Osteoarthritis and Cartilage (2007) **15,** 1348–1356

doi:10.1016/j.joca.2007.05.022

Osteoarthritis and Cartilage

International Cartilage Repair Society

OARSI OSTEOARTHRITIS RESEARCH SOCIETY INTERNATIONAL

A randomized placebo-controlled trial comparing the efficacy of etoricoxib 30 mg and ibuprofen 2400 mg for the treatment of patients with osteoarthritis[1,2]

A. Puopolo M.D.†, J. A. Boice Ph.D.‡*, J. L. Fidelholtz M.D.§, T. W. Littlejohn M.D.‖, P. Miranda M.D.#, A. Berrocal M.D.¶, A. Ko M.P.H.‡, N. Cichanowitz M.S.J.‡ and A. S. Reicin M.D.‡

† *Milford Emergency Associates, Milford, MA, United States*
‡ *Merck Research Laboratories, Rahway, NJ, United States*
§ *Hilltop Physicians, Inc., Hightop Medical Research Center, Cincinnati, OH, United States*
‖ *Piedmont Medical Research Associates, Winston-Salem, NC, United States*
¶ *Clinica Stella Maris, Lima, Peru*
# *Hospital San Juan De Dios, Santiago, Chile*

Summary

Objective: We compared the efficacy of etoricoxib 30 mg to placebo and ibuprofen 2400 mg for the treatment of osteoarthritis (OA) of the hip and knee.

Design: In this 12-week, randomized, double-blind, placebo- and active-comparator-controlled trial, 548 patients (median age 63 years) with OA of the hip or knee were randomized to receive placebo, etoricoxib 30 mg q.d., or ibuprofen 800 mg t.i.d. Demonstration of etoricoxib's efficacy vs placebo and comparison of its efficacy to ibuprofen were assessed using three co-primary endpoints: Western Ontario and McMaster's University Osteoarthritis Index (WOMAC) Pain Subscale (WOMAC-PS); WOMAC Physical Function Subscale (WOMAC-PFS); and Patient Global Assessment of Disease Status (PGADS). Each primary endpoint utilizes a 0–100 mm visual analog scale. To demonstrate comparable efficacy of etoricoxib vs ibuprofen, the 95% confidence intervals (CIs) for the difference in the least squares (LS) mean change over 12 weeks for all three co-primary endpoints had to fall within ±10 mm. Safety and tolerability data were collected throughout the study.

Results: Mean baseline values for the three co-primary endpoints ranged from 62.52 to 70.14 mm. Both etoricoxib and ibuprofen demonstrated superior ($P \leq 0.002$) efficacy for all primary endpoints. The LS mean (mm) changes (95% CI) over 12 weeks for etoricoxib and ibuprofen, respectively, compared to placebo were given as follows: WOMAC-PS: −11.66 (−16.31, −7.01) and −7.62 (−12.30, −2.94); WOMAC-PFS: −10.15 (−14.74, −5.57) and −7.23 (−11.85, −2.61); PGADS: −11.65 (−16.81, −6.50) and −8.11 (−13.30, −2.92). The efficacy of etoricoxib 30 mg was comparable to ibuprofen 2400 mg. All treatments were similarly well tolerated.

Conclusion: Treatment with etoricoxib 30 mg q.d. provides superior efficacy vs placebo and comparable clinical efficacy vs ibuprofen 2400 mg (800 mg t.i.d.) for the treatment of OA of the hip and knee.

Key words: Osteoarthritis, Etoricoxib, COX-2, Ibuprofen, Selective NSAID.

Abbreviations: AE adverse experience, ANOVA analysis of variance, ANCOVA analysis of covariance, ARA American Rheumatism Association, CHF congestive heart failure, CI confidence interval, COX cyclooxygenase, CV cardiovascular, CVA cerebrovascular accident, DVT deep vein thrombosis, GPAs gastroprotective agents, IGADS Investigator Global Assessment of Disease Status, IGART Investigator Global Assessment of Response to Therapy, LS least squares, MEDAL Multinational Etoricoxib and Diclofenac Arthritis Long-term, MITT modified intention-to-treat, Traditional NSAIDs Traditional nonsteroidal anti-inflammatory drugs, OA osteoarthritis, PGADS Patient Global Assessment of Disease Status, PGART Patient Global Assessment of Response to Therapy, q.d. once daily, t.i.d. three times daily, VA visual analog, VAS visual analog scale, WOMAC Western Ontario and McMaster's University Osteoarthritis Index, WOMAC-PS WOMAC Pain Subscale, WOMAC-PFS WOMAC Physical Function Subscale.

Introduction

Osteoarthritis (OA), generally considered a disease of aging, is the most common form of arthritis in older adults. In its severe form, the chronic pain of OA can lead to a significant reduction in the overall quality of life in patients of any age[1–4]. OA of the knee and hip can be quite disabling since these are major weight-bearing joints[5]. Given current projections indicating that OA could be the fourth leading cause of disability on a world-wide basis by the year 2020, the need for multiple treatment options exists[6].

[1] *Funded by*: This study was funded by Merck Research Laboratories. *Disclosures*: J. A. Boice, A. Ko, N. Cichanowitz, and A. S. Reicin are employees of Merck & Co., Inc., and own stock and/or hold stock options in the Company. *Previous Presentations of this Work*: None to-date.

[2] Clinical study protocol registered at http://www.clinicaltrials.gov/ct/show/NCT00092755.

*Address correspondence and reprint requests to: Dr Judith A. Boice, Ph.D., Merck Research Laboratories, Clinical Immunology and Analgesia, P.O. Box 2000, Rahway, NJ 07065, United States. Tel: 1-732-594-6297; Fax: 1-732-594-7435; E-mail: judith_boice@merck.com

Received 28 April 2006; revision accepted 26 May 2007.

Acetaminophen and non-pharmacologic approaches, such as exercise and improvement of joint biomechanics, are considered first-line treatment options for patients with OA[7,8]. However, traditional nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used to treat the pain and symptoms associated with this disease[7,9,10]. Nevertheless, there is a greatly elevated risk of gastrointestinal (GI) toxicity associated with traditional NSAIDs due to their additional inhibition of the cyclooxygenase-1 (COX-1) isoenzyme. This risk of NSAID-induced GI toxicity increases in a linear fashion with age[11].

Etoricoxib is a member of the COX-2 selective inhibitor class of NSAIDs and exhibits a reduced risk of GI toxicity compared to traditional NSAIDs[12,13]. Recent long-term randomized placebo-controlled trials have demonstrated an increased time-dependent risk of thrombotic cardiovascular (CV) events with other COX-2 selective NSAIDs compared with placebo[14,15]. Meta-analyses and reviews by regulatory authorities in the United States and Europe indicate that this risk likely extends to traditional NSAIDs[16–19].

