International Journal of Medicine Research
ISSN: 2455-7404; Impact Factor: RJIF 5.42
Received: 08-02-2019; Accepted: 09-03-2019
www.medicinesjournal.com
Volume 4; Issue 2; April 2019; Page No. 103-109

Effects of abexol and chondroitin sulfate/glucosamine in patients with osteoarthritis: A six-month comparative study

Roberto Puente-Rodríguez[1], Julio César Fernández-Travieso[2], José Illnait-Ferrer[3], Lilia Fernandez-Dorta[4], Dayana Ugarte-Moreno[5]

[1, 3, 5] Surgical Medical Research Centre, Havana, Caribbean, Cuba
[2, 4] National Centre for Scientific Research, Havana, Caribbean, Cuba

Abstract

Introduction: Osteoarthritis (OA) is a degenerative joint disease that affects undreds of millions worldwide, mainly the elderly. The management of OA included a combination of non-pharmacological interventions and pharmacologic agents. Symptomatic slow-acting drugs for OA, particularly glucosamine plus chondroitin sulfate (GS/CS), are effective for symptom relief, protect joint cartilage and delay OA progression, with a good safety profile. Abexol, a mixture of beeswax alcohols that inhibits both cyclooxygenase and 5-lipoxygenase activities, has been effective in experimental and clinical OA studies, showing also a chondroprotective effect.

Objective: To compare the effects of Abexol and GS/SC administered for 24 weeks on patients with OA symptoms.

Methods: Patients were randomized to Abexol (50 mg) or GS/CS (375/300 mg) once daily for 24 weeks. Symptoms were assessed by the Western Ontario and McMaster Individual Osteoarthritis Index (WOMAC) and the visual analogy scale (VAS) scores. The primary outcome was the reduction of the total WOMAC score. Secondary outcomes included WOMAC pain, stiffness and function scores, VAS score and rescue medication consumption.

Results: Of 60 randomized patients, 55 completed the study. Abexol and GS/SC reduced significantly total WOMAC score (71 % and 74 %, respectively), and pain, joint stiffness and physical function scores versus placebo. VAS scores decreased significantly with Abexol (66.4 %) and GS/SC (71.2 %). The reductions, significant from the six week, were enhanced over the trial. Rescue medications were consumed by 18/30 Abexol and 16/30 GS/SC patients. No differences between groups were found. Treatments were well tolerated.

Conclusions: Abexol and GS/SC administered for 24 weeks improved OA symptoms in patients with diagnostic osteoarthritis and both treatments shown comparable efficacy and safety.

Keywords: Abexol, beeswax alcohols, chondroitin sulfate, glucosamine, osteoarthritis, WOMAC score, VAS score

1. Introduction

Osteoarthritis (OA), the commonest musculoskeletal disorder, is a leading casue of disability worldwide, mainly in the elderly. According to the increasing life expectancy, OA is expected to become the fourth leading cause of disability by 2020 [1, 2]. OA is a progressive, painful and degenerative joint disease that affects every single tissue in the joint, characterized by localized cartilage loss, remodelling of adjacent bone and linked inflammation [3].

OA management requires non-pharmacological and pharmacological approaches [4-7]. While non-pharmacological is the pivotal treatment [4], it alone frequently is not enough for symptom relief and stopping OA progression. In turn, pharmacotherapy focuses on symptom relief with analgesics for pain, such as paracetamol, and non-steroidal anti-inflammatory drugs (NSAIDs) to treat both pain and associated inflammation. Analgesics and NSAIDs, however, are not only unable to solve the causal pathological process on the joint, but NSAIDs can produce gastrointestinal and cardiovascular adverse events, and paracetamol may cause hepatotoxicity [5-7]. In light of these sounds, there is updated interest in the search for safer alternatives to long-term manage OA.

Symptomatic slow-acting drugs for OA (SYSADOA) (glucosamine sulfate, glucosamine hydrochloride, chondroitin sulfate, hyaluronic acid, avocado soybean unsaponifiables, diacerein), second-line drugs for OA, improve the symptoms, decrease cartilage injury and are safer than NSAIDs and paracetamol for continuous or recurrent use [6].

