Journal of Ethnopharmacology 337 (2025) 118843

Contents lists available at ScienceDirect

Journal of Ethnopharmacology

journal homepage: www.elsevier.com/locate/jethpharm

Efficacy and safety of SKCPT in patients with knee osteoarthritis: A multicenter, randomized, double-blinded, active-controlled phase III clinical trial

Sung Il Bin [a], Myung Chul Lee [b], Seung-Baik Kang [c], Young-Wan Moon [d], Kyoung Ho Yoon [e], Seung-Beom Han [f], Yong In [g], Chong Bum Chang [h], Ki-Cheor Bae [i], Jae-Ang Sim [j], Jong-Keun Seon [k], Kwan Kyu Park [l], Sang Jin Lee [m], Young-Mo Kim [n,*]

[a] Department of Orthopedic Surgery, Asan Medical Center, 05505, Seoul, Republic of Korea
[b] Department of Orthopedic Surgery, Seoul National University Hospital, 03080, Seoul, Republic of Korea
[c] Department of Orthopedic Surgery, Seoul Metropolitan Government-Seoul National University Boramae Medical Center, 07061, Seoul, Republic of Korea
[d] Department of Orthopedic Surgery, Samsung Medical Center, 06351, Seoul, Republic of Korea
[e] Department of Orthopedic Surgery, Kyung Hee University Hospital, 02447, Seoul, Republic of Korea
[f] Department of Orthopedic Surgery, Korea University Anam Hospital, 02841, Seoul, Republic of Korea
[g] Department of Orthopedic Surgery, The Catholic University of Korea Seoul St. Mary's Hospital, 06591, Seoul, Republic of Korea
[h] Department of Orthopedic Surgery, Seoul National University Bundang Hospital, 13620, Seongnam, Republic of Korea
[i] Department of Orthopedic Surgery, Keimyung University Dongsan Hospital, 42601, Daegu, Republic of Korea
[j] Department of Orthopedic Surgery, Gachon University Gil Medical Center, 21565, Incheon, Republic of Korea
[k] Department of Orthopedic Surgery, Chonnam National University Hwasun Hospital, 58128, Hwasun, Republic of Korea
[l] Department of Orthopedic Surgery, Severance Hospital, 03722, Seoul, Republic of Korea
[m] Department of Orthopedic Surgery, Inje University Haeundae Paik Hospital, 48108, Busan, Republic of Korea
[n] Department of Orthopedic Surgery, Chungnam National University Hospital, Chungnam National University, College of Medicine, 35015, Daejeon, Republic of Korea

ARTICLE INFO

Keywords:
Celecoxib
Elderly
Knee osteoarthritis
Pain
SKCPT
Treatment

ABSTRACT

Ethnopharmacological relevance: Osteoarthritis (OA) is the most prevalent type of arthritis worldwide and a leading cause of years lost to pain and disability. Among the current pharmacological treatments for OA, symptomatic slow-acting drugs for OA (SYSADOA) induce pain relief and aim to improve joint function by relieving inflammation while causing fewer gastrointestinal and cardiovascular adverse events than non-steroidal anti-inflammatory drugs (NSAIDs). SKCPT is a herbal SYSADOA formulated from *Clematis mandshurica*, *Trichosanthes kirilowii*, and *Prunella vulgaris* powdered extracts. This preparation has been shown to induce cartilage protection and anti-inflammatory effects in preclinical studies and inhibit glycosaminoglycan degradation and catabolic gene expression in human OA chondrocytes and cartilage.

Aim of the study: We aimed to evaluate the non-inferiority of SKCPT to celecoxib and safety for treating knee OA.

Materials and methods: This multicenter, randomized, double-blind, phase III clinical trial enrolled adults with primary knee OA who were randomized (1:1) to SKCPT 300 mg twice daily or celecoxib 200 mg once daily for 12 weeks.

Results: In total, 278 patients were assigned to treatment (SKCPT, 136; celecoxib, 142) for approximately 12 weeks. The primary endpoint was the mean change of Korean Western Ontario and McMaster Universities Osteoarthritis Index (K-WOMAC) pain subscale scores from baseline to Day 84. The mean change (least squares [LS] mean ± standard error) from baseline to Day 84 was −23.74 ± 1.48 for SKCPT and −25.88 ± 1.44 for celecoxib. The two-sided 95% confidence interval of the difference (LS mean) between groups was [−1.94, 6.20], confirming that the upper limit was less than the non-inferiority margin of 10. Additionally, there were no significant differences in the secondary endpoints (mean changes of K-WOMAC pain, physical, stiffness subscale,

* Corresponding author.
E-mail addresses: sibin99@naver.com (S.I. Bin), leemc@snu.ac.kr (M.C. Lee), ossbkang@gmail.com (S.-B. Kang), yw1moon@gmail.com (Y.-W. Moon), kyoungho@khmc.or.kr (K.H. Yoon), oshan@korea.ac.kr (S.-B. Han), iy1000@catholic.ac.kr (Y. In), ccbknee@gmail.com (C.B. Chang), bkc@dsmc.or.kr (K.-C. Bae), sim_ja@gilhospital.com (J.-A. Sim), seonbell@jnu.ac.kr (J.-K. Seon), kkpark@yuhs.ac (K.K. Park), sjinnie@paik.ac.kr (S.J. Lee), osdr69@gmail.com (Y.-M. Kim).

https://doi.org/10.1016/j.jep.2024.118843
Received 21 March 2024; Received in revised form 29 July 2024; Accepted 17 September 2024
Available online 18 September 2024

and total score, and the frequency and number of doses of rescue medications) between groups at all time points. Differences between groups in adverse events and adverse drug reactions were not significant, and no serious adverse events occurred.

Conclusions: SKCPT efficacy was non-inferior, and its safety profile was similar, to celecoxib. Building on previous results showing that SYSADOA reduce NSAID intake, the present results suggest that the SYSADOA SKCPT could effectively replace NSAIDs in knee OA treatment while avoiding long-term side effects.

1. Introduction

Osteoarthritis (OA) is the most prevalent type of arthritis worldwide and a leading cause of years lost to pain and disability (O'Neill et al., 2018). OA seriously affects the life quality of patients. More than 500 million individuals are affected globally (Hunter et al., 2020). Over recent decades, there has been a trend toward increased OA prevalence, and the numbers are likely to increase as populations age (Safiri et al., 2020). Over 85% of the global burden of OA is attributed to knee OA (Safiri et al., 2020). Being primarily related to aging, the prevalence of OA will steadily increase and is expected to be the single greatest cause of disability in the general population by 2030 (Thomas et al., 2014). It is well known that the main factors that play crucial roles in the onset and progression of OA are mechanical stress, low-grade systemic inflammation, and metabolic imbalance (Courties et al., 2015).

Currently, OA is regarded as an inflammatory disease (Wang et al., 2011). Based on the research by Kang et al. (2019), the onset and progression of OA are attributed to various inflammatory cytokines in joint tissues and fluids that are produced by chondrocytes and/or interact with chondrocytes, as well as to low-grade inflammation in intra-articular tissues.

Current pharmacological treatments for OA (Kolasinski et al., 2020; Toupin April et al., 2019; Primorac et al., 2021) focus on pain relief, improving joint function and quality of life, and slowing disease progression. These are divided into two categories. The first comprises symptomatic rapid-acting drugs for OA, which include oral and topical non-steroidal anti-inflammatory drugs (NSAIDs), intra-articular corticosteroid injections, and opioid analgesics (Toupin April et al., 2019); these drugs are rapid-acting and highly effective but are limited in terms of long-term use (Primorac et al., 2021). The second group comprises symptomatic slow-acting drugs for OA (SYSADOA) (Dougados, 2006), which induce pain relief and aim to improve joint function by relieving inflammation, mainly by inhibiting proinflammatory and/or catabolic factors (Dougados, 2006). SYSADOA also seem capable of limiting the progression of, or aiding in the recovery from, joint damage and are classified as disease-modifying drugs (Oo et al., 2021). SYSADOA include various inflammatory cytokine blockers (e.g., diacerein) (Louthrenoo et al., 2007), joint tissue components (e.g., glucosamine sulfate, chondroitin sulfate, and hyaluronic acid) (Clegg et al., 2006), and natural plant or herb extracts (e.g., avocado soybean unsaponifiables [ASU] and JOINS®) (Appelboom et al., 2001; Kim et al., 2017). Although the therapeutic effects of SYSADOA have been subject to controversy, clinical study results suggest the efficacy of these drugs (Cho et al., 2019). A real-world analysis revealed that SYSADOA combined with NSAIDs significantly contributed to the discontinuation of NSAIDs (Cho et al., 2019). In particular, SYSADOAs from joint tissue components (glucosamine sulfate, chondroitin sulfate, and hyaluronic acid) and natural plant or herb extracts (ASU and JOINS®) are attracting attention because they act on several pathways of inflammation (Kang et al., 2019).

