

# Long-term effects of glucosamine sulphate on osteoarthritis progression: a randomised, placebo-controlled clinical trial

Jean Yves Reginster, Rita Deroisy, Lucio C Rovati, Richard L Lee, Eric Lejeune, Olivier Bruyere, Giampaolo Giacomelli, Yves Henrotin, Jane E Dacre, Christiane Gosset

## Summary

**Background** Treatment of osteoarthritis is usually limited to short-term symptom control. We assessed the effects of the specific drug glucosamine sulphate on the long-term progression of osteoarthritis joint structure changes and symptoms.

**Methods** We did a randomised, double-blind placebo controlled trial, in which 212 patients with knee osteoarthritis were randomly assigned 1500 mg sulphate oral glucosamine or placebo once daily for 3 years. Weightbearing, anteroposterior radiographs of each knee in full extension were taken at enrolment and after 1 and 3 years. Mean joint-space width of the medial compartment of the tibiofemoral joint was assessed by digital image analysis, whereas minimum joint-space width—ie, at the narrowest point—was measured by visual inspection with a magnifying lens. Symptoms were scored by the Western Ontario and McMaster Universities (WOMAC) osteoarthritis index.

**Findings** The 106 patients on placebo had a progressive joint-space narrowing, with a mean joint-space loss after 3 years of  $-0.31$  mm (95% CI  $-0.48$  to  $-0.13$ ). There was no significant joint-space loss in the 106 patients on glucosamine sulphate:  $-0.06$  mm ( $-0.22$  to  $0.09$ ). Similar results were reported with minimum joint-space narrowing. As assessed by WOMAC scores, symptoms worsened slightly in patients on placebo compared with the improvement observed after treatment with glucosamine sulphate. There were no differences in safety or reasons for early withdrawal between the treatment and placebo groups.

**Interpretation** The long-term combined structure-modifying and symptom-modifying effects of glucosamine sulphate suggest that it could be a disease modifying agent in osteoarthritis.

*Lancet* 2001; **357**: 251–56

See Commentary page 247

**Bone and Cartilage Metabolism Research Unit (WHO Collaborating Center for Public Aspects of Osteoarticular Disorders), University of Liege, B-4020 Liege Belgium** (J Y Reginster MD, R Deroisy PhD, E Lejeune PhD, O Bruyere PhD, Y Henrotin PhD, C Gosset MD); **Georgetown University Medical Center, Washington DC, USA** (J Y Reginster); **Department of Clinical Pharmacology, Rotta Research Laboratory, Monza, Italy** (L C Rovati MD, G Giacomelli PhD); **and Department of Rheumatology, Whittington Hospital, University College London, UK** (R L Lee MSc, J E Dacre MD)

**Correspondence to:** Dr Jean-Yves Reginster (e-mail: e-mail: jyreginster@ulg.ac.be)

## Introduction

Osteoarthritis is a major cause of disability and is among the most frequent forms of musculoskeletal disorders.<sup>1</sup> The goal of pharmacological treatment is usually to control symptoms of the disease, pain, and limitation of function, which is traditionally accomplished by the use of analgesic agents or non-steroidal antiinflammatory drugs (NSAIDs).<sup>2</sup> Drugs for the treatment of osteoarthritis have been classified as symptom-modifying drugs and also as structure-modifying drugs if they are able to alter the joint structure favourably and thus actually interfere with the progression of the disease.<sup>3,4</sup> Although no drug can be included in the second category as yet, compounds are being searched for that may exert more specific effects than those of NSAIDs, directly interfering with some of the possible disease processes. Thus, these compounds might also favourably affect joint structure changes during long-term treatment, contrary to what has been observed with some NSAIDs that could even worsen progression.<sup>5</sup>

Glucosamine sulphate is the sulphate derivative of the natural aminomonosaccharide glucosamine. Glucosamine, a normal constituent of glycosaminoglycans in cartilage matrix and synovial fluid,<sup>6</sup> could have various pharmacological actions in articular cartilage and joint tissues. Several short-term to medium-term clinical trials in osteoarthritis have shown the significant symptom-modifying effect of glucosamine sulphate and its good safety profile.<sup>7–10</sup> The need for long-term clinical trials with this compound has been emphasised.<sup>11,12</sup> We did a randomised double-blind placebo-controlled trial to establish whether glucosamine sulphate can affect progression of symptoms and joint structure changes in osteoarthritis.

