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Glucosamine Sulfate in the Treatment of Knee Osteoarthritis Symptoms

A Randomized, Double-Blind, Placebo-Controlled Study Using Acetaminophen as a Side Comparator

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Objective. **To assess the effects of the prescription formulation of glucosamine sulfate (1,500 mg administered once daily) on the symptoms of knee osteoarthritis (OA) during a 6-month treatment course.**

Methods. **Three hundred eighteen patients were enrolled in this randomized, placebo-controlled, double-blind trial in which acetaminophen, the currently preferred medication for symptomatic treatment of OA, was used as a side comparator. Patients were randomly assigned to receive oral glucosamine sulfate 1,500 mg once daily (n = 106), acetaminophen 3 gm/day (n = 108), or placebo (n = 104). The primary efficacy outcome measure was the change in the Lequesne index after 6 months. Secondary parameters included the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and response according to the Osteoarthritis Research Society International criteria. These outcome measures were assessed using an intent-to-treat analysis.**

Results. **At baseline, the study patients had moderately severe OA symptoms (mean Lequesne index ~11 points). Glucosamine sulfate was more effective than placebo in improving the Lequesne score, with a final decrease of 3.1 points, versus 1.9 with placebo (difference between glucosamine sulfate and placebo −1.2 [95% confidence interval −2.3, −0.8]) ($P = 0.032$). The 2.7-point decrease with acetaminophen was not significantly different from that with placebo (difference −0.8 [95% confidence interval −1.9, 0.3]) ($P = 0.18$). Similar results were observed for the WOMAC. There were more responders to glucosamine sulfate (39.6%) and acetaminophen (33.3%) than to placebo (21.2%) ($P = 0.004$ and $P = 0.047$, respectively, versus placebo). Safety was good, and was comparable among groups.**

Conclusion. **The findings of this study indicate that glucosamine sulfate at the oral once-daily dosage of 1,500 mg is more effective than placebo in treating knee OA symptoms. Although acetaminophen also had a higher responder rate compared with placebo, it failed to show significant effects on the algofunctional indexes.**

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Current treatment options for osteoarthritis (OA) include both nonpharmacologic and pharmacologic interventions (1,2). Published evidence-based recommendations for the treatment of knee OA (3) have attributed to oral glucosamine sulfate the highest level of evidence and strength of recommendation as a pharmacologic intervention, acknowledging the high quality of the trials performed; only 6 of 34 therapeutic interventions considered were ascribed the same degree of evidence and recommendation as glucosamine sulfate (3). Two 3-year clinical trials have independently provided evidence of efficacy in the long-term management of knee OA symptoms, and their results suggested that glucosamine sulfate may potentially delay joint structure changes in OA (4,5).

While the glucosamine sulfate substance and formulation used in those studies is a prescription drug in continental Europe and elsewhere, many glucosamine salts (e.g., glucosamine hydrochloride), formulations, and dosages are available as dietary supplements in the US, due to different regulations (6). In some studies using different glucosamine preparations (7,8), the favorable results in terms of symptom modification obtained in former trials, in which the prescription formulation was used, were not replicated. This drew attention to the pharmaceutical and pharmacologic differences, as noted in a recent Cochrane review (9), and to the limitations in study design (10) as possible explanations for the conflicting results.

Two recent randomized, controlled, double-blind trials have assessed the efficacy of different glucosamine preparations, compared with placebo, in the management of knee OA symptoms over a medium-term treatment course. Both studies used an active medication as a side comparator. In the Glucosamine/Chondroitin Arthritis Intervention Trial (GAIT study) celecoxib was used as the side comparator, while in the Glucosamine Unum In Die (once-a-day) Efficacy (GUIDE) trial acetaminophen was used, the latter being the currently preferred symptomatic medication in OA (2,3). The GAIT study was sponsored by the National Institutes of Health (NIH) and conducted in the US with glucosamine hydrochloride at a dosage of 500 mg 3 times daily, whereas the GUIDE trial is an industry-sponsored study conducted in Europe with the glucosamine sulfate prescription formulation of 1,500 mg once daily. Preliminary results of both studies were presented in 2005 (11,12), and the GAIT study report was recently published as a full article(13). We report herein the final results of the GUIDE trial.

PATIENTS AND METHODS

Study design. The GUIDE trial was conducted according to a prospective, randomized, placebo- and reference-controlled, double-blind, double-dummy, parallel-group design, in 13 rheumatology referral centers in Spain and Portugal. The study protocol was approved by the institutional review board of each participating center, and patients provided their written informed consent to participate. During the baseline period after screening, the results of routine laboratory tests were collected, radiographic assessments were conducted (if not performed during the previous 3 months), and symptomatic medications currently being taken were discontinued. Patients were then randomly assigned to 1 of the 3 treatment arms, i.e., glucosamine sulfate, acetaminophen, or placebo. Clinic visits were carried out after 15 days of treatment and then at monthly intervals from the time of randomization until the end of the 6-month treatment course.

Patient selection. Male and female outpatients who were seen in rheumatology clinics at the participating centers were selected if they had been diagnosed as having primary symptomatic knee OA (in 1 or both knees) according to the clinical and radiographic criteria of the American College of Rheumatology (14), and did not meet standard criteria for exclusion (15). Enrollment of patients who were obese (body mass index [BMI] >30 kg/m^2) was discouraged by the study protocol, to avoid any bias introduced by this factor. Disease stage was determined based on the Kellgren/Lawrence radiographic system (16) (either grade II or grade III as a condition of enrollment), and symptom severity was quantified with the algofunctional indexes selected as outcome measures (see below).

Treatment, blinding, and randomization. Crystalline glucosamine sulfate is a chemically well-characterized pure substance in which glucosamine, sulfate, chloride, and sodium ions are present in stoichiometric ratios of 2:1:2:2, and it is approved as a prescription drug in >45 countries (Dona, Viartril-S, Xicil, and other trade names of the Rottapharm Group, Monza, Italy); it is also available as a branded dietary supplement in the US (Dona). The product was used in its once-daily formulation (sachets of powder for oral solution, containing 1,500 mg of glucosamine sulfate). Acetaminophen was administered in 1-gm tablets 3 times per day, for a total daily dosage of 3 gm (the recommended daily dosage in Europe) (15).

