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# Comparison of Once-Daily and Twice-Daily Administration of Celecoxib for the Treatment of Osteoarthritis of the Knee

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## ABSTRACT

***Objective:*** The purpose of this study was to compare the efficacy and tolerability of a celecoxib 200 mg QD regimen with a 100 mg BID regimen in patients with osteoarthritis (OA) of the knee.

***Methods:*** Patients enrolled in this prospective, double-blind, placebo-controlled, parallel-group, multicenter study were randomly assigned to receive celecoxib 100 mg BID, celecoxib 200 mg QD, or placebo for 6 weeks. Assessments of OA severity (Patient's and Physician's Global Assessments of Arthritis, Patient's Assessment of Arthritis Pain–Visual Analog Scale, Lequesne Osteoarthritis Severity Index, and the Western Ontario and McMaster Universities Osteoarthritis Index) were performed at baseline and at week 2 and/or 6. Patients who discontinued treatment underwent assessments at the time of withdrawal from the study.

***Results:*** Of the 718 patients enrolled, 243 received celecoxib 100 mg BID, 231 received celecoxib 200 mg QD, and 244 received placebo. For all measures of efficacy, at all assessments, improvements from baseline in both celecoxib groups were superior to that seen in the placebo group ($P < 0.05$). No significant differences in efficacy between the celecoxib groups were observed. The overall incidence of adverse events was similar in the 2 celecoxib treatment groups.

***Conclusions:*** Dosing regimens of celecoxib 200 mg QD and 100 mg BID are equally effective and well tolerated in patients with OA of the knee. The availability of 2 effective regimens provides patients and physicians with increased flexibility in the selection of an appropriate dosing regimen for celecoxib therapy.

***Key words:*** osteoarthritis, COX-2 inhibitor, celecoxib, dosing regimen, efficacy, tolerability. (*Clin Ther.* 2001;23:213–227)

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## INTRODUCTION

Nonsteroidal anti-inflammatory drugs (NSAIDs) have both analgesic and anti-inflammatory properties and are widely prescribed for the treatment of painful musculoskeletal conditions such as osteoarthritis (OA). Each year in the United States, ~60 million people are prescribed NSAIDs.[1–3]

Conventional NSAIDs act by inhibiting both isoforms of cyclooxygenase (COX-1 and COX-2), the key enzyme required for prostaglandin production from arachidonic acid. COX-1 is constitutively expressed in many tissues and has a homeostatic role in the gastrointestinal (GI) tract, the kidneys, and platelets.[4–7] In contrast, COX-2 is undetectable or expressed at very low levels in most healthy tissues, is inducible by pro-inflammatory stimuli, and is expressed at high levels at sites of inflammation.[4]

The COX-1/COX-2 inhibitory action of conventional NSAIDs is associated with mild to life-threatening GI adverse events.[8] Indeed, severe NSAID-associated GI complications are the most commonly reported serious adverse drug reactions and a major cause of death in patients with rheumatoid arthritis (RA).[9–11]

Unlike conventional NSAIDs, celecoxib,* the first of the new class of COX-2–specific inhibitors, inhibits prostaglandin synthesis by inhibiting COX-2 while having minimal effect on COX-1 at therapeutic concentrations.[12,13] Celecoxib, which has the anti-inflammatory and analgesic properties of conventional NSAIDs without the associated adverse effects on the upper GI mucosa or platelets, is approved for the treatment of the signs and symptoms of OA and RA.[14–16]

*Trademark: Celebrex® (Pharmacia Corporation, Skokie, Illinois).

Preliminary efficacy studies of celecoxib in patients with OA and RA were undertaken with doses ranging from 40 to 400 mg BID.[14–16] However, the relatively long half-life of celecoxib (~11 hours)[17] and data from preclinical studies that show highly stable binding of celecoxib to the COX-2 active site[18] suggest that a once-daily regimen of the same total daily dose might be as effective as a twice-daily regimen.[14]

Numerous studies have indicated that compliance, particularly in elderly patients, is related to the number of coprescribed medications, daily dosing frequency, patient education, and tolerability or efficacy.[19–21] Because elderly patients are more likely than younger patients to be receiving polypharmacy for concomitant illnesses, the option of once-daily dosing may help improve compliance in this patient population and provide increased dose flexibility.

The aim of this study was to compare the efficacy and tolerability of a celecoxib 200 mg QD regimen with a 100 mg BID regimen and placebo in the treatment of the signs and symptoms of OA of the knee.

