

# The Effect of Glucosamine and/or Chondroitin Sulfate on the Progression of Knee Osteoarthritis

## A Report from the Glucosamine/Chondroitin Arthritis Intervention Trial

Allen D. Sawitzke,<sup>1</sup> Helen Shi,<sup>2</sup> Martha F. Finco,<sup>1</sup> Dorothy D. Dunlop,<sup>3</sup>  
Clifton O. Bingham, III,<sup>4</sup> Crystal L. Harris,<sup>5</sup> Nora G. Singer,<sup>6</sup> John D. Bradley,<sup>7</sup>  
David Silver,<sup>8</sup> Christopher G. Jackson,<sup>1</sup> Nancy E. Lane,<sup>9</sup> Chester V. Oddis,<sup>10</sup> Fred Wolfe,<sup>11</sup>  
Jeffrey Lisse,<sup>12</sup> Daniel E. Furst,<sup>13</sup> Domenic J. Reda,<sup>2</sup> Roland W. Moskowitz,<sup>6</sup>  
H. James Williams,<sup>1</sup> and Daniel O. Clegg<sup>1</sup>

**Objective.** Osteoarthritis (OA) of the knee causes significant morbidity and current medical treatment is

limited to symptom relief, while therapies able to slow structural damage remain elusive. This study was undertaken to evaluate the effect of glucosamine and chondroitin sulfate (CS), alone or in combination, as well as celecoxib and placebo on progressive loss of joint space width (JSW) in patients with knee OA.

**Methods.** A 24-month, double-blind, placebo-controlled study, conducted at 9 sites in the United States as part of the Glucosamine/Chondroitin Arthritis Intervention Trial (GAIT), enrolled 572 patients with knee OA who satisfied radiographic criteria (Kellgren/Lawrence [K/L] grade 2 or grade 3 changes and JSW of at least 2 mm at baseline). Patients with primarily lateral compartment narrowing at any time point were excluded. Patients who had been randomized to 1 of the 5 groups in the GAIT continued to receive glucosamine 500 mg 3 times daily, CS 400 mg 3 times daily, the combination of glucosamine and CS, celecoxib 200 mg daily, or placebo over 24 months. The minimum medial tibiofemoral JSW was measured at baseline, 12 months, and 24 months. The primary outcome measure was the mean change in JSW from baseline.

**Results.** The mean JSW loss at 2 years in knees with OA in the placebo group, adjusted for design and clinical factors, was 0.166 mm. No statistically significant difference in mean JSW loss was observed in any treatment group compared with the placebo group. Treatment effects on K/L grade 2 knees, but not on K/L grade 3 knees, showed a trend toward improvement

ClinicalTrials.gov identifier: NCT00032890.

Supported by the NIH (National Institute of Arthritis and Musculoskeletal and Skin Diseases and National Center for Complementary and Alternative Medicine, contract N01-AR-2236).

<sup>1</sup>Allen D. Sawitzke, MD, Martha F. Finco, MS, Christopher G. Jackson, MD, H. James Williams, MD, Daniel O. Clegg, MD: University of Utah School of Medicine, Salt Lake City; <sup>2</sup>Helen Shi, MS, Domenic J. Reda, PhD: Hines VA Cooperative Studies Program Coordinating Center, Hines, Illinois; <sup>3</sup>Dorothy D. Dunlop, PhD: Northwestern University Feinberg School of Medicine, Chicago, Illinois; <sup>4</sup>Clifton O. Bingham, III, MD: Johns Hopkins University, Baltimore, Maryland; <sup>5</sup>Crystal L. Harris, PharmD: Albuquerque VA Cooperative Studies Program Clinical Research Pharmacy Coordinating Center, Albuquerque, New Mexico; <sup>6</sup>Nora G. Singer, MD, Roland W. Moskowitz, MD: Case Western Reserve University, Cleveland, Ohio; <sup>7</sup>John D. Bradley, MD: Indiana University, Indianapolis; <sup>8</sup>David Silver, MD: Cedars Sinai Medical Center, Los Angeles, California; <sup>9</sup>Nancy E. Lane, MD: University of California, Davis, Sacramento; <sup>10</sup>Chester V. Oddis, MD: University of Pittsburgh, Pittsburgh, Pennsylvania; <sup>11</sup>Fred Wolfe, MD: Arthritis Research Center, Wichita, Kansas; <sup>12</sup>Jeffrey Lisse, MD: University of Arizona, Tucson; <sup>13</sup>Daniel E. Furst, MD: University of California, Los Angeles.

Dr. Bingham has received consulting fees from Merck and McNeil (less than \$10,000 each). Dr. Singer has received consulting fees, speaking fees, and/or honoraria from Bristol-Myers Squibb (less than \$10,000) and from Abbott Immunology (more than \$10,000); she has received grants and/or contracts through the University of California, Davis from the Alliance for Lupus Research, Pfizer, Merck, Endo, Zymogenetics, Serono, Genentech, Amgen, and Roche. Dr. Moskowitz has received speaking fees and honoraria from Bioiberica (more than \$10,000). Dr. Clegg has received consulting fees, speaking fees, and/or honoraria from Bioiberica (less than \$10,000), and has received grants and contracts through the University of Utah from Bioiberica.

Address correspondence and reprint requests to Allen D. Sawitzke, MD, University of Utah School of Medicine, 30E 1900 S SOM 4B200, Salt Lake City, UT 84132. E-mail: allen.sawitzke@hsc.utah.edu.

Submitted for publication March 11, 2008; accepted in revised form July 14, 2008.

relative to the placebo group. The power of the study was diminished by the limited sample size, variance of JSW measurement, and a smaller than expected loss in JSW.

**Conclusion.** At 2 years, no treatment achieved a predefined threshold of clinically important difference in JSW loss as compared with placebo. However, knees with K/L grade 2 radiographic OA appeared to have the greatest potential for modification by these treatments.

