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## BRIEF REVIEW

# A review of glucosamine for knee osteoarthritis: why patented crystalline glucosamine sulfate should be differentiated from other glucosamines to maximize clinical outcomes

Eugene J. Kucharz<sup>a</sup>, Volodymyr Kovalenko<sup>b</sup>, Sándor Szántó<sup>c</sup>, Olivier Bruyère<sup>d</sup>, Cyrus Cooper<sup>e,f</sup> and Jean-Yves Reginster<sup>d</sup>

<sup>a</sup>Department of Internal Medicine and Rheumatology, Medical University of Silesia, Katowice, Poland; <sup>b</sup>State Institution National Scientific Center, Strazhesko Institute of Cardiology, Department of Non-Coronary Heart Diseases and Rheumatology, National Academy of Medical Sciences of Ukraine, Kiev, Ukraine; <sup>c</sup>Internal Medicine Institute, Rheumatology Department, University of Debrecen, Debrecen, Hungary; <sup>d</sup>Department of Public Health, Epidemiology and Health Economics, University of Liège, Liège, Belgium; <sup>e</sup>MRC Lifecourse Epidemiology Unit, University of Southampton, Southampton, UK; <sup>f</sup>NIHR Musculoskeletal Biomedical Research Unit, University of Oxford, Oxford, UK

## ABSTRACT

The European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) treatment algorithm for knee osteoarthritis (OA) recommends symptomatic slow-acting drugs for osteoarthritis (SYSADOAs) first line for the medium to long term management of OA, due to their ability to control pain, improve function, and delay joint structural changes. Among SYSADOAs, glucosamine is probably the most widely used intervention. In the present review of glucosamine for knee OA, we have investigated whether the evidence is greater for the patented crystalline glucosamine sulfate (pCGS) preparation (Rottapharm/Meda) than for other glucosamine formulations. Glucosamine is actually widely available in many forms, as the prescription-grade pCGS preparation, generic and over-the-counter formulations of glucosamine sulfate (GS) and food supplements containing glucosamine hydrochloride (GH), which vary substantially in molecular form, pharmaceutical formulation and dose regimens. Only pCGS is given as a highly bioavailable once daily dose (1500 mg) with a proven pharmacological effect. pCGS consistently reaches the plasma levels of around 10 µM required to inhibit interleukin-1 induced expression of genes involved in the pathophysiology of joint inflammation and tissue destruction, compared with sub-therapeutic levels achieved with GH. It is evident, from careful consideration of the evidence base, that only the pCGS formulation of glucosamine reliably provides an effect size on pain that is higher than that of paracetamol and equivalent to that provided by non-steroidal anti-inflammatory drugs. In comparison, the effect size on pain of non-crystalline GS preparations and GH from randomized controlled trials is repeatedly demonstrated to be zero. In addition, there is evidence that chronic administration of pCGS has disease-modifying effects, with a reduction in the need for total joint replacement surgery lasting for at least 5 years after treatment cessation. Consequently, the pCGS preparation (Rottapharm/Meda) is the logical choice, with demonstrated medium-term control of pain and lasting impact on disease progression.

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## Introduction

Traditionally, the pharmacological management of osteoarthritis (OA) has focused on therapies that may improve or control symptoms, or at least provide rescue analgesia. More recently, the use of symptomatic slow-acting drugs for osteoarthritis (SYSADOAs), in particular prescription-grade glucosamine sulfate (GS) and chondroitin sulfate (CS), has been proposed as a first-line pharmacological treatment for slow-onset medium to long term control of symptoms in OA<sup>1</sup>. SYSADOAs have demonstrated symptomatic effects as well as potential disease-modifying effects, based upon reports of downregulation in the expression of several inflammatory and degenerative mediators resulting in an effect on pain and symptoms and also a slower degradation of the cartilage,

hence preventing disease progression<sup>2</sup>. The clinical impact of this molecular mechanism has been observed as a reduction of pain and increased function, and radiological measurement of reduced joint space narrowing (JSN)<sup>3,4</sup>.

While multiple international evidence-based guidelines for OA management exist, agreement on the different treatment modalities is lacking<sup>5–9</sup>. The main source of disagreement regarding the use of SYSADOAs derives from the fact that the regulatory status and, subsequently, the availability and labeling of these medications substantially differ in separate countries and regions of the world<sup>10</sup>. Glucosamine, in particular, is available as the high quality prescription-grade patented crystalline glucosamine sulfate (pCGS) formulation (Rottapharm/Meda)<sup>11</sup>, generic and over-the-counter (OTC) formulations of GS and food supplements mostly containing the glucosamine

hydrochloride (GH) salt. Glucosamine generics, OTC products and food/nutritional supplements vary substantially from pCGS in their molecular forms, pharmaceutical formulation and dose regimens. Only pCGS is given as a highly bioavailable once daily dose (1500 mg) with a proven pharmacological effect<sup>12</sup>.

