*Original Article*

# Patients' Real Life Experience in Using Glucosamine Sulfate for Treatment of Knee Osteoarthritis Under The Comptroller General's Department (CGD) Reimbursement Protocol: A Preliminary Report

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***Background:*** Knee osteoarthritis [OA] is one of the most common orthopedic diseases in Thailand. Glucosamine sulfate is an option for treatment of mild to moderate knee OA; however, this optional treatment has been restricted under the reimbursement protocol of the Comptroller General's Department [CGD]. The objective of this preliminary study was to evaluate both patient-reported and performance-based benefits of glucosamine for the treatment of knee OA when administered as specified by the CGD reimbursement protocol.

***Materials and Methods:*** We prospectively evaluated 100 knee OA patients who had been prescribed glucosamine sulfate and met CGD criteria for reimbursement. Outcomes of treatment were evaluated using conventional subjective measurements, including the Western Ontario and McMaster Universities Osteoarthritis Index [WOMAC], visual analog scale [VAS] for pain, and the Short form-12 [SF-12]. In addition, all patients had to complete two functional performance measures, the Timed Up and Go Test [TUGT] and the 5-time sit to stand [5XSST]. Measurements of all parameters were performed at pretreatment then again at week 6, 12, and 18.

***Results:*** Patients were divided in to into 3 groups according to Kellgren and Lawrence system: mild OA (KL 1), moderate OA (KL 2-3), and severe OA (KL 4) in accordance with the CGD reimbursement protocol. At the 18-week follow-up [FU], 57 of the 100 patients (50 females and 7 males) had completed evaluations of all parameters. Fifteen of the 57 patients were in the mild group (KL 1), 32 were in the moderate group (KL 2-3), and 10 were in the severe group (KL 4). The patients' mean age was 68.28 years, and the mean BMI was 26.03 kg/m$^2$. At the 18-week FU, values of all investigated parameters had significantly improved. However, improvement of the conventional clinical subjective parameters occurred later than those of objective functional performance, including TUGT improved from week 6; VAS, SF-12 (PCS), and 5XSST from week 12; and WOMAC and SF-12 (MCS) from week 18.

***Conclusion:*** At the 18-week FU, glucosamine sulfate treatment of knee OA administered following the CGD reimbursement protocol results in improvement in all evaluated parameters, especially performance-based measurements, which had no patient or surgeon bias. Whilst significant improvement was detected from week 6, at week 12, most of them were detected. Therefore, the results of this preliminary study supported the CGD reimbursement protocol, which defines that physicians have to evaluate the outcomes of treatment after 12 weeks.

***Keywords:*** Glucosamine sulfate, Osteoarthritis, Knee, Real life, Reimbursement

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Knee osteoarthritis [OA] is a common degenerative joint disease, which results in pain, inflammation, loss of range of motion, and limitation of daily activities. In the United States, the incidence of knee OA in people over 60 years old was 12.1%[1]. OA outpatients represented the highest proportion of outpatient department visits related to arthritis and other rheumatic conditions [AORC] during 2001 to 2005 in the US[2]. In 2010, the disability-adjusted life year [DALYs] increased by 26.2% relative to 1994[3]. Total health expenditure per year for the treatment of OA was more than 60 billion USD[4]. In Thailand in 2013, the reported incidence of knee OA in geriatric patients was 8.6%[5]. In 2004, among Thai females, the DALYs showed that knee OA ranked 7th and represented 3.1% of the DALY total[6].

Currently, several methods and medications are available for treatment of knee OA including lifestyle modification, exercise, body weight control, rehabilitation, acetaminophen, non-steroidal anti-inflammatory drugs [NSAIDs], tramadol, symptomatic slow-acting drugs for OA [SYSADOA], steroid injection, viscosupplement injection, and surgery[7-9]. The efficacy of treatment depends on several factors including severity of the disease, patient compliance, and type of treatment. NSAIDs have demonstrated good efficacy in treatment of knee OA, but they may have adverse effects on the cardiovascular and gastrointestinal systems[10,11].