Osteoarthritis (OA) is the most common form of arthritis, affecting at least 20 million Americans, and its prevalence is expected to double over the next 2 decades (1,2). Once considered a consequence of aging, OA is now thought to involve a complex interaction of biologic and pathologic processes influenced by a number of factors, including genetics, age, sex, obesity, joint injury, and muscle strength (3) together with mechanical factors such as repetitive microtrauma and instability (4). Although the pathogenesis of OA has yet to be clearly defined, failure of articular cartilage is central to disease development (5).

Loss of cartilage in OA is usually assessed radiographically, as an interbone distance. Precision and reproducibility in the measurement of this distance are improved by application of standardized acquisition protocols. Each protocol attempts to address difficulties inherent in obtaining reproducible positioning and projection of the joint. At the inception of this study, both anteroposterior (AP) and posteroanterior (PA) projection protocols, using various degrees of knee flexion with or without fluoroscopic guidance of positioning, were under scrutiny (6–12). In these protocols, fluoroscopy was not commonly used, due to its limited availability, difficulty in achieving and maintaining technician training, and the need to minimize cost and radiation exposure. Findings obtained with the available approaches indicated that a narrowing of the joint space of ~0.25 mm per year could be expected (9). The metatarsophalangeal (MTP) radiographic view used in a study by Buckland-Wright et al, which is a PA-directed, semiflexed-view of the knee joints, was thought to have a balance of ease, thrift, and precision adequate to detect the anticipated change in joint space width (JSW) over 2 years in knees with OA (10).

When the Glucosamine/Chondroitin Arthritis Intervention Trial (GAIT) (13) was initiated, the efficacy of glucosamine and chondroitin sulfate (CS) in the symptomatic treatment of knee OA had been suggested (14,15). Almost all available studies had evaluated these treatments singly, despite the fact that they were commonly marketed in combination, especially in the United

States. In addition, radiographic studies that were in progress were evaluating the effects of glucosamine or CS on JSW narrowing (16–18). The reported benefit observed in these studies remains controversial, due, in part, to methodologic concerns. The trial described herein was a prospective observational study of GAIT enrollees that was performed to evaluate whether glucosamine or CS, taken alone or in combination for 2 years, could be demonstrated to have a structure-modifying effect in OA of the knee. The primary end point was mean change in the minimum medial tibiofemoral JSW, as measured on films obtained using the standardized, nonfluoroscopic MTP radiographic protocol of Buckland-Wright et al (10).

## PATIENTS AND METHODS

**Study design.** Nine of the 16 GAIT centers participated in this ancillary study to assess structural changes in knee OA; participating centers were the Wichita Arthritis Research Center, the University of Arizona, Case Western Reserve University, Cedars-Sinai Medical Center, Indiana University, the University of California, Los Angeles, the University of California, San Francisco, the University of Pittsburgh, and the University of Utah. Eligible patients were at least 40 years of age, had knee pain for at least 6 months occurring on the majority of days in the month preceding their enrollment in GAIT, and had Kellgren/Lawrence (K/L) grade 2 or grade 3 knee OA (19) determined on a screening AP radiograph of the knee in a weight-bearing position. If both knees from an individual qualified, both were evaluated for structural change over time.

Qualifying patients received their blinded study treatment for a total of 24 months. The treatments consisted of glucosamine (500 mg 3 times daily), CS (400 mg 3 times daily), the combination of glucosamine and CS, celecoxib (200 mg daily), or placebo. Patients who had concurrent medical conditions that could confound evaluation of the knee joints or disease that would limit their successful completion of the trial were not eligible. Specific knees were excluded from evaluation if they had 1) a minimum baseline medial tibiofemoral JSW of <2 mm, 2) predominant lateral compartment OA on any film of the MTP joints, and 3) a history of significant trauma or surgery to the knee. The protocol was approved by the Institutional Review Board of each site, and all participants provided their written informed consent.

It was estimated that 791 patients would be eligible to participate at the 9 centers and that the rate of missing data would be 40%. The mean change in JSW at 2 years among patients taking placebo was expected to be 0.4 mm (9), with an SD of 0.388 mm. A reduction in JSW loss of at least 0.2 mm in the placebo group over 2 years was considered to be clinically meaningful. Thus, the study was designed to have 86% power to detect a difference between the groups, using a sample size of 95 persons per group, with the alpha level set at 0.0125.

**Radiographic technique.** All radiology technicians selected to participate in this trial were experienced musculo-

skeletal radiology technicians. The technicians from each site were trained at a 2-day session, conducted by Professor J. Christopher Buckland-Wright (King's College, London, UK), to perform nonfluoroscopic, weight-bearing radiographic assessment of the knee joints (10). Technicians were also given a training and reference manual and a quick reference sheet. Centers notified the National Coordinator Center (NCC) when a change in radiology technicians occurred. New technicians received training by the already trained technologist on site. Documentation of technologist training was maintained by the NCC.

MTP radiographs were obtained from patients at baseline, 12 months, and 24 months. Per protocol, a foot map was created by placing the subject's feet on a paper template and tracing an outline of the initial placement of the feet; this foot map was used to maintain similar positioning when repeat images had to be obtained. Over the course of the study, sites increasingly used digital image capture followed by film printing. All films were mailed to the central radiology center, where they were assessed by 2 readers for quality, including labeling, alignment of the x-ray beam, positioning of the knees on the film, and x-ray beam penetration. When indicated, repeat films were requested. Approved films were assigned a randomized code from a printed table, with randomization according to the order in which the films were received. Radiographic findings were digitized using a Lumisys 75 scanner and stored in archival form as 10 data bits in 16-bit DICOM files, using OsiriX software (20).

One observer (ADS) used the Mdisplay program from Buckland-Wright et al (10) to measure the minimum medial joint compartment JSW on coded films. The program requires the user to mark the end points of the tibial and femoral condyles for interpretation of the joint boundary, before the minimum JSW can be identified. Standard procedures ensure that the program does not measure osteophytes or disparate locations for a series of films. Each series of radiographic films was read together, but film sequence and treatment group remained masked. The standard error for the minimum JSW measurement obtained using the Mdisplay program was 0.025 mm. In order to estimate the error associated with the process of measurement, knees from 41 patients who were likely to show little or no progression of knee OA over a 1-year period were used (knees graded as K/L grade 0 or K/L grade 1). The within-knee SD for the standard error of repeated measurements showed an estimated precision error of 0.16 mm.

