Comparison of the efficacy and safety of CELBESTA® versus CELEBREX® in patients with rheumatoid arthritis: a 6-week, multicenter, double-blind, double-dummy, active-controlled, randomized, parallel-group, non-inferiority phase 4 clinical trial

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Abstract

Objectives: Celecoxib is a selective cyclooxygenase (COX)-2 inhibitor that is commonly used to reduce the incidence of gastrointestinal (GI) complications in patients with rheumatoid arthritis (RA). CELBESTA® is a generic equivalent to CELEBREX®, a celecoxib preparation. This study compared the efficacy and safety of CELBESTA® and CELEBREX® in patients with RA.

Methods: This was a multicenter, double-blind, double-dummy, active-controlled, randomized, parallel-group, non-inferiority clinical trial. The primary endpoint was a change from baseline in self-assessed pain intensity determined using a 100-mm visual analog scale after 6 weeks of treatment.

Results: After a washout period, 119 eligible subjects were randomized to one of two groups (CELBESTA® group, n = 61; CELEBREX® group, n = 58). CELBESTA® was not inferior to CELEBREX® because the upper limit of two-sided 95% confidence interval (CI) for the difference between the two groups (difference in the least square [LS] mean, −8.68 mm; two-sided 95% CI −16.59 mm to −0.77 mm) was less than the non-inferiority margin (10 mm). There were no significant differences in GI complications and renal toxicity.

Conclusions: CELBESTA® was not inferior to CELEBREX® with regard to the pain relief efficacy in RA patients, and the tolerability and safety profiles were excellent and at similar levels for both preparations.

Introduction

Nonsteroidal antiinflammatory drugs (NSAIDs) act rapidly to control inflammation and also provide analgesic effects in inflammatory arthritis. Although NSAIDs do not prevent the progression of joint destruction, they effectively relieve articular pain and control inflammation.[1,2] Patients with active rheumatoid arthritis (RA) often take NSAIDs primarily as adjuvant therapy for inflammatory pain control.[3] RA patients usually have a high economic burden for treatment duration.[4] Therefore, cost-effectiveness is an important issue for patients with RA who have long-term safety issues.[3,5,6]

The NSAID celecoxib is a selective cyclooxygenase (COX)-2 inhibitor that is commonly used to reduce the incidence of gastrointestinal (GI) complications in patients with active RA.[7–9] Many guidelines recommend the use of COX-2 inhibitors in elderly patients with GI problems.[10–12] The original commercial celecoxib drug, CELEBREX®, was developed by Pfizer, and it was patented in 1993 and approved for medical use in 1998. Upon expiry of the CELEBREX® patent in 2014, the US Food and Drug Administration (FDA) began to approve the first generic celecoxib preparations. CELBESTA®, developed by Dong-A ST (Seoul, Republic of Korea), is a generic celecoxib preparation that is produced in the Republic of Korea. Although it is considered to be similar to the original drug, the efficacy and safety of generic drugs

must be carefully verified in clinical settings. Bioequivalent formulations are expected to demonstrate similar efficacy and safety under identical circumstances. Although evidence for clinical inequivalence could not be identified, many patients and physicians have suspicions related to the quality, efficacy and safety of generic drugs, and they have a negative opinion of generic drug substitution.[13,14] If non-inferiority is clearly recognized, generic drugs can be prescribed more than they are currently prescribed to reduce a patient's economic burden. A previous study compared the efficacy and safety of the original non-selective NSAID and the generic non-selective NSAID in RA patients,[15] but there have been no studies involving a generic selective COX-2 inhibitor drug. The purpose of this study was to evaluate and compare the efficacy and safety of CELBESTA® and CELEBREX® after administering the drugs for 6 weeks to patients with RA, and to demonstrate that the therapeutic effects of CELBESTA® are not inferior to those of CELEBREX®.

Methods

This trial was structured in accordance with the Consolidated Standards of Reporting Trials (CONSORT) 2010 guidelines (http://www.consort-statement.org/consort-2010).

Registration

This trial was registered on ClinicalTrials.gov and the registration number is NCT02780323.

Trial design and participants

This multicenter, double-blind, double-dummy, active-controlled, randomized, parallel-group, non-inferiority clinical trial was conducted between November 2015 and December 2017 at ten centers throughout the Republic of Korea. This study was reviewed and approved by the institutional review board at each participating center, and written informed consent was obtained from all patients before participation in the study.

The inclusion criteria were adult patients 19 years of age or older with RA that was diagnosed in accordance with the 2010 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria or 1987 ACR classification criteria.[16] Patients had taken at least one type of disease-modifying antirheumatic drug (DMARD) for at least 3 months from the beginning of the screening test and an oral corticosteroid agent without dose change at a daily dose of <10 mg prednisolone for more than 4 weeks from the beginning of the screening test. Subjects who stopped taking other NSAIDs for 3 to 14 days before the randomization and who had an overall 100-mm visual analog scale (VAS) pain assessment after the washout period of at least 40 mm were enrolled into in this study.