Various clinical trials have been conducted with SYSADOA. In particular, combined therapy with glucosamine (GS) plus chondroitin sulfate (CS) (GS/CS), has shown to produce symptom relief, protect joint cartilage and delay OA progression, with a good safety profile [8-12]. A review of randomized trials, albeit most reported of low quality, concluded that short-term administration of chondroitin (alone or with glucosamine) was better than placebo in improving pain in OA patients. The benefit was estimated to be small to moderate, but clinically meaningful. Such efficacy, together with the low risk of their use, supports why these products are popular among OA sufferers [10]. Despite some negative data and controversy around [11], moderate to high quality evidence supports that GS/CS produce pain reduction and physical function improvement in OA patients with good safety. GS/CS treatment given for 6 months has demonstrated comparable efficacy to celecoxib, a COX2 inhibitor, for reducing pain, stiffness, functional limitation and joint swelling in patients with painful knee OA [12]. Hence, GS/CS is a good

comparator for new substances of natural origin that pretend help in OA management.

Abexol, a mixture of six high molecular weight aliphatic alcohols purified from beeswax [13], has demonstrated to inhibit both cycloxygenase (COX) and 5-lipooxygenase (5-LOX) activities *in vitro* [14]. Oral administration of Abexol has been effective in experimental inflammation [15] and in the model of monoiodoacetate (MIA)-induced OA in rats, in which Abexol displayed chondroprotective effects, decreasing cartilage injury [16]. Also, Abexol (50 mg/day) given for 6-12 weeks reduced significantly OA symptoms and the need of using rescue medications in OA subjects [17-19], being suggested the potential usefulness of Abexol for managing OA [20].

In light of these issues**,** this study compared the effects of Abexol and GS/SC, administered for 24 weeks, on patients with OA symptoms.

Methods

Study design: This randomized, open, comparator (GS/CS) controlled study was approved by the Institutional Ethics Committee of the Surgical and Medical Research Centre (Havana, Cuba) and registered on the Cuban Public Registry of Clinical Trials (RPCEC00000222).

The study was conducted according to the ethical standards of the Declaration of Helsinki. At enrolment, patients provided their informed written consent after received, in a plain and understabler language, oral and written explanations about the purpose and details of the trial.

Eligible patients were randomized, to GS/CS (375/300 mg) or 50 mg Abexol once daily for 24 weeks. Randomized patients attended to visits every six weeks. Physical examinations, treatment compliance, symptom assessment, use of rescue medications and AE were controlled at each visit post-randomization. Laboratory examinations were done at baseline and after 12 and 24 weeks on treatment.

Study participants: The study enrolled ambulatory women and men (20-80 years) previously diagnosed of suffering knee, hip or finger OA, supported by clinical and radiological criteria. Participants should have a diagnosis of functional class I, II or III (mild to moderate) according to the American College of Rheumatology Criteria (ACRC) [21] and a Western Ontario and McMaster Individual Osteoarthritis Index (WOMAC) ≥ 25 [22].

Exclusion criteria were other forms of arthritis, arthroscopy performed within the past year, intra-articular injection of steroids within the past 3 months, uncontrolled hypertension (diastolic pressure 120 Hg mm) or diabetes (fasting glucose > 7 mmol/L), active liver or renal disease, malignancies, any other serious illnesses, hospitalization during the 6 months prior to the study. Pregnant women, nursing women, and those not taking adequate contraceptive measures were also excluded.

Predefined premature discontinuations included unwillingness to follow-up, any AE supporting such decision and protocol violations (failure of tablets intake ≥ 10 days).

Treatment: Tablets of Abexol (50 mg) (MedSol Laboratories, Havana, Cuba) and GS/SC (375/300 mg) (Aspen Pharma Pty Ltd, NSW, Australia) were used in the trial. Treatments were packaged in plastic bottles.

Eligible patients were randomly allocated to receive Abexol or GS/SC tablets. The tablets should be taken one per day with the breakfast for 24 weeks.

The randomisation code was computer-generated with a fixed, not stratified randomisation method, using balanced blocks of 8 and allocation ratio of 1:1. The doses of Abexol and GS/SC whave been used in previous clinical studies in OA patients [17-19].

Treatment compliance was controlled by counting the remainder tablets and interviewing the patients. At study completion, non-used tablets were recovered. Compliance was considered good if the partitipants have taken at least 85% of the tablets scheduled from the previous visit.

Consumption of NSAIDs, steroids, cartilage or calcium supplements, or any other agent that may affect the study outcomes was forbidden, except that of rescue medications needed to treat persistent pain: acetaminophen (maximum 2 g/day) or metamizole (maximum 600 mg/day). Participants filled a daily record of their consumption of rescue medications, which was reported at each next scheduled visit, when the number of consumed rescue medication was recorded.

