Treatment of Osteoarthritis with Continuous Versus Intermittent Celecoxib

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ABSTRACT. ***Objective.*** To determine whether "continuous" celecoxib is more efficacious than "intermittent" use in preventing osteoarthritis (OA) flares of the knee and/or hip.

Methods. A double-blind, randomized, multicenter international study comparing efficacy and safety of continuous (daily) versus intermittent (as required during predefined OA flare) celecoxib 200 mg/day in 858 subjects, aged 18–80 years. The study consisted of 3 periods: (I) screening/washout visit; (II) open-label run-in with celecoxib; and (III) 22-week blinded treatment. Only subjects whose OA flares resolved in Period 2 (without subsequent flare) were randomized. The primary endpoint, number of flares per time of exposure during Period III (number of flares per month), was compared using analysis of variance with treatment as the independent variable. Acetaminophen was available as rescue medication.

Results. Of 875 subjects randomized to treatment, 858 subjects received treatment. At randomization > 70% were female; mean age 58.6 years; mean disease duration 6.5 years; total Western Ontario and McMaster Universities Osteoarthritis Index mean score 25.8; ~45% had hypertension; and ~20% were using aspirin (for cardiovascular prophylaxis). Subjects receiving continuous treatment reported 42% fewer OA flares/month than intermittent users ($p < 0.0001$) or 2.0 fewer OA flares over 22 weeks. Statistical and clinically meaningful benefits in secondary outcomes were also evident with continuous treatment. There were no differences in adverse events (AE) or new-onset/aggravated hypertension.

Conclusion. Continuous treatment with celecoxib 200 mg/day was significantly more efficacious than intermittent use in preventing OA flares of the hip and knee, without an increase in overall AE, including gastrointestinal disorders and hypertension, during 22 weeks of treatment. ClinicalTrials.gov identifier NCT00139776. (J Rheumatol First Release Nov 1 2011; doi:10.3899/jrheum.110636)

Key Indexing Terms:
COX-2 SELECTIVE NONSTEROIDAL ANTIINFLAMMATORY DRUGS CONTINUOUS
INTERMITTENT OSTEOARTHRITIS FLARE

Osteoarthritis (OA) is the most common form of arthritis[1] and is a painful and progressively debilitating condition characterized by "waxing and waning" symptoms. The amount of damage to the joints and severity of OA symptoms varies from person to person[2] and, although the majority of the 27 million people in the United States who have symptomatic OA[3] will have radiographic evidence of OA on or before 65 years of age[4,5,6,7], not all will have pain.

Some subjects with OA may experience asymptomatic periods, alternating with flares, while others demonstrate more continuous symptoms. Varying in length and severity, flares of OA may be unpredictable or occur following changes in activities of daily living, including exercise, stress, overexertion, treatment, and/or surgery[8]. Disease flares can negatively affect subjects' physical function and health-related quality of life ("multidimensional function")[9]; over time, with progressive disease, subjects report significant work disability, reduced ability to engage in activities at home, and limitations in participating in social and family activities. With an increasing burden of OA[6], safer and more efficacious treatments may lessen the influence of OA on society.

Although simple analgesics (i.e., acetaminophen) may be

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the first choice for symptomatic relief of OA[10,11,12], efficacy is variable and frequently short-lived. Ultimately, a majority of subjects will require other more efficacious treatments to control disease symptoms and flares, such as nonselective nonsteroidal antiinflammatory drugs (nsNSAID) and cyclooxygenase-2 selective NSAID (COX-2), either alone or in combination with nonpharmacologic therapies[13,14,15].

Concerns over cardiovascular (CV) and gastrointestinal (GI) adverse effects of nsNSAID and COX-2 selective therapy have led to the perception that intermittent therapy is generally a safer option. However, such use may result in subtherapeutic drug levels and preclude a durable symptomatic benefit in some patients. Therefore, in some subjects continuous daily treatment may offer more benefit. COX-2 selective therapy may be preferred to nsNSAID in some subjects, because of a more favorable GI tolerability profile[16,17,18,19,20,21,22]. In addition, many subjects with OA also require low-dose aspirin for its cardioprotective effects[23] and nsNSAID are generally not recommended with concomitant aspirin.

One previous 24-week pilot study (n = 123) found no significant clinical benefit with continuous versus intermittent treatment with celecoxib in OA[24]. While there was a consistent trend supporting the benefits of continuous treatment, only the percentage of days taking flare medication, a secondary endpoint, was significantly lower in the continuous versus intermittent treatment group. To better understand these results, we conducted a randomized controlled trial in 875 subjects to examine whether continuous celecoxib was more efficacious in preventing OA flares than intermittent celecoxib use.

MATERIALS AND METHODS

Subjects. Candidates for enrollment were aged 18 to 80 years with symptomatic OA of the hip/knee (according to American College of Rheumatology criteria[25]) and requiring NSAID treatment to control symptoms in the month preceding screening. Subjects had to demonstrate a screening flare of the index joint within 14 days of NSAID discontinuation (similar to a traditional flare-design study) and subsequent flare resolution during the open-label run-in period without flare recurrence (thus an enrichment design).

Major exclusion criteria included other etiologies for joint symptoms; any arthroscopic procedure or lavage, surgical, or other invasive procedure to the index knee or hip within 6 months before screening; use of oral corticosteroids within 4 weeks of screening; intraarticular injection of corticosteroids within 3 months of screening; and use of inhaled steroids > 2 g/day. Anticoagulant/antiplatelet agents other than aspirin ≤ 325 mg/day and lithium were also prohibited. Subjects were excluded if they had known sensitivities to acetaminophen/paracetamol, sulfonamides, aspirin, nsNSAID, or COX-2 selective NSAID; history of GI complications or active GI disease; renal, CV, or hepatic disease; uncontrolled hypertension (systolic blood pressure > 160 mm Hg and/or diastolic blood pressure > 95 mm Hg, at baseline visit); or body mass index ≥ 40 mg/kg^2.

