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Equivalence of a single dose (1200 mg) compared to a three-time a day dose (400 mg) of chondroitin 4&6 sulfate in patients with knee osteoarthritis. Results of a randomized double blind *placebo* controlled study

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SUMMARY

Objective: Evaluation of the efficacy and safety of a single oral dose of a 1200 mg sachet of chondroitin 4&6 sulfate (CS 1200) vs three daily capsules of chondroitin 4&6 sulfate 400 mg (CS 3*400) (equivalence study) and vs *placebo* (superiority study) during 3 months, in patients with knee osteoarthritis (OA).
Design: Comparative, double-blind, randomized, multicenter study, including 353 patients of both genders over 45 years with knee OA. Minimum inclusion criteria were a Lequesne index (LI) $\geq$ 7 and pain $\geq$ 40 mm on a visual analogue scale (VAS). LI and VAS were assessed at baseline and after 1–3 months. Equivalence between CS was tested using the per-protocol procedure and superiority of CS vs *placebo* was tested using an intent-to-treat procedure.
Results: After 3 months of follow-up, no significant difference was demonstrated between the oral daily single dose of CS 1200 formulation and the three daily capsules of CS 400. Patients treated with CS 1200 or CS 3*400 were significantly improved compared to *placebo* after 3 months of follow-up in terms of LI ($<$0.001) and VAS ($P < 0.01$). No significant difference in terms of security and tolerability was observed between the three groups.
Conclusion: This study suggests that a daily administration of an oral sachet of 1200 mg of chondroitin 4&6 sulfate allows a significant clinical improvement compared to a *placebo*, and a similar improvement when compared to a regimen of three daily capsules of 400 mg of the same active ingredient.

Introduction

Osteoarthritis (OA) is the most common form of arthritis and is a leading cause of morbidity and disability[1]. Treatment strategies for OA include both non-pharmacological and pharmacological therapies. Among pharmacological therapies, analgesics and non-steroidal anti-inflammatory drugs (NSAIDs) are current treatment options for OA because of their well-established efficacy[2,3]. However, long-term use of these drugs can induce a number of potentially serious side effects, particularly in the elderly. For this reason, attention has recently been focused on the investigation and development of new types of drugs and treatments that can improve the clinical symptoms of OA with better tolerability and safety profiles, such as symptomatic slow-acting drugs for OA (SYSADOAs)[4].

Chondroitin sulfate (CS) consists of repeating chains of glycosaminoglycans. It is a major component of cartilage, providing structure, holding water and nutrients and allowing other molecules to move through the cartilage providing resistance and elasticity to the cartilage[5,6]. It has been shown, in numerous short- and long-term double-blind clinical trials, to relieve pain and increase joint function and, to slow down progression of the disease[7–12].

CHONDROSULF® (Laboratoire Genevrier), a CS preparation that has been approved as a prescription drug, is marketed in several foreign countries under several forms (i.e., capsules, tablets and granules). The prescribed dosage, in France, is three intakes/day, corresponding to 1200 mg of active ingredient. Some patients might be interested in receiving a pharmaceutical form which allows the absorption of such a dose in a single daily intake, thus

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potentially improving the therapeutic compliance. For galenic reasons, the new dosage of 1200 mg/day needs a new pharmaceutical form, i.e., a 1200 mg CS oral gel sachet.

The objective of this phase III clinical trial was to assess the efficacy of a single daily intake of CHONDROSULF® 1200 mg oral gel sachet (CS 1200) vs CHONDROSULF® 400 mg three capsules/day (CS 3*400) vs *placebo* sachet or capsules during 3 months. The primary objective of this clinical trial was to confirm the equivalence of the efficacy of CS 1200 and of CS 3*400, compared to *placebo*. The secondary objective was to compare the equivalence of the safety of CS 1200, CS 3*400 and *placebo*.

