These results are supplied for informational purposes only.

Prescribing decisions should be made based on the approved package insert

Link to 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 Pharmaceuticals Inc.

Title of Study: Protocol I49-98-02-096

Final Report For Successive Celecoxib Efficacy And Safety Studies In Osteoarthritis (Success-1)

Study centre(s): 1142 sites in 39 countries.

Publication (reference, if applicable): None

Studied period 29 Dec 1998-18 Apr 2000 **Phase of development:** Phase 3B

Objectives:

The primary objectives of this study were:

- To compare the efficacy in various countries and/or geographic subregions; to evaluate the homogeneity of the efficacy between various countries and/or geographic regions;
- To compare the overall clinical tolerability and safety of celecoxib 100 mg BID or 200 mg BID with two non-steroidal anti-inflammatory drug (NSAID) comparators (diclofenac 50 mg BID and naproxen 500 mg BID) in the treatment of the signs and symptoms of osteoarthritis of the knee and hip.

The secondary objectives of this study were to compare celecoxib and the NSAID comparators with respect to:

- Incidences of changes in laboratory parameters: clinically significant changes in hemoglobin (≥1g/dL); clinically meaningful changes in ALT or AST (≥3 times the upper limit of normal); serum creatinine (>30% increase over pretreatment changes in serum creatinine);
- Patient and Physician Satisfaction and Pharmacoeconomic Assessments;
- Efficacy in osteoarthritis of the hand.

Methodology: Randomized, Parallel Group, Double-Blind, Active Comparator, Multiple Dose, Multicenter, Multinational Study

Number of patients (planned and analyzed):

It was planned that approximately 13,500 patients would be enrolled in approximately 1200 centers in 37 countries. Randomization was planned in a 1:1:1 ratio within each country and within each center: celecoxib 100 mg BID to celecoxib 200 mg BID to the NSAID comparator (diclofenac 50 mg BID[outside of North America] or naproxen 500 mg BID [US, Canada]).

13,274 patients were randomized at 1142 centers in 39 countries: 4421 to celecoxib 100 mg BID, 4429 to celecoxib 200 mg BID, and 4424 to an NSAID comparator. Of patients randomized to an NSAID comparator, 3510 were randomized to diclofenac 50 mg BID, and 914 were randomized to naproxen 500 mg BID.

All 13,194 patients (8800 on celecoxib, 4394 on an NSAID) who received at least one dose of study medication were evaluated for safety. 13,194 patients (4393 on celecoxib 100 mg BID, 4407 on celecoxib 200 mg BID, 905 on naproxen 500 mg BID, and 3489 on diclofenac 50 mg BID) were evaluated for efficacy in the intent-to-treat population. Patients randomized into the study who did not take any study medication and/or who had no efficacy assessments were excluded from the intent-to-treat population.

Diagnosis and main criteria for inclusion: Osteoarthritis of the knee, hip or hand of at least 6 months' duration, confirmed by ACR osteoarthritis criteria.

Duration of treatment: 12 weeks

Test product, dose and mode of administration:

Test product was packaged in yellow-label bottle ("Bottle A").

- Celecoxib capsules containing 100 mg celecoxib
- Celecoxib capsules containing 200 mg celecoxib
- Placebo capsules to match celecoxib capsules.

Patients were instructed to take one capsule orally (celecoxib capsule or matching placebo) from Bottle A twice a day, with the morning and evening meals.

Reference therapy, dose and mode of administration:

Reference therapy packaged in green-label bottle ("Bottle B")

Reference therapy in United States and Canada:

- Naprosyn (naproxen) 500 mg tablets
- Placebo tables to match naproxen

Reference therapy in all countries aside from U.S. and Canada:

- Voltaren (diclofenac) 50 mg tablets
- Placebo tablets to match diclofenac

Dosing Administration:

United States/Canada: Patients were instructed to take one capsule orally (encapsulated Naprosyn or its matching placebo) from Bottle B twice a day, with the morning and evening meals.

Rest of world: Patients were instructed to take one tablet orally (overcoated Voltaren or its matching placebo) from Bottle B twice a day, with the morning and evening meals.