## PATIENTS AND METHODS

### *Study Population*

Patients eligible for participation in this study were adults with a diagnosis of OA of the knee, as determined by the American College of Rheumatology clinical and radiographic criteria.[22,23] Eligible patients had a flare of OA of the knee and a Functional Capacity Classification of I, II, or III (I = good, IV = total or near incapacitation).[24]

Patients were excluded from participation if they had inflammatory arthritis, gout, or joint trauma at the knee in addition to OA; had received any oral, intramuscular, intra-articular, or soft-tissue in-

jection of corticosteroids within the 4 weeks before taking study medication; had taken any NSAID or analgesic agent (with the exception of aspirin ≤325 mg/d for conditions other than arthritis) within 48 hours of the baseline arthritis assessments; had an active GI, renal, hepatic, or coagulation disorder; had had esophageal or gastroduodenal ulceration within the previous 30 days; or had experienced NSAID hypersensitivity or any laboratory abnormalities considered by the investigator to be clinically significant within the previous 14 days. Women of childbearing age were excluded if they were pregnant or were not using adequate contraception. All patients provided written informed consent before entering the study.

### *Study Design*

This prospective, randomized, double-blind, placebo-controlled, parallel-group study was conducted at 98 clinical sites in the United States, in accordance with good clinical practice and the Declaration of Helsinki. An institutional review board at each site approved the study protocol.

At the screening visit, 2 to 14 days before the administration of the first dose of study medication, each prospective patient underwent a physical examination and laboratory tests. Assessments of OA disease severity, using the Patient's and Physician's Global Assessments of Arthritis, the Functional Capacity Classification, and the Lequesne Osteoarthritis Severity Index, were performed at screening, baseline, and weeks 2 and 6 of the 6-week treatment period. Additional laboratory tests and physical examinations were performed at each visit, with the exception of the week 2 visit, at which no physical examination was performed.

The Patient's and Physician's Global Assessments of Arthritis were both graded on a scale from 1 (very good) to 5 (very poor),[25] whereas the Functional Capacity Classification was graded on a scale of I (good) to IV (total or near incapacitation) according to Steinbrocker's criteria.[24] Patients with a Functional Capacity Classification score of IV were not eligible for participation. The Lequesne Osteoarthritis Severity Index was graded on a composite scale ranging from 0 to 24, with a lower score indicating a better condition.[26]

The following additional assessments were made: Patient's Assessment of Arthritis Pain–Visual Analog Scale (VAS) (at baseline and weeks 2 and 6), graded on a scale from 0 mm (no pain) to 100 mm (very severe pain), and the Western Ontario and McMaster Universities (WOMAC) Osteoarthritis Index (at baseline and week 6), which comprises 24 component items relating to pain (5 items), stiffness (2 items), and physical function (17 items), graded on a scale from 0 (good condition) to 96 (poor condition).[27]

After the screening procedures, patients were instructed to discontinue their current NSAID or analgesic (if applicable) and to notify the investigator when symptoms of a flare of OA began. All patients included in this study experienced an OA flare at the baseline visit (day 0, within 24 hours before the first dose of study medication). This visit occurred 2 to 14 days after screening for patients who had been receiving NSAIDs or analgesics, or 0 to 2 days after screening for those with poorly controlled OA who were not receiving treatment.

Patients were considered to have an OA flare if baseline scores on both the Patient's and Physician's Global Assessments of Arthritis indicated that their condition

was fair, poor, or very poor. Furthermore, baseline assessments had to meet the following criteria: Patient's Assessment of Arthritis Pain–VAS measurement of ≥40 mm; an increase of ≥2 points on the Lequesne Osteoarthritis Severity Index versus values at the screening visit; and an increase of ≥1 grade on the Patient's or Physician's Global Assessment of Arthritis versus values at the screening visit.

Patients with uncontrolled OA who were not receiving NSAIDs or analgesics before the study were considered to be experiencing an OA flare and therefore eligible for enrollment if they satisfied the following criteria: Patient's Assessment of Arthritis Pain–VAS measurement of ≥40 mm, a Lequesne Osteoarthritis Severity Index score of ≥7, and a score on the Patient's or Physician's Global Assessment of Arthritis of 4 (poor) or 5 (very poor).

Patients who satisfied the entry criteria were randomly assigned to receive celecoxib 100 mg BID, celecoxib 200 mg QD, or placebo for 6 weeks. The first dose was to be taken within 24 hours of the baseline visit. All regimens were masked and therefore unidentifiable to patients or study personnel. Patients assigned to receive celecoxib 100 mg BID took one 100-mg capsule with breakfast and a second with their evening meal. Patients assigned to celecoxib 200 mg QD took a placebo capsule with breakfast and a 200-mg capsule with their evening meal, and those assigned to placebo took a placebo capsule with both meals.

