Efficacy and Tolerability of GCSB-5 for Hand Osteoarthritis: A Randomized, Controlled Trial

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ABSTRACT

Purpose: The aim of this study was to investigate the efficacy and tolerability of GCSB-5, a mixture of 6 purified herbal extracts, in treating hand osteoarthritis (OA).

Methods: A randomized, double-blind, placebo-controlled trial enrolled 220 patients with hand OA who had baseline a visual analog scale joint pain score of >30 of 100 mm at 3 hospitals between September 2013 and November 2014. After randomization, patients were allocated to receive oral GCSB-5 600 mg or placebo, bid for 12 weeks. The primary end point was the change in the Australian/Canadian OA Hand Index (AUSCAN)-defined pain score at 4 weeks relative to baseline. Secondary end points included the frequency Outcome Measures in Rheumatology–OA Research Society International (OMERACT-OARSI)-defined response at 4, 8, 12, and 16 weeks after randomization.

Findings: The allocated treatment was received by 109 and 106 patients in the GCSB-5 and placebo groups, respectively. At 4 weeks, the median (interquartile range) change in AUSCAN pain score relative to baseline was significantly greater in the GCSB-5 group than in the placebo group (–9.0 [–23.8 to –0.4] vs –2.2 [–16.7 to 6.0]; $P = 0.014$), with sustained improvement at 8, 12, and 16 weeks ($P = 0.039$). The GCSB-5 group also had a significantly greater OMERACT-OARSI–defined response rate than did the placebo group at 4 weeks (44.0% vs 30.2%), 8 weeks (51.4% vs 35.9%), 12 weeks (56.9% vs 40.6%), and 16 weeks (50.5% vs 37.7%) ($P = 0.0074$). The 2 treatments exhibited comparable safety profiles.

Implications: GCSB-5 was associated with improved symptoms of hand OA, with good tolerability, in these patients. GCSB-5 may be a well-tolerated alternative of, or addition to, the treatment of hand OA. ClinicalTrials.gov identifier: NCT01910116. (*Clin Ther.* 2016;38:1858–1868) © 2016 The Authors. Published by Elsevier HS Journals, Inc.

Key words: GCSB-5, hand, osteoarthritis, randomized clinical trial.

INTRODUCTION

Osteoarthritis (OA) of the hand preferentially involves the proximal and distal interphalangeal joints and the first carpometacarpal joints in the middle-aged and elderly populations. Symptomatic hand OA is more prominent in women than in men.[1] It is often associated with considerable disability and a reduced quality of life that are comparable to the effects of rheumatoid arthritis.[2–4] The mainstay treatment of hand OA is to control the symptoms with a combination of nonpharmacologic and pharmacologic interventions.[5,6] An oral NSAID, acetaminophen, or an opioid-based analgesic is often recommended. However, findings from only a few well-designed

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randomized, controlled trials (RCTs) have supported the efficacy of these drugs in hand OA.[7] In addition, the increase in the prevalence of hand OA with age is problematic because long-term treatment with NSAIDs often is associated with serious gastrointestinal side effects, especially in elderly patients.[8–10] Moreover, in clinical practice, even the optimal combination of pharmacologic and nonpharmacologic managements fails to deliver comprehensive symptom control in a significant subset of patients.[7,11] Thus, there is an unmet need for new therapeutic options for hand OA.

GCSB-5 is a mixture of 6 purified herbal extracts at a fixed ratio.[12] These herbs have been used in traditional Chinese medicine for treating diverse inflammatory conditions. Their anti-inflammatory, analgesic, and chondroprotective effects have been observed in both animals and humans.[13,14] These properties suggest that GCSB-5 may be a useful addition to the management of hand OA.

This study was conducted to investigate the efficacy and tolerability of GCSB-5 for treating hand OA.

PATIENTS AND METHODS

Study Population

Patients with hand OA who were aged >40 years and had a visual analog scale (VAS) joint pain score exceeding 30 of 100 mm in the preceding 48 hours were included. Hand OA was diagnosed on the basis of the 1990 American College of Rheumatology–defined criteria for hand OA.[15] These classification criteria include hand pain, aching, and/or stiffness in the presence of bony enlargement or deformity in selected hand joints. The use of these criteria helped to recruit a relatively homogenous subset of patients with hand OA.

Patients who were taking an NSAID, analgesic agent, glucosamine, or other OA medication underwent washout for 2 weeks before receiving the allocated treatment. During the washout period, acetaminophen was allowed as a rescue medication until 24 hours before the screening visit. Patients were excluded if they had a history of any of the following: hand joint surgery; intra-articular injection of a hand joint with a corticosteroid or hyaluronic acid within the preceding 3 months; GCSB-5 use; stroke, myocardial infarction, or coronary angioplasty; gastrointestinal bleeding; and/or chronic kidney disease. Women who were pregnant or breast-feeding were also excluded.

