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PROPRIETARY DRUG NAME/INN: Celebrex/Celecoxib

THERAPEUTIC AREA AND FDA APPROVED INDICATIONS:

- 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

PROTOCOL NO. N49-96-02-012

PROTOCOL TITLE: A Pilot Dose-Ranging Study to Evaluate the Safety and Efficacy of SC-58635 (celecoxib) 40 mg BID, 200 mg BID, and 400 mg BID Versus Placebo in Treating the Signs and Symptoms of Rheumatoid Arthritis

Study Center(s): Twenty-eight (28) study centers in the United States.

Study Initiation and Completion Dates: 01 February 1996 to 28 May 1996

Phase of Development: Phase 2

Study Objective(s):

1. Evaluate the effectiveness of SC-58635 40 mg, 200 mg, and 400 mg BID versus placebo in treating the signs and symptoms of rheumatoid arthritis (RA);
2. Determine the effective dose range of SC-58635 in the treatment of the signs and symptoms of RA; and
3. Evaluate the safety of SC-58635 40 mg, 200 mg, and 400 mg taken BID for four weeks in patients with RA.

METHODS

Study Design: This was a double-blind, placebo-controlled, multi-center, parallel-group comparison of the efficacy of SC-58635 versus placebo in treating the signs and symptoms of RA. The study consisted of a Pre-Treatment Period defined as the interval from the screening visit up to the first dose of study drug (actually 2-7 days) and a four-week Treatment Period. Patients who met the entry criteria were randomly assigned to receive 40 mg, 200 mg, or 400 mg SC-58635 BID or placebo for four weeks.

A target sample size of 300 (75 patients per treatment arm) was selected to allow detection of a statistically significant difference in change from Baseline between an active treatment group

and the placebo group with 80% power at an alpha level of 0.05. A total of 330 patients were enrolled at 28 sites in this study and were randomized to receive one of four treatments: 85 patients received placebo, 81 patients received SC-58635 40 mg BID, 82 patients received SC-58635 200 mg BID, and 82 patients received SC-58635 400 mg BID. These patients constituted the ITT population. Arthritis assessments and safety evaluations were performed at Baseline and at Weeks 1, 2, and 4.

Diagnosis and Main Criteria for Inclusion: Male and female subjects 18 years of age and older were eligible if they had RA that was in a flare state and a Functional Capacity Classification of I - III, and had not received any non-steroidal anti-inflammatory drugs (NSAIDs) in the two days prior to the first dose of study medication.

Study Treatment: Investigational drug supplies consisted of the following: Capsules containing 20 mg SC-58635; capsules containing either 100 mg or 200 mg SC-58635, each identical in size and appearance; placebo capsules identical in size and appearance to the 20 mg SC-58635 capsules; and, placebo capsules identical in size and appearance to the 100 mg and 200 mg SC-58635 capsules. Study treatment was two capsules taken with breakfast AND two capsules taken with the evening meal for four weeks.

Efficacy Evaluations:
Primary measures of arthritis efficacy:

- Patient's Global Assessment of Arthritic Condition,
- Patient Assessment of Arthritis Pain,
- Assessment of Joint Tenderness/Pain, and
- Assessment of Joint Swelling.

Secondary measures of arthritis efficacy:

- Duration of Morning Stiffness,
- Categorical Change in Modified ACR Status from Baseline,
- Physician's Global Assessment of Arthritic Condition,
- SF-36 Health Survey,
- Incidence of Withdrawal Due to Lack of Arthritis Efficacy,
- Time to Withdrawal Due to Lack of Arthritis Efficacy, and
- Laboratory measurements of C-Reactive Protein (CRP), Erythrocyte Sedimentation Rate (ESR), and Serum Amyloid A (SAA) Protein.

Pharmacokinetic, Pharmacodynamic, and/or Other Evaluations: One 15 mL blood sample for pharmacokinetic testing was obtained during the Week 2 Study Visit, but was analyzed for plasma concentration of study drug only.

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

Statistical Methods: Summary statistics for all randomized patients were tabulated by treatment group. The Kruskal-Wallis test was performed to determine whether the randomization was successful in creating treatment groups that exhibited only chance variations at Baseline with respect to age, height, weight, and vital signs. Homogeneity of treatment groups in terms of

gender and race was analyzed by the Fisher's exact test. Differences between the treatment groups with respect to history of GI bleeding, gastroduodenal ulcer, cardiovascular disease, GI NSAID intolerance, and RA were also analyzed with Fisher's exact test. Baseline differences in duration of RA were analyzed with the Kruskal-Wallis test.