Patients receiving either of the 2 active treatments also received placebo for the other medication, while controls received double placebo consisting of once-daily sachets and 3-times-a-day tablets. The double-dummy placebo formulations were identical in appearance to the active medications, but contained only inactive excipients. Treatment compliance was checked at clinic visits by patient interview and by counting the number of unused doses of the study medications.

A block randomization list was generated by computer and was maintained by individuals who had no contact with investigators who assigned patients to their randomized treatments, performed any patient assessment, or conducted the statistical analysis. The block size was also kept secret to maintain blinding; each block consisted of only 3 patients, to avoid imbalances in treatment allocation at each clinical site. Patients were sequentially assigned their randomization number at each site, and the individual code was kept in single-

sealed, opaque envelopes to be opened only in case of a medical emergency. Double-blinding conditions were successfully achieved for all patients.

The pure analgesic acetaminophen was the side comparator treatment in the GUIDE study, and therefore it could not be used as a rescue medication as is the common procedure in OA clinical trials (15). Thus, the rescue medication consisted of the conventional nonsteroidal antiinflammatory drug (NSAID) ibuprofen, in 400-mg tablets. To avoid confounding in the efficacy assessments, the use of the rescue medication in case of persistent pain was carefully standardized according to the following sequential instructions: 1) leave the painful joint at rest for at least 1 hour; 2) take 1 ibuprofen tablet every 8 hours; 3) limit intake to a maximum of 3 days; 4) if needed, resume the rescue medication intake after a washout period of at least 7 days; and 5) in all cases, suspend any use of the rescue medication at least 7 days before a clinic visit. The use of rescue ibuprofen was recorded in a patient daily diary.

Prior analgesic (narcotic and non-narcotic) or antiinflammatory symptomatic medications, including topical agents, were discontinued for the duration of at least 5 half-lives or 72 hours, whichever was longer, before randomization and were prohibited during the study. The recommended duration of washout prior to randomization was at least 3 months for corticosteroids and 6 months for glucosamine or other drugs considered specific for OA. These and any other agents for the treatment of this condition were prohibited throughout the study. Physical and/or occupational therapy were allowed if the regimen had been stable for at least 3 months prior to randomization.

Assessment of efficacy. The Lequesne algofunctional index of severity for OA of the knee (17) was used for sample size calculation and was designated as the primary efficacy outcome in the GUIDE trial. It is a disease-specific, aggregated multidimensional index consisting of 5 questions addressing knee pain, 4 questions on knee function in activities of daily living, and a scale of maximum distance walked. The worst possible total index score is 24, but disease is considered extremely severe if the score is >13 (17). At randomization, after washout of previous symptomatic medications, patients had to have a Lequesne score that was at least as high as the score at the screening visit. For continuation in the study protocol, this score had to be ≥ 4, corresponding to at least mild-to-moderate disease severity (17).

The secondary efficacy end points were the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) (18) and the Osteoarthritis Research Society International (OARSI) responder criteria (19). The 0–4-point Likert scale (LK 3.0) WOMAC version was used, addressing severity of knee pain (5 questions), limitation of physical function (17 questions), and stiffness (2 questions) in the 48 hours before assessment. The worst possible scores on the WOMAC subscales are therefore 20, 68, and 8 in the 3 domains, respectively, and can be used to normalize the Likert scores to a 0–100 scale, i.e., similar to a 100-mm visual analog scale (VAS) (18). The OARSI-A responder criteria for oral OA-specific drugs consist of a dichotomous outcome measure that defines as responders those patients with either a high degree of improvement in pain (at least 55% relative change on the WOMAC pain subscale, with an absolute change of at least 30 on a 0–100 standardized scale) or moderate improvement in 2 of the 3 domains of pain, function (on the WOMAC physical function subscale), and patient global assessment (35%, 15%, and 15% relative changes, with 10, 20, and 15 standardized units of absolute change, respectively).

Additional efficacy outcomes included the OARSI-B responder criteria (high degree of improvement in pain or function, or moderate improvement in 2 of the 3 domains listed above) (19) and the proportion of patients reporting at least minimal clinically important improvement (MCII) or reaching the patient acceptable symptom state (PASS) in pain and function based on the WOMAC subscales, as recently described (20,21).

Assessment of safety. Reporting of adverse events was elicited with a nonleading question during clinic visits. All events were coded according to the Medical Dictionary for Regulatory Activities, as currently required by all regulatory authorities including the US Food and Drug Administration and the European Agency for the Evaluation of Medicinal Products. Routine laboratory tests, including measurement of serum glucose levels for estimating effects on glucose homeostasis and administration of liver function tests, were performed at enrollment and after 3 months and 6 months of treatment.

Statistical analysis. The primary comparison in this study was between glucosamine sulfate and placebo. The sample size was calculated on the basis of the difference between glucosamine sulfate and placebo in the change in the Lequesne index from baseline to end of treatment, which was at least 1 point in previous trials (9,22). With such a simulated difference, a standard deviation of the mean response of 2.25, a Type I error of 5%, and a Type II error of 20%, a sample size of 80 patients per group was calculated (23), and this was increased to at least 100 patients per group to take into account an expected dropout rate of $\sim$30%. The size of the group receiving acetaminophen was also set at 100 patients.

The GUIDE is a regulatory trial agreed upon by the sponsor (Rottapharm) and the relevant health authorities. Following protocol approval and implementation, the statistical analysis protocol was planned by the sponsor in June 2001. It was amended in December 2004, prior to database lock, only to add the MCII and PASS assessments that had become available in the summer of the same year (20,21).