Study Design

This prospective, multicenter (3 active sites), randomized, double-blind, placebo-controlled study (ClinicalTrials.gov identifier: NCT01910116) investigated the efficacy and tolerability of GCSB-5 600 mg BID in treating hand OA. The study was conducted at 3 tertiary medical centers between September 2013 and November 2014. The study protocol was approved by the institutional review boards at the participating centers. Written informed consent was received from all participating patients. The study was conducted in accordance with the recently revised Declaration of Helsinki.[16]

Randomization and Blinding

The Medical Research Collaboration Center of a participating medical center generated a randomization table that was stratified by center. The allocation ratio in this parallel-arm study was 1:1. The allocation table was given to independent pharmacists at each participating center and was concealed from the researchers who enrolled and assessed the study participants until the end of the study. The study design was not changed after commencement. The study medication and placebo were identical in appearance, odor, and taste, and were provided by Green Cross Corporation (Yongin, Republic of Korea).

Intervention

GCSB-5 is a powdered extract of 6 herbs at a fixed ratio (*Saposhnikovia divaricata* Schischkin, *Achyranthes bidentata* Blume, *Acanthopanax senticosus* Harms, *Cibotium barometz* J. Smith, *Glycine max* Merrill, and *Eucommia ulmoides* Oliver). The ingredients of the product were validated by HPLC analysis. GCSB-5 was further standardized for quality control according to the regulations imposed by the Korea Food and Drug Administration.[13] In Korea, GCSB-5 is indicated for the treatment of OA.

After randomization, patients received oral GCSB-5 600 mg or placebo, BID for 12 weeks. Independent pharmacists dispensed the study drugs according to the randomization table. For the evaluation of the residual effects of GCSB-5, patients in both groups were observed for an additional 4 weeks after the 12-week intervention period.

Prohibited Treatments

The use of medications that may have influenced the symptoms of OA was prohibited. These

medications included NSAIDs, analgesic agents, glucosamine sulfate, glucosamine hydrochloride, and chondroitin sulfate. Intra-articular injection was also prohibited. Acetaminophen 650 mg TID for up to 7 days was allowed as a rescue therapy.

Efficacy and Tolerability Assessments

All patients underwent comprehensive clinical and laboratory testing (including complete blood count, liver function testing, serum blood urea nitrogen, creatinine, and urinalysis) at baseline and at 4, 8, 12, and 16 weeks after randomization. The Korean version of the Australian/Canadian OA Hand Index (AUSCAN), which has been validated,[17] was the main tool used for measuring outcomes in this study. AUSCAN-defined pain and function scores were normalized according to a 0- to 100-point scale.[18] The AUSCAN index is a tri-dimensional, self-administered questionnaire that assesses pain, disability (dysfunction), and joint stiffness in hand OA. The questionnaire contains 15 items (5 on pain, 1 on stiffness, and 9 on disability) that were scored on a 100-mm VAS by each participant. AUSCAN pain and function scores were normalized according to a 0- to 100-point scale.

The primary efficacy end point was the change in AUSCAN pain score at 4 weeks relative to baseline. Secondary end points included the changes from the baseline in the following variables: AUSCAN pain score at 8, 12, and 16 weeks; AUSCAN stiffness score; AUSCAN function score; patient global assessment; physician global assessment; and Outcome Measures in Rheumatology–OA Research Society International (OMERACT-OARSI) response criterion D, at 4, 8, 12, and 16 weeks. General health was assessed by each patient using a patient global assessment tool, and by investigators using a physician global assessment tool. Both tools used the100-mm VAS, in which 0 mm represented the best health state, and 100 mm, the worst health state. The OMERACT-OARSI set of response criteria was used for determining clinically meaningful improvement on 3 symptom domains: pain, function, and patient global assessment. A patient was deemed to be an OMERACT-OARSI–defined *responder* if s/he showed an improvement of $\geq$50% relative to baseline on the pain or function domain, with an absolute change of $\geq$20, or an improvement of $\geq$20% relative to baseline in at least 2 of the 3 domains (pain, function, and patient global assessment), with an absolute change of $\geq$10.[19] The use of rescue medication was captured at each visit. The end points were not changed after study commencement.

All types of adverse events (AEs) were captured at each visit.

