Pierre Fabre Médicament
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1. TITLE PAGE

CLINICAL STUDY REPORT

Comparative study of efficacy and safety of Structum® and Chondrosulf® in patients with symptomatic osteoarthritis of the knee.
A Multicenter, Randomized, Double-Blind, Double Placebo-Controlled, Parallel Group Study.

Investigational product:	(L0023 / chondroitin sulfate (Structum®) / capsules 500 mg)
Study Design:	Multicenter, Randomized, Double-Blind, Double Placebo-Controlled, Parallel Group Study
Protocol number:	L00023 GE 409
Phase of development:	IV
Date of first enrolment:	15 September 2008
Date of last completed:	17 June 2009
Co-ordinating investigator:	Pr Patrice FARDELLONE Service de Rhumatologie CHU NORD 80054 AMIENS CEDEX 01 Phone: +33-(0)3-22-66-82-50 Fax: +33-(0) 3-22-66-82-59

Version 1 – 27 August 2009

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Date of report: 27 August 2009

Study performed in compliance with Good Clinical Practice.

L00023 GE 409

Clinical Study Report

SIGNATURE FORM

Co-ordinating investigator: Prof. Patrice FARDELLONE, M.D.	Date:	Signature:
Medical Project Leader: Mohammed ZAIM, MD	Date:	Signature:

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2. SYNOPSIS

Name of Company: Pierre Fabre Médicament	**Individual Study Table**	**(For National Authority Use Only)**
Name of finished product: Structum®	**Referring to Module 5 of the Dossier**	
Name of active substance *(or ingredient)***:** chondroitin sodium sulfate	**Vol.: .....Page: .....**	

Title of study:	Comparative study of efficacy and safety of Structum® and Chondrosulf® in patients with symptomatic osteoarthritis of the knee. A Multicenter, Randomized, Double-Blind, Double Placebo-Controlled, Parallel Group Study.	
Co-ordinating investigator:	Pr Patrice FARDELLONE Service de Rhumatologie CHU NORD 80054 AMIENS CEDEX 01 Phone: +33-(0)3-22-66-82-50 Fax: +33-(0) 3-22-66-82-59	
Study centre(s):	126 centres screened at least one patient	
Publication (reference):	NA	
Studied period *(years, months …)***:** **(date of first enrolment)** **(date of last completed)**	Duration: 9 months 15 September 2008 17 June 2009	**Phase of development:** IV
Objectives: **Primary:**	To demonstrate non-inferiority of Structum® to Chondrosulf® on pain relief and functional improvement in patients with symptomatic knee OA over 24 weeks.	
Secondary:	To compare the efficacy of Structum® and Chondrosulf® on : - Patient's and investigator's global assessment of the disease status, - Consumptions of analgesic medication (including NSAIDs), - Improvement in the patient's health related quality of life, To assess safety of the studied products in patients with symptomatic knee OA.	
Methodology:	Multicenter, Randomized, Double-Blind, Double Placebo-Controlled, Parallel Group Study	
Number of patients (planned and analysed):	Planned: 800 patients were required to demonstrate non-inferiority on both primary criteria. Selected: 839, Randomised: 837, Treated: 835, Analysed: 835	

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Diagnosis and main criteria for inclusion:	Patients aged from 50 to 80 years with symptomatic femorotibial knee OA fulfilling ACR criteria for knee OA, with a Kellgren-Lawrence radiological grade II or III, a global pain score greater than or equal to 40 on a 100mm VAS, and a Lequesne Index greater than or equal to 7.
Test product, **Dose,** **Mode of administration,** **Batch number:**	L0023 (Institut de Recherche Pierre Fabre), STRUCTUM® 500mg capsules 1 capsule bid, i.e. 1000 mg/day . oral route PC20080507, PC20080508, PC20080512
Other product, **Dose,** **Mode of administration,** **Batch number:**	Rescue medication: acetaminophen / paracetamol tablets On demand Oral route PC20080507, PC20080508, PC20080512 In the event that the course of acetaminophen / paracetamol proved inadequate, a NSAID with immediate symptomatic effect on OA might be prescribed from an established list [28].
Reference therapy, **Dose,** **Mode of administration,** **Batch number:**	Chondrosulf®: 400 mg capsules: 1 capsule tid, i.e.1200mg/day. Oral route PC20080507, PC20080508, PC20080512
	Patients self-administered the study products as from the inclusion visit, every day for 24 weeks: 2 capsules in the morning, at midday and in the evening. The double dummy method was used to preserve the blind: depending of the group on which the patient was randomized, the patients received: Group L0023 : Structum® (1000mg of chondroitin sulfate): 1 capsule of Structum® in the morning and in the evening, 1 capsule of placebo of Structum®, at midday, and 1 capsule of placebo of Chondrosulf® in the morning, at midday and in the evening Reference Group : Chondrosulf ® (1200mg of chondroitin sulfate): 1 capsule of Chondrosulf® in the morning, at midday and in the evening, and 1 capsule of placebo of Structum ® in the morning, at midday and in the evening

