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PROPRIETARY DRUG NAME/INN: Celebrex[®] / Celecoxib.

THERAPEUTIC AREA AND FDA APPROVED INDICATIONS: See USPI

PROTOCOL NO.: N49-01-02-145

PROTOCOL TITLE: A Randomized, Double-Blind, Multicenter Comparison of the Effects of Celecoxib 200 mg BID Versus Rofecoxib 25 mg QD and Dietary Sodium on Blood Pressure in Osteoarthritis (OA) Subjects With Treated Systolic Hypertension

Study Center(s): Eight (8) centers in the United States

Study Initiation and Completion Dates: 17 December 2001 to 31 October 2003

Phase of Development: Phase 3

Study Objective(s):

Primary: To compare the effects of celecoxib 200 mg twice a day (BID) to rofecoxib 25 mg once daily (QD) on 24-hour systolic blood pressure (SBP) as measured by ambulatory blood pressure monitoring (ABPM) with varying dietary sodium intake in systolic hypertensive OA patients treated with an angiotensin-converting enzyme (ACE) inhibitor, a beta-blocker and/or an angiotensin II receptor antagonist

Secondary:

- To compare the effects of celecoxib and rofecoxib in terms of safety and tolerability;
- To compare the effect of celecoxib to rofecoxib on 24-hour SBP and diastolic blood pressure (DBP) as measured by ABPM in response to a high-sodium die;
- To compare the effect of celecoxib to rofecoxib on 24-hour SBP and DBP as measured by ABPM in response to a low-sodium diet
- To compare the change in seated cuff diastolic and SBP in response to change in dietary sodium intake with background acetaminophen
- To evaluate the effect of celecoxib and rofecoxib on 24-hour DBP as measured by ABPM with varying dietary sodium intake
- To compare the effects of celecoxib 200 mg BID to rofecoxib 25 mg QD on seated cuff diastolic and SBP with varying dietary sodium intake

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METHODS

Study Design:

This was a multicenter, double-blind, randomized group study designed as a replicated factorial trial with 2 treatments (celecoxib and rofecoxib) each at 2 sodium intake levels (80 mEq/day [NaCl 4.65 gm] and 183.2 mEq/day [NaCl 10.65 gm]).

Screening procedures included a physical examination, vital signs, clinical laboratory tests, and an electrocardiogram. Patients underwent washout of previous nonsteroidal anti-inflammatory drugs (NSAID) therapy and followed their usual diet. At Baseline (Day -1), patients were randomized to 1 of 4 treatment groups: 80 mEq sodium/day (Days 1-21) and rofecoxib 25 mg QD (Days 7-20); 80 mEq sodium/day (Days 1-21) and celecoxib 200 mg BID (Days 7-20); 183.2 mEq sodium/day (Days 1-21) and rofecoxib 25 mg QD (Days 7-20); and 183.2 mEq sodium/day (Days 1-21) and celecoxib 200 mg BID (Days 7-20). All patients began a low-sodium diet (80 mEq) and were instructed to take 2 acetaminophen 500 mg capsules four times a day (QID). Patients assigned to the high-sodium diet were also provided with sodium chloride 1-gram tablets and were instructed to take 2 tablets three times a day (TID). On Day 6, patients took the last dose of acetaminophen prior to retiring and on Day 7 patients began blinded study medication (celecoxib or rofecoxib). The patient visited the clinic on Days 6 and 20 to initiate 24-hour ABPM and 24-hour urine collections, on Day 11 for the return of the 24-hour urine collections and on Days 7, 14, and 21 for seated cuff BP, monitoring for signs of edema, and physical examination including vital signs and clinical laboratory testing (Days 7 and 21 only); patients were to discontinue 24-hour ABPM on Days 7 and 21 only. On Days 6-7 and 20-21, the patient was instructed to complete an ABPM instructional worksheet to collect activities (time and date of dose(s), time and date of bedtime, time and date of awakening and time and date of getting out of bed) during the BP measurement procedure. Adverse events were monitored and concomitant medications were collected throughout the study.

Planned evaluations of the glomerular filtration rate (GFR), renal plasma flow (RPF) and water displacement at selected centers were not performed.

Due to enrollment difficulties, the study was terminated early.