The study was conducted between July 2005 and February 2008 and was approved by the applicable institutional review boards and performed in accord with Good Clinical Practice guidelines and the Declaration of Helsinki. All subjects provided written informed consent prior to enrollment. ClinicalTrials.gov identifier NCT00139776.

Study design. This was a double-blind, parallel-group, multicenter, international, randomized trial comparing the efficacy and safety of continuous versus intermittent use of celecoxib 200 mg daily in subjects with OA of the knee or hip. Occurrence and resolution of OA flares were based on specific criteria, noted below; subjects reported scores by telephone using an Interactive Voice Response System (IVRS). The trial consisted of 3 periods as follows (Figure 1).

Period I (14 ± 2 days): screening (Visit 1) and washout period during which discontinuation of NSAID treatment resulted in a documented OA flare. Subjects with an OA flare of the index joint within 14 days of NSAID discontinuation were allowed to enter Period II. An OA flare was demonstrated if subjects reported a score ≥ 4 but < 9 on the pain numeric rating score (NRS) and an increase ≥ 1 grade on the patient global assessment (PGA) of arthritis to "fair, poor, or very poor" between screening (Visit 1) and flare (Visit 2), and a score of "fair, poor, or very poor" on the physician global assessment of arthritis (MDGA) at Visit 2; all criteria had to be met for demonstration of a screening OA flare during Period I.

Period II (14 ± 2 days): included the visit when an OA flare was documented (Visit 2; flare). Only subjects in whom open-label run-in treatment with celecoxib 200 mg daily resulted in resolution of the screening OA flare, without additional flares, were eligible to enter double-blind treatment (Period III). Resolution of the OA flare was demonstrated if subjects reported scores < 4 on the pain NRS, and a ≥ 1-grade decrease on the PGA to "good or very good," and MDGA scores of "good or very good" at Visit 3. Recurrence of an OA flare was demonstrated if a subject reported a score ≥ 4 but < 9 on the pain NRS with a ≥ 1-grade increase on the PGA compared with Visit 1 (screening). Subjects with resolution of the screening OA flare with a subsequent recurrence of flare during Period II were not eligible to enter Period III. Use of rescue medication (acetaminophen/paracetamol) was not permitted during the run-in period.

Period III: included randomization (Visit 3) followed by double-blind treatment for 22 weeks, during which efficacy was evaluated, including recording of all OA flares. An OA flare was demonstrated if subjects reported a flare of the index joint ≥ 4 but < 9 on the pain NRS with a ≥ 1-grade increase on the PGA from Visit 3 (randomization) or use of rescue medication for > 2 consecutive days or > 2000 mg in a 24-hour period. Resolution of an OA flare was confirmed when subjects reported < 4 on the pain NRS and either no change or ≥ 1-grade decrease on the PGA from Visit 3. Use of acetaminophen/paracetamol was permitted, except within 12 hours of a scheduled visit.

Study treatment. Eligible subjects were randomly assigned by IVRS, using a computer-generated randomization schedule (permuted-block method stratified by study site), 1:1 to receive daily celecoxib 200 mg either (1) continuously, irrespective of whether they had a flare (i.e., continuous treatment) or (2) intermittently during periods of flare only (i.e., intermittent treatment). All subjects received 2 bottles containing capsules identical in appearance: Bottle A (to be taken each morning) and Bottle B [to be taken each morning only during an OA flare day(s)]. Those randomized to continuous treatment received Bottle A containing celecoxib capsules and Bottle B containing placebo; those randomized to intermittent use received Bottle A containing placebo and Bottle B containing celecoxib.

If a subject thought they were experiencing OA flare they were to report this by IVRS; if confirmed, they were instructed to take 1 capsule from Bottle B immediately and continue to do so on subsequent flare days, in addition to daily medication from Bottle A. Subjects were to report by IVRS when the flare resolved, and once confirmed, were to discontinue use of Bottle B, while continuing daily medication from Bottle A. Only flares that lasted ≥ 24 hours were included in the analysis.

Efficacy analysis. All efficacy assessments were performed during Period III. The primary outcome was the number of OA flares for each subject per time of exposure in Period III (mean number of flares per month).