Study outcomes: The primary study outcome was a significant reduction of the total WOMAC index ≥ 30% as compared to baseline. The WOMAC questionnaire consists of three sections, one that assess pain intensity (5 questions), other joint stiffness (2 questions), and the third the physical function (17 questions). Individual responses were scored on the following scale: 0 (none), 1 (slight), 2 (moderate), 3 (severe) and 4 (extreme). The total score ranges from 0 (the best) to 96 (the worst). This tool provides a validated assessment of the patient's functional capacity, specifically joint pain, stiffness and functional impairment, being useful for the evaluation of the effect of investigational products on OA symptoms [22, 23].

Significant decreases in pain, stiffness and physical function WOMAC scores [22, 23], as well as in the Visual analogy scale (VAS) score (specific for pain) [24] were secondary outcomes. In order to avoid biases, subjects answered to both WOMAC and VAS questionnaires in the doctor's office before their examination. The VAS-visual analogy scale score used a 100 mm linear measure of pain status with 0 representing no pain and 100 the worst suffered pain. Patients marked on the linear scale the relevant amount of pain they were suffering, and the value was noted. All primary and secondary outcome measures were assessed at each visit.

The subjective self-perception of symptom relief at trial completion was a collateral outcome. This matter was assessed according to 4 options: very good (complete symptoms relief), good (remarkable symptom relief, but some symptoms still remaining), fairly (modest symptom relief) and poor (no symptom relief or worsening of symptoms).

Safety and tolerability assessment: Safety variables included physical (body weight, pulse rate, blood pressure) and blood indicators (alanine aminotransferase –ALT-, aspartate aminotransferase–AST-, serum fasting glucose, creatinine, cholesterol, triglycerides). Blood biochemistry indicators were assessed by using reagent kits (Roche, Switzerland) and performed in the Hitachi 709 auto analyser (Tokyo, Japan). Analyses were done at the clinical laboratory. Controls of the precision and accuracy of the methods were performed.

An adverse event (AE) was defined as any new undesirable experience or change in physical or laboratory data or the worsening of any pre-existing condition occurred through

the trial, being or not drug-related. AE were classified according to their intensity in mild, moderate and serious. Mild AE were those AE not requiring treatment or withdrawal of study medication, moderate AE required withdrawal of study medication and/or specific treatment of the AE, and serious AE (SAE) was considered any AE leading to patient hospitalisation and/or death, independently of their nature [25].

Statistical Analysis: Data were analysed as per the Intention to treat approach. So, data of all randomized patients were included in all analyses. The sample size estimation assumed a difference of 20 % between the reductions of WOMAC total scores from baseline with each treatment at study completion. Then, 30 patients per arm (60 patients) would be sufficient to detect such difference with 80 % power and $\alpha = 0.05$.

The changes within each group of the continuous variables as well as the comparisons between groups were analyzed by Student's t test for paired samples and for independent samples, respectively. The categorical variables were analyzed with χ^2 test. For the statistical analyzes, the statistical systems SPSS 21 on Windows 10 and the EPIDAT 3.1 were used. All the statistical tests used were two tails. A priori a level of a = 0.05 was established for statistical significance.

Results

Baseline characteristics: Eighty (80) patients were recruited for the study. Of them, 60 were eligible for randomization. Twenty patients were not eligible because no confirmation of osteoarthritis by radiological criteria (11 patients), glucose values> 7 mmol/L (4 patients), incorporating nonsteroidal antiinflammatory drugs (2 patients), no laboratory tests or radiology (2 patients) and 1 patient due to presenting renal insufficiency.

Baseline characteristics were well balanced in the two groups (Table 1). The most frequent ≥ 20 % risk factor at baseline were sedentary life (75.0 %), overweight + obesity (68.3 %), hypertension (50 %) and hypercholesterolemia (28.3 %). In turn, the frequency of concomitant medications was high (80.0 %) and well matched in boths groups.

Of the 60 patients included, 55 completed the treatment, 4 patients (2 of each group) were discharged due to protocol violation (incorporation of NSAIDs) and only one patient of the Abexol group left the study due to moderate adverse events (redness and itching in the eyes).

Adherence to study protocol was excellent, and treatment compliance was very good (≥ 90%) and similar in both study groups.

