Efficacy and Safety of Celecoxib in Chinese Patients with Ankylosing Spondylitis: A 6-Week Randomized, Double-Blinded Study with 6-Week Open-Label Extension Treatment

CrossMark

Feng Huang, MD[1],*, Jieruo Gu, MD[2], Yi Liu, MD[3], Ping Zhu, MD[4], Yi Zheng, MD[5], Jin Fu, MD[6], Sharon Pan, PhD[7], Shi Le, MD[8]

[1] Department of Rheumatology, Chinese PLA General Hospital, Beijing, China
[2] Department of Rheumatology and Immunology, The Third Affiliated Hospital of Sun Yat-Sen University, Guangzhou, China
[3] Department of Rheumatology and Immunology, West China Hospital of Sichuan University, Sichuan, China
[4] Department of Rheumatology and Immunology, Xijing Hospital, Shanxi, China
[5] Department of Rheumatology and Immunology, Beijing Chaoyang Hospital, Capital University of Medical Science, Beijing, China
[6] Clinical Program Lead, Global Innovation Pharma, Clinical Science, Pfizer Investment Co, Ltd, Beijing, China
[7] Emerging Markets Business Unit, Pfizer Inc, New York, NY
[8] Former employee of Department of Clinical Development and Operation (China), Pfizer Investment Co, Ltd, Beijing, China

A R T I C L E   I N F O

A B S T R A C T

Background: Nonsteroidal anti-inflammatory drugs are the first-line option for treating ankylosing spondylitis (AS) in China. However, no large-scale controlled trials have been conducted in this ethnic population.
Objective: To evaluate the efficacy and safety of 6 weeks' treatment with celecoxib in patients with AS in China.
Methods: This Phase 3, double-blind, parallel-group study randomized patients with AS aged $\geq$ 18 to 65 years 1:1 to receive celecoxib 200 mg once daily or diclofenac sustained release 75 mg once daily. After 6 weeks, patients could use celecoxib 400 mg once daily or maintain blinded therapy. The primary efficacy end point was mean change from baseline at Week 6 for Patient's Global Assessment of Pain Intensity score (100-mm visual analog scale). Noninferiority was established if the upper bound of the CI was < 10 mm. Secondary objectives included patients' and physicians' assessments of disease activity, change from baseline in C-reactive protein level, and safety.
Results: In the per-protocol analysis set the least squares mean change from baseline in the Patient's Global Assessment of Pain Intensity score at Week 6 was –23.8 mm and –27.1 mm in patients receiving celecoxib (n = 111) and diclofenac (n = 108), respectively. The 2-sided 95% CI for the treatment difference (celecoxib – diclofenac) was –2.2 to 8.8. Overall, 4.2% and 6.7% of patients in the celecoxib and diclofenac groups, respectively, reported treatment-related adverse events. All were mild to moderate in severity.
Conclusions: Celecoxib 200 mg once daily is noninferior to diclofenac sustained release 75 mg once daily for pain treatment in Chinese patients with AS. ClinicalTrials.gov identifier: NCT00762463.

Introduction

Ankylosing spondylitis (AS) is a chronic inflammatory disease of the axial skeleton manifested by inflammatory back pain, progressive stiffness of the spine, arthritis, enthesitis, and acute anterior uveitis.[1,2] Symptoms of AS traditionally appear during late adolescence and early adulthood, and the condition is a significant health burden in young male adults.[3] If the disease is undiagnosed or inadequately treated, patients with AS may experience continuous pain, stiffness, fatigue, and a progressive loss of spinal mobility and function, which ultimately leads to a reduction in quality of life.[4] The 1984 modified New York criteria describe the classification criteria for AS.[5] Patients may be diagnosed with AS if characteristic radiologic changes of the sacroiliac joint are present, together with defined clinical symptoms and physical findings.

* Address correspondence to: Feng Huang, MD, Department of Rheumatology, Chinese PLA General Hospital, 28 Fuxing Rd, Beijing 100853, China.
E-mail address: fhuang1964@yahoo.com (F. Huang).

Nonsteroidal anti-inflammatory drugs (NSAIDs) are currently the mainstay of treatment for AS.[6] In China, where the prevalence of AS is 0.3%,[7] nonselective (ns) NSAIDs and tumor necrosis factor-α (TNFα) antagonists are approved AS treatments. In addition, a number of other medications, including disease-modifying anti-rheumatic drugs, opioids, and muscle relaxants are prescribed for the treatment of patients with AS.[7] However, evidence suggests that, particularly over the longer term, the use of nsNSAIDs and injectable TNFα antagonists may be limited by the concern for adverse events (AEs) and other undesirable effects.[8,9] The use of nsNSAIDs has been associated with AEs affecting the gastrointestinal (GI) tract[8] and cardiovascular system,[10–13] with diclofenac being associated with a particularly high risk of cardiovascular adverse events.[11] In addition, nsNSAIDs are also believed to exacerbate inflammatory bowel disease that often accompanies spondyloarthropathies.[14–18] Although injectable TNFα antagonists have been shown to be effective treatments for the signs and symptoms of AS,[19,20] the cost of use, inconvenience of administration, and possible safety concerns[9] may limit their use to refractory or severe cases.

Compared with nsNSAIDs, which inhibit both cyclooxygenase (COX)-1 and COX-2, the COX-2 selective NSAIDs are thought to have a superior GI safety profile[21] because they selectively inhibit COX-2–mediated production of inflammatory mediators while preserving the integrity of the gastroduodenal mucosa (through COX-1 mediated synthesis of prostanoids).[22] Furthermore, the rate of cardiovascular AEs has been demonstrated to be comparable to that of nsNSAIDs in a meta-analysis.[23]

Outside of China, the COX-2 selective NSAID celecoxib has been evaluated in 2 double-blind, randomized, controlled, active-comparator trials in patients with AS.[24,25] However, to date, no large-scale randomized controlled trials have been conducted in China, where there is a paucity of efficacy and safety data for this treatment. Therefore the primary objective of our study was to demonstrate noninferiority of celecoxib 200 mg once daily compared with diclofenac sustained release (SR) 75 mg once daily in the treatment of Chinese patients with AS in terms of pain assessment after 6 weeks of treatment.

Patients and Methods

Study design

Our study (ClinicalTrials.gov identifier NCT00762463) was a randomized, active-comparator, double-blind, parallel-group, non-inferiority study conducted at 5 centers across China. The protocol was approved by the institutional review board or independent ethics committee at each center, and the study was conducted in accordance with the principles of the Declaration of Helsinki, the International Conference on Harmonisation guidelines for Good Clinical Practice, and local regulatory requirements. The study consisted of a double-blind treatment period lasting 6 weeks, followed by a 6-week extension period. All patients provided written informed consent before any screening procedures were performed.

