

# PFIZER INC.

**These results are supplied for informational purposes only.  
Prescribing decisions should be made based on the approved package insert.  
For publications based on this study, see associated bibliography.**

**PROPRIETARY DRUG NAME/INN:** Celebrex®/Celecoxib

## **THERAPEUTIC AREA AND FDA APPROVED INDICATIONS:**

- For relief of the signs and symptoms of osteoarthritis.
- For relief of the signs and symptoms of rheumatoid arthritis in adults.
- For the management of acute pain in adults.
- For the treatment of primary dysmenorrhea.
- To reduce the number of adenomatous colorectal polyps in familial adenomatous polyposis (FAP), as an adjunct to usual care (e.g., endoscopic surveillance, surgery).

**PROTOCOL NO.** N49-96-02-020

**PROTOCOL TITLE:** Double-blind, Placebo-Controlled, Randomized Comparison Study of the Efficacy and Safety of SC-58635 (celecoxib) 50 mg, 100 mg and 200 mg BID and Naproxen 500 mg BID in Treating the Signs and Symptoms of Osteoarthritis of the Knee

**Study Center(s):** Sixty-eight (68) study centers in the United States and three (3) in Canada.

**Study Initiation and Completion Dates:** 05 August 1996 to 09 July 1997

**Phase of Development:** Phase 2-3

### **Study Objective(s):**

#### *Primary objectives:*

1. Compare the efficacy of SC-58635 50 mg, 100 mg, and 200 mg BID for 12 weeks with placebo in treating the signs and symptoms of OA of the knee; and
2. Evaluate the safety of SC-58635 50 mg, 100 mg, and 200 mg BID for 12 weeks in patients with OA of the knee.

#### *Secondary objectives of this study were to:*

1. Compare the efficacy of naproxen 500 mg BID and placebo in treating the signs and symptoms of OA of the knee; and
2. Compare the efficacy of SC-58635 50 mg, 100 mg, and 200 mg BID with naproxen 500 mg BID in treating the signs and symptoms of OA of the knee.

## **METHODS**

**Study Design:** The study consisted of Arthritis Assessments at pretreatment screening, at Baseline prior to dosing with study drug, and at treatment Week 2, Week 6 and Week 12 following the first dose of study drug. Patients who met the inclusion criteria were randomly

## CLINICAL STUDY SYNOPSIS

assigned to receive SC-58635 50 mg BID, SC-58635 100 mg BID, SC-58635 200 mg BID, naproxen 500 mg BID, or placebo. The Screening Visit occurred 2 to 14 days prior to the administration of the first dose of study medication. Each patient gave a medical history, including information about upper GI bleeding and/or gastroduodenal ulcers and previous NSAID GI intolerance, and underwent a physical examination, including measurement of weight and vital signs, as well as clinical laboratory tests.

Arthritis Assessments were performed immediately before the patient's discontinuation of his or her current NSAID or analgesic therapy and consisted of the Patient's Global Assessment of Arthritic Condition, Osteoarthritis Severity Index, Functional Capacity Classification and Physician's Global Assessment of Arthritic Condition. The physician assessed the Functional Capacity of the patient according to Steinbrocker's criteria. The patient was instructed to discontinue his/her current NSAID or analgesic and to notify the Investigator when flare symptoms began. All patients had to be in an OA flare at the Baseline Visit. The following procedures were performed: SF-36 Health Survey, WOMAC Osteoarthritis Index, Arthritis Assessments and Verification of Flare Criteria, Patient's Assessment of Pain (VAS). Patients were then asked to identify the joint with the most severe OA symptoms, either right knee or left knee: the "Index Joint," and assess the amount of arthritis pain there.

