**FULL MANUSCRIPT**

Review article

**Title: The differentiation of patented crystalline glucosamine sulfate from other glucosamine preparations will optimize osteoarthritis treatment**

Running title: Differentiation of glucosamines for OA

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**Abstract**

Symptomatic slow-acting drugs for osteoarthritis (SYSADOAs) are recommended for the medium to long term management of knee osteoarthritis (OA) due to their ability to control pain, improve function, and delay joint structural changes. Among SYSADOAs, evidence is greatest for the patented crystalline glucosamine sulfate (pCGS) formulation ( Mylan). Glucosamine is widely available as glucosamine sulfate (GS) and glucosamine hydrochloride (GH) preparations that vary substantially in molecular form, pharmaceutical formulation and dose regimen. Only pCGS is given as a highly bioavailable once-daily dose (1500 mg), which consistently delivers 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. Careful consideration of the evidence base reveals that only pCGS reliably provides a moderate effect size on pain that is higher than paracetamol and equivalent to non-steroidal anti-inflammatory drugs (NSAIDs), while non-crystalline GS and GH fail to reach statistical significance for pain reduction. Chronic administration of pCGS has disease-modifying effects, with a reduction in need for total joint replacement lasting for 5 years after treatment cessation. Pharmacoeconomic studies of pCGS demonstrate long-term reduction in additional pain analgesia and NSAIDs, with a 50% reduction in costs of other OA medication and healthcare consultations. Consequently, pCGS is the logical choice, with demonstrated medium-term control of pain and lasting impact on disease progression. Physician and patient education on the differentiation of pCGS from other glucosamine formulations will help to improve treatment selection, increase treatment adherence, and optimize clinical benefit in OA.

Keywords: Glucosamine, Osteoarthritis, Symptomatic slow-acting drugs for osteoarthritis

**Introduction**

Osteoarthritis (OA) is the most common joint disorder and is a leading cause of pain and disability worldwide. Most of the OA disability burden is attributable to the hip and knee, of which knee OA is the more frequent. Knee and hip OA ranked as the eleventh highest contributor to global disability in 2010 (measured as 17 million years lived with disability)1. It is estimated that 1 in 10 of the population aged 60 years or older has significant clinical problems that can be attributed to OA2. Knee and hip OA is a major contributor to global disability-adjusted life years (DALYs), with the Asian regions contributing to a large proportion of the disability; mean DALYs were estimated at 4.4 billion for East Asia, 2.5 billion for South Asia and 1.2 billion for Southeast Asia in 20101.

The prevalence of OA increases with age and generally affects women more frequently than men1. The prevalence of self-reported and/or symptomatic knee OA in European Health Surveys ranges from 4% to 20%, with rates of 30% to 50% among those aged ≥65 years2. By comparison, the Community-Oriented Program for the Control of Rheumatic Diseases (COPCORD) studies conducted in the Asian region provide estimates of the prevalence of knee pain ranging from 11% in those aged >45 years to 22% in those aged >55 years, and 24–41% in those aged >65 years among populations in the Philippines and Vietnam3. The prevalence of a diagnosis of knee OA ranges from 1% to 6% in both urban and rural populations of Thailand, Malaysia, the Philippines and Vietnam, and is likely to be an underestimate of OA prevalence if reliant on radiographically-confirmed diagnosis3. The proportion of people aged ≥65 years in Asia is estimated to double in the next two decades, from 7% in 2008 to 16% in 20403, and the proportion of people aged ≥65 years will increase by more than 250% in Singapore, Malaysia and the Philippines3.

OA has been associated with heavy physical occupational activity, a required livelihood for many people living in rural communities in developing countries. Unfortunately, joint replacement surgery, an effective intervention for people with severe OA involving the hips or knees, is inaccessible to most people in these regions3. Traditionally, the pharmacological management of 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 (SYSADOA), in particular prescription 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 OA4. 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 progression5. 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)6, 7.

While multiple international evidence-based guidelines for OA management exist, agreement on the different treatment modalities is lacking8-12. 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 world13. Glucosamine, in particular, is available on prescription as patented crystalline glucosamine sulfate (pCGS) ( Mylan)14, as generic and over-the-counter (OTC) formulations of GS and in 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 prescription-grade pCGS is given as a highly bioavailable once-daily dose (1500 mg) with a proven pharmacological effect15. The European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO) has recently developed a treatment algorithm recommendation that helps the prescribing physician to prioritize interventions in the management of knee OA, which is based upon the available evidence and is applicable across Europe and internationally4. As a step 1 therapy, 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 pCGS should be differentiated from other glucosamine preparations due to a clear divergence in the evidence base4.

