CLINICAL RESEARCH STUDY

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NSAIDs Are Associated with Lower Depression Scores in Patients with Osteoarthritis

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ABSTRACT

BACKGROUND: Studies have demonstrated the success of augmentation of antidepressant therapy with nonsteroidal anti-inflammatory drugs (NSAID) in decreasing depressive symptoms; however, little is known about the benefit of NSAID therapy on depressive symptoms.

METHODS: This study pooled data from 5 postapproval trials, each trial a 6-week, multicenter, randomized, double-blinded, placebo-controlled, active-comparator, parallel-group study in subjects with active osteoarthritis. Subjects were randomized to placebo group, ibuprofen 800 mg 3 times daily or naproxen 500 mg twice daily group, or Celebrex 200 mg daily group. Apart from different ethnicities enrolled, these trials had identical study designs. Depression was assessed using the Patient Health Questionnaire-9 (PHQ-9). Outcomes measured were change in PHQ-9 score after 6 weeks of NSAID therapy and change in classification of depression with a PHQ-9 score $\geq$10 as a marker of depression.

RESULTS: There were 1497 patients included. Median PHQ-9 score was similar in all 3 groups at baseline and after 6 weeks of treatment. Multivariable regression analysis demonstrated a detectable effect in lowering PHQ-9 score in the ibuprofen or naproxen group (−0.31) and Celebrex group (−0.61) ($P = .0390$). With respect to the change in classification of depression, logistic regression analysis demonstrated a trend towards significant treatment effect of all NSAIDs compared with placebo.

CONCLUSION: Our analysis of pooled data from 5 postapproval trials shows that NSAID usage demonstrates a trend towards reduction of depression symptoms in patients with osteoarthritis based upon PHQ-9 scores. Future clinical trials should investigate this association with maximum dosage of drugs, increased treatment duration, and monitoring of social and environmental changes.

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KEYWORDS: Celecoxib; Depression; Nonsteroidal anti-inflammatory drugs (NSAIDs); Osteoarthritis

Osteoarthritis and depression are debilitating comorbidities that lead to functional decline if inappropriately treated. Osteoarthritis results from articular cartilage failure induced by a complex interplay of genetic, metabolic, biochemical, and biomechanical factors with secondary components of inflammation.[1] This process involves interactive degradation, and repair processes of cartilage, bone, and synovium. Depression is a heterogeneous disorder that can manifest with symptoms at psychological, behavioral, and physiological levels. The magnitude of the problem, the delayed onset of action of antidepressants, adverse drug effects, and

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noncompliance with current drugs call for the development of effective management and preventive approaches to reduce the burden and morbidity associated with this illness.

Recent studies indicate that depression is 2 to 3 times more prevalent in patients with osteoarthritis.[2-5] However, a significant proportion of patients with osteoarthritis are not receiving appropriate treatment, suggesting a care gap.[6] The current target of drug therapy in depression is based upon the mechanism of a deficiency of serotonergic and noradrenergic neurotransmitters in the central nervous system. A recent hypothesis has emerged attributing aspects of depression to chronic systemic inflammation. Cytokines such as interleukin-1, interleukin-6, and tumor necrosis factor-α have been implicated in the response to stress and illness, also leading to depression and cognitive deficits in genetically susceptible hosts.[7-10] Under normal homeostasis, the cortisol release response of the body to stress modulates this cytokine response.[11] With sustained stress and inflammation, the feedback modulation of cytokines by cortisol becomes ineffective, leading to hypothalamus-pituitary-axis overactivity.[7,12,13] These elevated cortisol and cytokine levels lead to disordered tryptophan metabolism and 5-hydroxy-tryptamine (serotonin) production, and thus a predilection for clinical depression.[14]

CLINICAL SIGNIFICANCE

- Commonly, nonsteroidal anti-inflammatory drugs are used in patients with osteoarthritis, but little or no surveillance has been done on the effect of these drugs on clinical depression.
- Depression is 2 to 3 times more prevalent in patients with osteoarthritis.
- Use of nonsteroidal anti-inflammatory drugs in patients with osteoarthritis can improve depression.