Statistical Analysis

Sample Size Calculation

We reported previously that after 4 weeks of placebo administration, the mean (SD) improvement in AUSCAN pain score in patients with hand OA was +7.8 (23.6) (on a 0–100 scale).[20] Assuming that GCSB-5 improves the AUSCAN pain score by >10 relative to placebo, and assuming an α level of 0.05 (2-tailed), a power of 0.80, and a dropout rate of 20%, the sample size calculation revealed that 220 patients were needed for enrollment.[21–24]

Outcomes Analyses

A modified intent-to-treat analysis was performed using data from all randomized patients who received $\geq$1 dose of the allocated intervention. The last-observation-carried-forward method was used for imputing missing data. The 2 groups were compared in terms of demographic and clinical variables using an independent t test, χ^2 test, or Fisher exact test, as appropriate. The efficacy end points at 4, 8, 12, and 16 weeks did not follow a normal distribution ($P >$ 0.05 by both the Kolmogorov-Smirnov and Shapiro-Wilk tests). Therefore, differences between the 2 groups in terms of the primary end points were evaluated using the Wilcoxon rank-sum test. The primary and secondary efficacy end points measured at 4, 8 12, and 16 weeks were examined by nonparametric repeated measures of ANOVA for continuous variables and a generalized estimating equation for categorical variables.[25] The interactions between groups and time were examined. Sensitivity analyses were conducted on the primary end points using the complete dataset, and multiple imputation of the dataset by fully conditional specification. $P < 0.05$ was considered to indicate statistical significance. All analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC).

RESULTS

Patients' Demographic and Clinical Characteristics

In total, 230 patients with hand OA were screened. Of these, 220 (147, 43, and 30 patients from each of

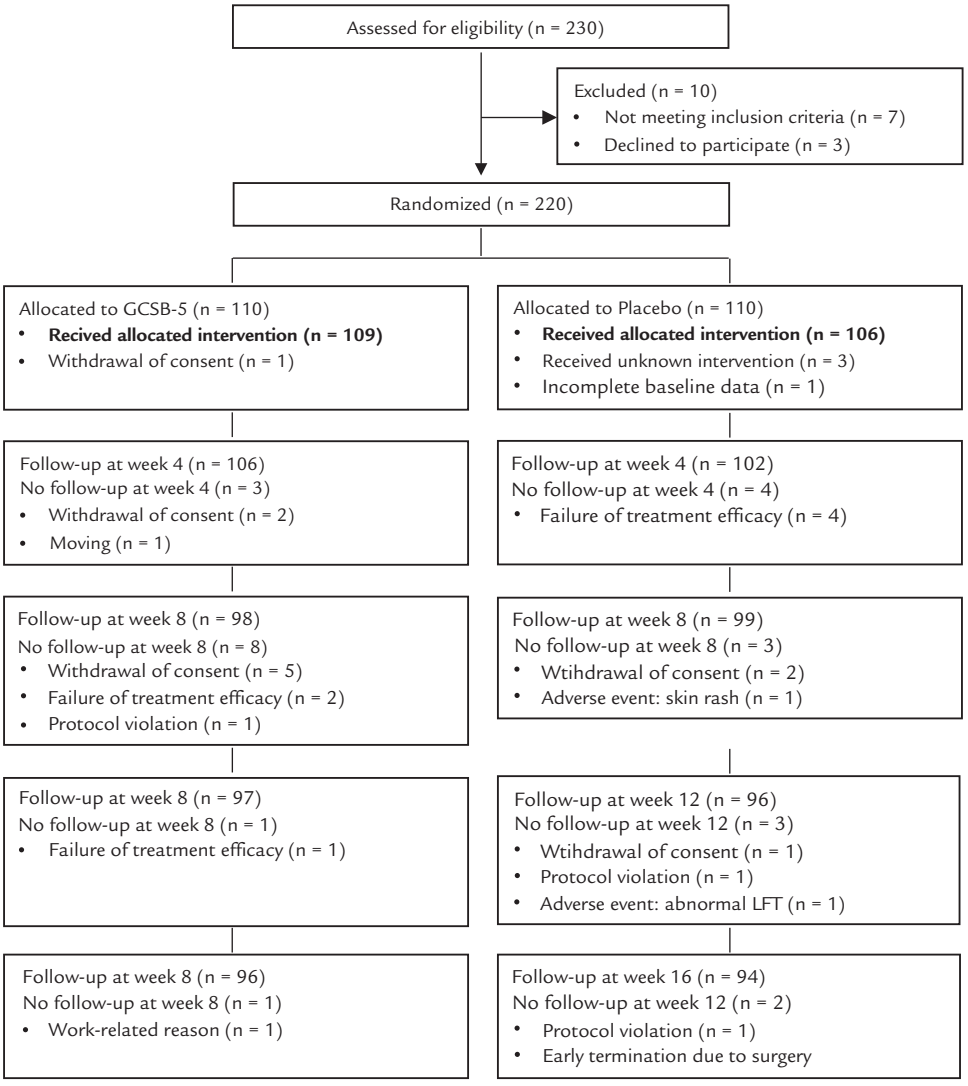

Figure 1. Flow diagram of patient disposition in this study in patients with hand osteoarthritis treated with GCSB-5 600 mg or placebo BID for 12 weeks. LFT = liver function test.

the 3 centers) were randomly assigned to the GCSB-5 arm (n = 110) or the placebo arm (n = 110). After randomization, 109 patients in the GCSB-5 arm and 106 in the placebo arm received the allocated treatment. The data from those patients were included in the analysis (Figure 1).