## Methods

### Study design and selection of patients

We recruited patients from the outpatient clinic of the Bone and Cartilage Metabolism Research Unit of the University Hospital Centre in Liege, Belgium. Inclusion criteria were age over 50 years and primary knee osteoarthritis of the medial femorotibial compartment, diagnosed according to the clinical and radiological criteria of the American College of Rheumatology.<sup>13</sup> Disease severity was graded on the basis of the Kellgren and Lawrence radiographic system.<sup>4</sup> Major exclusion criteria were: history or active presence of other rheumatic diseases that could be responsible for secondary osteoarthritis;<sup>3,4</sup> severe articular inflammation as confirmed by physical examination (excluded also by erythrocyte sedimentation rate  $<40$  mm/h and serum rheumatoid factor titre  $<1:40$ ); traumatic knee lesions; overweight defined as a body mass index  $>30$ ; substantial abnormalities in haematological, hepatic, renal, or

metabolic functions; and intra-articular or systemic corticosteroids in the 3 months preceding enrolment. The study was approved by the ethics committee of the University of Liege and all patients gave their oral and written informed consent to participate.

#### Treatment assignment

Crystalline glucosamine sulphate (Dona, Viartril-S, or Xicil, Rotta Research Group, Monza, Italy) is a defined pure substance that is synthesised from chitin, and in which glucosamine, sulphate, chloride, and sodium ions are present in stoichiometric ratios of 2:1:2:2. The net content of glucosamine sulphate in the dose form (powder for oral solution, with standard inactive excipients) is 1500 mg. This product has been approved at this once daily dosage as a prescription treatment for osteoarthritis in many countries in Europe and elsewhere.

Patients were randomly assigned to receive 1500 mg of glucosamine sulphate or placebo once daily for 3 years. For rescue analgesia, patients were allowed access to paracetamol in 500 mg tablets, or to one of the following NSAIDs (the most used in Belgium at the time of the trial): diclofenac in 50 mg tablets, piroxicam in 20 mg capsules, or proglumetacin in 150 mg tablets. Use of the rescue medications was recorded by the patients in a diary, with appropriate washout—ie, at least five half-lives of the selected medication were allowed before symptom assessment. Compliance with study treatment was established by asking the patients about missed doses and by counting unused sachets. No other co-interventions for osteoarthritis were allowed.

The randomisation list was generated by computer in blocks of four, and patients received their randomisation number in chronological order. The principal investigator was provided with individual envelopes, each containing patient codes, thus concealing treatment assignment.

#### Outcome measures

The primary outcome measure for joint structural changes was represented by the mean joint-space width of the medial compartment of the tibiofemoral joint. Weightbearing, anteroposterior, separate radiographs of each knee were taken at baseline, 1, and 3 years by a standardised technique.<sup>4</sup> In brief, patients stood with their knees fully extended and the posterior aspect of the knee in contact with the vertical cassette. The lower limbs were rotated until the patella was centralised over the lower end of the femur. Feet were positioned a small distance apart: foot maps were used for repositioning the patient. The X-ray beam was centred on the joint space and parallel to the tibial plateau. Fluoroscopy was used to correct lower limb positioning and X-ray beam alignment. The focus to film distance was 110 cm.

We digitised the radiographs and did the image analysis automatically by a validated system,<sup>14</sup> which located the proximal and distal joint margins excluding outlier points and calculated the mean joint-space width of the medial and lateral compartments of the tibiofemoral joint. We calculated the mean (SD) short-term and long-term coefficient of variation of this system for reproducing measurements as 1.82% (1.29) and 1.62% (1.31), respectively, for the medial compartment, which is in good agreement with the 1.84% coefficient of variation reported in the original validation of this method.<sup>15</sup> All radiographs obtained in a single radiological unit in Liege were measured in London by a single reader unaware of treatment assignment. A further masked analysis was visual determination of the minimum joint-

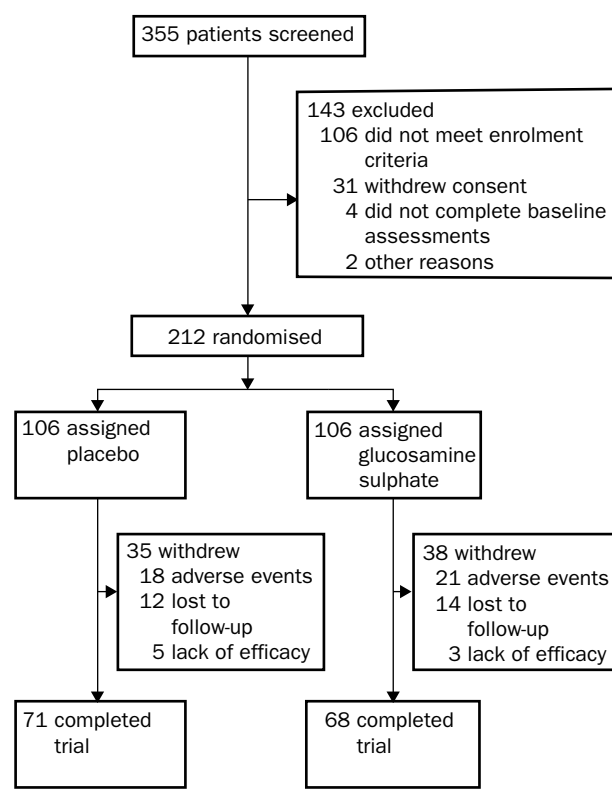


Figure 1: Trial profile

space width—ie, at the narrowest point—with a 0.1 mm graduated magnifying lens.<sup>16</sup>

