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# Efficacy and Safety of Glucosamine Sulfate versus Ibuprofen in Patients with Knee Osteoarthritis

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## Summary

A double-blind therapeutic investigation was performed on 178 Chinese patients suffering from osteoarthritis of the knee randomized into two groups, one treated for 4 weeks with glucosamine sulfate (GS, CAS 29031-19-4, Viartril-S®) at the daily dose of 1,500 mg and the other with ibuprofen (IBU, CAS 15687-27-1) at the daily dose of 1,200 mg. Knee pain at rest, at movement and at pressure, knee swelling, improvement and therapeutic utility as well as adverse events and drop-outs were recorded after 2 and 4 weeks of treatment. The variables were recorded also after 2 weeks of treatment discontinuation in order to appreciate the remnant therapeutic effect. Both GS and IBU significantly reduced the symptoms of osteoarthritis with the trend of GS to be more effective. After 2 weeks of drug discontinuation there was a remnant therapeutic effect in both groups, with the trend to be more pronounced in the GS group. GS was significantly better tolerated than IBU, as shown by the adverse drug reactions (6 % in the patients of the GS group and 16 % in the IBU group – $p = 0.02$) and by the drug-related drop-outs (0 % of the patients in the GS group and 10 % in the IBU group – $p = 0.0017$).

The better tolerability of GS is explained by its mode of action, because GS specifically curbs the pathogenic mechanisms of osteoarthritis and does not inhibit the cyclo-oxygenases as the non-steroidal anti-inflammatory drugs (NSAIDs) do, with the consequent anti-inflammatory analgesic activities but also with the several adverse reactions due to this not targeted effect.

The present study confirms that GS is a selective drug for osteoarthritis, as effective on the symtoms of the disease as NSAIDs but significantly better tolerated. For these properties GS seems particularly indicated in the long-term treatments needed in osteoarthritis.

## Zusammenfassung

*Wirksamkeit und Unbedenklichkeit von Glucosaminsulfat vs. Ibuprofen bei Patienten mit Gonarthrose*

Im Rahmen einer doppelblinden therapeutischen Untersuchung wurden 178 chinesische Patienten, die an Gonarthrose litten, 4 Wochen lang mit täglich 1.500 mg Glucosaminsulfat (GS, CAS 29031-19-4, Viartril-S®) oder 1.200 mg Ibuprofen (IBU, CAS 15687-27-1) behandelt. Die Zuteilung zu den beiden Behandlungsgruppen erfolgte randomisiert. Ruheschmerz, Bewegungsschmerz und Palpationsschmerz sowie unerwünschte Ereignisse und Drop-outs wurden 2 und 4 Wochen nach Behandlungsbeginn dokumentiert. Darüber hinaus wurden die Variablen zwei Wochen nach Behandlungsende erfaßt, um einen anhaltenden therapeutischen Effekt zu beurteilen.

Sowohl GS als auch IBU reduzierten signifikant die Symptome der Arthrose, wobei GS im Trend effektiver war. In beiden Gruppen war 2 Wochen nach Behandlungsende ein anhaltender therapeutischer Effekt vorhanden, der in der GS-Gruppe im Trend stärker ausgeprägt war. Die Verträglichkeit von GS war signifikant besser als die von IBU, wie die unerwünschten Arzneimittelwirkungen (6 % der Patienten in der GS-Gruppe und 16 % in der IBU-Gruppe –

p = 0,02) und die behandlungsbedingten Drop-outs (0 % der Patienten in der GS-Gruppe und 10 % in der IBU-Gruppe – p = 0,0017) zeigen. Die bessere Verträglichkeit von GS ist durch die unterschiedlichen Wirkungsmechanismen zu erklären. GS beeinflußt spezifisch den pathogenetischen Mechanismus der Arthrose, ohne – wie die nicht-steroidalen Antirheumatika (NSAR) – die Cyclooxygenase zu hemmen. Die Hemmung der Cyclooxygenase durch NSAR führt zu einer antiinflammatorischen und analgetischen Wirkung, aber auch – in Folge ihrer unspezifischen Aktivität – zu verschiedenen unerwünschten Wirkungen.
Die vorliegende Studie bestätigt, daß GS ein selektives Arzneimittel zur Behandlung der Arthrose ist, dessen symptomatische Wirksamkeit der der NSAR bei signifikant besserer Verträglichkeit entspricht. Auf Grund dieser Eigenschaften erscheint GS insbesondere zur Langzeitbehandlung der Arthrose angezeigt.

