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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 N49-96-02-047

Multicenter, double-blind, placebo controlled study to evaluate the efficacy and safety of SC-58635 (CELECOXIB) 25 MG, 100 MG, and 400 mg BID versus Placebo in treating the signs and symptoms of Osteoarthritis (OA) of the knee

Study centre(s): 26 centers in the United States

Publication (reference, if applicable): See attached bibliography

Studied period: 09 Jan 1997 - 19 Jun 1997

Phase of development: Not stated

Objectives: The objectives of this study were as follow:

1. Compare the efficacy of 25 mg, 100 mg, and 400 mg SC-58635 BID with placebo in treating the signs and symptoms of OA of the knee;

2. Further define the effective dose range of SC-58635 for the treatment of the signs and symptoms of OA of the knee;

3. Evaluate the safety of 25 mg, 100 mg, and 400 mg SC-58635, taken twice daily for four weeks, in patients with OA of the knee.

Methodology: This was a multicenter, double-blind, placebo-controlled, parallel group comparison of the efficacy and safety of SC-58635 versus placebo in treating the signs and symptoms of OA of the knee. The study consisted of a Pretreatment Period of at most 14 days prior to the start of study medication and a four-week Treatment Period. Patients who met the entry criteria were randomly assigned to receive SC-58635 25 mg BID, SC-58635 100 mg BID, SC-58635 400 mg BID, or placebo.

Number of patients (planned and analyzed): Three hundred sixty (360) patients were planned for this study (90 patients per treatment group). Four hundred and two patients were enrolled and were randomized to receive one of four treatments for four weeks: SC-58635 25 mg BID, SC-58635 100 mg BID, SC-58635 400 mg BID or placebo. One patient did not take study drug and was omitted from the ITT Cohort. A total of 101 patients withdrew from the study.

Diagnosis and main criteria for inclusion: Eligible patients had to have been diagnosed with OA of the knee with OA in a flare state at the Baseline visit and a Functional Capacity Classification of I-III.

Duration of treatment: 4 weeks

Test product, dose and mode of administration: Celecoxib (SC-58635) either 25 mg, 100 mg or 200 mg capsules taken orally daily. Placebo capsules (identical in size and appearance) taken orally daily.

Reference therapy, dose and mode of administration: NA

Criteria for evaluation:

Efficacy: The primary efficacy endpoints were:

1. Patient's Global Assessment of Arthritis;
2. Patient's Assessment of Arthritis Pain (VAS);
3. Physician's Global Assessment of Arthritis;

The secondary efficacy endpoints were:

1. Functional Capacity Classification;
2. WOMAC Osteoarthritis Index
3. Osteoarthritis Severity Index;
4. Incidence of Withdrawal due to Lack of Arthritis Efficacy;
5. Time to Withdrawal due to Lack of Arthritis Efficacy.

Safety: Safety was evaluated by:

1. Adverse events
2. Laboratory test values
3. Vital sign values

Statistical methods

Efficacy Analysis: All randomized patients who took at least one dose of drug were included in the ITT analyses.

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 (temperature, pulse rate, respiration rate, systolic and diastolic blood pressure). Homogeneity of treatment groups in terms of gender and race was analyzed by Chi-square test.

Differences between 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 Patient's and Physician'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 Patient's Assessment of Pain, OA Severity Index, SF-36 Health Survey, and WOMAC Health Status were analyzed using a two-way ANOVA with treatment and center as factors.

Safety analysis: Every randomized patient who received at least one dose of study medication was included in the safety analyses. Adverse events were classified into body system categories displayed by treatment groups. Severity and attribution to study drug for each episode were displayed by treatment group within body system, total number of incidences for each event reported were also displayed by treatment group. Changes in weight and vital signs from Baseline to the Final Visit (Week 4 or Early

Termination Visit) were calculated and compared across treatment groups using two-way ANOVA with treatment group and center as factors. Clinical laboratory data were examined within treatment groups in three ways:

1. A scatter diagram was created for each visit and for Early Termination depicting laboratory values at Baseline and at that visit for each patient;

2. A shift table was created for each visit and for Early Termination depicting numbers of patients whose values changed with respect to the normal range from Baseline to that visit. The data were analyzed using the Stuart-Maxwell Chi-square test. When appropriate, the tables were collapsed and the McNemar's Test was applied in place of the Stuart-Maxwell Test;

3. A display of descriptive statistics was created for each visit and for Early Termination, showing Baseline statistics, statistics at that visit, and statistics for mean changes from Baseline. The paired t-test was applied to the mean changes from Baseline.