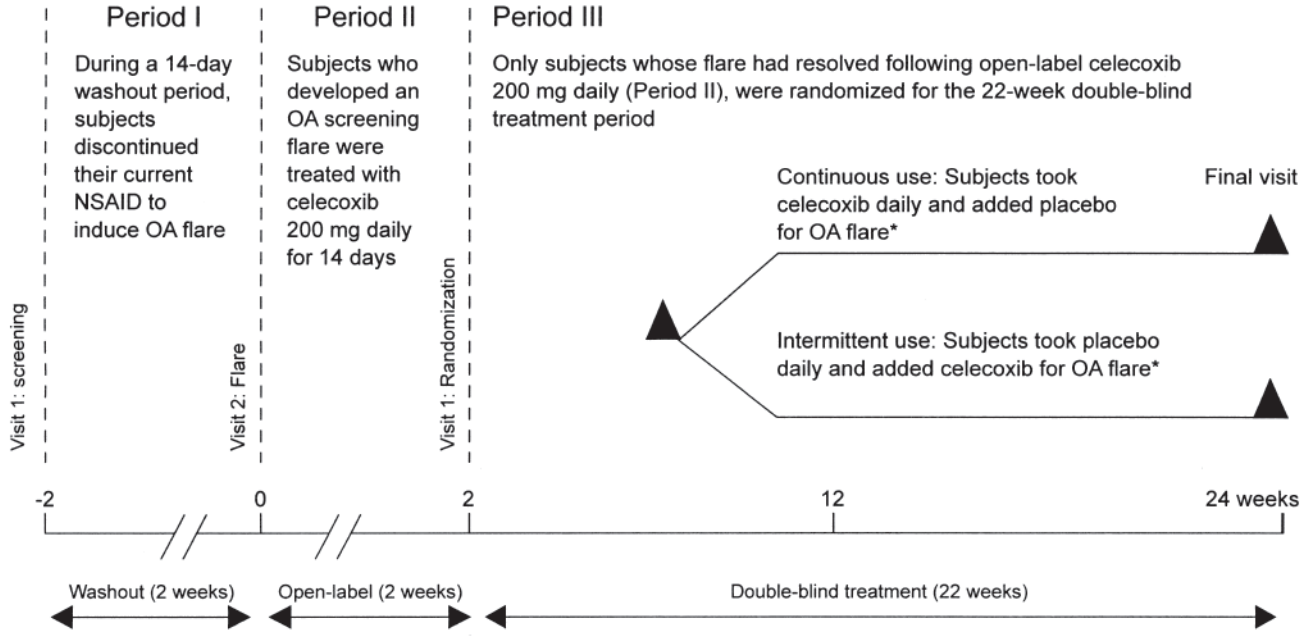

Figure 1. Study design. *Flare determined by study assessment of pain ≥ 4 to < 9 on Patient's Assessment of Arthritis Pain numerical rating scale (0—10 categorical pain scale) with an increase of ≥ 1 grade(s), or use of acetaminophen for pain > 2 days, or > 2000 mg acetaminophen use for pain in a 24-hour period. NSAID: nonsteroidal antiinflammatory drug; OA: osteoarthritis.

Secondary outcomes included Patient Assessment of Arthritis Pain NRS (scored 0, best, to 10, worst); PGA (1, very good, to 5, very poor); MDGA (1, very good, to 5, very poor); time in days from first dose of study medication in Period III to first OA flare; proportion of days subjects were free of OA flare; total amount of rescue medication taken; number of days on rescue medication; the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC; the total, pain, stiffness, and physical function subscores); and the Medical Outcomes SF-12 Health Survey (SF-12) as a health-related quality of life measure.

Using IVRS, subjects completed the pain NRS and PGA at about the same time each day, including 2 hours prior to randomization visit and then at all office visits (every 4 weeks from postflare visit to Week 4–24), and at post-flare visit (Weeks 3, 5, 6, 7, 9, 10, 11, 13, 14, 15, 17, 18, 19, 21, 22, and 23), in addition to reporting onset and resolution of OA flares. MDGA scores were assessed at Visit 1 (screening) and each monthly office visit. Subjects completed the WOMAC questionnaire prior to each scheduled office visit, and at onset and resolution of OA flares. IVRS data and information gathered from subjects during office visits (including subject's diary information) were used to assess all remaining secondary endpoints.

Safety evaluations, including physical examinations, laboratory tests, and monitoring of vital signs and adverse events (AE), were undertaken at each visit in Period II through to the end of Period III. Only those reported during Period III (blinded treatment) are presented.

Statistical analysis. It was estimated that 812 randomized subjects (406 per treatment arm) would provide at least 80% power to detect an effect size of 0.2 in terms of OA flares using a 2-sided t test with a 0.05 significance level. The last observation carried forward (LOCF) approach was used to impute missing data for pain NRS, PGA, MDGA, and WOMAC.

Prespecified primary and secondary efficacy analyses were conducted in the intent-to-treat (ITT), flare-modified ITT, and evaluable populations. The ITT population included all randomized subjects who received at least 1 dose of study medication during Period III; the flare-modified ITT population consisted of all ITT subjects with OA flares ≤ 14 ± 2 days' duration. The evaluable population included all ITT subjects with ≥ 80% compliance with daily medication, who had missed < 2 scheduled IVRS calls in any month during Period III or for ≤ 2 months during the study, had not missed any scheduled monthly visits, and had no major protocol violations. The flare-modified ITT population was designed to exclude subjects in whom prolonged OA flares may have reflected disease progression rather than spontaneous exacerbations.

The primary efficacy analyses used ANOVA with treatment as an independent variable. For secondary endpoints, area under the curve (AUC) was calculated for pain NRS and PGA, using analysis of covariance (ANCOVA) with treatment and baseline (randomization visit) values as covariates. MDGA was analyzed with a Cochran-Mantel-Haenszel test using modified rank-order statistic scores. Time to occurrence of first OA flare was analyzed using Kaplan-Meier methods. All other secondary efficacy endpoints used ANOVA. WOMAC scores were analyzed as change in WOMAC total, pain, stiffness, and physical function subscores from randomization to final visit (Visit 9).

For safety evaluations, only subjects who received ≥ 1 dose of study medication in Period III were included in the analyses.

RESULTS

Baseline demographics and characteristics. A total of 106/142 investigational centers across North and South America and Europe treated ≥ 1 subject during Period III. Of 875 subjects who entered Period III, 858 received treatment; 676 completed the study. One hundred eighty-two subjects (21.2%) discontinued (Figure 2) primarily for reasons unrelated to study medication. Twenty-four subjects (5.6%) in the intermittent group discontinued because of a lack of efficacy compared to 10 subjects (2.3%) in the continuous group. Similarly, 21 subjects (4.9%) in the intermittent group withdrew consent compared to 16 (3.7%) subjects in the continuous group.

Baseline demographics and clinical characteristics were similar in both treatment groups (Table 1). About 4 times more subjects presented with OA of the knee (81.7% and