Efficacy analysis: Table 2 summarizes the effects on total WOMAC scores. The mean baseline total WOMAC scores were 42.1 (Abexol) and 41.1 (GS/SC). After 6 weeks on treatment Abexol and GS/CS reduced significantly the total WOMAC score as compared to baseline. Thereafter, the decreases of the total score were not only persistent, but increased, so that significant ($p<0.001$) and marked reductions of 71.0% (Abexol) and 74.0 % (GS/SC) were seen at week 24. No significant differences between groups were found.

The baseline values of all WOMAC scores (mean ± SD) were similar in the two groups. Both treatments decreased significantly ($p<0.001$) pain (74.4% with Abexol, 76.0 % with GS/SC), stiffness (81.2% and 75.0%, respectively) and function (67.8% and 72.8%, respectively) WOMAC scores from the 24 week on therapy. The treatment effects did not wear off, but were enhanced during the trial.

The mean baseline WOMAC pain scores were 12.9 (Abexol) and 12.1 (GS/SC). At week 6 (first interim check-up), pain score had lowered significantly reduced with Abexol and GS/SC versus baseline for both comparisons. The effect was enhanced over the trial. At the end of the study the WOMAC pain scores lowered significantly to 3.3 (Abexol) and 2.9 (GS/SC). In turn, the mean stiffness WOMAC scores decreased significantly ($p<0.001$ versus baseline) from 3.2 to 0.6 (Abexol), and from 2.8 to 0.7 (GS/SC), and physical function WOMAC scores lowered ($p<0.001$ versus baseline) from 26.0 to 8.4 (Abexol) and from 26.1 to 7.1 (GS/SC) (Table 3). Comparisons did not show significant differences between Abexol and GS/SC WOMAC sub-scores.

Table 4 lists the effects on the mean VAS score. After 6 weeks on treatment Abexol and GS/SC reduced significantly ($p<0.001$) the VAS score versus baseline. The effects on VAS score, progressively enhanced thereafter, achieved percent decreases versus baseline of 66.4% (Abexol) and 71.2% (GS/SC) at the end of the study.

The proportion of patients who required analgesics during the study was similar in both groups: Abexol (18/30, 60.0%) and GS/SC (19/30, 63.3%).

In the Abexol group 9 patients (30.0%) and 16 (53.3%) perceived that the effectiveness of the treatment was very good and good, respectively, only 5 patients (16.7%) perceived that the efficacy was regular. Of the subjects treated with GS/SC, 11 (36.6%) reported the efficacy as very good and 14 (46.7%) as good, only 5 patients (16.7%) perceived that the efficacy was regular. Results in both groups were statistically comparable.

Safety and tolerability: Treatments were well safe and tolerated. Vital signs and blood parameters were not affected by the treatments, and individual values remained within normal ranges (data not shown for simplicity).

Two patients (1 from the Abexol group and 1 from the GS/SC group reported AE during the study, classified as moderate for requiring treatment) The patient from the Abexol group reported redness and stinging in the eyes and the GS/SC group debut of hypertension. In both cases, the relationship with the treatment was classified as doubtful. No significant differences between the groups were noted. Doctors rated tolerability as very good in 27 patients (90.0%) and regular in 3 patients (10.0%) of each group.

Table 1: Baseline characteristics of study population

	Abexol (n = 30)		**S/SC (n = 30)**		**Total (n = 60)**	
Age (years) (X ± SD)	61 ± 9		59 ± 9		60 ± 9	
Body mass index (kg/m^2) (X ± SD)	28.0 ± 4.6		26.7 ± 4.2		27.4 ± 4.4	
	n	%	n	%	n	%
Women	24	80.0	23	76.7	47	78.3
Men	6	20.0	7	23.3	13	21.7
Degree of OA according to ACRC						