Follow-up visits took place at week 2 (day 14 ± 2 days) and week 6 (day 42 ± 4 days) after the first dose of study medication. The week 6 visit took place no later than 2 days after the last dose of study medication. All arthritis assessments performed at baseline were repeated at weeks 2 and 6, with the exception of the WOMAC Osteoarthritis Index (week 6 only). The clinical laboratory tests used at screening were also repeated at weeks 2 and 6, and a complete physical examination was performed at week 6.

Patients could have been discontinued from the study for preexisting violations of study entry criteria, noncompliance with the study protocol, or adverse events. Investigators could withdraw a patient at any time if his or her arthritic condition did not improve or worsened. Patients withdrawing prematurely from the study completed an early-termination visit at the time of withdrawal, at which they underwent all assessments scheduled for the week 6 visit.

The use of NSAIDs, oral or injectable corticosteroids, analgesics, or anticoagulants was prohibited during the study. Patients taking aspirin ≤325 mg/d for reasons other than arthritis, for ≥30 days before the first dose of study medication, were permitted to continue with the same dosing regimen. Patients were permitted to take up to 2 g/d of acetaminophen, for 3 consecutive days, for reasons other than relief of arthritis symptoms. However, acetaminophen must not have been taken within 48 hours before OA assessments were performed at any visit.

### *Statistical Analysis*

All randomized patients were included in the baseline analyses. Homogeneity of treatment groups with respect to sex and race was assessed using the Pearson chi-square test. Two-way analysis of variance (ANOVA) with treatment and center as factors was used to assess homogeneity with respect to age, height, weight, and duration of OA.

The sample size was calculated assuming that 20% of patients receiving placebo and 35% of those given active drug would indicate an improvement in the Patient's Global Assessment of Arthritis. Improvement was defined as a reduction of ≥2 grades from baseline grades of 3 to 5, or a reduction from grade 2 to grade 1. Based on this definition, a sample of 200 patients per group was deemed sufficient to detect this difference using a 2-sided test with a 0.025 level of significance and 80% power. It was also sufficient to detect a difference of 0.37 in mean change from baseline at this level with 90% power.

Baseline results of the Patient's and Physician's Global Assessments of Arthritis were analyzed using the Cochran-Mantel-Haenszel (CMH) test stratified by center. Baseline scores for the Patient's Assessment of Arthritis Pain–VAS, Lequesne Osteoarthritis Severity Index, and WOMAC Osteoarthritis Index were compared using a 2-way ANOVA with treatment and center as factors.

All efficacy analyses were based on the intent-to-treat (ITT) cohort, which included all patients who were enrolled and took ≥1 dose of study medication. All missing observations were extrapolated using the last-observation-carried-forward approach.

Results from the Patient's and Physician's Global Assessments of Arthritis at weeks 2 and 6 were analyzed using 2 approaches. First, mean changes from baseline were compared between treatment groups by analysis of covariance (ANCOVA) with treatment and center as factors and the corresponding baseline score as a covariate. Second, each patient's disease state was classified as improved (a reduction of ≥2 grades from baseline grades of 3 to 5 or a change in grade from 2 to 1), worsened (an increase of ≥2 grades from baseline grades of 1 to 3 or a change in grade from 4 to 5), or unchanged compared with baseline. The CMH test, adjusted for center, was used to analyze distributions among the 3 categories.

ANCOVA analysis with treatment and center as factors and the corresponding baseline score as a covariate was used to analyze the results of the Patient's Assessment of Arthritis Pain–VAS, the WOMAC Osteoarthritis Index, and the Lequesne Osteoarthritis Severity Index. This enabled a comparison of changes in mean values from baseline among treatment groups. The Fisher exact test was used to compare the incidences of withdrawal due to lack of arthritis efficacy among treatment groups. Every randomized patient receiving ≥1 dose of study drug was included in the safety assessment, which included a summary of incidences of patient-reported adverse events as well as laboratory and physical examination findings.

## RESULTS

### *Baseline Characteristics*

A total of 718 patients with OA of the knee were enrolled at 98 clinical sites in the United States. There were no significant differences in baseline demographic characteristics between the treatment groups ($P \geq 0.300$) (Table I).

According to the Patient's Global Assessment of Arthritis, 73% of patients described their arthritis condition as either poor or very poor at baseline (Table II). There were no significant differences between groups for any baseline arthritis measures ($P \geq 0.116$).

