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A Randomized, Multicenter, Phase III Trial to Evaluate the Efficacy and Safety of Polmacoxib Compared with Celecoxib and Placebo for Patients with Osteoarthritis

Myungchul Lee, MD, Juhyung Yoo, MD*, Jin Goo Kim, MD†, Hee-Soo Kyung, MD‡, Seong-Il Bin, MD§, Seung-Baik Kang, MD‖, Choong Hyeok Choi, MD¶, Young-Wan Moon, MD#, Young-Mo Kim, MD**, Seong Beom Han, MD††, Yong In, MD‡‡, Chong Hyuk Choi, MD§§, Jongoh Kim, MD‖‖, Beom Koo Lee, MD¶¶, Sangsook Cho, PhD##

*Department of Orthopedic Surgery, Seoul National University Hospital, Seoul, *Department of Orthopedic Surgery, National Health Insurance Service Ilsan Hospital, Goyang, †Department of Orthopedic Surgery, Konkuk University Medical Center, Seoul, ‡Clinical Research Center, Kyungpook National University Hospital, Daegu, §Department of Orthopedic Surgery, Asan Medical Center, Seoul, ‖Department of Orthopedic Surgery, SMG-SNU Boramae Medical Center, Seoul, ¶Department of Orthopedic Surgery, Hanyang University Seoul Hospital, Seoul, #Department of Orthopedic Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, **Clinical Research Center, Chungnam National University Hospital, Daejeon, ††Department of Orthopedic Surgery, Korea University Anam Hospital, Seoul, ‡‡Department of Orthopedic Surgery, Seoul St. Mary's Hospital, Seoul, §§Department of Orthopedic Surgery, Severance Hospital, Yonsei University College of Medicine, Seoul, ‖‖Department of Orthopedic Surgery, Ewha Womans University Mokdong Hospital, Seoul, ¶¶Department of Orthopedic Surgery, Korean Armed Forces Capital Hospital, Seongnam, Korea, ##Clinical Research Department, CG Pharmaceuticals, Inc., Orinda, CA, USA*

Background: The aim of this study was to evaluate the safety and analgesic efficacy of polmacoxib 2 mg versus placebo in a superiority comparison or versus celecoxib 200 mg in a noninferiority comparison in patients with osteoarthritis (OA).

Methods: This study was a 6-week, phase III, randomized, double-blind, and parallel-group trial followed by an 18-week, single arm, open-label extension. Of the 441 patients with knee or hip OA screened, 362 were randomized; 324 completed 6 weeks of treatment and 220 completed the extension. Patients were randomized to receive oral polmacoxib 2 mg (n = 146), celecoxib 200 mg (n = 145), or placebo (n = 71) once daily for 6 weeks. During the extension, all participants received open-label polmacoxib 2 mg. The primary endpoint was the change in Western Ontario and McMaster Universities (WOMAC)-pain subscale score from baseline to week 6. Secondary endpoints included WOMAC-OA Index, OA subscales (pain, stiffness, and physical function) and Physician's and Subject's Global Assessments at weeks 3 and 6. Other outcome measures included adverse events (AEs), laboratory tests, vital signs, electrocardiograms, and physical examinations.

Results: After 6 weeks, the polmacoxib-placebo treatment difference was –2.5 (95% confidence interval [CI], –4.4 to –0.6; p = 0.011) and the polmacoxib-celecoxib treatment difference was 0.6 (CI, –0.9 to 2.2; p = 0.425). According to Physician's Global Assessments, more subjects were "much improved" at week 3 with polmacoxib than with celecoxib or placebo. Gastrointestinal and general disorder AEs occurred with a greater frequency with polmacoxib or celecoxib than with placebo.

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Correspondence to: Sangsook Cho, PhD
Clinical Research Department, CG Pharmaceuticals, Inc., 4 Orinda Way, Suite 100-D, Orinda, CA 94563, USA
Tel: +1-925-257-7036, Fax: +1-925-257-7036, E-mail: scho@cgxinc.com

Conclusions: Polmacoxib 2 mg was relatively well tolerated and demonstrated efficacy superior to placebo and noninferior to celecoxib after 6 weeks of treatment in patients with OA. The results obtained during the 18-week trial extension with polmacoxib 2 mg were consistent with those observed during the 6-week treatment period, indicating that polmacoxib can be considered safe for long-term use based on this relatively small scale of study in a Korean population. More importantly, the results of this study showed that polmacoxib has the potential to be used as a pain relief drug with reduced gastrointestinal side effects compared to traditional nonsteroidal anti-inflammatory drugs for OA.

Keywords: *Osteoarthritis, Polmacoxib, Placebo, Celecoxib, Cyclooxygenase 2 inhibitor*

Osteoarthritis (OA) is a progressive, whole joint, inflammatory disease that involves the breakdown and damage of cartilage and surrounding bone tissues and is associated with increased swelling and pain.[1] There are approximately 54.4 million adults with doctor-diagnosed arthritis in the United States, including over half of the population above 50 years old. The most common form of arthritis is OA and about 30% of adults with obesity have doctor-diagnosed arthritis.[2] Given the rapidly ageing population and widespread obesity problem, the prevalence of OA is predicted to increase.

As there is no cure for OA, treatment plans are based on ways to manage pain and improve function. These plans include exercise and weight control, rest and joint care, surgery, and medication for pain relief.[3] Currently, the most widely prescribed medications for OA are nonsteroidal anti-inflammatory drugs (NSAIDs); however, traditional NSAIDs carry a high risk of adverse events (AEs), including serious gastrointestinal (GI) diseases.[4]

NSAIDs inhibit cyclooxygenase (COX) enzymes, which play a role in the regulation of inflammation. COX-1 is thought to protect the GI mucosa by the synthesis of prostaglandin,[5,6] while COX 2 expression is increased by inflammation and involved in both inflammation and pain pathways.[7] Conventional first generation NSAIDs are nonselective, inhibiting both COX-1 and COX-2, meaning that GI lesions may accompany their effects to reduce inflammation and pain.[5]

Compounds exhibiting greater COX-2 selectivity are thought to reduce damage to the GI tract by allowing the synthesis of protective prostaglandins through COX-1, while simultaneously maintaining anti-inflammatory effects by inhibiting COX-2. This led to the development of COX-2 selective drugs such as celecoxib and rofecoxib, which were reported to reduce GI-related AEs compared with conventional NSAIDs.[8,9]

However, some studies have demonstrated an increased risk of adverse cardiovascular (CV) events, including blood pressure elevation and myocardial infarction, with COX inhibition.[10,11] The health concerns associated with traditional NSAIDs and COX-2 inhibitors have led to confusion around the use of COX-2 inhibitors[12] and provide strong rationale for the development of safer NSAIDs with fewer AEs on the GI tract and CV system.

Recently, a new COX-2 inhibitor, polmacoxib (CG100649; Acelex), has been developed.[13,14] Unlike other NSAIDs, polmacoxib has a dual mode of action: inhibition of COX-2 and binding to carbonic anhydrase (CA) with high affinity.[15] A key function of CA is to regulate the pH level in the body through the interconversion between carbon dioxide and bicarbonate. Where COX-2 and CA coexist, the high-affinity binding of polmacoxib to CA reduces the COX-2 inhibitory activity of polmacoxib. Preliminary experiments have shown the COX-2 inhibitory activities of polmacoxib with varying amounts of CA in the system.[16] Since the CV side effects of traditional NSAIDs and COX-2 inhibitors are associated with COX-2 inhibition in the CV system where CA is abundant,[17] it is theoretically possible that the dual action mechanism of polmacoxib may minimize the adverse CV effects of COX-2 inhibition, although supportive clinical evidence is currently lacking. Importantly, low-dose administration of polmacoxib is believed to have a negligible effect on overall CA function in the circulatory system, despite polmacoxib theoretically remaining in a combined state with CA.[18]

The aim of this study was to evaluate the safety and analgesic efficacy of polmacoxib 2 mg versus placebo in a superiority comparison or versus celecoxib 200 mg in a noninferiority comparison, when administered once daily over 6 weeks in subjects with OA of the hip or knee. To reflect the lowest value of expected outcome to show the clinical and statistically significant difference between treatment groups, a number of studies on OA pain use a 10% noninferiority margin for chronic pain; as such, a prespecified noninferiority margin of 10% was used for the noninferiority analysis between polmacoxib and cele-

coxib in this study. If the upper boundary of the one-sided 97.5% confidence interval (CI) is within the prespecified noninferiority margin, the null hypothesis can be rejected in favor of the alternative hypothesis, which means that the polmacoxib group is noninferior to the celecoxib group. An 18-week trial extension, in which all participants received open-label polmacoxib 2 mg once daily, was conducted to provide supporting safety and efficacy evidence.

METHODS

Study Design and Conduct

This was a multicenter, phase III, randomized, double-blind, double-dummy, placebo- and active comparator-controlled, and parallel-group trial. After providing informed consent, subjects who were referred from primary care, entered into a 14-day washout period, in which subjects were required to discontinue existing treatment with NSAIDs and/or other analgesic medications. Subjects could take rescue medication (acetaminophen 650 mg/day) during the washout and follow-up periods. Rescue medication was not allowed during the treatment period or within 24 hours before a clinic visit.