**Outcomes.** The primary outcome of the trial was mean change in JSW in the medial compartment of the knee over 2 years, assessed on films obtained using the Buckland-Wright nonfluoroscopic MTP protocol, with results read using computer-generated measurements from digitized images. The secondary outcome was the percentage of progressors at 2 years, defined as those knees with a loss in JSW that exceeded 0.48 mm (3 times the SD of the standard error of measurements) when compared with the baseline measurement of JSW, consistent with approaches used in other studies (8,18,21–23).

**Statistical analysis.** All analyses were done on a modified intent-to-treat basis. Baseline characteristics were compared across groups using a chi-square test for categorical variables, and analysis of variance for continuous variables. Statistical testing of treatment differences was adjusted for the

comparison of each of 4 treatments with a control (placebo) using multivariate *t*-test (analogous to Dunnett's *t*-test) to calculate 95% confidence intervals (95% CIs) (24). A 95% CI that excludes zero would indicate a statistically significant result. The analysis sample of 357 subjects, comprising 581 knees, had 55% power to detect the prespecified clinically important difference in mean JSW loss, defined as a mean reduction in JSW loss of at least 0.2 mm, allowing for an overall Type I error rate of 5% for the comparisons of the 4 treatment groups with the placebo group, based on a Dunnett's *t*-test.

The primary longitudinal analysis compared mean change in JSW in each intervention group compared with the placebo group over 2 years, while controlling for design factors (weeks of treatment, elapsed time from baseline radiograph, recruitment site) and clinical factors (baseline JSW, sex, baseline pain score, disease duration, normal/overweight/obese weight status, K/L grade), using the knee as the unit of analysis. A mixed-effects regression model using SAS version 9.1 (SAS Institute, Cary, NC) was used to validly compare each treatment group with the placebo group, accounting for repeated measures over time and for clustering due to the monitoring of both knees for some individuals. This widely accepted form of repeated-measures analysis utilizes all data collected on this cohort. Sensitivity analyses used mixed-effects regression to separately test for treatment differences at 1 year and 2 years.

The secondary longitudinal analysis compared the occurrence of disease progression, defined as a JSW loss exceeding 0.48 mm over the 2-year followup, in each intervention group as compared with the placebo group, while controlling for all of the above-mentioned design and clinical factors; again, the knee was the unit of analysis. Logistic regression analyses with generalized estimating equations were implemented using SAS version 9.1 to validly analyze repeated measures over time and to account for clustering due to monitoring of both knees.

## RESULTS

**Baseline characteristics.** The distribution of the 662 patients who consented to participate and for whom data were available is shown in Table 1, according to the treatment groups to which they were randomized in the GAIT. The 5 groups had no significant differences in baseline characteristics at the time of entry into the present study. Withdrawals were those patients who withdrew from the study prior to the first followup radiograph ( $n = 171$ ). Films for which change in JSW could not be accurately measured were rejected for quality, which accounted for most of the 44 technical losses. The final sample included 357 subjects, comprising 581 qualifying knees, for which there was both a baseline and at least 1 followup MTP film that met the radiographic criteria. This group of assessable patients was similar to the eligible group, except that significantly more women were in the eligible group. Sixty-six percent of patients had 2 knees qualifying for analysis.

**Table 1.** Distribution of patients randomized to the treatment groups\*

	Glucosamine	Chondroitin sulfate	Glucosamine + chondroitin sulfate	Celecoxib	Placebo
<b>Patients</b>					
Initial	134	123	128	143	134
Eligible	119	107	110	122	114
Withdrawal	33	30	40	32	36
Technical loss	9	6	11	10	8
Assessable	77	71	59	80	70
<b>Knees</b>	123	116	94	135	113
Single knee	31	24	25	25	27
Both knees	46	46	34	55	43

\* Values are the number of patients included or number of knees evaluated. The initial cohort comprised those patients who consented to participate and for whom data were available. Eligibility criteria were as follows: at least 40 years of age, having knee pain for at least 6 months on the majority of days in the month preceding enrollment in the trial, and having Kellgren/Lawrence grade 2 or grade 3 knee osteoarthritis (19) on a screening anteroposterior radiograph, with joint space width (JSW) determined to be  $\geq 2$  mm. Withdrawals were those patients who withdrew from the study prior to the first followup radiograph. Technical losses were those patients whose film quality did not allow measurement of JSW loss.

The study sample comprised 63.6% women, the mean  $\pm$  SD age was  $56.9 \pm 9.8$  years, and the mean  $\pm$  SD body mass index was  $32 \pm 6.9$  kg/m<sup>2</sup>. There were also no significant differences in the baseline characteristics between the placebo and treatment groups among the assessable patients, and there were no appreciable differences between this population and all participants in the GAIT (Table 2).

**Primary outcome.** There were no significant differences in mean JSW loss over 2 years between the

treatment groups and the placebo group (Table 3), as determined using mixed-effects model regression analysis. The glucosamine group had the least mean loss in JSW (0.013 mm at 2 years), whereas the glucosamine plus CS group had the greatest mean loss (0.194 mm at 2 years).