Criteria for evaluation:

Pharmacoeconomics:

The Patient's and Physician's Satisfaction with the assigned treatment was assessed and pharmacoeconomic data were analyzed using:

- Patient Satisfaction Assessment;
- Physician Satisfaction Assessment; and
- Pharmacoeconomic Data Collection Assessment.

Safety:

Safety assessments included:

- Adverse events (especially gastrointestinal symptoms such as abdominal pain/dyspepsia).
- Upper Gastrointestinal Serious Adverse Events.
- Other Serious adverse events.
- Withdrawal due to any adverse event.
- Clinical laboratory measurements (especially incidences of clinically significant changes in hemoglobin (≥1g/dL), in ALT or AST (≥3 times the upper limit of normal), and in serum creatinine (>30% increase over pretreatment changes in serum creatinine).

Efficacy:*

The primary arthritis efficacy variables were:

- Patient's Global Assessment of Arthritis;
- Patient's Assessment of Arthritis Pain (VAS); and
- WOMAC.

The secondary arthritis efficacy variables were:

- Physician's Global Assessment of Arthritis, and
- Patient's Assessment of Night Pain (from the WOMAC).

*WOMAC not assessed in countries where a validated version in the local language was not available, i.e., Asia and Greece.

Statistical methods:

Separate analyses were performed for selected individual countries, geographic subregions and for the study as a whole. Also, separate analyses were performed for patients with OA of the hip, knee, knee or hip, hand and all joints combined.

Pretreatment patient characteristics (demographics, vital signs, comorbidities, pharmacoeconomics OA history and assessments) were analyzed using the CMH test for categorical and linear models for continuous variables.

Changes from pretreatment in pharmacoeconomic variables and OA assessments were analyzed using the CMH test for categorical and linear models for continuous variables. Logistic and linear regression models were also used.

Homogeneity of changes from pretreatment in OA efficacy over individual countries and geographic subregions was performed using confidence intervals and the Whitehead and Whitehead approach.

Treatment differences in the incidences of clinically significant adjudicated upper gastrointestinal (UGI) events were assessed using the Fisher's Exact Test, the log rank test and odds ratios with associated confidence intervals. Log linear models were used to examine the relationship between treatments and cardio-prophylactic aspirin use for the same incidences. Incidences of NSAID related clinically significant changes and extreme values in specific laboratory tests were examined using the Fisher's Exact test.

General safety and tolerability was examined across treatments using the incidences of adverse events, adverse events leading to withdrawal (both using Fisher's Exact test), serious adverse events (no. events per 100 patient years), by attribution and by severity. Laboratory data was examined using shift tables and incidence of extreme laboratory values (Fisher's Exact test). Mean changes in laboratory values and vital signs from pretreatment were compared (ANCOVA with pretreatment value as covariate).

SUMMARY – CONCLUSIONS

EFFICACY RESULTS:

SUCCESS-1 represents one of the largest OA trials ever done with 39 countries in 6 continents participating. Given the magnitude of the study, assessments were performed on pre-specified countries and regions and no attempt was made to perform an analysis of efficacy across the entire population. Rather, assessments of homogeneity of treatment effect were performed to assess how celecoxib would perform over a broad range of clinical situations, specialists and populations. A number of efficacy assessments were used in the study including Patient's Global Assessment, Physician's Global Assessment, Pain VAS, WOMAC total and subscales and Patient's Assessment of Night Pain. Using these standard measures across different regions, celecoxib was shown to be as effective as diclofenac 50 mg BID and naproxen 500 mg BID in managing the signs and symptoms of OA in all measures. Moreover, celecoxib 100 mg BID and 200 mg BID are similar in efficacy in managing the signs and symptoms of OA.

In addition, celecoxib was shown to have a similar efficacy with regards to managing the signs and symptoms of OA of the hip, knee and hands. The efficacy across these three joints was similar to that seen with diclofenac and naproxen. For OA of the knee and hip, multiple assessments including the WOMAC were used. These assessments have been extensively studied and used in these forms of OA. For OA of the hand, similar assessments including the WOMAC were used to simplify data collection in such a large study. Assessment of efficacy in OA of the hand relied primarily on the Pain VAS, a widely used endpoint for OA. Patients with OA of the hand demonstrated an improvement with celecoxib that was similar to that of the comparator NSAIDs. In fact, in OA of the hand, the Patient's Pain VAS mirrored the other primary endpoints including the Patient's Global Assessment and WOMAC. The effect seen in OA of the hand was similar to that seen in OA of the hip and knee.