The GCSB-5 and placebo groups did not differ significantly in terms of baseline characteristics. They were, on average, 60.7 (7.2) and 59.4 (8.0) years of age, respectively, and females predominated in both groups (91.7% and 92.5%, respectively). The 2 groups did not differ significantly in terms of weight, height, body mass index, duration of hand OA, OA disease activity, or prior treatments (Table I).

Efficacy

The improvements in the AUSCAN pain score were significantly greater in the GCSB-5 group than in the placebo group over the 16-week study period (P = 0.0052). At 4 weeks, the median (interquartile range) improvement in the AUSCAN pain score relative to

Table I. Baseline characteristics of the study patients with hand osteoarthritis (OA) treated with GCSB-5 600 mg or placebo BID for 12 weeks (modified intent-to-treat population).

Characteristic	GCSB-5 (n = 109)	Placebo (n = 106)	*P*
Age, mean (SD), y	60.7 (7.2)	59.4 (8.0)	0.211
Female, no. (%)	100 (91.7)	98 (92.5)	0.847
Weight, mean (SD), kg	58.9 (7.4)	59.0 (8.1)	0.917
Height, mean (SD), cm	156.7 (6.7)	157.0 (6.0)	0.774
Body mass index, mean (SD), kg/m^2	23.9 (2.5)	23.9 (2.8)	0.927
Duration of hand OA, mean (SD), mo	28.6 (46.8)	31.7 (47.2)	0.631
Family history of OA, no. (%)	30 (27.5)	25 (23.6)	0.508
Baseline scores, mean (SD) (ranges, 1–100)			
AUSCAN pain score	49.7 (16.7)	48.2 (19.9)	0.529
AUSCAN stiffness score	55.2 (23.8)	60.4 (22.8)	0.103
AUSCAN function score	47.2 (21.8)	46.2 (23.9)	0.751
Patient global assessment	49.6 (16.5)	50.1 (16.3)	0.824
Physician global assessment	43.1 (11.1)	41.5 (13.0)	0.324
ESR, mean (SD), mm/h (normal, <20 mm/h)	14.2 (14.6)	13.3 (10.0)	0.593
hs-CRP,[†] mean (SD), mg/dL (normal, <0.5 mg/dL)	0.09 (0.11)	0.12 (0.26)	0.164
Prior treatment, no. (%)			
NSAIDs	36 (33.0)	36 (34.0)	0.885
Glucosamine	14 (12.8)	13 (12.3)	0.898
Acetaminophen	9 (8.3)	10 (9.4)	0.761
Tramadol	8 (7.3)	11 (10.4)	0.433
Diacerein	5 (4.6)	3 (2.8)	0.722[*]
Others	1 (0.9)	3 (2.8)	0.365[*]

AUSCAN = Australian/Canadian Osteoarthritis Hand Index; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; OA = osteoarthritis.
[*]Fisher exact test. Remaining *P* values were generated by using an independent *t* test for continuous variables or χ^2 test for categorical variables.
[†]CRP values were not available in 1 patient in the GCSB-5 group and in 1 patient in the control group.

baseline was greater in the GCSB-5 group than in the placebo group (–9.0 [–23.6 to –0.4] vs –2.2 [–16.6 to 6.0], respectively; $P = 0.014$) (Figure 2**A**). The improvement remained greater in the GCSB-5 group at 8 weeks (–13.4 [–26.2 to 0] vs –2.2 [–17.4 to 4.8]) and at 12 weeks (–14.6 [–30.4 to 0] vs –8.0 [–25.0 to 7.8]) (Table II). At 4 weeks after treatment discontinuation (week 16), the GCSB-5 group continued to exhibit improved AUSCAN pain scores relative to baseline, whereas the AUSCAN pain scores in the placebo group deteriorated after treatment discontinuation. Thus, at the 16-week time point, the GCSB-5 and placebo groups differed in terms of AUSCAN pain score improvement (–15.6 [–28.2 to 0] vs –4.4 [–24.8 to 7.2]). The improvements in the AUSCAN function scores relative to baseline were significantly greater in the GCSB-5 group than in the placebo group at 4 weeks (–6.8 [–18.9 to 3.6] vs –3.7 [–13.7 to 6.8]), 8 weeks (–9.8 [–26.9 to 2.6] vs –4.8 [–18.6 to 7.7]), 12 weeks (–11.0 [–27.8 to 0.8] vs –2.9 [–18.3 to 6.8]), and 16 weeks (–9.9 [–28.7 to 0.6] vs –4.8 [–18.7 to 9.1]) ($P = 0.039$). The 2 groups did not differ in terms of AUSCAN stiffness scores (Table II). Compared with patients who received placebo, more patients in the GCSB-5 group fulfilled the OMERACT-OARSI response criteria over the 16-week study period (proportions of fulfillment: 4 weeks, 44.0% vs 30.2%; 8 weeks, 51.4% vs 35.9%;