Etoricoxib's anti-inflammatory and analgesic efficacy for the treatment of acute and chronic pain have been established in multiple studies using a once daily dosing regimen and is reviewed elsewhere[20]. In countries where it is approved, the recommended once daily dose of etoricoxib for the treatment of OA is 60 mg. The purpose of this study, the second of two replicate, randomized, placebo- and active-comparator-controlled trials, was to examine the efficacy as well as the safety and tolerability of etoricoxib 30 mg q.d. compared to placebo and ibuprofen 800 mg t.i.d. in patients with OA of the knee or hip. In the first of these two studies (Sponsor protocol number 071), the efficacy of etoricoxib 30 mg was found to be superior to placebo and comparable to ibuprofen 2400 mg for the treatment of OA of the hip and knee[21]. The identification of lower effective doses of NSAIDs including selective COX-2 inhibitors is important in the context of mechanism-based side effects such as edema and hypertension, which are known to be dose-related.

Patients and methods

The protocol for this study was approved by the Institutional Review Board at each study center. All patients provided written informed consent prior to their participation in the study.

This 12-week, placebo- and active-comparator-controlled trial was conducted in 548 patients in 49 centers (41 in the United States and eight in Latin America) under double-blind (with in-house blinding) conditions to evaluate the efficacy, safety, and tolerability of etoricoxib 30 mg compared to placebo and ibuprofen 800 mg t.i.d. for the treatment of OA of the knee and hip. Otherwise healthy male and female OA patients 40 years or older, were enrolled. Women of child-bearing potential were determined to be in a nongravid state and were instructed to use contraceptive measures during the study. Eligible patients were required to have a clinical and radiographic diagnosis of OA of the knee or hip for at least the previous 6 months or were newly diagnosed patients with clinical symptoms consistent with OA of the study joint for at least the previous 6 months. All patients were required to have pain on motion or weight bearing for the majority of days during the previous month, which was partially relieved by rest. Radiographic criteria included joint space narrowing for hip OA. Patients with knee OA were required to have both tibiofemoral osteophytes and tibiofemoral joint space narrowing. All eligible patients met American Rheumatism Association (ARA) functional class I, II, or III criteria[22] and were required to have been using NSAIDs or acetaminophen to treat their OA. The primary source of pain for each patient was in the lower extremity. In cases where both knees and/or hips were affected, the most painful joint was selected for study evaluation. Patients who were regular users of NSAIDs (at least 25 of the last 30 days preceding enrollment) were required to have a prestudy score of less than 80 mm (based on the 0–100 mm visual analog scale [VAS]) for patient assessment of pain while walking on a flat surface. Following cessation of NSAID therapy (washout period) patients were instructed to return to the clinic upon experiencing a flare of OA pain. Prespecified washout periods for the various prior NSAIDs that were used ranged from 3 to 20 days. A sufficient flare within the washout period was defined as a patient-reported pain score of at least 40 mm while the patient walked on a flat surface, and was at least 15 mm greater than that recorded at the prestudy visit as well as a worsening of at least one point (0- to 5-point Likert scale) for Investigator Global Assessment of Disease Status (IGADS).

Patients who were classified as acetaminophen users (1.2–4 g of acetaminophen daily for at least 25 of the last 30 days preceding enrollment) reported no NSAID use for treatment of their OA and were required to have minimum scores of 40 mm for patient-reported pain while walking on a flat surface and Patient Global Assessment of Disease Status (PGADS), and an IGADS of fair, poor, or very poor. The number of acetaminophen users at each study site was limited to 20%, since this agent acts only as an analgesic, and unlike etoricoxib and ibuprofen, does not have anti-inflammatory activity.

All patients were required to stop taking rescue acetaminophen at least 12 h (24 h if they were using extended-release formulations) prior to all treatment visits and for acetaminophen users only, prior to screening.

EXCLUSION CRITERIA

Patients were excluded if they had medical conditions, such as recent joint injuries or rheumatologic, autoimmune, or musculoskeletal diseases that could confound or interfere with efficacy evaluations.

TREATMENT

Qualified patients were randomized to receive placebo, etoricoxib 30 mg q.d., or ibuprofen 800 mg t.i.d. for 12 weeks. Within each study center, patients were randomly allocated using a computer-generated allocation schedule; allocation was not stratified in this study. All study personnel, including investigators, study site personnel, patients, monitors, central laboratory and other study personnel, remained blinded to treatment allocation throughout the study. Study medication was supplied in two coded study bottles, labeled "bottle A" (containing either etoricoxib 30 mg tablets or matching placebo) and "bottle B" (containing either ibuprofen 800 mg tablets or matching placebo). Patients were instructed to take one tablet in the morning from bottle A and one tablet in the morning, afternoon, and evening from bottle B. Acetaminophen was provided as rescue medication for pain, if needed. Treatment compliance and amount of rescue acetaminophen use were determined by tablet counts.

INCLUDED AND EXCLUDED MEDICATIONS

Patients were allowed to continue use of chronic medications provided they remained on stable doses 2 weeks before and throughout the 12 weeks of the study. The use of intra-articular corticosteroids or hyaluronic acid injections to the study knee within the previous 3 months, use of immunosuppressants within the previous 3 months, corticosteroid use by any systemic route, and hyaluronic acid injections or intra-articular corticosteroids for any other joint in the previous month were not permitted. Patients taking stable doses of glucosamine or chondroitin sulfate for at least 6 months prior to the study were allowed to enroll. Low-dose aspirin ($\leq$100 mg daily) use for cardioprophylaxis was permitted; however, patients were excluded if they were required to take any other therapy to inhibit platelet aggregation. Gastroprotective agents (GPAs), such as proton pump inhibitors, H_2-receptor antagonists, sucralfate, and misoprostol, were allowed as necessary.

EFFICACY ASSESSMENTS

Efficacy was evaluated at 2, 4, 8, and 12 weeks following initiation of therapy. Primary endpoints included the Western Ontario and McMaster's University Osteoarthritis Index (WOMAC) visual analog (VA) 3.0 pain (WOMAC-PS) and physical function (WOMAC-PFS) subscales and the PGADS (0–100 mm VAS)[23–25]. Secondary and other endpoints included the Patient Global Assessment of Response to Therapy (PGART; 0–4 point Likert scale), the IGADS (0–4 point Likert scale), the WOMAC stiffness subscale (0–100 mm VAS), the WOMAC questionnaire overall score and subscale averages, the Investigator Global Assessment of Response to Therapy (IGART; 0–4 point Likert scale), joint tenderness (0–3 point Likert scale), the proportion of patients discontinuing due to lack of efficacy, rescue acetaminophen use, and the WOMAC pain while walking on a flat surface questionnaire (0–100 mm VAS). Exploratory endpoints included the WOMAC nighttime pain and WOMAC 3.0 stiffness upon first awakening subscales (0–100 mm VAS).

SAFETY AND TOLERABILITY ASSESSMENTS

Adverse experiences (AEs) were recorded throughout the study and for 14 days after the last dose of study drug. Physical examinations, clinical laboratory tests, and AEs were recorded throughout the study to assess safety.