Summary:

Disposition of Patients and Baseline Characteristics: A total of 402 patients received treatment as follows: placebo, 101 patients; SC-58635 25 mg BID, 101 patients; SC-58635 100 mg BID, 101 patients; and SC-58635 400 mg BID, 99 patients. The most common reason for withdrawal was lack of efficacy (sixty-one patients): 23 (23%) patients in the placebo group; 15 (15%) in the 25 mg group; 13 (13%) in the 100 mg group and 10 (10%) in the 400 mg group. There were statistically significantly fewer withdrawals due to lack of efficacy in the SC-58635 400 mg dose group than in placebo ($p=0.021$). There were no significant differences between treatment groups with respect to age, race, gender, height, weight or vital signs. For all patients, the age range was 29-91 years. Across treatment groups, 82-86% of the patients were Caucasian and 24-30% were male.

All treatment groups were comparable with respect to history of GI bleeding, gastroduodenal ulcer, NSAID GI intolerance, and cardiovascular disease. Across treatment groups, 2-8% of patients had a history of GI bleeding; 6-14% of patients had a history of gastroduodenal ulcers; 9-11% had a history of NSAID GI intolerance, and 57-65% of patients had a history of cardiovascular disease. All treatment groups were comparable with respect to OA duration and designation of left or right as Index Knee.

Efficacy Results:

Patient's Global Assessment of Arthritic Condition: At Week 2, improvement was reported by 40 (40%) patients at the SC-58635 100 mg dose and 39 (39%) at the SC-58635 400 mg dose as compared to 20 (20%) patients at the SC-58635 25 mg dose and 25 (25%) in the placebo group. A greater number of patients in the SC-58635 100 mg and 400 mg groups reported improvement at Week 2 as compared to placebo and SC-58635 25 mg dose and the differences in the distribution of patients classified as improved, worsened or unchanged were statistically significant ($p \leq 0.027$). At Week 4, improvement was reported by 36 (36%) patients at the SC-58635 100 mg dose and 40 (40%) patients at the SC-58635 400 mg dose as compared to 26 (26%) patients at the SC-58635 25 mg dose and 24 (24%) patients in the placebo group. At Week 2, no patients at the SC-58635 25 mg dose; three (3%) patients at the SC-58635 100 mg dose and two (2%) patients at the SC-58635 400 mg dose reported a worsening in their arthritic condition as compared to five (5%) placebo patients. The results were similar for Week 4. One (1%) patient in the SC-58635 25 mg dose; three (3%) patients at the SC-58635 100 mg dose and one (1%) patient at the SC-58635 400 mg dose reported a worsening as compared with four (4%) patients in the placebo group.

Based on mean changes from Baseline, the 100 mg and 400 mg dose levels of SC-58635 were more effective than the dose levels SC-58635 25 mg dose and placebo in improving the patients' arthritis at Week 2 and Week 4. This difference was statistically significant for the SC-58635 100 mg and 400 mg dose groups as compared to placebo at Week 2 ($p \leq 0.011$) and at Week 4 ($p \leq 0.012$). The difference between the SC-58635 100 mg dose group and the SC-58635 25 mg dose group was statistically significant at Week 2. The differences between the SC-58635 400 mg dose group and the SC-58635 25 mg dose group were statistically significant at Weeks 2 and 4. The differences in mean changes between the SC-58635 25 mg dose group and placebo were not statistically significant at Week 2 or Week 4 ($p \geq 0.574$).