The primary efficacy analysis performed was assessment of the difference between groups in the change from baseline in the Lequesne index after 6 months, in the intent-to-treat (ITT) population (i.e., including all randomized patients with at least 1 efficacy assessment after randomization). The last observation carried forward (LOCF) approach was used for patients who did not complete the study according to the protocol. A per-protocol completer analysis was also performed. To assess the differences between each of the active groups (glucosamine sulfate or acetaminophen) and placebo, a general linear model approach was applied in one-way analysis of variance, with treatments as fixed effect and application of Dunnett's 2-tailed test to adjust for multiple pairwise comparisons. Results were expressed as the difference between final group means and 95% confidence intervals (adjusted for multiple comparisons). In addition, the magnitude of each treatment effect was described as effect size, i.e., the difference between the mean change from baseline with the active drug and with placebo, divided by the pooled standard deviation (24).The same analysis was performed on the secondary efficacy outcome represented by the WOMAC,

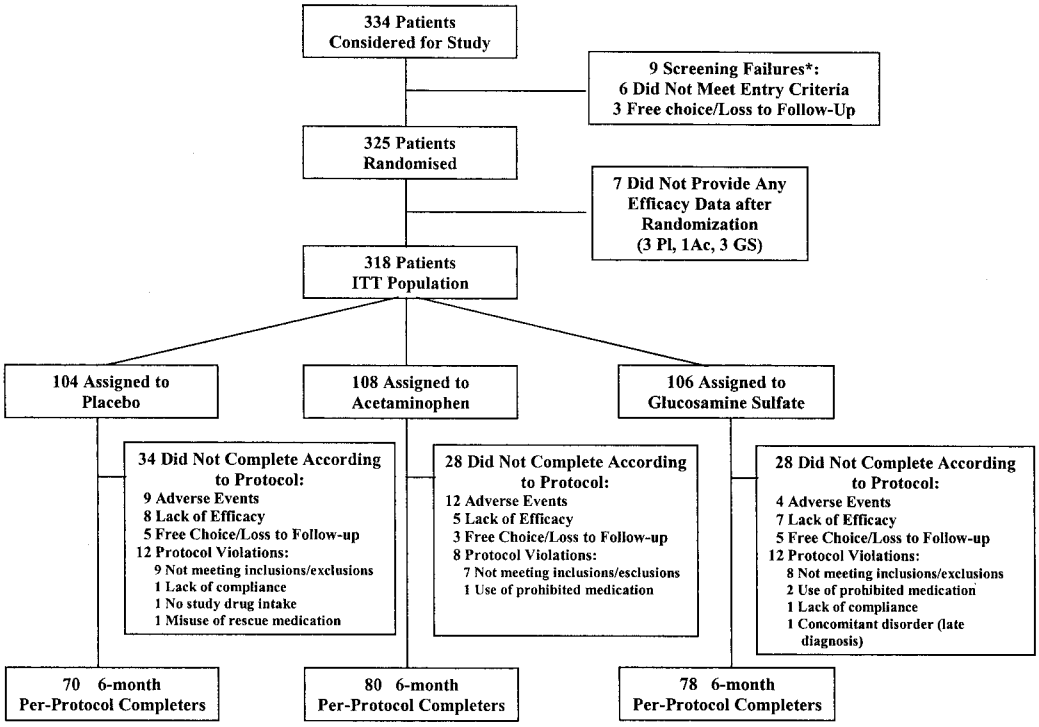

Figure 1. Study profile. * = patients who agreed to baseline evaluation but did not qualify for randomization. Pl = placebo; Ac = acetaminophen; GS = glucosamine sulfate; ITT = intent-to-treat.

while the difference between each active group and placebo in the proportion of OARSI-A responders in the ITT population was analyzed by 2-tailed chi-square test. The chi-square test was also used to compare each active group with placebo for the proportion of ITT patients satisfying the additional efficacy parameters, in the following order: OARSI-B responders, pain MCII, function MCII, pain PASS, and function PASS. To adjust for the multiplicity represented by the 2 active group comparisons with placebo for the dichotomous secondary outcome (OARSI-A) and additional efficacy parameters, the sequentially rejective Bonferroni method was applied, setting α at 0.05 divided by the number (n) of comparisons (0.05/2 = 0.025) for the lowest P value obtained in the 2 comparisons, and $\alpha = 0.05/(n - 1)$ (0.05/1 = 0.05) for the second comparison if the first yielded a significant result (25,26).

To achieve meaningful comparisons across groups over a standardized period, the use of the rescue medication was assessed in per-protocol completers over the 6-month treatment course. The mean number of days of use was tabulated for descriptive purposes, with calculation of the daily average ibuprofen tablet consumption, while the proportion of patients with any use of the rescue medication was compared between each active treatment group and the placebo group, by chi-square test.

RESULTS

Recruiting started in May 2000, and the last followup was performed in December 2002. Most of the patients considered for the study could be randomized. Seven patients did not provide any efficacy data after randomization and were not included in the analysis, leaving a total of 318 patients in the ITT population (Figure 1). Twenty-six percent of the patients receiving glucosamine sulfate or acetaminophen did not complete the 6-month treatment period according to the study protocol, compared with 33% of the patients in the placebo group.

There were no significant differences in the reasons for dropout (Figure 1). The acetaminophen group tended to have a higher number of dropouts due to adverse events, but there was a trend in this group toward fewer withdrawals due to other reasons; these observations are probably of minor clinical significance given the low number of events. Protocol deviations consisted mainly of patients not meeting some of the inclusion/exclusion criteria (mostly presence of concomitant diseases, insufficient symptom severity, or violation of required demographic characteristics); these patients were therefore withdrawn early from the protocol and were then assigned a negative efficacy outcome, often corresponding to no change from baseline. Other reasons for withdrawal were evenly distributed throughout

Table 1. Number of patients withdrawn from the protocol after each study visit

Time point	Treatment		
	Placebo (n = 104)	Acetaminophen (n = 108)	Glucosamine sulfate (n = 106)
Randomization	9	9	10
15 days	6	10	6
1 month	3	2	1
2 months	3	2	4
3 months	4	–	3
4 months	6	2	1
5 months	3	3	3

the study. The number of patients, by treatment group, who were withdrawn from the protocol at each study visit is shown in Table 1.