The study included a total of 6 study visits: screening visit (Visit 1), baseline visit (Visit 2), Week 2 (Visit 3), Week 4 (Visit 4), Week 6 (Visit 5), and Week 12 (Visit 6 for those enrolled in the extension period) or when the study drug was terminated (end-of-treatment visit) (Figure 1). However, unscheduled visits were possible at any time during the study treatment if required.

The primary objective was to demonstrate noninferiority of celecoxib 200 mg once daily compared with diclofenac SR 75 mg once daily in the treatment of patients with AS in the per-protocol analysis set population, in terms of their pain assessment at Week 6. Diclofenac was chosen as the active comparator in this study because it is commonly used to treat AS.[26] A dose of 75 mg diclofenac SR once daily was chosen to minimize the emergence of AEs that have been associated with the higher dose of 150 mg daily.[27,28]

Patients

Adult male and female patients aged 18 to 65 years were eligible for inclusion if they had AS according to the 1984 modified New York criteria for classification of AS.[5] In addition, all patients must have had a diagnosis of AS with axial involvement but without peripheral joint involvement (synovitis) at the time of study entry. Patients were required to have been receiving daily treatment with NSAIDs 30 days before study entry. Patients were excluded if they had known inflammatory enteropathy, the presence of other extra-articular manifestations, known vertebral compression, or the need to wear a corset during the study. In addition, patients were excluded if they required the use of concomitant muscle relaxants, hypnotics, anxiolytics, sedatives, tranquillizers, or antidepressant drugs, or the concomitant use of anticoagulants, ticlopidine, lithium, aspirin > 150 mg/d, methotrexate > 15 mg/wk, prednisolone > 10 mg/d (or equivalent dose of other corticosteroids), NSAIDs, or COX-2 inhibitors (other than study drug or biologics). Women with childbearing potential were required to have been using adequate contraception.

Treatment

Patients were randomized 1:1 to receive either celecoxib 200 mg once daily or diclofenac SR 75 mg once daily for 6 weeks
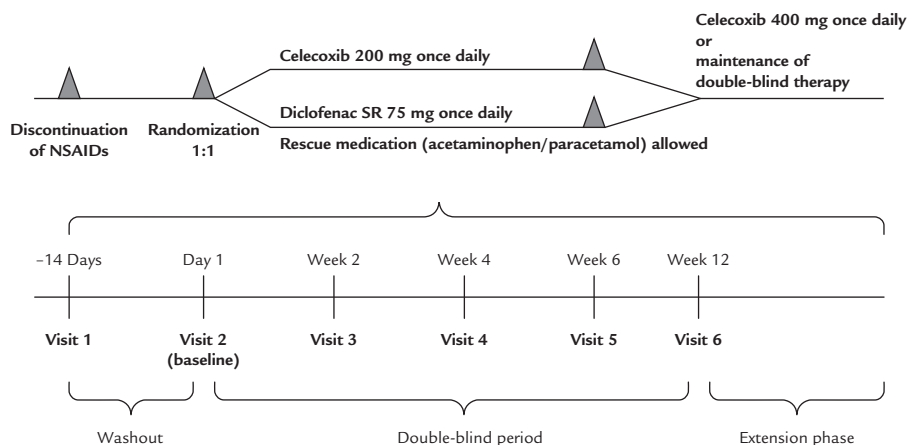

Figure 1. Study design. NSAID = nonsteroidal anti-inflammatory drug; SR = sustained release.

(Figure 1). Randomization was performed using a computer-generated schedule that generated a random permuted-blocks design. Each patient qualifying for a treatment assignment was given the next consecutive number within a center and was dispensed the corresponding study medication. To ensure that the treatment remained blinded to the investigators and patients during the double-blind period, a double-dummy method of blinding was used (celecoxib 200 mg capsules, diclofenac SR 75 mg tablets, and their respective matching placebos were similar in size, color, smell, taste, and appearance). Rescue medication in the form of acetaminophen/paracetamol could be taken on demand, but the dose could not exceed a total daily dose of 2 g.

All patients who exhibited no study medication-related AEs were offered extension treatment at the end of the 6-week, double-blind period; patients in the celecoxib 200 mg once daily (C200) and diclofenac SR 75 mg once daily (D75) groups received either open-label celecoxib 400 mg once daily (herein referred to as the C200/C400 or D75/C400 group) or continuation of their double-blind period therapies (herein referred to as the C200 or D75 no treatment change [NTC] groups) for an additional 6 weeks. In the extension phase, assignment to celecoxib 400 mg once daily was open to the investigators, patients, and the sponsor's study team. Patients who maintained their celecoxib 200 mg once daily or diclofenac SR 75 mg once daily therapies were dispensed medication in the same manner they had received medication during the double-blind phase. These patients remained blinded to the study medication assignments. Dose adjustments were not permitted during the study and extension period.

Efficacy evaluations

The primary end point was the mean change from baseline at Week 6 during the double-blind treatment period in the Patient's Global Assessment of Pain Intensity score. The Patient's Global Assessment of Pain Intensity score was based on a 100-mm visual analog scale (VAS) pain scale where 0 = no pain and 100 = worst possible pain. The secondary end points were the change from baseline at Weeks 2, 4, and 6 in the Patient's Global Assessment of Pain Intensity score, the Patient's Global Assessment of Disease Activity score (measured on a 5-point Likert scale where 1 = very good and 5 = very poor), the Physician's Global Assessment of Disease Activity score (measured on a 5-point Likert scale where 1 = very good and 5 = very poor), the Bath Ankylosing Spondylitis Functional Index score (comprising a series of 10 specific questions, each answered on a 100-mm VAS where 0 = easy and 100 = impossible), the Bath Ankylosing Spondylitis Disease Activity Index score (comprising a series of 6 questions), nocturnal pain, the distance from fingertips to floor (measured in centimeters), chest expansion (measured in centimeters), Assessment in Ankylosing Spondylitis (ASAS-20) score, and measures of the change from baseline at Week 6 in erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) level.

Safety evaluations

Safety evaluations included monitoring of AEs, treatment discontinuations, and the use of concomitant medications, measurement of vital signs, a physical examination, and the assessment of clinical laboratory investigations. The specific laboratory assessments included hematology measurements, urine tests, and clinical chemistry measurements.