Glucosamine is a water-soluble amino monosaccharide. It is found in high amount in articular cartilage and synovial fluid[12], and glucosamine sulfate has been proposed as a choice treatment for mild to moderate knee OA. In 2014, the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis [ESCEO] considered SYSADOA, including glucosamine sulfate, to be the first line drug for treating knee OA[13], although the efficacy of glucosamine sulfate is still controversial. Some researchers have reported that glucosamine sulfate can delay the progression of knee OA[14,15] and that it can reduce pain when compared to placebo, acetaminophen, and NSAIDs[16-18]. Other studies have reported that glucosamine sulfate does not decrease pain or delay the progression of knee OA[19,20]. In terms of cost-effectiveness, Scholtissen et al reported that glucosamine sulfate was highly cost-effective when compared to paracetamol for treatment of knee OA[21], while Black et al stated that they could not conclusively demonstrate that using glucosamine sulfate was cost-effective[22].

In Thailand, under the Comptroller General's Department [CGD] reimbursement protocol, the use of authorization for reimbursement for glucosamine for knee OA is restricted to patients meeting CGD criteria, including primary knee OA, prior failure of 3 months of conservative treatment, and age ≥56 years. Eligible patients can be prescribed reimbursed for treatment with glucosamine for an initial period of 6 weeks and can be renewed for a total of 24 weeks (one cycle) in order to be reimbursed for the glucosamine, the patients must undergo an evaluation of their clinical improvement at 3 months (12 weeks) after treatment. After the 1st cycle, the patients have to stop glucosamine for 12-week period. Only those patients who have shown improvement in clinical outcome will be able to continue the next to be reimbursed for another cycle of glucosamine treatment. To the best of our knowledge, there have been no published reports demonstrating that this protocol is useful to use patients evaluating the impact of this 12-week interval without glucosamine treatment. The objective of this preliminary study was to evaluate begin an evaluation of the results effect on patients of following the CGD reimbursement protocol in the treatment of knee OA in a real life situation.

## Materials and Methods

This study was approved by the Ethical Review Board of our institution. One hundred knee OA patients who met the CGD criteria were initially included in the study. For all patients, the diagnosis of primary knee OA was made following the American College of Rheumatology criteria and treatment was provided at the outpatient clinic. Exclusion criteria included a history of allergy to glucosamine, use of pain medications or SYSADOAs during the previous 2 weeks, use of pain medications for more than 2 weeks during the course of this study, and refusal to participate in the study.

Following initial screening, grading of the severity of knee OA of the patients was done using radiography in conjunction with clinical subjective parameters including the visual analogue scale [VAS] for pain, the Western Ontario and McMaster Universities Osteoarthritis Index [WOMAC][23], the 12-Item Short Form Health Survey [SF-12] including both the Physical Component Scores [PCS] and the Mental Component Scores [MCS] components[24], and 2 clinical objective functional performance measures, the Timed Up and Go Test [TUGT][25] and the Five Times Sit to Stand Test [5XSST][26].

The WOMAC[23], a disease-specific measurement of function, is composed of 3 domains consisting of a total of 24 items: pain (5 items), stiffness (2 items), and physical function (17 items). Each item was graded from 0 to 4 (0 = very well, 4 = very poor), with a maximum score of 96 points (the worst outcome) and a minimum score of 0 points (the best outcome). The Timed Up and Go Test [TUGT][25] measured the time that it took a patient to stand up from a chair and walk for 3 meters either with or without gait aid and return to the chair. The Five Times Sit to Stand Test [5XSST][26] measured the time it took a patient to stand up and sit down on a chair 5 times. Patients were divided into three groups based on the severity of their knee OA using the Kellgren and Lawrence classification [27]: mild (KL 1), moderate (KL 2-3), and severe (KL 4) following the 2011 Royal College of Orthopaedic Surgeons [RCOST] clinical practice guidelines for knee OA treatment[28].

The patients were then prescribed glucosamine sulfate sachet (Viartril-S 1,500 mg, Rottapharm Madaus, Confienza, Italy) to be taken once daily for an initial period of 6 weeks. As this is a study of the real-life impact of treatment, patients were allowed to continue all daily living activities. They were given an appointment for a follow-up visit every 6 weeks for a total of 4 additional visits over 24 weeks. At each follow-up visit, patients were reevaluated on the same parameters used in the pre-treatment evaluation. After the 2nd through the 3rd visits, they were prescribed glucosamine sulfate for an additional 6 weeks. Then after taking glucosamine for a total of 24 weeks, patients were required to stop taking glucosamine for 12 weeks (resting period) in order to maintain their eligibility for CGD reimbursement after which they started could start a new cycle of treatment with glucosamine for which they could be reimbursed.

In order to verified the CGD reimbursement protocol for its reliability to use in those patients who have eligible criteria. This study was intentionally reported patients outcomes when he/she finished the week 18 of treatment. However, this report would be a preliminary one, whilst the results of this cohort with longer follow-up was on the process of the study.