Serious AEs were defined as those events that resulted in death, were life threatening, resulted in or prolonged hospitalization, or caused persistent or significant disability or incapacity. AEs that were determined by the investigator to be possibly, probably, or definitely drug-related were classified as drug-related. Prespecified safety-related endpoints, including the proportion of patients with edema-related AEs; hypertension-related AEs; AEs of congestive heart failure (CHF), pulmonary edema, or cardiac failure; and discontinuation due to digestive system or abdominal pain AEs, edema-related AEs, or hypertension-related AEs were also recorded to more closely examine GI safety and possible clinical sequelae of modulating renal prostaglandin biosynthesis. Prior to initiation of the study, blinded, external adjudication committees were established to evaluate any investigator-reported thrombotic cardiovascular serious AEs (thrombotic CV events) or potential upper GI perforations, ulcers, or bleeds that occurred during the trial.

STATISTICAL ANALYSIS

For power calculations, the estimates for variability and assumed mean changes for each treatment group were based on results from three previous etoricoxib and two previous rofecoxib randomized, placebo-controlled studies in patients with OA[26–30]. Results from these studies suggested that the expected differences between responses to etoricoxib relative to placebo were approximately 11.9 mm for the WOMAC-PS, 10.0 mm for the WOMAC-PFS, and 13.5 mm for the PGADS. Using variability estimates from the two etoricoxib Phase III studies[27,28], it was predicted that planned sample sizes of 100 placebo patients and 200 etoricoxib 30 mg patients provided $>$97% power to detect ($\alpha = 0.050$, two-sided) these expected mean differences for the three co-primary endpoints. The modified intention-to-treat (MITT) population was used in all efficacy analyses and is defined as all randomized patients who received at least one dose of study medication and who provided a baseline and at least one post-baseline observation.

The time-weighted mean changes from baseline for each efficacy endpoint were analyzed using an analysis of covariance (ANCOVA) model with treatment and primary OA study joint as the main effects and the baseline value as the covariate. For endpoints without a relevant baseline measurement, the on-treatment response was analyzed using analysis of variance (ANOVA).

The between-treatment comparisons of interest were divided into three families of tests, using the Dunnett–Tamhane approach[31]; (1) testing of the efficacy of etoricoxib relative to placebo, (2) comparing the relative efficacy of etoricoxib 30 mg to ibuprofen 2400 mg, and (3) evaluating the study sensitivity, i.e., comparing ibuprofen to placebo. The different between-treatment comparisons in each family addressed related yet different questions. In addition, there was only one test within each family; therefore, no adjustment for multiple between-treatment comparisons was made between these three families of tests. Since the primary hypothesis had to be satisfied for each of the three primary endpoints, the overall alpha level was $<$0.050 and no adjustment was necessary. For comparisons to placebo, all three primary endpoints were required to reach statistical significance at $\alpha = 0.050$, two-tailed.

Statistical tests and estimators of the secondary endpoints and other secondary statistical analyses were supportive and helped in interpreting the primary analyses, establishing efficacy profiles, and checking the consistency of findings for the primary endpoints. Therefore, no multiple testing adjustments were made. All tests for difference in means were made at the customary two-sided $\alpha = 0.050$ level.

To demonstrate comparable efficacy of etoricoxib 30 mg q.d. and ibuprofen 800 mg t.i.d., the 95% confidence intervals (CIs) for the mean differences in the time-weighted average response between the two groups had to fall entirely within $\pm$10 mm on a 100 mm VAS for all three co-primary endpoints. The study was designed to provide greater than 95% power to yield all three CIs within $\pm$10 mm if true differences in efficacy between etoricoxib 30 mg and ibuprofen 2400 mg were zero.

The incidences of prespecified clinical AEs and laboratory AEs of interest in the two active treatment groups were individually compared with the incidence in the placebo group using Fisher's exact test. Differences between treatment groups in proportions of patients with AEs or those exceeding predefined limits of change in laboratory

safety parameters were evaluated using 95% CIs calculated by the Wilson's score method.

Results

PATIENTS

A total of 548 of the 861 patients screened met the eligibility criteria and were randomized (Fig. 1). Baseline patient characteristics were similar among the treatment groups (Table I). The majority of enrolled patients were female. The median age of the study population was 63 years, and the majority of patients (56%) were over 60 years and 22% were over 70 years. The mean duration of OA was 6.6 years, and the majority of patients were ARA functional class II. There were small insignificant differences among treatment groups in the proportions of patients who were classified as ARA functional class I, II, and III. Given the overlap between the diagnostic entry criteria used and those of the American College of Rheumatology (ACR) clinical and radiographic diagnostic criteria, all patients with hip OA and all patients >50 years of age with knee OA also met ACR diagnostic criteria[32]. Although it is likely that knee OA patients <50 years of age also met ACR criteria, this was not specifically documented as we did not specifically require patients to have one of the two ACR criteria of crepitus or stiffness <30 min. Of note, 88% of patients enrolled were >50 years of age.

Most patients (83%) had OA of the knee and 89% were NSAID users at screening. A small percentage of patients (4.2%) had a prior medical history of confirmed gastric or duodenal ulcer or upper GI bleeding. Baseline characteristics (e.g., percentage of patients with OA of the knee, ARA functional class, and mean duration of disease) for the patients in this study were similar to those in other studies of etoricoxib in patients with OA[26–28]. The most common secondary diagnosis at baseline was hypertension (46.4% of the patients). A total of four, seven, and four patients in the placebo, etoricoxib, and ibuprofen groups, respectively, were excluded from the MITT analysis for any of the three co-primary efficacy endpoints.

EFFICACY

Mean values for all efficacy endpoints were qualitatively similar among the treatment groups at baseline (Table II). Near-maximal efficacy was achieved with both active treatments by the first visit following initiation of treatments (week 2), followed by slight continued improvement for all primary endpoints through 12 weeks [Fig. 2(a)–(c)]. There were no significant treatment-by-baseline-covariate (i.e., age group [<65 years, ≥65 years], gender, racial background, ARA functional class, or duration of OA) or treatment-by-study-joint interactions observed. Results of the treatment comparisons of the last observed value were consistent with those of the time-weighted average responses over the 12-week treatment period.