Exclusion criteria included a history of symptomatic angina or congestive heart failure at rest or with minimal activity; myocardial infarction or atherosclerosis or a history of coronary angioplasty or coronary artery bypass graft within the past 1 year; cerebrovascular accidents within the past 2 years; gastroesophageal reflux surgery or gastrectomy; GI bleeding or peptic ulcer within the past 30 days; malignant tumors (except patients whose tumors were removed by surgery, and who had no recurrence within the past 5 years); and other major disorders of the GI tract, kidney, liver, and blood. Additionally, we excluded patients with a history of hypersensitivity to COX-2 inhibitors, sulfonamides, or other NSAIDs, and those taking medications including intraarticular corticosteroid injection within 4 weeks

before the screening visit; biological antirheumatic agents, such as infliximab, adalimumab, etanercept, anakinra, and abatacept within 6 months before randomization; or rituximab within 1 year before randomization.

Sample size

The estimated sample size was based on previous studies. To calculate the number of subjects, information from the most similar study design was used from the SKI306X 200 mg study[17] and the pelubiprofen 30 mg study,[18] which involved a comparison with CELEBREX® 200 mg. The non-inferiority margin of the difference in VAS change was defined as 10 mm based on statistical considerations and clinical judgement.[19,20] To define the non-inferiority margin for this study, two non-inferiority studies that were most similar to this study were reviewed.[17,18] In the same manner as in the previous two studies, we defined the non-inferiority margin as 10 mm, which is 10% of the VAS score based on clinical judgement. The target sample size was computed as 63 subjects in each group (126 subjects in total). Considering a drop-out rate of 20%, we aimed to recruit a total of 158 subjects.

Randomization and blinding

Before the recruitment phase, an independent statistician, who was unrelated to this study, generated random sequences using Proc PLAN procedure of SAS version 9.4 (SAS Institute, Cary, NC, USA).

The allocation table that was generated by the randomization results was delivered to the team that was involved in packaging the drug, and this packaging team was independent of team that was conducting the clinical trial. The study drugs were packaged based on the assigned participant number for each clinical trial institution, and they were delivered to the clinical trial institution in a blinded manner. At each clinical trial institution, the participant number was assigned by investigators in the order of participant registration, and each management pharmacist delivered the pre-packaged drug with the same number as the participant number that was given by investigators. Investigators determined the participant's eligibility, enrolled the participant, and assigned the participant number in the order of registration, and the investigators had no opportunity to access the clinical trial drugs. The test drug and the control drug were the same appearance and they were also delivered in a pre-packaged form to maintain the blinding for the investigators, management pharmacists, and participants.

Interventions

After a 3 to 14-day washout period, RA patients were randomized to receive either CELBESTA® (test group; Dong-A ST, Seoul, Republic of Korea) or CELEBREX® (active control group; Pfizer, New York, NY, USA) in a 1:1 ratio. To conduct the trial in a double-dummy manner, the test group took a capsule of active CELBESTA® 200 mg and a placebo CELEBREX® 200 mg capsule containing no drug twice a day (after breakfast and dinner) for 6 weeks, while the active control group took an active CELEBREX® 200 mg and a placebo CELBESTA® 200 mg capsule containing no drug in the same manner. The overall schedule of the study is shown in Figure 1. The patients attended four outpatient visits. Visit 1 confirmed the washout during the screening period and visit 2 (baseline) began by randomizing the patient to the study medication, which was prescribed in a double-blind, double-dummy manner. Visit 3 was performed as the midterm evaluation 2 weeks after the
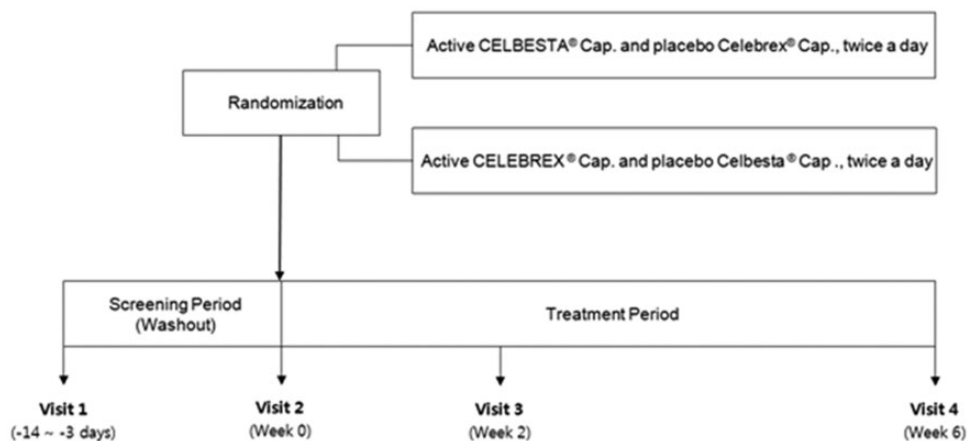
Figure 1. Overall schedule of the study.
Washout: period during which eligible subjects stopped taking any other NSAIDs before starting the study treatment.
CELBESTA®: generic celecoxib drug developed by Dong-A ST.
CELEBREX®: original celecoxib drug developed by Pfizer.
NSAID, non-steroidal anti-inflammatory.