We assessed symptoms of osteoarthritis by the Western Ontario and McMaster Universities (WOMAC) osteoarthritis index, a validated, disease-specific questionnaire addressing severity of joint pain (five questions), stiffness (two questions), and limitation of physical function (17 questions), and referring to the 48 h before assessment.<sup>17</sup> The visual analogue scale version of the index was used—ie, with the patient assessing each question by a 100 mm visual analogue scale, and the total index score being represented by the sum of the 24 component item scores. A higher WOMAC score represents worse symptom severity, with 2400 mm being the worst possible total score.

Secondary outcome measures were use of rescue medications as recorded in a daily diary; withdrawal rates; occurrence of adverse events; and routine safety laboratory tests, including testing for glucose homeostasis assessed by fasting glucose concentrations at yearly intervals in all patients still receiving the study treatment.

#### Statistical analysis

We calculated sample size on the basis of the recommendations available at the time of study planning, of a 0.5 mm target difference in joint-space narrowing between groups after 3 years,<sup>18</sup> given the validation data of the digital image analysis technique adopted as the principal outcome.<sup>15</sup> We calculated that a sample size of at least 60 patients in each group would give a power of 80% in detecting such a difference at the 5% significance level. We increased the sample size to at least 100 patients per group to allow an up to 40% dropout rate.

The primary efficacy outcome measure for structure modification was joint-space narrowing in the signal joint—ie, the change in joint-space width after 3 years in the narrowest medial tibiofemoral joint compartment at

| Characteristic                           | All randomised patients |                              | Patients assessed for 3 years |                             |
|--|-------------------------|------------------------------|-------------------------------|-----------------------------|
|  | Placebo (n=106)         | Glucosamine sulphate (n=106) | Placebo (n=71)                | Glucosamine sulphate (n=68) |
| Women                                    | 83 (78%)                | 79 (75%)                     | 55 (77%)                      | 53 (78%)                    |
| Age (years)                              | 65.5 (7.5)              | 66.0 (8.1)                   | 65.3 (7.4)                    | 65.5 (7.2)                  |
| Body-mass index (kg/m <sup>2</sup> )     | 27.4 (2.7)              | 27.3 (2.6)                   | 27.2 (2.8)                    | 27.2 (2.8)                  |
| Duration of knee osteoarthritis* (years) | 7.6 (7.5)               | 8.0 (7.5)                    | 7.9 (7.9)                     | 7.8 (6.8)                   |
| Kellgren and Lawrence grading†           |                         |                              |                               |                             |
| Grade 2                                  | 74 (70%)                | 75 (71%)                     | 51 (72%)                      | 51 (75%)                    |
| Grade 3                                  | 32 (30%)                | 30 (29%)                     | 20 (28%)                      | 17 (25%)                    |
| Total joint-space width‡ (mm)            | 5.39 (1.29)             | 5.23 (1.36)                  | 5.46 (1.23)                   | 5.39 (1.30)                 |
| Minimum joint-space width‡ (mm)          | 3.95 (1.24)             | 3.82 (1.32)                  | 4.01 (1.26)                   | 3.82 (1.23)                 |
| WOMAC index§                             |                         |                              |                               |                             |
| Total index (mm)                         | 939.7 (484.8)           | 1030.2 (473.8)               | 894.0 (494.8)                 | 1024.3 (486.1)              |
| Pain (mm)                                | 172.2 (104.5)           | 194.1 (101.9)                | 164.3 (105.1)                 | 189.2 (103.8)               |
| Function (mm)                            | 670.8 (367.8)           | 740.1 (364.2)                | 632.8 (376.9)                 | 739.8 (375.6)               |
| Stiffness (mm)                           | 96.7 (54.6)             | 96.0 (54.8)                  | 96.8 (54.8)                   | 95.3 (57.6)                 |

Values shown as mean (SD) unless otherwise indicated. \*Based on patient history. †The Kellgren and Lawrence system grades osteoarthritis on joint radiographs as 0=none, 1=doubtful, 2=mild, 3=moderate, 4=severe, based on the assumed sequential appearance of osteophytes, joint space loss, subchondral sclerosis, and cyst formation. ‡One baseline radiograph missing in the glucosamine sulphate group (n=105). §Sum of visual analogue scale scores.