Of the 718 patients randomized, 549 (76%) completed the study. Fewer patients in the placebo group (164/244, 67%) com-

Table I. Demographic and clinical characteristics at baseline.*

| | Placebo (n = 244) | Celecoxib 100 mg BID (n = 243) | Celecoxib 200 mg QD (n = 231) |
|---|---|---|---|
| Sex, no. (%) | | | |
| Female | 178 (73) | 167 (69) | 159 (69) |
| Male | 66 (27) | 76 (31) | 72 (31) |
| Age, y, mean ± SD | 61.3 ± 11.6 | 62.0 ± 11.8 | 61.3 ± 12.2 |
| Osteoarthritis duration, y, mean ± SD | 9.7 ± 8.7 | 9.5 ± 8.7 | 9.4 ± 8.1 |
| Race, no. (%) | | | |
| White | 210 (86) | 210 (86) | 196 (85) |
| Black | 27 (11) | 27 (11) | 23 (10) |
| Hispanic | 6 (2) | 5 (2) | 11 (5) |
| Asian | 0 (0) | 0 (0) | 1 (<1) |
| Other | 1 (<1) | 1 (<1) | 0 (0) |
| Height, cm, mean ± SD | 166.6 ± 9.5 | 167.2 ± 9.6 | 167.9 ± 10.2 |
| Weight, kg, mean ± SD | 88.8 ± 20.0 | 90.7 ± 22.9 | 91.8 ± 22.4 |

*No significant differences were observed between treatment groups.

pleted the study than in either the celecoxib 100 mg BID (194/243, 80%) or celecoxib 200 mg QD (191/231, 83%) group.

Only 3 patients, 1 from the placebo group and 2 from the celecoxib 100 mg BID group, failed to take ≥1 dose of study medication. The remaining 715 patients were included in the ITT cohort used for efficacy and safety analyses.

### *Efficacy*

At week 2, the results from the Patient's Global Assessment of Arthritis revealed that significantly more patients ($P < 0.01$) experienced a reduction in the severity of arthritis symptoms in the celecoxib treatment groups (41% [99/241], 100 mg BID; 31% [71/231], 200 mg QD) than in the placebo group (23% [56/243]; Figure 1). A similar significant trend was observed at week 6 ($P < 0.05$), with improvement occurring in 37% [90/241], 38% [87/231], and 27% [65/243] of patients in the celecoxib 100 mg BID, celecoxib 200 mg QD, and placebo groups, respectively (Figure 1). More patients in the placebo group reported that their OA was worse compared with baseline than in either celecoxib group at week 2 (5% [11/243] vs 1% [5/472]) and week 6 (7% [18/243] vs 3% [14/472]). Furthermore, when analyzed in terms of mean change in score from baseline on the Patient's Global Assessment of Arthritis, both celecoxib regimens significantly reduced the severity of arthritis symptoms relative to placebo at weeks 2 and 6 ($P < 0.01$) (Table III). No significant difference was observed between the celecoxib treatment groups in the percentage of patients with alleviation of symptoms ($P \geq 0.479$) or in the mean change in severity score from baseline on the Patient's Global Assessment of Arthritis ($P \geq 0.963$) at either time point.

Table II. Baseline measures of arthritis severity for all randomized patients (N = 718).

| Measure* | Placebo (n = 244) | Celecoxib 100 mg BID (n = 243) | Celecoxib 200 mg QD (n = 231) | *P* |
|---|---|---|---|---|
| Patient's Global Assessment of Arthritis | | | | 0.570† |
| Good | 0 (0%) | 1 (<1%) | 0 (0%) | |
| Fair | 61 (25%) | 62 (26%) | 68 (29%) | |
| Poor | 153 (63%) | 157 (65%) | 140 (61%) | |
| Very poor | 30 (12%) | 23 (9%) | 23 (10%) | |
| Mean score ± SD | 3.9 ± 0.6 | 3.8 ± 0.6 | 3.8 ± 0.6 | |
| Physician's Global Assessment of Arthritis | | | | 0.187† |
| Good | 0 (0%) | 1 (<1%) | 0 (0%) | |
| Fair | 68 (28%) | 57 (24%) | 73 (32%) | |
| Poor | 156 (64%) | 172 (71%) | 145 (63%) | |
| Very poor | 20 (8%) | 12 (5%) | 13 (6%) | |
| Mean score ± SD | 3.8 ± 0.6 | 3.8 ± 0.5 | 3.7 ± 0.6 | |
| Patient's Assessment of Arthritis Pain–Visual Analog Scale, mean mm ± SD | 68.2 ± 16.5 | 67.5 ± 16.5 | 65.2 ± 16.4 | 0.116‡ |
| WOMAC Osteoarthritis Index, mean score ± SD | | | | |
| Pain | 10.5 ± 3.3 | 10.1 ± 3.3 | 10.1 ± 3.5 | 0.172‡ |
| Stiffness | 4.8 ± 1.4 | 4.5 ± 1.5 | 4.6 ± 1.4 | 0.232‡ |
| Physical function | 37.5 ± 11.2 | 36.3 ± 11.2 | 35.9 ± 11.9 | 0.280‡ |
| Composite score | 52.8 ± 15.1 | 51.0 ± 15.1 | 50.7 ± 16.0 | 0.223‡ |
| Lequesne Osteoarthritis Severity Index | 15.1 ± 3.5 | 15.1 ± 3.4 | 15.0 ± 3.3 | 0.958‡ |

WOMAC = Western Ontario and McMaster Universities.