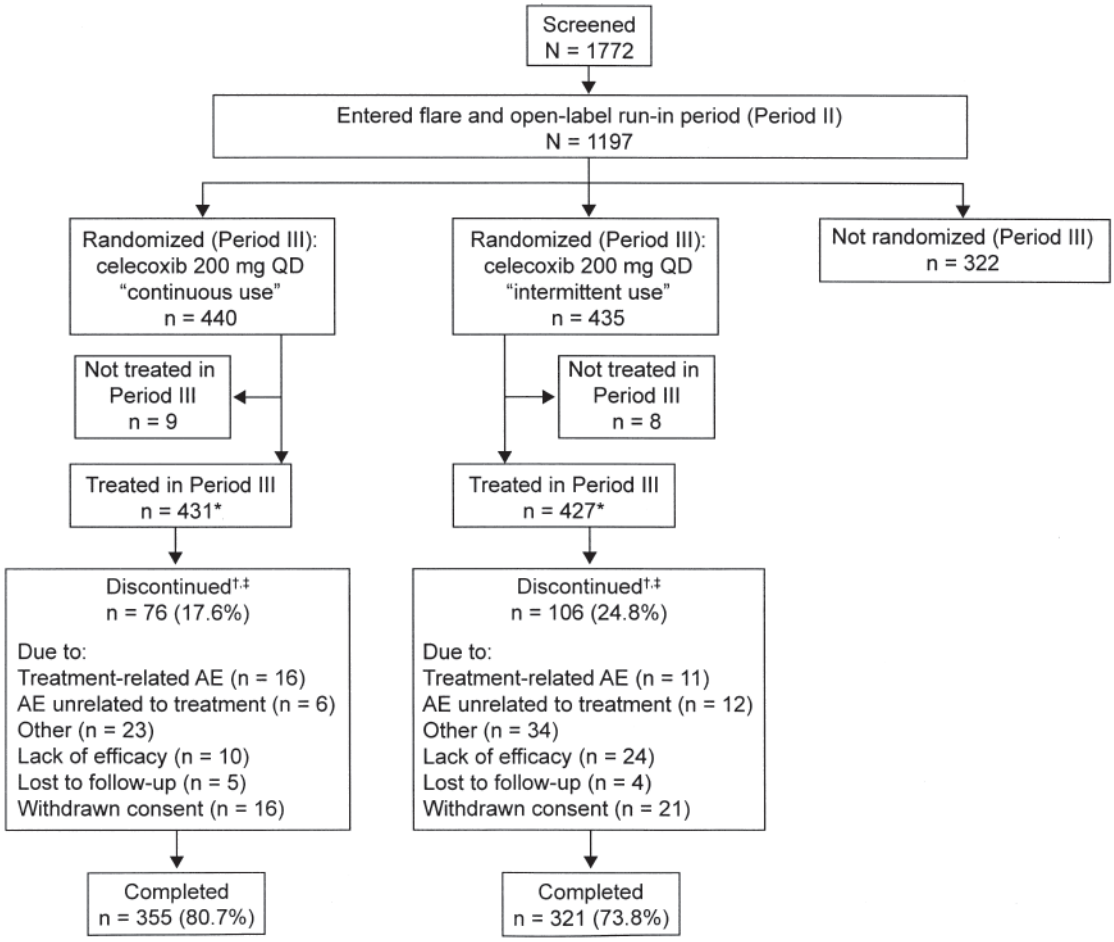

Figure 2. Disposition of subjects. *Subjects comprised both the safety and ITT populations. †Discontinuations that occurred 30 days after last dose of study medication were attributed to the last study treatment received. ‡Data for discontinuations presented here exclude 1 subject (described in text) who was discontinued due to an unconfirmed report of an adverse event (AE). Percentages were based on the number of subjects treated during Period III. QD: daily.

78.9%) than hip (18.3% and 21.1%); 44.8% and 45.2% had hypertension at randomization, and 18.6% and 19.9% of subjects were receiving low-dose aspirin for CV prophylaxis, in the continuous and intermittent use treatment groups, respectively.

Efficacy results: primary outcomes. Subjects receiving continuous celecoxib reported a 42% reduction in number of OA flares/month (or 2.0 fewer flares) over 22 weeks compared with those receiving intermittent treatment (0.54 vs 0.93 mean flares/mo, respectively; $p < 0.0001$; ITT population). A reduction in number of OA flares/month was also observed in the flare-modified ITT population and the evaluable population; subjects receiving continuous treatment reported 1.7 and 2.3 fewer flares over 22 weeks than those receiving intermittent treatment, respectively ($p < 0.0001$).

Figures 3A and 3B show scatterplot diagrams of the number of flares experienced by individual subjects in the continuous and intermittent groups, respectively. There were more subjects with an increased number of the flares, represented by the increased scatter, in the intermittent group than in the continuous group, demonstrated by the higher spread of data points.

Efficacy results: secondary outcomes. Subjects receiving continuous versus intermittent treatment reported significant improvements by pain NRS during Period III (ITT population: least-squares mean AUC; $p = 0.047$). A separate posthoc ANCOVA analysis for pain NRS demonstrated significant improvements with continuous use at all scheduled clinic visits over 22 weeks. Subjects receiving continuous treatment reported numerically lower (improved) global arthritis scores by PGA (using AUC) at all timepoints (statistically significant at Weeks 4 and 8; ITT population; $p < 0.01$).

The majority of subjects in each treatment group reported a score of "fair" or "good" by MDGA at visits during Period III. At the final visit, 16.0% of subjects in the continuous group reported their overall OA symptoms to be "very good" compared with 9.2% in the intermittent group (ITT population; $p = 0.0046$).

Median time to occurrence of first OA flare was longer in continuous versus intermittent use subjects (16 vs 8 days,

Table 1. Subject demographics and characteristics at randomization visit (Visit 3).

	"Continuous" Use Celecoxib 200 mg QD*, n = 431	"Intermittent" Use Celecoxib 200 mg QD*, n = 427	p
Female, n (%)	317 (73.5)	303 (71.0)	NS
Age, yrs, mean ± SD (range)	58.5 ± 10.0 (24–80)	58.7 ± 9.6 (29–80)	NS
Race, white, n (%)	338 (78.4)	333 (78.0)	NS
Weight, kg, mean ± SD	83.4 ± 19.0	83.7 ± 19.6	NS
Body mass index, n (%)			
< 30 kg/m^2	209 (48.5)	205 (48.0)	NS
≥ 30 kg/m^2	222 (51.5)	222 (52.0)	NS
Duration of OA, yrs, mean ± SD (range)	6.3 ± 6.4 (0–36)	6.8 ± 6.8 (0–47)	NS
Total WOMAC score, mean ± SD (range)	25.3 ± 14.8 (0–71)	26.3 ± 14.0 (0–72)	0.331
Localization of OA, n (%)			
Hip	79 (18.3)	90 (21.1)	—
Knee	352 (81.7)	337 (78.9)	—
Hypertension†, n (%)	193 (44.8)	193 (45.2)	—
Low-dose aspirin use, n (%)††	80 (18.6)	95 (19.9)	—