SKCPT (SK Chemicals Co., Ltd., Seongnam, Korea) is a herbal SYSADOA product formulated from a 30% ethanol dry extract of *Clematis mandshurica*, *Trichosanthes kirilowii*, and *Prunella vulgaris*, which have been widely used for the treatment of inflammatory diseases in East Asia. Preclinical studies showed that this preparation has biological effects, including cartilage protection and anti-inflammatory effects (Hartog et al., 2008; Choi et al., 2014; Kim et al., 2005) and inhibition of glycosaminoglycan degradation and catabolic gene expression in human OA chondrocytes and cartilage (Choi et al., 2014). SKCPT has been developed based on a previously licensed product developed in Korea in 1997 (JOINS® tablet [SKI306X, SK Chemicals Co., Ltd., Seongnam, Korea]) and approved in this country for the treatment of OA and rheumatoid arthritis (Kim et al., 2017). For SKCPT, the total daily dose is the same as that of the JOINS® tablet at 600 mg; however, SKCPT allows dosing of 300 mg twice daily rather than 200 mg three times daily. SYSADOA use was reported to be high in Korea, with 43.4% of patients using one or more to treat OA, according to a nationwide claims database; herbal SYSADOAs were used by 29.7% of patients. Regular SYSADOA users observed a reduction in NSAID use of 48.8% (Park et al., 2019).

We hypothesized that SKCPT is non-inferior to celecoxib (Celebrex, VIATRIS SPECIALTY LLC, Seoul, Korea) in the treatment of symptomatic knee OA; thus, the primary objective of this study was to evaluate the non-inferiority of SKCPT to celecoxib in dosing and safety for the treatment of knee OA.

2. Materials and methods

2.1. Study design, randomization, and blinding procedures

This was a multicenter, randomized, double-blind, active-controlled phase III clinical trial conducted from January 2021 to May 2022 at 14 participating institutions in Korea. The study protocol and related documents were approved by the Asan Medical Center Institutional Review Board (Songpa-gu, Seoul, Republic of Korea; approval number: S2020-2221-0001) and the Ministry of Food and Drug Safety. The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. Informed consent was provided by all patients at enrollment. The study was registered at ClinicalTrials.gov under the identifying number NCT05930080.

The study design is shown in Supplementary Fig. 1. Patients who met the inclusion criteria at screening (Visit 1) were required to undergo a washout period of ≥7 days for any medications taken for knee OA. At Visit 2, screened patients were randomly assigned 1:1 to receive either celecoxib or SKCPT. The treatment period, during which patients underwent efficacy and safety assessments, comprised Visit 2 to Visit 5, lasting 12 weeks. The rationale behind the study duration was based on the Ministry of Food and Drug Safety Guidelines, which indicate that trials of OA drugs should have at least a 3-month duration to demonstrate symptom relief (Ministry of Food and Drug Safety).

Patients were randomized using an interactive web-based system in a 1:1 ratio to receive SKCPT (Batch no. P012000) or celecoxib (Batch no. DL9334). Randomization was achieved using a permuted block randomization method with study site as a stratification factor; the allocation tables were maintained by unblinded study personnel. Treatment allocation was concealed from the investigators who enrolled and assessed the study participants, and from the patients themselves. To maintain double blinding, the study drug was packaged in the same form, with identical labelling, for all treatment groups and provided to the patients, who were required to take a specific form and quantity of the study drug daily. If a serious adverse event (AE) occurred, limited unblinding (for the investigator) would be permitted; however, no cases of unblinding occurred during the study.

2.2. Patients

The main inclusion criteria were as follows: men or women aged 20–75 years; individuals diagnosed with primary knee OA based on the following American College of Rheumatology (ACR) criteria: knee joint pain and presence of at least one of three criteria (age >50 years, morning stiffness <30 min, joint crepitus during activity); osteophytes; Kellgren–Lawrence Grade 1 to 3; patients with a Korean Western Ontario and McMaster Universities Osteoarthritis Index (K-WOMAC) (Bellamy et al., 1988; Bae et al., 2001) pain score of ≥40 mm and <80 mm at the screening visit when walking on a flat surface, and an increase of ≥10 mm in K-WOMAC pain score when walking on a flat surface at Visit 2 (baseline) compared with the screening visit; individuals who provided written informed consent; and individuals who understood and agreed to follow instructions and could participate in the study for the entire study period.

Patients were excluded if they had clear secondary OA; had undergone knee joint arthroplasty or open knee surgery within 3 years prior to the screening visit; had received intra-articular knee injections within 3 months prior to the screening visit; had received NSAIDs, COX-2 inhibitors, or botanical remedies for knee OA within 3 months prior to the screening visit but responded inadequately to the treatment; had received systemic corticosteroid administration (daily oral or inhaled corticosteroid dose exceeding 1500 μg) within 3 months prior to the screening visit; had received medication for conditions other than OA that could affect the study results; had a significant history of allergic diseases or hypersensitivity reactions to NSAIDs (including COX-2 inhibitors); had peptic ulcers, severe gastrointestinal disorders, or a history of gastrointestinal bleeding or perforation due to NSAIDs; had clinically significant kidney or liver function abnormalities; had any uncontrolled diseases or important systemic conditions; and were not suitable for study participation as determined by the investigator.

2.3. Intervention

Patients were administered SKCPT 300 mg twice daily or celecoxib 200 mg once daily for 12 weeks while undergoing efficacy and safety assessments. Patients could take rescue medication (acetaminophen; Tylenol immediate release (Batch no. 22845); maximum 4 tablets [2000 mg] per day) for pain relief. However, rescue medication was prohibited for 2 days before each visit for efficacy assessment. In the event of discontinuation or withdrawal from the study, the investigator discontinued administration of the study drug and reported the last administered dose, the date of withdrawal, and the reasons for discontinuation or withdrawal, together with all data obtained up to the time of discontinuation or withdrawal.

2.4. Efficacy endpoints

The primary efficacy endpoint was the mean change in the K-WOMAC pain subscale (assessing maximum knee pain over the previous 2 days from each visit) from pre-administration of the study drug (Visit 2, baseline) to 84 days after administration (Day 84, Visit 5). As secondary efficacy endpoints, we evaluated the mean changes in the K-WOMAC pain subscale (assessing maximum knee pain over the previous 2 days from each visit), as assessed by the patients, from pre-administration (Visit 2) to the assessments conducted at subsequent visits on Days 28 (Visit 3) and 56 (Visit 4) after administration; mean changes in the K-WOMAC total score at visits on Days 28, 56, and 84 after administration of the study drug compared with those at pre-administration (Visit 2); mean changes in the K-WOMAC physical function subscale as evaluated by the patients from pre-administration (Visit 2) to the assessments conducted at subsequent visits on Days 28, 56, and 84 after administration (assessing the severity of difficulties in performing daily activities over the previous 2 days from each visit); mean changes in the K-WOMAC stiffness subscale, as assessed by the patients, from pre-administration (Visit 2) to the assessments conducted at subsequent visits on Days 28, 56, and 84 after administration (assessing the maximum knee stiffness over the previous 2 days from each visit); and frequency of rescue medication usage.

2.5. Safety endpoints

Safety was assessed based on the number and incidence rate of AEs, adverse drug reactions (ADRs; i.e., considered as having a causal relationship with the drug), and serious AEs (SAEs), including abnormalities in physical examinations, vital signs, electrocardiograms, and laboratory tests, and subjective or objective symptoms. AEs were reported using MedDRA version 25.0. The duration of exposure was also measured.

2.6. Statistical analysis

The target sample size was ≥272 patients and ≥136 patients in each group. The sample size calculation was based on the results of previous clinical trials (Hochberg et al., 2011; Yoo MC et al., 2014a; Bingham III et al., 2007; Smugar et al., 2006) that confirmed the difference in effect between celecoxib and the placebo group. Assuming the mean change in the SKCPT and celecoxib groups was the same ($\mu_T = \mu_C = 29.8$), the standard deviation (SD) was set at 22.0, the non-inferiority margin was 10 mm, and the dropout rate was 25%. The number of subjects was calculated to be ≥ 136 in each administration group.

The analytical populations are defined in the **Supplementary Methods**. Demographic and baseline characteristics were analyzed using the intention-to-treat (ITT) set. The efficacy endpoint was analyzed in the full analysis set (FAS) and per-protocol set (PPS), and the main analysis set was the PPS. Safety endpoints, such as the duration of exposure and frequency of AEs, were analyzed using the safety set (SS).