**Key words** CAS 15687-27-1 · CAS 29031-19-4 · Glucosamine sulfate · Ibuprofen · Osteoarthritis · Viartril-S®, clinical studies, safety

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## 1. Introduction

Osteoarthritis is a disease characterized by alterations of the structure and function of the joints and is principally due to degenerative processes of the articular cartilage. Osteoarthritis affects a large proportion of the population all around the world with a progressive severity of joint pain and movement limitation that causes transient or permanent invalidity with very high social and economic costs.

To relieve pain and inflammation usually non-steroidal anti-inflammation drugs (NSAID) are used. These drugs, however, are only symptomatic because they do not act on the causes of osteoarthritis and do not stop the progression of the disease. Therefore as soon as the treatment with NSAIDs is discontinued the symptoms of the disease reappear. Furthermore the NSAIDs are not suitable for the long-term treatments required in osteoarthritis because their prolonged use provokes severe adverse reactions especially on the gastrointestinal tract and may even impair the underlying osteoarthritis disease.

A notable improvement of the therapy of osteoarthritis was achieved with the selective symptom modifying drugs for osteoarthritis, e.g. glucosamine sulfate (GS, CAS 29031-19-4), that are already extensively used in Europe and in some Asian countries. These drugs normalize and stimulate the biosynthesis of the proteoglycans of the cartilage matrix and stop the degenerative process of the articular cartilages which is the pathogenic mechanism of osteoarthritis.

GS is the amino-monosaccharide which is physiologically used by our body as substrate for the biosynthesis of the glycosaminoglycans and proteoglycans of the cartilage matrix. Endogenous GS is synthesized in the chondrocytes by amination of glucose. In osteoarthritis this synthesis is defective and insufficient, and the exogenous supply of GS has proven to be useful to manage the disease. GS stimulates and normalizes also the biosynthesis of the proteoglycans of the articular cartilage [2, 3, 16], inhibits certain enzymes which destroy the cartilage, e.g. collagenase and phospholipase A2 [15], and reduces the production of tissue damaging superoxide radicals [18]. By these actions GS blocks the pathogenic mechanisms that lead to articular degeneration, thus delaying the progression of the disease and relieving the symptoms of osteoarthritis, with persistent curative effects also after termination of the treatment courses.

We were interested to investigate the efficacy and safety of GS in comparison to a largely used NSAID, i.e. ibuprofen (IBU, CAS 15687-27-1), in Chinese patients suffering from osteoarthritis of the knee. We adopted a study protocol kindly outlined by the Chinese Bureau of Drug Administration & Policy, Ministry of Public Health. The study was performed in two Centers, the Department of Orthopaedics & Spine Surgery of the Peking Union Medical College Hospital (PUMCH) of Beijing and the Department of Orthopaedics of the Beijing Medical University First Attached Hospital (BMUFAH).

## 2. Objectives, patients, materials and methods

### 2.1. Objectives

Assessment of the efficacy and safety of GS orally administered in Chinese patients suffering from osteoarthritis of the knee in comparison with ibuprofen (IBU).

### 2.2. Study design

After having obtained their informed consent, the patients were randomized into 2 parallel groups treated for 4 weeks either with GS or with IBU in double-blind and controlled conditions. The treatment was followed by 2 drug-free weeks, during which the patients were

*Table 1:* Demographic data of enrolled patients.

| Group | GS | | Ibuprofen | | Total | |
|---|---|---|---|---|---|---|
| Gender | Males | Females | Males | Females | Males | Females |
| Number | 24 | 64 | 14 | 76 | 38 | 140 |
| Age mean ± SD | 58 ± 9 | 56 ± 9 | 58 ± 10 | 56 ± 10 | 58 ± 9 | 56 ± 10 |
| Range | 41–75 | 38–78 | 35–70 | 28–77 | 35–75 | 28–78 |

monitored for symptoms and possible adverse reactions in order to evaluate the effects of the two drugs and the evolution of the disease after discontinuation of therapy.

## 2.3. Patient population

A total of 178 patients was enrolled. Their demographic data and repartition in the treatment groups are given in Table 1.