* Subjects took flare medication (Bottle B) during a flare only. † Defined posthoc as having SBP ≥ 140 mm Hg and DBP ≥ 90 mm Hg documented at randomization visit (Visit 3); and/or diagnosis of hypertension; and/or receiving antihypertensive therapy in this analysis. †† ≤ 325 mg daily for cardiovascular prophylaxis; during the double-blind treatment period (Period III), 19.5% of subjects in the "continuous" group and 20.6% of subjects in the "intermittent" group took concomitant aspirin. QD: daily; NS: nonsignificant; WOMAC: Western Ontario and McMaster Universities OA score; SBP: systolic blood pressure; DBP: diastolic blood pressure.

respectively; $p < 0.0001$). In addition, 22.9% of subjects in continuous versus 10.6% of subjects in intermittent treatment groups reported they were flare-free during double-blind treatment in Period III ($p < 0.01$). Continuous use subjects also reported a significantly greater proportion of flare-free days [ITT population, 0.77 vs 0.67 days, respectively, ($p < 0.0001$) or 15.4 more flare-free days over 22 weeks].

Subjects receiving continuous treatment required less rescue medication than those receiving intermittent therapy (mean total rescue medication taken by patient per month 1566 vs 2428 mg/subject/month, respectively; $p = 0.0102$). The mean proportion of days on rescue medication was 0.044 versus 0.069 days, respectively ($p = 0.0012$), resulting in subjects on continuous treatment taking rescue medication for ~3.9 fewer days than the intermittent treatment group over the 22-week period. Although total WOMAC and subscores were comparable at randomization (Visit 3), mean (least-square) increases (worsening) in WOMAC total scores during double-blind treatment were significantly less in subjects receiving continuous than in those receiving intermittent treatment (1.60 vs 4.99, respectively; $p < 0.001$; Table 2). Reported increases in pain, stiffness, and physical function subscores were significantly less with continuous treatment ($p < 0.01$). Of interest, in the flare-modified ITT population, deteriorations in total WOMAC and the physical function subscore, from randomization to final visit, were not observed with continuous treatment (the pain subscore showed minimal change: 0.04), whereas in subjects receiving intermittent therapy, there were significant deteriorations in total WOMAC (3.22; 95% CI 1.53–4.91) and physical function (2.18; 95% CI 0.96–3.40) subscores. All results in the evaluable population were similar to those observed in the ITT population.

In a posthoc analysis, subjects were stratified by whether they had < 2 or ≥ 2 flares. These groups were correlated with WOMAC and the SF-12 scores. These data demonstrated that subjects with < 2 flares had statistically important differences in their WOMAC (total and subscores) and SF-12 scores (bodily pain, vitality, and physical component summary scale domains; Figures 4A, 4B). These data suggest subjects had worsening functional outcomes over the duration of 22 weeks if they had ≥ 2 flares.

Health-related quality of life measured by the SF-12 supports the differences observed in WOMAC scores. As shown in Figure 4B, SF-12 scores demonstrate a significant difference between those subjects with < 2 flares for physical component summary scores, as well as for the bodily pain and vitality domains, compared to those subjects with ≥ 2 flares.

Safety results. Serious adverse events and discontinuations were comparable between treatment groups. Discontinuations due to AE occurred in 5.1% of subjects in the continuous group and 5.6% in the intermittent group. Of these, GI-related AE, including abdominal pain, dyspepsia, and nausea, most commonly led to discontinuation in both groups. Serious AE were reported in 6 (1.4%) continuous use and 10 (2.3%) intermittent use subjects. No deaths were reported.

Overall, the frequency of AE during Period III was similar in both continuous and intermittent subjects (56.8% vs 58.8%, respectively). Headache accounted for the majority of AE in both groups (Table 3). Despite a high incidence of preexisting hypertension [defined posthoc as having systolic blood pressure (SBP) ≥ 140 mm Hg and diastolic blood