*Patient's and Physician's Global Assessments of Arthritis scale (1 = very good to 5 = very poor); Patient's Assessment of Arthritis Pain–Visual Analog Scale (0 mm = no pain to 100 mm = very severe pain); WOMAC Osteoarthritis Index subscales (pain 0–20; stiffness 0–8; physical function 0–68) and composite score (0 = good condition and 96 = poor condition); Lequesne Osteoarthritis Severity Index (0–24, with higher scores indicating poorer condition).

†Cochran-Mantel-Haenszel test.

‡Two-way analysis of variance.

Similar results were obtained for the Physician's Global Assessment of Arthritis. Although there was no significant difference between the 2 celecoxib groups, at weeks 2 and 6, the proportion of patients receiving celecoxib who were classified as improved or who had lower mean scores relative to baseline was significantly greater compared with patients receiving placebo ($P < 0.05$) (Table III). There was no significant difference in the mean change in score from baseline ($P > 0.5$) between celecoxib treatment groups at week 2, but there was a significant difference between groups in the percentage of patients classified as having improved symptoms (39% [93/241] with 100 mg BID vs 29% [66/231] with 200 mg QD, $P = 0.032$).

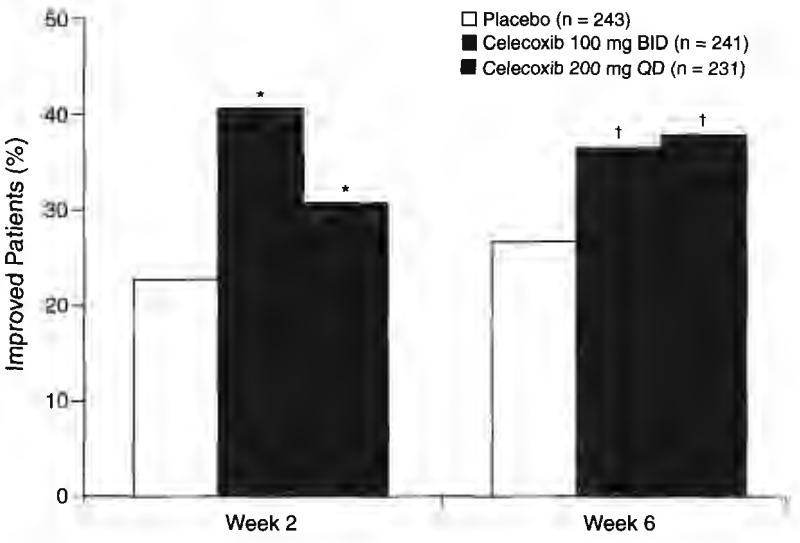


Figure 1. Patient's Global Assessment of Arthritis at weeks 2 and 6. On a scale of 1 (very good) to 5 (very poor), "improved" is defined as a reduction of ≥2 grades from baseline grades of 3 to 5 or a change in grade from 2 to 1. $^{*}P < 0.01$ versus placebo; $^{\dagger}P < 0.05$ versus placebo.

Both celecoxib regimens produced similar improvements in arthritis pain at weeks 2 and 6 as measured by the Patient's Assessment of Arthritis Pain–VAS (Figure 2). This improvement, measured as a change in mean VAS score from baseline, was significantly greater ($P \leq 0.01$) than that observed in the placebo group at both week 2 (difference of 22.5 with 100 mg BID, 21.1 with 200 mg QD, and 12.4 with placebo) and week 6 (21.2, 23.5, and 15.0, respectively). As with the other measures, the treatment effect was mainly achieved by week 2, with little or no further improvement occurring at week 6.

The WOMAC Osteoarthritis Index results are given in Figure 3 (individual measures) and Table III (composite score). At week 6, both celecoxib regimens led to amelioration of arthritis symptoms, as indicated by statistically significant decreases from baseline versus placebo in all 3 subscales ($P \leq 0.005$); there were no significant differences between celecoxib groups ($P \geq 0.276$) on any WOMAC subscale. The composite score showed similarly significant reductions relative to placebo for both celecoxib groups ($P \leq 0.001$). Significant improvements in symptom severity were demonstrated in both celecoxib groups compared with placebo at weeks 2 and 6, as indicated by a significant decrease in the Lequesne Osteoarthritis Severity Index ($P \leq 0.001$).