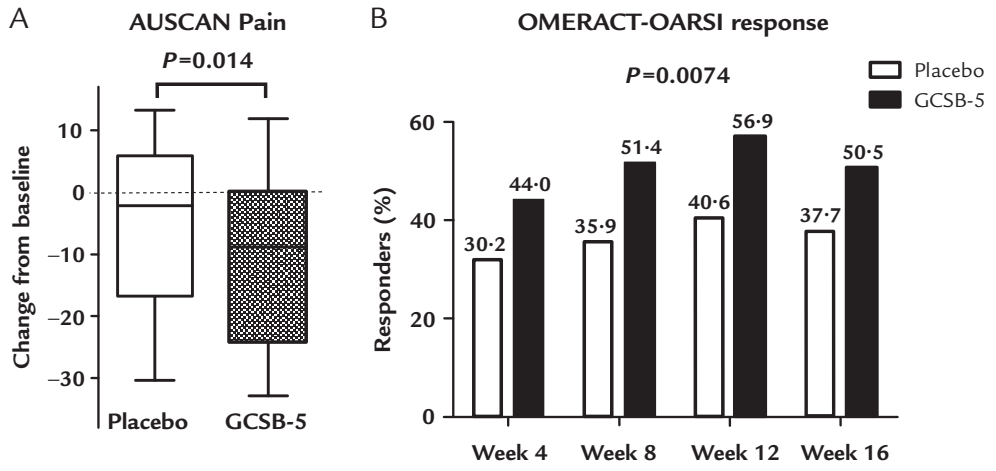

Figure 2. Outcomes in this study in patients with hand osteoarthritis treated with GCSB-5 600 mg or placebo BID for 12 weeks. (A) Change in Australian/Canadian Osteoarthritis Hand Index (AUSCAN) pain score at 4 weeks after randomization. *P* value for the primary outcome generated by the Mann-Whitney test. (B) Frequencies of Outcomes Measures in Rheumatology-Osteoarthritis Research Society International (OMERACT-OARSI)-defined response at various time points. *P* was generated using a generalized estimating equation.

12 weeks, 56.9% vs 40.6%; and 16 weeks, 50.5% vs 37.7% [$P = 0.0074$]) (Figure 2**B**).

The improvements in patient global assessment scores relative to baseline were significantly greater in the GCSB-5 group than in the placebo group, whereas the 2 groups did not differ in terms of physician global assessment scores. The 2 groups did not exhibit marked improvements relative to baseline in terms of the use of rescue medication (Table II) (Supplementary Table III).

Sensitivity Analysis

At 4 weeks, data were missing in 3 of 109 patients (2.8%) in the GCSB-5 group and in 4 of 106 patients (3.8%) in the placebo group. After multiple imputation of missing values using the fully conditional specification algorithm, the change in AUSCAN pain score at 4 weeks was significantly greater in the GCSB-5 group than in the placebo group ($P = 0.024$). The difference in the primary end point remained significant when the analysis was performed using the complete dataset ($P = 0.018$) (Table III).

Tolerability

The 2 groups had similar rates of AEs (Table IV). Severe AEs that led to early study withdrawal were not reported in the GCSB-5 arm. In the placebo group, two patients discontinued the study medication due to skin rash (n = 1) and liver function test abnormality (n = 1). The GCSB-5 group was more likely to develop upper respiratory infection (14.7% vs 4.7%; $P = 0.02$). The 2 groups had similar rates of gastrointestinal AEs.