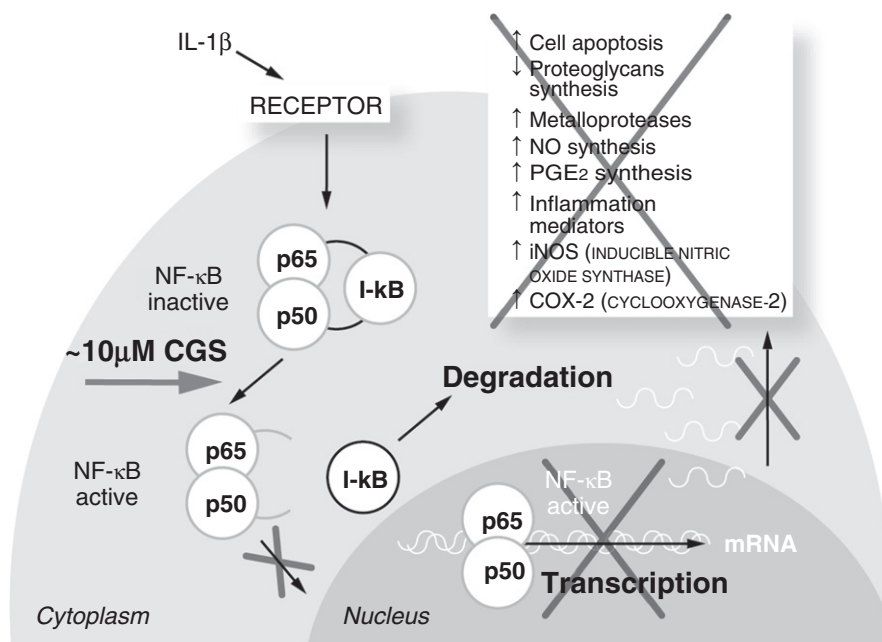
The European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO)<sup>13,14</sup> has recently developed a treatment algorithm recommendation which helps the prescribing physician to prioritize interventions in the management of knee OA, based upon the available evidence applicable across Europe and internationally<sup>1</sup>. The ESCEO Task Force acknowledged the variance in efficacy demonstrated with various glucosamine formulations in clinical studies, and recommends: "Among SYSADOAs, prescription [crystalline] glucosamine sulfate should be differentiated from other glucosamine preparations"<sup>1</sup>. In this review article on the use of glucosamine in the treatment of OA, we will explore the reasoning behind this distinction between glucosamine formulations by examination of the evidence base.

### Mechanism of action

Glucosamine is a naturally occurring building block for complex long-chain glycosaminoglycans that are linked to a core protein in proteoglycan molecules (aggrecans), and form part of the cartilage matrix. When administered exogenously, glucosamine exerts specific pharmacological effects on osteoarthritic cartilage and chondrocytes<sup>15,16</sup>. Glucosamine affects gene expression of OA cartilage, and the anti-catabolic activities of glucosamine are responsible for its therapeutic effects<sup>17</sup>. Glucosamine is demonstrated *in vitro* to reduce prostaglandin E<sub>2</sub> (PGE<sub>2</sub>) production and inhibit activation of the nuclear factor kappa B (NF- $\kappa$ B) pathway, thus inhibiting the cytokine intracellular signaling cascade in chondrocytes and synovial cells (Figure 1)<sup>2,16–19</sup>. In OA, glucosamine induces

reversal of the pro-inflammatory and joint-degenerating effects of interleukin-1 (IL-1)<sup>16</sup>. Interleukin-1 beta (IL-1 $\beta$ ) is a potent pro-inflammatory cytokine produced in high amounts in the OA joint, where it triggers the expression of inflammatory factors such as cyclooxygenase-2 (COX-2), inducible form of nitric oxide (iNOS), interleukin-6 (IL-6), and tumor necrosis factor alpha (TNF $\alpha$ ). IL-1 $\beta$  also induces cells to produce more IL-1 $\beta$  as well as matrix degradation factors, such as metalloproteinases (MMPs) and a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member TSs (ADAM-TSs). Most of these genes are under the transcriptional control of NF- $\kappa$ B. Glucosamine at clinically relevant concentrations reduces COX-2, iNOS, and microsomal prostaglandin E synthase-1 (mPGEs1) gene expression and PGE<sub>2</sub> synthesis after IL-1 $\beta$  stimulation, suggesting that glucosamine can control the cascade triggered by inflammatory stimuli<sup>20</sup>.