Table 1: Demographic and baseline clinical characteristics of all patients

enrolment. The medial tibiofemoral joint space is preferred in clinical trials, as opposed to the lateral space, since this is the area that is subjected to the greatest pressure and thus the most osteoarthritis cartilage loss, and for which outcome measures are better validated.<sup>3</sup> The 3-year % change in the total WOMAC score was taken for the primary assessment of symptom modification, with the final changes in the pain, physical function, and stiffness subscales analysed as secondary endpoints. Results were expressed as difference between the final group means and 95% CI, with p values based on analysis of variance. All primary efficacy analyses were done on patients who completed the 3-year observation period, and by intention-to-treat analysis for all randomised patients. Every effort was made to carry out the final examinations after 3 years, regardless of patient's compliance or whether the patient was still on the study treatment. When this was not possible, the intention-to-treat analysis was carried out according to three different approaches. First, we did a worst scenario analysis in which a poor outcome was assigned to patients in whom the final 3-year assessment was not completed, corresponding to the average change recorded in patients in the placebo group who were assessed for 3 years. For consistency we also used the last observation carried forward approach, and to avoid repeatedly assigning the same value to a series of missing values we used the random sampling method. In the random sampling approach, missing endpoint values were replaced with values selected randomly from the distribution of all known endpoint values—ie, glucosamine sulphate and placebo combined. To lower sampling error, 50 such datasets were constructed, analysed independently by analysis of variance and the median of the significance values was taken.

Among secondary analyses, we arbitrarily defined a cutoff point for marked structural damage progression as a joint-space narrowing of more than 0.5 mm, based on previous reports<sup>18</sup>—the proportion of all randomised patients reaching such a progression cutoff was compared between groups by the  $\chi^2$  test. The mean number of days

of rescue medication intake was assessed by analysis of variance. We used the Spearman correlation test to assess correlation between structure and symptom outcomes. Adverse event and dropout rates were analysed by  $\chi^2$  or Fisher's exact tests, as appropriate. Baseline characteristics were compared by the  $\chi^2$  test for categorical variables and by analysis of variance for continuous data. All reported p values are two sided with  $\alpha=0.05$ .

## Results

### Patients

Of 355 patients screened, 212 were enrolled in the study and randomly assigned to receive glucosamine sulphate or placebo (figure 1). A similar number of patients in the two groups did not complete the 3-year treatment course: 38 of 106 (36%) in the glucosamine sulphate group and 35 of 106 (33%) in the placebo group ( $p=0.77$ ), without significant differences in reasons for withdrawal. Patients in the two groups had similar demographic and baseline characteristics (table 1). Patients had similar mild to moderate osteoarthritis radiographic grading and joint-space widths at enrolment, with a degree of symptoms expressed by the WOMAC index that was also similar and of mild to moderate average severity. During the 6 months before enrolment, 51% of patients in both groups did not report any pharmacological treatment for osteoarthritis, whereas within the remaining patients 24% had received NSAIDs, 15% simple analgesics, 8% both NSAIDs and simple analgesics, 2% corticosteroids, without differences between groups. Compliance with study treatment was good: the proportion of patients who reported over 70% drug intake ranged between 81% and 91%, without significant differences between groups.

Table 2 shows the final joint-space narrowing in the medial compartment of the tibiofemoral joint for the patients assessed for 3 years and the intention-to-treat worst-scenario analysis. With both approaches there was no average loss of joint-space width in the patients receiving glucosamine sulphate. Conversely, patients on placebo had a significant mean and minimum joint-space

|                                    | Patients assessed for 3 years |                             |                     |       | Intention-to-treat analysis |                              |                     |       |
|------------------------------------|-------------------------------|-----------------------------|---------------------|-------|-----------------------------|------------------------------|---------------------|-------|
|                                    | Placebo (n=71)                | Glucosamine sulphate (n=68) | Difference (95% CI) | p     | Placebo (n=106)             | Glucosamine sulphate (n=106) | Difference (95% CI) | p     |
| Mean joint-space narrowing (mm)    | -0.31 (-0.57 to -0.04)        | 0.07 (-0.17 to 0.32)        | 0.38 (0.02 to 0.73) | 0.038 | -0.31 (-0.48 to -0.13)      | -0.06 (-0.22 to 0.09)        | 0.24 (0.01 to 0.48) | 0.043 |
| Minimum joint-space narrowing (mm) | -0.40 (-0.64 to -0.17)        | 0.11 (-0.10 to 0.33)        | 0.51 (0.20 to 0.83) | 0.002 | -0.40 (-0.56 to -0.24)      | -0.07 (-0.22 to 0.07)        | 0.33 (0.12 to 0.54) | 0.003 |