Material and methods

Study design and patients selection

This study is a multicentre, comparative, randomized, double-blind and double-dummy study. This study involved three parallel treatment groups with an allocation ratio of 1:1:1. Group 1 was the CS 1200 receiving one oral gel sachet of CS 1200 mg/day & one oral *placebo* capsule three times a day. Group 2 was the CS 3*400 receiving one oral *placebo* gel sachet/day & one oral capsule of CS 400 mg three times a day. Group 3 was the control group receiving one oral *placebo* gel sachet/day & one oral *placebo* capsule three times a day. All *placebos* were identical in form and appearance to the real drugs. The three different types of treatment were allocated according to a randomisation list balanced/blocks of three established by the sponsor with a randomisation method starting from a validated SAS® software. Treatment was allocated in ascending order as recruitment proceeded, by assigning the first available number. All these drug supplies were provided by the Institut Biochimique SA (IBSA)/Laboratoires Genévrier. No changes to methods after trial commencement have to be reported. This study was registered under the number EUDRACT 2005-005163-29 and was performed in compliance with the Helsinki Declaration.

The study group comprised patients from 10 centres in Belgium, three in France and two in Switzerland. The sponsor of the study delivered envelope to the investigators of these centres, who enrolled and assigned participants to interventions. The main inclusion criteria were outpatient status, aged over 45 years old with primary knee OA diagnosed according to the clinical and radiographic criteria of the American College of Rheumatology[13]. The symptomatic target knee should have a pain score of at least 40 mm on a 0–100 mm visual analogue scale (VAS) and a score ≥ 7 at the Lequesne index (LI). If both knees were symptomatic, the target knee was the most symptomatic knee.

The major exclusion criteria were destructive OA of the knee justifying a surgery in the following 6 months, important genu varum or valgum $>8^{\circ}$, knee joint surgery in the last 3 months, viscosupplementation, tidal lavage in the last 6 months, arthritis and metabolic arthropathies, Paget's illness, having consumed basic treatment of arthritis with SYSADOA (CSs, glucosamine sulfates, diacerein, hyaluronic acid) in the last 3 months and corticoids during the last month, presenting serious organic diseases (e.g., heart failure, renal or hepatic insufficiency, blood dyscrasia, serious infection), psychiatric illness hindering the protocol compliance, alcoholism, pregnant or likely to become it during clinical trial or lactating.

The only analgesic allowed during the study was paracetamol 500 mg, with a maximum consumption of 4 g a day (eight tablets/day). This treatment had to be stopped at least 10 h before every visit in order to ensure paracetamol elimination and thus to get the most accurate pain and functional discomfort evaluation.

The study was approved by the ethics committee of all participating study centres. All patients gave their written informed consent to participate.

Outcomes assessment

Clinical assessments of the patients were performed at the baseline and after a follow-up of 1–3 months.

The primary outcome measurement was the algo-functional LI[14,15]. This index consists of a 10-item investigator-administered questionnaire, which allows patients to rate pain or discomfort, stiffness, difficulty performing daily activities and their maximum walking capacity. The total score varies from 0 (no functional consequence) to 24 (major disability).

Global spontaneous pain was measured on a vertical VAS of 100 mm where zero = absent pain, and 100 = maximum pain. Consumption of paracetamol was recorded by the patient in a diary on a daily basis. The global efficacy assessment of the treatment was estimated, at each visit, by both the patient and the investigator, on a verbal semi quantitative four-point scale evaluation after 1–3 months of follow-up.

Treatment compliance was checked at each visit by counting the sachets and capsules. The compliance was considered as:

- excellent: no day of missed treatment,
- good: <3 days of missed treatment,
- fair: from 3 to 7 days of missed treatment,
- poor: >7 days of missed treatment.

Any adverse event and abnormal results of routine laboratory tests were reported. A serious adverse event was defined as an adverse event or reaction which could lead to death or is likely to jeopardize the life of the person participating in the study, required a hospitalization or the prolongation of hospitalization, caused an important or lasting inability or a disability, or led to a congenital anomaly or malformation, whatever the dose administered.