## 2.4. Investigated drugs

### Test drug GS

Capsules each containing 314 mg crystalline GS, corresponding to 250 mg GS[1].

### GS placebo

Capsules, indistinguishable from to those of GS, containing the excipients only.

### Reference drug IBU

Tablets, each containing 400 mg ibuprofen.

### IBU placebo

Tablets, indistinguishable from those of IBU, containing the excipients only.

## 2.5. Administration schedule

The drugs were administered according to the following dosage schedules.

### GS group

The patients received for 4 weeks daily t.i.d. 2 GS capsules and 1 IBU-placebo tablet (totally 6 capsules with 1,500 mg GS and 3 placebo tablets). After 4 weeks the treatment was discontinued and the patients were monitored for further 2 weeks for symptoms of osteoarthritis and possibly retarded adverse drug reactions.

### IBU group

The patients received for 4 weeks daily t.i.d. 1 IBU tablet and 2 GS-placebo capsules (totally 3 tablets with 1,200 mg IBU and 6 placebo capsules). After 4 weeks the treatment was discontinued and the patients were monitored for further 2 weeks as those in the GS Group.

## 2.6. Evaluation procedures

### Knee pain

Pain of the knee at rest, at movement and at pressure (tenderness) was scored before treatment, after 2 and 4 weeks of treatment, and after 2 weeks of follow-up without treatment. The following scores were used: 0 = Absent; 1 = Mild; 2 = Moderate; 3 = Severe.

### Knee swelling

Swelling of the knee was scored at the same time intervals used for scoring knee pain with the scores: 0 = Absent; 1 = Mild; 2 = Moderate; 3 = Severe.

### Improvement and therapeutic utility rating

Improvement was rated by the investigator as "Worsened", "Unchanged", "Improved" and "Definitely improved" (practical freedom of symptoms).

Therapeutic utility was the judgement by the investigator of the balance between benefits (efficacy on pain and mobility, positive judgement and good acceptance by the patient, practicality of administration), and disadvantages (adverse reactions, negative judgement and no good acceptance by the patient, poor practicality of administration) and was rated as "Unclear", "None", "Moderate" or "Good".

## 2.7. Adverse events and adverse drug reactions

Adverse events (AE) were defined as subjective or objective signs or symptoms happening or worsening during and after the course of the study, independently of causal relationships to the study drugs. Pathological changes of laboratory tests were also classified as AEs. Adverse drug reactions (ADR) were defined as AE related to the investigational drug.

At each visit the objective adverse events and those reported by the patient spontaneously and after questioning were recorded and the severity was classified as "Mild" (causing no limitation of usual activities with possible light discomfort and without need of therapeutic provisions), "Moderate" (causing some limitation of usual activities, some annoying discomfort and the need of therapeutic provisions), "Severe" (causing inability to carry out usual activities, with severe or intolerable discomfort or pain) and "Serious" (AE that were fatal, life threatening, permanently disabling, resulting in hospitalization or prolongation of hospitalization, congenital abnormalities, malignant tumors, or overdoses).

The relatedness with the investigational drug was classified as "Definite" (AE following in a reasonable temporal sequence the administration of the drug, with a known or expected response pattern to the suspected drug and confirmed by improvement on stopping or reducing the dose of the drug and by reappearance of the AE on repeated exposure), "Probable" (AE following in a reasonable temporal sequence the administration of the drug, showing a known or expected response pattern to the suspected drug and confirmed by improvement on stopping or reducing the dose of the drug and not reasonably explained by the known characteristics of the subject's clinical state, "Possible" (AE following in a reasonable temporal sequence the administration of the drug, showing a known or expected response pattern to the suspected drug but that could have been produced by other factors), "Unlike" (AE following in a reasonable temporal sequence the administration of the drug, showing a known or expected response pattern to the suspected drug but more likely due to the clinical state of the subject), "Not related" (AE not meeting the above criteria and with sufficient evidence that the AE could not be related to the investigational drug), "Unknown" (AE for which the judgement on the relationship with the investigational drug was not possible).

The evolution and outcome of each AE was also recorded.

### Overall evaluation of safety

The general safety of treatment was scored by the investigator as: Poor = 0; Moderate = 1; Good = 2; Very good = 3.

## 2.8. Laboratory tests

The following laboratory tests were performed on the patients at enrollement and after the 4-week treatment. In blood: red blood cell count, hemoglobin, platelets, glutamic-pyruvic transaminase, blood urea nitrogen. In urine: glucose, proteins, urobilinogen.