One design factor and 1 clinical covariate were significant predictors of JSW loss from baseline. JSW loss was greater in knees with K/L grade 3 radiographic OA than in knees with K/L grade 2 radiographic OA,

**Table 2.** Characteristics of the patients at baseline, by treatment group and by study\*

	Glucosamine	Chondroitin sulfate	Glucosamine + chondroitin sulfate	Celecoxib	Placebo	Structural (present study)	GAIT
<b>Patients</b>							
No. assessable	77	71	59	80	70	357	1,583
Age, mean $\pm$ SD years	$56.7 \pm 10.4$	$56.4 \pm 9.2$	$56.5 \pm 9.9$	$58.3 \pm 10.7$	$56.6 \pm 8.4$	$56.9 \pm 9.8$	$58.6 \pm 10.3$
HAQ pain score, mean $\pm$ SD (range 0–100)	$46.4 \pm 20.2$	$51.6 \pm 18.4$	$51.3 \pm 18.4$	$52.2 \pm 19.9$	$52.3 \pm 19.2$	$50.7 \pm 19.3$	$54.1 \pm 20.4$
Duration of OA symptoms, mean $\pm$ SD years	$9.2 \pm 9.4$	$8.8 \pm 8.9$	$10.5 \pm 9.8$	$10.3 \pm 9.5$	$9.4 \pm 8.7$	$9.6 \pm 9.2$	$10.0 \pm 9.8$
Female, %	61.0	71.8	55.9	63.8	64.3	63.6	64.1
<b>Weight status by BMI</b>							
<25 kg/m <sup>2</sup>	13.0	14.1	11.9	16.3	4.3	12.0	14.2
25–30 kg/m <sup>2</sup> (overweight)	28.6	39.4	35.6	31.3	40.0	34.7	33.8
>30 kg/m <sup>2</sup> (obese)	58.4	46.5	52.5	52.5	55.7	53.2	51.9
<b>Knees</b>							
No. assessable	123	116	94	135	113	581	–
Kellgren/Lawrence grade, %							
Grade 2	80.5	81.0	69.2	72.6	80.5	76.9	–
Grade 3	19.5	19.0	30.9	27.4	19.5	23.1	–
<b>JSW</b>							
Mean $\pm$ SD mm	$4.04 \pm 1.01$	$3.86 \pm 0.90$	$4.04 \pm 0.96$	$4.01 \pm 1.01$	$4.07 \pm 0.93$	$4.00 \pm 0.96$	–
Median (IQR) mm	3.95 (3.36–4.60)	3.90 (3.28–4.41)	3.97 (3.33–4.82)	4.01 (3.21–4.60)	4.02 (3.51–4.60)	3.95 (3.33–4.60)	–

\* GAIT = Glucosamine/Chondroitin Arthritis Intervention Trial; HAQ = Health Assessment Questionnaire; OA = osteoarthritis; BMI = body mass index; JSW = joint space width; IQR = interquartile range.

**Table 3.** Loss in JSW over 2 years, by treatment group\*

Therapy	No. of subjects	Mean JSW loss over 2 years, mm†	Difference from placebo (95% CI)‡
Glucosamine	77	0.013	-0.153 (-0.379, 0.074)
Chondroitin sulfate	71	0.107	-0.059 (-0.287, 0.169)
Glucosamine + chondroitin sulfate	59	0.194	0.028 (-0.214, 0.271)
Celecoxib	80	0.111	-0.055 (-0.279, 0.170)
Placebo	70	0.166	-

\* The minimum medial tibiofemoral joint space width (JSW) was measured over 2 years on nonfluoroscopic, weight-bearing radiographs of the metatarsophalangeal joints.

† Adjusted for baseline JSW, sex, baseline pain score, disease duration, weight status, Kellgren/Lawrence grade, weeks of treatment, elapsed time to followup radiograph, and recruitment site. In the mixed-effects regression model, 581 knees of 357 patients were analyzed.

‡ A negative difference from placebo indicates less JSW loss in the treatment group compared with the placebo group. 95% CI = 95% confidence interval.

and this difference increased with time (i.e., JSW loss was greater at year 2 than at year 1).

Sensitivity analyses performed to evaluate the measurement of JSW in only 1 knee per patient at 1 year and at 2 years yielded results nearly identical to those obtained in the main analysis. The unadjusted mean JSW loss in the placebo group was substantially less (0.34 mm) than had been anticipated by the study design (expected loss of 0.40 mm over 2 years), while the unadjusted mean JSW loss was 0.273 mm in K/L grade 2 knees and 0.523 mm in K/L grade 3 knees in the placebo group.

**Secondary outcome.** The likelihood of radiographic progression in any treatment group compared with the placebo group was not significant (Table 4). Radiographic progression (JSW loss exceeding 0.48 mm) was most frequent in the group treated with the combination of glucosamine and CS (24.4% experiencing progression at 2 years), whereas progression was least frequent in the group treated with glucosamine

alone (18.6% at 2 years). The overall order of progression across treatment groups paralleled that seen for mean JSW loss.

Figure 1 shows the difference in JSW loss in the treatment groups compared with the placebo group, stratified according to K/L grade (K/L grade 2 versus K/L grade 3 knees) and adjusted for design and clinical factors. Although the differences were not statistically significant, all treatment groups showed numerically less JSW loss than did the placebo group for knees with K/L grade 2 radiographic knee OA, but showed more JSW loss compared with the placebo group for knees with K/L grade 3 radiographic knee OA.

This effect of K/L grade on treatment is further examined in Figure 2. The estimated odds ratio for radiographic progression compared with the placebo group was <1 in patients with K/L grade 2 knees in all treatment groups, whereas it was >1 in patients with K/L grade 3 knees in all treatment groups. The overall pattern of treatment effect was remarkably constant in

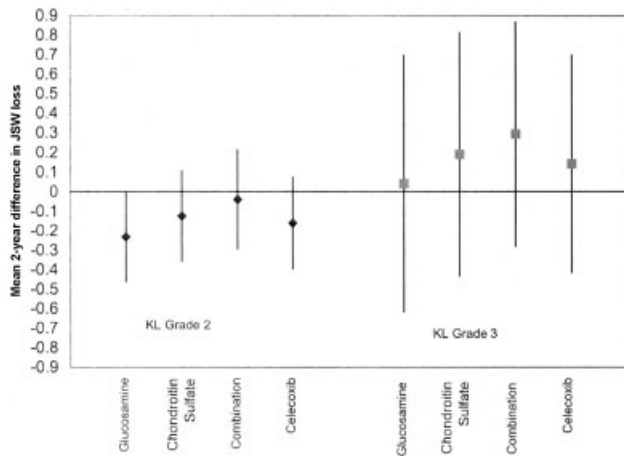
**Table 4.** Disease progression over 2 years, by treatment group\*

Therapy	No. of subjects	Progression, % of patients†	OR versus placebo (95% CI)‡
Glucosamine	77	18.6	0.79 (0.48-1.3)
Chondroitin sulfate	71	21.4	0.94 (0.57-1.55)
Glucosamine + chondroitin sulfate	59	24.4	1.12 (0.67-1.88)
Celecoxib	80	20.2	0.87 (0.53-1.43)
Placebo	70	22.4	-

\* Progression was defined as joint space width loss exceeding 0.48 mm when compared with the baseline measurement.