This association between cytokine release and prostaglandin synthesis in depression has led to the exploration of benefits of anti-inflammatory agents in depression. Nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit cyclooxygenase and impair the cascade of enzymatic reactions that transform arachidonic acid to prostaglandins, prostacyclins, and thromboxanes.[15] Selective cyclooxygenase-2 inhibitors such as celecoxib (Celebrex; Pfizer, New York, NY) possess anti-inflammatory and analgesic properties while offering the benefit of gastrointestinal protection compared with traditional NSAIDs. Recent studies have demonstrated benefit of NSAIDs as augmentation therapy, shown to reduce depressive symptoms in those taking concurrent antidepressant therapy.[16-18] However, the benefit of NSAID therapy in affecting depression in patients with osteoarthritis has not been studied. We performed a pooled analysis of 5 trials that examined NSAID (ibuprofen, naproxen, and Celebrex) usage in patients with established osteoarthritis. Subjects underwent screening for the presence or absence of depression, which was repeated following 6 weeks of NSAID therapy. We hypothesized that NSAID usage in patients with osteoarthritis would show a trend towards a decrease in depressive symptoms.

METHODS

Pooled data were included from 5 trials with identical protocols conducted by Pfizer Pharmaceuticals Inc., each of which was for a 6-week period, multicenter, randomized, double-blind, placebo-controlled, active-comparator, parallel-group study in subjects with osteoarthritis. The original data from these trials conducted in 2001-2003 have never been published (**Figure 1**, **Supplementary Table**).

In each trial, eligible subjects were randomized to 1 of 3 regimens: placebo group, ibuprofen 800 mg 3 times daily or naproxen 500 mg twice daily group, or Celebrex 200 mg daily group, in a 1:2:2 ratio. Apart from different ethnicities enrolled, these trials had identical study designs. Details are provided in the supplementary materials.

Subjects were eligible for study participation if at least 40 years of age and diagnosed with active and symptomatic osteoarthritis with a Functional Capacity Classification of I-III, including subjects in a flare state. Subjects taking NSAIDs or analgesic therapy were required to discontinue medications at least 48 hours before the baseline assessments.

All subjects were screened for major depression with the standard patient health questionnaire-9 (PHQ-9) scale at baseline. PHQ-9 score is a survey of functional impairment over the previous 2 weeks. Areas assessed in this survey include each of the *Diagnostic and Statistical Manual of Mental Disorders*, 4th Edition[19] criteria for depression, including interest or pleasure in daily activities, mood, sleep disturbance, eating habits, self-reflection/guilt, concentration, speech patterns, suicidal ideation, and overall severity of symptoms affecting function, rated on a scale of intensity of 0 ("not at all") to 3 ("nearly every day"). The diagnosis of major depression has been validated at a PHQ-9 sum $\geq$10 with a sensitivity of 88% and a specificity of 88%.

Patients were not eligible for participation in enrollment if age under 18 years or >50 years, past history of coronary artery disease, concurrent musculoskeletal disorders requiring NSAID therapy, pregnancy, current and past substance abuse, medical conditions leading to symptoms of depression including history of untreated or uncontrolled hypothyroidism, syphilis, human immunodeficiency virus, and current glucocorticoid therapy. Further exclusion in those with psychiatric comorbidities such as major depressive disorder or currently taking antidepressant therapy such as selective serotonin reuptake inhibitor (SSRI), selective norepinephrine reuptake inhibitor, and tricyclic antidepressants, as well those with bipolar disorder, schizophrenia, anxiety disorders, and *Diagnostic and Statistical Manual of Mental Disorders*, 4th Edition[19] axis II traits such as personality disorders (cluster A, B, and C).