baseline, and visit 4 completed the final evaluation 6 weeks after the baseline visit.

Concurrent use of methotrexate, sulfasalazine, hydroxychloroquine, leflunomide, or prednisolone was acceptable at the same dose as had been used before the study participation. Oral prednisolone was allowed at a dose of <10 mg/day and intra-articular corticosteroid injection and skin patches containing NSAIDs were not available.

Outcomes

The full analysis set (FAS) was used as the main analysis population for the efficacy evaluation, and the per-protocol set (PPS) was also analyzed. The FAS included all randomized subjects who receive at least one dose of study drug and had at least one valid post-baseline efficacy evaluation. The PPS was defined as a subset of the FAS, and it included subjects who completed the study without any major protocol violations. The major protocol violations were "violation of inclusion/exclusion criteria",

"did not meet the medication compliance criteria ($\geq 70\%$)", "missing of the primary efficacy endpoint", "concomitant administration of prohibited medication", "violation of randomization", and "not conducted washout".

The primary endpoint was a change in the self-assessed pain intensity using a 100-mm VAS from baseline until 6 weeks of treatment. The secondary endpoint was a change in the disease activity score in 28 joints (DAS28-ESR) from baseline until 6 weeks of treatment. Safety profiles and independent data were collected and laboratory testing was performed at each study visit, including GI symptoms, renal function, and other adverse events, using a questionnaire (Appendix 1). The safety analysis set of patients were grouped for analysis based on the treatment that they received, as opposed to the treatment they were allocated to receive at randomization. The compliance rate was calculated as follows: (Real number of treated capsules/Expected number of treated capsules) $\times 100$, where

the expected number of treated capsules was as follows: (Visit 4 − Visit 2) × 4. The premature discontinuation (PD) visit was used for withdrawn subjects.

Statistical analysis

Statistical analyses were performed using SAS version 9.4 (SAS Institute, Chicago, IL). Demographic and baseline data were analyzed using the chi-square test, two sample t-test, and Wilcoxon's rank-sum test. For comparison between the treatment groups, analyses of covariance (ANCOVA) or rank ANCOVA were performed depending on the predetermined satisfaction status of the normality assumption. Changes from baseline at Week 2 and Week 6 after dosing were compared within the treatment groups using the paired t-test or Wilcoxon's signed-rank test. Safety profiles and compliance were compared between the two groups with Wilcoxon's rank-sum test and Fisher's exact test. In all analyses, $p < 0.05$ was considered to indicate statistical significance.

Results

The scheme for enrollment and randomization throughout the study is shown in Figure 2. Between 2 November 2015 and 26 December 2017, 133 subjects were screened at 10 nationwide institutions in the Republic of Korea, and 119 subjects were randomized into the two groups (CELBESTA® group, n = 61; CELEBREX® group, n = 58). The FAS consisted of 60 patients in the CELBESTA® group and 58 patients in the CELEBREX® group. The PPS included 40 patients in the CELBESTA® group and 41 patients in the CELEBREX® group (Figure 2). The demographic and clinical characteristics of the patients at baseline were mostly balanced across the treatment groups (Table 1).

Both groups showed statistically significant reductions in 100-mm VAS score after 6 weeks of treatment compared with the respective baseline values (all $p < 0.0001$). The changes in the 100-mm VAS score between visit 2 (Week 0) and visit 4 (Week 6) are shown in Table 2 and Figure 3. The changes (least square [LS] mean ± standard error [SE]) in the full-set analyses were −29.1 ± 2.8 mm in the CELBESTA® group and −20.4 ± 2.9 mm in the CELEBREX® group and the difference between the two groups was −8.68 mm (two-sided 95% CI −16.59 mm to −0.77 mm). The changes (LS mean ± SE) in per-protocol analyses were −31.3 ± 3.2 mm in the CELBESTA® group and −22.3 ± 3.1 mm in the CELEBREX® group, and the difference between the two groups was −9.02 mm (95% two-sided CI −17.84 mm to −0.20 mm).