## 2.9. Statistical analysis

Descriptive statistics (arithmetic average, standard deviation, and standard error were calculated by conventional methods. Non-parametric tests such as a Mann-Whitney U test [19] and Wilcoxon matched-pairs signed-ranks test [19] were used to evaluate the significance of differences of effects.

[1] Viartril-S®; manufacturer: Rottapharm, Monza (Italy).

## 2.10. Ethical provisions

The investigated therapies and the conduct of the trial were consistent with the therapeutic provisions for osteoarthritis at the present status of the medical art. The protocol was approved by the Bureau of Drug Administration & Policy and by the ad hoc Commissions of PUMCH and BMUFAH. An informed consent to participate in the investigation was obtained from the subjects. The declaration of Helsinki (Venice Revision 1993) was observed in the conduct of the study. The patients were insured against risks and damages related to the study.

# 3. Results

## 3.1. Efficacy

One patient of the GS group dropped out for reasons not related to the drug and 9 patients of the IBU group dropped out for drug-related adverse events. The efficacy of the treatments could therefore be evaluated on a total of 168 patients, 87 treated with GS and 81 with IBU.

### Knee pain

Fig. 1 shows the averages of the recorded composite sum of scores and their 95 % confidence intervals. Both GS and IBU progressively and significantly reduced knee pain ($p < 0.0001$, Wilcoxon matched-pairs signed-rank test). In 4 weeks GS reduced knee pain by 57 % and IBU by 51 %. GS showed a trend of greater pain relieving efficacy, but the difference vs. IBU was not statistically significant (Mann-Withney U test).

After discontinuation of treatment both drugs exhibited a remnant efficacy because the knee pain scores did not increase significantly. The remnant efficacy had the trend to be greater with GS than with IBU, but the difference was not statistically significant ($p = 0.31$, Mann-Whitney U test).

### Knee swelling

Fig. 2 shows the average of the knee swelling scores and their 95 % confidence intervals. Both GS and IBU progressively and significantly reduced knee swelling ($p < 0.0001$, Wilcoxon signed-rank test).

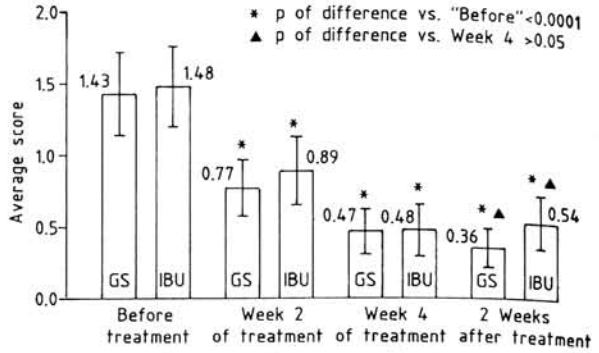


*Fig. 2:* Knee swelling score. Treatment with glucosamine sulfate (GS) or ibuprofen (IBU). Average scores (and 95 % confidence intervals) of knee swelling before starting the treatment, after 2 and after 4 weeks of treatment, and after 2 weeks of treatment discontinuation. The p of differences were calculated by the Wilcoxon matched-pairs signed-rank test.

In 4 weeks GS reduced knee swelling by 77 % and IBU by 78 %.

Both drugs exhibited a remnant efficacy on swelling after discontinuation of treatment. The remnant effect was notably greater after GS but the difference was not statistically significant ($p = 0.12$, Mann-Whitney U test).

### Improvement

The improvement ratings are shown in Fig. 3. GS tended to elicit a greater improvement especially with regard to freedom of symptoms, both after the 4 treatment weeks as after the 2 weeks of treatment-free follow-up. In the GS group there was also a lower percent of patients whose symptom worsened (4 % in the GS group vs. 6 % in the IBU group). The difference of improvement between the two treatments at week 4 was not yet significant (2-tailed $p = 0.09$), but was significantly better under GS after the 2-week treatment-free follow-up (2-tailed $p = 0.01$, Mann-Whitney U test).

### Therapeutic utility

Fig. 4 shows that GS had the trend to provide a better utility, especially with regard to the percent of "Good" utility ($p = 0.08$, Mann-Whitney U test).