Measures such as mean, SD, median, and range were reported for continuous data. A two-sample *t*-test was used to compare the differences between treatment groups. If the assumption of normality (using the Shapiro-Wilk test) was not satisfied, the difference was compared using Wilcoxon's rank sum test. The change from baseline within the group was analyzed using a paired *t*-test. If the assumption of normality was not satisfied, Wilcoxon's signed rank test was used. Frequencies and percentages were reported for categorical data, and the data were analyzed using the chi-square test. If ≥ 20% of all cells had an expected frequency less than five, then Fisher's exact test was used. McNemar's test was used to detect differences in the rate of change within a group.

To compare the mean change in the K-WOMAC pain subscale from pre-administration to 84 days after administration, an analysis of covariance (ANCOVA) was conducted with the treatment group and the pre-administration K-WOMAC pain subscale as covariates. The least squares (LS) mean, standard error (SE), and the two-sided 95% confidence interval (CI) and p-value for the difference between the SKCPT and celecoxib treatment groups was calculated using ANCOVA, with baseline values as covariates. If the upper limit of the 95% CI was less than the non-inferiority margin of 10, the SKCPT-treated group was considered non-inferior to the celecoxib group.

For the primary endpoint analysis, missing data were handled using the last observation carried forward method. Missing data were not replaced for laboratory parameters or other safety measures. Tests were two-sided at a 5% significance level. The statistical analysis software used was SAS, version 9.4 (SAS Institute Inc., Cary, NC, USA).

3. Results

3.1. Patient characteristics and duration of exposure

Of the 323 patients screened, 45 were excluded, resulting in 278 patients randomly assigned to treatment (ITT set), with 136 in the SKCPT group and 142 in the celecoxib group. All 278 patients in the ITT

set were included in the SS; the FAS included 275 patients (135 in the SKCPT group and 140 in the celecoxib group) and the PPS included 250 patients (122 in the SKCPT group and 128 in the celecoxib group). Nineteen patients (10 in the SKCPT group and nine in the celecoxib group) dropped out of the study, and 259 patients (126 in the SKCPT group and 133 in the celecoxib group) completed the study (Fig. 1).

FAS, full analysis set; ITT, intention-to-treat; PPS, per-protocol set; SS, safety set; K-WOMAC, Korean Western Ontario and McMaster Universities Osteoarthritis Index.

Patients had an age (median [range]) of 62.5 (30.0–75.0) years, 77.34% (n = 215) were female, with a duration of knee OA (mean ± SD) of 52.15 ± 52.66 months. In the SKCPT and celecoxib groups, 83.09% and 84.51% had morning stiffness <30 min, 53.68% and 51.41% had joint crepitus during activity, and 50.00% and 46.48% had Kellgren–Lawrence Grade 2 OA, followed by 33.82% and 38.03% with Kellgren–Lawrence Grade 3 OA (Table 1). Overall, there were no significant differences between groups in terms of baseline characteristics.

The overall compliance (mean ± SD) at the end of the study was 96.39 ± 6.31% and 96.05 ± 5.90% in the SKCPT and celecoxib groups, according to the following formula: overall compliance (%) = [number of completed doses during the clinical trial period]/[planned number of doses during the clinical trial period] × 100. The duration of exposure (mean ± SD) was 11.89 ± 1.90 weeks and 11.85 ± 2.01 weeks in the SKCPT and celecoxib groups, without significant difference in exposure between groups (p = 0.9946, Wilcoxon's rank sum test).

3.2. Efficacy

K-WOMAC pain subscale scores (mean ± SD) were 56.29 ± 13.07 in the SKCPT group and 56.64 ± 12.90 in the celecoxib group at baseline, and 32.60 ± 18.88 and 30.72 ± 18.44 on Day 84, respectively, with significant within-group differences from baseline (p < 0.0001 each; paired *t*-test; Table 2). LS mean ± SE were −23.74 ± 1.48 and −25.88 ± 1.44 in the SKCPT and celecoxib groups, respectively, with an LS mean difference of 2.13 ± 2.07 (95% CI for the LS mean difference: [−1.94, 6.20]; p = 0.3031; Fig. 2).

Mean changes from baseline in the K-WOMAC pain subscale to Days 28 and 56 and in the K-WOMAC total score, physical function subscale, and stiffness subscale to Days 28, 56, and 84 showed statistically significant improvements in the SKCPT and celecoxib groups (p < 0.0001 each). However, there were no differences between treatment groups at any time point. Similarly, the frequency and number of doses of rescue medication were numerically reduced in both treatment groups. The percentage of rescue medication adherence was 69.67% at baseline in the SKCPT group, and it was reduced to 34.43% at Day 84, and that in the celecoxib group was 64.06% at baseline and 36.72% at Day 84. At baseline, patients were taking a number of doses of rescue medicine (mean ± SD) of 4.40 ± 5.23 and 4.28 ± 4.84 doses, which were reduced to 2.39 ± 6.14 and 2.41 ± 5.35 doses by Day 84 in the SKCPT and celecoxib groups, respectively. There were no significant differences between treatment groups at any time point (Table 3).

3.3. Safety

In total, 89 AEs (23.02%) occurred in 64 patients; 26 patients (37 cases [19.12%]) in the SKCPT group and 38 patients (52 cases [26.76%]) in the celecoxib group presented with AEs, without significant differences between groups. ADRs occurred in three patients (three cases [2.21%]) in the SKCPT group and eight patients (eight cases [5.63%]) in the celecoxib group, without statistically significant differences between the groups (Table 4). No SAEs or serious ADRs occurred during the study.

Gastrointestinal AEs occurred in 6/136 (4.41%) patients and 9/142 (6.34%) patients in the SKCPT and celecoxib groups, without significant differences between groups (p = 0.4773, chi-square test).

One patient in the celecoxib group dropped out of the study because

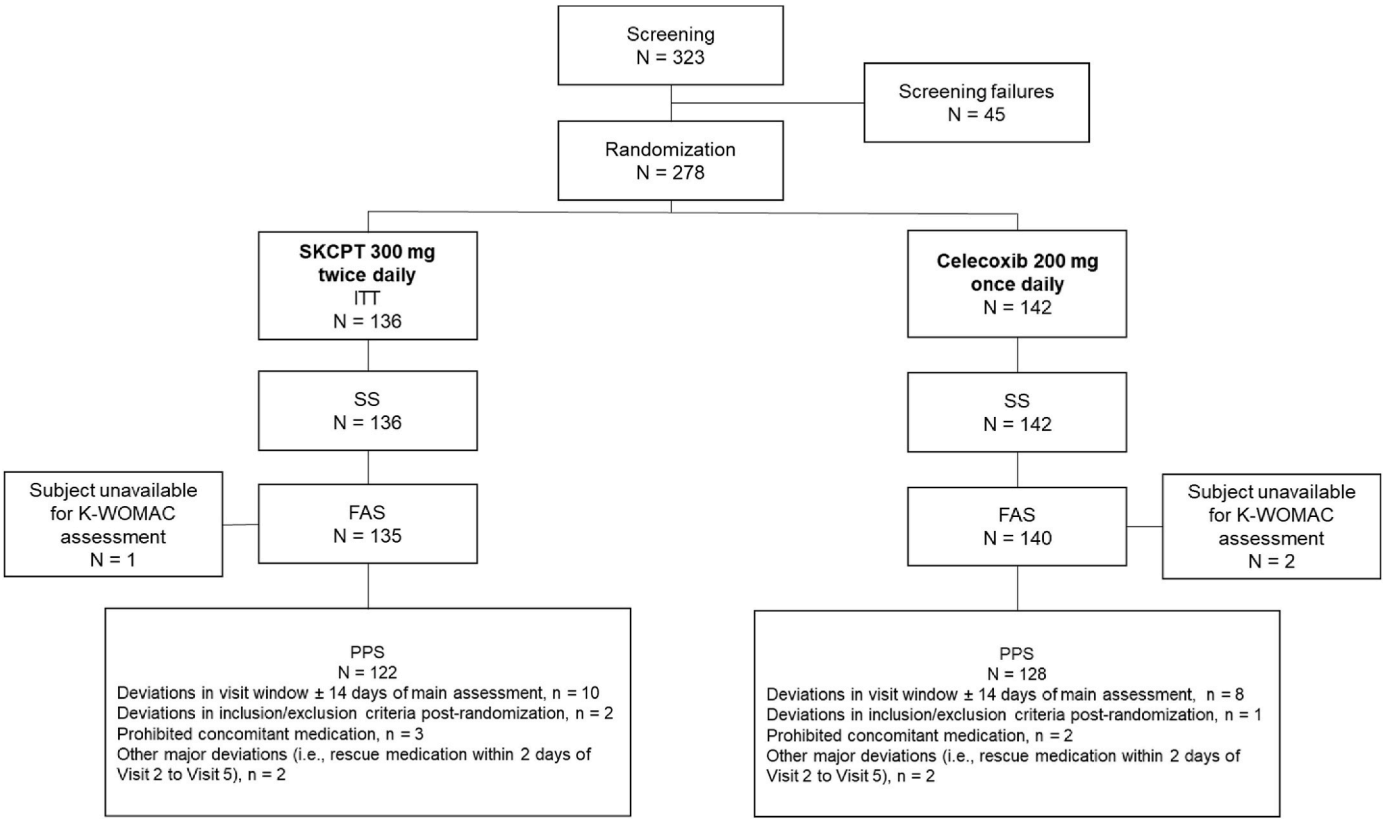

Fig. 1. CONSORT diagram In the PPS, patients were counted more than once for reasons for the exclusion.