The changes in the DAS28-ESR score between visit 2 (Week 0) and visit 4 (Week 6) are shown in Table 3 and Figure 3. The changes were −1.2 ± 0.1 in the CELBESTA® group and −0.9 ± 0.1 in the CELEBREX® group in full-set analyses and −1.2 ± 0.1 in the CELBESTA® group and −0.9 ± 0.1 in the CELEBREX® group in per-protocol analyses, which were both not statistically significant between the two groups.

This study showed that CELBESTA® was not inferior to CELEBREX® because the upper limit of the 95% two-sided CI for the difference between the two groups (difference in LS means, −8.68 mm; two-sided 95% CI −16.59 mm to −0.77 mm) was less than the non-inferiority margin (10 mm).

Safety profiles based on the safety set are shown in Table 4. There were no statistically significant differences in GI complications or renal toxicity between the two groups, and no unusual findings were observed in vital signs, clinical laboratory test, and ECG during the study.

For adverse events, GI disorders were the most common disorder in the CELBESTA® group (n = 7, 11.67%) and
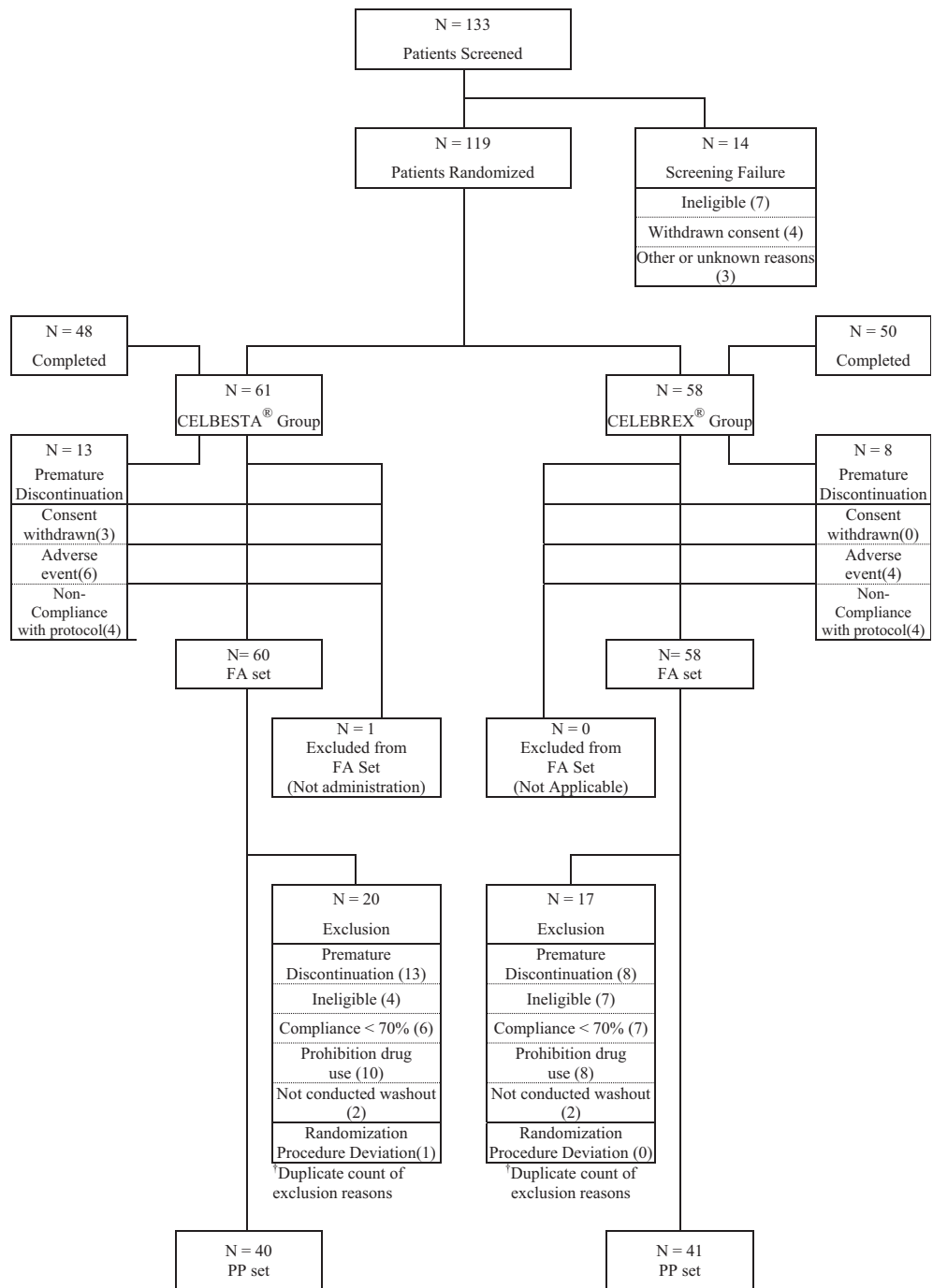
Figure 2. Scheme for enrollment and randomization along the overall schedule of the study.
PP: Per-protocol analysis, consisting of comparison of treatment groups including only those patients who completed the treatment originally allocated.
Compliance (%): (Real number of treated capsules/Expected number of treated capsules) × 100; Expected number of treated capsules: (Visit 4 − Visit 2) × 4; PD (premature discontinuation) visit was used for withdrawal subjects.