Table 2: Average (95% CI) joint-space narrowing after 3 years

|                      | Patients assessed for 3 years |                             |                      |       | Intention-to-treat analysis |                              |                      |       |
|----------------------|-------------------------------|-----------------------------|----------------------|-------|-----------------------------|------------------------------|----------------------|-------|
|                      | Placebo (n=71)                | Glucosamine sulphate (n=68) | Difference (95% CI)  | p     | Placebo (n=106)             | Glucosamine sulphate (n=106) | Difference (95% CI)  | p     |
| Total WOMAC % change | 9.8% (-14.6 to 34.3%)         | -24.3% (-37.0 to -11.6%)    | 34.1% (6.4 to 61.8%) | 0.016 | 9.8% (-6.2 to 25.8%)        | -11.7% (-20.3 to -3.2%)      | 21.6% (3.5 to 39.6%) | 0.020 |

Table 3: Average (95% CI) total WOMAC percent change after 3 years

narrowing after 3 years. Final differences between groups were significant in all instances. A similar effect was recorded when the intention-to-treat analysis was done by the last observation carried-forward approach (data not shown) and especially by the random sampling approach, in which the median of significant differences was  $p=0.044$  for the mean and  $p=0.013$  for the minimum joint-space narrowing.

After the first year of treatment, the intention-to-treat change in mean joint-space width with placebo was only  $-0.05$  mm (95% CI  $-0.23$  to  $0.14$ ), compared with the  $0.12$  mm ( $-0.06$  to  $0.29$ ) change with glucosamine sulphate (ie, only a non-significant favourable trend in the difference:  $0.17$  mm [95% CI  $-0.09$  to  $0.42$ ];  $p=0.21$ ). After 3 years, 32 of 106 patients (30%) randomised to placebo had a severe mean joint-space narrowing of more than  $0.5$  mm, compared with only 16 (15%) with glucosamine sulphate ( $p=0.013$ ).

There were similar mean joint-space narrowing trends after 3 years in the contralateral medial compartments of patients assessed for 3 years with bilateral involvement—ie, a significant loss with placebo and a non-significant change with glucosamine sulphate (final difference between groups:  $0.46$  mm [95% CI  $0.04$  to  $0.88$ ];  $p=0.033$ ;  $n=66$  and  $n=54$ , respectively). Changes in the same direction occurred also in the joint lateral compartments, but they were smaller and not significant.

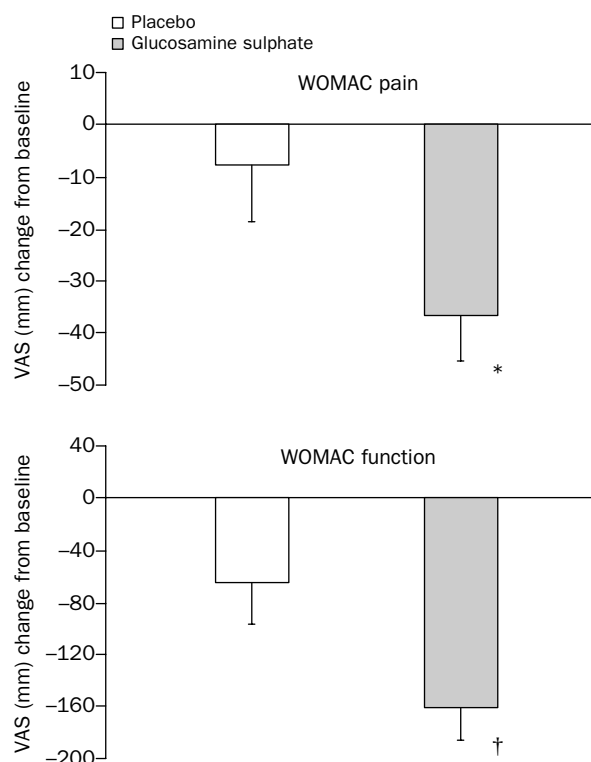


Figure 2: Intention-to-treat mean (SE) sum of VAS change subscales after 3 years

Upper: WOMAC pain Lower: WOMAC physical function. \* $p=0.047$ ; † $p=0.020$ . VAS=visual analogue scale.

### Symptoms

There was an improvement in the primary symptom outcome measure represented by the total WOMAC index (table 3) compared with baseline in the patients receiving glucosamine sulphate who were assessed for 3 years. However, symptoms of patients in the placebo group worsened and the difference between the final group averages was significant ( $p=0.016$ ). Results from the intention-to-treat, worst-scenario analysis were similar ( $p=0.020$ ), and when the last observation carried forward method was used (data not shown), and the median of significant differences by the random sampling approach was  $p=0.045$ . There were significant improvements in WOMAC pain and physical function subscales with glucosamine sulphate compared with placebo (figure 2). Minor changes in the stiffness subscale were not significantly different between groups. The general correlation between structure and symptom outcomes was poor and not significant. In particular, patients receiving glucosamine sulphate tended to improve their symptoms regardless of structure outcome—ie, even in those who had severe joint-space narrowing identified by the arbitrary cutoff point (data not shown).