Table 1
Baseline demographic and clinical characteristics of patients (ITT set).

	SKCPT 300 mg twice dailyN = 136	Celecoxib 200 mg once daily N = 142	Total N = 278
Age (years)			
Mean ± SD	61.1 ± 8.1	61.7 ± 8.5	61.4 ± 8.3
Median	62.0	63.0	62.5
Min, Max	32.0, 74.0	30.0, 75.0	30.0, 75.0
p-value [b]	0.4591[W]		
Age >50 years, n (%)			
Yes	125 (91.91)	129 (90.85)	254 (91.37)
No	11 (8.09)	13 (9.15)	24 (8.63)
p-value [b]	0.7516[C]		
Sex, n (%)			
Male	34 (25.00)	29 (20.42)	63 (22.66)
Female	102 (75.00)	113 (79.58)	215 (77.34)
p-value [b]	0.3621[C]		
Duration of knee osteoarthritis (months)			
Mean ± SD	54.42 ± 55.22	49.97 ± 50.18	52.15 ± 52.66
Median	40.00	42.00	41.00
Min, Max	0.00, 266.00	0.00, 255.00	0.00, 266.00
p-value [b]	0.7590[W]		
Location of knee osteoarthritis, n (%)			
Right	68 (50.00)	63 (44.37)	131 (47.12)
Left	68 (50.00)	79 (55.63)	147 (52.88)
p-value [b]	0.3469[C]		
Presence of knee joint pain, n (%)			
Yes	136 (100.00)	142 (100.00)	278 (100.00)
No	0 (0.00)	0 (0.00)	0 (0.00)
p-value [b]	NA		
Confirmation of diagnosis, n (%)			
Yes	136 (100.00)	142 (100.00)	278 (100.00)
No	0 (0.00)	0 (0.00)	0 (0.00)
p-value [b]	NA		
Morning stiffness <30 min, n (%)			
Yes	113 (83.09)	120 (84.51)	233 (83.81)
No	23 (16.91)	22 (15.49)	45 (16.19)
p-value [b]	0.7482[C]		
Joint crepitus during activity, n (%)			
Yes	73 (53.68)	73 (51.41)	146 (52.52)
No	63 (46.32)	69 (48.59)	132 (47.48)
p-value [b]	0.7050[C]		
Presence of osteophytes, n (%)			
Yes	136 (100.00)	142 (100.00)	278 (100.00)
No	0 (0.00)	0 (0.00)	0 (0.00)
p-value [b]	NA		
Kellgren–Lawrence grade, n (%)			
Grade 1	22 (16.18)	22 (15.49)	44 (15.83)
Grade 2	68 (50.00)	66 (46.48)	134 (48.20)
Grade 3	46 (33.82)	54 (38.03)	100 (35.97)
p-value [b]	0.7806[F]		
K-WOMAC pain subscale (score)			
Mean ± SD	56.83 ± 12.80	57.31 ± 13.09	57.08 ± 12.93
Median	56.50	57.80	57.20
Min, Max	21.20, 92.60	25.60, 94.20	21.20, 94.20
p-value [b]	0.7553[T]		
K-WOMAC stiffness subscale (score)			
Mean ± SD	55.23 ± 16.48	55.67 ± 16.42	55.46 ± 16.42
Median	55.00	55.00	55.00
Min, Max	9.00, 94.00	20.50, 94.50	9.00, 94.50
p-value [b]	0.8248[T]		
K-WOMAC physical function subscale (score)			
Mean ± SD	56.72 ± 14.05	56.53 ± 14.48	56.62 ± 14.25
Median	56.53	57.62	57.35
Min, Max	14.76, 93.88	24.00, 93.12	14.76, 93.88
p-value [b]	0.9099[T]		
K-WOMAC total score (score)			
Mean ± SD	56.62 ± 13.46	56.62 ± 13.88	56.62 ± 13.65
Median	56.23	57.98	57.02
Min, Max	16.96, 93.63	25.92, 92.38	16.96, 93.63
p-value [b]	1.0000[T]		

Note: Duration of knee osteoarthritis (month) = The SAS function (INTCK ('Month,' diagnosis date of knee osteoarthritis, first visit date, 'continuous')) is used to calculate the difference in calendar days between the first visit date and the diagnosis date of knee osteoarthritis.
Primary knee osteoarthritis according to ACR criteria: 1) Presence of knee joint pain, 2) presence of at least one of the following ([i] age >50 years, [ii] morning stiffness <30 min, [iii] joint crepitus during activity), 3) presence of osteophytes.
Confirmation of diagnosis: Presence of at least one of the following ([i] age >50 years, [ii] morning stiffness <30 min, [iii] joint crepitus during activity).
In cases of Kellgren–Lawrence Grade 1, the presence of suspected osteophytes is also considered as the presence of osteophytes.
p-value[b]: Test between treatment groups.
C: Chi-square test; F: Fisher's exact test; T: Two-sample *t*-test; W: Wilcoxon's rank sum test.
ACR, American College of Rheumatology; ITT, intention-to-treat; K-WOMAC, Korean Western Ontario and McMaster Universities Osteoarthritis Index; NA, not applicable; SD, standard deviation.

of a blood pressure-related ADR. Between-group comparison using Fisher's exact test showed no differences between the SKCPT and celecoxib groups regarding the incidence of systolic blood pressure reduction (SKCPT [0/136] vs celecoxib [1/142]; p = 1.0000). In the SKCPT group, there was a statistically significant reduction in systolic blood pressure from baseline to Days 56 and 84. There were no other clinically significant differences between groups in the results of physical examinations, vital signs, or laboratory tests, and electrocardiograms were normal in all patients.

4. Discussion

OA has a staggering impact on over 500 million individuals globally, making it the most prevalent type of arthritis. It is a primary cause of pain and disability, severely compromising patients' quality of life. Additionally, as populations age, the prevalence of OA is only increasing (O'Neill et al., 2018; Hunter et al., 2020; Safiri et al., 2020; Roser et al., 2021). The incidence and progression of knee OA are significantly more substantial in Korea compared with the West (Kim et al., 2010; Yoo et al., 2018), which underscores the need for prompt and effective interventions to mitigate the impact of this condition on affected individuals. Given the well-known long-term limitations of the current standard of care for patients with OA (da Costa et al., 2021), the current understanding of the pathogenesis of OA, and the role of inflammatory

Table 2
K-WOMAC pain subscale at baseline and Day 84 after administration (PPS).

	SKCPT 300 mg twice daily N = 122	Celecoxib 200 mg once daily N = 128
K-WOMAC pain subscale (score)		
Baseline		
Mean ± SD	56.29 ± 13.07	56.64 ± 12.90
Median	55.90	56.60
Min, Max	21.20, 92.60	25.60, 94.20
Day 84		
Mean ± SD	32.60 ± 18.88	30.72 ± 18.44
Median	29.50	28.00
Min, Max	1.80, 98.40	0.00, 94.20
Change from baseline to Day 84		
Mean ± SD	−23.69 ± 15.60	−25.93 ± 17.77
Median	−22.80	−24.10
Min, Max	−65.80, 20.80	−63.00, 13.80
p-value[w]	<0.0001[P−T]	<0.0001[P−T]
p-value[b]	0.2918[T]	
LS mean ± SE	−23.74 ± 1.48	−25.88 ± 1.44
LS mean difference ± SE	2.13 ± 2.07	
95% CI for LS mean difference	[−1.94, 6.20]	
p-value[b] for LS mean difference	0.3031	

Note: Covariance analysis. In the analysis, the change from baseline to Day 84 is the dependent variable, the treatment group is the independent variable, and the baseline K-WOMAC pain subscale is a covariate. Change = Day N − baseline.
p-value[b]: Test between treatment groups; p-value[w]: Test within treatment group.
P-T: Paired *t*-test; T: Two-sample *t*-test.
CI, confidence interval; LS, least squares; SD, standard deviation; SE, standard error; K-WOMAC, Korean Western Ontario and McMaster Universities Osteoarthritis Index; PPS, per-protocol set.