Patient's Assessment of Pain-Visual Analog Scale (VAS): The mean scores reported for the Patient's

Assessment of Pain on the VAS were similar for patients across all treatment groups and placebo at Baseline. Mean Baseline scores ranged from 64.7 to 67.3 across all groups. During the Treatment Period, mean VAS scores for patients in the 25 mg and placebo groups were similar. Patients in the 100 mg and 400 mg groups reported more improvement in pain from Baseline to Weeks 2 and 4 than patients in the 25 mg or placebo group. Patients in the 400 mg group reported the most improvement in mean scores from Baseline to Week 4.

Based on mean changes from Baseline, the 100 mg and 400 mg dose levels of SC-58635 were more effective as compared to the SC-58635 25 mg dose and placebo in improving the patients' arthritic pain at Week 2 and Week 4. This difference was statistically significant for the SC-58635 400 mg group as compared to placebo, SC-58635 25 mg and 100 mg dose groups at Week 2 ($p \leq 0.028$) and at Week 4 ($p \leq 0.020$). The differences in mean changes between the 25 mg dose group and placebo were not statistically significant at Week 2 or Week 4 ($p \geq 0.898$). Linear trend tests were significant at Weeks 2 and 4 ($p \leq 0.001$) indicating a dose response effect.

Physician's Global Assessment of Arthritic Condition: AtWeek 2, more patients in the SC-58635 100 mg and 400 mg treatment groups experienced improvement than patients in the SC-58635 25 mg or placebo group. At Week 2, improvement was experienced by 34 (34%) patients at the SC-58635 100 mg dose and 37 (37%) patients at the SC-58635 400 mg dose as compared to 23 (23%) patients at the SC-58635 25 mg dose and 26 (26%) patients in the placebo group. The differences in the distribution of patients classified as improved, worsened, or unchanged were statistically significant for the SC-58635 400 mg group as compared to placebo and SC-58635 25 mg dose ($p \leq 0.049$). At Week 4, improvement was experienced by 37 (37%) patients at the SC-58635 100 mg dose; 43 (43%) patients at the SC-58635 400 mg dose as compared with 30 (30%) patients at the SC-58635 25 mg dose and 25 (25%) patients in the placebo group. A greater number of patients in SC-58635 100 mg and 400 mg improved at Week 4 as compared to placebo and the differences in the distribution of patients classified as improved, worsened, or unchanged at Week 4 were statistically significant ($p \leq 0.043$).

The difference between the SC-58635 400 mg group and the SC-58635 25 mg group was statistically significant at Week 4 ($p=0.041$). There was no statistically significant difference in the number of patients experiencing an improvement in the SC-58635 25 mg group as compared with placebo at Week 2 or Week 4, or the SC-58635 100 mg group as compared with placebo at Week 2. Linear trend tests were significant at Weeks 2 and 4 ($p \leq 0.016$) indicating a dose response effect. At Weeks 2 and 4, no patients in the SC-58635 100 mg group experienced worsening of their arthritis symptoms from Baseline. One (1%) patient in the 400 mg group experienced worsening of arthritis symptoms at Week 2 and no patients experienced worsening of symptoms at Week 4. One (1%) patient in the SC-58635 25 mg group and three (3%) patients in the placebo group experienced worsening of their arthritis symptoms from Baseline at Week 2 and Week 4.

Based on mean changes from Baseline, the SC-58635 100 mg and 400 mg dose levels of SC-58635 were more effective than placebo in improving the patients' arthritis at Week 2 and Week 4. This difference was statistically significant for the SC-58635 100 mg and 400 mg dose as compared to placebo at Week 2 ($p=0.037$; $p=0.010$), and at Week 4 ($p=0.018$; $p=0.001$) respectively. The differences in mean changes between the 25 mg dose group and placebo were not statistically significant at Week 2 or Week 4 ($p \geq 0.576$). The differences between the SC-58635 100 mg and 400 mg groups and the SC-58635 25 mg were statistically significant at Week 2 ($p \leq 0.013$) and for the SC-58635 400 mg group at Week 4 ($p=0.008$)