Statistical analysis

SAS (version 9.0, SAS Institute Inc, Cary, North Carolina) was used for all analyses. The sample size calculation for this study was based on the primary end point, the Patient's Global Assessment of Pain Intensity score at Week 6, and the hypothesis that celecoxib 200 mg once daily was noninferior to diclofenac SR 75 mg once daily. Based on the following assumptions, the noninferiority margin was 10 mm, the SD of pain intensity change from baseline at Week 6 was no more than 25 mm (based on Week 6 data from previously published[25] and, as yet unpublished [COXA-0506-247], studies), and the power and significance level for the noninferiority test were 80% and 0.025 (1-sided), respectively, a sample size of 100 patients per-protocol analysis set in each treatment group was required. The noninferiority margin was selected a priori.

The primary efficacy analysis was performed on the per-protocol analysis set, which comprised all randomized and treated patients who had a global pain intensity assessment at Week 6 and had no major protocol deviations during the 6-week, double-blind period. The primary end point was analyzed using analysis of covariance with treatment group and study center as factors and the baseline Patient's Global Assessment of Pain Intensity score as a covariate. A 2-sided 95% CI was constructed for the least squares (LS) mean difference on the primary end point between celecoxib 200 mg once daily and diclofenac SR 75 mg once daily. Noninferiority was declared if the upper bound of the 95% CI was < 10 mm.

All secondary efficacy end point analyses were performed on the full analysis set, which comprised all randomized patients who received at least 1 dose of study treatment.

Safety analyses were performed on all randomized patients who received at least 1 dose of study medication. For the extension period the efficacy and safety analyses were analyzed separately.

Results

Patients

Overall, 255 patients were screened, of which 240 patients were randomized and received treatment (Figure 2). In total, 240 patients were included in the full analysis set, and 219 were included in the per-protocol analysis set for the efficacy analyses during the 6-week double-blind treatment phase.

A total of 218 patients entered the extension period, of which 6 withdrew from the celecoxib 400 mg once daily group (4 in the C200/C400 group and 2 in the D75/C400 group). Of patients in the NTC population, 3 withdrew from the C200 NTC group, and 1 withdrew from the D75 NTC group.

At baseline, 85.8% of patients (206 out of 240) were male. Other baseline characteristics were similar between the 2 treatment groups (Table I). In terms of prior NSAID use, 36.7% of patients (44 out of 120) in the celecoxib 200 mg once daily and 35.0% (42 out of 120) in the diclofenac SR 75 mg once daily groups were receiving either diclofenac or diclofenac sodium before the start of the study.

Efficacy

Patient's Global Assessment of Pain Intensity

For the primary end point in the per protocol analysis set, the LS mean change from baseline in the Patient's Global Assessment of Pain Intensity score (using a VAS) at Week 6 (per-protocol analysis set; Week 6 – baseline) was –23.8 mm and –27.1 mm in the celecoxib 200 mg once daily and diclofenac SR 75 mg once daily groups, respectively (Figure 3). The treatment difference (celecoxib – diclofenac SR) at Week 6 in the per-protocol analysis set was 3.3 mm and the 2-sided 95% CI for the treatment difference was (–2.2 to 8.8 mm). Because the upper bound of the 95% CI was < 10 mm, celecoxib was noninferior to diclofenac in the treatment of Chinese patients with AS.
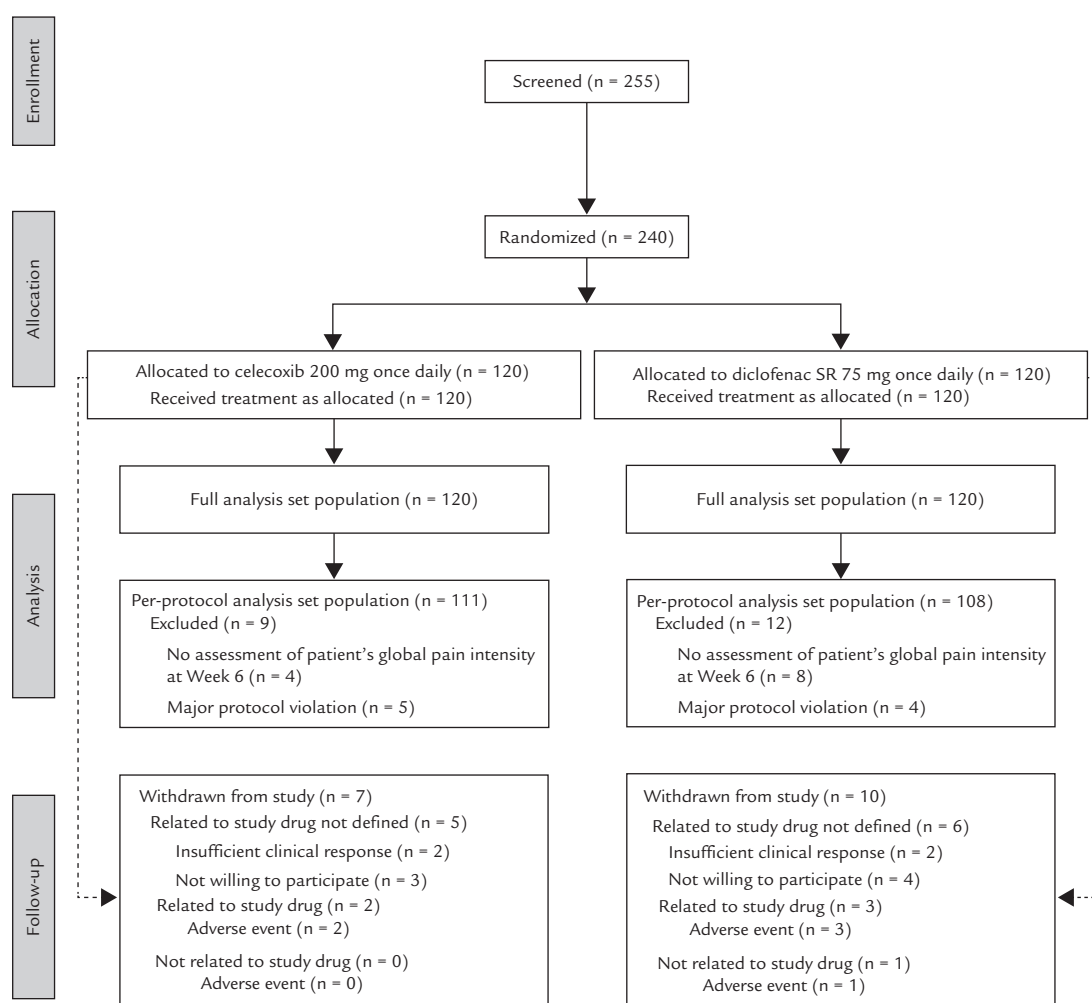
Figure 2. Flow of patients through the study. SR = sustained release.