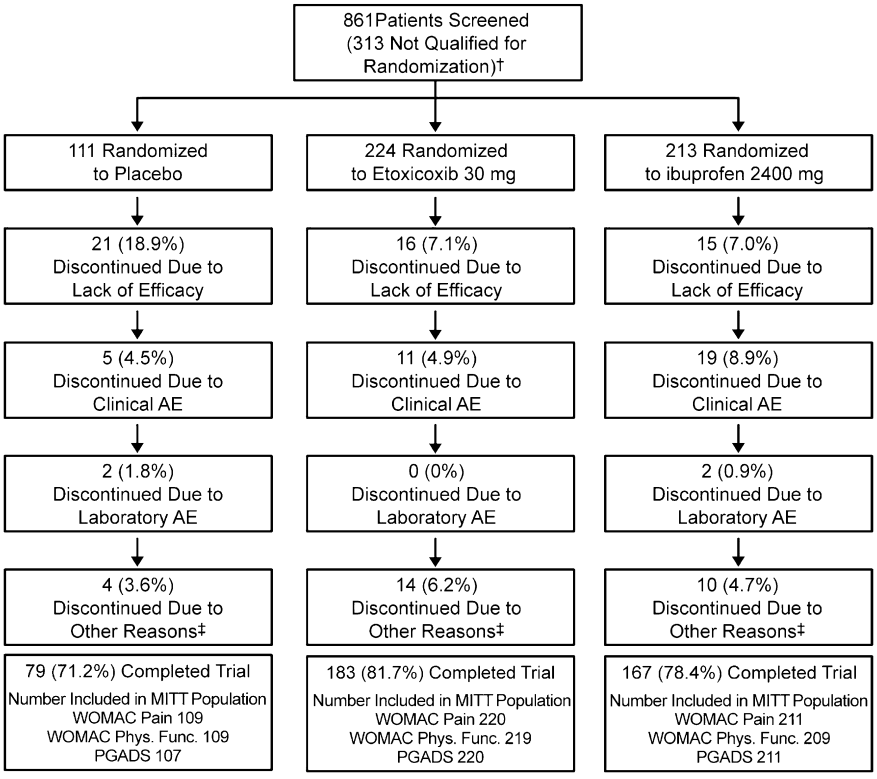

Fig. 1. Disposition of patients with OA enrolled in 12-week evaluation of etoricoxib 30 mg and ibuprofen 2400 mg vs placebo. †: The most common reasons patients were not randomized were due to failure to meet one or more inclusion criteria (i.e., not satisfying flare criteria and having a clinical diagnosis of OA based on clinical and radiographic criteria) or because one or more exclusion criteria were met (i.e., having an abnormal laboratory safety test result). ‡: Other reasons for discontinuation included lost to follow-up; unknown reason; patient moved; patient withdrew consent; and protocol deviation.

Table I
Baseline characteristics for patients enrolled in clinical study of etoricoxib and ibuprofen for treatment of OA

Characteristic	Placebo ($n=111$)	Etoricoxib 30 mg ($n=224$)	Ibuprofen 2400 mg ($n=213$)
Gender, *n* (%)			
Female	84 (75.7)	174 (77.7)	157 (73.7)
Male	27 (24.3)	50 (22.3)	56 (26.3)
Race, *n* (%)			
Asian	2 (1.8)	4 (1.8)	4 (1.9)
Black	5 (4.5)	10 (4.5)	3 (1.4)
Hispanic American	27 (24.3)	47 (21.0)	50 (23.5)
Multiracial	26 (23.4)	53 (23.7)	52 (24.4)
White	51 (45.9)	110 (49.1)	104 (48.8)
Age (years)			
Mean [standard deviation (SD)]	64.0 (10.1)	62.1 (9.0)	62.3 (9.6)
Median	65.0	62.0	62.0
Range	43–85	42–81	41–86
Primary OA joint, *n* (%)			
Knee	91 (82.0)	189 (84.4)	176 (82.6)
Hip	20 (18.0)	35 (15.6)	37 (17.4)
Mean duration of OA, years (SD)	6.5 (6.6)	6.6 (7.3)	6.7 (8.0)
ARA functional class, *n* (%)			
Class I	25 (22.7)	68 (30.4)	54 (25.4)
Class II	69 (62.7)	128 (57.1)	126 (59.2)
Class III	16 (14.5)	28 (12.5)	33 (15.5)
Mean height, cm (SD)	161.0 (11.2)	160.6 (12.1)	161.6 (11.8)
Mean weight, kg (SD)	80.1 (17.3)	81.9 (20.9)	79.2 (18.6)
Low-dose ($\leq$100 mg/day) aspirin use, *n* (%)	22 (19.8)	38 (17.0)	36 (16.9)

For all co-primary endpoints, both etoricoxib and ibuprofen were significantly more effective ($P \leq 0.002$) than placebo [Fig. 2(d) and Table II]. Etoricoxib met the predefined criteria for comparability to ibuprofen for all co-primary endpoints; additionally, etoricoxib demonstrated statistical superiority ($P < 0.05$) over ibuprofen for the WOMAC-PS, a co-primary endpoint. Analyses of key secondary endpoints, which included PGART, IGADS, WOMAC stiffness subscale, and WOMAC overall score and subscale averages, provided an additional perspective of etoricoxib's overall efficacy profile for the treatment of OA compared with the efficacy of ibuprofen and placebo. Etoricoxib and ibuprofen demonstrated comparable treatment effects, which were superior to placebo (Table II) for these secondary endpoints. These treatment effects were consistent with those of the co-primary endpoints.

From an exploratory *post hoc* analysis it was determined that 80.0%, 70.1%, and 55.1% of patients in the etoricoxib, ibuprofen, and placebo group, respectively, achieved what can be considered to be a minimally clinically important improvement[33] ($\geq$15% improvement from baseline) for the WOMAC-PS. Similar response rates of 72.6%, 66.5%, and 53.2% for WOMAC-PFS and 77.7%, 73.9%, and 61.7% for PGADS for etoricoxib, ibuprofen, and placebo, respectively, were observed.

Results for other secondary and exploratory endpoints were also consistent with results for the co-primary endpoints. Patients on etoricoxib experienced a 1.54 point (95% CI: 1.40, 1.68) improvement of IGART and −33.75 mm (95% CI: −37.17, −30.33 mm) improvement of pain status when walking on a flat surface (WOMAC score). This was similar to the improvements observed in patients taking ibuprofen (1.58 [95% CI: 1.44, 1.73] and −32.01 [95% CI: −35.44, −28.57] for IGART and pain status when walking on a flat surface, respectively). When compared with placebo, treatment with etoricoxib provided significant reduction of study joint tenderness ($P = 0.005$), whereas reduction of study joint tenderness following ibuprofen therapy only approached significance ($P = 0.076$). Both etoricoxib and ibuprofen significantly reduced night pain and stiffness upon awakening vs placebo ($P \leq 0.016$). Although the treatment effects for etoricoxib and ibuprofen were similar for stiffness upon awakening, the effect of etoricoxib on night pain was significantly greater than ibuprofen ($P = 0.041$).

Patients treated with etoricoxib or ibuprofen used significantly less acetaminophen than those receiving placebo ($P = 0.003$ for etoricoxib and $P = 0.029$ for ibuprofen) for the treatment of breakthrough pain. The amount of rescue acetaminophen use in the etoricoxib and ibuprofen groups was similar.

SAFETY AND TOLERABILITY

The incidences of 10 prespecified AEs were compared among the treatment groups (Table III). Etoricoxib and ibuprofen at the doses used in this study were generally safe and well tolerated. The percentage of patients experiencing an AE or a serious AE was similar among the three groups (Table III). The incidence of drug-related AEs in patients receiving ibuprofen was significantly greater than for patients treated with placebo ($P = 0.029$). The percentage of patients who discontinued due to any AE was higher in the ibuprofen group than in the placebo and etoricoxib groups but the difference was not significant. Only one serious AE (in the ibuprofen group) was considered drug-related.