While these effects can be demonstrated *in vitro* with most glucosamine salts or preparations, pCGS is the only glucosamine formulation for which such effects can be confirmed at the concentrations that are actually achieved in biological fluids after administration at therapeutic doses in humans. Indeed, while it is unknown whether these *in vitro* effects are relevant to the therapeutic activities observed in clinical trials, pCGS inhibits IL-1-stimulated gene expression of joint degeneration mediators in human chondrocyte cells at concentrations in the range of 10  $\mu$ M, similar to those found in the plasma or synovial fluid of knee OA patients after receiving pCGS at the therapeutic dose of 1500 mg once daily<sup>2</sup>. A dose-dependent effect of pCGS on IL-1 $\beta$ -induced gene expression of matrix degradation factors MMP-3 (stromelysin-1) and ADAM-TS5 (aggrecanase 2) was observed (Figure 2)<sup>2</sup>. Long-term oral administration of GS reduces the destruction of cartilage and upregulation of MMP-3 mRNA in *in vitro* models<sup>21</sup>. Furthermore, studies in a human osteoarthritic explant model demonstrate that GS is a stronger



**Figure 1.** The mechanism of action of patented crystalline glucosamine sulfate: inhibition of interleukin-1-stimulated signaling pathway and gene expression. Adapted from Chiusaroli *et al.* 2011<sup>2</sup>, Largo *et al.* 2003<sup>18</sup>, and Gouze *et al.* 2002<sup>19</sup>. CGS, crystalline glucosamine sulfate; IL-1 $\beta$ , interleukin-1 beta; I- $\kappa$ B, a cellular protein that inhibits NF- $\kappa$ B; NF- $\kappa$ B, nuclear factor kappa B.

inhibitor of gene expression than GH, when both are administered at 5 mM doses<sup>22</sup>.

Differences between GS and GH formulations may be important at both the pharmacokinetic and pharmacologic levels and may help to explain the divergent findings found in clinical trials with different glucosamine salts and formulations. Sulfate concentrations increase after administration of GS, which may overcome a deficiency in inorganic sulfur, caused by a low level of dietary proteins, essential for the synthesis of proteoglycans that are important for chondrocyte metabolism<sup>23,24</sup>. GS is effective in animal models of surgically induced OA<sup>25</sup>, and is demonstrated to improve OA histological changes with a 60% reduction in the synovitis score compared with controls<sup>26</sup>. However, surgically induced experimental OA may not reflect all aspects of spontaneous idiopathic OA in humans. When given chronically to STR/ort mice who develop spontaneous OA with age, in which the whole joint undergoes degenerative changes entirely similar to those described in human OA<sup>27</sup>, pCGS ameliorated the histological damage, the extent of lesion, and histomorphometry in this animal model<sup>2</sup>.

## Pharmacokinetics

Pharmacokinetic studies demonstrate that a once daily dose of pCGS at 1500 mg leads to mean plasma concentration at steady state of 9  $\mu\text{M}$  of glucosamine in healthy volunteers<sup>28</sup>, i.e., in the 10  $\mu\text{M}$  range shown to be effective in counteracting IL-1-induced gene expression, while administration of GH (500 mg tid) leads to steady state levels of only 1.2  $\mu\text{M}$ <sup>29</sup>. Peak plasma levels of glucosamine after single dose GH (1500 mg) are about one third of those measured after pCGS at the same dose (1500 mg), while GH dosing with the regimen used routinely in practice of 500 mg three times daily further lowers the peak levels by 50%, even at steady state (Table 1)<sup>29</sup>. In a cross-over study, change from pCGS to GH resulted in a 50% decrease in peak plasma