At the end of the extension phase (Week 12), the mean change from baseline was –28.4 mm in the C200 group and –30.9 mm in the D75 group. The treatment effect achieved by both treatment groups at the end of the 6-week double-blind period was maintained through Week 12.

The Patient's Global Assessment of Pain Intensity scores at Weeks 2, 4, and 6 for the full analysis set are summarized in **Table II**.
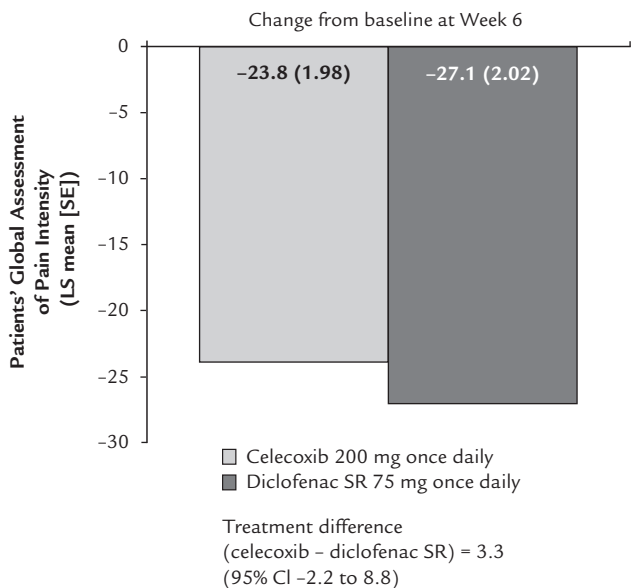
Patient's Global Assessment of Disease Activity

The Patient's Global Assessment of Disease Activity scores at Weeks 2, 4, and 6 are summarized in **Table III**. At the end of the extension phase (Week 12), the mean (SD) change from baseline was –0.6 (1.0) in the celecoxib group and –0.6 (0.8) in the diclofenac SR group. In patients who changed treatment during the extension period, the mean change from baseline at Week 6 in

Table I
Baseline patient demographics and disease characteristics (full analysis set).

Patient demographic	Celecoxib 200 mg once daily (n = 120)		Diclofenac SR 75 mg once daily (n = 120)		Total (N = 240)
	Men (n = 105)	Women (n = 15)	Men (n = 101)	Women (n = 19)	
Age, y					
18–44[*]	97 (92.4)	12 (80.0)	91 (90.1)	18 (94.7)	218 (90.8)
45–64[*]	8 (7.6)	3 (20.0)	10 (9.9)	1 (5.3)	22 (9.2)
Mean (SD)	29.5 (8.9)	31.6 (10.7)	28.8 (9.1)	29.5 (7.2)	29.3 (9.0)
Range	18–58	19–53	18–59	20–45	18–59
Weight, kg					
Mean (SD)	66.5 (11.8)	52.1 (7.3)	66.3 (11.8)	53.4 (9.7)	64.5 (12.3)
Range	47.0–108.0	35.0–62.0	46.0–93.0	42.0–75.0	35.0–108.0
Body mass index					
Mean (SD)	22.7 (3.6)	20.1 (2.3)	22.4 (3.5)	21.0 (3.5)	22.3 (3.6)
Range	17.2–34.5	15.6–23.4	16.0–31.5	16.2–27.9	15.6–34.5
Height, cm					
Mean (SD)	170.9 (5.4)	160.9 (5.5)	171.9 (5.9)	159.4 (4.5)	169.8 (6.8)
Range	158.0–185.0	150.0–175.0	150.0–184.0	150.0–170.0	150.0–185.0

SR = sustained release.

* Values are given as n (%) unless otherwise noted.

Figure 3. Changes from baseline in Patient's Global Assessment of Pain Intensity score (per-protocol analysis set) at Week 6. LS = least squares; SR = sustained release.

the C200/C400 group was noticeably smaller than in the C200 group. At Week 12 there was an improvement from Week 6 in the mean change from baseline in the C200/C400 group (–0.1 [0.7] at Week 6 vs –0.4 [0.7] at Week 12) and in the D75/C400 group (–0.4 [0.7] at Week 6 vs –0.6 [1.0] at Week 12).

Table II

Patient's Global Assessment of Pain Intensity score at baseline to Week 2, 4, and 6 in the double-blind period (full analysis set).

Characteristic	Celecoxib 200 mg once daily (n = 120)	Diclofenac SR 75 mg once daily (n = 120)	Difference (celecoxib 200 mg once daily – diclofenac SR 75 mg once daily)
Baseline			
N	117	115	
Mean (SD)	63.1 (12.84)	63.7 (13.28)	
Change from baseline to Week 2			
N	116	115	
Mean (SD)	–18.4 (19.39)	–17.7 (19.69)	
LS mean (SE)*	–18.6 (1.78)	–17.9 (1.79)	–0.7 (2.5)
95% CI†	–22.1 to –15.0	–21.4 to –14.3	–5.6 to 4.2
P value*	–	–	0.7849
Change from baseline to Week 4			
N	117	115	
Mean (SD)	–20.7 (20.52)	–23.4 (21.61)	
LS mean (SE)	–20.7 (1.86)	–23.3 (1.89)	2.6 (2.62)
95% CI	–24.4 to –17.0	–27.1 to –19.6	–2.6 to 7.8
P value	–	–	0.3223
Change from baseline to Week 6			
N	117	115	
Mean (SD)	–23.7 (20.61)	–26.7 (22.85)	
LS mean (SE)	–23.8 (1.92)	–26.8 (1.95)	3.1 (2.71)
95% CI	–27.5 to –20.0	–30.7 to –23.0	–2.3 to 8.4
P value	–	–	0.2598

LS = least squares; SR = sustained release.

   * Estimated from analysis of covariance model with treatment and center as factors and baseline as covariate.

   † Noninferiority considered if the upper bound of the CI < 10.

Table III

Patient's Global Assessment of Disease Activity score at baseline to Week 2, 4, and 6 in the double-blind period (full analysis set).