Table 1. Baseline characteristics of the patients.

	CELBESTA® (n = 61)	CELEBREX® (n = 58)	p-value
Sex Female, n (%)	47 (77.1)	48 (82.8)	0.44[a]
Age (years)	54.6 ± 12.3	56.1 ± 10.9	0.49[b]
BMI (kg/m²)	23.5 ± 3.7	24.0 ± 3.6	0.44[c]
Clinical status of rheumatoid arthritis			
2010 ACR/EULAR criteria, n (%)†	37 (60.7)	41 (70.7)	0.25[a]
1987 ACR criteria, n (%)†	27 (44.3)	22 (37.9)	0.48[a]
Duration of disease (months)	75.1 ± 81.8	79.6 ± 85.4	0.62[c]
X-ray findings other than RA Abnormal, n (%)	8 (13.8)	4 (7.6)	0.29[a]
100-mm VAS (mm)	56.0 ± 13.4	55.7 ± 14.0	0.75[c]
DAS 28-ESR	4.3 ± 1.1	4.3 ± 1.2	0.98[b]
Laboratory findings			
hs-CRP (mg/L)	4.2 ± 8.3	2.48 ± 4.3	0.91[c]
RF (IU/mL)	110.4 ± 217.7	110.8 ± 201.1	0.97[c]
RF positive, n (%)	41 (67.2)	37 (63.8)	0.69[a]
ACPA (U/mL)	95.9 ± 125.1	130.8 ± 170.9	0.38[c]
ACPA positive, n (%)	42 (68.9)	40 (69.0)	0.99[a]
Previous medication (previous 1 month)			
Prednisolone, n (%)†	50 (82.0)	45 (77.6)	
Mean dose (mg/day)	3.9 ± 1.8	4.1 ± 1.6	0.52[c]
Methotrexate, n (%)†	46 (75.4)	48 (82.8)	
Mean dose (mg/week)	9.8 ± 2.1	10.7 ± 2.2	0.06[c]
Sulfasalazine, n (%)†	11 (18.0)	6 (10.3)	
Mean dose (mg/day)	1,000.0 ± 387.3	750.0 ± 273.9	0.19[c]
Hydroxychloroquine, n (%)†	18 (29.5)	19 (32.8)	
Mean dose (mg/day)	311.1 ± 102.3	265.8 ± 97.3	0.17[c]
Leflunomide, n (%)†	10 (16.4)	7 (12.1)	
Mean dose (mg/day)	16.0 ± 5.2	14.3 ± 5.3	0.54[c]
DMARD monotherapy, n (%)	33 (54.1)	34 (58.6)	0.62[a]
DMARD combination, n (%)	25 (41.0)	23 (39.7)	0.88[a]

All data are presented as the mean ± SD.

n: number of patients.

VAS: 100-mm VAS; 0: no pain to 100: worst pain imaginable.

DAS28 (disease activity score using 28 joint count)-ESR: $0.56 \times \sqrt{TJC} + 0.28 \times \sqrt{SJC} + 0.70\ln ESR + 0.014 \times$ (100-mm VAS; 0: no pain to 100: worst pain imaginable).

Missing (n): CELBESTA® – height (1), weight (1), BMI (1), hs-CRP (1)/CELEBREX® – hs-CRP (2).

[a]Chi-square test.

[b]Two-sample t-test.

[c]Wilcoxon's rank-sum test.

†Duplicated.

VAS, visual analog scale; TJC, tender joint count; SJC, swollen joint count; BMI, body mass index; RA, rheumatoid arthritis; CRP, C-reactive protein; SD, standard deviation; RF, rheumatoid factor; ACPA, anti-citrullinated protein antibody; ESR, erythrocyte sedimentation rate; DMARD, disease modifying anti-rheumatic drug; ACR/EULAR, American College of Rheumatology/European League Against Rheumatism.

Table 2. Changes in the 100-mm VAS score before and after treatment in RA patients.