Functional Capacity Classification: AtWeek 2, more patients in the SC-58635 100 mg and 400 mg treatment groups showed improvement than did patients in the SC-58635 25 mg or placebo group. At Week 2, improvement was demonstrated by 21 (21%) patients at the SC-58635 100 mg dose and 20 (20%) at the SC-58635 400 mg dose as compared with 10 (10%) patients at the SC-58635 25 mg dose and 15 (15%) in the placebo group. For Week 4, improvement was reported by 22 (22%) patients at the SC-58635 100 mg dose and 19 (19%) patients at the SC-58635 400 mg dose as compared to 10 (10%) patients at the SC-58635 25 mg dose and 17 (17%) patients in the placebo group.

WOMAC Osteoarthritis Index: Based on mean changes from Baseline, there was an improvement in all SC-58635 treatment groups and placebo from Baseline to Week 4 in the subscales of Pain, Joint Stiffness, Physical Functioning, and Composite Score. The improvement was greater in the SC-58635 100 mg and

400 mg dose groups as compared to placebo and statistically significant for the SC-58635 400 mg dose group as compared to the SC-58635 25 mg group and placebo for all four subscales ($p \leq 0.013$). The differences in improvement between the SC-58635 100 mg and 25 mg dose group and placebo were not statistically significant ($p \geq 0.226$, $p \geq 0.347$, respectively).

The SC-58635 400 mg group demonstrated statistically significant improvement in Physical Functioning as compared to the SC-58635 100 mg group ($p=0.037$).

Incidence of Withdrawal Due to Lack of Arthritis Efficacy: Sixty-one patients withdrew due to treatment failure: 23 (23%) patients in the placebo group; 15 (15%) in the 25 mg group; 13 (13%) in the 100 mg group and 10 (10%) in the 400 mg group. There were statistically significantly fewer withdrawals due to lack of efficacy in the SC-58635 400 mg dose group than in placebo ($p=0.021$).

Time to Withdrawal Due to Lack of Arthritis Efficacy: The SC-58635 400 mg group was the only treatment group with statistically significant differences from placebo in the time to withdrawal due to lack of arthritis efficacy ($p \geq 0.017$).

Safety Results: Overall, 232 (58%) of the 401 patients receiving at least one dose of study drug reported one or more adverse event during the four-week duration of the study.

Adverse events were reported by 56 patients (55%) in the placebo group; 61 (61%) in the SC-58635 25 mg group, 59 (58%) in the SC-58635 100 mg group, and 56 (57%) in the SC-58635 400 mg group. The adverse events with the highest incidence in the SC-58635 groups were headache, dyspepsia, diarrhea, upper respiratory infection, back pain, pruritus, sinusitis, coughing and nausea. Twenty-four patients withdrew from study participation as a result of adverse events (five placebo, five SC-58635 25 mg, four SC-58635 100 mg, and 10 SC-58635 400 mg). Serious adverse events were reported for five patients. One patient from the placebo group (pulmonary carcinoma), one patient from the SC-58635 25 mg group (rectal bleeding), two patients from the SC-58635 100 mg group (Chest Pain, Aggravated Angina), and one patient from the SC-58635 400 mg group (Uremia). An SAE experienced by one patient receiving SC-58635 100 mg (chest pain) was considered by the Investigator to be related to study drug. There were no deaths reported during the study. There were no consistent clinically significant alterations in vital signs or mean laboratory test values; however, there were individual patients who had abnormal laboratory test results.

CONCLUSIONS:

It is therefore concluded that SC-58635 25, 100, 400 mg BID were safe and well tolerated in patients with OA of the knee; SC-58635 25 mg BID was not effective in the treatment of the signs and symptoms of OA of the knee and is a no-effect dose; and oral doses of SC-58635 100 and 400 mg BID were both efficacious in the treatment of the signs and symptoms of OA of the knee.

Based on a report completed on: 23 December 1997