Statistical analysis

The equivalence test was decided *a priori* and has been performed on the evolution of the LI between baseline and 3 months. The equivalence conclusion has been based on the comparison of the two-sided 95% confidence interval (CI) of the difference between the two treatments CS 1200 and CS 3*400. If this two-sided 95% CI was between the two equivalence threshold ($-\Delta$ and Δ), then the equivalence was demonstrated. If the lower margin of the two-sided 95% CI was above the lower equivalence margin, then the non-inferiority was demonstrated.

The averages of the LI variations were compared between groups at every visit by an analysis of variance (or a rank test if necessary) and the global evolution of this main criterion for different visits was compared by means of a two-way analysis of variance for repeated measures with two factors, time and treatment (with measurement of the interaction time*treatment). When a significant difference was become evident for all the groups, analysis of variance was completed with a test of Scheffé. The same procedure was followed for the evaluation of the variation, of pain measured on the VAS and for the total consumption of paracetamol. Patient's and investigator's assessments about product efficacy at different times were compared by means of the χ^2 test. The analysis of variance for repeated measures was performed taking into account the test multiplicity. The Scheffé's test was chosen in a view to analyse the origin of the global difference underlined by the repeated measure analysis of variance.

The number of patients involved in this clinical trial had to be sufficient so that the absence of difference between both groups taking CS could not be interpreted as due to a lack of test power caused by low enrolments and so that the power of the test was sufficient to point out a difference between the two groups of

treatments and the *placebo* group. As a consequence it was decided to determine the required minimum number of patients by group in order to test equivalence, ensuring that this enrolment would be sufficient to show a difference between CS groups and the *placebo* group. The sample size calculation was based on the results of several previous studies. The medium reduction of the LI after administration of CS for 3 months was 4.0 score points in a previous clinical trial[16], 2.8 score points in another clinical trial[17], 2.9 score points in a third clinical trial[18], 5.4 in a fourth clinical trial[19] and 4.6 score points in the fifth trial[20]. The medium reduction on the five studies was considered in the order of four score points and the standard deviation (SD) of this evolution in the order of three. The biggest acceptable difference as for equivalence between two groups was fixed, before the start of the study, to 1.0 score point of reduction of the LI in 3 months, i.e., 25% of the medium reduction obtained in the above-mentioned studies. The sample size calculation for equivalence trials showed that 112 subjects/group in a per-protocol (PP) analysis would ensure the equivalence between both formulations, with an alpha risk of 5 % and an 80% power. Equivalence between CS 1200 and CS 3*400 was tested using the PP procedure. However, for superiority assessment between CS and *placebo*, intent-to-treat (ITT) analyses were performed for all randomized patients, using the last observation carried forward approach. It has been verified by the use of the formula $n = \sigma 2/\Delta^2 2(Z\,1-\alpha + Z\,1-\beta)$ that this sample size was sufficient to show a difference of 1.5 score point with a 90% power and a difference of two points with more than 95% power between the groups taking CS and the group taking *placebo*, testing superiority at risk level of alpha = 0.05.

Results

Out of 354 patients screened, 353 were randomly assigned to receive CS 1200, CS 3*400 or *placebo* (Fig. 1). Less than 15% of dropout patients were observed leading to a PP analysis of 308 subjects. The study started on March 2nd 2006 and finished on April 9th 2008. Baseline characteristics of the studied population are reported in Table I. No significant differences appears between the three groups with regard to demographic and baseline characteristics.