Most patients took at least one dose of a rescue drug, with a similar proportion receiving the pure analgesic or a NSAID (about 40% and 60%, respectively, in both groups and without differences between the selected NSAIDs). However, consumption was variable and inconsistent between and within patients. On average, recourse to the rescue drugs was only needed on less than one of every 6 days throughout the study duration, without significant differences between groups in any respect. There was no apparent correlation between rescue drug intake and joint-space narrowing, or even symptom outcome, with a trend for larger intakes to be associated with poor symptom relief, again without differences between groups.

### Safety

Most patients reported at least one adverse event: 93% with placebo and 94% with glucosamine sulphate. There were no substantial differences between groups in

| Adverse event*           | Placebo (n=106) | Glucosamine sulphate (n=106) |
|--------------------------|-----------------|------------------------------|
| Abdominal pain           | 18 (17%)        | 13 (12%)                     |
| Dyspepsia                | 8 (8%)          | 4 (4%)                       |
| Diarrhoea                | 11 (10%)        | 10 (9%)                      |
| Increased blood pressure | 15 (14%)        | 15 (14%)                     |
| Decreased blood pressure | 8 (8%)          | 2 (2%)                       |
| Cardiac failure          | 7 (7%)          | 4 (4%)                       |
| Fatigue                  | 7 (7%)          | 10 (9%)                      |
| Headache                 | 4 (4%)          | 6 (6%)                       |
| Vertigo                  | 3 (3%)          | 7 (7%)                       |
| Neuritis                 | 6 (6%)          | 4 (4%)                       |
| Depressive mood          | 7 (4%)          | 4 (6%)                       |
| Allergic episode         | 7 (7%)          | 4 (4%)                       |

\*Seasonal/infective upper respiratory tract disorders were reported by 49% of patients on placebo and 51% on glucosamine sulphate, and influenza-like symptoms by 23% and 28% with placebo and glucosamine sulphate, respectively.

Table 4: Proportion of patients reporting adverse events recorded with an at least 5% frequency



frequency or pattern of events. Table 4 shows the frequencies of the most common adverse events recorded: most of them were transient and of mild to moderate severity. As shown in figure 1, adverse events were the cause of early withdrawal in 17% of patients receiving placebo and 20% of those receiving glucosamine sulphate ( $p=0.72$ ). In about half the cases, these events were referred to the gastrointestinal system (mainly including abdominal pain and disturbed defecation) and may be also referred to the rescue medication, without differences between groups. Among adverse events leading to patient's dropout, few single episodes were serious and were all judged as unrelated to the study treatment, mostly because such episodes were attributable to pre-existing or concomitant conditions in this elderly population, without significant differences between glucosamine sulphate and placebo.

Routine laboratory tests did not show any great abnormalities in system organs or metabolic functions in the two groups during the study. There was no change in glycaemic homeostasis, with fasting plasma glucose concentrations decreasing slightly in the glucosamine sulphate group (data not shown).

## Discussion

We have reported here that long-term administration of glucosamine sulphate over 3 years can prevent joint structure changes in patients with osteoarthritis of the knee with a significant improvement in symptoms.

Different validated methods have been proposed for measuring joint-space width from standardised radiographs, such as visual methods (using a caliper, ruler, or a magnifying lens) usually at the narrowest point of the joint, and computed readings of digitised radiographs, suggested to decrease observer-based error.<sup>4</sup> We used a validated method of digital image analysis to calculate mean joint-space width<sup>14</sup> and visual measurement of the narrowest point of the joint by a magnifying lens.<sup>16</sup> Both methods had very similar final results for joint-space narrowing, with the measurement at the narrowest point showing a slightly higher sensitivity to change, as previously suggested.<sup>4</sup> Although the two methods of measurements were similar, as indicated by other studies,<sup>19</sup> our decision to use digital image analysis to determine mean joint-space width as the primary outcome measure proved to be more conservative and allowed sounder conclusions.

Several studies have assessed the natural rate of joint-space narrowing in patients with knee osteoarthritis, but a wide spectrum of possible rates have been reported, ranging between 0.06 and 0.6 mm/year.<sup>20</sup> However, most of these studies had short follow-up periods, or a small number of observations. Other reasons for the differences in rates could include the varied radiographic or measurement procedures, different risk factors, or the population studied. Community-based studies such as the Baltimore Longitudinal Study of Aging<sup>21</sup> and the Framingham Study<sup>22</sup> yielded rates at the lower end of the spectrum—ie, in the 0.1 mm/year range. However, a large long-term study<sup>23</sup> has shown that the yearly rate of progression even in clinic-based populations should be in the 0.1 mm range. The final overall joint-space narrowing we recorded with placebo is in this range. However, the rate of joint-space narrowing we observed was not linear, since the loss in mean space width with placebo after the first year was only of 0.05 mm. When individual joint-space changes were analysed, twice as many patients receiving placebo had a striking joint-space narrowing, than those receiving glucosamine sulphate.