The most common drug-related AEs were epigastric discomfort, nausea, dyspepsia, and hypertension. Drug-related epigastric discomfort occurred most frequently in the ibuprofen group (9.4% vs 2.7% of those treated with etoricoxib and 1.8% of the placebo group; Table III) with 95% CIs for the difference between etoricoxib and ibuprofen as well as between ibuprofen and placebo that did not cross zero, consistent with the higher incidence for ibuprofen. Drug-related nausea occurred most frequently in the ibuprofen group, whereas dyspepsia was reported with similar frequency across all groups. Discontinuations due to AEs related to the digestive system or abdominal pain were similar in the placebo and ibuprofen groups and were slightly lower in the etoricoxib group. One patient in this study had a confirmed upper GI event. This patient, who was in the ibuprofen group, had a confirmed gastric ulcer that was deemed complicated due to hemorrhage. The investigator determined that this AE was probably drug-related.

The incidence of edema-related AEs was similar for etoricoxib and ibuprofen and was the lowest for placebo although this difference was not significant (Table III). The incidence of hypertension-related AEs was significantly higher in the etoricoxib (6.3%; $P < 0.05$) and ibuprofen (8.9%; $P < 0.005$) groups compared with placebo (0.9%; Table III). However, the rate of discontinuation due to hypertension-related AEs was low and similar among the groups. One patient each in the etoricoxib and ibuprofen groups experienced CHF.

Table II
Summary of results for primary and key secondary efficacy endpoints over the 12-week treatment period

	Baseline mean	LS mean (95% CI) change from baseline†	Difference from placebo in LS mean change (95% CI)†	Difference from ibuprofen in LS mean change (95% CI)†
Primary endpoints				
WOMAC-PS (0−100 VAS)				
Placebo ($n=109$)	64.66	−16.47 (−20.55, −12.40)	N/A	N/A
Etoricoxib 30 mg ($n=220$)	66.46	−28.14 (−31.23, −25.04)	−11.66 (−16.31, −7.01)	−4.04 (−7.86, −0.21)
Ibuprofen 2400 mg ($n=211$)	64.74	−24.10 (−27.20, −20.99)	−7.62 (−12.30, −2.94)	N/A
WOMAC-PFS (0−100 VAS)				
Placebo ($n=109$)	64.23	−13.56 (−17.59, −9.54)	N/A	N/A
Etoricoxib 30 mg ($n=219$)	64.27	−23.46 (−26.78, −20.65)	−10.15 (−14.74, −5.57)	−2.92 (−6.71, 0.87)
Ibuprofen 2400 mg ($n=209$)	62.52	−20.09 (−23.87, −17.72)	−7.23 (−11.85, −2.61)	N/A
PGADS (0−100 VAS)				
Placebo ($n=107$)	66.93	−17.85 (−22.41, −13.29)	N/A	N/A
Etoricoxib 30 mg ($n=220$)	70.14	−29.50 (−32.91, −26.10)	−11.65 (−16.81, −6.50)	−3.54 (−7.75, 0.67)
Ibuprofen 2400 mg ($n=211$)	69.88	−25.97 (−29.39, −22.54)	−8.11 (−13.30, −2.92)	N/A
Key secondary endpoints				
PGART (0−4 Likert scale)				
Placebo ($n=108$)	–	2.29 (2.09, 2.49)	N/A	N/A
Etoricoxib 30 mg ($n=220$)	–	1.61 (1.46, 1.76)	−0.68 (−0.91, −0.45)	−0.11 (−0.30, 0.08)
Ibuprofen 2400 mg ($n=210$)	–	1.72 (1.57, 1.87)	−0.57 (−0.80, −0.34)	N/A
IGADS (0−4 Likert scale)				
Placebo ($n=109$)	2.83	−1.00 (−1.15, −0.84)	N/A	N/A
Etoricoxib 30 mg ($n=220$)	2.85	−1.37 (−1.48, −1.25)	−0.37 (−0.54, −0.19)	−0.09 (−0.23, 0.06)
Ibuprofen 2400 mg ($n=211$)	2.88	−1.28 (−1.40, −1.16)	−0.28 (−0.46, −0.10)	N/A
WOMAC stiffness subscale (0−100 VAS)				
Placebo ($n=109$)	67.06	−16.26 (−20.61, −11.91)	N/A	N/A
Etoricoxib 30 mg ($n=218$)	65.68	−24.60 (−27.92, −21.28)	−8.34 (−13.30, −3.38)	−1.68 (−5.77, 2.41)
Ibuprofen 2400 mg ($n=209$)	65.32	−22.92 (−26.24, −19.60)	−6.66 (−11.66, −1.67)	N/A
WOMAC questionnaire overall score average (0−100 VAS)				
Placebo ($n=109$)	64.56	−14.43 (−18.39, −10.48)	N/A	N/A
Etoricoxib 30 mg ($n=218$)	64.95	−24.90 (−27.92, −21.87)	−10.46 (−14.97, −5.95)	−3.17 (−6.89, 0.56)
Ibuprofen 2400 mg ($n=209$)	63.18	−21.73 (−24.75, −18.71)	−7.29 (−11.84, −2.75)	N/A
WOMAC questionnaire overall subscale average (0−100 VAS)				
Placebo ($n=109$)	65.32	−15.53 (−19.50, −11.55)	N/A	N/A
Etoricoxib 30 mg ($n=218$)	65.49	−25.64 (−28.67, −22.60)	−10.11 (−14.64, −5.58)	−2.90 (−6.64, 0.84)
Ibuprofen 2400 mg ($n=209$)	64.13	−22.74 (−25.77, −19.70)	−7.21 (−11.77, −2.64)	N/A

Number of patients in the MITT analysis. †Lower values indicate a greater treatment effect. Where there is no baseline value, the mean on-treatment response is given.

There were a total of five investigator-reported thrombotic CV events (all nonfatal); one deep vein thrombosis (DVT) for placebo, two cerebrovascular accidents (CVAs) for etoricoxib, and an embolic stroke and DVT for ibuprofen. Of these events, three were confirmed thrombotic CV events; the DVT on placebo, one CVA on etoricoxib, and one embolic stroke on ibuprofen. None of these three thrombotic CV events was considered to be drug-related by the investigators.

Laboratory AEs were generally more frequent in the ibuprofen group than for placebo or etoricoxib. Overall laboratory AEs occurred in four (3.7%) patients treated with placebo, seven (3.2%) treated with etoricoxib, and 18 (8.5%) treated with ibuprofen. Drug-related laboratory AEs occurred in 1.9% of the placebo-treated patients, 2.3% of those treated with etoricoxib, and 7.1% of the patients treated with ibuprofen. The most common laboratory AE considered drug-related by investigators was increased alanine aminotransferase (ALT), the incidence of which was higher in the ibuprofen group (2.4%) than the placebo (0.9%) and etoricoxib (0%) groups. The next most common drug-related laboratory AEs were increased blood urea nitrogen and serum creatinine with the highest incidence in the ibuprofen group (both 1.9%), with both of these AEs occurring in 0.5% of patients in the etoricoxib group, and in no patients in the placebo group.