	CELBESTA® (n = 60)	CELEBREX® (n = 58)	p-value[a]
Full analysis set			
Week 0 (visit 2)	56.0 ± 13.5	55.7 ± 14.0	
Week 6 (visit 4)	26.8 ± 19.7	35.5 ± 23.8	
Change	−29.1 ± 2.8	−20.4 ± 2.9	0.03*
	CELBESTA® (n = 40)	CELEBREX® (n = 41)	p-value[a]
Per-protocol analysis set			
Week 0 (visit 2)	56.6 ± 13.6	54.0 ± 14.3	
Week 6 (visit 4)	24.2 ± 17.2	32.8 ± 22.1	
Change	−31.3 ± 3.2	−22.3 ± 3.1	0.05*

Values are presented as 100-mm VAS scores.
Values for visit 2 and visit 4 are shown as the mean ± SD.
Changes were calculated using the LS mean ± SE.
n, number of patients; VAS, visual analog scale (100-mm VAS; 0: no pain to 100: worst pain imaginable).
RA, rheumatoid arthritis; VAS, visual analog scale; SD, standard deviation; SE, standard error.
Week 0: visit 2 (baseline), Week 6: visit 4, change: value at visit 4 − value at visit 2 (baseline).
Missing (n): CELBESTA® − full analysis set: visit 4 (1).
[a]ANCOVA (covariate: baseline value).
*Statistically significant: $p < 0.05$.

Table 3. Changes in DAS28-ESR score before and after treatment in RA patients.

	CELBESTA® (n = 60)	CELEBREX® (n = 58)	p-value[a]
Full analysis set			
Week 0 (visit 2)	4.3 ± 1.1	4.3 ± 1.2	
Week 6 (visit 4)	3.1 ± 1.1	3.4 ± 1.2	
Change	−1.2 ± 0.1	−0.9 ± 0.1	0.09
Per-protocol analysis set			
Week 0 (visit 2)	4.2 ± 1.1	4.1 ± 1.2	
Week 6 (visit 4)	2.9 ± 1.0	3.2 ± 1.2	
Change	−1.2 ± 0.1	−0.9 ± 0.1	0.14

Values are presented as DAS28-ESR scores.
Values for visit 2 and visit 4 are shown as the mean ± SD.
Changes were calculated by the LS mean ± SE.
n: number of patients; DAS28 (disease activity score using 28 joint count)-ESR:
$0.56 \times \sqrt{TJC} + 0.28 \times \sqrt{SJC} + 0.70 \ln ESR + 0.014 \times$ (100-mm VAS; 0: no pain to 100: worst pain imaginable)
Week 0: visit 2 (baseline), Week 6: visit 4, change: value at visit 4 − value at visit 2 (baseline).
Missing (n): CELBESTA® − full analysis set: visit 4 (1).
[a]ANCOVA (covariate: baseline value).
TJC, tender joint count; SJC, swollen joint count; RA, rheumatoid arthritis; VAS, visual analog scale; SD, standard deviation; SE, standard error; LS, least square; ESR, erythrocyte sedimentation rate.

decreases in estimated glomerular filtration rate (eGFR) were the more common in the CELEBREX® group (n = 5, 8.62%). There were several serious adverse events. One serious adverse event was a maternal exposure during pregnancy (i.e. the participant took the drug without knowing about the pregnancy), which proceeded to abortion in the CELBESTA® group, but this case was determined as not related to
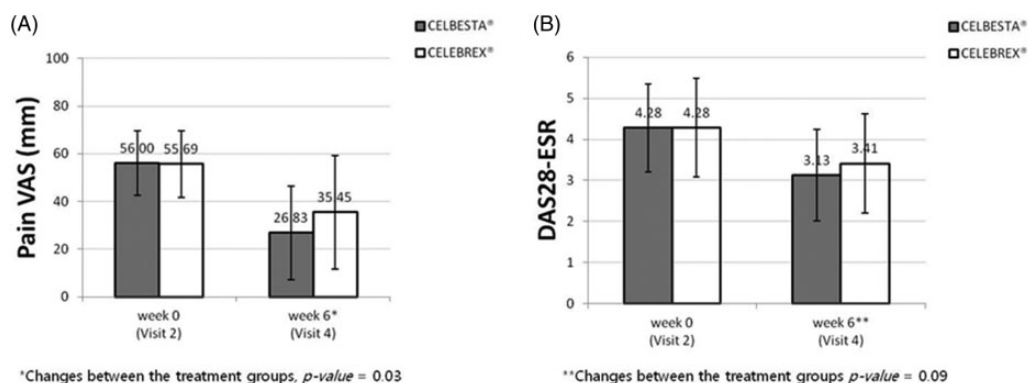
Figure 3. Changes in 100-mm VAS score and DAS28-ESR score before and after CELBESTA® and CELEBREX® treatments in RA patients (A) Changes in 100-mm VAS score (B) Changes in DAS28-ESR score. Values for visit 2 and visit 4 are shown as the mean ± SD.

VAS: 100-mm VAS; 0: no pain to 100: worst pain imaginable.