Statistical analysis was performed using Microsoft Excel 2013 software. Quantitative data are presented as either mean and range or mean $\pm$ SD. The paired t-test was performed for each measurement to compare before and after treatment with glucosamine. All $p$-values are 2-tailed. A $p$-value $<0.05$ was considered statistically significant.

## Results

Of the 100 patients initially identified, 57 completed evaluation of all investigated parameters for the entire 18 week study period. That group was comprised of 50 females and 7 males with an age range of 56 to 87 years (mean, 68.28 years). The mean BMI was 26.03 kg/m$^2$ (range, 19.56 to 38.54 kg/m$^2$). Assessment of the severity of knee OA found that 15 patients were in the mild group (KL 1), 32 patients were in the moderate group (KL 2-3), and 10 patients were in the severe group (KL 4) (Table 1).

Overall, the VAS for pain significantly improved beginning in week 12, although improvement was not uniform among the subgroups. There was significant improvement of VAS for pain in the moderate group (VAS at pretreatment, 3.63 and VAS at week 12, 2.66), but there were no differences in VAS for pain in either the mild or the severe subgroups at any of the time points (Table 2 and Figure 1).

**Table 1.** Demographic data of participating patients overall and by subgroups

| | All patients (n = 57) KL 1 | Mild (n = 15) KL 2-3 | Moderate (n = 32) KL 4 | Severe (n = 10) |
|---|---|---|---|---|
| Age (years) | 68.28 (56 to 87) | 64.67 (56 to 79) | 69.22 (56 to 84) | 70.7 (62 to 87) |
| Sex (%) | | | | |
| Female | 50 (87.72) | 14 (93.33) | 27 (84.38) | 9 (90) |
| Male | 7 (12.28) | 1 (6.67) | 5 (15.62) | 1 (10) |
| Height (cm) | 155.65±6.07 | 155.47±6.37 | 155.41±6.05 | 156.70±6.22 |
| Weight (kg) | 63.17±10.51 | 61.61±11.19 | 61.99±8.63 | 69.24±13.63 |
| BMI (kg/m$^2$) | 26.03±3.91 | 25.35±3.34 | 25.69±3.63 | 28.13±5.13 |

KL = Kellgren and Lawrence; BMI = body mass index

At the 18-week FU, functional performance of the combined group improved for both 5XSST and TUGT. However, TUGT showed improvement earlier, with significant gains being observed at week 6 and continuing through week 18: TUGT at pretreatment = 9.58 seconds, at week 6 = 8.42 seconds ($p = 0.001$), at week 12 = 8.27 seconds ($p = 0.0004$), and at week 18 = 7.70 seconds ($p<0.0001$). TUGT improved primarily in the mild and moderate subgroups. Overall, the 5XSST scores improved only from week 18 (5XSST at pretreatment = 9.58 seconds; 5XSST at week 18 = 7.70 ($p<0.0001$)), while the severe subgroup showed significant improvement from week 12 (Table 2 and Figure 2, 3).

Patient-reported outcomes or PROMs of

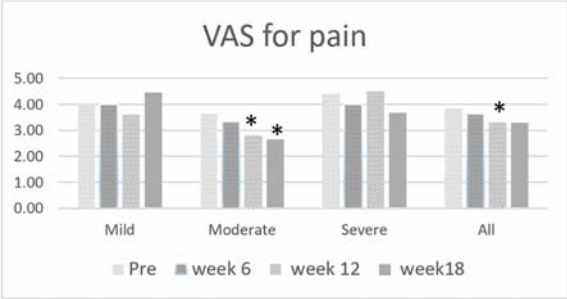


**Figure 1.** Graph comparing the mean values of each subgroup for VAS pain at pretreatment and at weeks 6, 12, and 18. * Statistically significant ($p<0.05$).