After completion of the washout period, at visit 2 (baseline), subjects meeting the inclusion and exclusion criteria were randomized into the study according to their order of enrollment, using a stratified block randomization method for each site. Subjects were randomly assigned in a 2:2:1 ratio by an independent statistician using the SAS ver. 9.1 (SAS Institute Inc., Cary, NC, USA) and distributed by Interactive Web Response Service to receive either polmacoxib 2 mg, celecoxib 200 mg, or placebo once daily after breakfast over a 6-week treatment period. Investigational drugs were produced and packaged to maintain study blinding, and were supplied by the sponsor to an institutional pharmacist at each investigational site. Polmacoxib 2 mg, celecoxib 200 mg, and their respective placebos were identical in appearance and weight. To maintain blinding for both the subjects and investigators, study medications were labeled in an identical manner. To maintain double-blinding, identical double dummy placebos were used. The specific codes for each treatment group were kept in a sealed place by the sponsor and investigators, and were not to be opened until database lock and completion of the treatment assignment unblinding procedure.

During the 6-week treatment period, subjects returned for study visits at week 3, week 6, and week 8, which was the final follow-up visit for subjects who did not agree to participate in the extended safety period. At each visit, efficacy was assessed by the Western Ontario and McMaster Universities (WOMAC)-OA index as well as the Subject's Global Assessment (SGA) and Physician's Global Assessment (PGA). Samples for evaluation of pharmacokinetics were collected at baseline, week 6, and week 8. Standard safety assessments, including serology testing, were conducted throughout the 6-week period.

The 6-week treatment period was followed by an 18-week open-label extended safety period in which subjects had the option to participate; for subjects who agreed, a separate informed consent was required at the week 6 visit. All subjects who participated received polmacoxib 2 mg. During this period, subjects returned for study visits at week 12, week 18, week 24, and week 26, which was the final follow-up visit for subjects participating in the extended safety period. Efficacy assessment, pharmacokinetic sample collection, and safety assessment were done at specified visits during the 18-week period. All subjects completed a follow-up visit 2 weeks after discontinuation of study treatment for any reason.

Eligibility Criteria

Subjects eligible for this trial were either male or female (aged ≥ 20 years) with a clinical diagnosis of knee or hip OA according to clinical and imaging criteria specified by the American College of Rheumatology (ACR) guidelines.[19,20] Subjects must have had chronic pain for ≥ 3 months from OA and an ACR global functional status of I, II, or III (excluding IV).[21] Other inclusion criteria were as follows: screening and baseline (predose) mean WOMAC-pain score in the index joint between 4 and 8; blood chemistry within twice the normal range; urinalysis within normal limits, macroscopic evaluation showing no blood; agreement to use double barrier contraception during the study period and for 3 months afterwards; able to read, understand and follow the study documents; willing to limit alcohol intake to ≤ 2 drinks per day.

Subjects were excluded, discontinued, removed from the trial and not considered in the per-protocol and modified intent-to-treat (ITT) populations for analysis if they met any of the following criteria: use of any analgesics except the study medication or acetaminophen during the study; use of anticoagulants within 2 weeks of screening; use of corticosteroids, herbal medicines, traditional Korean medicines, nutraceuticals, glucosamine, and/or chondroitin sulfate; requirement for knee or hip arthroplasty within 2 months of screening or anticipating any need for a surgical procedure on the index joint during the study; hypersensitivity or allergy to NSAIDs; history of nasal polyps, bronchospasm, urticaria, or anaphylactic shock;

history of New York Heart Association stage II–IV congestive heart failure, ischemic heart disease, uncontrolled hypertension, peripheral arterial disease, and/or cerebrovascular disease; pregnancy, breast-feeding, or expecting conception within the duration of the study; active ulcer, GI bleeding, ulcerative colitis, or severe renal, hepatic, or coagulant disorder within 6 months prior to randomization; ongoing chronic symptoms or psychiatric disorders preventing compliance with study procedures, except for subjects who were physically healthy and had been receiving the specified allowed drugs for ≥ 3 months; use of corticosteroids, intra-articular steroids or hyaluronic acid injections within 1 month of screening; chemotherapy within 5 years; or a Chinese traditional arthritis treatment within 1 week of screening.

Patients with stable hypertension for ≥ 3 months prior to screening, treated with antihypertensive medication, were permitted to participate in the study.

Efficacy Assessments

Efficacy was evaluated by the WOMAC arthritis index questionnaire (which was validated in OA patients and in Koreans),[22,23] the PGA and SGA,[24] and discontinuation from the study owing to a lack of analgesic efficacy. The numerical rating scale version of the WOMAC was used, with the subject assessing each question using an 11-point (0 to 10) numerical rating scale, and the total index score being represented by the sum of the component item scores. A higher WOMAC score represents worse symptom severity. The primary endpoint was the change in the WOMAC-pain subscale (five items, total score 0 to 50) in the index joint at week 6 versus day 1 (predose baseline). Secondary endpoints included the change in WOMAC-pain at week 3 and changes in WOMAC-stiffness (two items, total score 0 to 20), WOMAC-physical function (17 items, total score 0 to 170), WOMAC-OA index (24 items, total score 0 to 240), and SGA and PGA tests at both weeks 3 and 6. SGA and PGA tests were based on a 7-point Likert scale, assessing the overall condition asking the following question, "please choose a number that best represents the condition of the pain area during the past week."

Safety Assessments

Safety assessments included the number of AEs, including serious AEs (SAEs), treatment-emergent AEs (TEAEs; a condition that was not present prior to treatment with study medication, but appeared following treatment), deaths, and AEs leading to discontinuation. Other safety assessments included complete physical examinations, vital signs, 12-lead electrocardiograms and clinical laboratory tests (for hematology, clinical chemistry, coagulation, and urinalysis). Plasma and whole blood samples were taken for the pharmacokinetic assessment of polmacoxib after breakfast and administration of study drugs at day 1, weeks 6, and 8 for subjects who participated in the main 6-week treatment period only, and at day 1, weeks 6, 24, and 26 for extension period participants.

For subjects who participated in the 6-week treatment period only, safety assessments were conducted at weeks 3, 6, and 8 (follow-up visit). For trial extension participants, safety assessments were conducted at weeks 3, 6, 12, 18, 24, and 26.

Statistical Analysis

Calculation of sample size

Based on the International Conference on Harmonisation guideline E1,[25] guidelines for noninferiority clinical trials of the U.S. Food and Drug Administration,[26] and other similar study,[27] the standard deviation and noninferiority margin were conservatively chosen for the calculation of sample size. For evaluation of noninferiority between polmacoxib and celecoxib for analgesic efficacy, the following parameters were used to calculate the sample size needed: level of significance, $\alpha = 0.025$ (one-sided); statistical power, $1 - \beta = 0.95$; standard deviation = 11; noninferiority margin = 5 (10%); and difference between test group and comparison group, $\Delta = 0$, $\delta (> 0)$ = noninferiority margin. The calculated sample size for the noninferiority test (n = 126 for polmacoxib 2 mg and celecoxib 200 mg and n = 63 for placebo) was sufficient to fulfill the sample size needed for the superiority test for this trial at 93% statistical power.

Testing between drugs was conducted in the following order: (1) test for superiority between placebo versus polmacoxib or celecoxib, (2) test for noninferiority using upper CI between polmacoxib and celecoxib, and (3) test for superiority between polmacoxib and celecoxib. The primary endpoint was analyzed using a mixed effect analysis of covariance (ANCOVA), with terms for site as a random explanatory variable, treatment as a fixed explanatory variable, and baseline score as a covariate. Noninferiority was based on whether the upper limit of the one-sided 97.5% CI of the difference between the polmacoxib 2 mg and celecoxib 200 mg treatment groups, derived from the mixed effects ANCOVA, was less than or equal to the prespecified noninferiority margin of 10% (5 points on the WOMAC-pain subscale). Analysis of variance results were reported with least square (LS) means and their standard errors for the treatment group results, and estimates, their

standard errors, and 95% CIs for treatment differences. The secondary endpoints were analyzed using a repeated measurement ANCOVA, with terms for site as a random explanatory variable, treatment as a fixed explanatory variable, and baseline score as a covariate. Noninferiority for the secondary endpoints was predefined as 10% of the maximum score for each scale or subscale. Noninferiority was not evaluated for the SGA and PGA tests.

Continuous demographic parameters were summarized for the ITT population, defined as all randomized patients, using descriptive statistics. Categorical demographic parameters were summarized as a proportion of the ITT population. The primary and secondary efficacy evaluations were based on the ITT population using baseline observation carried forward (BOCF) method, regarded as the most conservative imputation method in pain subject analysis. Sensitivity analyses were made using various imputation methods in all analysis populations. All safety data were analyzed using the safety population. No data imputation was used for missing safety data.

Study populations are defined as follows: (1) ITT population: all randomized subjects; (2) modified ITT population: all randomized subjects who met all inclusion/exclusion criteria, received at least one dose of study product and returned for at least one postbaseline visit; (3) per-protocol population: all randomized subjects who met all inclusion/exclusion criteria, were at least 80% or more compliant with the assigned study treatment, returned to the study site for the primary endpoint visit within the specified time period or withdrew consent due to treatment failure, and had no major protocol violations; (4) safety population: all subjects who were administered any amount of study product. It was not possible to conduct statistical analysis for treatment comparisons beyond week 6 as there was only a single treatment arm during the 18-week trial extension.