DISCUSSION

The findings from this prospective, double-blind, randomized, placebo-controlled trial suggest that GCSB-5 treatment was clinically effective for hand OA and that it had a tolerable safety profile. AUSCAN pain scores were improved with GCSB-5 relative to placebo during the treatment period and at 4 weeks after discontinuation. Furthermore, the GCSB-5 group had a significantly greater rate of OMERACT-OARSI response than did the placebo group during the entire intervention period. This finding is important because the OMERACT-OARSI response has been proposed to be the preferred outcome measure in OA studies.[19]

Hand OA is one of the most common OA types: its prevalence ranges between 29% and 76%, and it has been associated with a serious disease burden.[2] However, the current guidelines were based mainly on the opinions of experts rather than on data from

Table II. Changes from baseline in efficacy outcomes in patients with hand osteoarthritis treated with GCSB-5 600 mg or placebo BID for 12 weeks. Data are given as median (interquartile range) unless otherwise noted.

Outcome	GCSB-5 (n = 109)	Placebo (n = 106)	*P*
AUSCAN pain			0.0052*
Week 4	−9.0 (−23.6 to −0.4)	−2.2 (−16.6 to 6.0)	
Week 8	−13.4 (−26.2 to 0.0)	−2.2 (−17.4 to 4.8)	
Week 12	−14.6 (−30.4 to 0.0)	−8.0 (−25.0 to 7.8)	
Week 16	−15.6 (−28.2 to 0.0)	−4.4 (−24.8 to 7.2)	
AUSCAN stiffness			0.2648*
Week 4	−9.0 (−22.0 to 3.0)	−6.0 (−23.0 to 6.0)	
Week 8	−12.0 (−28.0 to 2.0)	−6.0 (−27.0 to 4.0)	
Week 12	−14.0 (−36.0 to 0.0)	−11.0 (−29.0 to 5.0)	
Week 16	−10.0 (−27.0 to 2.0)	−8.0 (−27.0 to 5.0)	
AUSCAN function			0.0390*
Week 4	−6.8 (−18.9 to 3.6)	−3.7 (−13.7 to 6.8)	
Week 8	−9.8 (−26.9 to 2.6)	−4.8 (−18.6 to 7.7)	
Week 12	−11.0 (−27.8 to 0.8)	−2.9 (−18.3 to 6.8)	
Week 16	−9.9 (−28.7 to 0.6)	−4.8 (−18.7 to 9.1)	
Patient global assessment			0.0167*
Week 4	−9.0 (−24.0 to 2.0)	−3.0 (−15.0 to 6.0)	
Week 8	−10.0 (−24.0 to 0.0)	−6.0 (−18.0 to 12.0)	
Week 12	−11.0 (−30.0 to 1.0)	−6.0 (−24.0 to 6.0)	
Week 16	−10.0 (−29.0 to 3.0)	−8.5 (−21.0 to 9.0)	
Physician global assessment			0.0760*
Week 4	−12.0 (−21.0 to 0.0)	−7.0 (−19.0 to 1.0)	
Week 8	−16.0 (−26.0 to −4.0)	−11.5 (−25.0 to 0.0)	
Week 12	−19.0 (−29.0 to −5.0)	−13.0 (−27.0 to 0.0)	
Week 16	−12.0 (−23.0 to 0.0)	−6.5 (−20.0 to 1.0)	
Acetaminophen rescue, no. (%)			0.4216†
Week 4	7 (6.42)	4 (3.77)	
Week 8	10 (9.17)	7 (6.60)	
Week 12	4 (3.67)	4 (3.77)	
Week 16	4 (3.67)	2 (1.89)	

AUSCAN = Australian/Canadian Osteoarthritis Hand Index.
*Nonparametric repeated measure ANOVA.
†Generalized estimating equations were used for generate *P* values that represent the significance of group difference over 16 weeks.

well-designed clinical trials.[5–7] For example, the efficacy of acetaminophen, which is often suggested as the initial pharmacologic choice, in hand OA has not yet been proved by findings from an RCT. Among NSAIDs, only ibuprofen and lumiracoxib have been studied in RCTs in terms of their efficacy in hand OA to date.[26,27] However, ibuprofen can cause serious gastrointestinal complications in the elderly population,[28,29] and lumiracoxib, a selective cyclooxygenase-2 inhibitor with a lower risk for gastrointestinal AEs,

Table III. Sensitivity analysis of changes from baseline in Australian/Canadian Osteoarthritis Hand Index pain scores at 4 weeks in patients with hand osteoarthritis treated with GCSB-5 600 mg or placebo BID for 12 weeks. Data are given as median (interquartile range).