In clinical terms, the baseline values of the WOMAC index correspond to symptoms of mild to moderate severity—patients who completed treatment with glucosamine sulphate had a 20–25% improvement in symptoms, compared with the slight worsening of symptoms in the placebo group. Analysis of the WOMAC index subscales for pain and for physical function, confirmed the symptom improvement with glucosamine sulphate compared with placebo. Intention-to-treat analysis confirmed the beneficial effect of glucosamine sulphate on joint structure and symptoms reported when patients who completed the study treatment were assessed.

The precise mechanism of action of glucosamine sulphate has not been fully elucidated yet. Cartilage-unrelated effects, such as the inhibition of superoxide-radical generation<sup>24</sup> or the inhibition of inducible nitric oxide synthesis<sup>25</sup> have been suggested to explain the fast onset of action on symptoms noted in short-term clinical trials.<sup>7–9</sup> However, the long-term effects we recorded could be due to the reported effects of the compound on cartilage metabolism, including stimulation of anabolic activities, such as the synthesis of proteoglycans,<sup>26,27</sup> and the depression of catabolic activities, such as the effects of metalloproteases.<sup>27,28</sup>

Previous short-term studies have shown glucosamine sulphate is fairly safe<sup>7–9</sup> and more safe than standard NSAIDs, especially concerning the gastrointestinal tract.<sup>8,9</sup> We did not report any significant differences from placebo in safety, with no distinct adverse event pattern. Similarly, routine laboratory tests did not show any general system modification nor metabolic changes. The latter included no alteration of glycaemic homeostasis, contrary to what has been suggested by experimental models as a possible untoward target for aminomonosaccharides.<sup>12</sup>

In this study, glucosamine sulphate was approved as a prescription drug, therefore, our results cannot be generalised to other glucosamine products (or compound mixtures) such as those available in some countries as dietary supplements.

As a possible limitation of our trial, we should acknowledge that although current scientific and regulatory recommendations<sup>3,4</sup> still advise use of the fully extended, weightbearing radiographic view that we used to assess joint structural changes, more recent reports suggest that other radiographic views could be more efficient.<sup>29</sup> In particular, these views might avoid changes in patient positioning due to symptom changes during the study (eg, better knee extension and consequently lower apparent joint-space narrowing, due to symptom improvement in the glucosamine sulphate group). However, we believe it is unlikely that the symptom change observed in the two groups might have affected the results, given the mild to moderate disease and symptom conditions at baseline and throughout the study. Furthermore, the general correlation between symptom and structure changes was poor, as suggested by other studies.<sup>23</sup> Patients receiving glucosamine sulphate but with severe joint-space narrowing did have an improvement in their symptoms, which did not prevent the radiographic structure impairment.

Whether the effect of glucosamine sulphate on the average joint-space narrowing detected in our study and others<sup>21–23</sup> will be of clinical importance in the longer term cannot be concluded from the present data. Further studies, with longer follow-up and different designs are needed to assess whether these changes are predictive of further clinical progression of osteoarthritis—eg, modifying the indication for possible joint surgery or the time to substantial disability.

## Contributors

J Y Reginster contributed to the design of the study, analysed and interpreted the results, and did the patient assessments. R Deroisy, E Lejeune, and C Gosset coordinated patient clinic visits and assessments. O Bruyère and Y Henrotin were responsible for radiographic assessment of minimum joint-space width and contributed to analysis of the results. L C Rovati and G Giacovelli helped design the study and analyse the data. J E Darce had previously developed the radiograph digital image analysis system used for the primary analysis of efficacy. J E Darce and R L Lee did all the actual digital image analyses of mean joint-space width.

## Acknowledgments

The study was supported by a research grant from the Rotta Research Group, Monza, Italy.