Patients who did not demonstrate an OA flare within 14 days of discontinuing NSAID or analgesic treatment for OA were not eligible for enrollment. Patients satisfying all criteria were assigned a patient number and completed the Baseline Visit. Patients were issued American Pain Society (APS) Pain Measure questionnaires and Patient Assessment of Function questionnaires to be completed at Baseline and every evening for the first seven days of the study. Patients were instructed to return the questionnaires to the study site at the Week 2 Visit. The Treatment Period was defined as the 12-week period during which study medication was taken. Patients returned to the study site at the end of Week 2 (day 14±1 day), Week 6 (day 42±2 days), and Week 12 (day 84±2 days) after the first dose of study medication. The SF-36 Health Survey and WOMAC Osteoarthritis Index were repeated at the Week 2 and Week 12 Visits. The Arthritis Assessments (Patient's Global Assessment of Arthritic Condition, Osteoarthritis Severity Index, Functional Capacity Classification, Physician's Global Assessment of Arthritic Condition, and Patient's Assessment of Pain (VAS) were repeated at the Week 2, Week 6 and Week 12 Visits. With the exception of PT, PTT, and the serum pregnancy test, the clinical laboratory tests performed at screening were repeated at the Weeks 2, 6, and 12. The serum pregnancy test for women of childbearing potential was performed only at screening. PT and PTT were assessed at the Week 2 and the Week 12 Visits. A complete physical examination, including weight and vital signs, was completed at the Week 12 Visit.

At each follow-up visit, patients were asked: "Since your last visit, have you experienced any symptoms that are not associated with your arthritis?" Any symptom was recorded on the Adverse Signs and Symptoms CRF. Patients who withdrew before the end of the study had all final assessments performed at the time of withdrawal (Early Termination Visit).

Originally, a sample size of 1000 patients (200 per treatment group) was planned, but based on Protocol Amendment No. 5, patients with OA of the hip were to be excluded from the efficacy analysis. In order to compensate for patients with OA of the hip who had already entered the

## CLINICAL STUDY SYNOPSIS

study, the planned sample size was increased to 1070 patients. One thousand ninety-two (1092) patients received treatment.

**Diagnosis and Main Criteria for Inclusion:** Male and female patients of legal age with diagnosed, active OA of the knee in a flare state were enrolled and randomized. The original protocol also included patients with OA of the hip in this study. Based on communications with the FDA, the protocol was amended on 4 November 1996 (Amendment No. 5), to include only patients with OA of the knee. Patients with OA of the hip who were enrolled prior to this amendment were not included in the efficacy analyses.

**Study Treatment:** Investigational drug supplies consisted of the following:

- Hard gelatin capsules containing either SC-58635 50 mg, 100 mg or 200 mg, each identical in size and color;
- Hard gelatin placebo capsules, each identical in size and appearance to the SC-58635 50 mg, 100 mg and 200 capsules;
- Hard gelatin capsules containing naproxen 500 mg;
- Hard gelatin placebo capsules, identical in size and appearance to the naproxen 500 mg capsules.

Dosage and duration of study treatment was BID for 12 weeks.

### **Efficacy Evaluations:**

#### *Primary measures of arthritis efficacy:*

- Patient's Global Assessment of Arthritic Condition
- Patient's Assessment of Pain - Visual Analog Scale (VAS)
- Physician's Global Assessment of Arthritic Condition

#### *Secondary measures of arthritis efficacy*

- Functional Capacity Classification
- WOMAC Osteoarthritis Index
- Incidence of Withdrawal due to Lack of Arthritis Efficacy
- Time to Withdrawal due to Lack of Arthritis Efficacy
- Osteoarthritis Severity Index.

#### *Exploratory analyses:*

- American Pain Society (APS) Pain Measures (later validated as the mBPIsf)
- Patient Assessment of Function.

*Quality of life analysis* consisted of SF-36 Health Survey.

**Pharmacokinetic, Pharmacodynamic, and/or Other Evaluations:** Three 15-mL blood samples were to be collected from 200 patients (approximately 40 patients per treatment group) at selected study sites for determination of plasma concentrations of SC-58635. The blood samples were taken at the Week 2 Visit or at a separate visit between 7 and 28 days after the first dose of study medication. Upon reporting to the study site, information was taken regarding the

## CLINICAL STUDY SYNOPSIS

exact time of the most recent dose of study medication and the most recent meal. Blood samples were then drawn at one hour intervals for three hours and the plasma separated from each sample.