**Table 2.** Investigated parameters combined and by subgroup

| | Pre | Week 6 | *p*-value | Week 12 | *p*-value | Week 18 | *p*-value |
|---|---|---|---|---|---|---|---|
| VAS for pain | | | | | | | |
| Mild | 4.00±2.33 | 4.00±2.54 | 1 | 3.60±2.56 | 0.38 | 4.47±2.56 | 0.42 |
| Moderate | 3.60±2.20 | 3.34±2.36 | 0.26 | 2.81±2.38* | 0.003* | 2.66±2.65 | 0.01* |
| Severe | 4.40±2.17 | 4.00±2.00 | 0.10 | 4.50±2.22 | 0.91 | 3.70±2.45 | 0.51 |
| All | 3.86±2.21 | 3.63±2.33 | 0.20 | 3.32±2.44* | 0.03* | 3.32±2.67 | 0.06 |
| 5xSST (second) | | | | | | | |
| Mild | 17.35±3.76 | 16.77±6.05 | 0.60 | 16.34±4.29 | 0.41 | 17.33±6.26 | 0.99 |
| Moderate | 16.57±4.09 | 16.88±4.80 | 0.69 | 16.46±5.05 | 0.90 | 14.67±4.04* | 0.004* |
| Severe | 20.25±5.96 | 16.97±2.53 | 0.09 | 17.35±4.44* | 0.04* | 15.99±3.82* | 0.008* |
| All | 17.42±4.51 | 16.87±4.79 | 0.38 | 16.59±4.69 | 0.18 | 15.60±4.74* | 0.002* |
| TUGT (second) | | | | | | | |
| Mild | 9.57±2.83 | 8.51±3.02 | 0.26 | 7.35±2.27* | 0.007* | 7.82±2.45* | 0.007* |
| Moderate | 10.04±2.71 | 8.64±2.76* | 0.001* | 8.60±2.66* | 0.003* | 7.79±2.78* | <0.0001* |
| Severe | 8.11±1.93 | 7.61±1.78 | 0.33 | 8.58±2.13 | 0.41 | 7.23±1.76 | 0.12 |
| All | 9.58±2.68 | 8.42±2.68* | 0.001* | 8.27±2.50* | 0.0004* | 7.70±2.52* | <0.0001* |
| WOMAC | | | | | | | |
| Mild | 30.67±12.29 | 33.60±16.19 | 0.36 | 32.80±16.63 | 0.59 | 28.73±15.89 | 0.56 |
| Moderate | 34.25±20.00 | 32.72±20.35 | 0.45 | 34.03±22.21 | 0.93 | 30.31±18.41 | 0.055 |
| Severe | 36.10±18.78 | 32.50±12.98 | 0.29 | 30.40±14.89 | 0.16 | 26.30±15.18* | 0.01* |
| All | 33.63±17.88 | 32.91±17.95 | 0.64 | 33.07±19.49 | 0.77 | 29.19±17.03* | 0.005* |
| SF-12 PCS | | | | | | | |
| Mild | 48.96±14.38 | 47.52±14.23 | 0.55 | 50.30±14.99 | 0.69 | 53.49±13.70 | 0.20 |
| Moderate | 46.17±15.53 | 50.42±16.70* | 0.049* | 54.09±18.91* | 0.01* | 58.71±17.25* | 0.0003* |
| Severe | 47.07±11.88 | 47.77±10.95 | 0.80 | 50.85±12.78 | 0.45 | 51.90±11.35 | 0.26 |
| All | 47.06±14.47 | 49.19±15.04 | 0.14 | 52.52±16.84 | 0.01* | 56.14±15.53* | 0.0001* |
| SF-12 MCS | | | | | | | |
| Mild | 62.95±16.56 | 62.06±13.38 | 0.67 | 62.36±14.81 | 0.85 | 65.66±13.33 | 0.40 |
| Moderate | 60.83±14.41 | 64.32±12.52 | 0.09 | 62.87±13.06 | 0.44 | 66.84±13.01 | 0.04* |
| Severe | 61.97±18.33 | 58.60±15.68 | 0.58 | 64.98±12.05 | 0.46 | 65.04±11.61 | 0.43 |
| All | 61.59±15.44 | 62.72±13.25 | 0.49 | 63.11±13.17 | 0.40 | 66.22±12.66 | 0.02* |

Values presented as mean ± SD. The *p*-value corresponds to paired t-test, * statistically significant (*p*-value <0.05).
5XSST = 5 Times Sit to Stand; TUGT = Timed Up and Go Test; SF-12 PCS = SF-12 Physical Component summary; SF-12 MCS = SF-12 Mental Component summary


**Figure 2.** Graph comparing the mean values of each subgroup for 5XSST at pretreatment and at weeks 6, 12, and 18. *Statistically significant ($p$<0.05).