In this review article, we have set out the evidence for the differentiation of pCGS from other glucosamine formulations. Publication of this review will serve 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 program4. 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 formulation and maximize treatment outcomes.

**Glucosamine: 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 chondrocytes16, 17. Glucosamine inhibits gene expression of OA cartilage, and the anti-catabolic activities of glucosamine are responsible for its therapeutic effects18. GS is demonstrated *in vitro* to reduce prostaglandin E2 (PGE2) production and inhibit activation of the nuclear factor kappa-B (NFκB) pathway, thus inhibiting the cytokine intracellular signaling cascade in chondrocytes and synovial cells17-20. In OA, glucosamine induces reversal of the pro-inflammatory and joint-degenerating effects of interleukin-1 (IL-1)17. Interleukin-1 beta (IL-1β) 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 α (TNFα). IL-1β also induces cells to produce more IL-1β 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-κB. Glucosamine at clinically relevant concentrations reduces COX-2, iNOS, and microsomal prostaglandin E synthase-1 (mPGEs1) gene expression and PGE2 synthesis after IL-1β stimulation, suggesting that glucosamine can control the cascade triggered by inflammatory stimuli21.

These effects may be demonstrated *in vitro* with most glucosamine salts; however, pCGS is the only formulation for which these effects can be confirmed at the concentrations attained after administration of therapeutic doses in humans. pCGS inhibits IL-1-stimulated gene expression of joint degeneration mediators in human chondrocyte cells at concentrations in the range of 10 μM, similar to those found in plasma or synovial fluid of knee OA patients after receiving pCGS at the therapeutic dose of 1500 mg once-daily5. A dose-dependent effect of pCGS on IL-1β-induced gene expression of matrix degradation factors MMP-3 (stromelysin-1) and ADAM-TS5 (aggrecanase 2) was observed5. Long-term oral administration of GS reduces the destruction of cartilage and upregulation of MMP-3 mRNA in *in vitro* models22. Furthermore, studies in a human osteoarthritic explant model demonstrate that GS is a stronger inhibitor of gene expression than GH, when both are administered at 5 mM doses23.

**Glucosamine: Pharmacokinetics**

Studies measuring pharmacokinetic parameters demonstrate that a once daily dose of pCGS at 1500 mg leads to mean plasma concentration at steady state of 9 µM of glucosamine in healthy volunteers24, while administration of GH (500 mg tid) leads to steady state levels of only 1.2 µM (**Table 1**)25{Kucharz 2016}. In a cross-over study, change from pCGS to GH resulted in a 50% decrease in peak plasma concentration and 75% reduction in total bioavailability15, which might be explained by the differences in dosing regimen and pharmaceutical formulation. 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 placebo26. Importantly, in OA patients, peak glucosamine concentrations of 7.17 µM (range 3.35 to 22.7) in the plasma and 4.34 µM (range 3.22 to 18.1) in the synovial fluid have been measured at steady state after once-daily administration of pCGS for 14 days (1500 mg)27.

The quality of non-pCGS glucosamine formulations may be sub-optimal28, and a lack of appropriate stabilization of GS is shown to impact on the active ingredient availability. 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 dose28. The instability of glucosamine products other than pCGS has been observed in clinical practice in Asia. This may be due to the warm and humid climate conditions, which affects the chemical stability of some glucosamine formulations. 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 cultures5.

**Glucosamine: Efficacy**

The treatment of OA is based upon primary pain and loss of function control; thus, numerous studies of varying quality have been conducted to determine the effect of glucosamine on pain. A Cochrane review of 25 randomized controlled trials (RCTs) of all glucosamine formulations in 4,963 OA patients, when limited to studies with adequate concealment, failed to show any benefit of glucosamine for pain29. However, when the RCTs using the pCGS formulation were analyzed in isolation, pCGS 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 RCTs using a non-pCGS preparation of glucosamine failed to reach statistical significance for pain or function29. For example, an 8-week RCT of GH versus placebo failed to meet the primary endpoint of a statistically significant difference in Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain score; however, favorable differences were found in the secondary endpoints of cumulative pain reduction as measured by a daily diary question (*p*=0.018) and in the knee examination from Week 5 though to Week 8 (*p*=0.026){Houpt 1999}.