**Safety Evaluations:** Safety was measured by the record of treatment-emergent adverse events, clinical laboratory tests, and changes from Baseline vital signs and physical examinations.

**Statistical Methods:** Homogeneity of treatment groups in terms of gender and race was analyzed by Chi-square test. A two-way analysis of variance (ANOVA) with treatment and center as factors was used to examine homogeneity among the treatment groups with respect to age, height, weight, and vital signs. Differences among the treatment groups with respect to history of GI Index scores were analyzed with a two-way ANOVA. Differences among the treatment groups with respect to history of GI bleeding, gastroduodenal ulcer, cardiovascular disease, and GI-NSAID intolerance were analyzed using Fisher's exact test. Baseline differences in duration of OA were analyzed with a two-way ANOVA. Baseline results of Physician's and Patient's Global Assessments and Functional Capacity Classification were analyzed for homogeneity among the treatment groups with the Cochran-Mantel-Haenszel (CMH) test stratified by center.

The ITT Cohort included all patients with a knee identified as the index joint who took 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. Patients who did not have data for all primary efficacy variables at baseline were excluded from all analyses. A patient's data at a specific visit were included in this analysis if he or she satisfied the requirements for the ITT Cohort and the corresponding assessment days after the first dose of study medication fell in the following intervals: 14±5 days for Week 2; 42±7 days for Week 6; and 84±9 days for Week 12. The analyses were performed for Evaluable and Observed Data Cohorts at all scheduled visits and also at the 'Final Visit', which consisted of the last valid observation of the patient.

The Physician's and Patient's Global Assessments were analyzed by CMH stratified by center. Mean change analyses, including the linear trend test for all SC-58635 and placebo groups, and overall and pairwise comparisons for all five treatment groups were performed using analysis of covariance (ANCOVA) with treatment and center as factors and the corresponding Baseline score as covariate. Additionally, the Q-Ratio with 95% confidence intervals was calculated by taking the ratio of adjusted mean changes for each SC-58635 treatment groups versus the naproxen treatment group.

The results of the pairwise comparisons for the SC-58635 100 mg BID and 200 mg BID treatment groups versus placebo were interpreted using Hochberg's step-up procedure. P-values of comparisons between SC-58635 100 mg BID and SC-58635 200 mg BID versus placebo for the ITT Cohort were ordered from larger to smaller. The larger p-value was examined first, and, if  $p \leq 0.05$ , then it was declared that both doses were significantly different from placebo and no further examination was performed. If the larger p value was  $>0.05$ , the smaller p-value was checked. If the smaller p-value was  $\leq 0.025$ , then the corresponding dose was claimed to be

## CLINICAL STUDY SYNOPSIS

significantly different from placebo. For other comparisons, an alpha level of 0.05 was used to summarize the results of this report.

For the other effects or interactions, because of the multiplicity of testing involved in interpreting the significance, a p-value <0.100 observed across all visits was considered an indication of a significant interaction or effect trend and was further explored. Duration of OA was dichotomized as <5 years versus  $\geq 5$  years. Age was dichotomized as <65 years or  $\geq 65$  years. For all the primary efficacy measures, changes from Baseline were also analyzed by the CMA method, stratified by center, to confirm the results from corresponding analyses of covariance. Analyses on the Functional Capacity Classification and Osteoarthritis Severity Index were identical to analyses performed on the primary efficacy measures, except that the primary pairwise comparisons for the treatment groups versus placebo were not interpreted with Hochberg's step-up procedure. Mean change analyses, including the linear trend test for all SC-58635 and placebo groups, and overall and pairwise comparisons for all five treatment groups, were performed by using analysis of covariance (ANCOVA) with treatment and center as factors and the corresponding Baseline score as covariate.