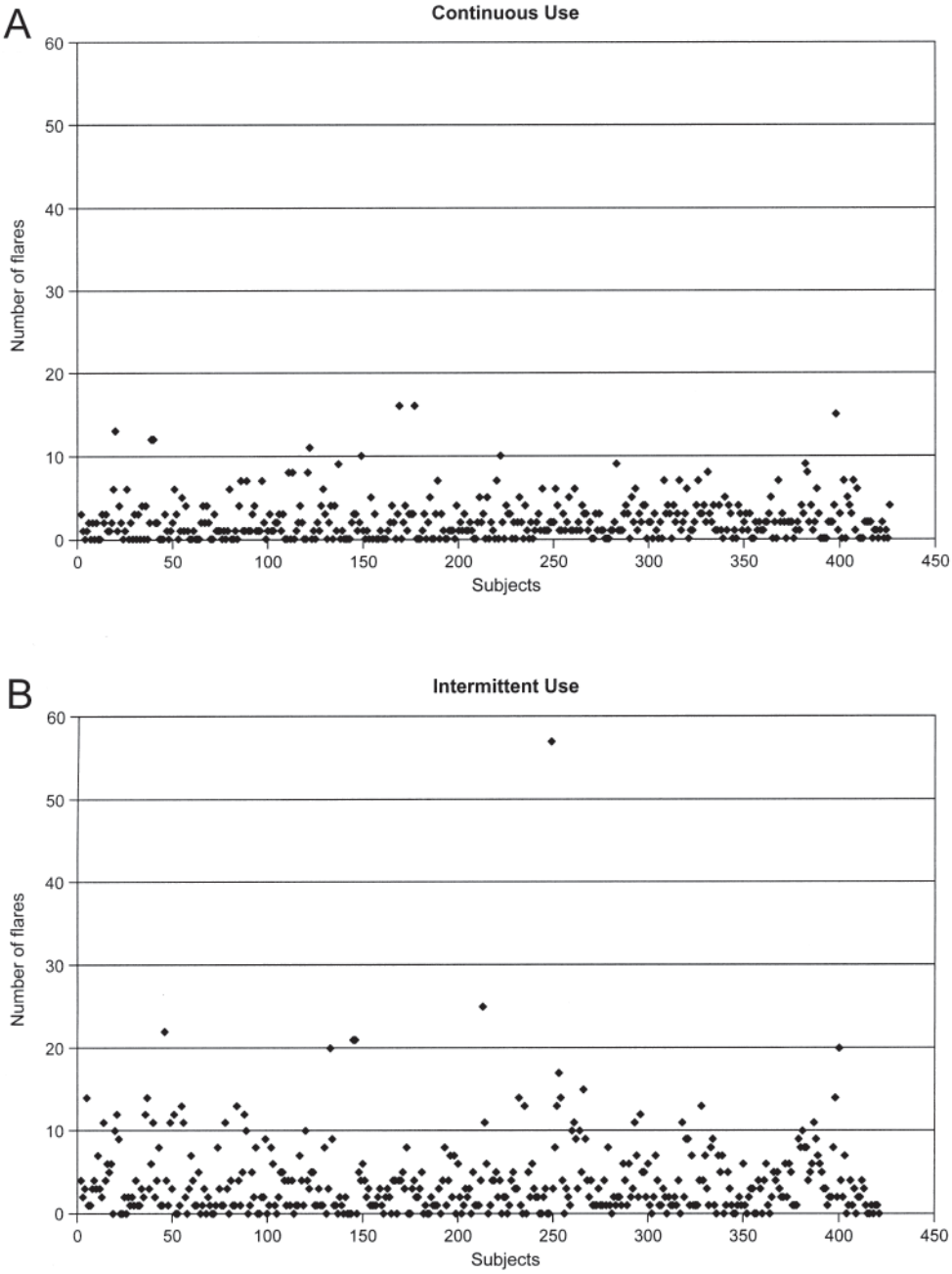

Figure 3. Number of flares experienced by individual subjects in the continuous (A) and intermittent (B) groups.

pressure (DBP) ≥ 90 mm Hg documented at randomization visit (Visit 3); and/or diagnosis of hypertension; and/or receiving antihypertensive therapy] in 44.8% and 45.2% of subjects at baseline for continuous and intermittent, respectively, there were no significant differences in incidence of new-onset (defined posthoc as having existing baseline hypertension and at least 1 postrandomization visit with SBP ≥ 140 mm Hg and DBP ≥ 90 mm Hg or a hypertension AE) or aggravated hypertension (defined posthoc as having no baseline hypertension and having either SBP ≥ 140 mm Hg and DBP ≥ 90 mm Hg documented during at least 2 post-randomization visits or a hypertension AE) in either treatment group (Table 3). Serum creatinine levels remained stable in both treatment groups, with the exception of increases < 2 times the upper limits of normal in 2 subjects receiving intermittent treatment.

DISCUSSION

Although the positive influence on health-related quality of life of treating OA symptoms and flares is well known[9], identifying the best treatment strategy remains a challenge for physicians. While numerous large-scale, randomized,

Table 2. Least-squares (LS) mean changes in WOMAC pain, stiffness, physical function, and total scores for the double-blind treatment period (Period III: 22 weeks duration; ITT population).

WOMAC	"Continuous" Use Celecoxib 200 mg QD*, n = 431	"Intermittent" Use Celecoxib 200 mg QD*, n = 427	p†
Total WOMAC score: change in LS mean from Visit 3 to Visit 9 (SE)††	1.60 (0.71)	4.99 (0.71)	
95% CI	0.21 to 2.99	3.60 to 6.38	< 0.001
WOMAC pain subscale: change in LS mean from Visit 3 to Visit 9 (SE)††	0.37 (0.15)	1.18 (0.15)	
95% CI	0.06 to 0.67	0.88 to 1.49	< 0.001
WOMAC stiffness subscale: change in LS mean from Visit 3 to Visit 9 (SE)††	0.12 (0.07)	0.40 (0.07)	
95% CI	–0.02 to 0.25	0.26 to 0.53	0.004
WOMAC physical function subscale: change in LS mean from Visit 3 to Visit 9 (SE)††	1.13 (0.51)	3.43 (0.51)	
95% CI	0.13 to 2.14	2.42 to 4.43	0.002

* Subjects took flare medication (Bottle B) only during flare. † Based on ANOVA with treatment as fixed effect and baseline (randomization visit) value as a covariate. †† Missing values at the final visit were imputed using the last observation carried forward approach. WOMAC: Western Ontario and McMaster Universities OA index; ITT: intent to treat; QD: daily.