Number of Patients (planned and analyzed):

Planned: Two hundred and twenty (220) patients

Analyzed: Sixty-five (65) patients were randomized with 35 being randomized to the celecoxib group and 30 to the rofecoxib group. A total 55 patients were treated.

Diagnosis and Main Criteria for Inclusion:

Patients with a clinical diagnosis of OA, as well as systolic hypertension with or without a diastolic component whose SBP was ≤ 140 mmHg and DBP < 95 mmHg, and who were stable on an ACE inhibitor, a beta-blocker, and/or an angiotensin II receptor antagonist for at least 30 days were eligible for randomization into the trial.

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Study Treatment:

Oral treatment with capsules of either celecoxib 200 mg BID and rofecoxib- matching placebo tablets QD or rofecoxib 25 mg QD and celecoxib-matching placebo tablets BID.

Efficacy Evaluations:

This was a safety study and thus, no efficacy data was collected.

Safety Evaluations:

For the purpose of reporting, safety measurements were divided into BP endpoints and general safety measures. Due to the small sample size, 24-hour excreted amounts of potassium, comparisons of incidence of peripheral edema across study medications, and sodium intake levels were not summarized.

Primary Endpoint: The change in the mean 24-hour ABPM SBP computed as the difference between the Day 21 assessment and the Day 7 with varying (pooled) sodium intake.

Secondary Endpoints:

- Change in the mean 24-hour ABPM SBP (computed as difference between the Day 21 assessment and the Day 7 assessment) in response to a high-sodium intake
- Change in the mean 24-hour ABPM DBP (computed as difference between the Day 21 assessment and the Day 7 assessment) in response to a high-sodium intake
- Change in the mean 24-hour ABPM SBP (computed as difference between the Day 21 assessment and the Day 7 assessment) in response to a low-sodium intake
- Change in the mean 24-hour ABPM DBP (computed as difference between the Day 21 assessment and the Day 7 assessment) in response to a low-sodium intake
- Change in the seated cuff SBP (computed as difference between the Day 7 observation and the Day -1 observation) with varying sodium intake with background acetaminophen
- Change in the seated cuff DBP (computed as difference between the Day 7 observation and the Day -1 observation) with varying sodium intake with background acetaminophen
- Change in the mean 24-hour ABPM DBP (computed as difference between the Day 21 assessment and the Day 7 assessment) with varying sodium intake
- Change in the seated cuff SBP (computed as difference between the Day 21 observation and the Day 7 observation) with varying sodium intake
- Change in the seated cuff DBP (computed as difference between the Day 21 observation and the Day 7 observation) with varying sodium intake

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- Change in the seated cuff SBP (computed as difference between the Day 21 observation and the Day –1 observation) with varying sodium intake
- Change in the seated cuff DBP (computed as difference between the Day 21 observation and the Day –1 observation) with varying sodium intake

General Safety Endpoints:

General safety was assessed by monitoring AEs by means of physical examinations, vital signs, and clinical laboratory testing throughout the study.

Statistical Methods:

Data sets analyzed included the Completer Population, the modified intent-to-treat (MITT) Population and the safety population. The MITT Population included patients randomized to treatment who took at least 1 dose of study medication. Patients without both a Baseline and a follow-up observation for a given endpoint were dropped from the analysis. The Completer Population included patients randomized to treatment who took study medication (either celecoxib or rofecoxib) for at least 11 days as measured by total duration from study drug start date to study drug stop date, and was indicated as completing treatment/study per protocol by the investigator per the End-of-Study CRF page.

Continuous variables were analyzed using a general linear model. Analyses required for binary variables were performed using Fisher's exact test. Center was not included as a factor in the analyses given that most centers randomized too few patients. All analyses on change from Baseline included the corresponding Baseline measurement as a covariate in the analysis of covariance (ANCOVA) model. For example, the primary endpoint included the 24-hour ABPM SBP measurement taken at Day 7 as a quantitative covariate in the model.

In the MITT analyses, the method of last observation carried forward (LOCF) was used for the changes in seated cuff SBP and DBP over Days -1 to 7, Days 7 to 21 and Days -1 to 21; 4-day cumulative sodium balance (Days 7-8, 8-9, 9-10, and 10-11) and 24-hour urine sodium and chloride (Days 7 to 21). When a patient did not have a final post Baseline measurement required for computing the change in a non-ABPM derived endpoint, the nearest non-missing post-baseline measurement was used.