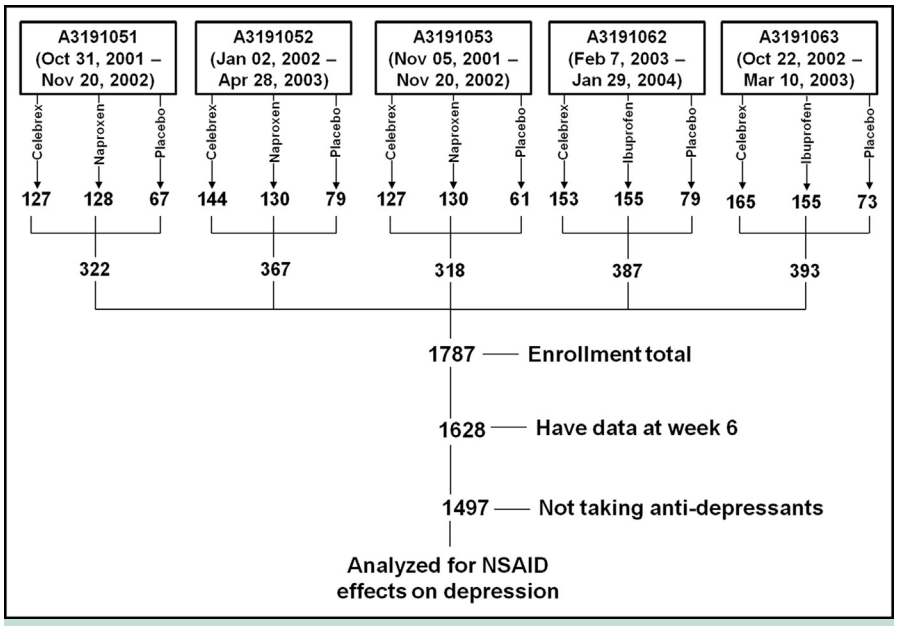

Figure 1 Selection criteria for population used this study.

Patients were assessed at 4 visits: Screening, Baseline, Week 2, and Week 6 (or early termination). The screening visit occurred within 1-14 days before the administration of the first dose of study medication. Between Screening and Baseline, subjects discontinued use of any NSAID or analgesic therapy. Acetaminophen (up to 2 g/day) was permitted as rescue analgesia for the treatment of arthritis symptoms during the pretreatment screening period. Subjects were to discontinue use of acetaminophen at least 24 hours before the Baseline arthritis assessments.

At screening, subjects had an abbreviated physical examination, underwent clinical laboratory testing, and if trial participant was a female of childbearing potential, she received a urine pregnancy test. An evaluation of arthritis consisting of both subject and physician assessments was performed, and subjects completed a PHQ-9 and a Complementary and Alternative Medicines Questionnaire. Eligible subjects returned for the Baseline visit. Study medication and the American Pain Society Pain Measure diary were dispensed. The use of analgesic medication, other than the study medication for treatment of arthritis symptoms, was prohibited throughout the study period.

At the Week 6 visit, each subject completed the PHQ-9 survey and arthritis assessments, and study medication was collected. In addition, concomitant medication and adverse event information was recorded. Patients with a PHQ-9 score $\geq$10 were diagnosed with persistent major depressive disorder. Changes in PHQ-9 score were recorded.

Outcome Measures

The outcome measured was a change in PHQ-9 score at week 6 (or early termination). Additional outcome was a change in classification of depression with a PHQ-9 score $\geq$10 as a marker for depression. Further outcome measures included measurement of visual analogue scale (VAS), patient's and physician's global assessments of arthritis, and change in Western Ontario and McMaster Universities (WOMAC) Osteoarthritis index.

Statistical Analysis

Statistical analysis was conducted in R version 2.14.0.[20] An intent-to-treat approach was used with respect to the treatment group assignments. Patients taking antidepressants at baseline were excluded. Because the amount of missing data was low, a complete case analysis was performed for the regression models.

There is a known strong association between the 24-item WOMAC scale and VAS pain scale. The WOMAC scale is a more standardized and representative interpretation of osteoarthritis than the VAS pain score and thus, was used in our model.[21]

The Week 6 PHQ-9 data were analyzed by multiple linear regression. In addition to the treatment variable, the model was adjusted for age, sex, body mass index (BMI), diabetes mellitus, baseline PHQ, and the difference in WOMAC between Baseline and Week 6. An interaction between Baseline PHQ and WOMAC difference also was considered. The possibility of nonlinear associations of baseline PHQ and WOMAC difference with the Week 6 PHQ were fit using restricted cubic splines with 3 knots.[22] The number of knots specifies the degree of smoothness, with fewer knots resulting in more smoothing. Because the associations appeared to change gradually, 3 knots was deemed sufficient. The interaction between Baseline PHQ and WOMAC difference was estimated between the splines as well.

The presence of a diagnosis of depression at Week 6 was analyzed by multivariate regression analysis. The same

adjusting variables as were used in the multiple regression model were used in the logistic regression model, with the exception that nonlinear associations were not evident, nor were any interactions considered.

P-values <.05 indicate statistically significant associations. However, all variables were retained in the models, irrespective of statistical significance to reduce potential bias and overfitting.[22] Model overfitting was assessed by bootstrapping and examining various model indexes (eg, R^2 for linear regression, $SommersD_{xy}$ for logistic regression, among others).[22] This method revealed no excessive overfitting. The residuals from the multiple regression model were examined and revealed mild nonnormality.