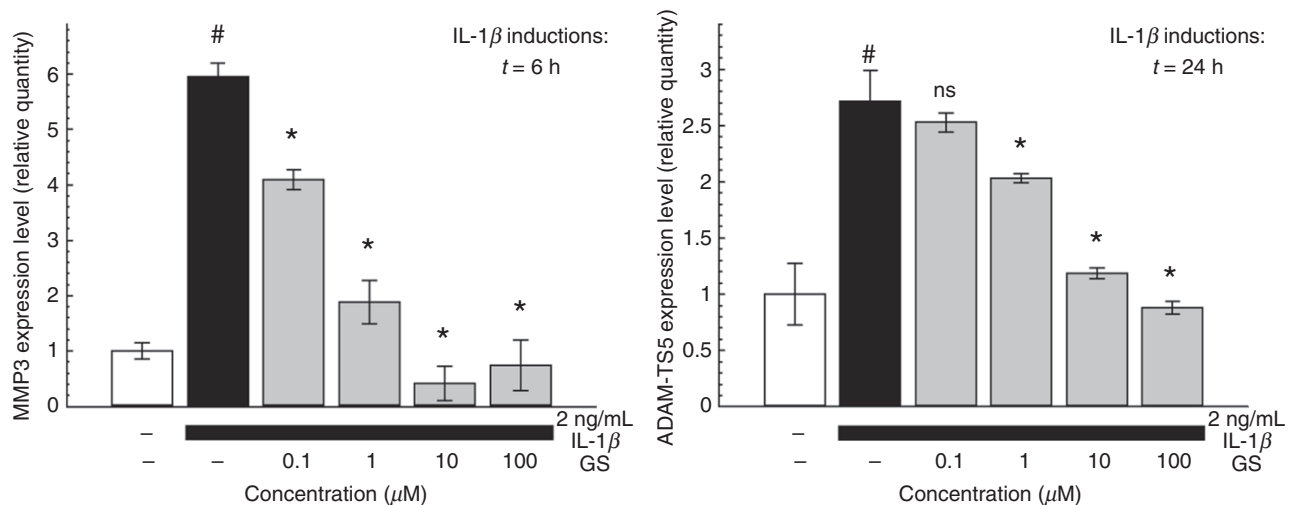
concentration and 75% reduction in total bioavailability<sup>12</sup>, which might be explained by the differences in dosing regimen and pharmaceutical formulation. Notably, the poor bioavailability obtained with GH may go some way to explain the poor results obtained with this formulation in the NIH-supported GAIT study (Glucosamine/chondroitin Arthritis Intervention Trial), which failed to demonstrate any efficacy for GH versus placebo<sup>30</sup>. Importantly, in OA patients, peak glucosamine concentrations at 7.17  $\mu\text{M}$  (range 3.35 to 22.7) in the plasma and 4.34  $\mu\text{M}$  (range 3.22 to 18.1) in the synovial fluid have been measured after once daily administration of pCGS (1500 mg)<sup>28,31</sup>.

A lack of appropriate stabilization of GS is shown to impact on the active ingredient availability; moreover, the quality of non-pCGS glucosamine formulations may be sub-optimal<sup>32</sup>. An investigation of 14 dietary supplements and OTC preparations of glucosamine found that only one contained the claimed amount of the active ingredient, while the others contained variable quantities ranging from 59 to 138% of the labeled dose<sup>32</sup>. Thus, only the pCGS formulation remains stable and reliably delivers sufficient plasma concentrations of glucosamine in the range that has been shown to be pharmacologically effective in reducing the expression of IL-1-induced cartilage degradation enzymes in human chondrocyte cultures<sup>2</sup>.

**Table 1.** Pharmacokinetic parameters for pCGS (1500 mg qd) and glucosamine hydrochloride (1500 mg qd or 500 mg tid). Adapted from Persiani *et al.* 2005<sup>28</sup> and Jackson *et al.* 2010<sup>29</sup>.

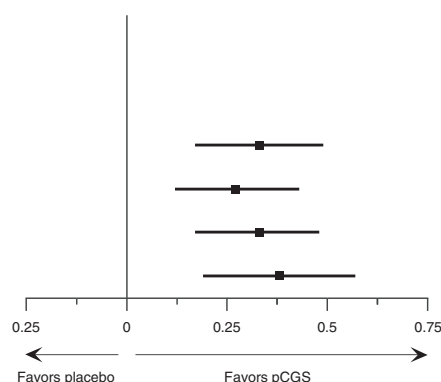
	pCGS 1500 mg qd Steady state	GH 1500 mg qd Single dose	GH 500 mg tid Steady state
$C_{max}$ (mean)			
ng/mL	1602 $\pm$ 425	492 $\pm$ 161	211 $\pm$ 93
$\mu\text{M}$	8.9 $\pm$ 2.4	2.7 $\pm$ 0.9	1.2 $\pm$ 0.5
$T_{1/2}$ (hours)	15	2.51 $\pm$ 1.84	3.94 $\pm$ 2.41

qd, once daily; tid, three times daily; GH, glucosamine hydrochloride; pCGS, patented crystalline glucosamine sulfate.



**Figure 2.** The dose-dependent effect of patented crystalline glucosamine sulfate on the IL-1 $\beta$ -induced gene expression of joint degeneration mediators MMP-3 (stromelysin-1) and ADAM-TS5 (aggrecanase 2) in human chondrocytes is optimized at clinically relevant concentrations ( $\sim 10$   $\mu\text{M}$ ). Reproduced from Chiusaroli *et al.* 2011<sup>2</sup>, with permission granted under the Creative Commons Attribution License. # $p < 0.001$  vs. untreated cells; \* $p < 0.001$  vs. IL-1 $\beta$  alone; ns, not significantly different from IL-1 $\beta$  alone.