Ethics

This study was registered with and approved by the Ministry of Food and Drug Safety of the Republic of Korea (IND 11004 CG100649-3-01; ClinicalTrials.gov: NCT01765296) and approved by the Independent Ethics Committee and Institutional Review Board at each of its 14 study sites: Seoul National University Hospital, National Health Insurance Service Ilsan Hospital, Inje University Seoul Paik Hospital, Kyungpook National University Hospital, Asan Medical Center, SMG-SNU Boramae Medical Center, Hanyang University Seoul Hospital, Samsung Medical Center, Chungnam National University Hospital, Korea University Anam Hospital, Seoul St. Mary's Hospital, Yonsei University, Ewha Womans University Mokdong Hospital, and Gachon University Gil Medical Center. All subjects provided written informed consent prior to participation in the study, and the study was conducted in compliance with principles of Good Clinical Practice.

RESULTS

Patients

The study was conducted in patients with OA at 14 tertiary care centers in Korea from March 25, 2013 to December 9, 2013. Of the 441 subjects screened for this study, 362 were randomized to three treatment groups as follows: 71 (16.1%) to placebo, 146 (33.1%) to polmacoxib 2 mg once daily, and 145 (32.9%) to celecoxib 200 mg once daily (Fig. 1). The majority of subjects in the study were females (85.4%) and the average age was 62.4 years (Table 1). All subjects were Asian, and the majority had knee joint OA (99.2%). Most subjects in each treatment group had ACR class II functional status, indicating that they could perform usual self-care activities, but had limited function in other activities. Alcohol use was limited to < 1 drink daily for 87.3% of subjects, and the majority had never smoked (95.9%). Other baseline patient demographics, concomitant medications, medical conditions or procedures reported, and baseline scores for efficacy assessments are shown in Table 1.

Efficacy

Primary efficacy outcome

The LS mean reductions from baseline to week 6 in WOMAC-pain subscale scores were significantly greater in both the polmacoxib group and the celecoxib group than the reduction observed in the placebo group (Tables 2-4 and Fig. 2A). The difference between the polmacoxib and celecoxib groups was not significant. The upper bound of the one-sided 97.5% CI was 2.2 (2.1 in the per-protocol population), less than the prespecified noninferiority margin of 5 for WOMAC-pain subscale. This result of noninferiority between polmacoxib and celecoxib groups was observed consistently with those from the sensitivity analyses based on different imputation methods. Results from the analysis of the per-protocol (Table 4) and observed cases without imputation in ITT population (Table 3) were also consistent with the results of the analysis of ITT population with BOCF imputation (Table 2).

Secondary efficacy outcomes

• Change in WOMAC-pain subscale at week 3: LS mean decreases from baseline were observed in all treatment

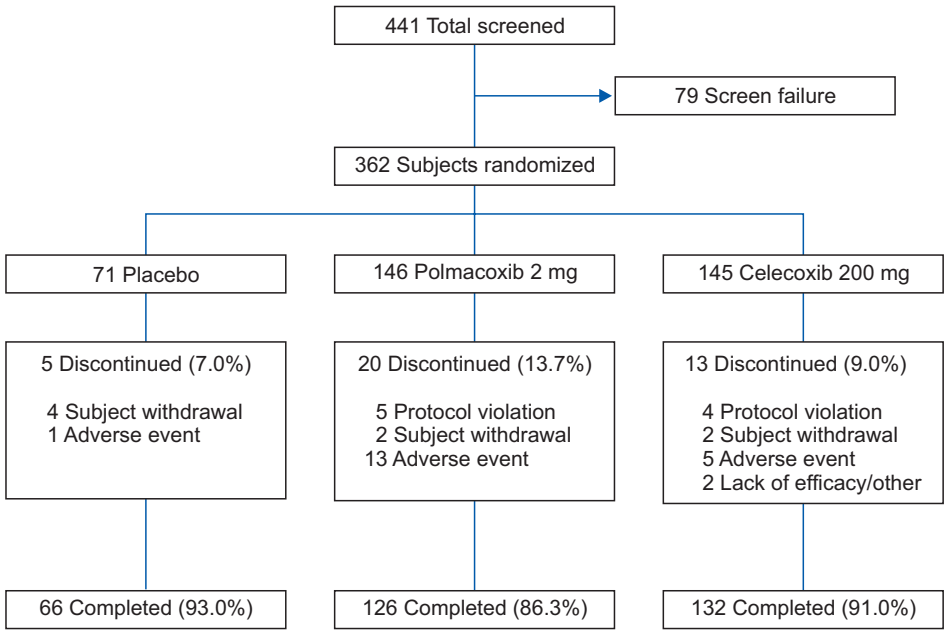

Fig. 1. Subject disposition throughout the 6-week period.

groups at week 3 (Tables 2-4 and Fig. 2A). The mean changes from baseline in both the polmacoxib group and the celecoxib group were significantly greater than the change observed in the placebo group. The difference between the polmacoxib and celecoxib groups was not statistically significant. Results from the analysis of the per-protocol population and sensitivity analyses using other imputation methods were similar to those observed using the BOCF imputation method.

• Change in WOMAC-OA index: LS mean decreases from baseline in WOMAC-OA index scores were observed in all treatment groups at week 3 (Tables 2-4 and Fig. 2B). LS mean decreases from baseline were significantly greater in both the polmacoxib group and the celecoxib group than the change observed in the placebo group for both weeks 3 and 6.

• Change in WOMAC-stiffness subscale: LS mean decreases from baseline in WOMAC-stiffness subscale scores were observed in all treatment groups at week 3 (Tables 2-4 and Fig. 2C). LS mean changes at week 6 were similar to those observed at week 3 in all treatment groups. At both time points, the LS mean changes in both the polmacoxib and the celecoxib groups were significantly greater than the change observed in the placebo group, while the difference between the polmacoxib and celecoxib groups was not statistically significant.

• Change in WOMAC-physical function subscale: LS mean decreases in WOMAC-physical function subscale scores from baseline were observed in all treatment groups at week 3 (Tables 2-4 and Fig. 2D). The difference in the LS mean change from baseline between the placebo and celecoxib groups was not statistically significant at this time point, while the difference between the placebo and polmacoxib groups was statistically significant. Similar results were also observed in all treatment groups in the per-protocol (Table 4) and modified ITT populations, and in the sensitivity analyses using other imputation methods, including analysis of observed cases without imputation. LS mean decreases were also observed at week 6 in all treatment groups (Tables 2-4 and Fig. 2D). The mean changes from baseline in both polmacoxib and celecoxib groups were greater than the change observed in the placebo group at week 6. The difference between the polmacoxib and celecoxib groups was not statistically significant. Similar results were observed in all analysis populations, including all sensitivity analyses.

• Change in SGA and PGA: Across all treatment groups, most subjects reported minimal improvement in their condition at week 3 (Table 5). However, 20.0% of subjects in the polmacoxib group and 14.9% of subjects in the celecoxib group reported their condition as "much improved" or "very much improved" by week 3 compared with 3.0% of subjects in the placebo group; similar results were observed at week 6 for subjects in the polmacoxib (16.7%), celecoxib (12.1%), and placebo (1.5%) groups.

Based on the PGA, by week 3, 22.9% of subjects in the polmacoxib group and 17.1% of subjects in the celecoxib group were considered by the investigator to be "much improved" or "very much improved" compared with 4.5% of subjects in the placebo group (Table 5). A

Table 1. Demographic and Baseline Characteristics (ITT Population)

Characteristic	Placebo (n = 71)	Polmacoxib 2 mg (n = 146)	Celecoxib 200 mg (n = 145)	Total (n = 362)
Age (yr)				
Mean ± SD	62.9 ± 9.0	62.5 ± 7.5	62.1 ± 7.6	62.4 ± 7.8
Median (range)	63 (28–83)	63 (40–78)	62 (44–82)	63 (28–83)
Sex				
Male	10 (14.1)	21 (14.4)	22 (15.2)	53 (14.6)
Female	61 (85.9)	125 (85.6)	123 (84.8)	309 (85.4)
Race (Asian)	71	146	145	362
Smoking status				
Never	69 (97.2)	139 (95.2)	139 (95.9)	347 (95.9)
Former	1 (1.4)	5 (3.4)	3 (2.1)	9 (2.5)
Current	1 (1.4)	2 (1.4)	3 (2.1)	6 (1.7)
Drinking status				
< 1 Drink per day	62 (87.3)	129 (88.4)	125 (86.2)	316 (87.3)
1–2 Drinks per day	3 (4.2)	2 (1.4)	3 (2.1)	8 (2.2)
≥ 3 Drinks per day	6 (8.5)	15 (10.3)	17 (11.7)	38 (10.5)
Concomitant medication				
Anti-inflammatory and anti-rheumatic drugs, non-steroids	28 (39.4)	76 (52.1)	54 (37.2)	158 (43.6)
Drugs for peptic ulcers and gastroesophageal reflux disease	20 (28.2)	61 (41.8)	28 (19.3)	109 (30.1)
Lipid-modifying drugs, single agents	14 (19.7)	33 (22.6)	32 (22.1)	79 (21.8)
Selective calcium channel blockers with mainly vascular effects	14 (19.7)	21 (14.4)	16 (11.0)	51 (14.1)
Blood glucose-lowering drugs, excluding insulins	12 (16.9)	12 (8.2)	26 (17.9)	50 (13.8)
Propulsives	8 (11.3)	21 (14.4)	16 (11.0)	45 (12.4)
Angiotensin II antagonists, combination	6 (8.5)	12 (8.2)	15 (10.3)	33 (9.1)
Angiotensin II antagonists, plain	4 (5.6)	18 (12.3)	11 (7.6)	33 (9.1)
Medical condition or procedure				
Hypertension	22 (31.0)	55 (37.7)	42 (29.0)	119 (32.9)
Hyperlipidaemia	10 (14.1)	31 (21.2)	29 (20.0)	70 (19.3)
Osteoporosis	8 (11.3)	17 (11.6)	13 (9.0)	38 (10.5)
Diabetes mellitus	8 (11.3)	9 (6.2)	19 (13.1)	36 (9.9)
Meniscus injury	3 (4.2)	15 (10.3)	17 (11.7)	35 (9.7)
Gastritis	5 (7.0)	14 (9.6)	13 (9.0)	32 (8.8)
WOMAC-pain subscale				
Mean ± SD	26.8 ± 4.58	27.9 ± 5.01	27.7 ± 5.08	27.6 ± 4.96
Median (range)	26.0 (20–40)	27.0 (20–40)	27.0 (20–40)	27.0 (20–40)
WOMAC-OA index				
Mean ± SD	129.2 ± 26.52	132.6 ± 26.44	131.6 ± 25.94	131.5 ± 26.21
Median (range)	130.0 (74–194)	132.0 (72–196)	130.0 (73–197)	131.0 (72–197)
WOMAC-stiffness subscale				
Mean ± SD	10.4 ± 3.52	11.1 ± 3.44	11.1 ± 3.23	10.9 ± 3.37
Median (range)	11.0 (0–17)	11.0 (0–18)	11.0 (0–18)	11.0 (0–18)
WOMAC-physical function subscale				
Mean ± SD	92.0 ± 19.87	93.6 ± 19.50	92.8 ± 19.26	93.0 ± 19.43
Median (range)	92.0 (46–139)	92.0 (46–138)	92.0 (51–144)	92.0 (46–144)