† Adjusted for baseline joint space width, sex, baseline pain score, disease duration, weight status, Kellgren/Lawrence grade, weeks of treatment, elapsed time to followup radiograph, and recruitment site. In the mixed-effects regression model, 581 knees of 357 patients were analyzed.

‡ An odds ratio (OR) value of <1 indicates less progression in the treatment group compared with the placebo group. 95% CI = 95% confidence interval.



**Figure 1.** Mean 2-year difference in joint space width (JSW) loss (in mm) in the treatment groups relative to the placebo group, according to Kellgren/Lawrence (K/L) radiographic severity grade (K/L grade 2 versus K/L grade 3 knee osteoarthritis). Negative values (those below the horizontal line) indicate less JSW loss in the treatment groups than in the placebo group. Symbols show the mean, and bars show the 95% confidence intervals.

the 2 subsets of K/L grade, for both JSW loss (Figure 1) and progression of OA (Figure 2).

**DISCUSSION**

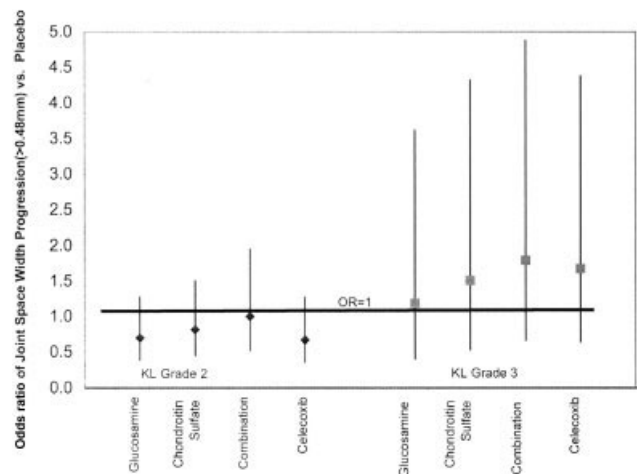
This study assessed radiographic outcomes in OA of the knee in patients being treated with glucosamine, CS, glucosamine plus CS, celecoxib, or placebo. Over 2 years, no treatment achieved the predefined clinically important difference from placebo in terms of JSW loss. The power of the study was limited by a smaller than anticipated sample size, increased variability of measurement, and a smaller than expected loss in JSW.

Controlled studies have demonstrated slowing of JSW loss among patients receiving glucosamine (17,18). In particular, in a long-term study by Reginster and colleagues, 106 glucosamine-treated patients and 106 placebo-treated patients were followed up for radiographic progression (18), with results indicating a mean JSW loss of 0.06 mm and 0.31 mm, respectively. When those authors defined progression as a JSW loss of >0.5 mm, twice as many progressors were observed in the placebo-treated group as in the glucosamine-treated group. A randomized trial by Pavelka et al examined 101 glucosamine-treated patients and 101 placebo-treated patients over 3 years (17). Those investigators found a mean JSW increase of 0.04 mm with glucosamine treatment and a decrease of 0.19 mm with placebo therapy. A

meta-analysis performed by Richy et al summarized these types of studies with respect to JSW loss and found an effect size of 0.41 SD units when patients were treated with glucosamine (25). Our glucosamine treatment group had 0.153 mm less JSW loss over 2 years as compared with the placebo group, yielding a smaller effect size of 0.25 SD units (26). In part, this may be related to the increased variability associated with multicenter trials.

Similar approaches have been used to examine the effect of CS on JSW loss (16,27–30). A meta-analysis performed by Reichenbach et al summarized the minimum JSW loss values from 5 trials that had included treatment with CS. Those authors found a mean effect size of 0.18 SD units, an effect size that was not clearly considered to be of clinical significance (31). In our study, the CS group had an even smaller effect size of 0.10 SD units, with 0.059 mm less JSW loss at 2 years.

No prior studies have examined the effects of the combination of glucosamine and CS on JSW loss, even though this is a combination therapy commonly taken by patients. Our study observed similar JSW loss in the combination treatment group compared with the placebo group, but the JSW loss was greater than that seen in patients treated with glucosamine or CS alone, raising the possibility of interference associated with their combined use. Pharmacokinetic studies have shown decreased absorption of glucosamine when given concur-



**Figure 2.** Odds ratio (OR) for the likelihood of progression of joint space width loss in the treatment groups relative to the placebo group, according to Kellgren/Lawrence (K/L) radiographic severity grade (K/L grade 2 versus K/L grade 3 knee osteoarthritis). Progression was defined as knees with a loss in JSW that exceeded 0.48 mm when compared with the baseline measurement. Symbols show the mean, and bars show the 95% confidence intervals.

rently with CS (32), which could effectively lower the blood levels of glucosamine. Alternatively, the higher proportion of subjects with K/L grade 3 knee OA who were treated with combination therapy might have altered the results; in general, K/L grade 3 knees demonstrated more progression and may have had less treatment benefit (Figures 1 and 2).

Patients treated with celecoxib might have been predicted to have more progression than placebo patients, since results from previous trials of nonsteroidal antiinflammatory agents have suggested that increased JSW loss occurs with their use (33); however, other trials have not yielded this finding (34,35). No significant difference between the celecoxib group and the placebo group was observed in the present trial, and the direction of the changes was consistent with those observed in the glucosamine or CS groups.