Continuous Baseline demographic and vital signs variables were analyzed using an analysis of variance (ANOVA), and categorical variables were analyzed using Pearson's chi-square test. Two ANOVA models were employed for each continuous Baseline variable. The initial model contained factors for study medication and sodium intake and their interaction; a second only contained a factor for study medication. In a similar manner, 2 Pearson's chi-square tests were employed for each categorical Baseline demographic variable. The test contained 4 groups, each treatment at low and high sodium levels. The second test compared the two treatments irrespective of sodium level.

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The primary analysis was based on the Completer Population. The general linear model included factors for study medication, sodium intake, the interaction between those 2 factors, and the mean 24-hour ABPM SBP from Day 7 as a covariate.

The mean, standard deviation, least squares means (LS mean) and standard error of the primary endpoint were presented by study medication and sodium intake level, as well as by study medication only. The difference between the LS means between the study medications (celecoxib minus rofecoxib), the corresponding standard error, 2-sided 95% confidence intervals, and p-value were presented.

No analysis was performed on the MITT Population since patients who terminated early did not have the ABPM performed.

Secondary endpoints were analyzed using a model similar to the primary analysis. All analyses of change from Baseline included the corresponding Baseline measurement as a covariate in the ANCOVA model.

No interim analyses were planned or performed.

All patients who received at least 1 dose of study medication were included in the analyses of adverse events. The incidence of adverse events were tabulated by treatment group and system organ class (SOC) and displayed by severity, attribution, those causing withdrawal, and serious adverse events. The incidences of adverse events by treatment group within SOC and causing withdrawal were compared between treatment groups using a Fisher's exact test.

Clinical laboratory data were summarized and compared across the treatment groups. An ANCOVA with study medication and assigned sodium intake as factors, as well as the interaction between these 2 factors, and the Day -1 value as a covariate, was used to analyze between-treatment differences from Days -1 to 21 (or early termination). The incidences were compared between treatment groups using a Fisher's exact test.

Changes in vital signs (pulse, respiration, temperature, and weight) from Day -1 to Day 21 or early termination were calculated and compared between treatment groups using an ANCOVA.

RESULTS

Subject Disposition and Demography:

A total of 65 patients were randomized. Eight patients in the celecoxib treatment group and 2 patients in the rofecoxib treatment group did not take study medication. Fifty-four (54) patients completed the study and 1 patient in the rofecoxib treatment group was terminated from the study early due to a protocol violation.

Subject disposition is displayed in Table S1.

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Table S1 Subject disposition

	Celecoxib 200 mg BID			Rofecoxib 25mg QD		
	Low NaCl	High NaCl	Overall	Low NaCl	High NaCl	Overall
Randomized/ No Study Medication, n (%)	4 (20.0)	4 (26.7)	8 (22.9)	1 (7.7)	1 (5.9)	2 (6.7)
Randomized/ Took Study Medication/ Completed, n (%)	16 (80.0)	11 (73.3)	27 (77.1)	11 (84.6)	16 (94.1)	27 (90.0)
Randomized/ Took Study Medication/ Withdrawn, n (%)	0	0	0	1 (7.7)	0	1 (3.3)
Reason for Withdrawal ^a						
Adverse Event, n (%)	0	0	0	0	0	0
Protocol Violation, n (%)	0	0	0	1 (7.7)	0	1 (3.3)
Consent Withdrawn, n (%)	0	0	0	0	0	0
Lost to Follow-up, n (%)	0	0	0	0	0	0
Sponsor's Decision, n (%)	0	1 (6.7) ^b	1 (2.9)	0	0	0

Note: Percentages are based on the number of randomized patients in each treatment group.

Na = Sodium.

^aMutually exclusive and exhaustive categories.

^bPatient 00082 did not take study medication.

Twenty-five (25) celecoxib-treated patients and 27 rofecoxib-treated patients formed the Completer Population. The primary analysis was performed on all patients who met the Completer Population criteria and who had both a baseline and a follow-up measure. This analysis included 18 celecoxib treated patients and 20 rofecoxib-treated patients. One patient randomized to the celecoxib 200 mg BID plus high-sodium treatment group received a low-sodium diet without NaCl supplementation. Therefore, the patient was included in the celecoxib plus low-sodium treatment group for analysis purposes.