Baseline results of Patient's Global Assessment of Arthritic Condition, Physician's Global Assessment of Arthritic Condition, and Functional Capacity Classification were analyzed for differences among treatment groups with the Cochran-Mantel-Haenszel (CMH) test stratified by center. Patient's Assessment of Arthritis Pain, Assessment of Joint Tenderness/Pain (Number of Tender/Painful Joints and Tender/Painful Joint Score), Assessment of Joint Swelling (Number of Swollen Joints and Swollen Joint Score), Duration of Morning Stiffness, CRP, ESR, and SAA were analyzed with a Kruskal-Wallis test. Baseline SF-36 Health Survey scores were analyzed with an analysis of variance (ANOVA) with treatment group and center as factors.

The primary analyses for the primary measures of efficacy consisted of: Analyses of mean change at each post-Baseline Visit performed by ANCOVA with treatment and center as factors and the corresponding Baseline Arthritis Assessment score as the covariate; a linear trend test to investigate dose response; and an overall and pairwise comparison for all four treatment groups. The linear trend tests and pairwise comparisons were carried out using contrasts based on the above ANCOVA model. Effects of treatment by Baseline interaction, treatment by center interaction, age, and gender were investigated. If significant effects were observed consistently for Week 1, Week 2, and Week 4, then subgroup analyses based on the effect were performed using SAS general linear models procedures with contrast statements for the pairwise treatment group comparisons for the following efficacy variables: Patient's Global Assessment; Patient's Assessment of Arthritis Pain; Number of Tender/Painful Joints; Tender/Painful Joint Score; Number of Swollen Joints; and Swollen Joint Score. CMH analyses stratified by center were used for linear dose trend tests and treatment group comparisons.

For the Assessment of Tenderness/Pain and the Assessment of Joint Swelling, the number of "improved" joints was analyzed on the ITT Cohort only by ANCOVA with treatment and center as factors and the Baseline number of joints with a score greater than zero as the covariate. The number of "worsened" joints was similarly analyzed. A categorical analysis of change from Baseline as defined according to the ACR criteria was performed to examine the overall effect of the study drug on the patient's condition. A patient was classified as "improved" if the patient experienced at least a 20% improvement from Baseline in the Number of Tender/Painful Joints and in the Number of Swollen Joints as well as at least a 20% improvement from Baseline in at least three of the following four assessments: Physician's Global Assessment of Arthritic Condition (a secondary efficacy measure), Patient's Global Assessment of Arthritic Condition, Patient's Assessment of Arthritis Pain, and CRP (a secondary efficacy measure). CMH tests stratified by center were performed on this categorical change on the ITT Cohort only.

Incidence of Withdrawal Due to Lack of Arthritis Efficacy was analyzed for the ITT Cohort by Fisher's exact test for overall and pairwise comparisons. The Time to Withdrawal Due to Lack of Arthritis Efficacy was analyzed for the ITT Cohort by the method of survival analyses, and the log-rank test was used to test for the treatment differences. For the Quality of Life analyses, scores from the SF-36 Health Survey were analyzed with an ANCOVA with treatment group and

center as factors. The analyses of mean changes on the SF-36 Health Survey scores were conducted only for the ITT Cohort.

Every randomized patient receiving at least one dose was included in the safety analysis. Clinical laboratory data were summarized and treatment groups compared using the Kruskal-Wallis test applied to change from the Baseline to the end of the study. Shift tables and the Stuart-Maxwell test, or McNemar's test, were used to determine significant distribution changes over the course of the study. Shifts in laboratory values were compared across treatment groups in terms of the number of patients showing an increase, decrease, or no change with respect to the normal range using the chi-square test. Changes in vital signs from Baseline to Week 4 were calculated and compared across treatment groups using the Kruskal-Wallis test. All statistical testing was two-sided at the 5% level. All analyses in this study were performed using SAS version 6.09. For efficacy data that were missing or not in the window of the scheduled visit day, the last observed value was carried forward.

RESULTS

Subject Disposition and Demography: Of the 330 patients in the ITT population, 265 (80%) completed the study, while 65 patients withdrew prior to completing the study. A higher proportion of placebo patients (31%) withdrew from the study as compared to SC-58635 patients (23% 40 mg; 11% 200 mg; 13% 400 mg). Also, a higher proportion of placebo patients (15 [18%]) withdrew because of treatment failure than SC-58635 patients in the 200 mg BID (3 [4%]), and 400 mg BID (5 [6%]) treatment groups. Fourteen patients (17%) withdrew because of treatment failure in the SC-58635 40 mg BID group.