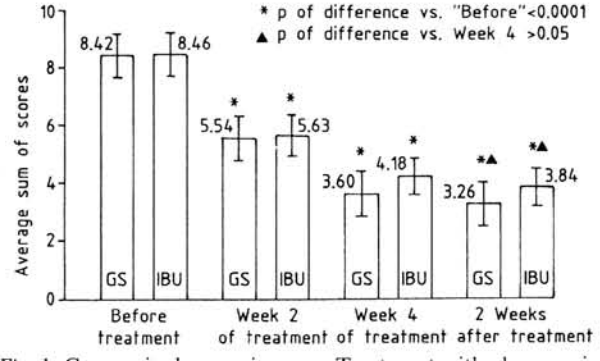


*Fig. 1:* Composite knee pain score. Treatment with glucosamine sulfate (GS) or ibuprofen (IBU). Averages of sum of scores (and 95 % confidence intervals) of knee pain at rest, at movement and at pressure before starting the treatment, after 2 and after 4 weeks of treatment, and after 2 weeks of treatment discontinuation. The p of differences were calculated by the Wilcoxon matched-pairs signed-rank test.

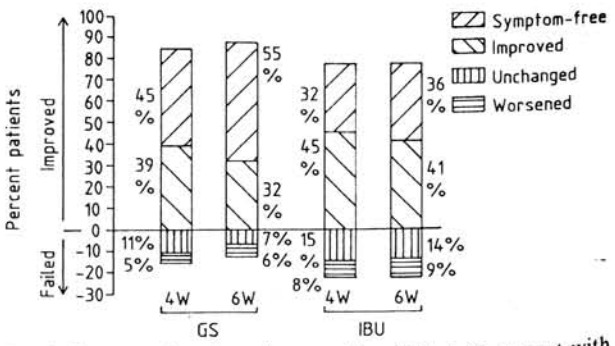


*Fig. 3:* Percent of patients improved or failed. Treatment with glucosamine sulfate (GS) or ibuprofen (IBU). Percent of patients with improvement or therapeutic failure after 4 treatment weeks (4W) and after 2 weeks of treatment discontinuation (6W).

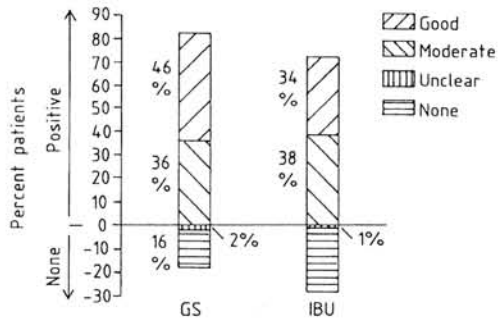


*Fig. 4:* Utility. Treatment with glucosamine sulfate (GS) or ibuprofen (IBU). Percent of patients in whom utility was rated "Good", "Moderate", "Unclear" or "None" after a 3-week treatment.

## 3.2. Safety

The tolerability of the treatments could be evaluated on 88 patients of the GS group and in 90 patients in the IBU patients.

### Adverse drug reactions and drop-outs

In the GS group 5 patients complained drug-related adverse events, i.e. 3 complained mild stomach discomfort, 1 mild sleepiness, 1 mild nausea. In the IBU group 14 patients complained drug-related adverse events, i.e. 1 mild abdominal pain, 1 severe stomach discomfort*, 1 mild swelling legs, 1 moderate vomiting, 1 severe hypertension*, 1 sleepiness*, 1 severe hematuria*, 2 mild sleepiness, 1 severe vomit*, 1 severe abdominal discomfort*, 1 severe edema eyelids and lips*, 1 severe skin rush*, 1 severe edema of face and legs* (the adverse events marked with * required drug discontinuation).

The ADRs and drop-outs are summarized in Table 2 and show that GS was significantly better tolerated than IBU because it provoked a significantly lower incidence of drug-related AEs and drop-outs.

### The overall evaluation of safety

The overall evaluation of safety given by the investigators of the two centers after 4 weeks treatment with GS or IBU is shown in Table 3. Table 4 gives the average rank of safety scores and the p value of the difference of ranking between GS and calculated with the Mann-Withney U test. The overall rank of safety resulted 18 % better for GS. The difference vs. IBU is statistically significant ($p = 0.01$) and confirms the better tolerability of GS evaluated from the incidence of drug-related adverse events and drop-outs.