The 95% CIs for the difference between the etoricoxib and ibuprofen groups for overall laboratory AEs (95% CI: −10.2, −0.9) and drug-related laboratory AEs (95% CI: −9.3, −0.8) did not cross zero which is consistent with a higher incidence on ibuprofen. Discontinuations due to laboratory AEs occurred in two patients in the placebo and two patients in the ibuprofen groups. The increased incidence of laboratory AEs in the ibuprofen group was mainly due to increases of ALT, blood urea nitrogen, and serum creatinine. Decreases in hemoglobin values were rare and occurred in 0.9%, 0.0%, and 1.9% of patients in the placebo, etoricoxib, and ibuprofen groups, respectively.

Discussion

This study used validated clinical endpoints for the assessment of treatment efficacy in patients with OA[34,35]. The demographic characteristics of the patient population

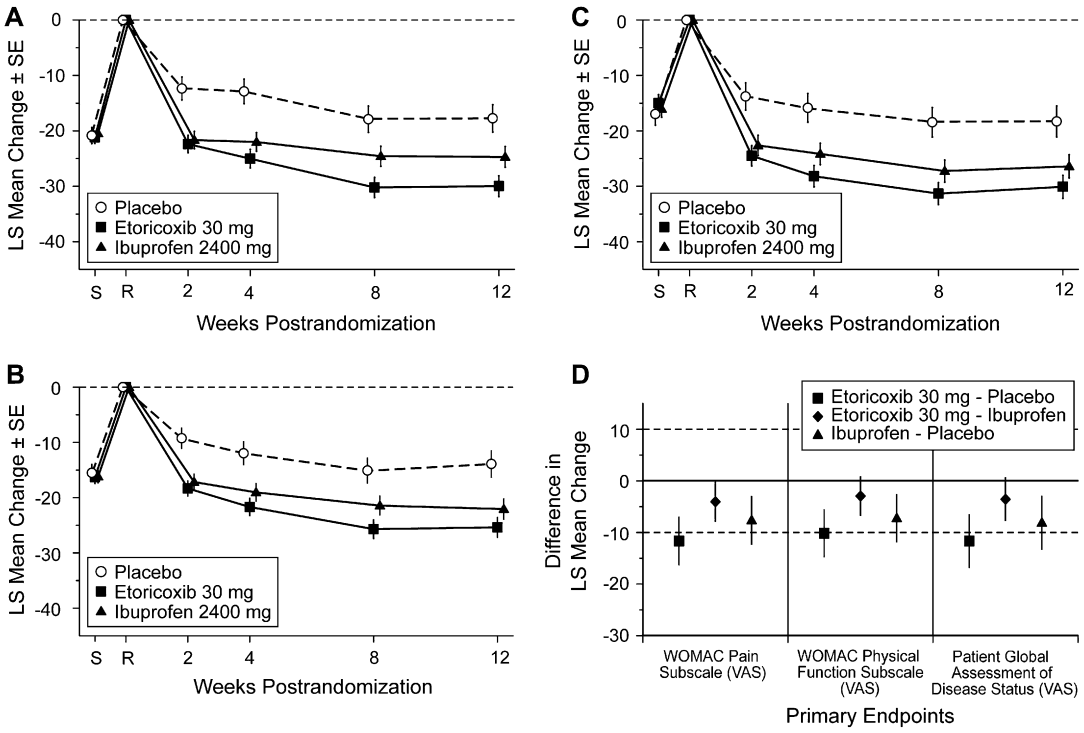

Fig. 2. Co-primary endpoints evaluated (0−100 mm VAS) over 12-week period of treatment with placebo, etoricoxib 30 mg/day, or ibuprofen 2400 mg/day in patients with OA of the knee or hip. (a) WOMAC-PS; (b) WOMAC-PFS; (c) PGADS; and (d) pairwise treatment differences (VAS) in co-primary endpoints for patients with OA treated daily with etoricoxib 30 mg, ibuprofen 2400 mg, or placebo. *Note*: the week number for each group has been shifted along the horizontal scale to improve legibility. Error bars are standard errors. S = screening and R = randomization.

at baseline were similar to those of OA patients in the general population that seek treatment[5,7]. Consistent with other clinical studies, the results of this trial confirm the superior clinical efficacy of etoricoxib 30 mg q.d. compared with placebo[21,26] and its comparable efficacy to ibuprofen 2400 mg daily[21]. Improvement of all co-primary endpoints for etoricoxib and ibuprofen was evident within 2 weeks of the initial dose of study medication and was maintained throughout the 12 weeks of active therapy.

It is important in trials of this nature to determine whether the magnitude of the observed changes compared to placebo for indices of pain and physical function is actually clinically meaningful. In this and a similar study[21], the magnitude of the treatment responses for WOMAC subscales of pain and physical function in the etoricoxib group was in the range of changes recognized to be clinically meaningful to patients with OA of the knee or hip[36]. The significant efficacy of etoricoxib 30 mg vs placebo across the range of efficacy domains, including pain, stiffness, and physical function, clearly demonstrates its overall clinical effectiveness for the treatment of OA. Relief of morning stiffness for patients taking etoricoxib 30 mg is indicative of its sustained efficacy over the 24-h dosing interval and consistent with its pharmacokinetic profile[37].

Etoricoxib 30 mg and ibuprofen 2400 mg were both generally well tolerated in this study. The concomitant use of GPAs in this study does not allow for a rigorous comparison of GI safety and tolerability between treatments. However, the numerically lower incidence of GI AEs, despite the use of GPAs, is consistent with previous comparisons of GI safety and tolerability of etoricoxib to traditional NSAIDs[12,13,38,39].

The occurrence of renovascular AEs was closely monitored in this study because the role of prostaglandins in the regulation of renal homeostasis is well recognized[40]. Data from the third National Health and Nutrition Examination Survey indicate that approximately 40% of adults with OA also have hypertension, which is similar to the baseline status of the population in the present study[41]. In this study, the incidence of hypertension-related AEs was significantly higher for patients taking either ibuprofen or etoricoxib compared with placebo, with the highest incidence occurring in patients on ibuprofen. The incidence of edema-related AEs was similar in patients treated with etoricoxib 30 mg and ibuprofen 2400 mg and was numerically higher in patients receiving either active treatment compared with placebo. These data point out the importance of monitoring blood pressure in all patients on NSAID therapy.

This clinical trial was not designed to assess the thrombotic CV safety of etoricoxib or ibuprofen relative to placebo. However, a large, long-term non-inferiority clinical trials program, the Multinational Etoricoxib and Diclofenac Arthritis Long-term (MEDAL) Program[42,43], designed to assess the thrombotic CV risk of etoricoxib (60 or 90 mg) relative to the traditional NSAID diclofenac 150 mg in OA and rheumatoid arthritis patients, has recently been completed. The MEDAL Program demonstrated that rates of confirmed thrombotic CV events were comparable, yielding a hazard ratio of 0.95 (95% CI: 0.81, 1.11)[43]. These data help to inform the benefits and risks of treatment with a selective COX-2 inhibitor such as etoricoxib.