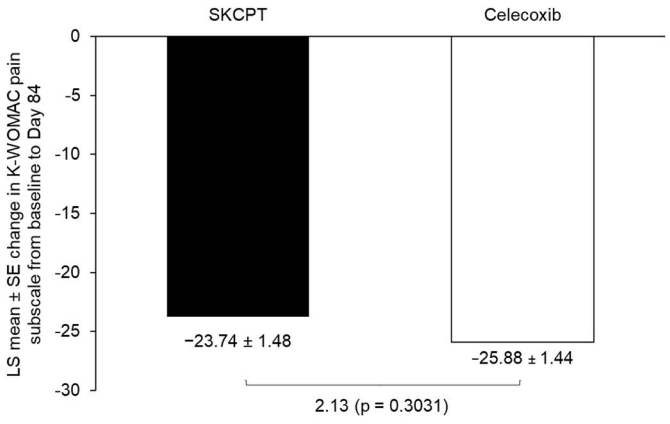

Fig. 2. Difference in K-WOMAC pain subscale at Day 84 (PPS) PPS, per-protocol set; K-WOMAC, Korean Western Ontario and McMaster Universities Osteoarthritis Index; LS, least squares; SE, standard error.

pathways and proteins, research on new drugs, including herbal SYSADOA, such as SKCPT, targeting these pathways, is underway.

The SKCPT formulation is based on a previously approved OA treatment in Korea (JOINS® tablet), with the sole difference being that SKCPT allows for twice-daily dosing. SKI306X has the same composition as SKCPT and is the active ingredient in the JOINS® tablet. SKI306X is composed of three crude herbal extracts: oleanolic acid from *Clematis mandshurica* (Li et al., 2021), rosmarinic acid (RosA) (Luo et al., 2020), and ursolic acid (UA) from *Prunella vulgaris* (Wang et al., 2020), and 4-hydroxybenzoic acid, 4-hydroxy-3-methoxybenzoic acid and *trans*-cinnamic acid from *Trichosanthes kirilowii* (Hartog et al., 2008). Oleanolic acid is a natural triterpenoid found to be beneficial for treating diabetes and inflammation (Li et al., 2021). RosA showed antiviral,

Table 3
Secondary efficacy assessments at Days 28, 56, and 84 after administration (PPS).

	SKCPT 300 mg twice daily N = 122	Celecoxib 200 mg once daily N = 128	p-value [b]
K-WOMAC pain subscale			
Day 28			0.3477[T]
Mean ± SD	42.47 ± 16.90	40.51 ± 16.06	
Median	43.10	39.00	
Min, Max	4.00, 86.00	8.00, 85.40	
Day 56			0.6429[W]
Mean ± SD	35.72 ± 17.79	36.88 ± 17.77	
Median	34.10	34.00	
Min, Max	4.00, 97.00	2.00, 90.00	
Change from baseline to Day 28			0.2300[W]
Mean ± SD	−13.81 ± 13.41	−16.13 ± 13.05	
Median	−12.60	−13.80	
Min, Max	−53.00, 26.00	−50.20, 15.60	
p-value[w]	<0.0001[P−T]	<0.0001[W−S]	
Change from baseline to Day 56			0.6877[T]
Mean ± SD	−20.56 ± 15.67	−19.77 ± 15.50	
Median	−20.40	−18.00	
Min, Max	−68.20, 29.00	−62.00, 14.00	
p-value[w]	<0.0001[P−T]	<0.0001[P−T]	
K-WOMAC total score			
Day 28			0.2395[T]
Mean ± SD	43.73 ± 16.64	41.33 ± 15.43	
Media	43.85	39.38	
Min, Max	4.58, 87.13	10.71, 83.88	
Day 56			0.6637[W]
Mean ± SD	37.45 ± 18.30	38.39 ± 17.51	
Median	34.56	36.25	
Min, Max	3.42, 96.42	3.75, 91.67	
Day 84			0.3611[W]
Mean ± SD	34.40 ± 18.94	32.67 ± 18.69	
Median	32.77	30.52	
Min, Max	2.00, 98.29	2.54, 95.71	
Change from baseline to Day 28			0.1496[W]
Mean ± SD	−12.39 ± 13.33	−14.96 ± 12.48	
Median	−10.58	−11.08	
Min, Max	−50.33, 31.13	−45.08, 10.88	
p-value[w]	<0.0001[P−T]	<0.0001[W−S]	
Change from baseline to Day 56			0.3717[W]
Mean ± SD	−18.67 ± 16.50	−17.90 ± 15.06	
Median	−17.02	−14.92	
Min, Max	−68.75, 26.54	−58.04, 18.88	
p-value[w]	<0.0001[P−T]	<0.0001[W−S]	
Change from baseline to Day 84			0.5236[W]
Mean ± SD	−21.72 ± 16.17	−23.62 ± 16.86	
Median	−20.60	−21.92	
Min, Max	−69.88, 17.58	−60.17, 10.54	
p-value[w]	<0.0001[P−T]	<0.0001[W−S]	
K-WOMAC physical function subscale			
Day 28			0.2356[T]
Mean ± SD	44.15 ± 16.67	41.73 ± 15.50	
Median	43.74	39.82	
Min, Max	4.12, 87.71	11.47, 83.29	
Day 56			0.6822[W]
Mean ± SD	38.13 ± 18.63	38.93 ± 17.66	
Median	35.68	37.03	
Min, Max	3.00, 96.35	4.12, 91.94	
Day 84			0.4184[W]
Mean ± SD	35.01 ± 19.06	33.49 ± 18.99	
Median	33.76	30.91	
Min, Max	2.06, 98.47	2.41, 95.88	
Change from baseline to Day 28			0.2266[W]
Mean ± SD	−12.11 ± 13.86	−14.59 ± 12.93	
Median	−10.03	−10.74	
Min, Max	−49.29, 32.24	−46.00, 10.29	

(*continued on next page*)

Table 3 (*continued*)

	SKCPT 300 mg twice daily N = 122	Celecoxib 200 mg once daily N = 128	p-value [b]
p-value[w]	<0.0001[P–T]	<0.0001[W–S]	
Change from baseline to Day 56			0.3855[W]
Mean ± SD	−18.12 ± 17.28	−17.39 ± 15.38	
Media	−15.76	−14.29	
Min, Max	−69.24, 29.41	−58.12, 20.65	
p-value[w]	<0.0001[P–T]	<0.0001[W–S]	
Change from baseline to Day 84			0.6669[W]
Mean ± SD	−21.25 ± 16.71	−22.82 ± 17.00	
Median	−20.62	−21.21	
Min, Max	−70.94, 20.12	−62.18, 13.71	
p-value[w]	<0.0001[P–T]	<0.0001[W–S]	
K-WOMAC stiffness subscale			
Day 28			0.1315[W]
Mean ± SD	43.27 ± 19.24	40.04 ± 18.39	
Median	44.75	35.00	
Min, Max	5.00, 90.00	0.00, 85.00	
Day 56			0.6006[W]
Mean ± SD	36.00 ± 19.39	37.68 ± 19.73	
Median	35.00	34.75	
Min, Max	0.00, 95.50	0.00, 93.50	
Day 84			0.1582[W]
Mean ± SD	33.79 ± 20.72	30.57 ± 20.30	
Median	30.25	25.50	
Min, Max	0.00, 96.50	0.00, 98.00	
Change from baseline to Day 28			0.0573[W]
Mean ± SD	−11.28 ± 16.94	−15.17 ± 15.71	
Median	−10.00	−14.50	
Min, Max	−70.00, 34.50	−59.50, 30.00	
p-value[w]	<0.0001[W–S]	<0.0001[W–S]	
Change from baseline to Day 56			0.5166[W]
Mean ± SD	−18.55 ± 18.12	−17.53 ± 17.58	
Median	−17.00	−15.00	
Min, Max	−66.00, 36.00	−61.50, 45.00	
p-value[w]	<0.0001[W–S]	<0.0001[W–S]	
Change from baseline to Day 84			0.1366[W]
Mean ± SD	−20.76 ± 19.16	−24.63 ± 19.05	
Median	−19.50	−21.25	
Min, Max	−71.00, 21.50	−66.50, 22.00	
p-value[w]	<0.0001[P–T]	<0.0001[W–S]	
Rescue medication adherence rate			p-value [c]
Baseline	85(69.67)	82(64.06)	0.3465[C]
Day 28	55(45.08)	43(33.59)	0.0629[C]
Day 56	44(36.07)	49(38.28)	0.7171[C]
Day 84	42(34.43)	47(36.72)	0.7051[C]
Frequency of rescue medication			
Baseline			0.8448[W]
Mean ± SD	4.40 ± 5.23	4.28 ± 4.84	
Median	2.00	3.00	
Min, Max	0.00, 23.00	0.00, 19.00	
Day 28			0.1028[W]
Mean ± SD	3.19 ± 5.59	2.57 ± 5.12	
Median	0.00	0.00	
Min, Max	0.00, 30.00	0.00, 28.00	
Day 56			0.7583[W]
Mean ± SD	2.57 ± 5.78	2.70 ± 5.62	
Median	0.00	0.00	
Min, Max	0.00, 42.00	0.00, 30.00	
Day 84			0.6352[W]
Mean ± SD	2.39 ± 6.14	2.41 ± 5.35	
Median	0.00	0.00	
Min, Max	0.00, 50.00	0.00, 37.00	

Note: Change = Day N − baseline.
p-value[b]: Test between treatment groups; p-value[w]: Test within treatment group.
C: Chi-square test; P-T: Paired *t*-test; T: Two-sample *t*-test; W-S: Wilcoxon's signed rank test; W: Wilcoxon's rank sum test.
PPS, per-protocol set; SD, standard deviation; K-WOMAC, Korean Western Ontario and McMaster Universities Osteoarthritis Index.