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Criteria for evaluation:

Evaluations were performed at inclusion (V2), week 6 (V3), week 12 (V4), week 18 (V5) and week 24 – end of study (V6)

Efficacy:

Primary criteria: Two co-primary efficacy endpoints [23] :

Mean variation of the global pain score (VAS) over 24 weeks,

Mean variation of Lequesne Index [29] over 24 weeks,

Secondary criteria:

Mean changes of pain scores (on motion and at rest) over 24 weeks,

Responders (OARSI-OMERACT criteria [30]) at Weeks12 and 24 in each group,

Mean changes on patient's and investigator's global assessment scores

Mean consumption in each group, of analgesics medication (including NSAIDs) over 24 weeks.

Quality of life assessment

Medical Outcomes Study 12-item Short-Form General Health Survey (SF12) questionnaire: mean changes of Physical Component Summary (PCS) and Mental Component Summary (MCS) of SF12 [32], between baseline and week 12 and 24, in each group.

OsteoArthritis of Knee and Hip Quality of Life Scale (OAKHQOL): mean changes of each OAKHQOL dimension score [31], between baseline and weeks 12 and 24, in each group,

Safety:

Adverse Events

Global physical examination

Weight and height

Vital signs: systolic and diastolic blood pressure and heart rate

Statistical methods:

Analyses have been conducted on the following patients data sets:

- The Full Analysis Set (FAS): patients having received at least one administration of the product and having at least one evaluation of the primary criteria post administration,

- The "Per Protocol" (PP) data set: subset of the FAS composed of all patients without any major protocol deviations.

- The Safety data set: composed of all randomized patients having received one administration of the product. This data set has been used to perform the analysis of safety.

Primary criteria

Change from baseline was calculated as Baseline-Mean (week 6, week 12, week 18, week 24)

The 95% confidence interval of the difference test-reference for both criteria has been calculated. The test product was to be declared non-inferior to the reference product if the lower limit of the 95% CI was above -5mm for pain and -1 for Lequesne index both in the PP and the FAS populations.

No adjustment of the Type I error rate was required since the four analyses must demonstrate each non-inferiority.

Statistical methods (continued):

Secondary criteria

Analyses of the secondary criteria have been performed on the FAS and PP data sets.

For all the secondary criteria, the 95% CI of the difference test-reference has been calculated.

The analysis was purely descriptive: no test of hypotheses (non-inferiority or superiority) has been made.

For the consumption of analgesics, the criterion analyzed was the percentage of days with intake of analgesics relatively to the number of days on treatment.

Safety analysis

The safety data set has been used to perform all analyses of the safety criteria. The safety analyses were purely descriptive.

Summary - Conclusions:

847 patients were screened to enter the study, 839 were selected, 837 were randomised and 835 treated (412 in the Structum® group and 425 in the Chondrosulf® group. 23 patients prematurely discontinued the treatment in the Structum® group (5.6%) and 39 (9.2%) in the Chondrosulf® group.

The population analyzed for safety consists in the 835 patients treated, the FAS analysis population counts 817 patients and the PP population 692 patients.

	Structum (n=412)	Chondrosulf (n=425)	Total (N=837)
	n (%)	n (%)	n (%)
SAF dataset	411 (99.8)	424 (99.8)	835 (99.8)
FAS dataset	403 (97.8)	414 (97.4)	817 (97.6)
PP dataset	348 (84.5)	344 (80.9)	692 (82.7)

Demographics (PP population): 68.2% of the patients are females, mean age (SD) is 65.1 (8.6) years, mean weight 75.5 (12.8) kgs, mean BMI 27.7 (3.7) kg/m². Overall knee osteoarthritis duration is 5.6 (5.3) years.

Efficacy results

The main efficacy analysis, shows that the lower limits of the 95% confidence intervals of the differences between Structum® and Chondrosulf® mean changes between baseline and mean over 24 weeks in both co-primary criteria (global pain VAS and Lequesne Index) are both above the predefined non inferiority margins (-5 and -1 respectively). It can be concluded that non inferiority of Structum® over Chondrosulf® is demonstrated on the PP dataset.

The analysis of the two co-primary endpoints on the FAS dataset, leads to the same conclusion.