Outcome	Effect size (95% CI) <sup>†</sup>
WOMAC scale	
Total	0.33 (0.17-0.49)
Pain	0.27 (0.12-0.43)
Function	0.33 (0.17-0.48)
Lequesne index <sup>‡</sup>	0.38 (0.19-0.57)
Test for heterogeneity, $I^2 = 0.00$	



**Figure 3.** Symptom outcomes for patented crystalline glucosamine sulfate formulation in knee osteoarthritis: pooled effect size from three pivotal trials. Adapted from Reginster 2007<sup>36</sup>. <sup>†</sup>Estimates and 95% confidence intervals (CIs) from fixed-model meta-analysis method using the pooled standard deviation in each study/outcome<sup>3,4,35</sup>; the data in the table have been depicted as a forest plot in the right-hand panel. <sup>‡</sup>Not assessed in one study<sup>3</sup>.

## Efficacy

The current treatment of OA is based upon primary pain and loss of function control. Numerous studies of varying quality have been conducted to determine the effect of glucosamine on pain. A Cochrane review of 25 randomized controlled trials of all glucosamine formulations in 4963 OA patients, when limited to studies with adequate concealment, failed to show any benefit of glucosamine for pain<sup>33</sup>. However, when the trials using pCGS were analyzed in isolation, it was found to be superior to placebo for pain (standardized mean difference [SMD]  $-1.11$ ; 95% confidence interval [CI]  $-1.66$  to  $-0.57$ ) and function (Lequesne index SMD  $-0.47$ ; 95% CI  $-0.82$  to  $-0.12$ ). Conversely, analysis of those trials using a non-pCGS preparation of glucosamine failed to reach statistical significance for pain or function<sup>33</sup>.

Possible explanations for the difference in efficacy found between different glucosamine formulations have focused on the poor quality of some trials included in the meta-analyses and the potential risk of bias which may distort the results. The Cochrane review found superiority for the pCGS formulation on pain in OA, but with high heterogeneity between trials ( $I^2 = 92\%$ )<sup>33</sup>. One solution is to focus only on the high quality trials of glucosamine. A subgroup analysis in the Cochrane review of three pivotal trials found pCGS to be significantly superior to placebo in terms of Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain subscale score (SMD  $-0.17$ ; 95% CI  $-0.32$  to  $-0.01$ ;  $p = 0.037$ ), with zero heterogeneity between trials<sup>33</sup>.

Eriksen and colleagues performed a stratified meta-analysis to address the potential risk of bias due to unsatisfactory handling of the data, i.e. during randomization and concealment and statistical analyses<sup>34</sup>. They found that only eight studies met the standard for 'low risk of bias'. This analysis confirmed that the five studies with non-pCGS even with a 'low risk of bias' found a non-significant effect on pain reduction (0.02; 95% CI  $-0.08$  to  $0.12$ ). In contrast, analysis of the three 'low risk of bias' studies with pCGS confirmed a reduction in pain with effect size of 0.27 (95% CI  $-0.43$  to  $-0.12$ )<sup>3,4,34,35</sup>. This recent finding is in total agreement with an earlier analysis of the same three trials of pCGS judged to be of highest quality using the Jadad quality score for clinical trials<sup>36,37</sup>. In the absence of industry bias, several other factors may explain the difference in efficacy observed between quality clinical

trials of glucosamine preparations. The superiority of pCGS may be explained by the unique stabilized formulation of glucosamine, single once daily dosing regimen (1500 mg) and high bioavailability, reaching higher glucosamine concentration in the plasma, compared with other preparations<sup>12</sup>.

The impact of pCGS formulation on other symptom outcomes is demonstrated in further analysis of results from the pivotal three trials, with a significant effect size on WOMAC total score, WOMAC pain and function subscale scores, and Lequesne index, with a complete absence of heterogeneity (Figure 3)<sup>36</sup>.

The effect size for pCGS on pain may be considered as only moderate at 0.27. However, it is notable that pCGS has a greater effect on pain than that of paracetamol (with effect size of 0.14; 95% CI 0.05 to 0.22)<sup>38</sup>, which may still be used as first-line rescue analgesia for OA<sup>1</sup>. In addition, the effect size of pCGS on pain over treatment periods ranging between 6 months and 3 years is equivalent to that achieved with oral non-selective or COX-2 selective non-steroidal anti-inflammatory drugs (NSAIDs), at 0.29 (95% CI 0.22 to 0.35) for much shorter treatment courses<sup>39</sup>, which are recommended as step 2 treatments in persistently symptomatic OA patients<sup>1</sup>. Thus, although it would be desirable to have interventions available in OA that provide more than a moderate effect, it is still a major finding that some interventions can indeed provide such a reliable and consistent efficacy pattern.

## Safety

For all treatments, the balance of risk versus benefits must be considered prior to administration. Oral NSAIDs are recommended for intermittent or cyclical use due to concerns over gastrointestinal (GI) and cardiovascular adverse events<sup>1</sup>. There is also accumulating evidence for an increased risk of GI adverse events with paracetamol use, with elevation in liver enzymes<sup>38</sup>. Conversely, pCGS may be taken safely in the long term with an adverse event rate comparable with that of placebo<sup>3,4,33,35</sup>.