I	18	60.0	17	56.7	35	58.3
II	12	40.0	13	43.3	25	41.7
OA diagnosis						
Knee	22	73.3	21	70.0	43	71.7
Hip	16	53.3	20	66.7	36	60.0
Hand/fingers	20	66.7	23	76.7	43	71.7
Mixed	29	96.7	27	90.0	56	93.3
Visible inflammation of joints	25	83.3	21	70.0	46	76.7
Main concomitant conditions						
Overweight and obesity	22	73.3	19	63.3	41	68.3
Hypertension	18	60.0	12	40.0	30	50.0
Hypercholesterolemia	11	36.7	6	20.0	17	28.3
Thyroid dysfunction	4	13.3	3	10.0	7	11.7
Orthopedic surgery	1	3.3	4	13.3	5	8.3
Coronary heart disease	2	6.7	2	6.7	4	6.7
Diabetes mellitus	0	0.0	2	6.7	2	3.3
Lifestyle factors						
Sedentary life	24	80.0	21	70.0	45	75.0
Smoking	3	10.0	5	16.7	8	13.3
Concomitant therapy*						
Consumers of at least one concomitant drug	27	90.0	21	70.0	48	80.0
Angiotensin converting enzyme inhibitors	10	33.3	10	33.3	20	33.3
Diuretics	11	36.7	8	26.7	19	31.7
Calcium antagonists	5	16.7	4	13.3	9	15.0
Antiplatelet drugs	6	20.0	2	6.7	8	13.3
Antiulcers	3	10.0	4	13.3	7	11.7
Thyroid hormones	3	10.0	3	10.0	6	10.0
β-blockers	3	10.0	1	3.3	4	6.7
Cholesterol-lowering drugs	3	10.0	0	0.0	3	5.0
Oral hypoglycemic drugs	0	0.0	3	10.0	3	5.0
Psychopharmaceutical	1	3.3	2	6.7	3	5.0
Anti-asthmatic Anxyolitics	1	3.3	2	6.7	3	5.0

X mean, SD standard deviation, OA osteoarthritis, ACRC American College of Rheumatology Criteria;
*The table includes only those consumed by ≥ 5 patients; No significant between groups differences were found (Student's-t test for independent samples, χ^2 test for categorical variables)

Table 2: Changes in the total Western Ontario and McMaster Individual Osteoarthritis Index (WOMAC) scores

Week	WOMAC Index scores+	
	Abexol	GS/SC
0 (baseline)	42.1 ± 5.2	41.1 ± 5.9
6	26.3 ± 4.5**	25.3 ± 3.6**
12	17.4 ± 6.6**	15.5 ± 4.2**
18	13.8 ± 6.7**	13.0 ± 3.7**
24	12.2 ± 7.4**	10.7 ± 4.3**
Changes (%)	- 71.0	- 74.0

Values are means ± SD, GS/CS glucosamine/chondroitin sulfate
+Divided into three domains: pain, stiffness and physical function. Each domain has several items and each one is graded in a scale of 0 (none) to 4 (extreme), the lowest being the better, the highest the worst.
There were a total of 24 items in the total WOMAC score
**p<0.001 Comparisons versus baseline (Student's-t test for paired samples)

Table 3: Changes in pain, stiffness and physical function WOMAC scores

Treatment	Baseline	6 weeks	12 weeks	18 weeks	24 weeks	Changes (%)
Pain score+						
Abexol	12.9 ± 2.1	8.2 ± 1.0**	4.5 ± 2.4**	3.9 ± 2.2**	3.3 ± 2.4**	-74.4
GS/SC	12.1 ± 2.4	7.6 ± 1.4**	3.8 ± 1.9**	3.3 ± 1.6**	2.9 ± 2.1**	-76.0
Stiffness score+						
Abexol	3.2 ± 1.6	1.4 ± 1.2**	1.0 ± 1.3**	0.6 ± 1.1**	0.6 ± 1.1**	-81.2
GS/SC	2.8 ± 1.4	1.1 ± 0.7**	0.8 ± 0.7**	0.7 ± 0.6**	0.7 ± 0.7**	-75.0
Physical function+						
Abexol	26.0 ± 3.1	16.8 ± 3.3**	11.9 ± 4.0**	9.2 ± 3.9**	8.4 ± 4.6**	-67.8
GS/SC	26.1 ± 4.3	16.7 ± 2.8**	10.9 ± 2.8**	9.1 ± 2.4**	7.1 ± 2.4**	-72.8

Values are means ± Standard Deviation, GS/CS glucosamine/chondroitin sulfate
+Measured on the following scale (0-4, where 0=none, 1=slight, 2=moderate, 3=severe, 4=extreme)
The lowest the better, the highest the worst
**p<0.001 Comparisons versus baseline (Student's-t test for paired samples)

Table 4: Changes in visual analogy scale (VAS) scores[+]