For the ITT Cohort with LOCF approach, differential effects of gender, age and duration of disease were, for selected secondary measures of efficacy, examined by ANCOVA models. For Functional Capacity Classification and Osteoarthritis Severity, changes from Baseline were analyzed by CMH method, stratified by center, to confirm the results from the corresponding analyses of covariance. Linear trend tests (excluding the naproxen group) and pairwise comparisons among all treatment groups were conducted. These analyses were performed on the ITT Cohort with LOCF approach. For the WOMAC Osteoarthritis Index, mean change from Baseline observed at Week 2 and Week 12 or Early Termination was analyzed using ANCOVA with treatment and center as factors and corresponding Baseline as covariate. Incidence of withdrawal due to lack of arthritis efficacy was analyzed by Fisher's Exact test. Overall and pairwise comparisons were performed for the ITT Cohort. CMH test of linear dose trend (nonzero correlation) was performed excluding the naproxen group. Time to withdrawal due to lack of arthritis efficacy was calculated as the difference between the last dose date and the first dose date. Patients who completed the study according to the protocol or withdrew for reasons other than lack of arthritis efficacy were censored at the Week 12 Visit or at the withdrawal time, respectively. Log-rank test was used for the overall and pairwise comparisons for the ITT Cohort. Patients assessed their overall functional ability at the Baseline Visit and then daily for the first seven days of dosing with study medication. Treatment by center interaction and treatment by Baseline interaction were examined. Pairwise comparisons between treatments were performed based on the corresponding statistical methods. Scores of eight domains for the SF-36 Health Survey were calculated at Baseline, Week 2, and Week 12 (or Early Termination). Mean change from Baseline for quality of life data observed at Week 2 and Week 12 or Early Termination was analyzed using ANCOVA with treatment and center as factors and corresponding Baseline score as covariate. This analysis was performed on the ITT Cohort only.

All patients, including those with OA of the hip, who were randomized and took at least one dose of study medication were included in the safety analysis. The incidence of treatment-emergent adverse events was tabulated by treatment group and body system. Changes in weight and vital signs from the Baseline Visit to the Final Visit were calculated and compared across treatment groups using one-way ANOVA with pairwise comparisons. Clinical laboratory data

## CLINICAL STUDY SYNOPSIS

were examined within treatment groups at Weeks 2, 6, 12, or Early Termination in three ways: a scatter diagram depicting laboratory values at Baseline and at that visit for each patient; a shift table for Early Termination depicting numbers of patients whose values changed with respect to the normal range from Baseline to that visit analyzed using the Stuart-Maxwell Chi-square test (or when appropriate, the McNemar's Test); a display of descriptive statistics showing Baseline statistics, statistics at that visit, and statistics for mean changes from Baseline. Shifts in laboratory test values at each visit were compared pairwise among treatment groups in terms of the numbers of patients showing an increase, decrease, and no change from Baseline using the Chi-square test. Mean changes from Baseline were compared among the treatment groups using one-way ANOVA with pairwise treatment contrasts. For all analyses of laboratory results, Early Termination results were considered as Week 2, Week 6, or Week 12 results if the Early Termination Visit date was within the following time intervals: Day 14±5 for Week 2; Day 42±7 for Week 6; and Day 84±9 for Week 12 and included all laboratory results. Baseline values, posttreatment values, and changes in weight and vital signs from Baseline to posttreatment were calculated and compared across treatment groups using the one-way ANOVA with pairwise treatment contrasts.

For purposes of statistical analyses of the efficacy variables, a derived SAS efficacy dataset containing demographic characteristics and all the primary and secondary measures of efficacy was created with a one patient, one record structure. All statistical testing was two-sided at the 5% level, except for comparisons that were adjusted using Hochberg's step-up procedure. All analyses in this study were performed using SAS version 6.09.

### **RESULTS**

**Subject Disposition and Demography:** A total of 1004 patients with OA of the knee were randomized to study treatment, including 204 patients in the placebo group, 203 in the SC-58635 50 mg BID treatment group, 197 in the in the SC-58635 100 mg BID treatment group, 202 in the SC-58635 200 mg BID treatment group, and 198 in the naproxen 500 mg treatment group. One thousand and three (1003) of these patients received at least one dose of study medication and were included in the Intent-to-Treat (ITT) Cohort. Of the 1004 patients with OA of the knee, 570 (57%) completed the study. Of the 1003 patients in the ITT Cohort, 806 were included in the Evaluable Cohort for Week 2, 598 were included in the Evaluable Cohort for Week 6, and 483 were included in the Evaluable Cohort for Week 12. The Observed Data Cohort contained 945 patients at Week 2, 699 patients at Week 6, and 569 patients at Week 12.