On average, patients were between 62.4 and 64.5 years of age. The majority of patients (80%) were Caucasian. The majority (60%) of patients randomized to celecoxib were male while the majority (70%) of patients randomized to rofecoxib were female. Gender assignment to treatment groups was statistically significantly different ($p=0.016$ overall). On average, patients weighed between 85.5 kg and 88.8 kg at Baseline.

Efficacy Results:

This was a safety study and no efficacy evaluations were performed.

Safety Results:

Analysis of sodium excretion at Baseline (Day 6) indicated that several patients in both treatment groups ingested sodium in excess of their assigned intake. Overall, the lack of compliance with the assigned sodium level resulted in many patients not achieving sodium balance at the desired sodium intake prior to introduction of study medication. Because patients were noncompliant with sodium intake, no inferences can be made with respect to the potential difference between the 2 treatment groups in the presence of low- and high-sodium levels. Thus, discussion focuses on the celecoxib and rofecoxib treatment groups with pooled sodium intake.

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Primary Endpoint: The results of the change in the mean 24-hour ABPM SBP from Days 7 to 21 are summarized in Table S2.

Table S2 Change in the Mean 24-Hour ABPM SBP From Days 7 to 21 for the Completer Population for patients who had both a baseline and a follow-up measure

	Celecoxib Overall (N = 25)	Rofecoxib Overall (N = 27)
N analyzed (patients who had both a baseline and a follow-up measure)	18	20
Day 7 Mean (SD)	134.6 (16.15) mmHg	134.5 (11.66) mmHg
Day 21 Mean (SD)	135.7 (17.48) mmHg	135.3 (12.16) mmHg
LS Mean Change From Baseline	1.2 mmHg	0.3 mmHg
p-value ^a	0.716	

^aFrom ANCOVA model with factors study medication, sodium intake, and their interaction, and the Day 7 value as a covariate.

Secondary Endpoints:

Change in Seated Cuff Blood Pressure – Low and High Sodium Intake With Background Acetaminophen (Days –1 to 7) For the seated cuff SBP, the LS mean changes from Baseline were 2.5 mmHg and 5.0 mmHg for the low-sodium and high-sodium intake groups, respectively. No statistically significant difference was demonstrated between the sodium intake levels ($p = 0.389$). For the seated cuff DBP, the LS mean changes from Baseline were 2.1 mmHg and 0.3 mmHg for the low-sodium and high-sodium intake groups, respectively. There was no statistically significant difference between sodium intake levels ($p = 0.304$).

Change in Mean 24-Hour ABPM DBP – Varying (Pooled) Sodium Intake The results of the change in the mean 24-hour ABPM DBP for pooled sodium intake from Days 7 to 21 are summarized below in Table S3.

Table S3 Change in the Mean 24-Hour ABPM DBP From Days 7 to 21 for the Completer Population

	Celecoxib Overall (N = 25)	Rofecoxib Overall (N = 27)
N analyzed	18	20
Day 7 Mean (SD)	78.6 (8.61) mmHg	77.1 (8.85) mmHg
Day 21 Mean (SD)	80.0 (10.40) mmHg	76.5 (8.49) mmHg
LS Mean Change From Baseline	1.4 mmHg	-1.0 mmHg
p-value ^a	0.124	

^aFrom ANCOVA model with factors study medication, sodium intake, and their interaction, and the Day 7 value as a covariate.

Change in Seated Cuff Blood Pressure – Varying (Pooled) Sodium Intake (Days 7 to 21) Changes in seated cuff systolic and diastolic blood pressure are summarized in Table S4.

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Table S4 Change in the Seated Cuff Systolic and Diastolic Mean Blood Pressure From Days 7 to 21 for the Completer Population

	Celecoxib Overall (N = 25)	Rofecoxib Overall (N = 27)
Systolic Blood pressure		
Day 7		
Mean (SD)	130.3 (14.28) mmHg	133.1 (12.31) mmHg
Day 21		
Mean (SD)	130.7 (13.83) mmHg	137.5 (15.02) mmHg
LS Mean Change From Baseline	0.0 mmHg	4.7 mmHg
p-value ^a	0.152	
Diastolic Blood pressure		
Day 7		
Mean (SD)	78.5 (9.90) mmHg	78.9 (10.51) mmHg
Day 21		
Mean (SD)	77.7 (10.72) mmHg	79.9 (8.93) mmHg
LS Mean Change From Baseline	-0.8 mmHg	1.30 mmHg
p-value ^a	0.244	

^aFrom ANCOVA model with factors study medication, sodium intake, and their interaction, and the Day 7 value as a covariate.