Logistic regression or linear model analyses were performed for the primary and secondary efficacy assessments to determine if pretreatment assessments as outlined in Section 10.3.4 influenced subsequent assessments. A review of the results on a global basis for Week 12 did not demonstrate any consistent influence of pretreatment assessments across the primary and secondary endpoints, with the exception of the pretreatment value of the dependent variable.

SAFETY RESULTS:

Adverse events

Celecoxib is associated with fewer adverse events and clinically significant UGI events than the NSAID group. Overall, celecoxib is associated with a risk reduction of approximately 49-92% compared to the NSAID group, whether or not patients used aspirin for cardiovascular prophylaxis.

Upper Gastrointestinal Serious Adverse Events (SAE).

The most common body system leading to a SAE was gastrointenstinal (GI) with rates of 0.68% in the celecoxib 100 mg BID group, 1.09% in the celecoxib 200 mg BID group, 2.8% in the naproxen group and 0.9% in the diclofenac group. The most common GI SAE was abdominal pain occurring in 0.27% in the celecoxib 100 mg BID group, 0.41% in the celecoxib 200 mg BID group, 1% in the naproxen group and 0.4% in the diclofenac group.

Other SAEs:

There were 10 deaths during the study, five in the celecoxib group and five in the NSAID group (all on diclofenac). Four of the deaths (2 celecoxib, 2 diclofenac) resulted from SAEs that occurred between 4 and 16 weeks after study completion. Deaths that occurred within 30 days of the study or were due to SAEs reported within 30 days of the study included 3 on celecoxib (sudden death/MI, gastric ulcer hemorrhagic, pulmonary carcinoma) and 3 on diclofenac (sudden death/subarachnoid hemorrhage, cerebrovascular disorder/hemorrhagic stroke,bile duct carcinoma).

The numbers and percent of subjects with SAEs in each treatment group were:

	Celecoxib 100 mg BID	Celecoxib 200 mg BID	Diclofenac 50 mg BID	Naproxen 500mg BID
No. treated	4393	4407	3489	905
No. (%) with SAE	119 (2.7%)	146 (3.3%)	95 (2.7%)	48 (5.3%)

There were 4 (0.09%) celecoxib 100 mg BID, 3 (0.07%) celecoxib 200 mg BID subjects 3 (0.33%) naproxen subjects and 6 (0.17%) diclofenac subjects who had SAEs in the WHO class Cardiovascular Disorders. Cardiac failure was the most frequently reported SAE in this category: 1 (0.02%) each in celecoxib 100 mg BID and 200 mg BID, 2 (0.22%) naproxen and 2 (0.06%) diclofenac. Sudden death was reported in 1 (0.02%) celecoxib 100 mg BID, 0 celecoxib 200 mg BID, 0 naproxen and 1 (0.03%) diclofenac subjects. SAEs classed as Heart Rate and Rhythm Disorders were reported in the celecoxib 100 mg BID group at 7 (0.16%), 200 mg BID (5, 0.11%), naproxen 3 (0.33%) and diclofenac 3 (0.09%). SAEs classed as Myo-Endo Pericardial & Valve Disorders were reported in 11 (0.25%) of celecoxib 100 mg BID subjects, 8 (0.18%) of celecoxib 200 mg BID, 1 (0.11%) of naproxen subjects and 3 (0.09%) of diclofenac subjects. Coronary artery disorder and myocardial infarction were the most frequently reported SAEs in this category: coronary artery disorder - celecoxib 100 mg BID 2 (0.05%), 200 mg BID 3 (0.07%), naproxen 0 and diclofenac 1 (0.03%); MI - celecoxib 100mg BID 8 (0.18%), celecoxib 200 mg BID 2 (0.05%), naproxen 1 (0.11%) and diclofenac 0. There was no statistical difference between the celecoxib, diclofenac, and naproxen group in the number of MI events. SAEs classed as Vascular (Extracardiac) Disorders were reported in 5 (0.11%) celecoxib 100 mg BID subjects, 10 (0.23%) celecoxib 200 mg BID subjects, 3 (0.33%) naproxen subjects and 7 diclofenac subjects (0.20%). The most frequently reported SAE in this category was cerebrovascular disorder, which was reported in 1 (0.02%) celecoxib 100 mg BID; 7 (0.15%) celecoxib 200 mg BID subjects, 2 (0.22%) naproxen subjects and 4 (0.11%) diclofenac subjects, (additionally, 6 cerebrovascular disorders (mostly transient ischemic attacks) were reported as non-serious for Celebrex).