In total, 106 patients withdrew from the study due to a lack of treatment effect. Of these, 55 were in the placebo group, 27 in the celecoxib 100 mg BID group, and 24

Table III. Results of assessments of arthritis treatment efficacy.

| Measure* | Week 2 | | | Week 6 | | |
|---|---|---|---|---|---|---|
| | Placebo (n = 243) | Celecoxib 100 mg BID (n = 241) | Celecoxib 200 mg QD (n = 231) | Placebo (n = 243) | Celecoxib 100 mg BID (n = 241) | Celecoxib 200 mg QD (n = 231) |
| Patient's Global Assessment of Arthritis, mean score ± SD | 3.0 ± 0.06 | 2.7 ± 0.06† | 2.7 ± 0.06† | 3.0 ± 0.07 | 2.8 ± 0.06‡ | 2.6 ± 0.06† |
| Physician's Global Assessment of Arthritis | | | | | | |
| Improved, no. (%) | 47 (19) | 93 (39)† | 66 (29)‡ | 59 (24) | 84 (35)§ | 80 (35)‡ |
| Worsened, no. (%) | 8 (3) | 3 (1) | 1 (<1) | 12 (5) | 5 (2) | 0 (0) |
| Mean score ± SD | 3.0 ± 0.05 | 2.6 ± 0.05† | 2.7 ± 0.05† | 3.0 ± 0.06 | 2.7 ± 0.06‡ | 2.6 ± 0.06† |
| WOMAC Osteoarthritis Index composite score, mean ± SD | – | – | – | 44.0 ± 1.2 | 37.6 ± 1.3† | 37.0 ± 1.3† |
| Lequesne Osteoarthritis Severity Index, mean ± SD | 13.0 ± 0.3 | 11.3 ± 0.3† | 11.5 ± 0.3† | 12.8 ± 0.3 | 11.5 ± 0.3† | 11.5 ± 0.3† |
| Withdrawal due to treatment failure or adverse events, no. (%) | – | – | – | 67 (28) | 36 (15)‡ | 30 (13)‡ |

WOMAC = Western Ontario and McMaster Universities.

*Patient's and Physician's Global Assessments of Arthritis scale (1 = very good to 5 = very poor); WOMAC Osteoarthritis Index composite score (0 = good condition and 96 = poor condition); Lequesne Osteoarthritis Severity Index (0–24, with higher scores indicating poorer condition).

†$P \leq 0.001$ versus placebo.

‡$P < 0.01$.

§$P < 0.05$.

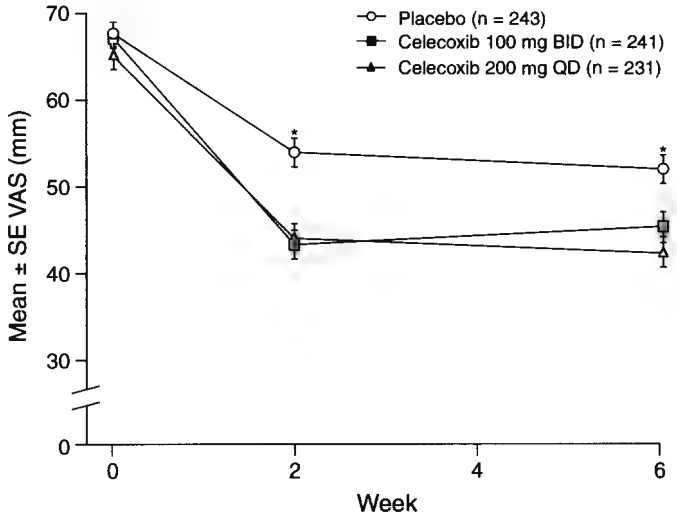


Figure 2. Patient's Assessment of Arthritis Pain–Visual Analog Scale (VAS) at weeks 2 and 6. Scale ranges from 0 mm (no pain) to 100 mm (very severe pain). $^{*}P \leq 0.01$ for both doses of celecoxib versus placebo.