Although the optimal method of documenting disease progression in OA is unknown, the standard at present remains the measurement of JSW on plain radiographs (36–40). Many investigators believe that magnetic resonance imaging (MRI) may replace radiographs (41) in the future, especially if the substantial costs of MRI can be offset by a reduction in the required sample size and trial duration due to enhanced precision and sensitivity. When this study was designed, it was believed that weight-bearing, PA-based films had the best overall performance characteristics. Fluoroscopic guidance for placement was not used at the time of this trial, due to cost and the difficulty of standardization in a multicenter trial. The Buckland-Wright nonfluoroscopic MTP view was chosen to balance these issues and was considered to be adequate to detect a clinically important difference at 2 years of followup (10,12,42). In the time elapsed since the initiation of this trial, fluoroscopic methods have been tested and validated (36–38,43–45), and may now be considered more advantageous, even in multicenter trials (40,46), because they allow increased sensitivity for the detection of JSW loss, due to better alignment of the tibial plateau (6,39,44,47).

In this study, the rate of JSW loss over 2 years was less than the conservative estimate of 0.20 mm of JSW loss per year, determined with the radiographic technique available at the time of study design (9). Other recent, large studies have also demonstrated significantly less JSW loss. For example, Michel et al observed a JSW loss close to 0.1 mm/year in patients treated with CS (16), and a trial of risedronate demonstrated a JSW loss in the placebo group, using a fluoroscopically aligned MTP view, of only 0.088 mm per year in the European cohort, and 0.13 in the North American

cohort (21). These results are even smaller than the annual JSW loss of 0.14 mm observed in our placebo group. It is likely that the expected rate of loss differs according to the radiographic technique used, and is affected by the quality of the alignment of the tibial plateau, with better alignment associated with improved detection of JSW loss (40,44). Overall, it appears that a rate of progression of JSW loss of 0.1 mm/year should be used for planning of future OA radiographic progression studies.

Since a substantial number of individuals may experience little or no JSW loss, the mean loss may not even be the best measure to compare treatment groups (36,38). As in other trials (18,23), we defined progressors as those who experienced a JSW loss that was more than 3 times the mean SD of the standard error of measurement. Although we had a greater proportion of progressors using this definition in the placebo group (22.4%) than was reported in the placebo group of the risedronate study (14%) (21), the frequency of progression in the treatment groups was not statistically significantly different from that in the placebo group in our study. Overall, the order of effect was similar to that observed when progression was examined in the mixed-effects regression model.

Although the use of state-of-the-art statistical methods allowed us to utilize all of the collected data to obtain the most robust estimates of treatment effect possible, the power of this study was limited by several factors. First, the number of qualifying individuals whose followup films were considered acceptable was less than expected (i.e., 14.1% of patients were excluded because of this effect, rather than the expected 3–10% [36]). Second, the magnitude of JSW loss in the placebo group was less than anticipated from the literature at the time (0.14 mm/year versus a reported 0.2 mm/year [9]). Third, the variability of JSW measurement was larger than expected (0.16 mm versus a reported 0.09 mm in the available literature [11,12]). The SDs of JSW measurement from radiographs in the MTP view were 2–3 times the measured JSW differences in this study, the latter of which compare favorably to that obtained in other examinations of this technique (12) but are higher than the data available at the time that the study was designed. Although these factors limit the power of the present study, the results do provide valuable information for the design of future OA studies.

In summary, no therapy resulted in predefined thresholds for either statistically significant or clinically meaningful structural modification. The effect of the combination of glucosamine plus CS may be less active

than the effect of each treatment singly. The validity and mechanisms of this novel observation are uncertain but could be related to altered absorption of glucosamine. In future OA trials evaluating structural modification, K/L grade 2 knees may represent a more potentially responsive population; however, a larger sample size, longer study duration, and/or improved methods of measurement will be required, since the rate of JSW loss identified on plain radiographs is much slower than was previously recognized.

### ACKNOWLEDGMENTS

We would like to thank Drs. J. Christopher Buckland-Wright and Rupert Ward for their expert advice and for reworking the computer JSW measurement system to work with DICOM files, Ms Allison Sawitzke for scanning all of the films, and Drs. Julia Crim and Grant W. Cannon for reviewing all films for qualification and quality. We are indebted to McNeil Consumer and Specialty Pharmaceuticals (Fort Washington, PA) for donating acetaminophen; to Bioiberica, S.A. for donating sodium chondroitin sulfate; and to Ferro Pfanstiehl Laboratories (Waukegan, IL) for donating a portion of the glucosamine through Wilke Resources.

### AUTHOR CONTRIBUTIONS

Dr. Sawitzke had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Study design.** Sawitzke, Bingham, Jackson, Lane, Reda, Moskowitz, Williams, Clegg.

**Acquisition of data.** Sawitzke, Shi, Finco, Harris, Singer, Bradley, Silver, Jackson, Lane, Oddis, Wolfe, Lisse, Furst, Moskowitz, Clegg.

**Analysis and interpretation of data.** Sawitzke, Shi, Finco, Dunlop, Bingham, Harris, Bradley, Jackson, Lane, Wolfe, Furst, Reda, Moskowitz, Williams, Clegg.

**Manuscript preparation.** Sawitzke, Finco, Dunlop, Bingham, Harris, Singer, Bradley, Jackson, Lane, Wolfe, Furst, Reda, Moskowitz, Williams, Clegg.