Table III
Summary of AEs in 12-week study of etoricoxib and ibuprofen in patients with OA

AE	Number of patients (%)		
	Placebo ($n=111$)	Etoricoxib 30 mg ($n=224$)	Ibuprofen 2400 mg ($n=213$)
Prespecified clinical AEs			
Any AE	57 (51.4)	113 (50.4)	123 (57.7)
Any drug-related AE	24 (21.6)	64 (28.6)	71 (33.3)*
Any serious AE	1 (0.9)†	3 (1.3)‡	5 (2.3)§
Discontinued due to an AE	5 (4.5)	11 (4.9)	18 (8.5)
Discontinued due to digestive or abdominal pain AE	4 (3.6)	4 (1.8)	10 (4.7)
Edema-related AE	2 (1.8)	8 (3.6)	7 (3.3)
Discontinued due to edema-related AE	0 (0)	1 (0.4)	1 (0.5)
Hypertension-related AE	1 (0.9)	14 (6.3)*	19 (8.9)**
Discontinue due to hypertension-related AE	0 (0)	2 (0.9)	2 (0.9)
CHF, pulmonary edema, or cardiac failure	0 (0)	1 (0.4)	1 (0.5)
Discontinued due to serious AE	0 (0)	1 (0.4)	4 (1.9)
Serious drug-related AE	0 (0)	0 (0)	1 (0.5)
Discontinued due to a drug-related AE	5 (4.5)	8 (3.6)	13 (6.1)
Discontinued due to serious drug-related AE	0 (0)	0 (0)	1 (0.5)
Most common drug-related AEs			
Epigastric discomfort	2 (1.8)	6 (2.7)	20 (9.4)
Nausea	3 (2.7)	4 (1.8)	9 (4.2)
Dyspepsia	4 (3.6)	7 (3.1)	7 (3.3)
Hypertension	1 (0.9)	9 (4.0)	14 (6.6)

*$P<0.05$ vs placebo. **$P=0.005$ vs placebo. †DVT. ‡CVA; CHF; and seizure/CVA. §Perforated appendicitis; musculoskeletal chest pain; embolic stroke; dental infection; and DVT (considered drug-related).

Conclusion

In this trial, treatment with etoricoxib 30 mg q.d. for the treatment of OA is well tolerated and provides therapeutic effectiveness that is superior to placebo and comparable to ibuprofen 2400 mg (800 mg t.i.d).

Acknowledgements

The authors would like to thank Mr Anish Mehta and Dr Paul Cavanaugh of Merck Research Laboratories for their assistance with preparation of this manuscript.

References

1. Elliott AM, Smith BH, Penny KI, Smith WC, Chambers WA. The epidemiology of chronic pain in the community. Lancet 1999 Oct 9;354(9186):1248–52.
2. Guccione AA. Arthritis and the process of disablement. Phys Ther 1994 May;74(5):408–14.
3. Guccione AA, Felson DT, Anderson JJ, Anthony JM, Zhang Y, Wilson PW, *et al*. The effects of specific medical conditions on the functional limitations of elders in the Framingham Study. Am J Public Health 1994 Mar;84(3):351–8.
4. Breedveld FC. Osteoarthritis—the impact of a serious disease. Rheumatology (Oxford) 2004 Feb;43(Suppl 1):i4–8.
5. Felson DT, Lawrence RC, Dieppe PA, Hirsch R, Helmick CG, Jordan JM, *et al*. Osteoarthritis: new insights. Part 1: The disease and its risk factors. Ann Intern Med 2000 Oct 17;133(8):635–46.
6. Woolf AD, Pflieger B. Burden of major musculoskeletal conditions. Bull World Health Organ 2003;81: 646–56.
7. Felson DT, Lawrence RC, Hochberg MC, McAlindon T, Dieppe PA, Minor MA, *et al*. Osteoarthritis: new insights. Part 2: Treatment approaches. Ann Intern Med 2000;133(9):726–37.
8. Towheed TE, Judd MJ, Hochberg MC, Wells G. Acetaminophen for osteoarthritis. Cochrane Database Syst Rev 2003;(2):CD004257.
9. Hochberg MC, Altman RD, Brandt KD, Clark BM, Dieppe PA, Griffin MR, *et al*. Guidelines for the medical management of osteoarthritis: Part I. Osteoarthritis of the hip. Arthritis Rheum 1995;38(11):1535–40.
10. Hochberg MC, Altman RD, Brandt KD, Clark BM, Dieppe PA, Griffin MR, *et al*. Guidelines for the medical management of osteoarthritis: Part II. Osteoarthritis of the knee. Arthritis Rheum 1995;38(11):1541–6.
11. Wolfe MM, Lichtenstein DR, Singh G. Gastrointestinal toxicity of nonsteroidal antiinflammatory drugs. N Engl J Med 1999;340(24):1888–99.
12. Hunt RH, Harper S, Watson DJ, Yu C, Quan H, Lee M, *et al*. The gastrointestinal safety of the COX-2 selective inhibitor etoricoxib assessed by both endoscopy and analysis of upper gastrointestinal events. Am J Gastroenterol 2003 Aug;98(8):1725–33.
13. Hunt RH, Harper S, Callegari P, Yu C, Quan H, Evans J, *et al*. Complementary studies of the gastrointestinal safety of the cyclo-oxygenase-2-selective inhibitor etoricoxib. Aliment Pharmacol Ther 2003 Jan; 17(2):201–10.
14. Bresalier RS, Sandler RS, Quan H, Bolognese JA, Oxenius B, Horgan K, *et al*. Cardiovascular events associated with rofecoxib in a colorectal adenoma chemoprevention trial. N Engl J Med 2005 Mar 17; 352(11):1092–102.
15. Bertagnolli MM, Eagle CJ, Zauber AG, Redston M, Solomon SD, Kim K, *et al*. Celecoxib for the prevention of sporadic colorectal adenomas. N Engl J Med 2006 Aug 31;355(9):873–84.
16. Kearney PM, Baigent C, Godwin J, Halls H, Emberson JR, Patrono C. Do selective cyclo-oxygenase-2 inhibitors and traditional non-steroidal anti-inflammatory drugs increase the risk of atherothrombosis? Meta-analysis of randomised trials. Br Med J 2006;332:1302–8.
17. EMEA. European Medicines Agency review concludes positive benefit-risk balance for nonselective NSAIDs. Doc Ref EMEA/413136/2006, http://www.emea.europa.eu/pdfs/general/direct/pr/41313606.pdf; 2006 Oct 24. accessed December 14, 2006.
18. Jenkins JK, Seligman PJ. Analysis and recommendations for agency action regarding nonsteroidal anti-inflammatory drugs and cardiovascular risk, http://www.fda.gov/cder/drug/infopage/COX2/NSAIDdecisionMemo.pdf; 4.6.2005. 1–19.
19. Food and Drug Administration. COX-2 selective (includes Bextra, Celebrex, and Vioxx) and non-selective non-steroidal anti-inflammatory drugs (NSAIDs), http://www.fda.gov/cder/drug/infopage/COX2/default.htm; 15.6.2005. accessed July 5, 2005.
20. Matsumoto AK, Cavanaugh PF Jr. Etoricoxib. Drugs Today (Barc) 2004 May;40(5):395–414.