The demographic and clinical characteristics of the randomized patients were comparable at baseline (Table 2). As expected, the majority of patients were female. The mean age was between 60 and 65 years. On average, patients were overweight, and 5% of them were obese (BMI >30 kg/m^2). The mean duration of knee OA was ~7 years, and slightly more than half of the patients had a Kellgren/Lawrence radiographic grade of 2, although grading of 2 or 3 was not firmly assigned to ~10% of the patients. Inflammatory joint disease was an exclusion criterion, but signs of modest inflammation, i.e., mild joint effusion, were present in 12–15% of the patients. The mean Lequesne index score at baseline was

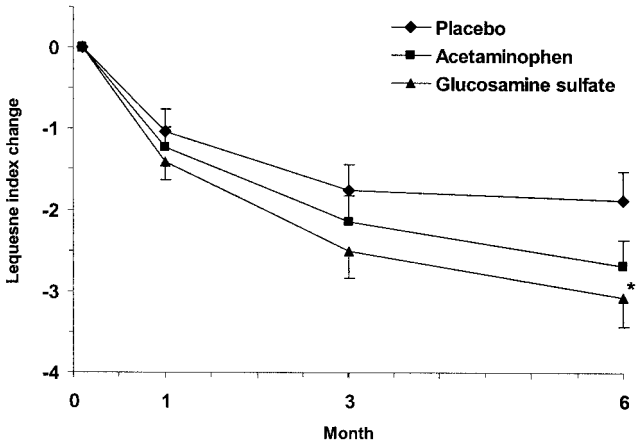

Figure 2. Mean and SEM changes in the Lequesne index after 1, 3, and 6 months of treatment, in the intent-to-treat population (n = 104 in the placebo group, 108 in the acetaminophen group, and 106 in the glucosamine sulfate group). * = $P = 0.032$ versus placebo.

~11, indicating disease with moderate symptom severity. This was confirmed by the baseline WOMAC pain and function subscale scores, which averaged ~40 when normalized to a 0–100 scale (i.e., similar to 40 mm on a 100-mm VAS).

Compliance with the study medication regimen was good in all treatment groups. In trial completers, the rate of compliance was >95%.

The changes in the Lequesne index after 1, 3, and 6 months of treatment in the ITT population are reported in Figure 2. The primary outcome measure was

Table 2. Demographic and baseline clinical characteristics of patients in the intent-to-treat population*

	Treatment		
	Placebo (n = 104)	Acetaminophen (n = 108)	Glucosamine sulfate (n = 106)
Women, no. (%)	89 (86)	93 (86)	96 (91)
Age, years	64.5 ± 7.2	63.8 ± 6.9	63.4 ± 6.9
Body mass index, kg/m^2	27.6 ± 2.4	27.9 ± 2.3	27.7 ± 2.3
Duration of knee osteoarthritis, years	7.2 ± 5.8	6.5 ± 5.3	7.4 ± 6.0
Mild knee joint effusion, no. (%)	13 (13)	16 (15)	13 (12)
Kellgren/Lawrence grade, no. (%)			
2	52 (50)	61 (56)	53 (50)
3	41 (39)	34 (31)	43 (41)
2/3 unspecified	11 (11)	13 (12)	10 (9)
Lequesne index	10.8 ± 2.6	11.1 ± 2.7	11.0 ± 3.1
WOMAC score			
Total	37.9 ± 14.3	40.4 ± 14.8	38.3 ± 15.2
Pain	7.9 ± 3.0	8.0 ± 2.9	7.8 ± 3.0
Function	27.2 ± 10.9	29.4 ± 11.0	27.8 ± 11.4

* Except where indicated otherwise, values are the mean ± SD. WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

Table 3. Mean (95% confidence interval) change from baseline in the primary outcome measure (Lequesne index) and the secondary outcome measure (WOMAC)*

	Intent-to-treat population			Per-protocol completers		
	Placebo (n = 104)	Acetaminophen (n = 108)	Glucosamine sulfate (n = 106)	Placebo (n = 70)	Acetaminophen (n = 80)	Glucosamine sulfate (n = 78)
Lequesne index						
Change	−1.9 (−2.6, −1.2)	−2.7 (−3.3, −2.1)	−3.1 (−3.8, −2.3)	−2.8 (−3.6, −2.0)	−3.6 (−4.2, −3.0)	−4.3 (−5.1, −3.6)
Difference vs. placebo	–	−0.8 (−1.9, 0.3)	−1.2 (−2.3, −0.8)	–	−0.7 (−1.9, 0.4)	−1.5 (−2.6, −3.1)
P		0.18	0.032		0.26	0.01
WOMAC						
Total						
Change	−8.2 (−11.3, −5.1)	−12.3 (−14.9, −9.7)	−12.9 (−15.6, −10.1)	−11.7 (−15.1, −8.4)	−16.0 (−18.7, −13.4)	−17.3 (−20.3, −14.4)
Difference vs. placebo	–	−4.1 (−8.5, 0.4)	−4.7 (−9.1, −0.2)	–	−4.2 (−9.0, 0.4)	−5.6 (−10.4, −0.9)
P		0.08	0.039		0.08	0.018
Pain						
Change	−1.8 (−2.6, −1.1)	−2.4 (−3.0, −1.8)	−2.7 (−3.3, −2.1)	−2.4 (−3.3, −1.6)	−3.3 (−3.9, −2.7)	−3.8 (−4.5, −3.1)
Difference vs. placebo	–	−0.5 (−1.6, 0.5)	−0.9 (−1.9, 0.2)	–	−0.9 (−2.0, 0.3)	−1.4 (−2.5, −0.2)
P		0.41	0.12		0.16	0.014
Function						
Change	−5.5 (−7.7, −3.3)	−8.7 (−10.6, −6.8)	−9.2 (−11.2, −7.2)	−8.2 (−10.5, −5.8)	−11.3 (−13.3, −9.3)	−12.3 (−14.5, −10.0)
Difference vs. placebo	–	−3.2 (−6.5, −0.008)	−3.7 (−6.9, −0.5)	–	−3.1 (−6.6, 0.3)	−4.1 (−7.6, −0.6)
P		0.049	0.022		0.08	0.018

* *P* values and 95% confidence intervals of the differences versus placebo were derived by Dunnett's 2-tailed test with adjustment for multiple comparisons. WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

the 6-month change in the index. There was a change of almost −2 with placebo treatment, but the change was −3.1 with glucosamine sulfate ($P = 0.032$ versus placebo) (Table 3). The 2.7-point decrease in the acetaminophen group was not significantly different from the decrease observed with placebo ($P = 0.18$). For all 3 treatments, the degree of improvement in per-protocol completers was higher than that in the ITT population; compared with placebo, the difference in the degree of improvement was significant in the glucosamine sulfate group ($P = 0.01$), but not in the acetaminophen group ($P = 0.26$).