Proposed explanations for the difference in efficacy found between various 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. A systematic quality assessment and meta-analysis of glucosamine and chondroitin preparations for OA symptoms initially found moderate to large effect sizes for both treatments, although only one study described adequate allocation concealment and the effects were diminished when only high quality or large trials were considered{McAlindon 2000}. The Cochrane review found superiority for the pCGS formulation on pain in OA, but with high heterogeneity between trials (I2=92%)29. One solution is to focus only on the high quality trials of glucosamine. A subgroup analysis in the Cochrane review of 3 pivotal RCTs found pCGS to be significantly superior to placebo in terms of WOMAC pain subscale score (SMD -0.17; 95% CI -0.32 to -0.01; *p*=0.037), with zero heterogeneity between trials29.

A stratified meta-analysis was performed by Eriksen and colleagues to address the potential risk of bias due to unsatisfactory handling of the data, i.e. during randomization and concealment and statistical analyses30. They found that only 8 studies met the standard for ‘low risk of bias’. This analysis confirmed that the 5 studies with non-pCGS formulations 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 3 ‘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)6, 7, 30, 31. This recent finding is in total agreement with an earlier analysis of the same 3 RCTs of pCGS judged to be of highest quality using the Jadad quality score for clinical trials32, 33. 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 preparations15.

The impact of pCGS formulation on other symptom outcomes is demonstrated in further analysis of results from the pivotal 3 RCTs, 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 1**)32{Kucharz 2016}.

While the effect size for pCGS on pain may be considered as only moderate at 0.27, 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)34, which may still be used as first-line rescue analgesia for OA4. 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 courses35, which are recommended as step 2 treatments in persistently symptomatic OA patients4.

**Glucosamine: Safety**

The balance of risk versus benefits must be considered prior to administration of all treatments. Oral NSAIDs are recommended for intermittent or cyclical use due to concerns over gastrointestinal (GI) and cardiovascular adverse events4. There is also accumulating evidence for an increased risk of GI adverse events with paracetamol use, with elevation in liver enzymes34. Conversely, pCGS may be taken safely in the long term with an adverse event rate comparable with that of placebo6, 7, 29, 31.

In Thailand, the concomitant prescription of a COX-2 inhibitor plus pCGS is recommended for not more than 2 weeks due to safety concerns (related to the COX-2 inhibitor). In this case, an NSAID with an improved risk: benefit ratio may be considered, such as nabumetone, which is associated with a 10-fold lower risk of GI adverse events compared with other NSAIDs36.

**Glucosamine: Disease-modifying effects**

Two RCTs provide evidence that the long-term administration of pCGS over 3 years delays joint structure changes, suggesting a potential benefit of pCGS beyond symptom control when used early in the treatment algorithm6, 7. Analysis of joint space width (JSW) at trial enrollment and after 3 years of treatment in the 2 RCTs 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)6. 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**)7{Kucharz 2016}. Subsequent analysis demonstrated that the relief of knee pain did not bias the report of a structure-modifying effect of pCGS in these two trials37.

A lack of progression of JSN over 2–3 years (determined at a threshold of 0.5 mm [>0.3–0.7 mm]) has demonstrated predictive value of >90% for not having joint replacement surgery38, and is proposed as a surrogate marker for total joint replacement (TJR)39. In two studies, fewer patients treated with pCGS experienced predefined severe JSN (>0.5 mm) compared with patients treated with placebo6, 7. After 3 years, in the first study 30% of patients randomized to placebo had a severe mean JSN of >0.5 mm compared with 15% with pCGS (*p*=0·013)6. In the second study, the proportion of patients experiencing severe JSN was 14% in the placebo group and 5% in the pCGS group (*p*=0.05)7. Long-term follow-up of knee OA patients who had participated in the two 3-year RCTs of pCGS and received treatment for at least 12 months in a post-hoc analysis revealed that 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)40. Treatment with pCGS significantly delayed the need for TJR surgery (*p*=0.026) (**Figure 2**)40.

**Glucosamine: Cost-effectiveness**

Few studies have considered the economic costs of OA in Southeast Asia. The economic burden of OA to society and patients was found to increase 3-fold among patients who received total joint replacement surgery at the Singapore General Hospital41. The indirect cost of OA, including work absence and productivity loss, was estimated at around US$1000–1200 in Singapore, or around 3% of the annual household income42. The actual cost is likely to be higher as the estimate did not include caregiver burden. Further, the intangible cost of OA, calculated as the maximum amount a person would be willing to pay, sacrifice or exchange in order to avoid the pain and suffering of OA was estimated at US$1200 per year42. 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)31, 43. The incremental cost per QALY gain for adding pCGS to current care over a lifetime horizon is estimated at around £21,33544. The cost-effectiveness of pCGS therapy is dependent on the magnitude of the quality of life gain, the change in knee TJR probability, and the discount rate.