Values are presented as number (%) unless otherwise indicated.
ITT: intent-to-treat, SD: standard deviation, WOMAC: Western Ontario and McMaster Universities, OA: osteoarthritis.

Table 2. Summary Results* of Noninferiority and Superiority Tests on Change in WOMAC Index from Baseline to Weeks 3 and 6 as Primary and Secondary Endpoints in ITT Population: Baseline Observation Carried Forward

Variable	Week 3			Week 6		
	Placebo (n = 71)	Polmacoxib 2 mg (n = 146)	Celecoxib 200 mg (n = 145)	Placebo (n = 71)	Polmacoxib 2 mg (n = 146)	Celecoxib 200 mg (n = 145)
WOMAC-pain						
LS mean change	–2.0 ± 0.85 (–3.7 to –0.4)	–4.9 ± 0.68 (–6.2 to –3.6)	–4.4 ± 0.68 (–5.7 to –3.1)	–2.6 ± 0.90 (–4.4 to –0.8)	–5.1 ± 0.70 (–6.5 to –3.7)	–5.7 ± 0.70 (–7.1 to –4.4)
Comparisons vs. placebo		–2.9 ± 0.87 (–4.6 to –1.2)	–2.4 ± 0.87 (–4.1 to –0.7)		–2.5 ± 0.98 (–4.4 to –0.6)	–3.1 ± 0.98 (–5.1 to –1.2)
p-value		0.001	0.007		0.011	0.001
Polmacoxib vs. celecoxib		–0.5 ± 0.70 (–1.9 to 0.9)			0.6 ± 0.79 (–0.9 to 2.2)	
p-value		0.471			0.425	
Noninferiority (NI margin = 5)	Yes, UCI (0.9) is less than NI margin (5)			Yes, UCI (2.2) is less than NI margin (5)		
WOMAC-stiffness						
LS mean change	–0.4 ± 0.32 (–1.0 to 0.3)	–1.7 ± 0.25 (–2.2 to –1.2)	–1.2 ± 0.25 (–1.7 to –0.7)	–0.5 ± 0.42 (–1.3 to 0.3)	–1.6 ± 0.33 (–2.3 to –1.0)	–1.7 ± 0.33 (–2.3 to –1.0)
Comparisons vs. placebo		–1.4 ± 0.36 (–2.1 to –0.7)	–0.9 ± 0.36 (–1.6 to –0.2)		–1.1 ± 0.43 (–2.0 to –0.3)	–1.2 ± 0.43 (–2.0 to –0.3)
p-value		< 0.001	0.014		0.008	0.007
Polmacoxib vs. celecoxib		–0.5 ± 0.29 (–1.0 to 0.1)			0.0 ± 0.35 (–0.7 to 0.7)	
p-value		0.102			0.934	
Noninferiority (NI margin = 2)	Yes, UCI (0.1) is less than NI margin (2)			Yes, UCI (0.7) is less than NI margin (2)		
WOMAC-physical function						
LS mean change	–5.7 ± 2.49 (–10.6 to –0.8)	–13.7 ± 1.92 (–17.5 to –9.9)	–10.7 ± 1.92 (–14.5 to –6.9)	–7.9 ± 2.83 (–13.4 to –2.3)	–14.3 ± 2.18 (–18.6 to –10.0)	–14.9 ± 2.18 (–19.1 to –10.6)
Comparisons vs. placebo		–8.0 ± 2.71 (–13.3 to –2.6)	–5.0 ± 2.71 (–10.3 to 0.4)		–6.5 ± 3.08 (–12.5 to –0.4)	–7.0 ± 3.08 (–13.1 to –0.9)
p-value		0.003	0.069		0.036	0.024
Polmacoxib vs. celecoxib		–3.0 ± 2.20 (–7.3 to 1.3)			0.5 ± 2.49 (–4.4 to 5.4)	
p-value		0.17			0.833	
Noninferiority (NI margin = 17)	Yes, UCI (1.3) is less than NI margin (17)			Yes, UCI (5.4) is less than NI margin (17)		
WOMAC-OA index						
LS mean change	–8.0 ± 3.51 (–14.9 to –1.1)	–20.4 ± 2.73 (–25.8 to –15.0)	–16.4 ± 2.73 (–21.7 to –11.0)	–10.8 ± 3.97 (–18.6 to –3.0)	–21.2 ± 3.07 (–27.2 to –15.2)	–22.4 ± 3.07 (–28.4 to –16.3)
Comparisons vs. placebo		–12.4 ± 3.77 (–19.8 to –5.0)	–8.3 ± 3.77 (–15.8 to –0.9)		–10.4 ± 4.31 (–18.8 to –1.9)	–11.5 ± 4.31 (–20.0 to –3.1)
p-value		0.001	0.027		0.016	0.008
Polmacoxib vs. celecoxib		–4.0 ± 3.05 (–10.0 to 2.0)			1.2 ± 3.48 (–5.7 to 8.0)	
p-value		0.187			0.740	
Noninferiority (NI margin = 24)	Yes, UCI (2.0) is less than NI margin (24)			Yes, UCI (8.0) is less than NI margin (24)		

Values are presented as mean ± standard error (95% confidence interval).
WOMAC: Western Ontario and McMaster Universities, ITT: intent-to-treat, LS: least square, NI: noninferiority, UCI: upper confidence interval, OA: osteoarthritis.
*Data obtained from a mixed-effects analysis of covariance model with fixed effects for treatment group and baseline pain score and a random effect for pooled site.

Table 3. Summary Results* of Noninferiority and Superiority Tests on Change in WOMAC Index from Baseline to Weeks 3 and 6 as Primary and Secondary Endpoints in ITT Population: Observed Cases