Similar results were observed for the secondary outcome measure represented by change in the WOMAC total index (Table 3), for which the difference between the glucosamine sulfate group and the placebo group was statistically significant in both the ITT and per-protocol analyses ($P = 0.039$ and $P = 0.018$, respectively). Conversely, the improvement observed with acetaminophen just failed to reach statistical significance when compared with placebo ($P = 0.08$ in both the ITT and per-protocol populations), although it was only marginally lower than that achieved with glucosamine sulfate. Both glucosamine sulfate and acetaminophen were significantly more effective than placebo in terms of improvement in the WOMAC function subscales, but for the WOMAC pain subscale, the difference from placebo, for both glucosamine sulfate and acetaminophen, failed to reach statistical significance in the ITT analysis. However, the better trend shown with glucosamine sulfate ($P = 0.12$ versus placebo in the ITT analysis) was statistically significant in per-protocol completers ($P = 0.014$). The small improvements in the low scores on the WOMAC stiffness subscale (<3 points on average at baseline) did not differ significantly among the 3 groups (data not shown).

As shown in Figure 3, the effect size of glucosamine sulfate relative to placebo was 0.32, based on the ITT analysis of the Lequesne index results. This effect size was similar to that for the WOMAC total index (0.31), and only slightly lower than that for the WOMAC function subscale (0.34). The effect sizes of glucosamine sulfate according to the per-protocol analysis were larger and exceeded 0.40 in all analyses. This included the WOMAC pain subscale, for which the ITT analysis yielded a small effect size of 0.25 with 95% confidence limits that crossed the zero line. Effect sizes in the acetaminophen group were smaller and, in most analyses, crossed the zero line.

As assessed using the OARSI-A responder criteria, which are characterized by high improvement in knee pain as the first threshold to qualify as a responder, the proportion of responders in the glucosamine sulfate group was almost 40%, i.e., 18.4% more than with placebo ($P = 0.004$) (Table 4). The response rate was also higher with acetaminophen than with placebo, with a difference of 12.1% ($P = 0.047$). When the OARSI-B responder criteria were considered, i.e., when the first threshold for response was a high degree of improvement in either knee pain or function, similar results were obtained for this additional efficacy outcome (Table 4).

Almost 50% of the patients in the glucosamine sulfate group reported a decrease in pain above the threshold for MCII, compared with slightly more than 30% of the patients treated with placebo ($P = 0.023$). More than 40% of the patients in the acetaminophen group achieved the MCII for pain, but the difference from placebo was not significant ($P = 0.11$). Conversely, the difference between acetaminophen and placebo was significant for the proportion of patients achieving the

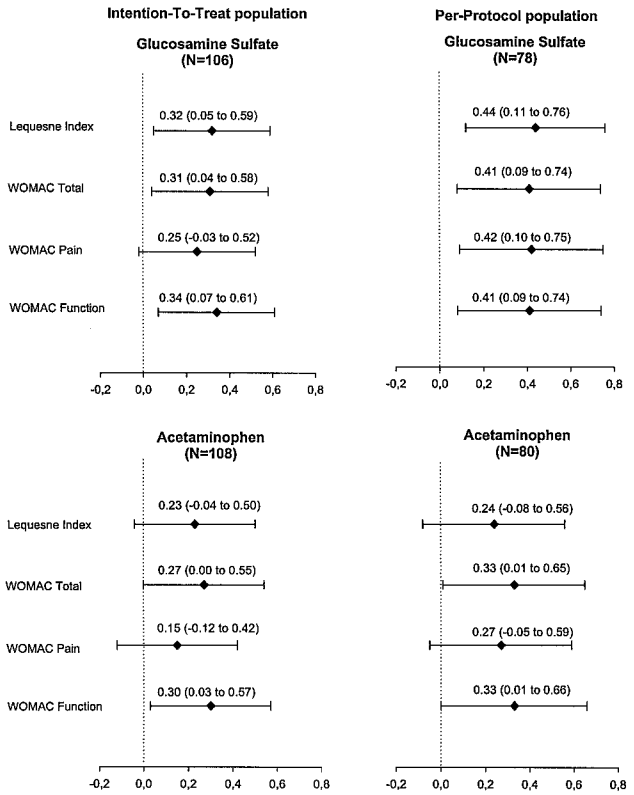

Figure 3. Effect size of glucosamine sulfate and acetaminophen in the intent-to-treat and per-protocol completer populations. Diamonds show the effect size point estimate; bars show the 95% confidence interval. WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

Table 4. Proportion of patients meeting the dichotomous secondary efficacy outcome measure (responders according to the OARSI-A criteria), or the additional efficacy outcome measures (OARSI-B responders, achievement of MCII in pain and function, or achievement of PASS in pain and function) at the end of treatment, in the intent-to-treat population*

	Treatment		
	Placebo (n = 104)	Acetaminophen (n = 108)	Glucosamine sulfate (n = 106)
OARSI-A responders	21.2	33.3 ($P = 0.047$)	39.6 ($P = 0.004$)
Additional outcome measures			
OARSI-B responders	19.2	32.4 ($P = 0.047$)	35.8 ($P = 0.004$)
Pain MCII	32.7	43.5 ($P = 0.11$)	48.1 ($P = 0.023$)
Function MCII	37.5	52.8 ($P = 0.025$)	55.7 ($P = 0.008$)
Pain PASS	46.2	54.6 ($P = 0.22$)	67.9 ($P = 0.001$)
Function PASS	43.3	54.6 ($P = 0.10$)	62.3 ($P = 0.006$)

* P values are versus placebo; all P values less than 0.05 are significant after correction for multiple comparisons according to the sequential Bonferroni method (see Patients and Methods). OARSI = Osteoarthritis Research Society International; MCII = minimal clinically important improvement; PASS = patient acceptable symptom state. See Patients and Methods for explanation of OARSI-A and OARSI-B responder criteria.