## Disease-modifying effects

Evidence that long-term administration of pCGS over 3 years delays joint structure changes is provided by two trials,



**Table 2.** Prevention of joint space narrowing in knee osteoarthritis with pCGS formulation over 3 years' treatment. Reproduced from Bruyere et al. 2016<sup>40</sup>, with permission granted under the Creative Commons Attribution License.

Reginster et al. 2001 <sup>3</sup>	Placebo (n = 106)	pCGS (n = 106)	Difference	p value
JSW at enrolment, mm (mean ± SD)	3.95 ± 1.24	3.82 ± 1.32	–	–
3 year JSN, mm (mean and 95% CI)	–0.40 (–0.56 to –0.24)	–0.07 (–0.22 to 0.07)	0.33 (0.12 to 0.54)	0.003
Pavelka et al. 2002 <sup>4</sup>	Placebo (n = 101)	pCGS (n = 101)	Difference	p value
JSW at enrolment, mm (mean ± SD)	3.63 ± 1.57	3.89 ± 1.48	–	–
3 year JSN, mm (mean and 95% CI)	–0.19 (–0.29 to –0.09)	+0.04 (–0.06 to 0.14)	0.23 (0.09 to 0.37)	0.001

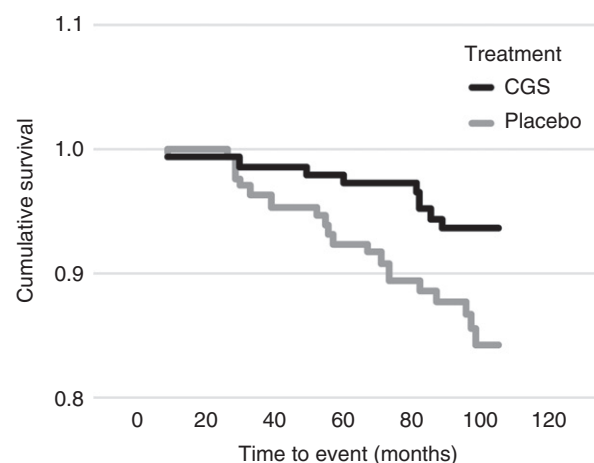
CI, confidence interval; JSN, joint space narrowing; JSW, joint space width; pCGS, patented crystalline glucosamine sulfate; SD, standard deviation.

suggesting a potential benefit of pCGS beyond symptom control when used early in the treatment algorithm. Analysis of joint space width (JSW) at trial enrollment and after 3 years of treatment in the two trials of pCGS versus placebo demonstrates a reduction in JSN with pCGS. In one study, a significant difference in JSN of 0.33 mm (95% CI 0.12 to 0.54) was observed with pCGS versus placebo after 3 years ( $p = 0.003$ )<sup>3</sup>. In the second study, pCGS treatment for 3 years was shown to completely prevent narrowing of the joint (JSN +0.04 mm; 95% CI –0.06 to 0.14;  $p = 0.001$ ) (Table 2)<sup>40</sup>. It should be noted that these trials used a radiological technique that is no longer considered state of the art today (although it was at the time the studies were performed). Nonetheless, post-hoc analysis of these findings demonstrates (i.e. demonstrates) that there was no bias determined by patient positioning or radiological view, thus confirming the validity of these results<sup>41</sup>.

A lack of progression of JSN (determined at a threshold of 0.5 mm [ $>0.3$ – $0.7$  mm]) has demonstrated predictive value of  $>90\%$  for not having joint replacement surgery<sup>42</sup>. In both studies, fewer patients treated with pCGS experienced predefined severe JSN ( $>0.5$  mm) compared with patients treated with placebo: 15% vs. 30% ( $p = 0.013$ )<sup>3</sup> and 5% vs. 14% ( $p = 0.05$ )<sup>4</sup>. Long-term follow-up of knee OA patients who had participated in the two 3 year trials of pCGS and received treatment for at least 12 months revealed in a post-hoc analysis that total joint replacement (TJR) had occurred in over twice as many patients from the placebo group (14.5%) in the 5 years of follow up compared with those patients formerly receiving pCGS (6.3%;  $p = 0.024$ ), demonstrating a 57% reduction in risk of TJR with pCGS (relative risk 0.43; 95% CI 0.20 to 0.92)<sup>43</sup>. Treatment with pCGS significantly delayed the need for TJR surgery ( $p = 0.026$ ) (Figure 4)<sup>43</sup>.