Treatment	Baseline	6 weeks	12 weeks	18 weeks	24 weeks	Changes (%)
Abexol	75.0 ± 20.9	57.5 ± 18.2[**]	38.0 ± 22.6[**]	31.2 ± 20.0[**]	25.2 ± 20.9[**]	-66.4
GS/SC	68.5 ± 18.5	49.8 ± 14.7[**]	37.0 ± 17.9[**]	31.3 ± 15.1[**]	19.7 ± 17.5[**]	-71.2

Values are means ± Standard Deviation, GS/CS glucosamine/chondroitin sulfate

[+]Measured on a 100 mm scale of 0 to 100, where 0 = no pain and 100 was the worst possible pain

[**]p<0.001 Comparisons versus baseline (Student's-t test for paired samples)

Discussion

The progression of OA affects the quality of life of the sufferers [1, 2]. Pain decrease and improved function are the main objectives in OA management, which mainly involves medical treatment and lifestyle modifications. The consumption of NSAIDs for pain management in OA is highly frequent, but they increase the risk of gastrointestinal bleeding and cardiovascular adverse events [3]. Second-line treatments (SYSADOA), not included in all guidelines, improve OA symptoms, reduce cartilage degradation, and have a better gastrointestinal profile as compared to NSAIDs, but the onset of their effects is more delayed [6, 7].

This study demonstrates that administration of Abexol (50 mg/day) and GS/SC (375/300 mg) for 24 weeks produce a significant improvement in the total WOMAC score, main study outcome, in patients with mild to moderate OA. Similar effects were seen on pain, stiffness, and physical function WOMAC scores, and on the VAS score for pain. The score decreases were significant from the first interim-ckeck up conducted after concluding 6 weeks on therapy, and were enhanced throughout the study.

The efficacy of both treatments was remarkable and comparable. Since the two study groups were homogeneous at baseline, the randomized allocation of treatments should be accepted as adequate and the results here seen as attributable to the treatmenst, not to initial differences between them.

The patients included (average age: 60 years) were mostly women (78.3%), which coincides with reports of higher incidence of the disease in women and more marked in the post-menopause [26], characteristic that by their age they were 33/47 (70.2%) of the included patients.

The studied population presented a high frequency of risk factors, results that agree with the reports of coexistence of osteoarthritis and hypertension, overweight, obesity, dyslipidemia, smoking and diabetes in people with middle or advanced age and that can influence the development of osteoarthritis [26, 27].

Both treatments produced comparable reductions in the primary and secondary efficacy variables in all evaluations of the WOMAC and VAS surveys conducted during the 24 weeks of treatment.

Regarding the consumption of analgesics, there were no significant differences between groups, since the proportion of patients who required consumed them was similar in both groups.

In this study, the consumption of analgesics was higher than the previous three-month study [19], where in the group Abexol and GS/SC consumed analgesics 12/30 (40%) and 11/30 (36.7%), respectively. On the other hand, four of the five study losses were due to the incorporation of NSAIDs by patients due to exacerbation of OA symptoms. The fact of the increase in the consumption of analgesics or NSAIDs could be related to the temporal course of the disease that becomes more evident in a medium-term study (6 months).

The subjective perception of efficacy in both groups was similar, with no significant differences between groups. The highest percentage of subjects classified the efficacy as very good or good (90%) and only 6 patients, three of each group rated it as regular.

In this study, the efficacy of GS/SC was superior to that reported by other authors. A double-blind randomized trial comparing the efficacy of GS/SC (500 mg/450 mg) administered three times a day and colecoxib (200 mg) administered once a day for six months significantly decreased the WOMAC scale in the pain domains (50.1% vs. 50.2%), stiffness (46.9% vs. 49.2%) and physical capacity (45.5%, 46.4%), respectively [12].

In this clinical trial, despite the administration of GS/SC at lower doses, the effect achieved was higher (reductions greater than 65%), perhaps because in this study only patients with mild to moderate symptoms were included.

The percentages of reduction of the total score of the WOMAC and VAS scale of Abexol and the GS/SC reached in this trial are similar to those obtained in the previous three-month study[19] and corroborates the efficacy of Abexol in subjects with symptoms of OA mild to moderate [17, 18].

The mechanism by which Abexol and GS/SC improve symptoms in patients with OA is not an objective of study. However, SC and glucosamine produce anti-inflammatory and chondroprotective effects that involve the inhibition of metalloproteinase activity, the release of prostaglandins E2, the production of nitric oxide and the degradation of glycosaminoglycans, as well as an increase in the synthesis of hyaluronic acid in the joint. SC stimulates the synthesis of collagen while glucosamine inhibits the release of prostaglandins, the administration of both substances exhibits synergistic effects [9]. In contrasts, in experimental studies it has been shown that Abexol inhibits the activity of COX and LOX [14] in addition to chondroproctector effects [16].