MCII on the WOMAC function scale ($P = 0.025$), although the proportion of patients in the glucosamine sulfate group who reached this end point was even higher ($P = 0.008$ versus placebo). Indeed, PASS was achieved in well over 60% of the patients receiving glucosamine sulfate, with highly significant differences from the placebo group for pain (difference of 21.7% compared with placebo; $P = 0.001$) and function (difference of 19.0% compared with placebo; $P = 0.006$). The differences between the acetaminophen and placebo groups in these PASS outcomes did not reach statistical significance ($P = 0.22$ and $P = 0.10$, respectively).

When a sensitivity analysis was performed on the primary and the 2 principal secondary outcome measures, in which the 7 patients for whom there were no efficacy data after randomization were included (assigning to them no changes on all outcomes, according to the LOCF approach), the results were virtually identical and the differences between glucosamine sulfate and placebo were significant for all parameters (Lequesne index $P = 0.034$, WOMAC total index $P = 0.041$, and OARSI-A responder criteria $P = 0.004$). A significant difference between the acetaminophen group and the placebo group was again found only for the OARSI-A criteria ($P = 0.039$).

During the 6-month treatment period, the need for recourse to the rescue medication was low, occurring an average of 1 in every 5–6 days, with a mean consumption of 0.20–0.26 tablets of 400 mg ibuprofen per day across groups. Compared with the placebo group, there was a trend toward a lower number of days of use in the glucosamine sulfate and acetaminophen groups (both 28 days, versus 35 days with placebo). Only 9% of the completers in the placebo group did not use rescue medication at all, compared with 21% in the acetaminophen and 22% in the glucosamine sulfate group ($P = 0.045$ and $P = 0.027$, respectively, versus placebo).

The number of adverse events reported during treatment was similar in all 3 groups: 89 with placebo, 96 with acetaminophen, and 95 with glucosamine sulfate. The most frequent adverse events were of minor clinical significance and did not differ in frequency between groups. Table 5 summarizes the adverse events reported by at least 3 patients in any group. There were 5 serious adverse events in the placebo group (precordial chest pain, apnea, pneumonia, elective surgery, and lumbar pain), 5 in the acetaminophen group (atrial flutter, carpal tunnel syndrome, vertebral fracture, meniscus rupture, and crush injury), and 2 in the glucosamine sulfate group (meniscus rupture and elective surgery).

Routine laboratory examinations indicated that more patients in the acetaminophen group developed abnormalities in liver function (as reflected by levels of transaminases and gamma glutamyl transferase [GGT]); abnormalities were detected in 21 patients in the acetaminophen group versus 2 and 6 in the glucosamine sulfate and placebo groups, respectively. These abnormalities were the cause of study withdrawal after the 3-month assessment in only 2 patients, whose baseline values were found to be increased almost 2-fold above the normal range (alanine aminotransferase in 1 patient

Table 5. Summary of adverse events occurring in at least 3 patients in any group during treatment*

	No. of events		
	Placebo group	Acetaminophen group	Glucosamine sulfate group
Gastrointestinal disorders			
Dyspepsia	4	2	5
Abdominal pain	4	4	3
Diarrhea	4	4	3
Infections			
Respiratory tract infections	9	4	8
Gastroenteritis	2	0	4
Respiratory disorders			
Coughing and associated symptoms	0	4	1
Nervous system disorders			
Headache	4	6	2
Dizziness	1	4	1
Musculoskeletal disorders			
Back pain	5	4	7
Neck pain	0	2	3
Injuries			
Fall	2	3	5
Injury	0	4	2

* Adverse events are grouped by system organ class and reported as Medical Dictionary for Regulatory Activities (MedDRA) lower-level term except for respiratory tract infections and respiratory disorders, for which similar events were grouped under MedDRA high-level term.

receiving placebo) and almost 3-fold above the normal range (GGT in 1 patient receiving acetaminophen), respectively. Clinically significant abnormalities in GGT, i.e., levels 2–3 times above the upper reference limit, were found in an additional 2 patients receiving acetaminophen and 1 patient in the glucosamine sulfate group, but did not necessitate treatment withdrawal. The remaining abnormalities were mostly transient and mild (i.e., from slightly above the normal range to less than twice the maximum normal values) and were recorded as adverse events in only 2 patients taking acetaminophen. In no cases were these alterations judged to necessitate any particular followup that might have interfered with the study procedures or blinding.

Serum glucose levels were virtually unaltered in acetaminophen- and glucosamine sulfate–treated patients who completed the protocol and had both baseline and 6-month assessments (mean ± SD 99 ± 14 mg/dl at baseline and 99 ± 13 mg/dl at 6 months in the acetaminophen group, and 98 ± 15 mg/dl at both time points in the glucosamine sulfate group). A minimal increase was seen in patients receiving placebo (99 ± 15 at baseline and 102 ± 16 mg/dl at 6 months). Similarly, there was no clinically significant change in the serum glucose level in any individual patient, either among those who completed the protocol or among those in whom treatment was withdrawn. One patient taking placebo had an abnormal serum glucose level (132 mg/dl) at the time of screening and was withdrawn after 3 months because the level was still 139 mg/dl. There were no significant changes in other routine laboratory parameters.

DISCUSSION

The results of the GUIDE trial show that crystalline glucosamine sulfate, administered once daily at a dose equivalent to 1,500 mg glucosamine sulfate, is more effective than placebo in relieving knee OA symptoms. These data confirm the results obtained in previous long-term (3-year) clinical studies (4,5) and the general clinical trial experience with this particular glucosamine formulation (9). However, compared with these previous trials, the GUIDE is the first trial with this glucosamine preparation to be conducted over a 6-month treatment period, which is currently regarded to be the minimum trial duration for study of a symptomatic medication in OA (27). In addition, the study explored a complete panel of symptom outcomes and included an active medication, acetaminophen, as a side comparator.