## References

- 1 Creamer P, Hochberg MC. Osteoarthritis. *Lancet* 1997; **350**: 503–09.
- 2 American college of rheumatology subcommittee on osteoarthritis guidelines: recommendations for the medical management of osteoarthritis of the hip and knee. *Arthritis Rheum* 2000; **43**: 1905–15.
- 3 Dougados M for the Group for the Respect of Ethics and Excellence in Science: recommendations for the registration of drugs used in the treatment of osteoarthritis. *Ann Rheum Dis* 1996; **55**: 552–57.
- 4 Altman R, Brandt K, Hochberg M, Moskowitz R. Design and conduct of clinical trials of patients with osteoarthritis: recommendations from a task force of the Osteoarthritis Research Society. *Osteoarthritis Cartilage* 1996; **4**: 217–43.
- 5 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.
- 6 Hamerman D. The biology of osteoarthritis. *N Engl J Med* 1989; **320**: 1322–30.
- 7 Noack W, Fischer M, Förster KK, Rovati LC, Setnikar I. Glucosamine sulfate in osteoarthritis of the knee. *Osteoarthritis Cartilage* 1994; **2**: 51–59.
- 8 Müller-Faßbender H, Bach GL, Haase W, Rovati LC, Setnikar I. Glucosamine sulfate compared to ibuprofen in osteoarthritis of the knee. *Osteoarthritis Cartilage* 1994; **2**: 61–69.
- 9 Rovati LC. The clinical profile of glucosamine sulfate as a selective symptom modifying drug in osteoarthritis: current data and perspectives. *Osteoarthritis Cartilage* 1997; **5** (suppl A): 72.
- 10 McAlindon TE, La Valley MP, Gulin JP, Felson DT. Glucosamine and chondroitin for treatment of osteoarthritis: a systematic quality assessment and meta-analysis. *JAMA* 2000; **283**: 1469–75.
- 11 Towheed TE, Anastassiades TP. Glucosamine and chondroitin for treating symptoms of osteoarthritis: evidence is widely touted but incomplete. *JAMA* 2000; **283**: 1483–84.
- 12 Adams ME. Hype about glucosamine. *Lancet* 1999; **354**: 353–54.
- 13 Altman R, Asch E, Bloch D, et al. Development of criteria for the classification and reporting of osteoarthritis: classification of osteoarthritis of the knee. *Arthritis Rheum* 1986; **29**: 1039–49.
- 14 Dacre JE, Huskisson EC. The automatic assessment of knee radiographs in osteoarthritis using digital image analysis. *Br J Rheumatol* 1989; **28**: 506–10.
- 15 Byrne J, Heald G, James MF, Kay M, Shorter J, Dacre JE. Digital image analysis, a rapid and reproducible method for joint space measurement. *Osteoarthritis Cartilage* 1993; **1**: 60–61.
- 16 Lequesne M. Quantitative measurements of joint space width during progression of osteoarthritis: chondrometry. In: Kuetter KE, Goldberg VM, eds. Osteoarthritic disorders. Rosemont, USA: American Academy of Orthopedic Surgeons, 1995: 427–44.
- 17 Bellamy N, Buchanan WW, Goldsmith CH, Campbell J, Stitt LW. Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. *J Rheumatol* 1988; **15**: 1833–40.
- 18 Lequesne M, Brandt K, Bellamy N, et al. Guidelines for testing slow acting drugs in osteoarthritis. *J Rheumatol* 1994; **21**: 65–73.
- 19 Piperno M, Heliö Le Graverand MP, Conrozier T, Bochu M, Mathieu P, Vignon E. Quantitative evaluation of joint space width in femorotibial osteoarthritis: comparison of three radiographic views. *Osteoarthritis Cartilage* 1998; **6**: 252–59.
- 20 Mazzuca SA, Brandt KD, Katz BP. Is conventional radiography suitable for evaluation of a disease-modifying drug in patients with knee osteoarthritis? *Osteoarthritis Cartilage* 1997; **5**: 217–26.
- 21 Lethbridge-Cejku M, Hockberg MC, Scott WW Jr, Plato CC, Tobin JD. Longitudinal change in joint space of the knee: data from the Baltimore Longitudinal Study of Aging. *Arthritis Rheum* 1995; **38** (suppl): S262.
- 22 Neuhauser KB, Anderson JJ, Felson DT. Rate of joint space narrowing in normal knees and knees with osteoarthritis. *Arthritis Rheum* 1994; **37** (suppl): S423.
- 23 Dieppe PA, Cushnaghan J, Shepstone L. The Bristol “OA500” Study: progression of osteoarthritis (OA) over 3 years and the relationship between clinical and radiographic changes at the knee joint. *Osteoarthritis Cartilage* 1997; **5**: 87–97.
- 24 Setnikar I, Cereda R, Pacini MA, Revel L. Antireactive properties of glucosamine sulfate. *Arzneimittelforschung* 1991; **41**: 157–61.
- 25 Shikhman AR, Alaaeddine N, Lotz MK. N-acetylglucosamine prevents IL-1 mediated activation of chondrocytes. *Arthritis Rheum* 1999; **42** (suppl): S381.
- 26 Bassleer C, Rovati LC, Franchimont P. Glucosamine sulfate stimulates proteoglycan production in human chondrocytes in vitro. *Osteoarthritis Cartilage* 1998; **6**: 427–34.
- 27 Dodge GR, Hawkins DF, Jimenez SA. Modulation of aggrecan, MMP1, and MMP3 production by glucosamine sulfate in cultured human osteoarthritis articular chondrocytes. *Arthritis Rheum* 1999; **42** (suppl): 253.
- 28 Sandy JD, Gamett D, Thompson V, Verscharen C. Chondrocyte-mediated catabolism of aggrecan: aggreganase-dependent cleavage induced by interleukin-1 or retinoic acid can be inhibited by glucosamine. *Biochem J* 1998; **335**: 59–66.
- 29 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.