Abexol produces gastro protection unlike the gastrotoxicity induced by NSAIDs. The gastro protective effects involve the increase of the secretion and improvement of the composition of the gastric mucus that acts as a defensive factor of the gastric mucosa and reduces the generation of hydroxyl radicals, lipid peroxidation and protein oxidation in the gastric mucosa [28-30].

In this study, Abexol and GS/SC showed a good safety and tolerability profile, which is consistent with reported data for both treatments.

The results of the present study can be extrapolated to patients with mild to moderate OA. These data demonstrate that the efficacy and safety of Abexol are comparable to those of GS/SC in the management of these patients and suggests that Abexol could be an alternative, mainly in those patients who have contraindications for the treatment with NSAIDs and paracetamol.

Conclusions
Abexol and GS/SC administered for 24 weeks improved OA symptoms in patients with diagnostic osteoarthritis and both treatments shown comparable efficacy and safety.

Acknowledgements
We thank the Dr. Sarahí Mendoza-Castaño (National Centre for Scientific Research), Dr. Ernesto Lopez-González, Dr. Yolanda Cruz-Gomez, Bcs. Meilis Mesa-Angarica (Surgical Medical Research Centre), Carlos Sanchez-Texido, Bcs. Victoria Sanchez-Pedroso, Bcs. Gladys Jiménez-Rivero (National Centre for Clinical Trials Coordinator), Havana, Cuba, for his contribution in the realization of this study.