## Pharmacoeconomics

Evaluation of the cost-effectiveness of treatments and impact on healthcare budgets is increasingly important. Economic evaluation allows comparison of different strategies in terms of cost (intervention costs and disease costs) and consequences, e.g. quality-adjusted life years (QALYs). Six months' treatment with pCGS is shown to be a highly cost-effective therapy compared with paracetamol and placebo in the treatment of knee OA, in terms of incremental cost-effectiveness ratio (ICER)<sup>35,44</sup>. Further, a systematic review and economic evaluation has determined the incremental cost per QALY gain for adding GS to current care over a lifetime horizon to be around £21,335<sup>45</sup>. Sensitivity analysis determined that the



**Figure 4.** Effect of prior patented crystalline glucosamine sulfate formulation on cumulative incidence of total joint replacement surgery for up to 5 years following treatment. Reproduced from Bruyère et al. 2008<sup>43</sup>, with permission. CGS, crystalline glucosamine sulfate.

cost-effectiveness of GS therapy was particularly dependent on the magnitude of the quality of life gain, the change in knee TJR probability, and the discount rate.

Continuous treatment with pCGS results in a reduction in intake of other concomitant medication for OA and in a reduction in healthcare consultations and examinations, as demonstrated in a long-term follow up of OA patients<sup>43</sup>. A subset of patients who had previously taken part in a randomized trial attended a follow-up clinic visit at which the total average cost of OA-related resources per year was calculated to have approximately halved among those that had received pCGS versus placebo (€292 versus €605;  $p = 0.024$ ) (Table 3). The total cost of OA medications taken among the placebo group (including analgesics and NSAIDs) was almost double that of the pCGS group (€204 with placebo vs. €108 with pCGS); while the number of specialist, general practitioner (GP) and paramedic visits, and examinations (radiographs, gastroscopies and non-OA exams) were consistently higher among the placebo group compared with pCGS patients<sup>43</sup>.

Further evidence for a reduction in the need for rescue pain analgesia achieved with continuous pCGS is provided by a recent study, which is representative of all OA patients in everyday life. The Pharmacoeconomics of GonArthroSis (PEGASus) study was conducted by the French Health Authorities in collaboration with a panel of French rheumatologists and epidemiologists; the primary objective of the study was to assess the impact of SYSADOAs on the use of NSAIDs<sup>46</sup>. Adults with knee and/or hip OA consulting a rheumatologist or GP for symptom flare were recruited into

the PEGASus study and assigned to a SYSADOA treatment according to the physician's or patient's choice. During up to 24 months' follow-up, SYSADOA switching, continuation or discontinuation was permitted. Among all SYSADOA treatments, including GH, CS, avocado soybean unsaponifiables, and diacerein, in the primary analysis only pCGS achieved a significant reduction in NSAID use of 36% (odds ratio [OR] 0.64; 95% CI 0.45 to 0.92) (Figure 5). The reduction in NSAID use was even greater, approaching a 50% reduction, when patients who received >4 months of treatment with pCGS were considered alone (OR 0.52; 95% CI 0.28 to 0.95)<sup>46</sup>. It may be expected that similar findings in support of the cost-effectiveness of pCGS will be found in other countries, despite the different financing of healthcare systems.

# Discussion

The ESCEO treatment algorithm for knee OA recommends chronic SYSADOA treatment, specifically the patented crystalline glucosamine sulfate (pCGS) formulation and prescription

**Table 3.** Use of health resources per patient per year among osteoarthritis patients who had received pCGS formulation 5 years previously versus placebo. Adapted from Bruyère *et al.* 2008<sup>43</sup>.

Mean costs, €(US\$)*	Placebo (n = 43)	pCGS (n = 58)
Cost of analgesics	59 (77)	19 (25)
Cost of NSAIDs	116 (151)	63 (82)
Total cost of OA drugs (including analgesics, NSAIDs, etc.)	204 (265)	108 (140)
Number of visits to specialist, mean (SE)	2.1 (0.5)	1.8 (0.3)
Number of paramedic visits for OA	17.4 (6.3)	6.6 (2.0)
Number of radiographs for OA	0.60 (0.14)	0.44 (0.09)
Number of gastroscopies	0.30 (0.07)	0.10 (0.04)
Total cost calculated for OA-related resources†	605 (786)	292 (380)‡

\*1 €(euro) = approximately 1.3 US\$(2007).

†Total cost calculation includes costs of secondary healthcare visits (paramedic, specialist), examinations (radiographs, gastroscopies) and medication costs (analgesics, NSAIDs etc.).

‡*p* = 0.024 vs. placebo.