Characteristic	Celecoxib 200 mg once daily (n = 120)	Diclofenac SR 75 mg once daily (n = 120)	Difference (celecoxib 200 mg once daily – diclofenac SR 75 mg once daily)
Baseline			
N	117	115	
Mean (SD)	3.2 (0.73)	3.1 (0.67)	
Change from baseline to Week 2			
N	116	115	
Mean (SD)	–0.4 (0.72)	–0.4 (0.72)	
LS mean (SE)*	–0.4 (0.06)	–0.4 (0.06)	0.0 (0.08)
95% CI†	–0.5 to –0.3	–0.5 to –0.3	–0.15 to 0.17
P value*	–	–	0.8938
Change from baseline to Week 4			
N	117	115	
Mean (SD)	–0.3 (0.74)	–0.4 (0.67)	
LS mean (SE)	–0.3 (0.06)	–0.4 (0.06)	0.2 (0.08)
95% CI	–0.4 to –0.2	–0.5 to –0.3	0.01 to 0.31
P value	–	–	0.0426
Change from baseline to Week 6			
N	117	115	
Mean (SD)	–0.3 (0.76)	–0.4 (0.74)	
LS Mean (SE)	–0.3 (0.06)	–0.4 (0.06)	0.1 (0.09)
95% CI	–0.4 to –0.2	–0.5 to –0.3	–0.05 to 0.29
P value	–	–	0.1502

LS = least squares; SR = sustained release.

   * Estimated from analysis of covariance model with treatment and center as factors and baseline as covariate.

   † Noninferiority considered if the upper bound of the CI < 10.

Physician's Global Assessment of Disease Activity

The Physician's Global Assessment of Disease Activity scores at Weeks 2, 4 and 6 are summarized in **Table IV**. At the end of the extension phase (Week 12), the mean (SD) change from baseline was –0.7 (0.6) in the C200 group and –0.5 (0.6) in the D75 group. At Week 12 there was an improvement from Week 6 in the mean change from baseline in the C200/C400 group (–0.2 [0.6] at Week 6 vs –0.5 [0.5] at Week 12) and in the D75/C400 group (–0.5 [0.7] at Week 6 vs –0.7 [0.8] at Week 12).

Bath Ankylosing Spondylitis Functional Index

The LS mean (SE) change from baseline at Week 6 in Bath Ankylosing Spondylitis Functional Index score was –0.5 (0.2) and –0.8 (0.2) in the celecoxib and diclofenac SR groups, respectively (treatment difference and 2-sided 95% CI; 0.3 [–0.1 to 0.7]). At Week 12, the mean change from baseline was –0.9 (1.8) in the C200 group and –1.0 (1.6) in the D75 group. In patients who changed treatment during the extension period, the mean change from baseline at Week 6 in the C200/C400 group was noticeably smaller than in the C200 group. At Week 12, there was an improvement from Week 6 in the mean change from baseline in the C200/C400 group (–0.2 [1.8] at Week 6 vs –0.6 [2.0] at Week 12) and in the D75/C400 group (–0.8 [2.1] at Week 6 vs –1.0 [2.3] at Week 12).

Bath Ankylosing Spondylitis Disease Activity Index

The LS mean (SE) change from baseline at Week 6 in Bath Ankylosing Spondylitis Disease Activity Index was –1.1 (0.2) in the celecoxib group and –1.4 (0.2) in the diclofenac SR group (treatment difference = 0.3; 2-sided 95% CI, –0.1 to 0.8). At Week 12, the mean change from baseline was –1.7 (1.9) in the C200 group and –2.1 (1.9) in the D75 group. In patients who changed treatment

Table IV
Physician's Global Assessment of Disease Activity score at baseline to Week 2, 4, and 6 in the double-blind period (full analysis set).

Characteristic	Celecoxib 200 mg once daily (n = 120)	Diclofenac SR 75 mg once daily (n = 120)	Difference (celecoxib 200 mg once daily – diclofenac SR 75 mg once daily)
Baseline			
N	117	115	
Mean (SD)	3.2 (0.51)	3.2 (0.52)	
Change from baseline to Week 2			
N	116	115	
Mean (SD)	–0.4 (0.65)	–0.3 (0.56)	
LS mean (SE)[*]	–0.4 (0.05)	–0.4 (0.05)	0.0 (0.07)
95% CI[†]	–0.5 to –0.3	–0.5 to –0.3	–0.2 to 0.1
P value[*]			0.5945
Change from baseline to Week 4			
N	117	115	
Mean (SD)	–0.4 (0.62)	–0.5 (0.64)	
LS mean (SE)	–0.4 (0.05)	–0.5 (0.05)	0.1 (0.07)
95% CI	–0.5 to –0.3	–0.6 to –0.4	–0.1 to 0.2
P value	–	–	0.3427
Change from baseline to Week 6			
N	117	115	
Mean (SD)	–0.5 (0.68)	–0.5 (0.70)	
LS mean (SE)	–0.5 (0.06)	–0.5 (0.06)	0.0 (0.08)
95% CI	–0.6 to –0.4	–0.6 to –0.4	–0.1 to 0.2
P value	–	–	0.6522

LS = least squares; SR = sustained release.

[*] Estimated from analysis of covariance model with treatment and center as factors and baseline as covariate.

[†] Noninferiority considered if the upper bound of the CI < 10.

during the extension period, the mean change from baseline at Week 6 in the C200/C400 group was noticeably smaller than in the C200 group. At Week 12, the change in baseline in the C200/C400 group was maintained (–0.6 [1.6] at Week 6 vs –0.6 [1.9] at Week 12) and in the D75/C400 group (–1.3 [2.1] at Week 6 vs –1.4 [2.1] at Week 12).

ASAS-20 responders

The percentage of ASAS-20 responders at Week 6 was 30.2% in the celecoxib group and 34.2% in the diclofenac SR group (**Table V**). The 2-sided 95% CI for the treatment difference was (–16.5 to 7.9). At the end of the extension phase (Week 12), the percentage of ASAS-20 responders was 49.0% in the C200 group and 47.2% in the D75 group.

ESR and CRP

The LS mean (SE) change from baseline at Week 6 in ESR was –2.5 (1.3) mm/h in the celecoxib group and –1.8 (1.3) mm/h in the diclofenac SR group (treatment difference and 2-sided 95% CI; –0.7 mm/h [–4.3 to 2.9 mm/h]). At Week 12, the mean (SD) change from baseline was –3.5 (14.0) mm/h in the C200 group and –1.3 (11.1) mm/h in the D75 group. In patients who changed treatment during the extension period, the mean (SD) change from baseline at Week 12 was –6.3 (13.5) mm/h in the C200/C400 group and –0.7 (19.5) mm/h in the D75/C400 group. For CRP, the LS mean (SE) change from baseline at Week 6 was –4.2 (1.6) mg/L in the celecoxib group and –2.7 (1.6) mg/L in the diclofenac SR group (treatment difference and 2-sided 95% CI; –1.4 mg/L [–5.8 to 2.9 mg/L]). At Week 12, the mean (SD) change from baseline was –4.6 (9.7) mg/L in the C200 group and –3.0 (13.2) mg/L in the D75 group. In patients who changed treatment during the extension

Table V
Analyses of Assessment in Ankylosing Spondylitis responders at Week 6 and Week 12 (extension phase).