Statistical Set	GCSB-5, *n*	Placebo, *n*	*P*
LOCF*	−9.0 (−23.8 to −0.2), 109	−2.2 (−16.7 to 6.0), 106	0.014
FCS†	−9.8 (−24.0 to −0.8), 109	−3.8 (−17.2 to 6.0), 106	0.024
Complete dataset	−9.8 (−24.0 to −0.8), 106	−3.7 (−17.0 to 6.0), 102	0.018

*Missing data were imputed using last observation carried forward (LOCF).
†Missing data handled with multiple imputation using fully conditional specification (FCS). *P* values were generated by using Wilcoxon rank sum test.

has been withdrawn from the market due to its potential for severe hepatotoxicity.[30] Moreover, although NSAIDs are effective in hand OA, their association with considerable gastrointestinal and cardiovascular toxicity limits their long-term use.[31] Opioid analgesics, which are also frequently associated with gastrointestinal discomfort, have not yet been studied in an RCT. The data on corticosteroid use in hand OA are conflicting: 1 small observational study in 36 patients reported that 120 mg of methylprednisolone IM effectively ameliorated OA symptoms, and an RCT in 83 patients reported that with the drug Crx-102 (a combination of dipyridamole and low-dose prednisolone), hand pain was significantly reduced, whereas an RCT in 70 patients reported that 5 mg of oral prednisolone had no effect on hand pain.[24,32,33] However, various complications associated with glucocorticoid limit its long-term use.[34] In short, the oral pharmacologic agents currently recommended for hand OA require a more solid scientific background regarding efficacy and tolerability. Only topical

Table IV. Adverse events (AEs) in patients with and hand osteoarthritis treated with GCSB-5 600 mg or placebo BID for 12 weeks. Data are given as no. (%).

Parameter	GCSB-5 (n = 109)	Placebo (n = 106)
Any AE	55 (50.5)	45 (42.5)
AEs leading to treatment discontinuation	0	2 (1.9)
Serious AEs	1 (0.9)	4 (3.8)
Surgery	1 (0.9)	1 (0.9)
Fracture	0	1 (0.9)
Liver function abnormality	0	1 (0.9)
Skin rash	0	1 (0.9)
AEs occurring in >5% of patients		
Abdominal discomfort	17 (15.6)	11 (10.4)
Upper respiratory infection	16 (14.7)	5 (4.7)
Skin rash	8 (7.3)	10 (9.4)
Leukopenia	9 (8.3)	7 (6.6)
Liver function abnormality	7 (6.4)	7 (6.6)
Nausea	6 (5.5)	6 (5.7)

diclofenac gel has been reported to be effective for hand OA in a well-designed trial.[35]

That GCSB-5 was associated with a greater OMERACT-OARSI response rate than was placebo throughout the intervention period suggests that GCSB-5 has meaningful clinical efficacy. This finding is consistent with those from a prior study that reported that GCSB-5 was noninferior to celecoxib in treating knee OA.[12] Another finding from the present study was that the clinical response to GCSB-5 continued after the treatment was stopped: in the GCSB-5 group, the improvement in AUSCAN pain score was unabated 4 weeks after treatment discontinuation, whereas the AUSCAN pain score in the placebo group had started to increase at the same time point (Table II). Whether GCSB-5 may be a disease-modifying OA drug—as GCSB-5 has been reported in an animal OA model to protect cartilage structures[13]—needs further investigation. Longer-term studies are needed to further investigate the potential of GCSB-5 as a disease-modifying OA drug—in particular, studies that assess the optimal GCSB-5 treatment duration and the effect of this agent on structural changes in hand OA. The low placebo response in the current study was surprising. A possible explanation is that placebo responses vary from study to study, as the clinical characteristics of the enrolled patients might differ between studies. A similarly low placebo response in a study in hand OA was reported previously.[24]

Although the exact mechanism of action of GCGB-5 is still under investigation, the extracts contained in GCSB-5 have been reported to have several biological effects. They exhibit antioxidative effects and reduce oxidative stress. The anti-inflammatory effects are elicited through the suppression of cyclooxygenase 2 expression; down-regulation of inflammatory mediators, including interleukin 1β and tumor necrosis factor α; and inhibition of nitrite oxide. In addition, GCSB-5 might improve OA-induced cartilage damage by inhibiting matrix metalloproteinase activity (see **Supplemental Table I** in the online version at http://dx.doi.org/10.1016/j.clinthera.2016.06.016).

Because GCSB-5 and celecoxib have exhibited comparable efficacy in the treatment of knee OA, and because the analgesic effect of NSAIDs is usually clinically apparent within 1 to 2 weeks, we chose the change in pain at 4 weeks relative to baseline as the primary end point. Furthermore, changes in pain and other clinical outcomes measures up to 16 weeks were included as secondary end points for evaluating treatment sustainability. However, as long-term effects (ie, efficacy and AEs) are crucial for the management of chronic disease, a prospective, long-term study (beyond a 52-week period) is needed for evaluating the exact role of GCSB-5 in the management of hand OA.