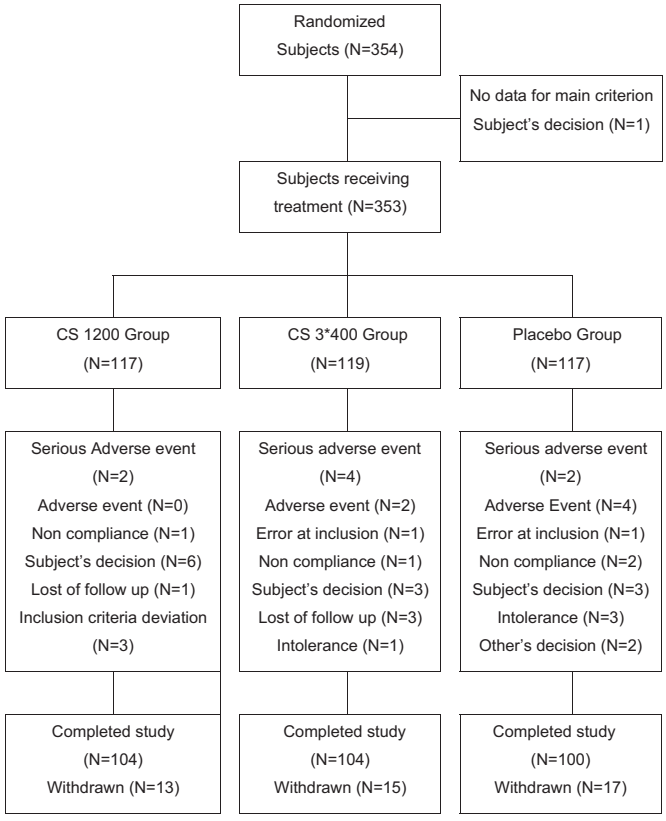

Fig. 1. Disposition of subjects.

Table I
General clinical examination and algo-functional LI

	All subjects	CS 1200	CS 3*400	*Placebo*	*P*-value
	N = 352	*N* = 117	*N* = 119	*N* = 117	
Age (years) mean ± SD	65.2 ± 9.9	65.4 ± 10.4	65.3 ± 8.8	64.9 ± 10.6	0.94
Male gender *N* (%)	125 (35.4)	40 (34.2)	47 (39.5)	38 (32.5)	0.50
BMI (kg/m^2) mean ± SD	28.6 ± 5.3	28.8 ± 5.2	28.4 ± 4.4	28.6 ± 6.1	0.80
Lequesne's score (target knee) mean ± SD	11.4 ± 3.0	11.9 ± 3.1	11.2 ± 2.6	11.2 ± 3.2	0.13

Primary outcomes

After 3 months of follow-up, no significant difference was demonstrated in PP analysis between the oral daily single dose of CS 1200 and the three daily capsules of CS 400 in the algo-functional LI. Indeed, as shown in Table II, the CI of the difference between the average variation of the LI score under treatment with CS 1200 and CS 3*400 is [−0.81; 1.08]. The lower limit of this CI is above the non-inferiority threshold −1 and leads to the conclusion that CS 1200 is not inferior compared to CS 3*400.

Using the ITT procedure, the Scheffé test showed that CS 1200 and CS 3*400 are significantly more effective than the control in decreasing the algo-functional LI after the 3-month treatment period ($P = 0.0001$) (Table III). In the CS groups, the reduction of the LI was almost of 40% compared to baseline. Interestingly, all these difference in LI between CS groups and *placebo* were already statistically significant after 2 months of follow-up (Table III).

Secondary outcomes

Among secondary outcome assessment, the Scheffé test showed a statistical significant difference between the two study treatment groups and the *placebo* group; i.e., CS 1200 and CS 3*400 are more effective than the control in decreasing the VAS pain score ($P = 0.02$) (Table IV). In the CS groups, the reduction of VAS score was near to 45%. The total consumption of paracetamol along the study treatment period was quite similar in the three treatment groups. More specifically, the mean (SD) number of capsules of paracetamol used was 75.3 (103.9) in the CS 1200, 70.2 (93.1) in the CS 3*400 and 73.5 (107.4) for the *placebo* ($P = 0.93$

Table II
Equivalence for the change in the total score of algo-functional index of Lequesne between M_0 and M_3 ($n = 104$ for CS 1200 and CS 3*400 and $n = 100$ for *placebo*)

