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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. 635-IFL-0508-002

PROTOCOL TITLE: A Double-Blind, Randomized, Parallel-Group Comparison Study of the Safety and Efficacy of Celecoxib, Rofecoxib and Naproxen in Stable, Treated Hypertensive Patients with Osteoarthritis and Type 2 Diabetes Mellitus (CRESCENT Trial)

Study Center(s): Sixty-five (65) centers, including: 34 in the United States, 12 in Canada, 11 in Germany, 3 each in Spain and Chile, and 1 each in Austria and the United Kingdom.

Study Initiation and Completion Dates: 11 May 2001 to 19 July 2002

Phase of Development: Phase 4

Study Objective(s):

Primary:
The primary objective of this study was to evaluate the effects of celecoxib 200 mg QD, rofecoxib 25 mg QD, and naproxen 500 mg BID on the mean change from Baseline to Week 6 of the average 24-hour systolic blood pressure by ambulatory blood pressure monitoring (ABPM) in patients with stable, treated hypertension, Type 2 diabetes, and osteoarthritis (OA).

Secondary:
The secondary objectives of this study were to evaluate the effects on systolic blood pressure at Week 12; diastolic blood pressure; arterial pressure; fluid retention; pulse pressure; the incidence of clinically diagnosed heart failure; and several standard OA efficacy assessments.

METHODS

Study Design: The trial was conducted in patients with stable, controlled, treated hypertension, Type 2 diabetes mellitus, and OA of the hip or knee. Following a Pretreatment screening and NSAID washout period of seven to 10 days, patients meeting eligibility criteria were randomized

to receive either celecoxib 200 mg QD, rofecoxib 25 mg QD, or naproxen 500 mg BID for 12 weeks. Visits occurred at Screening, Baseline, Week 1, Week 2, Week 6, and Week 12 or Early Termination. Cardiorenal function was assessed by the use of 24-hour ABPM performed at the Baseline, Week 6, and Week 12 Visits; by cuff blood pressure evaluations performed at all visits; and by monitoring fluid retention as indicated by edema and changes in weight. Efficacy in treating OA signs and symptoms was assessed using measures of pain, physical function, and quality of life that are standard in arthritis trials. General safety was assessed with standard monitoring of physical examinations, vital signs, and adverse signs and symptoms.

The planned enrollment was approximately 360 patients. A total of 404 patients were enrolled and randomized to treatment; eight of these patients did not receive study medication. Therefore, the Intent-to-Treat (ITT) Cohort consisted of 396 patients: 136 patients receiving celecoxib 200 mg QD, 132 receiving rofecoxib 25 mg QD, and 128 receiving naproxen 500 mg BID.

Diagnosis and Main Criteria for Inclusion: Patients were eligible for this study if they had documented OA of the hip or knee by ACR criteria; stable, controlled hypertension being treated with a fixed-dose regimen including at least one angiotensin-converting enzyme inhibitor or an angiotensin II receptor blocker; and Type 2 (non-insulin dependent) diabetes mellitus under good medical care. Patients with significant comorbidity were not eligible.

Study Treatment:

- Celecoxib 200 mg capsules, administered 200 mg QD.
- Rofecoxib 25 mg tablets, encapsulated in unmarked, hard gelatin capsules, administered 25 mg QD.
- Naproxen 500 mg tablets, encapsulated in unmarked, hard gelatin capsules, administered 500 mg BID.
- Placebo capsules identical in size and appearance to the celecoxib capsules, the rofecoxib capsules, and the naproxen capsules.
- Additionally, open label acetaminophen was supplied for dosing at 1000 mg TID during the Pretreatment/Screening Period

Total treatment duration was 12 weeks (84+7 days).

Efficacy Evaluations: WOMAC Osteoarthritis Index, Patient's Assessment of OA Pain-VAS, Patient's Global Assessment of Arthritis, incidence of withdrawal due to lack of efficacy, and Patient Satisfaction Survey.

Pharmacokinetic, Pharmacodynamic, and/or Other Evaluations: No pharmacokinetic or pharmacodynamic evaluations were performed.

Cardiorenal Evaluations:

Primary outcome variable:

- Mean change from Baseline to Week 6 in the average 24-hour systolic blood pressure measured by ABPM.

Secondary outcome variables:

- Mean change from Baseline to Week 6 in the average 24-hour diastolic blood pressure measured by ABPM;
- Mean change from Baseline to Week 12 in the average 24-hour systolic and diastolic blood pressures measured by ABPM;
- Mean change from Baseline to Weeks 6 and 12 in the average 24-hour arterial pressure measured by ABPM;
- Incidence of discontinuation due to changes in blood pressure and/or edema medications;
- Incidence of clinically significant edema;
- Incidence and magnitude of pretibial edema and weight changes (fluid retention);
- Mean change from Baseline to Weeks 6 and 12 in the average 24-hour pulse pressure measured by ABPM;
- Incidence of clinically diagnosed heart failure; and
- Incidence of elevated systolic or diastolic blood pressure.