Hand OA is a chronic disease that exhibits great variation. The disease inevitably progresses in half of patients, leading to high levels of functional limitation.[36] These patients might require lifelong treatment, making the long-term tolerability of oral pharmacologic treatments a major issue. GCSB-5 was comparable to placebo in terms of overall safety profile. In particular, the GCSB-5 and placebo groups exhibited similar frequencies of abdominal discomfort (16.5% and 12.3%, respectively). Interestingly, the GCSB-5 group experienced upper respiratory tract infection more frequently than did the placebo group (14.7% vs 4.7%) (Table IV). However, an association between leukopenia and the increased rate of upper respiratory tract infection was not found (see **Supplemental Table II** in the online version at http://dx.doi.org/10.1016/j.clinthera.2016.06.016). A larger-scale study is needed for confirming whether GCSB-5 use is associated with increased risks for upper respiratory tract infection and leukopenia. The clinical efficacy and tolerability of GCSB-5 suggest that it may be a well-tolerated alternative in patients with hand OA who cannot tolerate other oral pharmacologic treatments.

Study Limitations

A major limitation of the present RCT was that the study population was composed of ethnic Koreans only. Whether the present findings can be generalized to other ethnic groups requires further investigation. In addition, a study with longer follow-up is needed to investigate long-term efficacy and tolerability issues.

CONCLUSION

The use of GCSB-5 was associated with meaningful clinical improvement and was well-tolerated in these patients with hand OA.

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The corresponding author had full access to all of the data in the study and had final responsibility for the decision to submit the manuscript for publication.

CONFLICT OF INTEREST

E.B. Lee has received consultant's fees from Pfizer Inc. The authors have indicated that they have no other conflicts of interest with regard to the content of this article.

SUPPLEMENTARY MATERIAL

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.clinthera.2016.06.016.

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SUPPLEMENTARY MATERIAL

Supplementry Tables S1–S3.

Supplementary Table 1. Summary of the biologic effects of the 6 extracts in GCSB-5.

Extracts	Biologic effect
Saposhnikovia divaricata Schischkin	Anti-inflammatory[*,†,‡]
Achyranthes bidentata Blume	Anti-inflammatory and reduction of metalloproteinases matrix (MMP)-3 release[§]
Acanthopanax senticosus Harms	Anti-oxidative effect[‖] Anti-inflammatory: inhibition of AP-1 and/or NF-κB activities[¶]
Cibotium barometz J. Smith	Anti-oxidative effect[#] Inhibition of osteoclast formation and activation of osteoblast[**]
Glycine max Merrill	Anti-nocieptive and anti-inflammatory effect[††]
Eucommia ulmoides Oliver	Anti-oxidative[‡‡] Anti-inflammatory: COX-2 suppression[§§], Suppression of IL-1, TNF production[‖‖]

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Supplementary Table 2. Association between leukopenia and URI in GCSB-5 group.

	Leukopenia (+)	Leukopenia (-)	Total
URI (+)	0	16	16
URI (-)	9	84	93
Total	9	100	109

P=0.3512 by Fisher's exact test.
URI, upper respiratory infection.

Supplementary Table 3. Mean change from baseline in efficacy outcomes in the two study groups

Outcomes	GCSB-5 (n =109)	Placebo (n = 106)
AUSCAN pain change from baseline, mean (SD)		
Week 4	-10.2 (17.1)	-5.7(19.3)
Week 8	-12.4 (19.2)	-6.7 (21.9)
Week 12	-14.6 (21.5)	-8.8 (23.5)
Week 16	-14.4 (19.5)	-6.5(25.7)
AUSCAN stiffness, change from baseline, mean (SD)		
Week 4	-10.2 (24.4)	-9.3 (23.5)
Week 8	-13.6 (25.0)	-10.1 (28.0)
Week 12	-17.0 (27.4)	-12.8 (28.1)
Week 16	-12.4 (26.6)	-9.7 (29.6)
AUSCAN function, change from baseline, mean (SD)		
Week 4	-8.3 (21.3)	-4.4 (18.1)
Week 8	-9.6 (22.9)	-6.0 (21.8)
Week 12	-12.0 (25.5)	-7.3 (24.1)
Week 16	-11.0 (23.6)	-5.4 (26.4)
Patient global assessment, change from baseline, mean (SD)		
Week 4	-9.7 (21.6)	-4.7 (19.3)
Week 8	-11.8 (23.1)	-4.1 (22.9)
Week 12	-13.8 (23.9)	-7.5 (25.8)
Week 16	-10.4 (24.2)	-6.0 (25.4)
Physician global assessment, change from baseline, mean (SD)		
Week 4	-12.5 (16.1)	-9.7 (15.4)
Week 8	-17.3 (17.8)	13.0 (17.8)
Week 12	-18.5 (17.8)	-14.3 (18.2)
Week 16	-13.4 (17.5)	-9.6 (17.7)