Variable	Week 3			Week 6		
	Placebo (n = 67)	Polmacoxib 2 mg (n = 135)	Celecoxib 200 mg (n = 134)	Placebo (n = 66)	Polmacoxib 2 mg (n = 126)	Celecoxib 200 mg (n = 132)
WOMAC-pain						
LS mean change	–2.2 ± 0.90 (–3.9 to –0.4)	–5.3 ± 0.74 (–6.7 to –3.8)	–4.8 ± 0.74 (–6.2 to –3.3)	–2.7 ± 1.02 (–4.7 to –0.7)	–6.0 ± 0.84 (–7.6 to –4.3)	–6.3 ± 0.83 (–7.9 to –4.7)
Comparisons vs. placebo		–3.1 ± 0.90 (–4.9 to –1.3)	–2.6 ± 0.90 (–4.4 to –0.9)		–3.2 ± 1.03 (–5.3 to –1.2)	–3.6 ± 1.02 (–5.6 to –1.6)
p-value		0.001	0.004		0.002	0.001
Polmacoxib vs. celecoxib		–0.5 ± 0.73 (–1.9 to 0.9)			0.4 ± 0.85 (–1.3 to 2.0)	
p-value		0.501			0.669	
Noninferiority (NI margin = 5)	Yes, UCI (0.9) is less than NI margin (5)			Yes, UCI (2.0) is less than NI margin (5)		
WOMAC-stiffness						
LS mean change	–0.3 ± 0.34 (–1.0 to 0.4)	–1.9 ± 0.26 (–2.4 to –1.3)	–1.4 ± 0.26 (–1.9 to –0.8)	–0.5 ± 0.45 (–1.4 to 0.4)	–1.9 ± 0.38 (–2.7 to –1.2)	–1.9 ± 0.37 (–2.6 to –1.2)
Comparisons vs. placebo		–1.6 ± 0.37 (–2.3 to –0.8)	–1.0 ± 0.37 (–1.8 to –0.3)		–1.5 ± 0.46 (–2.4 to –0.6)	–1.4 ± 0.45 (–2.3 to –0.5)
p-value		< 0.001	0.005		0.002	0.002
Polmacoxib vs. celecoxib		–0.5 ± 0.30 (–1.1 to 0.1)			–0.0 ± 0.37 (–0.8 to 0.7)	
p-value		0.094			0.941	
Noninferiority (NI margin = 2)	Yes, UCI (0.1) is less than NI margin (2)			Yes, UCI (0.7) is less than NI margin (2)		
WOMAC-physical function						
LS mean change	–6.1 ± 2.67 (–11.3 to –0.8)	–14.9 ± 2.11 (–19.0 to –10.7)	–11.6 ± 2.11 (–15.7 to –7.4)	–8.4 ± 3.17 (–14.6 to –2.1)	–16.7 ± 2.59 (–21.8 to –11.6)	–16.2 ± 2.56 (–21.3 to –11.2)
Comparisons vs. placebo		–8.8 ± 2.85 (–14.4 to –3.2)	–5.5 ± 2.85 (–11.1 to 0.1)		–8.3 ± 3.29 (–14.8 to –1.9)	–7.9 ± 3.26 (–14.3 to –1.5)
p-value		0.002	0.055		0.012	0.016
Polmacoxib vs. celecoxib		–3.3 ± 2.32 (–7.8 to 1.3)			–0.4 ± 2.70 (–5.8 to 4.9)	
p-value		0.16			0.868	
Noninferiority (NI margin = 17)	Yes, UCI (1.3) is less than NI margin (17)			Yes, UCI (4.9) is less than NI margin (17)		
WOMAC-OA index						
LS mean change	–8.5 ± 3.75 (–15.9 to –1.1)	–22.1 ± 2.99 (–28.0 to –16.2)	–17.8 ± 2.99 (–23.7 to –11.9)	–11.5 ± 4.46 (–20.3 to –2.7)	–24.7 ± 3.66 (–31.9 to –17.5)	–24.5 ± 3.61 (–31.6 to –17.4)
Comparisons vs. placebo		–13.6 ± 3.94 (–21.3 to –5.8)	–9.3 ± 3.94 (–17.0 to –1.5)		–13.2 ± 4.59 (–22.2 to –4.2)	–13.0 ± 4.55 (–22.0 to –4.1)
p-value		0.001	0.019		0.004	0.004
Polmacoxib vs. celecoxib		–4.3 ± 3.21 (–10.6 to 2.0)			–0.2 ± 3.76 (–7.5 to 7.2)	
p-value		0.183			0.967	
Noninferiority (NI margin = 24)	Yes, UCI (2.0) is less than NI margin (24)			Yes, UCI (7.2) is less than NI margin (24)		

Values are presented as mean ± standard error (95% confidence interval).
WOMAC: Western Ontario and McMaster Universities, ITT: intent-to-treat, LS: least square, NI: noninferiority, UCI: upper confidence interval, OA: osteoarthritis.
*Data obtained from a mixed-effects analysis of covariance model with fixed effects for treatment group and baseline pain score and a random effect for pooled site.

Table 4. Summary Results* of Noninferiority and Superiority Tests on Change in WOMAC Index from Baseline to Weeks 3 and 6 as Primary and Secondary Endpoints in Per-Protocol Population

Variable	Week 3			Week 6		
	Placebo (n = 61)	Polmacoxib 2 mg (n = 112)	Celecoxib 200 mg (n = 121)	Placebo (n = 61)	Polmacoxib 2 mg (n = 112)	Celecoxib 200 mg (n = 121)
WOMAC-pain						
LS mean change	–2.3 ± 0.99 (–4.3 to –0.4)	–5.4 ± 0.84 (–7.0 to –3.7)	–5.0 ± 0.82 (–6.6 to –3.4)	–2.6 ± 1.07 (–4.7 to –0.5)	–6.3 ± 0.89 (–8.0 to –4.6)	–6.6 ± 0.87 (–8.3 to –4.9)
Comparisons vs. placebo		–3.0 ± 0.99 (–5.0 to –1.1)	–2.7 ± 0.98 (–4.6 to –0.8)		–3.7 ± 1.12 (–5.9 to –1.5)	–4.0 ± 1.11 (–6.2 to –1.8)
p-value		0.002	0.006		0.001	< 0.001
Polmacoxib vs. celecoxib		–0.3 ± 0.81 (–1.9 to 1.3)			0.3 ± 0.92 (–1.5 to 2.1)	
p-value		0.682			0.727	
Noninferiority (NI margin = 5)	Yes, UCI (1.3) is less than NI margin (5)			Yes, UCI (2.1) is less than NI margin (5)		
WOMAC-stiffness						
LS mean change	–0.4 ± 0.37 (–1.1 to 0.4)	–1.9 ± 0.29 (–2.5 to –1.3)	–1.5 ± 0.28 (–2.1 to –0.9)	–0.6 ± 0.49 (–1.6 to 0.3)	–2.1 ± 0.41 (–2.9 to –1.3)	–2.1 ± 0.40 (–2.9 to –1.3)
Comparisons vs. placebo		–1.6 ± 0.41 (–2.4 to –0.7)	–1.2 ± 0.41 (–2.0 to –0.4)		–1.5 ± 0.48 (–2.4 to –0.5)	–1.4 ± 0.48 (–2.4 to –0.5)
p–value		< 0.001	0.005		0.003	0.003
Polmacoxib vs. celecoxib		–0.4 ± 0.34 (–1.1 to 0.3)			0.0 ± 0.40 (–0.8 to 0.8)	
p-value		0.24			0.962	
Noninferiority (NI margin = 2)	Yes, UCI (0.3) is less than NI margin (2)			Yes, UCI (0.8) is less than NI margin (2)		
WOMAC-physical function						
LS mean change	–6.6 ± 2.90 (–12.3 to –0.9)	–14.7 ± 2.35 (–19.3 to –10.1)	–11.7 ± 2.29 (–16.2 to –7.2)	–8.4 ± 3.33 (–15.0 to –1.8)	–17.4 ± 2.71 (–22.7 to –12.0)	–17.1 ± 2.64 (–22.3 to –11.9)
Comparisons vs. placebo		–8.1 ± 3.15 (–14.3 to –1.9)	–5.1 ± 3.11 (–11.2 to 1.0)		–9.0 ± 3.59 (–16.0 to –1.9)	–8.7 ± 3.54 (–15.6 to –1.7)
p-value		0.011	0.1		0.013	0.015
Polmacoxib vs. celecoxib		–3.0 ± 2.59 (–8.1 to 2.1)			–0.3 ± 2.96 (–6.1 to 5.5)	
p-value		0.254			0.917	
Noninferiority (NI margin = 17)	Yes, UCI (2.1) is less than NI margin (17)			Yes, UCI (5.5) is less than NI margin (17)		
WOMAC-OA index						
LS mean change	–9.3 ± 4.08 (–17.3 to –1.2)	–22.1 ± 3.34 (–28.6 to –15.5)	–18.3 ± 3.25 (–24.7 to –11.9)	–11.5 ± 4.68 (–20.8 to –2.3)	–25.9 ± 3.83 (–33.4 to –18.3)	–25.8 ± 3.74 (–33.2 to –18.5)
Comparisons vs. placebo		–12.8 ± 4.36 (–21.4 to –4.2)	–9.1 ± 4.30 (–17.5 to –0.6)		–14.3 ± 5.00 (–24.2 to –4.5)	–14.3 ± 4.93 (–24.0 to –4.6)
p-value		0.004	0.036		0.004	0.004
Polmacoxib vs. celecoxib		–3.7 ± 3.59 (–10.8 to 3.3)			–0.1 ± 4.11 (–8.2 to 8.0)	
p-value		0.299			0.988	
Noninferiority (NI margin = 24)	Yes, UCI (3.3) is less than NI margin (24)			Yes, UCI (8.0) is less than NI margin (24)		

Values are presented as mean ± standard error (95% confidence interval).
WOMAC: Western Ontario and McMaster Universities, ITT: intent-to-treat, LS: least square, NI: noninferiority, UCI: upper confidence interval, OA: osteoarthritis.
*Data obtained from a mixed-effects analysis of covariance model with fixed effects for treatment group and baseline pain score and a random effect for pooled site.