	C200	D75	C200/C400	D75/C400
Week 6				
Total[*]	54	54	54	54
Responders[†]	22 (40.7)	23 (42.6)	12 (22.2)	16 (29.6)
Week 12				
Total[*]	51	53	46	51
Responders[†]	25 (49.0)	25 (47.2)	15 (32.6)	19 (37.3)

C200 = celecoxib 200 mg once daily during double-blind and extension phase; D75 = diclofenac sustained release 75 mg once daily during double-blind and extension phase; C200/C400 = celecoxib 200 mg once daily during double-blind phase and celecoxib 400 mg once daily during extension phase; D75/C400 = diclofenac sustained release 75 mg once daily during double-blind phase and celecoxib 400 mg once daily during extension phase.

[*] Total number of patients with data at baseline and week.

[†] Those patients showing improvement of at least 20% from baseline and absolute improvement of at least 10 mm on a 0 to 100 scale in at least 3 of the following 4 domains: Patient's Global Assessment of Disease Activity, Patient's Assessment of Global Pain Intensity, Functional impairment according to Bath Ankylosing Spondylitis Functional Index, Inflammation (defined as mean value for Bath Ankylosing Spondylitis Disease Activity Index morning stiffness intensity and morning stiffness duration). In any domain for which a patient did not demonstrate improvement, the patient must not have shown deterioration, with deterioration defined as a reduction that was both ≥ 20% and ≥ 10 mm. Values are presented as n (%).

period, the mean (SD) change from baseline at Week 12 was –4.8 (24.7) mg/L in the C200/C400 group and –2.1 (20.9) mg/L in the D75/C400 group.

Nocturnal pain, fingertips to floor distance, and chest expansion

The LS mean (SE) change from baseline at Week 6 in nocturnal pain was –15.4 (2.0) and –19.4 (2.0) in the celecoxib and diclofenac SR groups, respectively (treatment difference and 2-sided 95% CI; 4.0 [–1.4 to 9.5]). At Week 12, the mean change from baseline was –19.4 (22.5) in the C200 group and –27.5 (25.6) in the D75 group.

The LS mean (SE) change in fingertips to floor distance from baseline at Week 6 was –2.8 (0.7) and –3.1 (0.7) in the celecoxib and diclofenac SR groups, respectively. At Week 12, the mean (SD) change from baseline was –3.0 (9.4) cm in the C200 group and –3.7 (6.8) cm in the D75 group. The mean (SD) change from baseline at Week 12 was –2.2 (8.0) in the C400 group.

The LS mean (SE) change from baseline at Week 6 in chest expansion was 0.7 (0.1) in the celecoxib group and 0.6 (0.1) in the diclofenac SR group. At Week 12, the mean change from baseline was 0.8 (1.3) cm in the C200 group and 0.8 (1.4) cm in the D75 group. The mean change from baseline at Week 12 was 0.8 (1.2) cm in the C400 group.

Safety profile

AEs occurring in both treatment phases by patient treatment group are summarized in **Table VI**. All were mild to moderate in intensity; no serious AEs or deaths were reported during our study. There were no clinically significant changes in vital signs during the double-blind period and 6-week extension period in any of the treatment groups. During the double-blind period, rescue medication in the form of acetaminophen/paracetamol was taken by 3 patients in the celecoxib 200 mg once daily group and 0 patients in the diclofenac SR 75 mg once daily group.

Discussion

Effective treatment of AS should meet the following 3 goals: relief of back pain and stiffness, reduction of the underlying

Table VI
The incidence of treatment-emergent adverse events (AEs) (all causality and treatment-related) during the double-blind and extension phase.[*]

	All causality		Treatment-related	
	Celecoxib 200 mg once daily (n = 120)	Diclofenac SR 75 mg once daily (n = 120)	Celecoxib 200 mg once daily (n = 120)	Diclofenac SR 75 mg once daily (n = 120)
Double-blind phase				
Number of patients				
With AEs	11 (9.2)	9 (7.5)	5 (4.2)	8 (6.7)
Discontinued due to AEs	2 (1.7)	4 (3.3)	2 (1.7)	3 (2.5)
Number of patients with AEs by system organ class				
Blood and lymphatic system disorders	1 (0.8)	0	1 (0.8)	0
Cardiac disorders	0	1 (0.8)	0	1 (0.8)
Eye disorder	0	1 (0.8)	0	0
Gastrointestinal disorders	3 (2.5)	4 (3.3)	2 (1.7)	4 (3.3)
Hepatobiliary disorders	0	2 (1.7)	0	2 (1.7)
Infections and infestations	4 (3.3)	2 (1.7)	0	1 (0.8)
Musculoskeletal and connective tissue disorders	1 (0.8)	0	0	0
Nervous system disorders	1 (0.8)	0	1 (0.8)	0
Respiratory, thoracic and mediastinal disorders	1 (0.8)	0	0	0
Skin and subcutaneous tissue disorders	1 (0.8)	0	1 (0.8)	0

	All causality				Treatment-related			
Extension phase	C200 (n = 54)	D75 (n = 55)	C200/C400 (n = 53)	D75/C400 (n = 54)	C200 (n = 54)	D75 (n = 55)	C200/C400 (n = 53)	D75/C400 (n = 54)
Number of patients								
With AEs	0	6 (10.9)	5 (9.4)	6 (11.1)	0	4 (7.3)	3 (5.7)	3 (5.6)
Discontinued due to AEs	0	0	0	0	0	0	0	0
Number of patients with AEs by system organ class								
Blood and lymphatic system disorders	0	1 (1.8)	0	0	0	0	0	0
Gastrointestinal disorders	0	0	0	1 (1.9)	0	0	0	0
Hepatobiliary disorders	0	1 (1.8)	0	1 (1.9)	0	1 (1.8)	0	1 (1.9)
Infections and infestations	0	0	1 (1.9)	2 (3.7)	0	0	0	0
Laboratory investigations[†]	0	4 (7.3)	4 (7.5)	2 (3.7)	0	3 (5.5)	3 (5.7)	2 (3.7)

C200 = celecoxib 200 mg once daily during double-blind and extension phase; C200/C400 = celecoxib 200 mg once daily during double-blind phase and celecoxib 400 mg once daily during extension phase; D75 = diclofenac sustained release 75 mg once daily during double-blind and extension phase; D75/C400 = diclofenac sustained release 75 mg once daily during double-blind phase and celecoxib 400 mg once daily during extension phase.