## 4. Discussion

The medicinal therapy of osteoarthritis is usually directed to suppress the secondary inflammatory component of the disease, mainly with NSAID or with corticosteroids. These drugs are able to suppress inflammation and pain, but do not act on the causes and on the natural evolution of the disease, that may even worsen under these therapies [8, 13]. An alternative and perhaps more rational therapeutic approach is that using selective drugs for

*Table 2:* Adverse events and drop-outs. Number and percent (in parentheses) of patients.

| Group | GS | IBU | P of diff.[a)] |
|---|---|---|---|
| No. of patients | 88 (100) | 90 (100) | |
| AE related to drug | 5 (6) | 14 (16) | 0.02 |
| AE unrelated to drug | 2 (2) | 0 (0) | NS |
| Drop-outs related to drug | 0 (0) | 9 (10) | 0.0017 |
| Drop-outs unrelated to drug | 1 (1) | 0 (0) | NS |

[a)] Fisher exact probability.

*Table 3:* Overall evaluation of safety. Number and percent (in parentheses) of patients.

| Group | GS | IBU |
|---|---|---|
| Poor | 1 (1) | 9 (10) |
| Moderate | 1 (1) | 1 (1) |
| Good | 11 (13) | 17 (19) |
| Very good | 75 (85) | 65 (70) |

*Table 4:* Mann-Whitney U test on the rank of safety at the 4th week of treatment.

| Mean rank | | p 2-tailed |
|---|---|---|
| GS | Ibuprofen | |
| 97 | 82 | 0.010 |

osteoarthritis that suppress the pathogenic mechanisms of the disease rather than the symptoms only.

Glucosamine sulfate (GS) is one of the selective drugs for osteoarthritis. In fact GS is a preferred and essential substrate for the synthesis of proteoglycans by the chondrocytes [6, 16, 21, 22] and is able to normalize and stimulate this biosynthesis [2, 3]. In addition GS inhibits the generation of superoxide radicals and of lysosomal enzymes [18] and inhibits the activity of cartilage destroying enzymes such as collagenase and phospholipase A2 [15]. By these mechanisms GS selectively blocks the pathogenic processes of osteoarthritis, stops the evolution of the disease and relieves from symptoms as shown by a large clinical experience [4, 5, 7, 9, 10, 11, 12, 14, 17, 20].

In the investigations performed in comparison with NSAIDs, e.g. with ibuprofen [9], phenylbutazone [10] or piroxicam [17], GS at a daily dose of 1500 mg/d was equally effective on the symptoms of osteoarthritis as the reference NSAID, but was significantly better tolerated. This feature of GS is due to the fact that GS curbs selectively the pathogenic mechanisms of osteoarthritis and, unlike the NSAIDs, has not general non-specific effects such as the inhibition of the cyclo-oxygenases that trigger also several systemic effect with sometimes severe gastrointestinal or neurological adverse reactions.

For these properties GS is presently considered one the most important representative of the selective symptom modifying drugs for osteoarthritis, previously known as slow acting drugs [1]. The efficacy of GS on symptoms need some time to appear (1–2 weeks) because GS has no direct analgesic effects

but improves the biochemical and functional conditions of the joints. However, once the therapeutic effect is achieved it persists for a notable time also after discontinuation of treatment, contrary to the NSAIDs which need a continuous administration. This is the so-called remnant effect which allows cyclic therapeutic courses lightening the drug burden of the patients. In addition GS is a physiological substance used by our body for the biosynthesis of the proteoglycans, and this explains the safety of GS because our body is already used to it and does not adversely react for its disposal.

In our clinical study we have fully confirmed the efficacy of GS in the 80 patients with osteoarthritis of the knee who were treated for 4 weeks with a daily dose of 1500 mg GS. We have also confirmed the results of Müller-Fassbender et al. [9], i.e. that GS was significantly better tolerated than the reference ibuprofen, both with regard to the incidence of drug-related adverse reactions and drop-outs. Finally we confirmed the remnant benefits of the GS after therapy discontinuation.

We therefore conclude that GS is a drug which selectively curbs the pathogenic mechanisms of osteoarthritis and combines efficacy on symptoms with a good tolerability. GS appears therefore particularly useful in the long-term therapeutic courses needed in this chronic disease in which for good clinical practice any load with xenobiotic substances should be kept to a minium.

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