Safety Evaluations: Adverse events, serious adverse events, vital signs, and clinical laboratory test results.

Statistical Methods: Analyses of Screening and Baseline data used Fisher's Exact Test or chi-square test for categorical variables, and two-way analysis of variance (ANOVA) for continuous variables.

For all results of 24-hour ABPM, pretibial edema assessments, and weight assessments, mean changes from Baseline to Week 6 or 12 were compared using analysis of covariance (ANCOVA). Incidences of clinically significant edema, elevated blood pressure, and discontinuations due to change in blood pressure and/or edema medication were compared using Fisher's Exact test. Pretibial edema assessments and incidences of clinically significant edema and of elevated blood pressure were also analyzed categorically using logistic regression with treatment, gender, and race as covariates.

Continuous efficacy variables were analyzed using ANOVA or ANCOVA. Categorical efficacy variables were analyzed using Cochran-Mantel-Haenszel test and logistic regression with treatment, gender, and race as covariates. Incidences of withdrawal due to lack of efficacy were compared using Fisher's Exact test.

Overall percentages of patients experiencing adverse events were compared using Fisher's Exact test. Changes from Baseline in laboratory values were analyzed using ANOVA, and in vital signs using ANCOVA.

RESULTS

Subject Disposition and Demography: A total of 404 patients were enrolled into this study, with 136 randomized to the celecoxib 200 mg QD group, 138 to the rofecoxib 25 mg QD group, and 130 to the naproxen 500 mg BID group. Eight of the randomized patients did not receive study medication; six of these were originally assigned to the rofecoxib group and two to the naproxen group. Therefore, 136 received celecoxib, 132 received rofecoxib, and 128 received

naproxen. The three treatment groups were generally similar with respect to demographics, arthritis assessments, and results of ABPM at Baseline, although some statistically significant differences were seen.

Efficacy Results: The three treatments demonstrated similar efficacy across all measures. With only one exception (a difference in favor of celecoxib over naproxen in WOMAC Stiffness at Week 12), pairwise comparisons in all efficacy measures indicated that none of the differences among the groups was statistically significant. As a representative measure, the WOMAC Total Domain results are shown below:

WOMAC Total Domain Results (ITT Cohort)

	Celecoxib 200 mg QD (n=136)	Rofecoxib 25 mg QD (n=132)	Naproxen 500 mg BID (n=128)	P Value
Baseline	46.2±21.51	50.4±19.91	51.4±19.83	
Week 6	32.7±21.33	35.7±21.29	38.3±20.75	
Week 12 / Final	29.9±22.09	33.9±24.44	37.1±21.51	
Week 6 change	-13.6±18.44	-14.7±20.72	-12.8±19.81	Overall: 0.400 C vs R: 0.869 C vs N: 0.211 R vs N: 0.267
Week 12 change	-16.3±19.33	-16.4±24.30	-14.7±20.43	Overall: 0.398 C vs R: 0.668 C vs N: 0.183 R vs N: 0.362

Values are mean ±SD, and represent the means of the 24 scores on the 100-mm VAS.
C=celecoxib R=rofecoxib N=naproxen

Pharmacokinetic, Pharmacodynamic, and/or Other Results: No pharmacokinetic or pharmacodynamic evaluations were performed.

Cardiorenal Results: Results in the primary outcome variable are shown below, along with other blood pressure results from ABPM:

ABPM Blood Pressure Results at Weeks 6 and 12 (ITT Cohort)

	Celecoxib 200 mg QD (n=136)	Rofecoxib 25 mg QD (n=132)	Naproxen 500 mg BID (n=128)	P Value
Week 6 systolic blood pressure (*primary outcome variable*)				
Baseline	132.0±13.95	130.3±12.87	133.7±14.59	
Week 6	131.9±13.93	134.5±14.40	133.0±13.52	
Change	-0.1±9.29	4.2±10.87	-0.8±10.12	Overall: 0.005 C vs R: 0.005 C vs N: 0.956 R vs N: 0.005
Week 12 systolic blood pressure				
Baseline	131.8±13.95	130.2±12.77	133.7±14.76	
Week 6	132.2±14.49	133.9±13.97	133.0±13.64	
Change	0.3±10.98	3.7±11.02	-0.7±10.45	Overall: 0.056 C vs R: 0.068 C vs N: 0.627 R vs N: 0.023
Week 6 diastolic blood pressure				
Baseline	75.7±8.31	75.4±8.67	76.0±9.05	
Week 6	75.6±8.45	76.9±9.50	75.1±8.35	
Change	-0.1±5.66	1.5±6.58	-1.0±6.09	Overall: 0.013 C vs R: 0.088 C vs N: 0.194 R vs N: 0.003
Week 12 diastolic blood pressure				
Baseline	75.7±8.50	75.5±8.78	75.9±8.93	
Week 6	75.6±9.38	77.2±8.10	74.9±8.89	
Change	-0.1±6.69	1.7±6.74	-1.0±7.18	Overall: 0.010 C vs R: 0.089 C vs N: 0.166 R vs N: 0.003