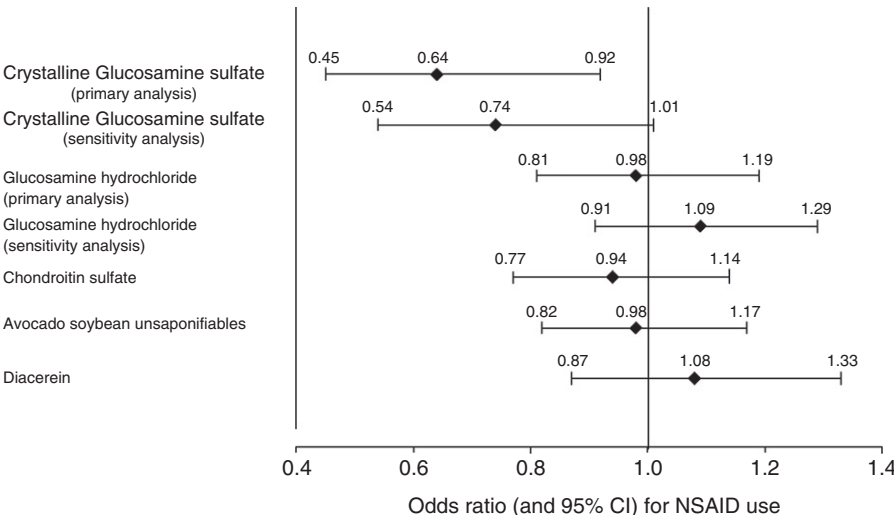
NSAIDs, non-steroidal anti-inflammatory drugs; OA, osteoarthritis; pCGS, patented crystalline glucosamine sulfate.

CS, as first line therapy for slow-onset medium to long term control of symptoms<sup>1</sup>. The ESCEO guidelines recognize that glucosamine is available in many forms, and yet not all formulations of glucosamine provide equivalent effects. Thus, the ESCEO Task Force recommends that the pCGS formulation should be differentiated from other glucosamine preparations due to a clear divergence in the evidence base<sup>1</sup>.

In this paper, we have set out the evidence for differentiation of pCGS from other glucosamine formulations. Publication of this review serves to educate and inform physicians as to this difference; however, we are aware that patient education is an essential element of successful disease management. The ESCEO algorithm, along with other guidelines, recommends a core set of initial measures that each knee OA patient should undergo, including information access and education, weight loss if overweight and an appropriate exercise program<sup>1</sup>. The patient should be informed that while OA cannot as yet be cured, an improvement in symptoms and a control of disease progression may be obtained with the correct use of appropriate medications. Educating the patient on the difference between pCGS and the many other glucosamine formulations widely available will help to ensure treatment adherence to the correct preparation and maximize treatment outcomes.

Mechanistic studies support the role of pCGS as both a symptom- and structure-modifying agent in OA, via glucosamine-induced reversal of the pro-inflammatory and joint-degenerating effects of IL-1. Specifically, pCGS inhibits IL-1-induced expression of genes involved in the pathophysiology of joint inflammation and tissue destruction at a plasma concentration of 10 µM. Only the pCGS formulation given as a highly bioavailable once daily dose (1500 mg) reliably reaches the plasma level of around 10 µM required to deliver a therapeutic effect.

Randomized controlled trials and meta-analyses consistently show a moderate effect size on pain for pCGS of 0.27, which is higher than that of paracetamol (0.14), considered as the gold standard first-line rescue analgesic medication, and



**Figure 5.** Odds ratio (with 95% confidence interval) for NSAID use with symptomatic slow-acting osteoarthritis drugs in the Pharmaco-Epidemiology of GonArthroSis (PEGASus) study. Reproduced from Rovati *et al.* 2016<sup>46</sup>, with permission granted under the Creative Commons Attribution License. CI, confidence interval; NSAID, non-steroidal anti-inflammatory drug (NSAID).

comparable with the effect size obtained for oral NSAIDs of 0.29. In comparison, the effect size on pain obtained with non-crystalline GS preparations and GH from randomized trials and meta-analyses is repeatedly demonstrated to be zero<sup>33</sup>.

## Conclusion

The goals of treatment for OA are to reduce symptoms and ultimately slow disease progression, which may in turn reduce the impact of OA on the patient's mobility and quality of life, and lead to a reduction in the need for rescue analgesia and joint replacement surgery in the long-term, with consequent reduction in healthcare resource needs<sup>47</sup>. As well as a moderate effect on pain, there is evidence that chronic administration of pCGS can have disease-modifying effects, delaying joint structural changes and leading to a reduction in need for knee replacement surgery. Furthermore, real-life pharmacoeconomic studies demonstrate a long-term reduction in the need for pain analgesia and NSAIDs with pCGS therapy over 12 months, with significant reduction in costs associated with medication, healthcare consultations and examinations. Consequently, exposing patients to a non-pCGS glucosamine preparation (sulfate or hydrochloride salt) which is not expected to provide any clinical benefit may be considered as unethical and, from a socioeconomic point of view, a waste of economic resources both in terms of direct drug costs and increased utilization of healthcare systems. Thus, the pCGS formulation (1500mg once daily) is the logical choice to maximize clinical benefit in OA patients with demonstrated medium-term control of pain and lasting impact on disease progression.

## Transparency

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