The multivariable regression was adjusted for age, sex, BMI, diabetes mellitus, baseline PHQ-9, and WOMAC that yielded this significant *P* value. Before choosing the best-fit model, a decision to adjust for age, sex, and BMI was made. This decision was based on previous studies that have demonstrated that age, sex, and BMI are strongly associated with depression in osteoarthritis.[23] Before model selection, the decision to adjust for diabetes mellitus was based upon the relationship between metabolic syndrome and osteoarthritis.[24] The WOMAC and PHQ-9 Baseline scores also were adjusted for in this best-fit model selection.

RESULTS

There were 1497 patients included in this analysis. Baseline demographics including race and ethnicity, comorbidities, vital signs, and medications taken at screening were similar among all 3 groups (**Tables 1**, **2**). No significant increase in systolic or diastolic blood pressure and heart rate were observed between Baseline and Week 6 in the placebo and treatment groups. The WOMAC and VAS pain sum differences were reduced in all 3 groups at Week 6 (**Table 2**).

PHQ-9 Score at Week 6 of NSAID Treatment

In this study, change in PHQ-9 score over 6 weeks with NSAID treatment was assessed. Treatment was divided into 3 groups: placebo, ibuprofen/naproxen, and Celebrex groups (**Table 3**). Median PHQ-9 score was similar in all 3 groups at Baseline and Week 6 (**Table 4**). Multivariable regression analysis demonstrated a detectable difference in PHQ-9 score dependent on treatment groups: ibuprofen/naproxen (−0.31) or Celebrex treatment (−0.61) ($P = .0390$) compared with placebo (**Table 4**).

Figure 2 shows the interaction between the PHQ-9 at Week 6 with WOMAC difference score (WOMAC at Week 6 − WOMAC at Baseline) and PHQ-9 baseline. The interaction fit increases with PHQ-9 at Week 6 and increased WOMAC difference and increased Baseline PHQ-9, therefore as PHQ-9 increases, the greater effect baseline PHQ-9 and WOMAC difference (**Figure 2**).

The occurrence of depression as defined by a PHQ-9 score ≥10 also was assessed. After 6 weeks of treatment, 9% of subjects in the ibuprofen or naproxen group and 9% of the Celebrex group compared with 14% of the placebo group were classified as depressed, with a PHQ-9 score ≥10 (**Table 3**). Logistic regression analysis showed a trend

Table 1 Baseline Characteristics and Medications

	Placebo (n = 297)	Ibuprofen or Naproxen (n = 593)	Celebrex (n = 607)
Demographics			
Age (years)*	61 (52, 69)	61 (54, 68)	61 (52, 69)
Body mass index (kg/m^2)*	29 (25, 35)	29 (26, 34)	30 (26, 34)
Female (%)	67	69	68
White (%)	33	33	33
Black (%)	22	23	22
Asian (%)	26	25	24
Hispanic (%)	16	18	17
Other race (%)	3	2	4
Medical conditions			
Alcohol or tobacco abuse	1	0	0
Depression or anxiety (%)	3	5	3
Angina (%)	3	2	2
Arrhythmia (%)	3	2	2
Congestive heart failure (%)	1	0	1
Cardiovascualr disease (%)	4	5	5
Diabetes mellitus (%)	16	13	17
Dyslipidemia (%)	2	3	3
Heartburn (%)	3	4	5
Hyperglycemia (%)	0	0	0
Hyperlipidemia (%)	16	10	20
Hypertension (%)	45	52	48
Myocardial infarction (%)	1	1	2
Overweight/obese (%)	3	2	3
Pericarditis (%)	0	0	0
Peripheral vascular disease/ thrombosis/ deep vein thrombosis (%)	4	5	4
Transient ischemic attack/stroke/ aneurysm (%)	1	1	0
Medications			
Antithyroid (%)	6	7	7
Cardiovascular system (%)	44	52	51
Analgesics (%)	39	34	38
Medication affecting nutrition or blood (%)	9	13	11
Anesthetics (%)	0	0	0
Endocrine system disorder (%)	13	15	14
Diabetic (%)	15	10	13
Muscle relaxant (%)	60	62	62

*Median (25^{th}, 75^{th} percentile).