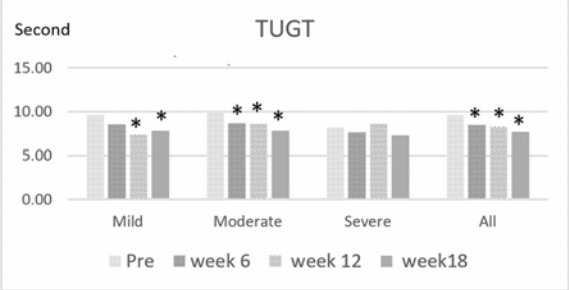


**Figure 3.** Graph comparing the mean values of each subgroup for WOMAC at pretreatment and at weeks 6, 12, and 18. * Statistically significant ($p$<0.05).

the studied group, including WOMAC, SF-12 PCS, and SF-12 MCS, significantly improved at week 18 (WOMAC: pretreatment, 33.63 vs. week 18, 29.19 (p 0.005), SF-12 PCS: pretreatment, 47.06 vs week 18, 56.14 ($p$ = 0.0001) and SF-12 MCS: pretreatment, 61.59 vs week 18, 66.22 ($p$ = 0.02)). However, in subgroup analyses, the WOMAC only improved in the severe subgroup at week 18 (pretreatment = 36.10 vs. week 18 = 26.30 ($p$ = 0.01)), while SF-12 PCS and SF-12 MCS only improved for patients in the moderate subgroup (Table 2 and Figure 4 to 6).

## Discussion

When knee OA in geriatric patients progresses, resulting in a decrease in quality of life[6], most patients search for a variety of non-surgical treatments, the cost of which ranges from low to expensive[4]. Among the several available methods of non-surgical treatment of OA knee, glucosamine sulfate is one commonly used option; however, its efficacy

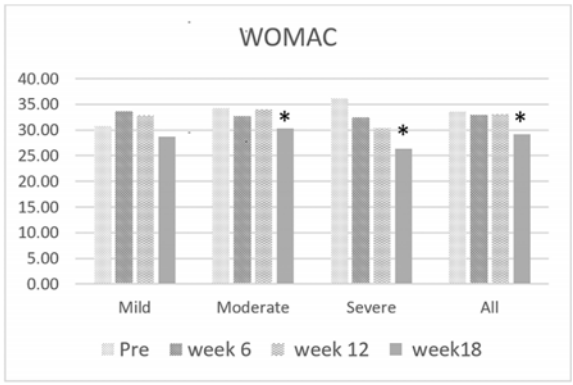


**Figure 4.** Graph comparing the mean values of each subgroup for SF-12 PCS at pretreatment and at weeks 6, 12, and 18. *Statistically significant ($p$<0.05).

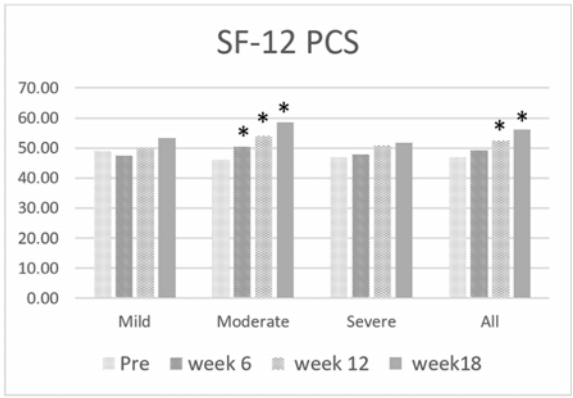


**Figure 5.** Graph comparing the mean values of each subgroup for SF-12 PCS at pretreatment and at weeks 6, 12, and 18. * Statistically significant ($p$<0.05).

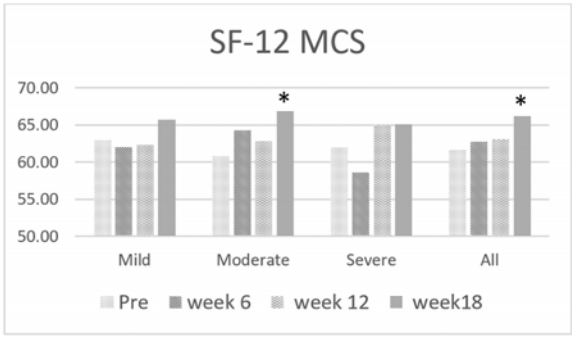


**Figure 6.** Graph comparing the mean values of each subgroup for SF-12 MCS at pretreatment and at weeks 6, 12, and 18. *Statistically significant ($p$<0.05).

in relation to the cost of treatment is somewhat controversial[14,19,21,22]. For that reason, in Thailand prescription of glucosamine sulfate is restricted to certain groups of patients under the CGD reimbursement protocol, although all patients can receive the medication if they pay for it themselves. The present study intended to report real-life outcomes after a 18-week course of glucosamine treatment under the Thai CGD protocol.