According to current OA practice guidelines (2,3), acetaminophen is the oral analgesic that should be tried first and, if successful, the preferred long-term symptomatic medication, due to its safety profile and common use. For this reason, and not for its efficacy, acetaminophen was chosen as a side comparator in the present study. In fact, acetaminophen failed to show a statistically significant difference from placebo in the primary efficacy outcome (Lequesne algofunctional index of severity) and in some of the secondary end points, including pain outcomes. A marginally significant difference between acetaminophen and placebo was seen in function outcomes, and the response rate was higher in the acetaminophen group than in the placebo group. Conversely, glucosamine sulfate was significantly more effective than placebo in the primary and virtually all secondary efficacy outcomes, with a trend toward superiority compared with acetaminophen, although directly comparing these 2 active treatments was not an aim of the present study.

In most but not all previous trials, acetaminophen was globally more effective than placebo but less effective than NSAIDs in the treatment of OA pain, especially in patients whose pain was moderate to severe; acetaminophen and NSAIDs showed similar efficacy in patients with mild OA pain (28). In contrast, acetamin-

ophen exerted no significant effects on the Lequesne or WOMAC score (28), consistent with the present findings in the GUIDE study. It should be noted that the dosage of acetaminophen used in this study was 3 gm/day as is most commonly used in Europe, whereas up to 4 gm/day is usually advised in the US (15). The 4 gm daily dosage was used in the majority of previous clinical trials, and there are insufficient data to determine whether daily dosages of 3 gm and 4 gm have comparable effects; use of this lower dosage might have further compromised the efficacy of acetaminophen in the present study. On the other hand, safety considerations with regard to acetaminophen dosage selection also had to be taken into account, since there were no previous OA clinical trials in which acetaminophen at 4 gm/day had been administered for periods longer than 12 weeks (28) at the time the present trial was designed and conducted; in addition, the gastrointestinal safety of acetaminophen at >2 gm/day has been questioned (29).

The efficacy results observed with glucosamine sulfate in the present study were clinically relevant. The effect size on the primary outcome measure, represented by the Lequesne index, was 0.32 compared with placebo, while the minimal difference that is considered clinically relevant is achieved with an effect size of 0.20 (30). Effect sizes between 0.20 and 0.50 are considered "small" (30), but this is a common finding for interventions in OA. An effect size of 0.32 or lower was even described for NSAIDs for their principal use in knee OA, i.e., short-term pain relief, while the effect size was 0.29 for the reduction in functional disability (31). Unlike NSAIDs, glucosamine sulfate is not a drug for short-term analgesia, but is intended for medium- to long-term management of the disease. In this respect, the small but clinically relevant effect size on symptoms found in the GUIDE study, being of the magnitude observed with purely symptomatic medications administered on a short-term basis, further supports the long-term trial data (4,5).

The Lequesne index is a combined measure of pain and functional disability, in which pain parameters account for one-third of the total score and functional parameters for the rest (17). Glucosamine sulfate exhibited efficacy in all physical function outcome measures in the GUIDE study, with an effect size of 0.34 on the relevant WOMAC subscale. Therefore, functional improvement might be the main determinant of glucosamine sulfate's effectiveness in knee OA. However, efficacy of glucosamine sulfate was also demonstrated for several of the pain outcomes. In fact, although the improvement on the WOMAC pain subscale failed to reach statistical significance in comparison with placebo in the ITT population, the change was significant in per-protocol completers. Furthermore, the threshold for minimally clinically important improvement in pain (20) was reached by significantly more ITT patients in the glucosamine sulfate group, and almost 70% of them reported an acceptable pain state (21) at the end of the trial, with a significant difference from placebo (>20%). A nearly 20% difference from placebo was also found for the proportion of patients who were classified as treatment responders based on the OARSI composite pain and function criteria (19).

The results of GUIDE study are at variance with those of the recently reported GAIT study (13), in which glucosamine failed to show a significant difference in efficacy compared with placebo over a similar 6-month treatment period. However, the editorial accompanying the report of the GAIT study (32) states that this finding was not surprising given the nonconventional glucosamine preparation used in the NIH-sponsored study, which differed from the glucosamine sulfate formulation used in previous successful trials of glucosamine treatment and in the present study. Indeed, the regimen of glucosamine hydrochloride at a dosage of 500 mg 3 times per day used in the GAIT study (13) is not approved as a prescription formulation and was previously used in only 1 randomized controlled trial, which yielded mostly negative results (33).

The glucosamine sulfate prescription formulation used in the GUIDE trial and in most previous glucosamine trials, i.e., once-daily administration of 1,500 mg (4,5), yielded steady-state plasma and synovial fluid glucosamine concentrations in the 10 μM range (34,35). While these levels may be insufficient to directly stimulate the synthesis of cartilage glycosaminoglycans (36), they have been found to be effective in inhibiting interleukin-1–induced gene expression (37), which has been proposed as the most probable, although hypothetical, mechanism of action of glucosamine sulfate in OA (38). Conversely, the glucosamine hydrochloride preparation used in the GAIT study resulted in plasma glucosamine levels that were at least 3-fold lower (39) and therefore might have fewer pharmacologic effects.

In addition, while no relationship was found between OA development and fasting serum sulfate levels (40), sulfates have been suggested to be an important component of glucosamine's mechanism of action (41,42). Interestingly, the most significant results in the GAIT study were achieved in a subgroup analysis of patients with more severe symptoms when glucosamine hydrochloride was combined with chondroitin

sulfate (13), presumably increasing sulfate plasma levels (42), and possibly even levels of glucosamine metabolites, to concentrations closer to those achieved with the prescription glucosamine sulfate formulation used in the GUIDE trial.