[*] Patients were only counted once per treatment row; AEs occurring during the double-blind phase and up to 30 days after last dose (in double-blind phase) included. Values are presented as n (%).

[†] Laboratory investigations include alanine aminotransferase increased, aspartate aminotransferase increased, red blood cells urine positive, transaminases increased, weight decreased, and white blood cell count decreased.

inflammation, and improvement in physical function. Although NSAIDs are widely used in the treatment of AS, a number of safety and tolerability concerns surrounding their use (particularly over the longer term) still exist. Meanwhile, data supporting the use of alternative therapeutic options, such as COX-2 selective NSAIDs, are lacking. In the absence of direct head-to-head comparisons between COX-2 selective and nonselective NSAIDs in China, the present study was conducted. Diclofenac SR was selected as the active control because it is widely used by patients who have AS.[26] The double-blind treatment duration of 6 weeks was chosen because celecoxib has been shown to be statistically superior to placebo in placebo-controlled clinical studies of 6 to 12 weeks' duration in patients with AS.[24,25] Using the ASAS-20 response criteria, no changes in the response rates at Week 12 compared with Week 6 were demonstrated. A 6-week extension was also conducted to observe the safety profile and to collect efficacy data for celecoxib 400 mg in Chinese patients.

Our study demonstrated that celecoxib 200 mg once daily was noninferior to diclofenac SR 75 mg once daily in the treatment of Chinese patients with AS. In addition, patients in the celecoxib 200 mg once daily group experienced similar improvements in pain relief, disease activity, and physical function compared with patients receiving diclofenac SR 75 mg once daily. This finding is consistent with those of similarly designed studies in AS using the same comparator treatment.[24,25]

According to previous reports,[24,25] celecoxib 400 mg once daily reduces some parameters of inflammation more effectively than celecoxib 200 mg once daily, suggesting a possible dose-

dependent effect and potentially better treatment outcomes with the higher dose. The results of our analysis support this. At the end of the extension period (Week 12), celecoxib 400 mg once daily noticeably advanced the extent of improvements in patients who did not achieve satisfactory improvement in signs and symptoms after 6 weeks of treatment with celecoxib 200 mg once daily.

GI disorders are a well-known side effect of NSAID use;[29,30] however, celecoxib, a selective inhibitor of the inducible form of the COX enzyme (ie, COX-2), is thought to be better tolerated and associated with fewer AEs than the more traditional nsNSAIDs that act via nonselective inhibition of both COX-1 and COX-2.[31–35] Notably, in the Celecoxib versus Omeprazole and Diclofenac for at-Risk Osteoarthritis and Rheumatoid Arthritis Patients trial, the rate of predefined and adjudicated clinically significant upper and lower GI events (the primary end point) was 4 times higher in patients with arthritis at increased GI risk who were receiving diclofenac SR 75 mg twice daily plus omeprazole 20 mg once daily than in those receiving celecoxib 200 mg twice daily during 6 months of treatment.[36]

In our study, although GI disorders were the most frequently reported treatment-related AEs in both treatment groups during the double-blind phase, a similar number of GI AEs and discontinuations due to GI AEs were reported in patients receiving celecoxib 200 mg once daily compared with diclofenac SR 75 mg once daily. Furthermore, patients receiving the higher celecoxib 400 mg once daily dose throughout the 6-week extension phase also reported a similar number of GI AEs and discontinuations compared with patients receiving diclofenac SR 75 mg once daily. Our results, which suggest that treatment with celecoxib is not only well

tolerated but associated with a low frequency of GI AEs are also consistent with those of previous study outcomes in patients with AS[24,25] and arthritis.[29,30,36]

Conclusions

Consistent with previous findings in AS, our results suggest that the efficacy of celecoxib 200 mg once daily is noninferior to diclofenac SR 75 mg once daily over 6 weeks of treatment in Chinese patients with AS. Furthermore, the use of celecoxib 400 mg once daily was not associated with any additional AEs or tolerability issues compared with diclofenac SR 75 mg once daily over a 6-week treatment extension.

Acknowledgments

Conflicts of Interest

This study was sponsored by Pfizer Inc., who were responsible for the collection, analysis and interpretation of the data. Authors affiliated with Pfizer Inc. assisted with the writing and submission of the manuscript. Jin Fu and Sharon Pan are full-time employees of Pfizer Inc. Shi Le was a full-time employee of Pfizer Inc during the study and the manuscript development. The authors have indicated that they have no other conflicts of interest regarding the content of this article.