The results for the MITT Population were similar to those for the Completer Population. There were no notable differences for the seated cuff SBP ($p = 0.112$) or seated cuff DBP ($p = 0.250$).

Change in Seated Cuff Blood Pressure – Varying (Pooled) Sodium Intake (Days –1 to 21) In the Completer Population, no notable treatment difference was observed in seated cuff SBP ($p = 0.114$) or seated cuff DBP ($p = 0.458$). The LS mean changes from Baseline for the celecoxib and rofecoxib groups were 3.4 mmHg and 9.3 mmHg, respectively for SBP and 0.9 mmHg and 2.3 mmHg, respectively, for DBP. The results for the MITT Population were similar to those for the Completer Population. There were no notable differences for the seated cuff SBP ($p = 0.083$) or seated cuff DBP ($p = 0.487$).

General Safety Results:

There were 10 patients (37%) in the celecoxib treatment group and 9 (32.1%) in the rofecoxib treatment group reporting at least 1 adverse event. Adverse events reported in more than one patient in either treatment group (irrespective of sodium levels) are presented in Table S5.

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Table S5 Adverse Events Reported in more than One Patient in Either Treatment Group (Safety Population)

System Organ Class Adverse event	Celecoxib 200 mg BID			Rofecoxib 25 mg OD		
	Low Na ^a (N=16)	High Na ^b (N=11)	Overall (N=27)	Low Na ^a (N=12)	High Na ^b (N=16)	Overall (N=28)
Any event	5 (31.3)	5 (45.5)	10 (37.0)	2 (16.7)	7 (43.8)	9 (32.1)
Gastrointestinal disorders						
Abdominal pain NOS	0	1 (9.1)	1 (3.7)	1 (8.3)	1 (6.3)	2 (7.1)
Nausea	0	0	0	0	2 (12.5)	2 (7.1)

^a80 mEq/day ^b183.2 mEq/day

All adverse events for patients in the celecoxib treatment group were reported as mild to moderate in intensity. One patient (3.6%) in the rofecoxib plus high-sodium treatment group experienced a severe headache and the event was determined to be unrelated to study medication by the investigator.

There were no deaths, serious adverse events or discontinuations due to adverse events recorded during this study.

There were statistically significant differences between treatment groups in mean changes from Baseline for alkaline phosphatase (mean change -4.222 U/L and 2.667 U/L for the celecoxib and rofecoxib treatment groups, respectively) and aspartate aminotransferase (AST) (mean change -1.926 U/L and 1.115 U/L for the celecoxib and rofecoxib treatment groups, respectively). A borderline statistically significant ($p = 0.074$) difference between treatment groups was also observed for alanine aminotransferase (ALT) (mean change -2.407 U/L and 1.296 U/L for the celecoxib and rofecoxib treatment groups, respectively). However, none of the mean changes in biochemistry parameters were clinically significant. There were no patients with hematology or biochemistry values outside the extreme lower limits at minimum value or at the Final Visit.

One patient in the celecoxib plus low-sodium treatment group experienced a blood urea nitrogen level (BUN) that was above the upper limit of normal (ULN) (15.0 mmol/L) during the study; however, the patient's Baseline value was above the ULN (10.0 mmol/L) and no associated adverse event was reported with the increase in BUN. The patient's serum creatinine remained normal throughout study participation. No patients had values outside the extreme lower limits. The frequencies of normal-to-high or normal-to-low shifts were similar for the treatment groups for most analyses.

CONCLUSION(S):

- There is insufficient power to adequately address the objectives of the study. Additionally, noncompliance with sodium intake precluded accurate measurement of the potential antinatriuretic effects of celecoxib and rofecoxib.
- No difference in mean change from Baseline for 24-hour ABPM SBP was detected between the rofecoxib 25 mg QD and celecoxib 200 mg BID treatment groups.
- There were no overall differences observed between treatment arms for general safety.

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Based on a report completed on: 24 December 2004

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