The response to placebo in the GUIDE study ranged from 20–25% (for the primary end point and the responder rate) to 40–45% (for the additional efficacy outcomes). This placebo response rate was therefore in the expected range for OA trials and much lower than the rate of >60% observed in the GAIT trial (13). Such a high rate of response to placebo is difficult to interpret and might have partly clouded the results concerning efficacy of the experimental treatments in the GAIT study. OA trials are often add-on studies of test treatments with a rescue analgesic medication, whose indiscriminate use might increase the placebo response. The use of the rescue medication was strictly regulated in the present study, and this might account for its low consumption and the observed low rate of response to placebo.

A possible limitation of the present study may be the requirement of a 6-month washout from prior glucosamine sulfate use, since patients who had potentially had a poor response to previous glucosamine treatment would not be as willing to participate as those who had not previously been treated with this agent. However, appropriate washout from previous treatment is mandatory in clinical trials of compounds such as glucosamine sulfate, which are thought to have a persistent effect after drug withdrawal (43).

Among other possible limitations of the present study, it should be noted that although >90% of the patients were overweight (BMI 25–30 kg/m^2), only 5% were actually obese (BMI >30 kg/m^2), due to the protocol restrictions, and the average BMI was slightly lower than 28 kg/m^2. In most knee OA trials the average BMI is higher than this, and it was even >30 kg/m^2 in some North American trials, including, e.g., the GAIT study (13). This is due to the high prevalence of obesity among patients with symptomatic knee OA in the US. The results of the GUIDE trial therefore might not be generalizable to obese patients, and the effectiveness of glucosamine sulfate in such patients would require further assessment. We also enrolled a slightly higher proportion of female patients, i.e., almost 90% compared with almost 80% in previous glucosamine sulfate trials (4,5), but the results seem to have been in the same direction.

Additional differences in the study populations of the GUIDE and GAIT trials include genetic and ethnic backgrounds, reflecting differences between the European and North American continents. Finally, the level of pain at the time of enrollment was apparently lower in the GUIDE trial than in the GAIT study (~40 versus ~47, on a 0–100 normalized scale). However, the baseline Lequesne index scores indicated at least moderate symptomatic disease severity in the GUIDE study (17), and the present results are therefore applicable to this subset of patients with knee OA. Conversely, previous long-term trials have focused on the effects of glucosamine sulfate in patients with milder disease (4,5,44).

Early withdrawal from the study occurred in 26–33% of patients. Protocol violations were among the most frequent reasons for this, and they were mainly represented by patients not meeting the inclusion/exclusion criteria suggested by current guidelines (14,15), who were thus misrandomized. The proportion of such patients was comparable in all 3 treatment groups, and they were conservatively and appropriately accounted for in the statistical analysis. Their early withdrawal immediately after randomization necessitated assigning them a negative efficacy outcome for all assessments, according to the LOCF approach.

Adverse events were the other main reason for dropout, although treatment safety was good throughout the study. Glucosamine sulfate was well tolerated, and did not differ from placebo in terms of frequency of adverse events or abnormal findings of laboratory evaluations, including glucose serum levels. These observations confirm the good safety profile of this agent, as observed in all previous meta-analyses (3,9,45,46) and long-term trials (4,5).

To our knowledge, the GUIDE is the first OA trial to assess the safety of acetaminophen in comparison with placebo over a treatment period of 6 months. Previous trials using naproxen as a comparator documented the good safety profile of acetaminophen at doses of 2,600 mg/day for 2 years (47) and 4 gm/day for 6–12 months (48); acetaminophen was also well tolerated in the present study, with no findings that would cause concern with regard to gastrointestinal safety (29). However, abnormalities in liver function were found in ~20% of the acetaminophen-treated patients, even though the drug was used at a relatively low dosage of 3 gm/day, further supporting this dosage selection. The alterations in liver function were mostly mild and transient, and in only 5 patients were they either deemed clinically significant, reported as adverse events, or the reason for treatment withdrawal (compared with 1 each in the placebo and glucosamine sulfate groups).

In conclusion, the results of the GUIDE trial

demonstrate that glucosamine sulfate at the once-daily dosage of 1,500 mg is an effective medication for knee OA symptoms, compared with placebo. These data were obtained during a 6-month period, which is the currently recommended minimum treatment duration for the management of OA, and they complement those obtained over long-term treatment periods of 3 years (4,5). To date, no studies have demonstrated any other pharmacologic treatment to have the same efficacy as glucosamine sulfate for the long-term treatment of OA symptoms (49). The efficacy results obtained with glucosamine sulfate were significant and clinically relevant in the present study in which acetaminophen, the currently recommended preferred medication (2,3), was used as a side comparator. A trial specifically designed to directly compare it with acetaminophen and possibly an NSAID would be needed in order to assess whether glucosamine sulfate could be regarded as the preferred medication in OA.

AUTHOR CONTRIBUTIONS

Dr. Herrero-Beaumont 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. Dr. Herrero-Beaumont.

Acquisition of data. Drs. Herrero-Beaumont, Ivorra, Trabado, Blanco, Benito, Martín-Mola, Paulino, Marenco, Porto, Laffon, Araújo, Figueroa, and Branco.

Analysis and interpretation of data. Drs. Herrero-Beaumont, Ivorra, Trabado, Blanco, Benito, Martín-Mola, Paulino, Marenco, Porto, Laffon, Araújo, Figueroa, and Branco.

Manuscript preparation. Drs. Herrero-Beaumont, Ivorra, Trabado, Blanco, Benito, Martín-Mola, Paulino, Marenco, Porto, Laffon, Araújo, Figueroa, and Branco.

Statistical analysis. Dr. Giampaolo Giacovelli (nonauthor; Rottapharm).

ROLE OF THE STUDY SPONSOR

GUIDE is a regulatory trial agreed upon by the sponsor (Rottapharm) and the relevant health authorities and designed with the principal investigator (Dr. Herrero-Beaumont). Following protocol approval and implementation, the statistical analysis plan was prepared and executed by the sponsor. The statistical analysis was supervised by the principal investigator, and each author had the opportunity to review the data and the analysis. The sponsor provided the study medication and funding for the trial. In addition, it monitored the study according to Good Clinical Practice standards and according to all applicable laws and guidelines, to preserve the integrity of the data and their collection. However, Rottapharm as a corporate entity had no control over the writing, contents, or decision to submit the present manuscript for publication.

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