All treatment groups were comparable for age (range 21 - 86), ethnic origin (78% to 89% were Caucasian), height, weight, and vital signs at Baseline. 11% to 33% were males. The distribution of males (11% to 33%) and females across all treatment groups was uneven and this difference between groups with respect to gender distribution was significant.

All treatment groups were comparable with respect to history of GI bleeding, gastroduodenal ulcer, cardiovascular disease, and NSAID GI intolerance. All treatment groups were comparable with respect to RA duration.

There was no statistically significant difference between treatment groups in the Baseline mean for the Duration of Morning Stiffness and for the Patient's Assessment of Pain on the VAS. Neither was there a statistically significant difference between treatment groups at Baseline in the Physician's Global Assessment of the Arthritic Condition, nor in the Patient's Global Assessment scores. The Baseline mean for both the Assessment of the Number of Joint Tenderness/Pain, and the Assessment of Swollen Joints was not statistically significantly different for all treatment groups. None of the Baseline means for Tender/Painful Joints Score; Swollen Joints Score; ESR; SAA; and CRP were statistically significantly different across treatment groups. No statistically significant differences among the treatment groups were noted for any domain in the SF-36 Health Survey at Baseline.

Efficacy Results: In the Patient's Global Assessment of Arthritic Condition, the Patient Assessment of Arthritis Pain, the Assessment of Tender/Painful Joints, and the Assessment of

Swollen Joints, SC-58635 produced a reduction in the signs and symptoms of RA. This improvement was statistically significant for the 200 mg and 400 mg BID dose groups at Week 1, Week 2, and Week 4; the only exception to this was the Number of Swollen Joints at Week 2 which was not statistically significant for either the 200 or 400 mg BID dose groups. The 40 mg SC-58635 dose group was statistically significant only at Week 1 only for the Patient's Global Assessment of Arthritic Condition and the Patient's Assessment of Arthritis Pain.

All dose levels of SC-58635 were statistically more effective in reducing the signs and symptoms of RA as determined by the Physician's Global Assessment of the Arthritic Condition, and the Duration of Morning Stiffness. At Week 2 and Week 4, the 200 and 400 mg BID dose levels continued to produce a statistically significant reduction in the Duration of Morning Stiffness.

Patients at all dose levels of SC-58635 reported greater improvement than the placebo group in each of the eight domains of the SF-36 Health Survey (Physical Function, Role-Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role-Emotional, and Mental Health). This reported improvement was statistically significant for Physical Function and Bodily Pain for all dose levels of SC-58635. The improvement reported by the 200 and 400 mg BID dose groups was statistically significant for six of the eight and all eight of the domains, respectively.

Pharmacokinetic, Pharmacodynamic, and/or Other Results: Other than plasma concentration testing at Week 2, no additional pharmacokinetic or pharmacodynamic evaluations were performed.

Safety Results: Adverse events were reported by 53 (63%) of the patients in the placebo group; 45 (56%) of the patients receiving 40 mg BID SC-58635; 48 (59%) of the patients receiving 200 mg BID SC-58635; and 43 (53%) of the patients receiving 400 mg BID SC-58635. The adverse events with the highest incidence (i.e. =5% reported in any of the treatment groups) in the SC-58635 groups were headache, diarrhea, sinusitis, nausea, upper respiratory tract infection, dyspepsia, rash, pharyngitis, coughing, accidental injury, pruritus, abdominal pain, back pain, pain, and nervousness. Sixteen patients withdrew from study participation as a result of adverse events (five placebo, three 40 mg BID, four 200 mg BID and four 400 mg BID). Adverse events which led to withdrawal of more than one subject in a treatment group were: rash (2 placebo subjects, and 2 SC-58635 200 mg BID patients), diarrhea (2 SC-58635 40 mg BID patients).

There were no serious adverse events or deaths reported during the study. There were no consistent clinically significant alterations in laboratory test values.

Conclusion(s):

- In this study, SC-58635 doses of 40, 200 and 400 mg BID were safe.
- SC-58635 200 and 400 mg BID were efficacious
- SC-58635 40 mg BID was noneffective.

Based on a report completed on: 31 December 1997