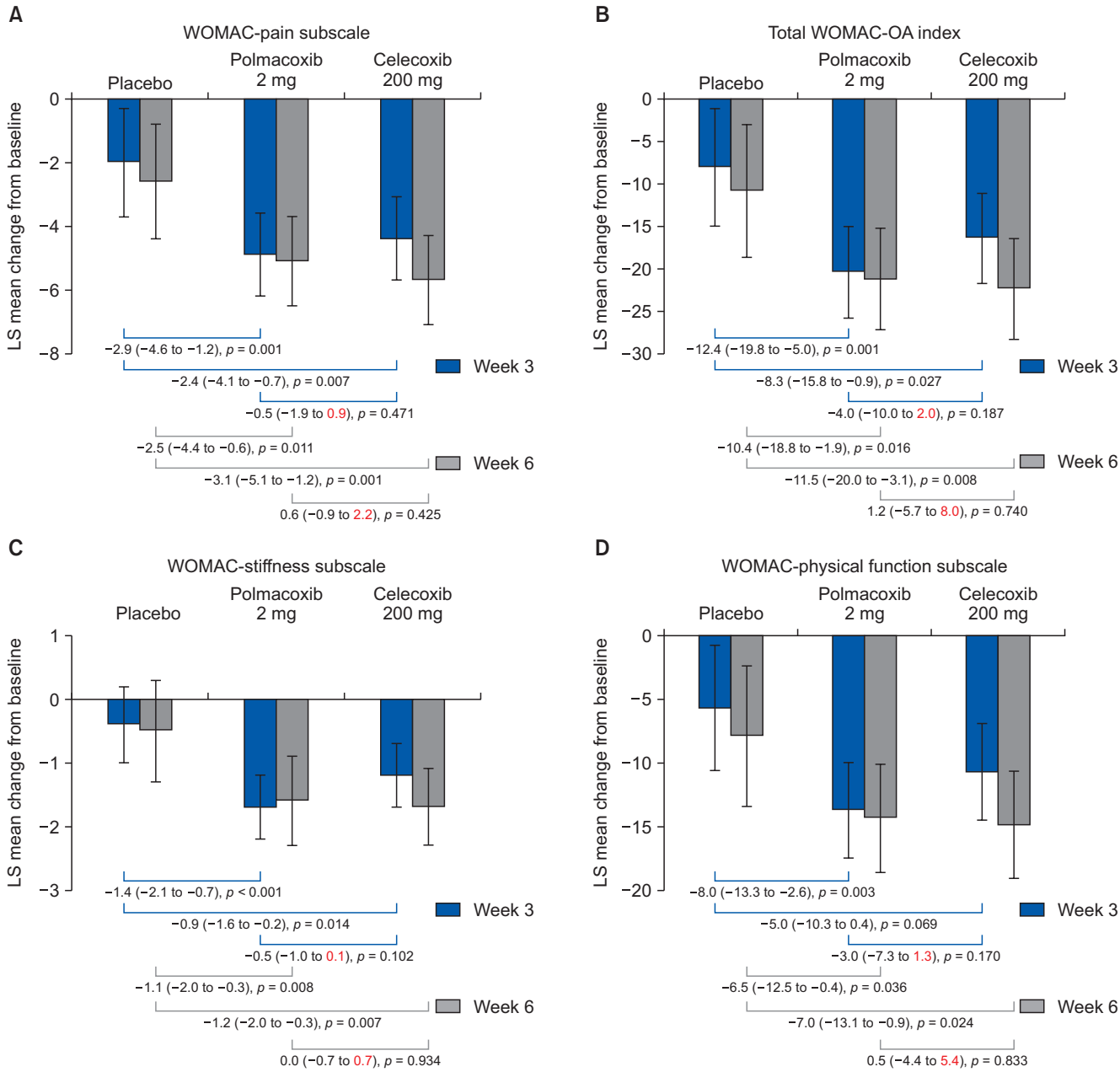

Fig. 2. Efficacy endpoints among treatment groups: least square (LS) mean changes from baseline in the WOMAC-pain subscale (A), total WOMAC-OA index score (B), WOMAC-stiffness subscale (C), and WOMAC-physical function subscale (D) at weeks 3 and 6 (intent-to-treat population, baseline observation carried forward). Data shown below the brackets are estimated treatment differences with 95% confidence intervals and *p*-values. The text in red indicates the upper confidence interval. Noninferiority can be inferred, as the predefined noninferiority margin for the WOMAC-pain subscale (A) was a score of 5 (10% of the total score), total WOMAC-OA index (B) was a score of 24 (10% of the total score), WOMAC-stiffness subscale (C) was a score of 2 (10% of the total score), and WOMAC-physical function subscale (D) was a score of 17 (10% of the total score). WOMAC: Western Ontario and McMaster Universities, OA: osteoarthritis.

similar trend was observed at week 6 in all treatment groups. A slightly higher proportion of subjects in the polmacoxib group (18.3%) compared with the celecoxib group (12.9%) were considered to be "much improved" and "very much improved" by week 6. Only 4.5% of subjects in the placebo group were considered to be as such.

Withdrawal due to lack of analgesic efficacy

Only one subject, who was treated with celecoxib, withdrew from the study owing to a lack of analgesic efficacy.

Table 5. Change from Baseline at Week 3 in the Subject's Global Assessment and Physician's Global Assessment (ITT Population-Observed Cases and Per-Protocol Population)

Variable	ITT population (week 3)			Per-protocol population (week 3)		
	Placebo (n = 71)	Polmacoxib 2 mg (n = 146)	Celecoxib 200 mg (n = 145)	Placebo (n = 71)	Polmacoxib 2 mg (n = 146)	Celecoxib 200 mg (n = 145)
Subject's Global Assessment						
Number	67	135	134	61	112	121
Very much improved	0	0	2 (1.5)	0	0	2 (1.7)
Much improved	2 (3.0)	27 (20.0)	18 (13.4)	2 (3.3)	23 (20.5)	18 (14.9)
Minimally improved	33 (49.3)	74 (54.8)	65 (48.5)	32 (52.5)	60 (53.6)	59 (48.8)
No change	24 (35.8)	29 (21.5)	44 (32.8)	20 (32.8)	24 (21.4)	37 (30.6)
Minimally worse	7 (10.4)	3 (2.2)	4 (3.0)	6 (9.8)	3 (2.7)	4 (3.3)
Much worse	1 (1.5)	2 (1.5)	1 (0.7)	1 (1.6)	2 (1.8)	1 (0.8)
Very much worse	-	-	-	-	-	-
Comparisons vs. placebo (*p*-value)*		< 0.001	0.013		0.001	0.025
Polmacoxib vs. celecoxib (*p*-value)*		0.058			0.189	
Physician's Global Assessment						
Number	67	135	134	61	112	121
Very much improved	0	1 (0.7)	1 (0.7)	0	1 (0.9)	1 (0.8)
Much improved	3 (4.5)	30 (22.2)	22 (16.4)	3 (4.9)	27 (24.1)	22 (18.2)
Minimally improved	30 (44.8)	74 (54.8)	56 (41.8)	29 (47.5)	58 (51.8)	51 (42.1)
No change	29 (43.3)	28 (20.7)	51 (38.1)	24 (39.3)	24 (21.4)	43 (35.5)
Minimally worse	5 (7.5)	1 (0.7)	3 (2.2)	5 (8.2)	1 (0.9)	3 (2.5)
Much worse	0	1 (0.7)	1 (0.7)	0	1 (0.9)	1 (0.8)
Very much worse	-	-	-	-	-	-
Comparisons vs. placebo (*p*-value)*		< 0.001	0.034		<0.001	0.042
Polmacoxib vs. celecoxib (*p*-value)*		0.003			0.020	

Values are presented as number (%).
ITT: intent-to-treat.
**p*-values obtained from an ordinal logistic regression model with effects for treatment and pooled site.

Safety

Overall, 79 subjects (21.8%) experienced at least one TEAE during the 6-week treatment period. The incidence of TEAEs (95% CI) was 28.6% (21.4% to 36.6%) in the polmacoxib group, 18.8% (12.7% to 26.1%) in the celecoxib group and 14.1% (7.0% to 24.4%) in the placebo group. TEAEs relating to GI disorders and general disorders occurred with a numerically greater frequency in the polmacoxib and celecoxib groups compared with the placebo group (Table 6). The difference in TEAEs was primarily influenced by a few events of peripheral edema, edema, and abdominal pain that occurred more frequently in the polmacoxib group. However, all of these events occurred in < 5% of subjects.

Similarly, the most commonly reported TEAEs considered to be related to treatment in the polmacoxib and celecoxib groups were associated with GI and general disorders (Table 7). These events, however, were reported

Table 6. Treatment-Emergent Adverse Events Occurring in ≥ 2% of Subjects by Treatment Group and Preferred Term during the 6-Week Treatment Period (Safety Population)

System Organ Class Preferred Term	Placebo (n = 71)	Polmacoxib 2 mg (n = 147)*	Celecoxib 200 mg (n = 144)*
Gastrointestinal disorders	3 (4.2)	15 (10.2)	14 (9.7)
Comparisons vs. placebo (*p*-value)†		0.190	0.189
Polmacoxib vs. celecoxib (*p*-value)†		1.000	
Abdominal pain	1 (1.4)	3 (2.0)	0
Diarrhoea	0	3 (2.0)	3 (2.1)
Dyspepsia	1 (1.4)	7 (4.8)	5 (3.5)
Abdominal pain, upper	1 (1.4)	1 (0.7)	4 (2.8)
General disorders and administration site conditions	2 (2.8)	16 (10.9)	8 (5.6)
Comparisons vs. placebo (*p*-value)†		0.063	0.503
Polmacoxib vs. celecoxib (*p*-value)†		0.135	
Face oedema	1 (1.4)	3 (2.0)	2 (1.4)
Oedema	0	4 (2.7)	0
Oedema peripheral	0	7 (4.8)	3 (2.1)
Musculoskeletal and connective tissue disorders	3 (4.2)	2 (1.4)	2 (1.4)
Comparisons vs. placebo (*p*-value)†		0.333	0.335
Polmacoxib vs. celecoxib (*p*-value)†		1.000	
Musculoskeletal pain	2 (2.8)	0	0
Skin and subcutaneous tissue disorders	2 (2.8)	5 (3.4)	2 (1.4)
Comparisons vs. placebo (*p*-value)†		1.000	0.600
Polmacoxib vs. celecoxib (*p*-value)†		0.448	
Urticaria	2 (2.8)	1 (0.7)	0
Swelling face	0	3 (2.0)	0

Values are presented as number (%).
*Due to an error from one site, one subject was administered with polmacoxib instead of celecoxib. Safety results are therefore presented based on the actual number of subjects treated with the drug. This error did not make any numerical differences in the presentation of results. †*p*-values obtained from Fisher exact test.

for ≤ 2% of subjects in both treatment groups. The GI events with a "probable" relationship to polmacoxib treatment were abdominal pain (one subject), upper abdominal pain (one subject), diarrhea (one subject), enteritis (one subject) and dyspepsia (two subjects). Other TEAEs with a "possible" or "probable" relationship to polmacoxib treatment included face edema, edema, peripheral edema, headache, face swelling, urticaria, pruritus and increased blood creatinine. The GI disorders with a "probable" or "possible" relationship to celecoxib treatment were upper abdominal pain (three subjects) and dyspepsia (two subjects). Other TEAEs with a "possible" or "probable" relationship to celecoxib treatment included generalized edema, peripheral edema, headache, somnolence, and depression. One subject in the celecoxib group had upper abdominal pain considered to have a "certain" relationship to treatment; there were no such TEAEs in the polmacoxib group.