Withdrawal due to any adverse event:

Celecoxib was associated with fewer withdrawals due to adverse events than NSAIDs. In addition, celecoxib was associated with fewer withdrawals due to GI adverse events than NSAIDs.

Clinical laboratory measurements :

Celecoxib was associated with fewer decreases in hemoglobin and hematocrit compared to NSAIDs. Clinically significant changes in transaminases and serum creatinine were seen less frequently with celecoxib compared to NSAIDs.

RESULTS OF PHARMACOECONOMIC AND SATISFACTION ASSESSMENTS:

No improvement with any of the treatment arms was noted in percentage of patients working at a paid job. All treatment arms demonstrated overall improvement in number of work days missed due to their arthritis, days less effective at work due to their arthritis, difficulty performing daily routine activities due to arthritis, reliance on help from other people to perform daily activities, and visits to a physician or other healthcare professional.

The results of the pharmacoeconomics assessments show no statistically significant differences between celecoxib or the NSAID comparators, further demonstrating the efficacy of celecoxib in OA. This suggests the overall benefit of chronic anti-inflammatory therapies in OA.

The results of the Patient's and Physician's Satisfaction Assessments, including Patient's Willingness to Continue Study Medication demonstrated improvement with all anti-inflammatory therapies over the 12 week duration of the study.

No statistically significant differences were noted for any of the Satisfaction Assessments between celecoxib and the comparator NSAIDs, further supporting the efficacy of celecoxib.

Conclusion: The results of the pharmacoeconomics and satisfaction assessments show no statistically significant differences between celecoxib or the NSAIDs, further supporting the findings of the primary and secondary efficacy endpoints: Celecoxib at either dose level is comparable in efficacy to either naproxen or diclofenac

CONCLUSIONS:

SAFETY AND TOLERABILITY:

- Celecoxib was better tolerated than diclofenac or naproxen, especially in upper gastrointestinal symptoms such as dyspepsia, abdominal pain and other typical NSAID-related UGI events
- Celecoxib was associated with fewer withdrawals due to adverse events than NSAIDs. In addition, celecoxib was associated with significantly fewer withdrawals due to GI adverse events than NSAIDs.
- Celecoxib was associated with SAEs similar to the NSAIDs. However, celecoxib is associated with

significantly fewer GI serious adverse events than NSAIDs.

- Celecoxib was associated with significantly fewer clinically significant UGI events than the NSAID group. Overall, celecoxib was associated with a risk reduction of approximately 49% to 92% compared to NSAIDs, whether or not patients was using aspirin for cardiovascular prophylaxis.
- Celecoxib was associated with significantly fewer decreases in hemoglobin and hematocrit compared to NSAIDs.
- Celecoxib was associated with rates of cardiovascular and peripheral vascular adverse events similar to NSAIDs; however, 8 MIs were observed in celecoxib 200mg, 2 in the 400mg group, and 1 in the NSAID group.
- Celecoxib 100 mg BID and celecoxib 200 mg BID had similar safety profiles.
- Celecoxib was safely used with concomitant aspirin for cardiovascular prophylaxis

EFFICACY:

Celecoxib at dose levels of either 100 mg BID or 200 mg BID had comparable efficacy to diclofenac 50 mg BID or naproxen 500 mg BID in OA of the hip, knee, or hand. Celecoxib 100 mg BID and 200 mg BID have similar efficacy.

PHARMACOECONOMIC AND PATIENT AND PHYSICIAN SATISFACTION ASSESSMENTS:

The results of these pharmacoeconomics and satisfaction assessments show no statistically significant differences between celecoxib or the NSAIDs, further supporting the findings of the primary and secondary efficacy endpoints: Celecoxib at either dose level is comparable in efficacy to either naproxen or diclofenac.

Date of Report: 24 April 2001