The treatment groups were comparable for age (age range 21-89), race, and gender. Across treatment groups, 84-89% of the patients were Caucasian and 25-31% were male. All treatment groups were comparable ( $p \geq 0.215$ ) with respect to height, weight, vital signs (temperature, pulse rate, and respiration rate), and systolic and diastolic blood pressures at Baseline.

All treatment groups were comparable ( $p \geq 0.089$ ) with respect to history of GI bleeding, gastroduodenal ulcer, NSAID GI-intolerance, and cardiovascular disease. Across the treatment groups, <1%-4% of patients had a history of GI bleeding; 7-12% of patients had a history of gastroduodenal ulcer; 6-9% of patients had a history of NSAID GI-intolerance; and 53%-64% of patients had a history of cardiovascular disease. All treatment groups were comparable with respect to duration of OA and designation of index joint.

## CLINICAL STUDY SYNOPSIS

All treatment groups were comparable at Baseline with regard to the Patient's Global Assessment of Arthritic Condition, the Physician's Global Assessment of Arthritic Condition scores, Baseline Functional Capacity classification, the mean Osteoarthritis Severity Index score at Baseline, the mean scores for the Baseline WOMAC Health Survey, the APS Pain Measures at Baseline, the Patient Assessment of Function scores, and for all domains on the SF-36 Health Survey at Baseline.

**Efficacy Results:** SC-58635 at doses of 50, 100 and 200 mg BID was consistently better than placebo in treating the signs and symptoms of OA of the knee. For the primary efficacy variables (Patient's Global Assessment of Arthritic Condition, Patient's Assessment of Pain [VAS], and Physician's Global Assessment of Arthritic Condition), SC-58635 100 mg BID and SC-58635 200 mg BID were statistically superior to placebo at all visits based on an adjustment for multiplicity using Hochberg's step-up procedure. SC-58635 50 mg BID was numerically better than placebo for each primary efficacy assessment at all visits, and statistically superior to placebo at some visits. In addition, both SC-58635 100 mg BID and SC-58635 200 mg BID were numerically better than SC-58635 50 mg BID for each primary efficacy assessment at all visits, and statistically superior to SC-58635 50 mg BID at some visits. There were no statistically significant differences between SC-58635 100 mg BID, SC-58635 200 mg BID and naproxen 500 mg BID for each primary efficacy assessment at most visits.

Similar results were seen for the secondary measures of efficacy. The mean changes from Baseline in the Functional Capacity Classification were statistically significantly greater for SC-58635 100 mg BID at Weeks 2 and 12 and for SC-58635 200 mg BID at all timepoints as compared to placebo, indicating that SC-58635 provided greater improvement in functional capacity compared to placebo. Mean changes from Baseline in WOMAC scores were statistically significantly greater for all SC-58635 treatment groups compared to placebo at all timepoints. In addition, at Weeks 2 and 12, both SC-58635 100 mg BID and SC-58635 200 mg BID showed greater improvement in WOMAC scores than SC-58635 50 mg BID. Results of the Osteoarthritis Severity Index demonstrated statistically significant improvement for all SC-58635 treatment groups compared to placebo at Weeks 2, 6, and 12. There were no statistically significant differences between any of the SC-58635 treatment groups for this variable.

A total of 281 patients withdrew from study participation due to lack of efficacy (79 placebo, 61 SC-58635 50 mg BID, 40 SC-58635 100 mg BID, 49 SC-58635 200 mg BID, and 52 naproxen 500 mg BID). The number of patients withdrawing due to lack of efficacy was statistically significantly lower for the SC-58635 100 mg BID, SC-58635 200 mg BID, and naproxen 500 mg BID doses compared to placebo. There was no statistically significant difference in the number of withdrawals due to lack of efficacy between SC-58635 50 mg BID and placebo. All active treatment groups were statistically significantly different from placebo with regard to time to withdrawal due to lack of arthritis efficacy.