Table 2 Vital Signs and Functional Parameters

	Placebo (n = 297)	Ibuprofen or Naproxen (n = 593)	Celebrex (n = 607)
HR baseline (beats per minute)*	76 (70, 80)	74 (68, 80)	74 (68, 80)
HR difference*(Week 6—baseline)	0 (−4, 4)	0 (−4, 4)	0 (−4, 5)
WOMAC sum difference*(Week 6—baseline)	−19 (−36, −5)	−23 (−37, −9)	−24 (−39, −8)
VAS pain sum difference*(Week 6—baseline)	−29 (−52, −7)	−37 (−57, −16)	−41 (−56, −18)
Functional capacity classification at week 6			
Class I (%)	4	3	4
Class II (%)	66	70	67
Class III (%)	30	27	29
Class IV (%)	0	0	0

HR = heart rate; VAS = visual analogue scale; WOMAC = Western Ontario and McMaster Universities.
*Median (25th, 75th percentile).

towards significant treatment effect for the NSAIDs treatment groups compared with placebo ($P = .087$).

DISCUSSION

Our study has shown through new analysis of pooled data from 5 postapproval trials that NSAID usage demonstrates a trend towards reduction of depression symptoms in patients with osteoarthritis based upon PHQ-9 scores. Our data support the findings of previous studies that assessed the effects of NSAIDs on depression. A multicenter prospective study including 2228 patients with osteoarthritis treated with 25 mg daily of rofecoxib resulted in a 12% absolute reduction in comorbid depressive symptoms.[16] A prospective study of 40 patients suffering from an acute depressive episode revealed that SSRI reboxetine combined with Celebrex significantly improved depressive symptoms compared with reboxetine alone.[17] A simultaneous study of depressed patients who had not responded to at least 4 weeks of SSRI treatment found that adding 160 mg daily of aspirin to this regimen resulted in a response rate of 52.4%. This response rate was comparable to classic augmentation strategies such as lithium or triiodothyronine supplementation.[18]

Several aspects of the trial design may have potentially reduced the treatment effect observed. Patients in the ibuprofen or naproxen group received maximum effective dose at 800 mg 3 times daily and 500 mg twice daily, respectively. The Celebrex group received only 200 mg daily, compared with previous studies that demonstrated therapeutic benefit with a dose of 400 mg daily. This lower dose may have potentially underestimated the prospective benefit of Celebrex on depressive symptoms. The length of observation was only 6 weeks without continuous observation; measurements were taken only upon study commencement and termination. Six weeks of therapy in both NSAID groups demonstrated a treatment effect, and longer follow-up may demonstrate even greater therapeutic benefit with progressive decrease in PHQ-9 depression scores. The baseline demographics of this study did not take into account social and economic factors. Generalizability of these results is limited as potential confounders are still unknown, which may precipitate depression or mood changes in all groups. It also is likely that symptomatic

Table 3 PHQ-9 Score at Baseline and Week 6 and Depression at Week 6

	Placebo (n = 297)	Ibuprofen or Naproxen (n = 593)	Celebrex (n = 607)
PHQ-9 baseline*	3 (1, 7)	3 (1, 7)	3 (1, 7)
PHQ-9 week 6*	2 (0, 6)	2 (0, 5)	2 (0, 5)
Not depressed (<10)† (%)	86	91	91
Depressed (≥10)† (%)	14	9	9

The effect of nonsteroidal antiinflammatory drugs (NSAIDs) treatment on depression. Percentage of trial population classified as depressed. Bivariate analysis of Patient Health Questionnaire (PHQ-9) score after 6 weeks of NSAIDs treatment, yielding depressed population in this analysis.
*Median (25th, 75th percentile).
†Percentage of those depressed at week 6 of analyzed population of each study arm.

Table 4 Multivariate Regression and ANOVA Analysis of Effects on PHQ-9 Score

	Effect	95% CI	*P* Value
Treatment			
Ibuprofen or naproxen vs placebo	−0.31	−0.80 to 0.17	.039
Celebrex vs placebo	−0.61	−1.10 to −0.13	
Age (per 10 years)	−0.0068	−0.181 to 0.168	.939
Body mass index (per 8.5)	0.31	0.09 to 0.54	.0072
Sex: male vs female	−0.25	−0.64 to 0.13	.194
Diabetes mellitus: yes vs no	0.26	−0.24 to 0.76	.316

ANOVA = analysis of variance; CI = confidence interval.
The adjusted model for prediction of depression in nonsteroidal antiinflammatory drugs (NSAIDs) groups compared with those on placebo. For every 10 years of increased age, there was increase of Patient Health Questionnaire (PHQ-9) at Week 6. Adjusted model for prediction of depression in NSAIDs groups compared with placebo.