Across all treatment groups, most TEAEs were mild in intensity. Events reported as moderate in intensity occurred with a similar frequency in all treatment groups. Severe events occurred in 4.1% of subjects in the polma-

Table 7. Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Relationship to Treatment (Certain, Probable, Possible) during the 6-Week Treatment Period (Safety Population)

System Organ Class Preferred Term and Relationship	Placebo (n = 71)	Polmacoxib 2 mg (n = 147)	Celecoxib 200 mg (n = 144)
Gastrointestinal disorders	3 (4.2)	15 (10.2)	14 (9.7)
Certain	0	0	1 (0.7)
Probable	1 (1.4)	4 (2.7)	2 (1.4)
Possible	1 (1.4)	2 (1.4)	1 (0.7)
Abdominal pain	1 (1.4)	3 (2.0)	0
Probable	0	1 (0.7)	0
Abdominal pain, upper	1 (1.4)	1 (0.7)	4 (2.8)
Certain	0	0	1 (0.7)
Probable	0	1 (0.7)	2 (1.4)
Possible	1 (1.4)	0	1 (0.7)
Diarrhea	0	3 (2.0)	3 (2.1)
Probable	0	1 (0.7)	0
Dyspepsia	1 (1.4)	7 (4.8)	5 (3.5)
Probable	1 (1.4)	2 (1.4)	1 (0.7)
Possible	0	1 (0.7)	1 (0.7)
Enteritis	0	1 (0.7)	0
Probable	0	1 (0.7)	0
Epigastric discomfort	0	1 (0.7)	0
Possible	0	1 (0.7)	0
General disorders and administration site conditions	2 (2.8)	16 (10.9)	8 (5.6)
Probable	0	2 (1.4)	1 (0.7)
Possible	0	4 (2.7)	2 (1.4)
Face oedema	1 (1.4)	3 (2.0)	2 (1.4)
Probable	0	2 (1.4)	0
Generalized oedema	0	2 (1.4)	1 (0.7)
Probable	0	0	1 (0.7)
Oedema	0	4 (2.7)	0
Possible	0	3 (2.0)	0
Oedema, peripheral	0	7 (4.8)	3 (2.1)
Probable	0	2 (1.4)	0
Possible	0	1 (0.7)	2 (1.4)
Investigation	1 (1.4)	3 (2.0)	2 (1.4)
Possible	1 (1.4)	1 (0.7)	0
Alanine aminotransferase increased	1 (1.4)	0	0
Possible	1 (1.4)	0	0
Aspartate aminotransferase increased	1 (1.4)	0	0
Possible	1 (1.4)	0	0
Blood creatinine increased	0	1 (0.7)	0
Possible	0	1 (0.7)	0
Gamma-glutamyltransferase increased	1 (1.4)	0	0
Possible	1 (1.4)	0	0
Nervous system disorders	0	1 (0.7)	5 (3.5)
Possible	0	1 (0.7)	1 (0.7)
Headache	0	1 (0.7)	2 (1.4)
Possible	0	1 (0.7)	1 (0.7)
Somnolence	0	0	1 (0.7)
Possible	0	0	1 (0.7)
Psychiatric disorders	0	0	1 (0.7)
Possible	0	0	1 (0.7)
Depression	0	0	1 (0.7)
Possible	0	0	1 (0.7)
Skin and subcutaneous tissue disorders	2 (2.8)	5 (3.4)	2 (1.4)
Possible	1 (1.4)	3 (2.0)	0 (0.0)
Pruritus	1 (1.4)	1 (0.7)	1 (0.7)
Possible	0	1 (0.7)	0
Swelling face	0	3 (2.0)	0
Possible	0	1 (0.7)	0
Urticaria	2 (2.8)	1 (0.7)	0
Possible	1 (1.4)	1 (0.7)	0

Values are presented as number (%).

coxib treatment group (hypertension, abdominal pain, diarrhea, gastritis, and spinal compression fracture), 0.7% of subjects in the celecoxib group (increased blood pressure), and 1.4% of subjects in the placebo group (spinal column stenosis). Of the TEAEs occurring in the polmacoxib group, only abdominal pain and diarrhea were deemed related to treatment. There were no deaths during the study and SAEs were reported in four subjects, none of which were reported as related to treatment.

More subjects treated with polmacoxib discontinued the study drug due to TEAEs (9.5% for polmacoxib and 2.8% for celecoxib and placebo); however, investigators determined that the AEs were not related or unlikely related to the study drug. The observed difference in treatment discontinuation was primarily influenced by GI disorders in three more subjects treated with polmacoxib (3.4%) than in subjects treated with celecoxib (1.4%).

There were no clinically relevant findings in the analysis of clinical laboratory tests, vital signs, electrocardiograms, or physical examination results. Ten subjects experienced changes from baseline in corrected QT interval by Fridericia (QTcF) greater than 30 ms at week 6: two of these subjects were treated with polmacoxib; three were treated with placebo; and five were treated with celecoxib. One subject in the celecoxib group experienced a change in QTcF interval from baseline to week 6 of greater than 78 ms.

Results from the Extended Observation Period

Of the 324 subjects who completed the 6-week treatment period, 303 (93.5%) participated in the extended observation period and received at least one dose of polmacoxib 2 mg once daily. Originally, 62 had been randomized to receive placebo (placebo/polmacoxib), 116 to receive polmacoxib 2 mg once daily (polmacoxib/polmacoxib) and 125 to receive celecoxib 200 mg once daily (celecoxib/polmacoxib). A total of 220 subjects (72.6%) completed the 18-week trial extension.

The results observed during the 18-week safety extension were consistent with those observed during the 6-week treatment period. The incidences (95% CIs) of TEAEs over 24 weeks were similar between groups: placebo/polmacoxib, 38.0% (19.0% to 37.5%); polmacoxib/polmacoxib, 47.6% (26.1% to 38.9%); and celecoxib/polmacoxib, 45.8% (25.2% to 38.2%). There were no statistically significant differences among these three groups (p = 0.693). Overall, 12.7% of subjects had at least one AE that led to study drug discontinuation; although fewer subjects (8.5%) in the placebo/polmacoxib group had AEs leading to study drug discontinuation compared to subjects in the polmacoxib/polmacoxib group (13.6%) and the celecoxib/polmacoxib group (13.9%), the differences were not statistically significant (p = 0.535).

In particular, the most frequently occurring TEAEs over the combined 24-week treatment period (abdominal pain, 7.2%; dyspepsia, 6.1%) were reported in 6.9% and 3.3% of subjects, respectively, during the 18-week safety extension. Peripheral edema, which was reported in 3.6% of subjects over the combined period, occurred in 1.0% of subjects during the safety extension period. There were no notable increases in the incidence of any TEAEs. During the 18-week extension, seven SAEs were reported: SAEs of angina pectoris, palpitations, and dyspnea were reported in the polmacoxib/polmacoxib group, and SAEs of pneumonia, concussion, contusion, ruptured ligament, and ligament sprain were reported in the celecoxib/polmacoxib group. None of the SAEs were considered by the investigator to be related to the study drug. There were no deaths during the trial extension.

The improvements from baseline in WOMAC subscale scores were maintained over 24 weeks in the polmacoxib/polmacoxib group (Fig. 3). Subjects initiating polmacoxib after 6 weeks (placebo/polmacoxib and celecoxib/polmacoxib groups) experienced numerical improvements in WOMAC subscale scores during the 18-week trial extension (Fig. 3).

DISCUSSION

In this study, we investigate the safety and efficacy of a new pain relief drug, polmacoxib, which was developed with the intent to reduce the risk of side effects associated with most NSAIDs. Patients with OA were given polmacoxib, placebo, or celecoxib (the current standard for moderate to serious pain relief from OA). An evaluation was done after 6 weeks of treatment to assess the patients' pain, stiffness, and physical function using a specially designed questionnaire for OA assessment. The goal was to assess whether polmacoxib performs better in terms of improving OA signs and symptoms including lowering pain compared to placebo, and whether polmacoxib has similar performance to celecoxib. We also investigated long-term safety concerns. This trial has demonstrated that polmacoxib 2 mg once daily has analgesic superiority to placebo and analgesic noninferiority to celecoxib 200 mg once daily in patients with OA over 6 weeks. Treatment effects were confirmed by various sensitivity analyses, including per-protocol population and observed cases without imputation for missing values.