Similar results were also seen in the exploratory and quality of life analyses. Analysis of the APS Pain Measure indicated that SC-58635 100 mg BID and SC-58635 200 mg BID were generally more efficacious than SC-58635 50 mg BID or placebo in reducing arthritis pain. Mean changes from Baseline in Patient's Assessment of Function showed that changes in scores were small across treatment groups but that there were significant treatment effects for all of the SC-58635 treatment groups compared to placebo. Analysis of the SF-36 Health Survey data demonstrated

## CLINICAL STUDY SYNOPSIS

an improved quality of life in patients receiving SC-58635 100 mg BID and 200 mg BID compared with SC-58635 50 mg BID or placebo.

**Pharmacokinetic, Pharmacodynamic, and/or Other Results:** Plasma concentrations of SC-58635 were generally higher in patients dosed with higher doses of SC-58635. After 7-28 days of dosing, the mean plasma concentration was 232.48 ng/ml for SC-58635 50 mg BID patients, 406.44 ng/ml for SC-58635 100 mg BID patients, and 916.56 ng/ml for SC-58635 200 mg BID patients. These values were within the ranges predicted by single and multiple dose PK studies.

**Safety Results:** Adverse events were reported by a total of 711 patients: 130 patients (59%) in the placebo group; 150 (69%) in the SC-58635 50 mg BID group, 150 (69%) in the SC-58635 100 mg BID group, 144 (65%) in the SC-58635 200 mg BID group, and 137 (63%) in the naproxen 500 mg BID group. The adverse events with the highest incidence (i.e.  $\geq 5\%$  reported in one of the active treatment groups) were headache, upper respiratory tract infection, dyspepsia, diarrhea, abdominal pain, sinusitis, nausea, accidental injury, and constipation.

GI-related adverse events were reported by 291 patients: 49 (22%) placebo patients, 61 (28%) SC-58635 50 mg BID patients, 58 (27%) SC-58635 100 mg BID patients, 54 (24%) SC-58635 200 mg BID patients, and 69 (32%) naproxen 500 mg BID 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 ( $\geq 5\%$  in any active treatment group) were, in descending order of total incidence in the SC-58635 200 mg BID treatment group, dyspepsia, diarrhea, abdominal pain, nausea, and constipation. A total of 112 patients withdrew from the study due to an adverse event (17 placebo, 19 SC-58635 50 mg BID, 35 SC-58635 100 mg, 23 SC-58635 200 mg BID, and 18 naproxen 500 mg BID).

Serious adverse events were reported for four patients in the placebo group (one each: bowel obstruction, coronary artery disorder, basal cell carcinoma, colitis hemorrhagic), one in the SC-58635 50 mg BID group (patient experienced both super ventricular tachycardia and cardiac failure), five in the SC-58635 100 mg BID group (one each: arthrosis, carcinoma, injury-accidental, pulmonary carcinoma, skin carcinoma), four in the SC-58635 200 mg BID group (3 patients experienced myocardial infarction, 1 neoplasm malignant), and three in the naproxen 500 mg BID group (one each: gastric ulcer, back pain, pleural effusion).

There were no deaths during the treatment period.

There were no consistent alterations in mean laboratory test values; however, there were individual patients who had abnormal laboratory test results and there were shifts in laboratory values within treatment groups which were not clinically significant.

### Conclusion(s):

- SC-58635 doses of 50, 100 and 200 mg BID were safe, well tolerated, and efficacious in treating the signs and symptoms of osteoarthritis of the knee;
- SC-58635 100 and 200 mg BID were comparable and maximally efficacious doses;
- SC-58635 50 mg BID was a submaximally efficacious dose; and



## CLINICAL STUDY SYNOPSIS

- Naproxen 500 mg BID was efficacious in treating the signs and symptoms of osteoarthritis of the knee, and the efficacy of SC-58635 doses of 100 and 200 mg BID were comparable to that of naproxen.

**Based on a report completed on:** 27 February 1998.