Comparison between the three groups two by two	Delta	*t*-test CI (95%)	Equivalence limit
Group CS 1200 − group CS 3*400 (main criteria)	0.13	[−0.81; 1.08]	[−1; 1]
Group CS 1200 − *placebo* group	2.59	[1.68; 3.49]	[−1; 1]
Group CS 3*400 − *placebo* group	2.45	[1.54; 3.36]	[−1; 1]

Table III
Change in LI during the treatment period

LI score	CS 1200	CS 3*400	*Placebo*	*P*-value between groups	Scheffé test
ITT	$N = 117$	$N = 119$	$N = 117$		
Pre-treatment (M_0)	11.9 ± 3.1	11.2 ± 2.6	11.2 ± 3.2		
Follow-up (M_1)	9.8 ± 3.7	9.4 ± 3.1	10.1 ± 3.7	0.32	
Follow-up (M_2)	8.4 ± 3.8	8.4 ± 3.6	9.9 ± 4.3	0.003	$(1, 2 \neq 3)$
Final visit (M_3)	7.8 ± 4.2	7.5 ± 3.9	9.7 ± 4.6	0.0001	$(1, 2 \neq 3)$

between groups). The global efficacy evaluation did not show a statistical difference between CS 1200 and CS 3*400. However, a significant superiority was observed in both CS groups compared to *placebo* after 2 and 3 months, when evaluated by patients or by investigators (all $P < 0.05$). Global compliance was comparable between the three treatment groups along the treatment period (Table V).

Safety

A total number of 260 adverse events were reported in 161 subjects during the study. The CS 1200 group reported 26.4% of adverse events related to the treatment, the CS 3*400 group reported 26.0% and the *placebo* group 41.7%. Eight serious adverse events, all related to hospitalization, occurred during the study: two in the *placebo* arm (i.e., endourethral prostate resection, surgery related to frequent angina and snoring), two in the CS 1200 group (i.e., cystitis, radical prostatectomy) and four in the CS 3*400 group (i.e., transient ischaemic attack, acute intermediate syndrome, surgery on lumbar spinal stenosis, myocardial infraction). No statistically significant difference was demonstrated between the three treatment groups in the mean number of adverse events or in the number of subjects in each group with at least one adverse event.

Discussion

This study suggests that a daily administration of an oral sachet of 1200 mg of chondroitin 4&6 sulfate allows a significant clinical improvement compared to a *placebo*, and a similar improvement when compared to a regimen of three daily capsules of 400 mg of the same active ingredient.

Chronic illness requiring ongoing pharmacotherapy, such as OA, continues to challenge health care systems. Patient adherence to (taking the correct dose at the appropriate times, as prescribed) and persistence with (continuing with chronic medication over long periods of time) medications become an important issue in efforts to improve patient outcomes and decrease health care costs[21]. Many physicians consider medication non-adherence to be one of the most serious problems facing current medical practice[22]. Several studies have highlighted the potential tradeoffs between efficacy, days of missed medication, and adverse events[21]. Despite the development of therapeutically optimal dosing regimens, medication doses are not always taken correctly. Dosing is one of several factors affecting patient adherence[23]. Reducing the frequency of dosing has been shown to improve patient adherence to medication regimens, across a variety of therapeutic classes. In addition, several studies have shown that using single-dose regimens improves patient adherence[21,23]. Once- or twice-daily regimens are associated with better adherence than thrice-daily regimens[24,25]. We could then expect that the once a day oral sachet of 1200 mg of CS will improve patient's compliance compared to a regimen of three daily capsules of 400 mg of the same active ingredient. However, a study designed for this purpose is needed before final conclusion.