Table 4
Overall adverse events and adverse drug reactions (SS).

	SKCPT 300 mg twice daily N = 136	Celecoxib 200 mg once daily N = 142	Total N = 278
Adverse events	26 (19.12), [37]	38 (26.76), [52]	64 (23.02), [89]
95% CI	[12.51,25.73]	[19.48,34.04]	[18.07,27.97]
p-value[b]	0.1302[C]		
Adverse drug reactions	3 (2.21), [3]	8 (5.63), [8]	11 (3.96), [11]
95% CI	[0.00,4.67]	[1.84,9.43]	[1.67,6.25]
p-value[b]	0.1428[C]		
Serious adverse events	0 (0.00), [0]	0 (0.00), [0]	0 (0.00), [0]
95% CI	[0.00,0.00]	[0.00,0.00]	[0.00,0.00]
p-value[b]	NA		
Serious adverse drug reactions	0 (0.00), [0]	0 (0.00), [0]	0 (0.00), [0]
95% CI	[0.00,0.00]	[0.00,0.00]	[0.00,0.00]
p-value[b]	NA		

Data are shown as number of patients (%), [number of events], unless otherwise specified.
95% CI: 95% normal approximation confidence interval.
p-value[b]: Test between treatment groups.
C: Chi-square test.
CI, confidence interval; NA, not applicable; SS, safety set.

antibacterial, antioxidant, antimutagenic, and anti-inflammatory effects in *in vitro* and *in vivo* studies of inflammatory diseases like arthritis, colitis, and atopic dermatitis (Luo et al., 2020). UA decreases the expression of MMP13, IL-1β, IL-6, and prostaglandin-endoperoxide synthase-2, and down-regulates type II collagen and aggrecan after tumor necrosis factor (TNF)-α stimulation (Wang et al., 2020). Therefore, unlike other plant oils and herbal extracts, JOINS® components mentioned above are widely known to act as SYSADOA and are involved in cartilage protection and inflammation reduction (Kim et al., 2005, 2017; Hartog et al., 2008; Choi et al., 2014; Li et al., 2021; Luo et al., 2020; Wang et al., 2020). The JOINS® tablet has proven to be beneficial for pain relief, largely owing to the anti-inflammatory effects of its components (Li et al., 2021; Luo et al., 2020; Wang et al., 2020) due to inhibition of IL-1β, prostaglandin E2, and TNF-α (Hartog et al., 2008). Although clinical data on the efficacy and safety of SYSADOA are scarce, the active ingredients of SKCPT and their roles as SYSADOA are clearly known. The present phase III clinical trial on the efficacy and safety of SKCPT showed that, indeed, SKCPT was non-inferior to celecoxib, a well-established, safe, and highly effective treatment for OA (Puljak et al., 2017). Both the SKCPT and celecoxib groups showed statistically significant reductions in K-WOMAC pain subscale at Day 84 (primary efficacy endpoint) from baseline after study drug administration, without a statistically significant difference between the groups, indicating that SKCPT yielded the same effects as celecoxib by Day 84.

The secondary efficacy endpoints, including mean changes in the K-WOMAC pain subscale, K-WOMAC total score, physical function subscale, and stiffness subscale, as well as the frequency and number of doses of rescue medication, significantly decreased in both the SKCPT and celecoxib groups at all time points compared with baseline, without any statistically significant difference between the groups. Of note, the K-WOMAC pain subscale scores improved by more than 20 mm in both groups during approximately 12 weeks. To determine whether these results are clinically significant, we compared the degree of K-WOMAC improvement with the minimal clinically important improvement (MCII) criteria reported in existing literature (Bellamy et al., 1988). This analysis showed that by 4 weeks, OA symptoms were clinically

significantly improved in overall subscales after taking SKCPT (MCII vs SKCPT group change) in the pain subscale: −9 vs −13.81; stiffness subscale: −7 vs −11.28; physical function subscale: −6 vs −12.11; and total score: −7 vs −12.39) (Bellamy et al., 1988).

The frequency of AEs was low in both groups, without any statistically significant differences between SKCPT and celecoxib during the study period. Moreover, AEs in the SKCPT group tended to be 29% lower in incidence compared with AEs in the celecoxib group. All reported ADRs in the SKCPT group were within the expected safety profile based on the JOINS® tablet label (Ministry of Food and Drug Safety, 2023) and previous literature (Kim et al., 2005, 2017; Hartog et al., 2008; Choi et al., 2014). Based on the AEs and ADRs reported in the phase III clinical studies of comparable herbal products (i.e., GCSB-5 [Shinbaro®] and PG201 [Layla®]), it was noted that the SKCPT group had a lower incidence of AEs (19.12%) and ADRs (2.21%) compared with the GCSB-5 group, with an incidence of AEs of 41.4% and ADRs of 21.2% (Park et al., 2013), and that of the PG201 group with an incidence of AEs of 28.6% and ADRs of 14.9% (Yoo WH et al., 2014b). This suggests that SKCPT may be a safer option than those herbal products. Gastrointestinal AEs in the present study were infrequent, at 4.41% in the SKCPT group and 6.34% in the celecoxib group. These results are similar to those reported for similar products in the market, such as JOINS® (Kim et al., 2017) and Layla® (Yoo WH et al., 2014b).

Although NSAIDs are a standard treatment for knee OA, their long-term use can result in dyspepsia, mucosal damage, peptic ulcer disease, and complications such as gastrointestinal bleeding and perforation (Tai and McAlindon, 2021). Most OA patients are elderly (>65 years old) and advanced age is a risk factor for gastrointestinal-related side effects from NSAIDs (Chi et al., 2018). Although selective COX-2 inhibitors like celecoxib are less harmful than NSAIDs in the gastrointestinal tract, they have been linked to an increased risk of cardiovascular events (Spiegel et al., 2006; Trelle et al., 2011; Nissen et al., 2016). Therefore, decreasing or even sparing their use can be highly beneficial. However, considering that OA is a chronic disease, it is difficult to reduce the dose of NSAIDs.

In addition to safety, in terms of treating OA symptoms, this study shows that the use of SKCPT led to a 50% decrease in the need for rescue medication over 12 weeks, as well as a reduction in the mean dose of rescue medication for knee OA. This suggests that SKCPT may be able to replace NSAIDs, going one step further compared with several reports indicating that SYSADOA can reduce NSAID use (Louthrenoo et al., 2007; Clegg et al., 2006; Hochberg et al., 2011). When dealing with chronic conditions, such as knee OA, it is crucial to maintain consistent medication compliance over the long term. Switching to a twice-daily administration from the current three times daily routine can increase compliance by reducing the number of tablets needed. Our SKCPT tablet, which contains 300 mg of the same active ingredients as JOINS®, can be taken twice daily. The overall compliance at the end of the study was high with both SKCPT and celecoxib (96.39% and 96.05%, respectively), suggesting that twice-daily administration improved ease of use.

This study has some limitations. The population solely comprised Korean patients, which limits the generalizability of the results. Long-term (e.g., 1 year or more) research results on the efficacy of SKCPT are scarce; thus, the follow-up period was set at 12 weeks considering the difficulty of long-term administration of NSAIDs (control group: celecoxib) and the MFDS guidelines (Ministry of Food and Drug Safety). Nonetheless, the study duration was considered sufficient to evaluate the efficacy of SKCPT. JOINS® tablet, with the same components as SKCPT, is known to be safe for long-term use. Thus, SKCPT is expected to yield similar results (Kim et al., 2017). The patient sample in the phase IV study was somewhat small. Based on the present findings, conducting a large-scale study to evaluate the long-term efficacy and safety of SKCPT may be necessary.

5. Conclusion

SKCPT was found to be non-inferior in efficacy to celecoxib and was safe and well tolerated. Therefore, SKCPT can be considered a safe and effective treatment option for OA. These study findings suggest that SKCPT is a SYSADOA that could replace the use of NSAIDs for the treatment of knee OA.

Funding

This research was funded by SK Chemicals Co., Ltd., Seongnam, Korea. SK Chemicals Co., Ltd., had no role in the study design; collection, analysis, and interpretation of data; writing of the report; or the decision to submit the article for publication.