To avoid potential bias from subjective evaluations by the patient, including pain perception (VAS) and PROMs measurements (WOMAC and SF-12), we also included performance-based measurements, including the TUGT and 5XSST, which are objective measures of functional ability. It is thus possible that a patient could exhibit no measurable clinical improvement but still have a positive attitude regarding the perceived benefits of glucosamine sulfate. In fact, the present study found clinical significant improvement in both VAS, PROMs measurements (WOMAC and SF-12) as well as in performance-based measurements (TUGT and 5XSST) at 18 weeks after treatment of knee OA with glucosamine sulfate, especially for performance-based outcomes with performance-based measures of improvement occurring earlier than subjective measures.

Functional performance outcomes improved significantly at week 6 (TUGT), earlier than significant improvement of VAS and PROMs which was first detected at week 12 and week 18. These findings implied that patients' objectively measured functional abilities improved before they noticed subjective improvement in their daily activities. As noted above, we believe that significant improvement of objectively measured functional performance is a reliable measure that avoids possible patient bias. Therefore, it appeared that treatment of knee OA with glucosamine sulfate following the CGD protocol provided reliable cost-effectiveness. The current CGD reimbursement protocol for knee OA requiring the physician to perform an evaluation of clinical improvement after 3 months of treatment without supporting scientific information. This study was the first domestic study to evaluate the requirement for compulsory outcome evaluation after 3-months of treatment with glucosamine sulfate.

The findings of this study were in agreement with previous studies, which reported WOMAC score improvement after a few months of treatment. In knee OA with moderate severity, Korkmaz et al[29] reported significant improvement of WOMAC scores from a baseline of 51.56 to 33.12 at week 12 of treatment. However, a domestic study by Wangroongsub et al[30] found only insignificant improvement in WOMAC scores after treatment with glucosamine sulfate from a baseline of 79.44 to 77.73 at 12 weeks. As glucosamine sulfate is made by several manufacturers, conflict outcome of different studies might relate to the differences in study results may be related to the use of glucosamine from different manufacturers.

This study had some limitations. Firstly, the initial final sample size was small due to lack of patient cooperation in submitting WOMAC and SF-12 data at each follow-up visit and a high dropout rate. Secondly, the duration of this study was limited to 18 weeks. However, this preliminary study was designed to investigate the CGD protocol requirement for pateint evaluation after 3 months of glucosamaine treatment. in addition, we are continuing to collect data on the patients in this study until they finish their 2nd round of treatment (60 weeks) of treatment and we are also increasing the number of patients included in the next phase of study. Finally, this study was a real-life study which means we did not attempt to control either patient activities or other confounding factors, rather we wanted to observe the impact of glucosamine sulfate on the patients' lives.

## Conclusion

Glucosamine sulfate is an effective treatment for knee OA as demonstrated by both objective and subjective measures. Improvement in objective measures tended to occur earlier than improvement in subjective measures. At 18 weeks of treatment of knee OA with glucosamine sulfate administered following the CGD reimbursement protocol, it resulted in improvement in most evaluation parameters, both subjective measures (VAS, PCS of SF-12), and performance-based measure (TUGT). At 18 weeks of treatment, the rest investigated parameters were found improved (5XSST, WOMAC, and MCS of SF-12). This preliminary study supported the use of the CGD reimbursement protocol for evaluation of outcomes after 12 weeks of for treatment with glucosamine sulfate.

## What is already known on this topic?

Knee osteoarthritis [OA] is one of the most common orthopedic diseases in Thailand. Glucosamine sulfate is a treatment of choice for mild to moderate knee OA. However, the efficacy of glucosamine sulfate for treatment knee OA is still controversial. In Thailand,

the reimbursement for cost of treatment of glucosamine for knee OA is restricted to patients who meet the Comptroller General's Department [CGD] criteria, as well as CGD protocol for outcome evaluation.

## What this study adds?

At 18-week FU, glucosamine sulfate for the treatment of the knee OA in real-life situation under the CGD reimbursement protocol improved most evaluated parameters, especially performance-based measurements. The present study supported the CGD reimbursement protocol that the patient must be evaluated for outcome improvement after 12-week treatment.

## Potential conflicts of interest

The authors declare no conflict of interest.

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