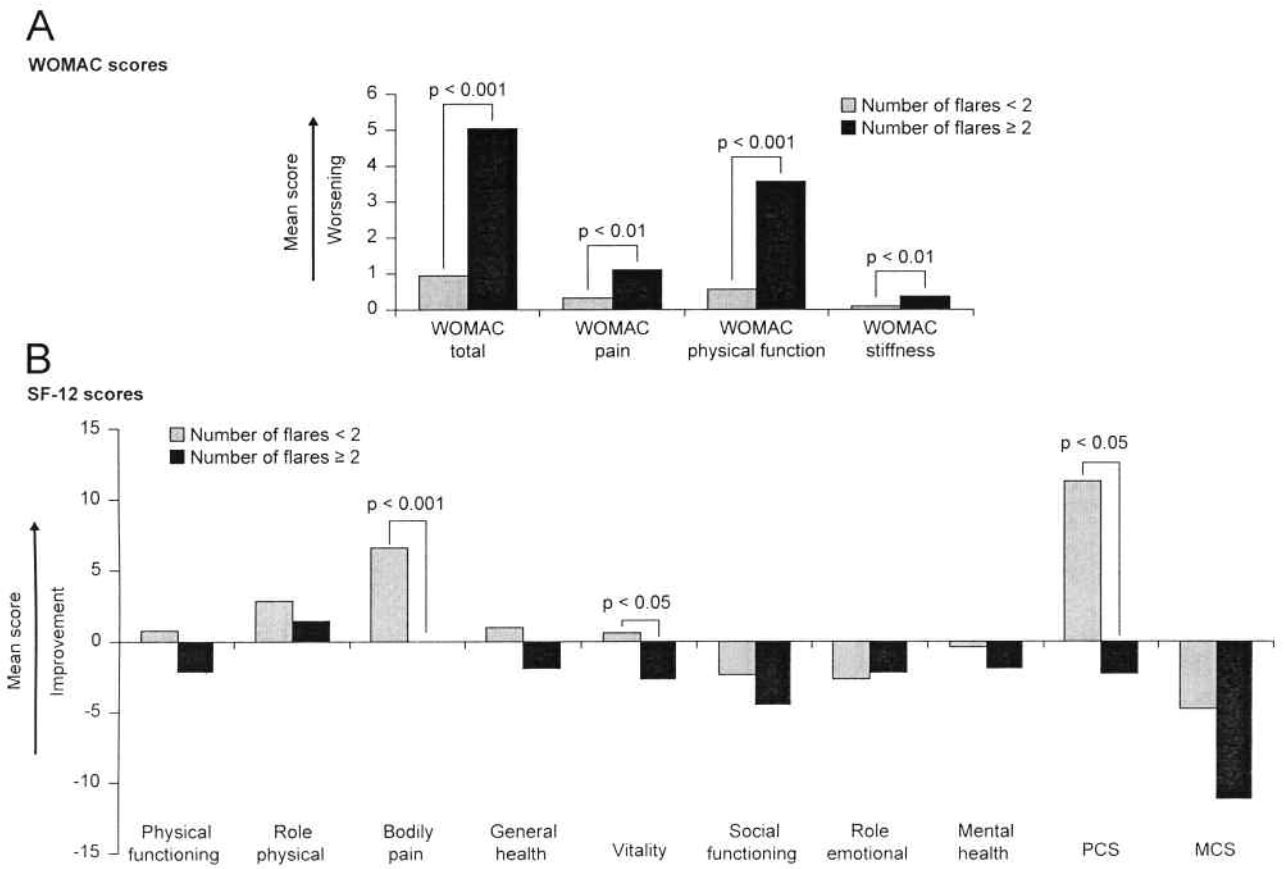

Figure 4. Improvement in mean (A) WOMAC and (B) SF-12 scores in subjects with < 2 or ≥ 2 flares (posthoc analysis). WOMAC: Western Ontario and McMaster Universities OA Score; SF-12: Medical Outcomes Survey; PCS: physical component summary scale; MCS: mental component summary scale.

Table 3. Summary of treatment-emergent adverse events (AE); all causalities ≥ 2% of subjects in either treatment group) and hypertension for safety population for the double-blind treatment period (Period III: 22 weeks' duration). Data are n (%).

Adverse Events	"Continuous" Use Celecoxib 200 mg QD*, n = 431	"Intermittent" Use Celecoxib 200 mg QD*, n = 427
Total no. subjects with treatment-emergent AE	245 (56.8)	251 (58.8)
AE ≥ 2% subjects in either treatment group by preferred term		
Headache	65 (15.1)	68 (15.9)
Back pain	20 (4.6)	31 (7.3)
Arthralgia	17 (3.9)	25 (5.9)
Pain in extremity	18 (4.2)	21 (4.9)
Nasopharyngitis	19 (4.4)	20 (4.7)
Upper respiratory tract	14 (3.2)	19 (4.4)
Diarrhea	7 (1.6)	17 (4.0)
Dyspepsia	17 (3.9)	6 (1.4)
Hypertension	9 (2.1)	13 (3.0)
Insomnia	11 (2.6)	8 (1.9)
Sinusitis	11 (2.6)	10 (2.3)
Abdominal pain	10 (2.3)	4 (0.9)
Influenza	10 (2.3)	9 (2.1)
Muscle spasms	10 (2.3)	5 (1.2)
Myalgia	10 (2.3)	9 (2.1)
Musculoskeletal pain	7 (1.6)	12 (2.8)
Upper abdominal pain	7 (1.6)	10 (2.3)
Nausea	5 (1.2)	9 (2.1)
Fatigue	6 (1.4)	9 (2.1)
Peripheral edema	4 (0.9)	12 (2.8)
Pain	6 (1.4)	9 (2.1)
Bronchitis	3 (0.7)	9 (2.1)
Hypertension		
Baseline hypertension†	193 (44.8)	193 (45.2)
Aggravated hypertension††	51 (11.8)	45 (10.5)
Change in BP postrandomization		
SBP ≥ 20 mm Hg	18 (4.2)	15 (3.5)
DBP ≥ 10 mm Hg	26 (6.0)	24 (5.6)
New-onset hypertension#	10 (2.3)	13 (3.0)

* Subjects took flare medication (Bottle B) during a flare only. † Defined posthoc as having SBP ≥ 140 mm Hg and DBP ≥ 90 mm Hg documented at randomization visit (Visit 3); and/or diagnosis of hypertension; and/or receiving antihypertensive therapy in this analysis. †† Defined posthoc as having existing baseline hypertension and at least 1 postrandomization visit with SBP ≥ 140 mm Hg and DBP ≥ 90 mm Hg or a hypertension AE. # Defined posthoc as having no baseline hypertension and having either SBP ≥ 140 mm Hg and DBP ≥ 90 mm Hg documented during at least 2 postrandomization visits or a hypertension AE. BP: blood pressure; SBP: systolic BP; DBP: diastolic BP; QD: daily.

controlled trials have demonstrated the efficacy and safety of celecoxib and nsNSAID for controlling signs and symptoms of OA[15,22,26,27,28,29,30,31], none have directly compared continuous daily versus intermittent daily dosing regimens. Although Luyten, *et al* compared these dosing regimens in a smaller pilot study, they were able to demonstrate numerical superiority only with continuous use of celecoxib compared with "on-demand" use for the treatment of OA flares[24]. Our current trial was designed to clarify these observations by using a greater number of subjects and using the number of OA flares for each subject per time of exposure in Period III as the primary endpoint.