Table IV
Change in the global spontaneous pain during the treatment period

VAS score (mm)	CS 1200	CS 3*400	*Placebo*	*P*-value between groups	Scheffé test
ITT	$N = 117$	$N = 119$	$N = 117$		
Pre-treatment (M_0)	65.2 ± 13.7	62.7 ± 14.8	62.5 ± 15.0		
Follow-up (M_1)	52.5 ± 21.0	48.9 ± 20.9	50.3 ± 21.2	0.43	
Follow-up (M_2)	43.0 ± 22.9	43.1 ± 23.5	47.9 ± 22.9	0.18	
Final visit (M_3)	39.4 ± 24.2	38.8 ± 25.5	47.1 ± 24.8	0.02	$(1, 2 \neq 3)$

Table V
Global compliance

	All subjects	CS 1200	CS 3*400	*Placebo*	*P*-value
	$N = 175$	$N = 63$	$N = 61$	$N = 51$	
Poor	5.1%	1.6%	6.6%	7.8%	0.20
Fair	7.4%	9.5%	11.5%	0%	
Good	8.6%	9.5%	6.6%	9.8%	
Excellent	78.9%	79.4%	75.4%	82.4%	

N = number of subjects.

This study also shows a significantly better symptomatic improvement with CS compared to *placebo*. This confirms previous studies showing that CS could be considered as a SYSADOA[4] and that CS could be a cost-effective treatment in patients with knee OA[26]. A previous study has compared CS 1200, CS 3*400 and *placebo* but not with the objective to assess the equivalence or the non-inferiority of CS 1200 over CS 3*400[16]. This previous 3-month study randomized 127 patients with mono or bilateral knee OA to CS 1200, CS 3*400 or *placebo*. In the CS groups, the LI and VAS showed a significant reduction of clinical symptoms ($P < 0.01$ for both parameters), while only a slight reduction was observed in the *placebo* group ($P =$ ns for LI and $P < 0.05$ for VAS).

Previous short- and long-term studies have demonstrated that CS is fairly safe[7,27]. In the present study, no significant clinical or laboratory differences between the CS and *placebo* groups were observed, showing a similar tolerance and tolerability.

The validity of the study is supported by the design (double blind *placebo* controlled trial) and the relatively low dropout rate. One limitation in this study is the use of a specific CS preparation (Chondrosulf® 400◦mg) that has been approved as a prescription drug and therefore our results cannot be generalized to other CS products. Another limitation is that we have no data on joint structure, including Kellgren and Lawrence score or joint space width assessment. At last, our study was limited to a 3-month period.

In conclusion, this study shows the non-inferiority of CS 1200 mg once a day compared to CS 400 mg three times a day and the superiority of CS over *placebo* during a 3 months period of follow-up.

Author contributions

Study design: B. Zegels and J.Y. Reginster.

Data collection, analysis and interpretation: B. Zegels, P. Crozes, D. Uebelhart, O. Bruyère and J.Y. Reginster.

Writing of the manuscript: B. Zegels and J.Y. Reginster.

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Conflict of interest
This study was conducted in the framework of a product registration. B. Zegels, P. Crozes, D. Uebelhart, O. Bruyère and J.Y. Reginster received support (grants or reimbursement for attending meetings) from IBSA.

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List of participating centres:

In France: HIA Desgenettes in Lyon (Dr Crozes and Dr Dubourg). HIA Laveran in Marseilles Armees (Dr Chouc and Dr Fulpin). HIA Begin in Saint Mande (Dr Lechevalier, Dr Magnin and Dr Voisin).

In Belgium: Galerie Centrale in Arlon (Dr Lefebvre). Hôpital Erasme – Service de Rhumatologie in Brussels (Dr Appelboom). Université Catholique de Louvain in Brussels (Dr Devogelaer). Clinique du Parc Leopold in Brussels (Dr Wouters). Centre hospitalier de Dinant in Dinant (Dr Mahty). Private Practice in Liège (Dr Fraikin) Policliniques Universitaires L-Brull in Liège (Dr Reginster, main investigator). Clinique St Pierre in Ottignies Louvain La Neuve (Dr Toussaint). Cabinet Médical in Saive (Dr Halleux). Cliniques Universitaires (UCL) de Mont Godinne in Yvoir (Dr Boutsen).

In Switzerland: Stadtspital Triemli Zürich in Zürich (Dr Theiler). Universitäts Spital Zürich in Zürich (Dr Uebelhart).

Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.joca.2012.09.017.

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