**Statistical analysis.** Sawitzke, Shi, Finco, Dunlop, Reda, Clegg.

### REFERENCES

- Helmick CG, Felson DT, Lawrence RC, Gabriel S, Hirsch R, Kwoh CK, et al, for the National Arthritis Data Workgroup. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part I. *Arthritis Rheum* 2008;58:15–25.
- Lawrence RC, Felson DT, Helmick CG, Arnold LM, Choi H, Deyo RA, et al, for the National Arthritis Data Workgroup. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part II. *Arthritis Rheum* 2008;58:26–35.
- Felson DT, Lawrence RC, Dieppe PA, Hirsch R, Helmick CG, Jordan JM, et al. Osteoarthritis: new insights. Part 1: the disease and its risk factors. *Ann Intern Med* 2000;133:635–46.
- Brandt KD, Radin EL, Dieppe PA, van de Putte L. Yet more evidence that osteoarthritis is not a cartilage disease. *Ann Rheum Dis* 2006;65:1261–4.
- Wollheim FA. Early stages of osteoarthritis: the search for sensitive predictors. *Ann Rheum Dis* 2003;62:1031–2.
- Brandt KD, Mazzuca SA, Conrozier T, Dacre JE, Peterfy CG, Provvedini D, et al. Which is the best radiographic protocol for a clinical trial of a structure modifying drug in patients with knee osteoarthritis? *J Rheumatol* 2002;29:1308–20.
- Mazzuca SA, Brandt KD, Buckwalter KA, Lane KA, Katz BP. Field test of the reproducibility of the semiflexed metatarsophalangeal view in repeated radiographic examinations of subjects with osteoarthritis of the knee. *Arthritis Rheum* 2002;46:109–13.
- Ravaud P, Giraudeau B, Auleley GR, Drape JL, Rousselin B, Paolozzi L, et al. Variability in knee radiographing: implication for definition of radiological progression in medial knee osteoarthritis. *Ann Rheum Dis* 1998;57:624–9.
- Lequesne M, Brandt K, Bellamy N, Moskowitz R, Menkes CJ, Pelletier JP, et al. Guidelines for testing slow acting drugs in osteoarthritis. *J Rheumatol Suppl* 1994;41:65–71.
- Buckland-Wright JC, Wolfe F, Ward RJ, Flowers N, Hayne C. Substantial superiority of semiflexed (MTP) views in knee osteoarthritis: a comparative radiographic study, without fluoroscopy, of standing extended, semiflexed (MTP), and schuss views. *J Rheumatol* 1999;26:2664–74.
- Wolfe F, Lane NE, Buckland-Wright C. Radiographic methods in knee osteoarthritis: a further comparison of semiflexed (MTP), schuss-tunnel, and weight-bearing anteroposterior views for joint space narrowing and osteophytes. *J Rheumatol* 2002;29:2597–601.
- Buckland-Wright JC, Ward RJ, Peterfy C, Mojcik CF, Leff RL. Reproducibility of the semiflexed (metatarsophalangeal) radiographic knee position and automated measurements of medial tibiofemoral joint space width in a multicenter clinical trial of knee osteoarthritis. *J Rheumatol* 2004;31:1588–97.
- Clegg DO, Reda DJ, Harris CL, Klein MA, O'Dell JR, Hooper MM, et al. Glucosamine, chondroitin sulfate, and the two in combination for painful knee osteoarthritis. *N Engl J Med* 2006;354:795–808.
- McAlindon TE, LaValley MP, Gulin JP, Felson DT. Glucosamine and chondroitin for treatment of osteoarthritis: a systematic quality assessment and meta-analysis. *JAMA* 2000;284:1469–75.
- Jordan KM, Arden NK, Doherty M, Bannwarth B, Bijlsma JW, Dieppe P, et al. EULAR Recommendations 2003: an evidence based approach to the management of knee osteoarthritis: report of a Task Force of the Standing Committee for International Clinical Studies Including Therapeutic Trials (ESCISIT). *Ann Rheum Dis* 2003;62:1145–55.
- Michel BA, Stucki G, Frey D, De Vathaire F, Vignon E, Bruehlmann P, et al. Chondroitins 4 and 6 sulfate in osteoarthritis of the knee: a randomized, controlled trial. *Arthritis Rheum* 2005;52:779–86.
- Pavelka K, Gatterova J, Olejarova M, Machacek S, Giacovelli G, Rovati LC. Glucosamine sulfate use and delay of progression of knee osteoarthritis: a 3-year, randomized, placebo-controlled, double-blind study. *Arch Intern Med* 2002;162:2113–23.
- Reginster JY, Deroisy R, Rovati LC, Lee RL, Lejeune E, Bruyere O, et al. Long-term effects of glucosamine sulphate on osteoarthritis progression: a randomised, placebo-controlled clinical trial. *Lancet* 2001;357:251–6.
- Kellgren JH, Lawrence JS. Radiological assessment of osteoarthritis. *Ann Rheum Dis* 1957;16:494–502.
- Rosset A, Spadola L, Ratib O. OsiriX: an open-source software for navigating in multidimensional DICOM images. *J Digit Imaging* 2004;17:205–16.
- Buckland-Wright JC, Messent EA, Bingham CO III, Ward RJ, Tonkin C. A 2 yr longitudinal radiographic study examining the effect of a bisphosphonate (risedronate) upon subchondral bone loss in osteoarthritic knee patients. *Rheumatology (Oxford)* 2007;46:257–64.
- Mazzuca SA, Brandt KD, Katz BP, Lane KA, Buckwalter KA.