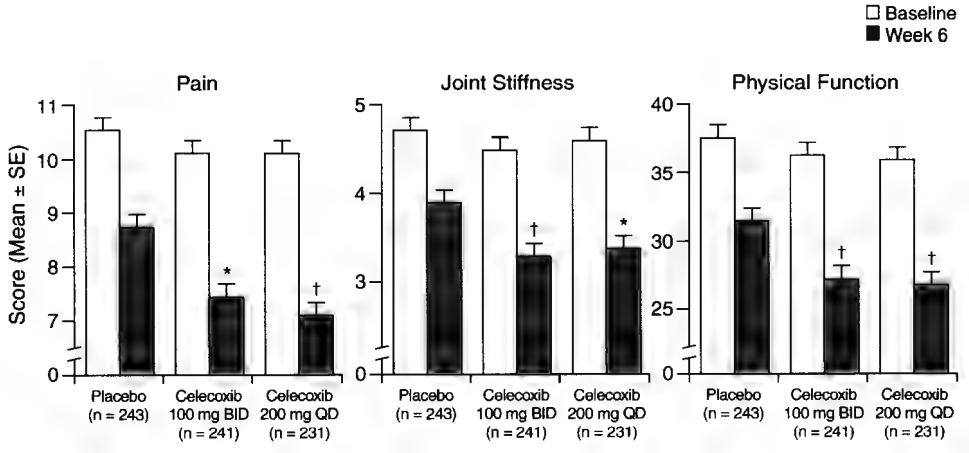


Figure 3. Scores on the subscales of the Western Ontario and McMaster Universities Osteoarthritis Index at baseline and week 6. Scales are from 0 to 20 for pain, 0 to 8 for joint stiffness, and 0 to 68 for physical function. $^{*}P \leq 0.005$ versus placebo; $^{\dagger}P \leq 0.001$ versus placebo.

Table IV. Incidence* of adverse events.

| | Placebo (n = 243) | Celecoxib 100 mg BID (n = 241) | Celecoxib 200 mg QD (n = 231) |
|---|---|---|---|
| Adverse events | | | |
| Total | 116 (48) | 119 (49) | 124 (54) |
| Causing withdrawal | 12 (5) | 9 (4) | 6 (3) |
| Most common adverse events† | | | |
| Headache | 42 (17) | 39 (16) | 39 (17) |
| Upper respiratory tract infection | 12 (5) | 17 (7) | 17 (7) |
| Dyspepsia | 12 (5) | 15 (6) | 9 (4) |
| Sinusitis | 6 (2) | 13 (5) | 8 (3) |
| Diarrhea | 3 (1) | 12 (5) | 7 (3) |
| Gastrointestinal adverse events | | | |
| Total | 34 (14) | 49 (20) | 34 (15) |
| Causing withdrawal | 3 (1) | 3 (1) | 0 (0) |

*Reported as number (%) of patients experiencing the adverse event.
†Includes all events with an incidence ≥5% in any treatment group.

in the 200 mg QD group. The difference in withdrawal rates between the 2 celecoxib groups and the placebo group was significant ($P < 0.001$). The time to withdrawal due to lack of effect or adverse events was significantly different in the celecoxib groups versus the placebo group ($P < 0.001$). Similarly, significantly fewer patients withdrew due to a combination of treatment failure and adverse events in the celecoxib 100 mg BID and 200 mg QD groups (36/241 [15%] and 30/231 [13%], respectively) relative to the placebo group (67/243 [28%], $P \leq 0.001$) (Table III). No significant difference in the incidence of withdrawal due to treatment failure and adverse events was observed between celecoxib treatment groups ($P = 0.596$).

### *Tolerability*

The overall incidence of adverse events was similar among the treatment groups (Table IV). Fifty percent (359/715) of the patients reported ≥1 adverse event during the study (48% [116/243] with placebo, 49% [119/241] with 100 mg BID, 54% [124/231] with 200 mg QD). More than 85% of adverse events were either mild or moderate in severity (ie, they did not result in an inability to carry out normal activities). Headache was the most frequently reported adverse event in all 3 groups (16%–17%). Although more patients receiving placebo withdrew (12/243 [5%]) than in either celecoxib group (9/241 [4%] with 100 mg BID, 3/231 [1%] with 200 mg QD), this difference was not statistically significant ($P \geq 0.232$).

GI adverse events, which consisted predominantly of dyspepsia and diarrhea, were generally mild to moderate in severity and were evenly distributed among all groups (14% [34/243] with placebo; 20% [49/241] with celecoxib 100 mg BID; 15% [34/231] with celecoxib 200 mg QD).

None of these events was considered serious or clinically significant (ie, upper GI bleeding, perforation, or obstruction).