CRediT authorship contribution statement

Sung II Bin: Writing – review & editing, Formal analysis, Data curation, Conceptualization. **Myung Chul Lee:** Writing – review & editing, Formal analysis, Data curation, Conceptualization. **Seung-Baik Kang:** Writing – review & editing, Formal analysis, Data curation, Conceptualization. **Young-Wan Moon:** Writing – review & editing, Formal analysis, Data curation, Conceptualization. **Kyoung Ho Yoon:** Writing – review & editing, Formal analysis, Data curation, Conceptualization. **Seung-Beom Han:** Writing – review & editing, Formal analysis, Data curation, Conceptualization. **Yong In:** Writing – review & editing, Formal analysis, Data curation, Conceptualization. **Chong Bum Chang:** Writing – review & editing, Formal analysis, Data curation, Conceptualization. **Ki-Cheor Bae:** Writing – review & editing, Formal analysis, Data curation, Conceptualization. **Jae-Ang Sim:** Writing – review & editing, Formal analysis, Data curation, Conceptualization. **Jong-Keun Seon:** Writing – review & editing, Formal analysis, Data curation, Conceptualization. **Kwan Kyu Park:** Writing – review & editing, Formal analysis, Data curation, Conceptualization. **Sang Jin Lee:** Writing – review & editing, Formal analysis, Data curation, Conceptualization. **Young-Mo Kim:** Writing – review & editing, Writing – original draft, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Young Mo Kim received honoraria from SK Chemicals Co. Ltd. The remaining authors have no competing interests to declare.

Data availability

Anonymized individual patient data will not be shared. Aggregate data will be shared upon request dependent upon the request nature, proposed research merit, data availability and its intended use.

Acknowledgments

The authors would like to personally thank all the principal investigators and study coordinators for their help with subject recruitment and data collection. The authors also wish to thank Keyra Martinez Dunn, MD, of Edanz for providing medical writing support, in accordance with Good Publication Practice 2022 guidelines (https://www.ismpp.org/gpp-2022).

Glossary

Arthroplasty joint surgery to restore joint function
Chondrocytes cells that make up the cartilage
Glycosaminoglycans a key component in biological functions ranging from anticoagulation and growth pathways to the ability of

cartilage to sustain stress during compression

Inflammatory cytokines small protein signaling molecules derived from immune system cells that upregulate inflammatory response

Joint crepitus a popping, clicking, or cracking sound that is made when the joint is moved

Kellgren–Lawrence grade a grading system used to classify the severity of osteoarthritis

Korean Western Ontario and McMaster Universities Osteoarthritis Index an instrument used to assess outcomes (pain/stiffness/function) in patients with knee osteoarthritis

Osteoarthritis the most common form of arthritis characterized by joint inflammation and cartilage destruction, usually starting in an isolated joint

Osteophytes bone spurs or bony projections that form along the ends of bones (joints)

Rheumatoid arthritis an inflammatory autoimmune disease that affects the tissues lining the joints on both sides of the body

Abbreviations

ACR	American College of Rheumatology
ADR	adverse drug reaction
AE	adverse event
ANCOVA	analysis of covariance
ASU	avocado soybean unsaponifiables
CI	confidence interval
FAS	full analysis set
ITT	intention-to-treat
K-WOMAC	Korean Western Ontario and McMaster Universities Osteoarthritis Index
LS	least squares
MCII	minimal clinically important improvement
NSAID	non-steroidal anti-inflammatory drug
OA	osteoarthritis
PPS	per-protocol set
RosA	rosmarinic acid
SAE	serious adverse event
SD	standard deviation
SE	standard error
SS	safety set
SYSADOA	symptomatic slow-acting drugs for osteoarthritis
TNF	tumor necrosis factor
UA	ursolic acid

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jep.2024.118843.

References

Appelboom, T., Schuermans, J., Verbruggen, G., Henrotin, Y., Reginster, J.Y., 2001. Symptoms modifying effect of avocado/soybean unsaponifiables (ASU) in knee osteoarthritis. A double blind, prospective, placebo-controlled study. Scand. J. Rheumatol. 30, 242–247. https://doi.org/10.1080/030097401316909602.

Bae, S.C., Lee, H.S., Yun, H.R., Kim, T.H., Yoo, D.H., Kim, S.Y., 2001. Cross-cultural adaptation and validation of Korean Western Ontario and McMaster Universities (WOMAC) and Lequesne osteoarthritis indices for clinical research. Osteoarthritis Cartilage 9, 746–750. https://doi.org/10.1053/joca.2001.0471.

Bellamy, N., Buchanan, W.W., Goldsmith, C.H., Campbell, J., Stitt, L.W., 1988. Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. J. Rheumatol. 15, 1833–1840.

Bingham III, C.O., Sebba, A.I., Rubin, B.R., Ruoff, G.E., Kremer, J., Bird, S., et al., 2007. Efficacy and safety of etoricoxib 30 mg and celecoxib 200 mg in the treatment of osteoarthritis in two identically designed, randomized, placebo-controlled, non-inferiority studies. Rheumatology 46, 496–507. https://doi.org/10.1093/rheumatology/kel296.

Chi, T.Y., Zhu, H.M., Zhang, M., 2018. Risk factors associated with nonsteroidal anti-inflammatory drugs (NSAIDs)-induced gastrointestinal bleeding resulting on people over 60 years old in Beijing. Medicine (Baltim.) 97 (18), e0665. https://doi.org/10.1097/MD.0000000000010665.

Cho, S.K., Kim, H., Park, H.R., Choi, W., Choi, S., Jung, S.Y., et al., 2019. Nonsteroidal anti-inflammatory drugs-sparing effect of symptomatic slow-acting drugs for osteoarthritis in knee osteoarthritis patients. J. Rheum. Dis. 26, 179–185.

Choi, C.H., Kim, T.H., Sung, Y.K., Choi, C.B., Na, Y.I., Yoo, H., et al., 2014. SKI306X inhibition of glycosaminoglycan degradation in human cartilage involves down-regulation of cytokine-induced catabolic genes. Korean J. Intern. Med. 29, 647–655. https://doi.org/10.3904/kjim.2014.29.5.647.

Clegg, D.O., Reda, D.J., Harris, C.L., Klein, M.A., O'Dell, J.R., Hooper, M.M., et al., 2006. Glucosamine, chondroitin sulfate, and the two in combination for painful knee osteoarthritis. N. Engl. J. Med. 354. https://doi.org/10.1056/NEJMoa052771, 795–708.

Courties, A., Gualillo, O., Berenbaum, F., Sellam, J., 2015. Metabolic stress-induced joint inflammation and osteoarthritis. Osteoarthritis Cartilage 23, 1955–1965. https://doi.org/10.1016/j.joca.2015.05.016.

da Costa, B.R., Pereira, T.V., Saadat, P., Rudnicki, M., Iskander, S.M., Bodmer, N.S., et al., 2021. Effectiveness and safety of non-steroidal anti-inflammatory drugs and opioid treatment for knee and hip osteoarthritis: network meta-analysis. BMJ 375, n2321. https://doi.org/10.1136/bmj.n2321.

Dougados, M., 2006. Symptomatic slow-acting drugs for osteoarthritis: what are the facts? Joint Bone Spine 73, 606–609. https://doi.org/10.1016/j.jbspin.2006.09.008.

Hartog, A., Hougee, S., Faber, J., Sanders, A., Zuurman, C., Smit, H.F., et al., 2008. The multicomponent phytopharmaceutical SKI306X inhibits in vitro cartilage degradation and the production of inflammatory mediators. Phytomedicine 15, 313–320. https://doi.org/10.1016/j.phymed.2007.09.005.

Hochberg, M.C., Fort, J.G., Svensson, O., Hwang, C., Sostek, M., 2011. Fixed-dose combination of enteric-coated naproxen and immediate-release esomeprazole has comparable efficacy to celecoxib for knee osteoarthritis: two randomized trials. Curr. Med. Res. Opin. 27, 1243–1253. https://doi.org/10.1185/03007995.2011.580340.

Hunter, D.J., March, L., Chew, M., 2020. Osteoarthritis in 2020 and beyond: a lancet commission. Lancet 396, 1711–1712. https://doi.org/10.1016/S0140-6736(20)32230-3.

Kang, Y.H., Lee, H.J., Lee, C.J., Park, J.S., 2019. Natural products as sources of novel drug candidates for the pharmacological management of osteoarthritis: a narrative review. Biomol. Ther. (Seoul) 27, 503–513. https://doi.org/10.4062/biomolther.2019.139.

Kim, I., Kim, H.A., Seo, Y.I., Song, Y.W., Jeong, J.Y., Kim, D.H., 2010. The prevalence of knee osteoarthritis in elderly community residents in Korea. J. Kor. Med. Sci. 25, 293–298. https://doi.org/10.3346/jkms.2010.25.2.293.