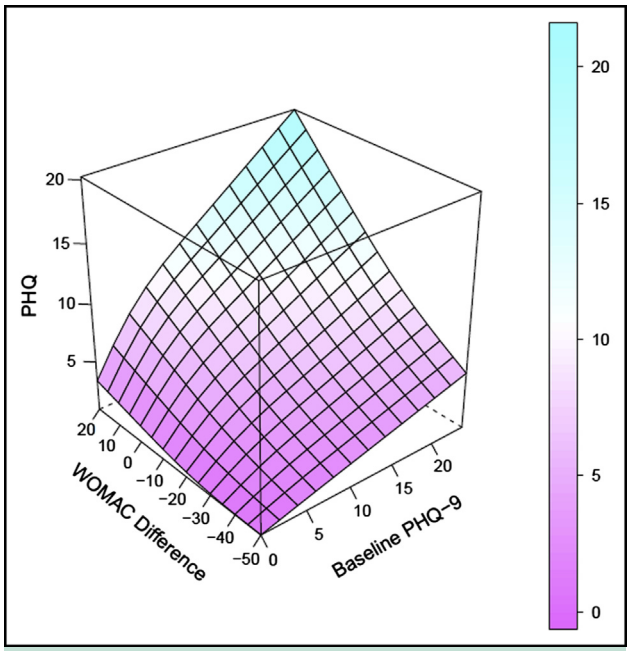

Figure 2 Joint relationship of baseline PHQ and WOMAC difference on Week 6 PHQ depression scale. Adjusted to reference groups = ibuprofen or naproxen, mean age = 61 years, body mass index = 29.47, reference sex = female, diabetes diagnosis = no as reference. PHQ = Patient Health Questionnaire; WOMAC = Western Ontario and McMaster Universities.

osteoarthritis may have limited patient function, which was improved by NSAID usage. This also may have resulted in an improvement in PHQ-9 scores, which are markers of functional impairment.

The results of our study are intriguing, as after 6 weeks of therapy with NSAIDs, there was a significant trend towards reduction in PHQ-9 scores, and a trend towards change in classification of depression based upon PHQ-9 scores. The results of this study suggest a prospective reduction in the development of depressive symptoms in this high-risk population of patients with osteoarthritis. This has important implications from an epidemiologic and public policy standpoint because of the high costs associated with the management of depressive disorders. Our exploratory study supports the putative connection between depression and inflammation; however, based upon our results, we do not recommend routine population-based screening for depression and prophylactic NSAID use in those at high risk for the development of depression. Our study does confirm the importance of NSAID therapy in osteoarthritis, as the benefit is likely to be beyond anti-inflammatory properties acting only on synovial cartilage. Future large, randomized clinical trials should investigate the benefits of NSAIDs on depression in osteoarthritis with dosages that have maximal anti-inflammatory effects, study period >6-week duration used in these clinical trials, and with monitoring of covariates such as social and environmental changes.

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Supplementary Table Phase 4 Development Trials Conducted by Pfizer Pharmacetuicals Inc.

Protocol	Title of Study	Study Center(s)	Study Period	Treatment Groups
A3191051/ N49-01-02-209	A study of the efficacy and tolerability of once daily Celebrex (celecoxib) and twice daily naproxen vs placebo in the treatment of African American subjects with osteoarthritis of the knee	28 centers, United States	31 Oct 2001—20 Nov 2002	(1) Celebrex (2) Naproxen (3) Placebo
A3191052/ I49-01-02-210	A study of the efficacy and tolerability of once daily Celebrex (celecoxib) and twice daily naproxen vs placebo in the treatment of Asian American subjects with osteoarthritis of the knee	24 centers, United States	02 Jan 2002—28 Apr 2003	(1) Celebrex (2) Naproxen (3) Placebo
A3191053	A study of the efficacy and tolerability of once daily Celebrex (celecoxib) and twice daily naproxen vs Placebo in the treatment of Hispanic subjects with osteoarthritis of the knee	31 centers, United States	05 Nov 2001—20 Nov 2002	(1) Celebrex (2) Naproxen (3) Placebo
A3191062	A study of the efficacy and tolerability of once daily Celebrex (celecoxib) and three times daily Ibuprofen vs placebo in the treatment of subjects with osteoarthritis of the knee	34 investigators; Germany (12), Spain (10), and United Kingom (12)	7 February 2003—29 January 2004	(1) Celebrex (2) Ibuprofen (3) Placebo
A3191063	A study of the efficacy and tolerability of once daily Celebrex (celecoxib) and three times daily Ibuprofen vs placebo in the treatment of subjects with osteoarthritis of the knee	32 centers, United States	22 Oct 2002—10 Mar 2003	(1) Celebrex (2) Ibuprofen (3) Placebo