C=celecoxib R=rofecoxib N=naproxen

Results in the other secondary outcome variables were consistent with the blood pressure results. Elevations in arterial pressures in the rofecoxib group were statistically significant compared with celecoxib at Week 6 and compared with naproxen at Weeks 6 and 12. No difference was seen between the groups in heart rate. Pulse pressures were elevated in the rofecoxib group, but the only statistically significant difference in this measure was seen between celecoxib and

rofecoxib at Week 6. Although more rofecoxib patients withdrew due to antihypertensive medication changes (4% vs. 1% for celecoxib and 2% for naproxen), the differences were not statistically significant. Incidences of clinically significant edema were 5% for celecoxib, 8% for rofecoxib, and 3% for naproxen (not statistically significant). In fluid retention, no differences were seen among groups in pretibial edema, but statistically significantly larger weight gains were seen in the rofecoxib group than in the celecoxib group (Week 1) and the naproxen group (Weeks 1, 2, and 6). No patients in the study had heart failure.

Safety Results: Adverse event results are shown in the following table:

Summary of Adverse Events (% of patients)			
	Celecoxib 200 mg QD (n=136)	**Rofecoxib 25 mg QD (n=132)**	**Naproxen 500 mg BID (n=128)**
Any event	53	54	57
Most common events (≥3% in any one treatment group):			
Upper resp. tract inf.	11	9	6
Headache	10	10	8
Coughing	4	3	2
Diarrhea	4	8	3
Bronchitis	3	6	2
Leg cramps	3	1	3
Dizziness	3	3	2
Nausea	3	5	6
Upper abdominal pain	2	4	4
Back pain	1	1	5
Edema of extremities	1	4	1
Influenza-like symptoms	1	2	3
Accidental injury	1	3	3
Peripheral pain	1	2	5
Heartburn	1	2	4
Constipation	0	2	8
Any event causing withdrawal:	5	8	9
Any serious adverse event	3	4	2

No safety or tolerability concerns were evident from the laboratory or vital sign data. Cuff blood pressures were slightly higher than ABPM measurements, but showed similar effects of treatment.

The 12 serious adverse events that occurred are listed in the following table:

Summary Incidence Serious Adverse Events

All SAEs experienced	Celecoxib 200 mg QD (n=136)	Rofecoxib 25 mg QD (n=132)	Naproxen 500 mg BID (n=128)
Chest pain	2	0	0
Carcinoma	1	0	0
Dislocation	1	0	0
Angina pectoris	0	0	1
Anxiety	0	1	0
Drug abuse	0	1	0
Hypertension aggravated	0	1	0
Myocardial infarction	0	1	0
Neoplasm	0	1	0
Tachycardia	0	0	1
Transient ischemic attack	0	0	1

Conclusion(s):

Cardiorenal Safety:

- Administration of celecoxib had no effect on blood pressure either at six or 12 weeks. In contrast, at both time points rofecoxib was associated with increases of approximately 4 mm Hg in systolic and 1.5 mm Hg in diastolic blood pressure. In the primary end point, the increase was statistically significant compared with celecoxib. All of the blood pressure effects of rofecoxib were statistically significant compared with naproxen.
- No cardiorenal effect of celecoxib was seen in the other secondary end points. An effect of rofecoxib was suggested in most end points, but the results were not consistently distinguished from celecoxib or naproxen statistically.
- None of the differences between celecoxib and naproxen in any cardiorenal end point were statistically significant.
- Clinically significant edema occurred in all groups. The highest incidence was seen in the rofecoxib group, but the difference was not statistically significant. Women were more susceptible to this outcome than men.
- Exploratory analysis showed statistically significant differences between celecoxib and rofecoxib in daytime ABPM results at Week 6. At Week 12, differences in both daytime and nighttime results were seen between rofecoxib and naproxen.

Efficacy:

- Substantial improvements from Baseline occurred in all treatment groups.
- The three treatments demonstrated similar efficacy across all measures. With only one exception, all pairwise comparisons in all efficacy measures indicated no statistically significant differences among the groups.

- The similarity of the three treatments was shown consistently across all types of measures: pain, stiffness, physical function, withdrawals, global assessments, and patient satisfaction.

General Safety:

- All treatments were safe and well tolerated in this study.
- Overall incidences of adverse events and of adverse events causing withdrawal were similar among the three groups. The incidence of the latter was lowest for celecoxib, but the difference was not statistically significant.
- The frequency and character of the adverse events experienced by patients were consistent with events seen in other trials of similar populations and duration. No pattern of deleterious effect of treatment was suggested by the types of adverse events.
- No preponderance of severity of events was seen with active treatments. However, the proportion of events in the celecoxib group considered by the Investigator to be drug-related was smaller than in the other two groups, and the difference was statistically significant.
- Serious adverse events occurred with low frequency in all treatment groups.

Based on a report completed on: 07 August 2003**.**