In our study, subjects receiving continuous celecoxib reported on average 2.0 fewer OA flares during 22 weeks of double-blind treatment than those randomized to intermittent treatment, as well as significant improvements in pain NRS, PGA, and MDGA. They also reported more flare-free days, spent fewer days taking rescue medication, and in general, required less rescue medication. Overall, subjects receiving intermittent treatment reported statistically significant higher least-squares mean total WOMAC and WOMAC subscores than those in the continuous group, suggesting they were experiencing worsening of their OA symptoms.

There was also a statistically significant difference between subjects with fewer (< 2) and more flares (≥ 2), irrespective of treatment group, for WOMAC total and

WOMAC subscores for pain, physical function, and stiffness. Similarly, SF-12 scores for bodily pain, vitality domains, and the physical component summary scale showed statistically significant differences in those with < 2 flares, compared with ≥ 2 flares ($p < 0.05$). There were no differences for the other SF-12 scores.

While reporting fewer flares, it appears the continuous use group experienced better preservation of physical function; whether longer-term studies will confirm this is unknown. WOMAC and SF-12 data showed subjects reported less pain, were better able to perform activities of daily living, and demonstrated improved health-related quality of life when receiving continuous rather than intermittent celecoxib treatment. As patient-reported WOMAC and SF-12 scores were balanced at baseline, the only differences over time were whether they were exposed to continuous or intermittent administration of study medication. Further, the lesser use of rescue medication in the continuous treatment group supports these findings.

Results in the flare-modified ITT population suggest flares ≤ 16 days' duration were more likely to represent transient disease exacerbations, whereas those > 16 days were more logically consistent with disease progression. Continuous therapy demonstrated improvement over 22 weeks of treatment in WOMAC total and the physical function subscore, with the pain subscore showing minimal change (0.04) in the flare-modified ITT population. In the ITT population, in those subjects with flares ≤ 16 days, mean flare length was shorter in those subjects receiving continuous compared to intermittent treatment [3.7 (SD 4.01) vs 4.6 (SD 3.93) days, respectively ($p = 0.0120$)]. Use of the flare-modified ITT definition of duration of flare (< 16 days) may be considered a reasonable distinction between intermittent exacerbations and disease progression for future OA trials.

It has been suggested that intermittent or "on-demand" treatment may be safer compared with continuous therapy. Although our study was not designed or powered to address this question, the incidence of AE was similar in both treatment arms over the 22 weeks of double-blind randomized treatment. Despite a high incidence of preexisting hypertension, there were no significant differences in new-onset or aggravated hypertension between the treatment groups. These results indicate that over 22 weeks' treatment, increased symptomatic benefit can be obtained with continuous use, with no observed increased incidence of AE. The observed lack of difference in AE between these 2 populations is of interest. However, a longer trial designed to investigate this with a greater number of subjects is required to demonstrate the clinical robustness of these observations.

Study limitations. An important criterion for inclusion in this study was that subjects were to have been taking daily NSAID to control OA symptoms in the month before screening and develop a symptomatic OA flare during the washout period. Subsequently, they successfully treated their flare during the celecoxib open-label treatment period before randomization into blinded study treatment. This study design therefore includes subjects successfully treating their OA flare with celecoxib and, along with the flare design, yields an enriched study population with demonstrated efficacy and tolerability to the therapy. These results are likely to be specific to this type of OA population, rather than to a more general OA population frequently seen by many general practitioners. Nonetheless, this trial population represents subjects who have failed simple analgesic and/or intermittent treatment, likely to reflect those with more severe OA, whose disease was most likely to progress.

It is likely not all subjects need to be treated continuously; these results suggest there are some subjects with OA appropriate for such therapy. We do not suggest this trial explains how to select those subjects; rather, it demonstrates that some subjects will have a better response and benefit from such continuous therapy.

The evidence of clinical relevance for a decrease of 2.0 flares during 22 weeks in the continuous treatment arm compared with the intermittent treatment arm is supported by the improvements in WOMAC function scores, in pain scores including both WOMAC and SF-12, in the PGA, and in the decreased use of rescue medications.

We arbitrarily chose more or less 2 flares in the 22-week randomized component of the trial for our posthoc analysis. This analysis was informative in demonstrating that regardless of the type of therapy, those subjects with fewer flares fared better in terms of function and symptoms over the 22 weeks, whereas those with more flares did less well. These observations further support the benefits of decreasing the numbers of flares that subjects may experience.

We did not perform different types of sensitivity analyses to further test the robustness of our findings, such as a baseline carried forward model instead of the last observation carried forward imputation, since there were many performed analyses defined *a priori*. Remarkably, these analyses were in similar direction of effect supporting the primary hypothesis that continuous therapy would for some subjects result in fewer OA flares and improved functional assessments, and lessen the amount of rescue therapy required.

Because of the preponderance of subjects with OA of the knee in this trial, it was not possible to ascertain whether there would be differences in flare events between knee and hip — a larger trial would be required.

This randomized, multicenter, international trial has demonstrated continuous celecoxib 200 mg daily is more efficacious than intermittent use of celecoxib 200 mg daily in preventing flares in subjects with OA of the knee or hip who have successfully treated their flare during the celecoxib open-label treatment period. Overall AE (including GI disorders and hypertension) were similar between the 2 treatment arms, over 22 weeks of double-blind treatment.

These subjects, taking continuous celecoxib, also reported significantly less pain and improved physical function.

Physicians may consider continuous NSAID therapy in appropriate subjects with OA, as this trial demonstrated it led to significantly fewer OA flares and less pain with significantly improved physical function.

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