21. Wiesenhutter CW, Boice JA, Ko A, Sheldon EA, Murphy FT, Wittmer BA, *et al*. Evaluation of the comparative efficacy of etoricoxib and ibuprofen for treatment of patients with osteoarthritis: a randomized, double-blind, placebo-controlled trial. Mayo Clin Proc 2005 Apr;80(4):470–9.
22. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, *et al*. The American rheumatism association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988;31(3): 315–24.
23. Altman R, Brandt K, Hochberg M, Moskowitz R, Bellamy N, Bloch DA, *et al*. Design and conduct of clinical trials in patients with osteoarthritis: recommendations from a task force of the Osteoarthritis Research Society. Osteoarthritis Cartilage 1996;4(4):217–43.
24. Bellamy N. WOMAC osteoarthritis index: a user's guide. Western Ontario and McMaster Universities, 1995.
25. Bellamy N. WOMAC: a 20-year experiential review of a patient-centered self-reported health status questionnaire. J Rheumatol 2002 Dec;29(12):2473–6.
26. Gottesdiener K, Schnitzer T, Fisher C, Bockow B, Markenson J, Ko A, *et al*. Results of a randomized, dose-ranging trial of etoricoxib in patients with osteoarthritis. Rheumatology (Oxford) 2002;41:1052–61.
27. Leung AT, Malmstrom K, Gallacher AE, Sarembock B, Poor G, Beaulieu A, *et al*. Efficacy and tolerability profile of etoricoxib in patients with osteoarthritis: a randomized, double-blind, placebo and active-comparator controlled 12-week efficacy trail. Curr Med Res Opin 2002;18(2):49–58.
28. Reginster J, Malmstrom K, Mehta A, Bergman G, Ko AT, Curtis SP, *et al*. Evaluation of the efficacy and safety of etoricoxib compared with naproxen in two, 138-week randomized studies of osteoarthritis patients. Ann Rheum Dis 2007;66:945–51.
29. Day R, Morrison B, Luza A, Casteneda O, Strusberg A, Nahir M, *et al*. A randomized trial of the efficacy and tolerability of the COX-2 inhibitor rofecoxib vs ibuprofen in patients with osteoarthritis. Arch Intern Med 2000;160:1781–7.
30. Saag K, van der Heijde D, Fisher C, Samara A, DeTora L, Bolognese J, *et al*. Rofecoxib, a new cyclooxgenase 2 inhibitor shows sustained efficacy, comparable with other nonsteroidal anti-inflammatory drugs: a 6-week and a 1-year trial in patients with osteoarthritis. Arch Fam Med 2000;9:1124–34.
31. Dunnett CW, Tamhane AC. Comparisons between a new drug and active and placebo controls in an efficacy clinical trial. Stat Med 1992;11:1057–63.
32. Altman R, Alarcon G, Appelrouth D, Bloch D, Borenstein D, Brandt K, *et al*. The American College of Rheumatology criteria for the classification and reporting of osteoarthritis of the hip. Arthritis Rheum 1991 May;34(5):505–14.
33. Ehrich EW, Davies GM, Watson DJ, Bolognese JA, Seidenberg BC, Bellamy N. Minimal perceptible clinical improvement with the Western Ontario and McMaster Universities Osteoarthritis index questionnaire and global assessments in patients with osteoarthritis. J Rheumatol 2000;27(11):2635–41.
34. Bellamy N, Buchanan WW, Goldsmith CH, Campbell J, Stitt LW. Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. J Rheumatol 1999;15(12):1833–40.
35. Dougados M, LeClaire P, Van der Heijdet D, Bloch DA, Bellamy N, Altman RD. Response criteria for clinical trials on osteoarthritis of the knee and hip: a report of the osteoarthritis research society international standing committee for clinical trials response criteria initiative. Osteoarthritis Cartilage 2000;8(6):395–403.
36. Tubach F, Ravaud P, Baron G, Falissard B, Logeart I, Bellamy N, *et al*. Evaluation of clinically relevant changes in patient reported outcomes in knee and hip osteoarthritis: the minimal clinically important improvement. Ann Rheum Dis 2005 Jan;64(1):29–33.
37. Agrawal NG, Porras AG, Matthews CZ, Rose MJ, Woolf EJ, Musser BJ, *et al*. Single- and multiple-dose pharmacokinetics of etoricoxib, a selective inhibitor of cyclooxygenase-2, in man. J Clin Pharmacol 2003 Mar;43(3):268–76.
38. Laine L, Curtis SP, Cryer B, Kaur A, Cannon CP. Assessment of upper gastrointestinal safety of etoricoxib and diclofenac in patients with osteoarthritis and rheumatoid arthritis in the Multinational Etoricoxib and Diclofenac Long-term (MEDAL) programme: a randomised comparison. Lancet 2007;369:465–73.
39. Baraf HS, Fuentealba C, Greenwald M, Brzezicki J, O'Brien K, Soffer B, *et al*. Gastrointestinal side effects of etoricoxib in patients with osteoarthritis: results of the etoricoxib versus Diclofenac Sodium Gastrointestinal Tolerability and Effectiveness (EDGE) Trial. J Rheumatol 2007 Feb;34(2):408–20.
40. Brater DC, Harris C, Redfern JS, Gertz BJ. Renal effects of COX-2-selective inhibitors. Am J Nephrol 2001;21:1–15.
41. Singh G, Miller JD, Lee FH, Pettitt D, Russell MW. Prevalence of cardiovascular disease risk factors among US adults with self-reported osteoarthritis: data from the Third National Health and Nutrition Examination Survey. Am J Manag Care 2002 Oct;(15 Suppl):S383–91.
42. Cannon CP, Curtis SP, Bolognese JA, Laine L. Clinical trial design and patient demographics of the Multinational Etoricoxib and Diclofenac Arthritis Long-term (MEDAL) Study Program: cardiovascular outcomes with etoricoxib vs. diclofenac in patients with osteoarthritis and rheumatoid arthritis. Am Heart J 2006; 152(2):237–45.
43. Cannon CP, Curtis SP, FitzGerald GA, Krum H, Kaur A, Bolognese JA, *et al*. Cardiovascular outcomes with etoricoxib and diclofenac in patients with osteoarthritis and rheumatoid arthritis in the Multinational Etoricoxib and Diclofenac Arthritis Long-term (MEDAL) programme: a randomised comparison. Lancet 2006 Nov 18;368(9549):1771–81.