Three patients reported serious adverse events, 1 in the placebo group (bullous eruption and facial edema) and 2 in the celecoxib 200 mg QD group. One patient in the celecoxib 200 mg QD group developed a lesion on her back that was subsequently diagnosed as a basal cell carcinoma. She was successfully treated by excision biopsy and went on to complete the study. The second patient, who had a history of asthma, diabetes mellitus, and obesity, died as a result of arteriosclerotic cardiovascular disease. Neither event was considered by the investigator to be related to the study drug.

There were no consistent differences in mean laboratory test values between the treatment groups. No more than 3% of patients in any group were reported to have abnormal laboratory test results, and none of these patients' laboratory abnormalities were considered clinically significant.

## DISCUSSION

This 6-week study in a representative population of patients with OA of the knee demonstrates that 2 regimens of the COX-2–specific inhibitor celecoxib (200 mg QD and 100 mg BID) have efficacy and safety profiles that are essentially indistinguishable.[28]

The determination of a drug's dosing regimen is usually based on pharmacokinetic parameters such as serum half-life, tissue distribution, and local concentrations at sites of action. However, pharmacodynamic factors, such as affinity and binding kinetics, may also play an important role in determining the optimal dosing interval. In addition to its relatively long half-life (~11 hours), celecoxib has been shown to demonstrate partially irreversible binding to COX-2 in preclinical studies.[18] This implies that celecoxib may have a duration of action that is longer than might be predicted by its pharmacokinetic profile and suggests the potential efficacy of a once-daily regimen, a suggestion fully supported by the present study.

The efficacy of celecoxib 100 mg BID in treating OA has already been established.[14,15] However, the ability to administer 200 mg/d in a single dose without loss of efficacy or tolerability would afford the physician the dosing flexibility necessary to treat individual patients according to their needs. This added flexibility is of particular importance for elderly patients, for whom compliance issues are often significant.

In the present study, the equivalent efficacy of the twice-daily and once-daily celecoxib regimens was confirmed by improvements in both the Patient's and Physician's Global Assessments of Arthritis. Despite the stringent nature of these assessments, both celecoxib regimens significantly reduced the severity of OA symptoms in terms of mean change in score from baseline ($P \leq 0.01$) and a favorable shift in the distribution of worsened/improved patients ($P < 0.05$) relative to placebo at weeks 2 and 6. By week 6, 36% of all patients receiving celecoxib were classified as improved in both assessments. Furthermore, both celecoxib treatments significantly ($P \leq 0.01$) reduced the severity of OA symptoms according to all other assessments at weeks 2 and 6. The comparability of the twice-daily and once-daily celecoxib regimens was further highlighted by the low rates of withdrawal due to treatment failure (<11% in each celecoxib group vs 23% in the placebo group).

There were no significant differences in efficacy measures between the 2 treatment regimens, with the exception of the Physician's Global Assessment of Arthritis at week 2, in which a higher percentage of patients reported improvement in the 100 mg BID group ($P = 0.032$). It is important to note that the time between the last dose of celecoxib and the arthritis assessments was much greater for the celecoxib 200 mg QD group (12–24 hours) than for the celecoxib 100 mg BID group (3–4 hours), yet comparable efficacy was still observed.

These efficacy results are similar to those of a previous multicenter study in which celecoxib 200 mg QD and 100 mg BID were compared with placebo in 686 patients with OA of the knee in a flare state.[29]

In the present study celecoxib 200 mg QD and 100 mg BID were equally well tolerated. The overall incidence of adverse events and the incidence of withdrawal due to adverse events in the celecoxib groups were similar to those in the placebo group. Furthermore, there was no significant difference in the incidence of GI adverse events between the celecoxib groups and the placebo group. The comparable tolerability of the 2 celecoxib regimens in patients with OA supports the results of a previous clinical study of 200 mg QD versus 100 mg BID dosing[29] and a second study with celecoxib dosages up to 200 mg BID.[30]

Whether the anti-inflammatory and analgesic effects of celecoxib are sustained over longer treatment periods remains to be addressed. However, previous studies with various celecoxib regimens (including 100 mg BID) have shown that the maximum analgesic or anti-inflammatory effect is reached within 2 weeks in arthritis patients.[15,16,30] Similarly, in the present study, optimum efficacy was reached at 2 weeks, with little or no change at 6 weeks. Moreover, previous studies have also shown that once the maximum benefit has been achieved it is sustained for ≥3 months.[15,16,30] Therefore, it would be expected that the benefits of celecoxib 200 mg QD would be sustained over longer periods.

## CONCLUSIONS

The results of this 6-week study suggest that 200 mg QD and 100 mg BID regimens of the COX-2 inhibitor celecoxib are equally well tolerated and effective in treating the signs and symptoms of OA, thereby providing flexibility to both patients and physicians in choosing a celecoxib dosing regimen.

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