75 mg BID group; and 131 (38%) of the patients in the ibuprofen 800 mg TID treatment group. The majority of all reported GI-related adverse events were mild to moderate in severity. The most commonly reported events in the GI system (≥5% in any treatment group) were: dyspepsia, abdominal pain, diarrhea, and nausea. The withdrawal rate due to GI adverse events was lower in SC-58635 treated patients than in the diclofenac or ibuprofen group (SC-58635 3% compared to diclofenac 6% and ibuprofen 8%). One clinically significant GI event occurred in each of the treatment groups: hemorrhagic gastric ulcer (SC-58635 200 mg BID), decreased hematocrit and erosive duodenitis (diclofenac 75 mg BID), and hemorrhagic gastric ulcer (ibuprofen 800 mg TID).

Several important potential risk factors were analyzed for their effect on ulcer rate in this study. In SC-58635 treated patients, age (65 years or older), history of cardiovascular disease, NSAID intolerance, gastroduodenal ulcer, or GI bleeding were associated with an increase in cumulative crude gastroduodenal ulcer rate over 12 weeks. In diclofenac 75 mg BID treated patients concurrent aspirin use, age (65 years or older), history of cardiovascular disease, gastroduodenal ulcer, or disease status (OA) were associated with an increase in cumulative crude gastroduodenal ulcer rate over 12 weeks. In ibuprofen treated patients, age (65 years or older), a history of gastroduodenal ulcer, or GI bleeding were associated with an increase in cumulative gastroduodenal rate over 12 weeks. For each treatment group, generally similar interactions were seen for gastric and duodenal ulcers separately. The ulcer data were also analyzed by *H. pylori* status, as determined by CLOtest and histology or FlexSure. Based on analyses of Week 0-12 crude ulcer rates (gastroduodenal, gastric, and duodenal), there were no statistically significant increases in ulcer rates in any of the treatment groups in patients who were H. pylori positive by the FlexSure test compared to patients who were H. pylori negative by FlexSure test. However, it is recognized that serological measurement of *H. pylori* antibodies is an imperfect measure of *H. pylori* infection and therefore these results do not provide definitive data on a possible relationship between ulcers and *H. pylori* infection.

Analyses of arthritis efficacy results indicated that patients treated with either SC-58635 200 mg BID, diclofenac 75 mg BID, or ibuprofen 800 mg TID showed improvement from Baseline in Patient's Global Assessment of Arthritic Condition and Physician's Global Assessment of Arthritic Condition scores. Based on a one-grade categorical analysis, there were no statistically significant differences between the SC-58635 200 mg BID, diclofenac 75 mg BID, and ibuprofen 800 mg TID treatment groups in the number of patients who showed improvement, no change, or worsening in arthritis condition at Weeks 4, 8, and 12 in these arthritis efficacy parameters except for Week 4 of the Patient's Global Assessment of Arthritic Condition. There were no statistically significant differences in the incidence or time of withdrawal due to lack of arthritis efficacy between the three treatment groups. These data support the conclusion that SC-58635 200 mg BID was comparable to diclofenac 75 mg BID and ibuprofen 800 mg TID in treating the signs and symptoms associated with OA and RA.

The results of the quality of life analyses were consistent with those of the arthritis efficacy analyses. Results of the SF-36 Health Survey showed that the SC-58635 200 mg BID group was statistically significantly different from the diclofenac 75 mg BID group for the Role-Physical, Bodily Pain, and Vitality domains; however, the SC-58635 200 mg BID group was not statistically different from the ibuprofen 800 mg TID group in any of the SF-36 domains.

Safety Results: No unexpected adverse events related to study drug were reported. Adverse events were reported by 709 patients: 214 (59%) in the SC-58635 200 mg BID group; 258 (67%) in the diclofenac 75 mg BID group; and 237 (69%) in the ibuprofen 800 mg TID group. The adverse events with the highest incidence (i.e., ≥5% reported in either treatment group) were headache, dyspepsia, upper respiratory tract infection, abdominal pain, sinusitis, diarrhea, and nausea. The incidences of adverse events causing withdrawal were 22 (6%) in the SC-58635 200 mg BID group, 37 (10%) in the diclofenac 75 mg BID group, and 37 (11%) in the ibuprofen 800 mg TID group. Serious adverse events were reported for 21 patients: 9 patients in the SC-58635 200 mg BID group; 8 patients in the diclofenac 75 mg BID group; and

4 patients in the ibuprofen 800 mg TID group. The SAEs reported in these groups were:

NO. OF PATIENTS WITH SERIOUS ADVERSE EVENTS

Adverse event	SC-58635 200mg bid (n= 365)	Diclofenac 75mg bid (n= 387)	Ibuprofen 800mg tid (n= 345)
Basal cell carcinoma	1	0	0
Depression aggravated	1	0	0
Gastric ulcer hemorrhagic	1	0	0
Hypertension aggravated	1	0	0
Lymphoma malignant	1	0	0
Previously scheduled surgery	1	1	0
Renal calculus	1	0	0
Treatment emergent surgery	1	0	1
Urinary tract infection	1	0	0
Angina pectoris	0	1	0
Arrhythmia atrial	0	1	0
Arteriosclerosis	0	1	0
Carcinoma	0	1	0
Emphysema	0	1	0
Fracture accidental	0	1	0
Myocardial infarction	0	0	1
Pleural effusion	0	1	0
Pyelonephritis	0	0	1
Sudden death	0	0	1

There were 2 deaths during the study. The first patient was found dead at home 15 days after starting treatment with diclofenac 75 mg BID. The coroner listed the cause of death as arteriosclerotic cardiovascular disease. The second patient withdrew from the study after 35 days of treatment with ibuprofen 800 mg TID due to ankle edema. Twenty-four days after stopping study medication the patient collapsed and expired. No autopsy was performed. It was the opinion of both the Investigator and the Searle Medical Monitor that neither event was associated with study medication. There were no consistent alterations in mean laboratory test values; however; individual abnormal laboratory test results occurred, and there were shifts in laboratory values within treatment groups. None of these findings were considered to be clinically significant nor did there appear to be a pattern suggesting a drug-related process in the nature of the changes.

Conclusions: It is concluded that, in this study: SC-58635 200 mg BID was safe and well tolerated in patients with osteoarthritis or rheumatoid arthritis; based on the gastroduodenal ulcer rate determined by serial endoscopies over 12 weeks, the GI safety profile of SC-58635 200 mg BID was superior to ibuprofen 800 mg TID. The gastroduodenal ulcer rate for SC-58635 200 mg BID was numerically lower than that for diclofenac 75 mg BID; and the efficacy of SC-58635 200 mg BID was comparable to diclofenac 75 mg BID and ibuprofen 800 mg TID in treating the signs and symptoms associated with osteoarthritis or rheumatoid arthritis.

Based on a report completed on: 30 April 1998