- Comparison of quantitative and semiquantitative indicators of joint space narrowing in subjects with knee osteoarthritis. *Ann Rheum Dis* 2006;65:64–8.
23. Bingham CO III, Buckland-Wright JC, Garner P, Cohen SB, Dougados M, Adami S, et al. Risedronate decreases biochemical markers of cartilage degradation but does not decrease symptoms or slow radiographic progression in patients with medial compartment osteoarthritis of the knee: results of the two-year multinational knee osteoarthritis structural arthritis study. *Arthritis Rheum* 2006;54:3494–507.
  24. Hochberg Y, Tamhane AC. Multiple comparison procedures. New York: John Wiley & Sons; 1987.
  25. Richy F, Bruyere O, Ethgen O, Cucherat M, Henrotin Y, Reginster JY. Structural and symptomatic efficacy of glucosamine and chondroitin in knee osteoarthritis: a comprehensive meta-analysis. *Arch Intern Med* 2003;163:1514–22.
  26. Kazis LE, Anderson JJ, Meenan RF. Effect sizes for interpreting changes in health status. *Med Care* 1989;27(3 Suppl):S178–89.
  27. Conrozier T. Anti-arthritis treatments: efficacy and tolerance of chondroitin sulfates (CS 4&6). *Presse Med* 1998;27:1862–5. In French.
  28. Malaise MG, Marcolongo R, Uebelhart D, Vignon E. Efficacy and tolerability of 800 mg chondroitin 4&6 sulfate in the treatment of knee osteoarthritis: a randomised, double-blind, multicentre study versus placebo. *Litera Rheumatologica* 1999;24:21–30.
  29. Uebelhart D, Thonar EJ, Delmas PD, Chantraine A, Vignon E. Effects of oral chondroitin sulfate on the progression of knee osteoarthritis: a pilot study. *Osteoarthritis Cartilage* 1998;6 Suppl A:39–46.
  30. Kahan A. STOPP (Study on Osteoarthritis Progression Prevention): a new two-year trial with chondroitin 4&6 sulfate (CS) [abstract]. European League Against Rheumatism: Abstracts from the 2006 Annual Scientific Meeting. URL: [www.ibsa-ch.com/eular-2006.amsterdam-vignon-2.pdf](http://www.ibsa-ch.com/eular-2006.amsterdam-vignon-2.pdf).
  31. Reichenbach S, Sterchi R, Scherer M, Trelle S, Burgi E, Burgi U, et al. Meta-analysis: chondroitin for osteoarthritis of the knee or hip. *Ann Intern Med* 2007;146:580–90.
  32. Jackson CG, Plaas AH, Barkhill JG, Harris CL, Clegg DO. The pharmacokinetics of oral glucosamine and chondroitin sulfate in humans [abstract]. *Arthritis Rheum* 2005;52:4062–3.
  33. Rashad S, Revell P, Hemingway A, Low F, Rainsford K, Walker F. Effect of non-steroidal anti-inflammatory drugs on the course of osteoarthritis. *Lancet* 1989;2:519–22.
  34. Williams HJ, Ward JR, Egger MJ, Neuner R, Brooks RH, Clegg DO, et al. Comparison of naproxen and acetaminophen in a two-year study of treatment of osteoarthritis of the knee. *Arthritis Rheum* 1993;36:1196–206.
  35. Tindall EA, Sharp JT, Burr A, Katz TK, Wallemark CB, Verburg K, et al. A 12-month, multicenter, prospective, open-label trial of radiographic analysis of disease progression in osteoarthritis of the knee or hip in patients receiving celecoxib. *Clin Ther* 2002;24:2051–63.
  36. Cline GA, Meyer JM, Stevens R, Buckland-Wright C, Peterfy C, Beary JF. Comparison of fixed flexion, fluoroscopic semi-flexed and MTP radiographic methods for obtaining the minimum medial joint space width of the knee in longitudinal osteoarthritis trials. *Osteoarthritis Cartilage* 2006;14 Suppl A:A32–6.
  37. Buckland-Wright C. Review of the anatomical and radiological differences between fluoroscopic and non-fluoroscopic positioning of osteoarthritic knees. *Osteoarthritis Cartilage* 2006;14 Suppl A:A19–31.
  38. Nevitt MC, Sharma L. OMERACT workshop radiography session 1. *Osteoarthritis Cartilage* 2006;14 Suppl A:A4–9.
  39. Mazzuca SA, Brandt KD, Buckwalter KA. Detection of radiographic joint space narrowing in subjects with knee osteoarthritis: longitudinal comparison of the metatarsophalangeal and semi-flexed anteroposterior views. *Arthritis Rheum* 2003;48:385–90.
  40. Brandt KD. Translating osteoarthritis into numbers: the importance of alignment in knee radiography for clinical trials of structure-modifying drugs [editorial]. *Arthritis Rheum* 2005;52:1343–5.
  41. Amin S, LaValley MP, Guermazi A, Grigoryan M, Hunter DJ, Clancy M, et al. The relationship between cartilage loss on magnetic resonance imaging and radiographic progression in men and women with knee osteoarthritis. *Arthritis Rheum* 2005;52:3152–9.
  42. Dupuis DE, Beynon BD, Richard MJ, Novotny JE, Skelly JM, Cooper SM. Precision and accuracy of joint space width measurements of the medial compartment of the knee using standardized MTP semi-flexed radiographs. *Osteoarthritis Cartilage* 2003;11:716–24.
  43. Mazzuca SA, Brandt KD, Buckwalter KA, Lequesne M. Pitfalls in the accurate measurement of joint space narrowing in semiflexed, anteroposterior radiographic imaging of the knee. *Arthritis Rheum* 2004;50:2508–15.
  44. Conrozier T, Mathieu P, Piperno M, Favret H, Colson F, Vignon M, et al. Selection of knee radiographs for trials of structure-modifying drugs in patients with knee osteoarthritis: a prospective, longitudinal study of Lyon schuss knee radiographs with the definition of adequate alignment of the medial tibial plateau. *Arthritis Rheum* 2005;52:1411–7.
  45. Le Graverand MP, Mazzuca S, Lassere M, Guermazi A, Pickering E, Brandt K, et al. Assessment of the radioanatomic positioning of the osteoarthritic knee in serial radiographs: comparison of three acquisition techniques. *Osteoarthritis Cartilage* 2006;14 Suppl A:A37–43.
  46. Hunter DJ, Zhang YQ, Niu JB, Tu X, Amin S, Clancy M, et al. The association of meniscal pathologic changes with cartilage loss in symptomatic knee osteoarthritis. *Arthritis Rheum* 2006;54:795–801.
  47. Vignon E, Piperno M, Le Graverand MP, Mazzuca SA, Brandt KD, Mathieu P, et al. Measurement of radiographic joint space width in the tibiofemoral compartment of the osteoarthritic knee: comparison of standing anteroposterior and Lyon schuss views. *Arthritis Rheum* 2003;48:378–84.