DAS28 (disease activity score using 28 joint count)-ESR: $0.56 \times \sqrt{TJC} + 0.28 \times \sqrt{SJC} + 0.70 \ln ESR + 0.014 \times$ (100-mm VAS; 0: no pain to 100: worst pain imaginable).

TJC, tender joint count; SJC, swollen joint count; VAS, visual analog scale; SD, standard deviation.

Table 4. Safety profiles according to the safety set in patients with RA.

	CELBESTA® ($n = 60$)	CELEBREX® ($n = 58$)	*p-value*
GI symptom, score (*n*)			
Change at visit 3	0.2 ± 2.2 (51)	0.2 ± 2.8 (51)	0.23[a]
Change at visit 4	0.6 ± 3.2 (60)	0.7 ± 2.9 (58)	0.62[a]
≥ G3 Chronic kidney disease, *n* (%)‡			
Visit 1	1 (1.7)	2 (3.5)	0.62[b]
Visit 3	1 (2.0)	3 (5.9)	0.62[b]
Visit 4†	1 (1.7)	3 (5.3)	0.36[b]
eGFR (mL/minute/1.73 m²) (*n*)			
Change at visit 3	−0.5 ± 40.2 (51)	2.7 ± 13.2 (51)	0.43[a]
Change at visit 4	−0.2 ± 38.1 (59)	0.9 ± 13.4 (57)	0.29[a]

visit 1: screening period; visit 3: Week 2; visit 4: Week 6. Change: value at follow-up visit − value at baseline.

GI symptom score: evaluation of the nine gastrointestinal symptoms (abdominal pain, diarrhea, bloody stool, chest pain (heartburn), nausea, vomiting, abdominal bloating, loss of appetite, and constipation); G3: Grade 3 (eGFR < 60 mL/minute/1.73 m²); eGFR: estimated glomerular filtration rate.

Missing (*n*): CELBESTA® − GI symptom: visit 3 (9), ≥G3 chronic kidney disease: visit 3 (9), visit 4 (1), eGFR: visit 3 (9), visit 4 (1)/CELEBREX® − GI safety: visit 3 (7), ≥G3 chronic kidney disease: visit 3 (7), visit 4 (1), eGFR: visit 3 (7), visit 4 (1)

[a]Wilcoxon's rank-sum test.

[b]Fisher's/ exact test.

†PD (premature discontinuation) visit was used for withdrawn subjects.

‡Subjects with chronic kidney disease stage 3, 4, 5 according to National Kidney Foundation (NKF): eGFR < 60 mL/minute/1.73 m² at each visit.

GI, gastrointestinal; RA, rheumatoid arthritis; eGFR, estimated glomerular filtration rate; SD, standard deviation; SE, standard error.
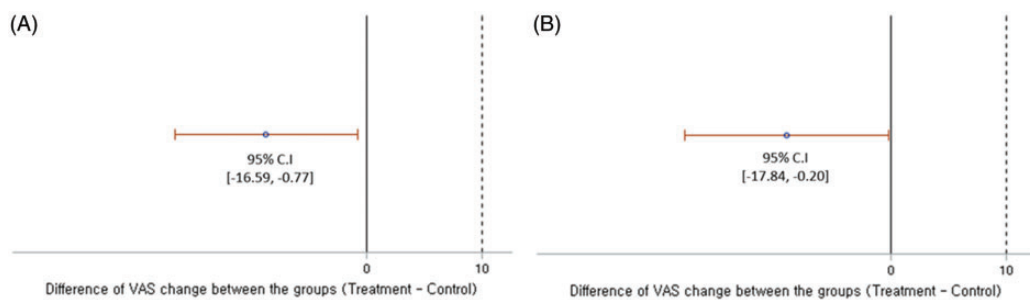
Figure 4. The 95% confidence interval for the difference between groups for the 100-mm VAS (A) Full analysis set (B) Per-protocol analysis set.
The full analysis set comprises comparison of the treatment groups including all patients as they were originally allocated after randomization.
Per-protocol analysis set comprises comparison of treatment groups including only those patients who completed the treatment to which they were originally allocated.
VAS: 100-mm VAS (0: no pain to 100: worst pain imaginable).
10: 10 mm was the non-inferiority margin of the difference in the VAS change.
VAS, visual analog scale.

CELBESTA® by the attending physician. Another serious adverse event was a urinary tract infection (UTI) in the CELEBREX® group, which was not considered to be related to the study drug. Adverse events of special interest were defined as GI ulcer, bleeding, perforation, and eGFR reduction. There was also one serious adverse event of drug-related eGFR reduction that occurred in the CELEBREX® group.

The compliance rates were 92.8% in the CELBESTA® group and 91.6% in the CELEBREX® group in the full-set analyses. In the per-protocol analyses, the CELBESTA® group and CELEBREX® group showed compliance rates of 97.8% and 96.6%, respectively.