Kim, J.H., Ryu, K.H., Jung, K.W., Han, C.K., Kwak, W.J., Cho, Y.B., 2005. SKI306X suppresses cartilage destruction and inhibits the production of matrix metalloproteinase in rabbit joint cartilage explant culture. J. Pharmacol. Sci. 98, 298–306. https://doi.org/10.1254/jphs.fpj04058x.

Kim, J.I., Choi, J.Y., Kim, K.G., Lee, M.C., 2017. Efficacy of JOINS on cartilage protection in knee osteoarthritis: prospective randomized controlled trial. Knee Surg. Relat. Res. 29, 217–224. https://doi.org/10.5792/ksrr.17.004.

Kolasinski, S.L., Neogi, T., Hochberg, M.C., Oatis, C., Guyatt, G., Block, J., et al., 2020. 2019 American College of Rheumatology/Arthritis Foundation guideline for the management of osteoarthritis of the hand, hip, and knee. Arthritis Care Res. 72, 149–162. https://doi.org/10.1002/acr.24131.

Li, W., Zeng, H., Xu, M., Huang, C., Tao, L., Li, J., et al., 2021. Oleanolic acid improves obesity-related inflammation and insulin resistance by regulating macrophages activation. Front. Pharmacol. 12, 697483. https://doi.org/10.3389/fphar.2021.697483.

Louthrenoo, W., Nilganuwong, S., Aksaranugraha, S., Asavatanabodee, P., Saengnipanthkul, S., Thai Study Group, 2007. The efficacy, safety and carry-over effect of diacerein in the treatment of painful knee osteoarthritis: a randomised, double-blind, NSAID-controlled study. Osteoarthritis Cartilage 15, 605–614. https://doi.org/10.1016/j.joca.2007.02.021.

Luo, C., Zou, L., Sun, H., Peng, J., Gao, C., Bao, L., et al., 2020. A review of the anti-inflammatory effects of rosmarinic acid on inflammatory diseases. Front. Pharmacol. 11, 153. https://doi.org/10.3389/fphar.2020.00153.

Ministry of Food and Drug Safety. Available at: https://www.mfds.go.kr/eng/index.do (accessed 21 March 2024).

Ministry of Food and Drug Safety, 2023. [JOINS tablet label]. https://www.skchemicals.com/imgup/ls/products/pdf/ls_05.pdf. (Accessed 21 March 2024) [In Korean].

Nissen, S.E., Yeomans, N.D., Solomon, D.H., Lüscher, T.F., Libby, P., Husni, M.E., et al., 2016. Cardiovascular safety of celecoxib, naproxen, or ibuprofen for arthritis. N. Engl. J. Med. 375, 2519–2529. https://doi.org/10.1056/NEJMoa1611593.

O'Neill, T.W., McCabe, P.S., McBeth, J., 2018. Update on the epidemiology, risk factors and disease outcomes of osteoarthritis. Best Pract. Res. Clin. Rheumatol. 32, 312–326. https://doi.org/10.1016/j.berh.2018.10.007.

Oo, W.M., Little, C., Duong, V., Hunter, D.J., 2021. The development of disease-modifying therapies for osteoarthritis (DMOADs): the evidence to date. Drug Des. Dev. Ther. 15, 2921–2945. https://doi.org/10.2147/DDDT.S295224.

Park, H.R., Cho, S.K., Im, S.G., Jung, S.Y., Kim, D., Jang, E.J., et al., 2019. Treatment patterns of knee osteoarthritis patients in Korea. Korean J. Intern. Med. 34, 1145–1153. https://doi.org/10.3904/kjim.2017.304.

Park, Y.G., Ha, C.W., Han, C.D., Bin, S.I., Kim, H.C., Jung, Y.B., et al., 2013. A prospective, randomized, double-blind, multicenter comparative study on the safety and efficacy of Celecoxib and GCSB-5, dried extracts of six herbs, for the treatment of osteoarthritis of knee joint. J. Ethnopharmacol. 149, 816–824. https://doi.org/10.1016/j.jep.2013.08.008.

Primorac, D., Molnar, V., Matišić, V., Hudetz, D., Jeleč, Ž., Rod, E., et al., 2021. Comprehensive review of knee osteoarthritis pharmacological treatment and the

latest professional societies' guidelines. Pharmaceuticals 14, 205. https://doi.org/10.3390/ph14030205.

Puljak, L., Marin, A., Vrdoljak, D., Markotic, F., Utrobicic, A., Tugwell, P., 2017. Celecoxib for osteoarthritis. Cochrane Database Syst. Rev. 5, CD009865. https://doi.org/10.1002/14651858.CD009865.pub2.

Roser, M., Ritchie, H., Spooner, F., 2021. Burden of disease. Published online at OurWorldInData.org. Available at: https://ourworldindata.org/burden-of-disease.

Safiri, S., Kolahi, A.A., Smith, E., Hill, C., Bettampadi, D., Mansournia, M.A., et al., 2020. Global, regional and national burden of osteoarthritis 1990-2017: a systematic analysis of the Global Burden of Disease Study. Ann. Rheum. Dis. 79, 819–828. https://doi.org/10.1136/annrheumdis-2019-216515.

Smugar, S.S., Schnitzer, T.J., Weaver, A.L., Rubin, B.R., Polis, A.B., Tershakovec, A.M., 2006. Rofecoxib 12.5 mg, rofecoxib 25 mg, and celecoxib 200 mg in the treatment of symptomatic osteoarthritis: results of two similarly designed studies. Curr. Med. Res. Opin. 22, 1353–1367. https://doi.org/10.1185/030079906X104876.

Spiegel, B.M., Farid, M., Dulai, G.S., Gralnek, I.M., Kanwal, F., 2006. Comparing rates of dyspepsia with Coxibs vs NSAID+PPI: a meta-analysis. Am. J. Med. 119, 448. e27–448.e36. https://doi.org/10.1016/j.amjmed.2005.11.020.

Tai, F.W.D., McAlindon, M.E., 2021. Non-steroidal anti-inflammatory drugs and the gastrointestinal tract. Clin. Med. 21, 131–134. https://doi.org/10.7861/clinmed.2021-0039.

Thomas, E., Peat, G., Croft, P., 2014. Defining and mapping the person with osteoarthritis for population studies and public health. Rheumatology 53, 338–345. https://doi.org/10.1093/rheumatology/ket346.

Toupin April, K., Bisaillon, J., Welch, V., Maxwell, L.J., Jüni, P., Rutjes, A.W., et al., 2019. Tramadol for osteoarthritis. Cochrane Database Syst. Rev. 5, CD005522. https://doi.org/10.1002/14651858.CD005522.pub3.

Trelle, S., Reichenbach, S., Wandel, S., Hildebrand, P., Tschannen, B., Villiger, P.M., et al., 2011. Cardiovascular safety of non-steroidal anti-inflammatory drugs: network meta-analysis. BMJ 342, c7086. https://doi.org/10.1136/bmj.c7086.

Wang, C., Gao, Y., Zhang, Z., Chen, C., Chi, Q., Xu, K., et al., 2020. Ursolic acid protects chondrocytes, exhibits anti-inflammatory properties via regulation of the NF-κB/NLRP3 inflammasome pathway and ameliorates osteoarthritis. Biomed. Pharmacother. 130, 110568. https://doi.org/10.1016/j.biopha.2020.110568.

Wang, Q., Rozelle, A.L., Lepus, C.M., Scanzello, C.R., Song, J.J., Larsen, D.M., et al., 2011. Identification of a central role for complement in osteoarthritis. Nat. Med. 17, 1674–1679. https://doi.org/10.1038/nm.2543.

Yoo, J.J., Kim, D.H., Kim, H.A., 2018. Risk factors for progression of radiographic knee osteoarthritis in elderly community residents in Korea. BMC Muscoskel. Disord. 19, 80. https://doi.org/10.1186/s12891-018-1999-5.

Yoo, M.C., Yoo, W.H., Kang, S.B., Park, Y.W., Kim, S.S., Moon, K.H., et al., 2014a. Etoricoxib in the treatment of Korean patients with osteoarthritis in a double-blind, randomized controlled trial. Curr. Med. Res. Opin. 30, 2399–2408. https://doi.org/10.1185/03007995.2014.955169.

Yoo, W.H., Yoo, H.G., Park, S.H., Baek, H.J., Lee, Y.J., Shim, S.C., et al., 2014b. Efficacy and safety of PG201 (Layla(®)) and celecoxib in the treatment of symptomatic knee osteoarthritis: a double-blinded, randomized, multi-center, active drug comparative, parallel-group, non-inferiority, phase III study. Rheumatol. Int. 34, 1369–1378. https://doi.org/10.1007/s00296-014-2964-8.