The continuous use of 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 patients40. A subset of patients who had previously taken part in an RCT 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**)40{Kucharz 2016}. 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 patients40.

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 Pharmaco-Epidemiology 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 NSAIDs45. 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 3**)45. 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)45.

**Conclusions**

Treatment goals for OA are to reduce symptoms and ultimately slow disease progression. In this respect, pCGS (1500 mg once-daily) is the logical choice to optimize OA treatment with demonstrated medium-term control of pain and lasting impact on disease progression. As well as a moderate effect on pain, chronic administration of pCGS over 12 months has disease-modifying effects, delaying joint structural changes and leading to a reduction in need for knee TJR surgery. There is also evidence for a reduction in the need for pain analgesia and NSAIDs with pCGS therapy over 12 months, with significant reduction in costs associated with medications, healthcare consultations and examinations. Finally, examination of the evidence base identifies that exposing patients to a non-pCGS glucosamine preparation (sulfate or HCl) which may not provide any clinical benefit might be considereda waste of economic resources both in terms of direct drug costs and increased utilization of healthcare systems.

New references to be added (as cited in revised text) and references re-numbered:

Kucharz EJ et al. A review of glucosamine for knee osteoarthritis: why patented crystalline glucosamine sulfate should be differentiated from other glucosamines to maximize clinical outcomes. Curr Med Res Opin 2016; 32(6):997-1004

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**Table 1** Pharmacokinetic parameters for patented crystalline glucosamine sulfate (pCGS) (1500 mg qd) and glucosamine hydrochloride (1500 mg qd or 500 mg tid). Adapted from Persiani et al. 200524 and Jackson et al. 201025; Reproduced with permission from Kucharz et al. 2016{Kucharz 2016}.

|  |  |  |  |
| --- | --- | --- | --- |
|  | **pCGS  1500 mg qd  Steady state** | **GH  1500 mg qd  Single dose** | **GH  500 mg tid  Steady state** |
| Cmax (mean)  ng/mL  μM | 1,602 ± 425  8.9 ± 2.4 | 492 ± 161  2.7 ± 0.9 | 211 ± 93  1.2 ± 0.5 |
| T1/2 (hours) | 15 | 2.51 ± 1.84 | 3.94 ± 2.41 |

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

**Table 2** Prevention of joint space narrowing in knee osteoarthritis with patented crystalline glucosamine sulfate (pCGS) over 3 years’ treatment. Adapted from Reginster et al. 20016 and Pavelka et al. 20027; Reproduced with permission from Kucharz et al. 2016{Kucharz 2016}.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Reginster et al. 20016 | **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. 20027 | **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.

**Table 3** Use of health resources per patient per year among OA patients who had received patented crystalline glucosamine sulfate (pCGS) formulation 5 years’ previously versus placebo. Adapted from Bruyère 200840; Reproduced with permission from Kucharz et al. 2016{Kucharz 2016}.

|  |  |  |
| --- | --- | --- |
| **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) = approx. 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.

**Figure legends**

**Figure 1** Symptom outcomes for patented crystalline glucosamine sulfate (pCGS) formulation in knee osteoarthritis: pooled effect size from three pivotal trials. Adapted from Reginster 200732; Reproduced with permission from Kucharz et al. 2016{Kucharz 2016} †Estimates and 95% confidence intervals (CIs) from fixed-model meta-analysis method using the pooled standard deviation in each study/outcome6, 7, 31: the data in the table have been depicted as a forest plot in the right-hand panel; ‡Not assessed in 1 study6. WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

**Figure 2** Effect of prior patented crystalline glucosamine sulfate (CGS) taken for at least 12 months on cumulative incidence of total joint replacement surgery for the subsequent 5 years following treatment, compared with placebo (received in two prior randomized controlled trials). Reproduced with permission from Bruyère et al. 200840.

**Figure 3** Odds ratio (with 95% confidence interval) for NSAID use with symptomatic slow-acting osteoarthritis drugs in the Pharmaco-Epidemiology of GonArthroSis (PEGASus) study. Adapted from Rovati et al. 201645, with permission granted under the Creative Commons Attribution License. CI, confidence interval; NSAID, non-steroidal anti-inflammatory drug (NSAID).