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Primary Analysis : change between baseline and the mean of global pain VAS and Lequesne Index over 24 weeks on the PP population:

Description	Statistic	STRUCTUM (N=348)	CHONDROSULF (N=344)	Difference and [95% CI]
Global pain (VAS)				
Baseline *	n / Missing	348 / 0	344 / 0	
	Mean (SD)	61.61 (11.62)	62.36 (11.69)	
	[95% CI]	[60.38, 62.83]	[61.12, 63.60]	
	Median [Q1,Q3]	60.50 [52.00, 70.00]	61.00 [53.00, 71.00]	
	[Min., Max.]	[40.00, 95.00]	[40.00, 94.00]	
Mean over 24 weeks *	n / Missing	348 / 0	344 / 0	
	Mean (SD)	37.76 (16.99)	38.53 (17.14)	
	[95% CI]	[35.97, 39.55]	[36.71, 40.35]	
	Median [Q1,Q3]	39.25 [24.00, 49.81]	38.31 [25.00, 50.38]	
	[Min., Max.]	[2.25, 82.00]	[2.25, 81.63]	
Change (Baseline - Mean over 24 weeks*)	n / Missing	348 / 0	344 / 0	0.012 [-2.58, 2.61]
	Mean (SD)	23.85 (17.54)	23.84 (17.24)	
	[95% CI]	[22.00, 25.70]	[22.01, 25.66]	
	Median [Q1,Q3]	21.88 [11.13, 34.88]	22.13 [10.00, 36.88]	
	[Min., Max.]	[-12.75, 87.50]	[-12.00, 73.75]	
Lequesne Index				
Baseline *	n / Missing	348 / 0	344 / 0	
	Mean (SD)	11.05 (2.60)	11.03 (2.42)	
	[95% CI]	[10.77, 11.32]	[10.77, 11.28]	
	Median [Q1,Q3]	10.50 [9.00, 12.50]	11.00 [9.00, 12.50]	
	[Min., Max.]	[7.00, 21.00]	[7.00, 20.00]	
Mean over 24 weeks *	n / Missing	348 / 0	344 / 0	
	Mean (SD)	7.82 (3.07)	7.94 (3.11)	
	[95% CI]	[7.49, 8.14]	[7.61, 8.27]	
	Median [Q1,Q3]	7.75 [5.88, 9.38]	7.63 [5.81, 10.13]	
	[Min., Max.]	[0.38, 18.13]	[0.00, 17.88]	
Change (Baseline - Mean over 24 weeks*)	n / Missing	348 / 0	344 / 0	0.139 [-0.22, 0.50]
	Mean (SD)	3.23 (2.42)	3.09 (2.43)	
	[95% CI]	[2.97, 3.48]	[2.83, 3.35]	
	Median [Q1,Q3]	2.81 [1.59, 4.75]	2.63 [1.50, 4.63]	
	[Min., Max.]	[-3.13, 11.50]	[-2.50, 15.00]	

* Calculated data

Analyses of the secondary efficacy endpoints (pain on motion, pain at rest, global assessment of disease status by the patient and the investigator, responders rate according to OARSI-OMERACT criteria, dimensions of SF12 and OAKHQOL questionnaires) show similar results: a statistically significant, as evidenced by the 95% CI of the change from baseline, and medically relevant improvement in both groups with no evidence of difference between the groups. The SF12 Mental component summary and the OAKHQOL mental health, social support and social activities scores show small within group variations unlikely to be medically relevant in the context of knee OA.

Use of rescue medication (paracetamol and/or NSAID) is similar between the two groups and cannot have biased the results of the efficacy analyses either by modifying the within group estimates of treatment effects or by biasing the between groups comparisons.

The analyses conducted either on the PP dataset or the FAS dataset give similar results.

Safety results

One hundred and seventy seven (177) patients of the Structum® group (43.1%) and 190 patients of the Chondrosulf® group (44.8%) reported at least one TEAE.

Twenty-nine (29) patients (10 patients, 2.4% in the Structum® group and 19 patients, 4.5% in the Chondrosulf® group) definitively discontinued the study drug treatment due to an AE.

No death occurred in the study.

Twenty (20) serious adverse events (SAEs) were reported in 19 patients (5 patients, 1.2% in the Structum® group and 14 patients, 3.3% in the Chondrosulf® group). For all the SAEs reported, relationship to study treatment was rated as excluded by the investigator.

No relevant findings regarding physical examination and vital signs have to be mentioned.

On some parameters (frequency of patients definitively discontinuing study treatment due to an AE, frequency of patients presenting at least one SAE, cardiac disorders, infections and infestations general disorders and administration site conditions, migraine and insomnia) between groups differences, possibly indicative of a lesser tolerance of the treatment in the Chondrosulf® group are observed:

Overall, 24 weeks treatment with both Structum® and Chondrosulf® can be considered as safe and well tolerated.

Conclusion

Overall the conclusion on efficacy are that the two drugs are equally effective on pain relief an functional improvement in patients with symptomatic knee OA over a 6 month period of time. Improvement is obtained as early as week 6 and persists over the 24 weeks of the study.The overall improvement (pain and function) is translated into an improvement on some components of quality of life (physical functioning and pain, and also mental functioning, where the magnitude of the change is smaller). Effectiveness is also confirmed by the high rate of responders, which is about 3 out of 4 patients in each group.

Treatment by either Structum® 500 mg bid or Chondrosulf® 400 mg tid in patients suffering from knee OA has been well tolerated.

In summary, this non-inferiority randomised, active-controlled trial has demonstrated that Structum® was not inferior to Chondrosulf® in reducing OA symptoms in patients with knee OA.

Date of report: 27 August 2009