References
1. Briggs AM, Cross MJ, Hoy DG, Sanchez-Riera L, Blyth FM, Woolf AD, March L. Musculoskeletal health conditions represent a global threat to healthy aging: A report for the 2015 World Health Organization World Report on Ageing and Health. Gerontologist. 2016; 56(2):S243-S55.
2. Marshall DA, Vanderby S, Barnabe C, MacDonald KV, Maxwell C, Mosher D, *et al*. Estimating the Burden of Osteoarthritis to Plan for the Future. Arthritis Care Res. 2015; 67(10):1379-1386.
3. Allen KD, Bierma-Zeinstra SM, Foster NE, Golightly YM, Hawker G. Osteoarthritis Cartilage. 2015; 23(5):826-838.
4. Hochberg MC, Altman RD, April KT, Benkhalti M, Guyatt G, McGowan J, *et al*. American College of Rheumatology recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee. Arthritis Care Res. 2012; 64:465-74.
5. McCarberg B, Tenzer P. The complexities in the pharmacologic management of osteoarthritis pain. Curr Med Res Opin. 2013; 29:539-548.
6. Cutolo M, Berenbaum F, Hochberg M, Punzi L, Reginster JY. Commentary on recent therapeutic guidelines for osteoarthritis. Semin Arthritis Rheum. 2015; 44(6):611-617.
7. Yeomans ND. Consensus about managing gastrointestinal and cardiovascular risks of nonsteroidal anti-inflammatory drugs? BMC Med. 2015; 13:56-60.
8. Lee YH, Woo JH, Choi SJ, Ji JD, Song GG. Effect of glucosamine or chondroitin sulfate on the osteoarthritis progression: a meta-analysis. Rheumatol Int. 2010; 30:357-363.
9. Henrotin Y, Lambert C. Chondroitin and glucosamine in the management of osteoarthritis: an update. Curr Rheumatol Rep. 2013; 15:361-364.
10. Singh JA, Noorbaloochi S, MacDonald R, Maxwell LJ. Chondroitin for osteoarthritis. Cochrane Database Syst Rev. 2015; 1:CD005614.
11. Yang S, Eaton CB, McAlindon TE, Lapane KL. Effects of glucosamine and chondroitin supplementation on knee osteoarthritis: an analysis with marginal structural models. Arthritis Rheumatol. 2015; 67:714-723.
12. Hochberg MC, Martel-Pelletier J, Monfort J, Möller I, Castillo JR, Arden N, *et al*. on behalf of the MOVES Investigation Group. Combined chondroitin sulfate and glucosamine for painful knee osteoarthritis: a multicentre, randomised, double-blind, non-inferiority trial versus celecoxib. Ann Rheum Dis. 2016; 75(1):37-44.
13. Mas R. D-002: A product obtained from beeswax. Drugs of the Future. 2001; 26:731-744.
14. Pérez Y, Oyarzábal A, Ravelo Y, Mas R, Jiménez S, Molina V. Inhibition of COX and 5-LOX enzymes by D-002 (beeswax alcohols). Curr Top Nutraceutical Res. 2014; 12(1/2):13-18.
15. Ravelo Y, Molina V, Carbajal D, Fernández L, Fernández J, Arruzazabala ML, et al. Evaluation of anti-inflammatory and antinociceptive effects of D-002 (beeswax alcohols). J Nat Med. 2010; 65:330-335.
16. Mendoza S, Noa M, Valle M, Mendoza N, Mas R. Ameliorating effects of D-002, a mixture of beeswax alcohols, on monosodium iodoacetate-induced osteoarthritis in rats. IJPSRR2013; 19:10-15.
17. Rodríguez I, Mendoza S, Illnait J, Mas R, Fernández JC, Fernández L, Mesa M, Gámez R. Effects of Abexol, a mixture of beeswax alcohols, on osteoarthritis symptoms: a randomized placebo-controlled study. IOSRPHR. 2012; 2:1-9.
18. Puente R, Illnait J, Mas R, Carbajal D, Mendoza S, Fernández JC, *et al*. Evaluation of the effect of Abexol, a mixture of beeswax alcohols, on osteoarthritis symptoms. Korean J Intern Med 2014; 29(2):191-202.
19. Puente R, Illnait J, Mas R, Lopez E, Mendoza S, Carbajal D, *et al*. Comparison of the efficacy and tolerability of chondroitin plus glucosamine and D-002 (beeswax alcohols) in subjects with osteoarthritis symptoms. Rev Facultad Ciencias Médicas de Cordova 2017; 74(2):107-118.
20. Kim HS. Can natural products serve as potential treatments for osteoarthritis? Korean J Intern Med 2014; 29(2):173-175.
21. Altman R, Alarcón G, Appelrouth D, Bloch Borenstein D, Brandt K, *et al*. The American College of Rheumatology Criteria for the classification and reporting of osteoarthritis of the hip. Arthritis Rheum. 1991; 34:505-514.
22. Batlle-Gualda E, Esteve-Vives J, Piera MC, Hargreaves R, Cutis J. Adaptación transcultural al cuestionario WOMAC especifico para artrosis de rodilla y cadera. Rev Esp Reumatol. 1999; 26:38-45.
23. Jinks C, Jordan K, Croft P. Measuring the population impact of knee pain and disability with the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC). Pain. 2002; 100:55-64.
24. Gruenwald J, Petzold E, Busch R, Petzold HP, Graubaum HJ. Effect of glucosamine sulfate with or without omega-3 fatty acids in patients with osteoarthritis. Advances in Therapy. 2009; 26:858-871.
25. Requerimientos para la notificacion y el reporte de eventos adversos graves e inesperados en los ensayos clínicos. Regulación No. 45-2007, Centro para el Control Estatal de los Medicamentos, Equipos y Dispositivos Médicos (CECMED), MINSAP, La Habana, Cuba, 2007.
26. Rizzoli R, Boonen S, Brandi ML, Bruyère O, Cooper C, Kanis JA, *et al*. Vitamin D supplementation in elderly or postmenopausal women: a update of the recommendations from the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO). Curr Med Res Opin 2013; 29:305-313.
27. Singh G, Miller D, Lee FH, Pettitt D, Russell MW.

Prevalence
28.
29. of cardiovascular disease risk factors among US adults with self-reported osteoarthritis: data from the Third National Health and Nutrition Examination Survey. Am J Manag Care 2002; 8:S383-S391.
30. Carbajal D, Molina V, Noa M, Valdes S, Arruzazabala ML, Aguiar A, Más R. Effects of D-002 on gastric mucus composition in ethanol induced ulcer. Pharmacol Res 2000; 42:329-332.
31. Pérez Y, Oyárzabal A, Mas R, Molina V, Jiménez S. Protective effect of D-002, a mixture of beeswax alcohols, against indomethacin-induced gastric ulcers and mechanism of action. J Nat Medicine. 2013; 67:182-189.
32. Molina V, Valdes S, Carbajal D, Arruzazabala ML, Menéndez R, Mas R. Antioxidant effects of D-002, on gastric mucosa of rats with experimentally-induce injury. J Med Food. 2001; 4:79-83.