References

[1] Arnett FC. Seronegative spondylarthropathies. *Bull Rheum Dis.* 1987;37:1–12.
[2] Dougados M, Behier JM, Jolchine I, et al. Efficacy of celecoxib, a cyclooxygenase 2-specific inhibitor, in the treatment of ankylosing spondylitis: a six-week controlled study with comparison against placebo and against a conventional nonsteroidal antiinflammatory drug. *Arthritis Rheum.* 2001;44:180–185.
[3] Chen HH, Chen TJ, Chen YM, Ying-Ming C, Chen DY. Gender differences in ankylosing spondylitis-associated cumulative healthcare utilization: a population-based cohort study. *Clinics (Sao Paulo).* 2011;66:251–254.
[4] Zink A, Braun J, Listing J, Wollenhaupt J. Disability and handicap in rheumatoid arthritis and ankylosing spondylitis–results from the German rheumatological database. German Collaborative Arthritis Centers. *J Rheumatol.* 2000;27:613–622.
[5] van der Linden S, Valkenburg HA, Cats A. Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria. *Arthritis Rheum.* 1984;27:361–368.
[6] Wanders A, Heijde D, Landewé R, et al. Nonsteroidal antiinflammatory drugs reduce radiographic progression in patients with ankylosing spondylitis: a randomized clinical trial. *Arthritis Rheum.* 2005;52:1756–1765.
[7] Chinese Association of Rheumatology. Diagnosis and treatment guideline for Ankylosing Spondylitis. *Chin J Rheumatol.* 2010;14:557–559.
[8] Garcia Rodriguez LA, Jick H. Risk of upper gastrointestinal bleeding and perforation associated with individual non-steroidal anti-inflammatory drugs. *Lancet.* 1994;343:769–772.
[9] Khanna D, McMahon M, Furst DE. Safety of tumour necrosis factor-alpha antagonists. *Drug Saf.* 2004;27:307–324.
[10] 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. *BMJ.* 2006;332:1302–1308.
[11] McGettigan P, Henry D. Cardiovascular risk and inhibition of cyclooxygenase: a systematic review of the observational studies of selective and nonselective inhibitors of cyclooxygenase 2. *JAMA.* 2006;296:1633–1644.
[12] McGettigan P, Henry D. Cardiovascular risk with non-steroidal anti-inflammatory drugs: systematic review of population-based controlled observational studies. *PLoS Med.* 2011;8:e1001098.
[13] Solomon DH, Glynn RJ, Rothman KJ, et al. Subgroup analyses to determine cardiovascular risk associated with nonsteroidal antiinflammatory drugs and coxibs in specific patient groups. *Arthritis Rheum.* 2008;59:1097–1104.
[14] Bonner GF, Walczak M, Kitchen L, Bayona M. Tolerance of nonsteroidal antiinflammatory drugs in patients with inflammatory bowel disease. *Am J Gastroenterol.* 2000;95:1946–1948.
[15] De Keyser F, Elewaut D, De VM, et al. Bowel inflammation and the spondyloarthropathies. *Rheum Dis Clin North Am.* 1998;24:785–813 (ix-x).
[16] Evans JM, McMahon AD, Murray FE, McDevitt DG, MacDonald TM. Non-steroidal anti-inflammatory drugs are associated with emergency admission to hospital for colitis due to inflammatory bowel disease. *Gut.* 1997;40:619–622.
[17] Felder JB, Korelitz BI, Rajapakse R, Schwarz S, Horatagis AP, Gleim G. Effects of nonsteroidal antiinflammatory drugs on inflammatory bowel disease: a case-control study. *Am J Gastroenterol.* 2000;95:1949–1954.
[18] Gibson GR, Whitacre EB, Ricotti CA. Colitis induced by nonsteroidal anti-inflammatory drugs. Report of four cases and review of the literature. *Arch Intern Med.* 1992;152:625–632.
[19] Brandt J, Haibel H, Cornely D, et al. Successful treatment of active ankylosing spondylitis with the anti-tumor necrosis factor alpha monoclonal antibody infliximab. *Arthritis Rheum.* 2000;43:1346–1352.
[20] Gorman JD, Sack KE, Davis J Jr.. Treatment of ankylosing spondylitis by inhibition of tumor necrosis factor alpha. *N Engl J Med.* 2002;346:1349–1356.
[21] Deeks JJ, Smith LA, Bradley MD. Efficacy, tolerability, and upper gastro-intestinal safety of celecoxib for treatment of osteoarthritis and rheumatoid arthritis: systematic review of randomised controlled trials. *BMJ.* 2002;325:619.
[22] Dougados M, Dijkmans B, Khan M, Maksymowych W, van der Linden S, Brandt J. Conventional treatments for ankylosing spondylitis. *Ann Rheum Dis.* 2002;61 (Suppl 3):iii40–iii50.
[23] White WB, West CR, Borer JS, et al. Risk of cardiovascular events in patients receiving celecoxib: a meta-analysis of randomized clinical trials. *Am J Cardiol.* 2007;99:91–98.
[24] Barkhuizen A, Steinfeld S, Robbins J, West C, Coombs J, Zwillich S. Celecoxib is efficacious and well tolerated in treating signs and symptoms of ankylosing spondylitis. *J Rheumatol.* 2006;33:1805–1812.
[25] Sieper J, Klopsch T, Richter M, et al. Comparison of two different dosages of celecoxib with diclofenac for the treatment of active ankylosing spondylitis: results of a 12-week randomised, double-blind, controlled study. *Ann Rheum Dis.* 2008;67:323–329.
[26] Zochling J, Bohl-Buhler MH, Baraliakos X, Feldtkeller E, Braun J. Nonsteroidal anti-inflammatory drug use in ankylosing spondylitis–a population-based survey. *Clin Rheumatol.* 2006;25:794–800.
[27] 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 Arthritis Long-term (MEDAL) programme: a randomised comparison. *Lancet.* 2007;369:465–473.
[28] Kellner HL, Li C, Essex MN. Efficacy and safety of celecoxib versus diclofenac and omeprazole in elderly arthritis patients: a subgroup analysis of the CONDOR trial. *Curr Med Res Opin.* 2012;28:1537–1545.
[29] Allison MC, Howatson AG, Torrance CJ, Lee FD, Russell RI. Gastrointestinal damage associated with the use of nonsteroidal antiinflammatory drugs. *N Engl J Med.* 1992;327:749–754.
[30] Lanas A, Sopena F. Nonsteroidal anti-inflammatory drugs and lower gastrointestinal complications. *Gastroenterol Clin North Am.* 2009;38:333–352.
[31] Bensen WG, Zhao SZ, Burke TA, et al. Upper gastrointestinal tolerability of celecoxib, a COX-2 specific inhibitor, compared to naproxen and placebo. *J Rheumatol.* 2000;27:1876–1883.
[32] Goldstein JL, Silverstein FE, Agrawal NM, et al. Reduced risk of upper gastrointestinal ulcer complications with celecoxib, a novel COX-2 inhibitor. *Am J Gastroenterol.* 2000;95:1681–1690.
[33] McKenna F, Arguelles L, Burke T, Lefkowith J, Geis GS. Upper gastrointestinal tolerability of celecoxib compared with diclofenac in the treatment of osteoarthritis and rheumatoid arthritis. *Clin Exp Rheumatol.* 2002;20:35–43.
[34] Silverstein FE, Faich G, Goldstein JL, et al. Gastrointestinal toxicity with celecoxib vs nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis: the CLASS study: A randomized controlled trial. Celecoxib Long-term Arthritis Safety Study. *JAMA.* 2000;284:1247–1255.
[35] Singh G, Fort JG, Goldstein JL, et al. Celecoxib versus naproxen and diclofenac in osteoarthritis patients: SUCCESS-I Study. *Am J Med.* 2006;119:255–266.
[36] Chan FK, Lanas A, Scheiman J, Berger MF, Nguyen H, Goldstein JL. Celecoxib versus omeprazole and diclofenac in patients with osteoarthritis and rheumatoid arthritis (CONDOR): a randomised trial. *Lancet.* 2010;376:173–179.