The difference in LS mean change in WOMAC-pain

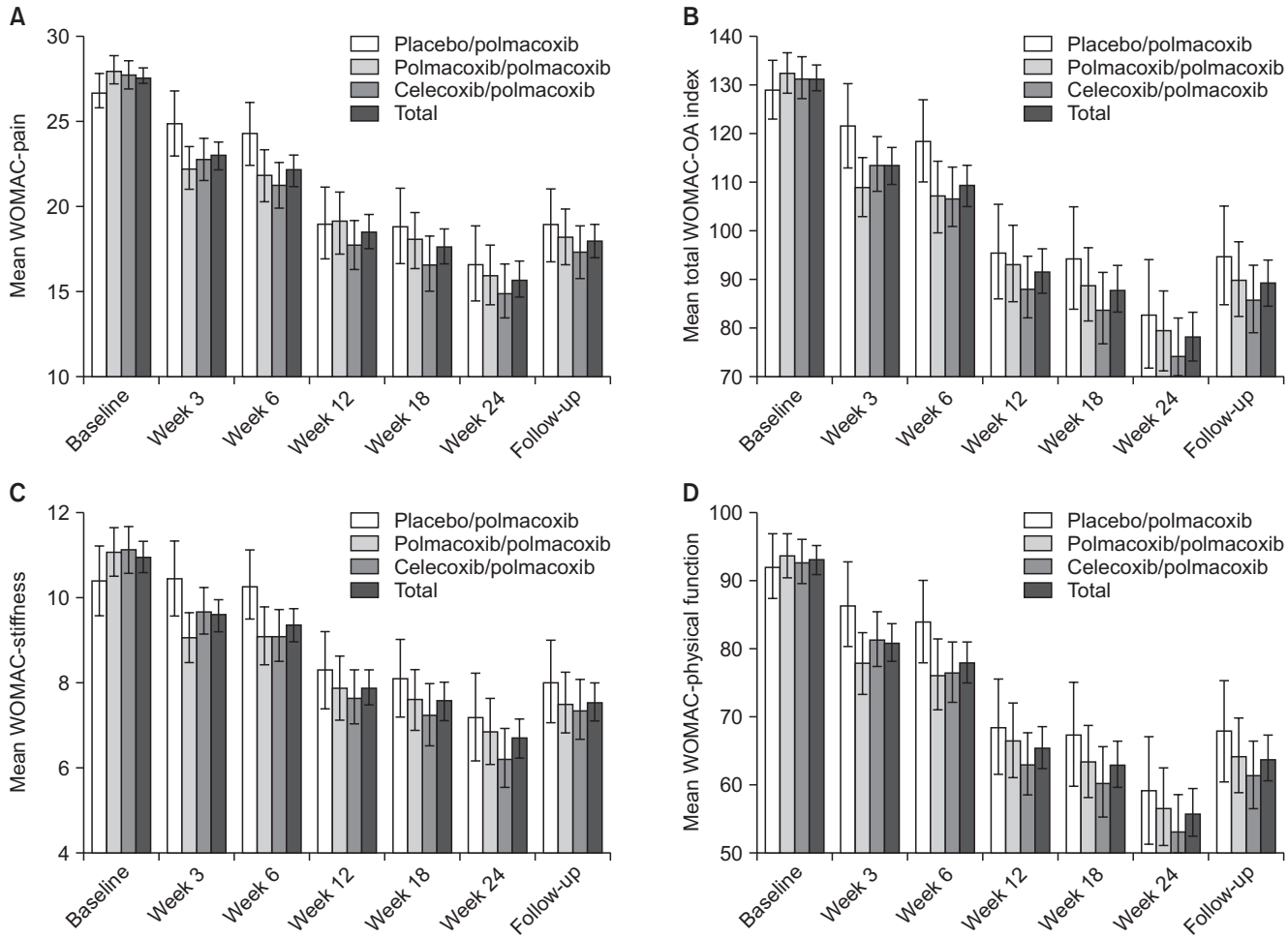

Fig. 3. Efficacy endpoints among treatment groups: mean WOMAC questionnaire scores by time point and treatment group (intent-to-treat population). (A) WOMAC-pain subscale. (B) Total WOMAC-OA index score. (C) WOMAC-stiffness subscale. (D) WOMAC-physical function subscale. WOMAC: Western Ontario and McMaster Universities, OA: osteoarthritis.

at week 6 between polmacoxib and placebo was –2.5 (95% CI, –4.4 to –0.6) based on the ITT (BOCF) population, and –3.7 (95% CI, –5.9 to –1.5) based on the per-protocol population. Although these differences are statistically significant (p = 0.011 and p = 0.001, respectively), these changes can be interpreted as minimal. However, overall improvements in OA signs and symptoms were reported by both subjects and physicians and were evident in the WOMAC-stiffness and WOMAC-physical function subscales, which evaluated difficulty in performing daily activities using questions such as "how much difficulty have you had while going up stairs?" In addition, a placebo effect can be observed, as the placebo group showed a 9.6% reduction in pain from baseline to week 6 in per-protocol population compared with a 23.0% reduction in the polmacoxib group. As a result, the 9.6% reduction for placebo should not be interpreted as a baseline score for clinical improvement for polmacoxib or celecoxib. The perception of pain is subjective and as WOMAC-pain scores are considered the most objective method of quantifying clinical improvements in pain, statistically significant improvements in scores were considered to be clinically relevant.

The difference in LS mean change in WOMAC-pain scores between polmacoxib and celecoxib from baseline to week 6 was 0.6 (95% CI, –0.9 to 2.2, p = 0.425) based on ITT (BOCF) population, with the upper CI of 2.2 clearly within the prespecified noninferiority margin of 5. The use of BOCF in efficacy analyses to manage treatment discontinuation can be limiting; baseline observation is treated as the missing data point for a patient without considering the reason for withdrawal from the trial. As such, all combinations of imputation and analysis population were used to confirm the results of the trial, obtaining similar results and conclusions.

After 3 weeks, polmacoxib was associated with significantly superior PGA scores compared with celecoxib, indicating that physicians perceived greater patient improvements in terms of OA signs and symptoms. These findings suggest that polmacoxib 2 mg provides rapid relief from OA signs and symptoms and may have a faster onset of action than celecoxib. It is noteworthy that these effects with polmacoxib were observed at the low dose of 2 mg per day, the lowest effective dose among all known NSAIDs.

The TEAEs reported in this study were generally mild and of the type expected for COX-2 inhibitor drugs. The most commonly occurring TEAEs in the polmacoxib and celecoxib groups were GI-related, which occurred more frequently in both treatment groups when compared with the placebo group. As polmacoxib had similar safety profiles with celecoxib and other COX-2 inhibitors that have shown a reduced incidence of GI disorders compared with other NSAIDs,[8] polmacoxib was considered to have an acceptable GI safety profile in this study. Besides *p*-values for comparison for the occurrences of adverse events between polmacoxib and celecoxib (Table 6), we set no higher than the 5% incidence rate for any adverse events to be an "acceptable" safety profile for polmacoxib. Through extensive literature review on celecoxib in similar and lager studies, we considered this 5% limit could be applicable for polmacoxib as an "acceptable" safety profile. The increased edema observed with polmacoxib is associated with the well-known side effects of NSAIDs: increased sodium and fluid retention due to the reduction of prostaglandin[28] often leads to mild general peripheral edema within the first few weeks of therapy. In this study, incidences of peripheral edema (< 5%) in subjects treated with polmacoxib were observed within the first 2 weeks of therapy, with most subjects recovering within a week without any intervention. To further evaluate the safety of polmacoxib in patients with OA, a trial extension was conducted in which all participants received open-label polmacoxib 2 mg daily and were followed for up to 26 weeks, including an off-treatment period of 2 weeks. Over this 6-month period, polmacoxib was well tolerated and demonstrated an acceptable profile that was comparable to the 6-week treatment period and other available COX-2 inhibitors.[8] In addition, over the safety extension, peripheral edema did not occur in the polmacoxib-only group, with three events observed in subjects who switched from celecoxib (n = 2) and placebo (n = 1).

A limitation of this trial is its relatively short duration. The main treatment period of 6 weeks with active comparator and placebo groups was considered sufficient to evaluate the treatment differences among study groups and to satisfy the OA guidelines provided by Ministry of Food and Drug Safety of Korea. However, additional follow-up is needed to establish the long-term efficacy and safety of polmacoxib, including its CV safety profile. This study was also limited by the fact that all patients were Korean, and many were female. Further studies with larger and more diverse populations are needed to extrapolate these findings to different populations. In addition, the results of this study were limited to knee joint OA only due to very low enrolment of patients with hip joint OA. The prevalence of hip joint OA is low among the Korean community compared with knee or hand OA.[29,30]

In conclusion, polmacoxib 2 mg was relatively well tolerated and demonstrated superior efficacy to placebo and noninferior efficacy to celecoxib after 6 weeks of treatment in patients with OA. The results obtained during the additional 18-week trial extension with polmacoxib 2 mg were consistent with those observed during the 6-week treatment period, indicating that polmacoxib can be considered safe for long-term use based on this relatively small scale of study with a Korean population. More importantly, the results of this study showed that polmacoxib has the potential to be used as a pain relief drug with reduced GI side effects compared to traditional NSAIDs for OA.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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