Discussion

This study demonstrated that CELBESTA® was not inferior to CELEBREX®. The results showed that the upper limit of the two-sided 95% CI for the difference between the two groups was less than the non-inferiority margin (10 mm).

RA is a type of inflammatory arthritis that is characterized by autoantibody production and synovitis causing erosion of cartilage and bone destruction.[2,21] Long-term management of RA patients requires optimal pain relief from treatment, which is associated with improvements in pain symptoms, function, and quality of life.[4,5] Because of their analgesic effect, NSAIDs are commonly used in acute articular pain management.[1,3] RA requires long-term treatment, so cost-effectiveness is important to patients.[5,6] Therefore, cheaper drugs with appropriate safety profiles are needed to reduce the economic burden. Generic drugs contain the same chemical components as the original drugs that were protected by patents. Because the components are the same, the medical profile of generics is thought to be equivalent to the original drugs in practice. However, although a generic may have the same pharmaceutical components as the original drug, it may differ in some characteristics, such as the manufacturing process, formulation, and excipients. Therefore, the efficacy and safety of generic drugs should be confirmed.

In this study, CELBESTA® and CELEBREX® treatment resulted in rapid reduction of pain in RA patients as assessed by the 100-mm VAS score and DAS28-ESR score. In RA patients, the overall pain relief effect of CELBESTA® was not inferior to that of CELEBREX®. There was no clinically significant worsening of GI symptoms in both groups, and no significant intergroup differences in the changes were found. No significant changes were found in the calculated eGFR in both groups; the eGFR values at baseline, Week 2, and Week 6 were all at least $90 \, mL/minute/1.73 \, m^2$, indicating that renal function remained normal after administration of both drugs.

Our study has several limitations. The generalizability of the findings from this study is limited by its short study period of 6 weeks and by the small enrollment number. The primary endpoint of this study was to determine the non-inferiority of CELBESTA, which was shown in this study. This study showed superiority beyond non-inferiority, but the results should be interpreted with caution (Figure 4). The study began with the assumption that bioequivalence would be predicted to have similar efficacy and safety because the study drugs were synthetic drugs. Although it showed superiority and statistical significance, these results may be because of a sampling error based on the small sample size. It is necessary to evaluate more real-world data. In addition, it remains unknown whether treatment was effective even at low doses <400 mg per day of CELBESTA®. Our results reconfirm the safety of moderate celecoxib doses, but not the safety of high doses exceeding 400 mg per day.

In conclusion, CELBESTA® is not inferior to CELEBREX® with regard to efficacy in RA patients. Both drugs also have excellent tolerability and safety at similar doses.

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Appendix 1. Gastrointestinal symptoms questionnaire.

Gastrointestinal symptoms questionnaire

☐ Visit 1 / ☐ Visit 3 / ☐Visit 4 / ☐ Visit premature discontinuation)

Symptoms	Question	Answer
Abdominal pain	Does your stomach hurt like a squeeze? If yes, how many times per week did you experience it?	Times
Diarrhea	Have you ever had diarrhea? If yes, how many times per week did you experience it?	Times
Bloody stool	Have you ever had bloody stool? If yes, how many times per week did you experience it?	Times:
Chest pain (Heartburn)	Have you ever had chest pain or heartburn? If yes, how many times per week did you experience it?	☐0 (No symptom) ☐1 (Mild) ☐2 (Moderate) ☐3 (Severe)
Nausea	Have you ever had nausea? If yes, how many times per week did you experience it?	☐0 (No symptom) ☐1 (Mild) ☐2 (Moderate) ☐3 (Severe)
Vomiting	Have you ever vomited? If yes, how many times per week did you experience it?	☐0 (No symptom) ☐1 (Mild) ☐2 (Moderate) ☐3 (Severe)
Abdominal bloating	Have you ever had abdominal bloating? If yes, how many times per week did you experience it?	☐0 (No symptom) ☐1 (Mild) ☐2 (Moderate) ☐3 (Severe)
Loss of appetite	Have you lost your appetite? If yes, how many meals do you skip per week?	☐0 (No symptom) ☐1 (Mild) ☐2 (Moderate) ☐3 (Severe)
Constipation	Is it hard to have a bowel movement? If yes, how many times do you have stool per week?	☐0 (No symptom) ☐1 (Mild) ☐2 (Moderate) ☐3 (Severe)

Score	Symptom severity
0 (No symptoms)	No symptoms
1 (Mild)	Symptoms less than twice a week
2 (Moderate)	Symptoms two or more times a week, but no limitation of daily activity
3 (Severe)	Almost daily symptoms, and marked limitation of daily activity
Abdominal pain, diarrhea, and bloody stool are scored as the number of occurrences per week.	