**Pierre Fabre Médicament**
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**45, Place Abel Gance**
**F-92100 Boulogne**

# 1. TITLE PAGE

# CLINICAL STUDY REPORT

**Efficacy and tolerability of chondroitin sulphate 1000 mg, twice daily in patients with symptomatic knee osteoarthritis.**

**Investigational product**: L0023 (chondroitin sulphate, Structum®)

**Study Design**: A multicentre, randomised, double-blind, placebo-controlled, parallel-group study.

**Protocol number**: L00023 GE 3 03
**Eudract number**: 2009-014516-35

**Phase of development**: III

**Date of first enrolment**: January 7, 2010

**Date of last completed**: July 4, 2011

**Coordinating Investigator:** F. Berenbaum, MD
Hôpital Saint-Antoine,
184 rue du Faubourg Saint-Antoine
F-75012 PARIS

**Sponsor Representative for study report**: Head of Therapeutic Area: A. Bouroubi, MD,
IRPF, 3, avenue Hubert Curien
31035 TOULOUSE CEDEX – France

**Date of report**: **July 25, 2012**

Study performed in compliance with Good Clinical Practice.

# 2. SYNOPSIS

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

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|---|---|
| **Title of study:** | **Efficacy and tolerability of chondroitin sulphate 1000 mg, twice daily in patients with symptomatic knee osteoarthritis.** |
| **Investigators:** | 43 investigators coordinated by F. Berenbaum MD. |
| **Study centres** | 41 centres in 7 countries, respectively 2 in Belgium, 7 in Czech republic, 1 in Estonia, 16 in France, 3 in Lithuania, 4 in Poland, 8 in Romania. |
| **Publication (reference):** | No publication based on this study has been written to date. |
| **Studied period:** | January 07, 2010<br>July 04, 2011 — **Phase of development: III** |
| **Objectives:** | **Primary objective**<br>To assess the efficacy of chondroitin sulphate (L0023) 1000 mg twice daily on pain relief and additionally functional improvement in patients with symptomatic knee OA at 6 months.<br>Secondary objectives<br>to assess the efficacy over 12 months on:<br>– patient's and investigator's global assessment of the disease status,<br>– consumptions of analgesic medication (including NSAID),<br>– improvement in the patient's health related quality of life,<br>– pain relief and functional improvement<br>– knee structural changes over 12 months.<br>to evaluate<br>– the safety and tolerability of L0023 over 12 months,<br>– knee structural changes over 12 months,<br>– biological tolerance over 12 months. |
| **Methodology:** | A multicentric, randomised, double-blind, placebo-controlled, parallel-group study. |
| **Number of patients** | Planned: 460 randomised patients,<br>Analysed: 508 randomised and FAS patients (255 on placebo, 253 on L0023), 360 Per Protocol (PP) patients (188 on placebo, 172 on L0023). |
| **Diagnosis and main criteria for randomisation** | – male or female between 50 and 75 years of age,<br>– presenting with medial femorotibial osteoarthritis (OA) of the knee fulfilling ACR criteria (knee pain + crepitus + morning stiffness < 30 minutes),<br>– evolving for more than 6 months,<br>– with a WOMAC pain score ≥ 45 mm on a 100 mm VAS,<br>– patients taking analgesic medications for at least 3 months prior to randomisation (Day1/V2) and dissatisfied with their current therapy,<br>– with a grade II or III according to the Kellgren and Lawrence radiological classification on a posterio-anterior weight-bearing X-ray image of both knees performed at screening visit (V1),<br>– having given their written consent to take part in the study,<br>– covered by social security or a health insurance policy (if required by local requirements). |
| **Test product, Dose, Mode of administration, Batch number:** | L0023 capsules of chondroïtin sulphate 500 mg, 1000 mg twice daily, *per os*,<br>Batch No G01263, expiry date August 2012. |
| **Other product, Dose, Mode of administration, Batch number:** | paracetamol tablets (Doliprane®), *per os*,<br>Batch No 4444, expiry date August 2012. |
| **Duration of treatment:** | 12 months ± 7 days. |
| **Reference therapy, Dose, Mode of administration, Batch number:** | Placebo capsules, matching L0023 capsules, 2 capsules twice daily, *per os*,<br>Batch No SB0737, expiry date August 2013. |

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**Criteria for evaluation:**

**Efficacy**

Primary criteria:

- percentage of pain responders (patients with reduction in WOMAC pain score from randomisation (Day1/V2) of ≥ 30%) at Month 6 (V5),
- percentage of function responders (patients with reduction in WOMAC function score from Day1/V2 of ≥ 20%) at Month 6 (V5).

Secondary criteria:

- percentage of pain responders (patients with reduction in WOMAC pain score from Day1/V2 of ≥ 30%), and function responders (patients with reduction in WOMAC function score from Day1/V2 of ≥ 20%) at months 2 (V3), 4 (V4), 9 (V6) and 12 (V7),
- mean variation of WOMAC pain score, WOMAC function, WOMAC stiffness score at Months 2, 4, 6, 9 and 12 in each group,
- percentage of responders according to Omeract-Oarsi criteria at Months 2, 4, 6, 9 and 12 in each group,
- percentage of patients with a Minimal Clinically Important Improvement (MCII) at Months 2, 4, 6, 9 and 12 in each group,
- percentage of patients who met the threshold for Patient Acceptable Symptom State (PASS) at Months 2, 4, 6, 9 and 12 in each group,
- mean changes on patient's and investigator's global assessment scores at Months 2, 4, 6, 9 and 12 in each group,
- mean changes of Physical Component Summary (PCS) and Mental Component Summary (MCS) of SF12, between Day 1/V2, Month 6 and Month 12 in each group,
- mean changes of Intermittent and Constant Osteoarthritis Pain (ICOAP) questionnaire between Day1/V2, Month 6 and Month 12 in each group,
- mean changes of Knee injury and Osteoarthitis Outcome Score - Physical Function Shortfom (KOOS-PS) between Day1/V2, Month 6 and Month 12 in each group,
- percentage of days with NSAIDs intake and percentage of days with any analgesics intake,
- mean NSAIDs intake (diclofenac equivalent) and mean paracetamol intake,
- mean changes of joint space narrowing between Day 1/V2 and Month 12 in each group

**Safety**

- Adverse events recording
- Physical examination at screening visit and at each visit (from V2 to V7) including weight (at V1 and V7 only) and height (atV1 only),
- Vital signs at each visit (from V1 to V7),
- Biological safety (haematology, biochemistry) at V1, Month 6 and Month 12,
- Percentage of patients with a joint space narrowing between Day 1/V2 and Month 12 greater than 0.3 mm and greater than 0.7 mm; the analyses were performed on both the target knee and the non target knee.

**Statistical methods**

**Efficacy**

- For quantitative parameters measured at baseline: the change from randomisation (Day1/V2) were compared using an analysis of covariance (ANCOVA) with treatment effect, centre effect and baseline as a covariate. An additional analysis of covariance using a likelihood-based MMRM was carried out on mean of WOMAC different score changes from baseline separately.
- categorical or ordinal parameters were compared using a Cochran-Mantel-Haenszel (CMH) test adjusting for centre, with modified ridit score. For binary variables, a check of the validity condition of Mantel and Fleiss was performed.

**Safety**: descriptive statistics summarizing adverse events, vital signs, laboratory tests and joint space narrowing by treatment group

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**Summary - Conclusions:** The FAS population was composed of 508 patients, respectively 399 women (78.5%) and 109 men (21.5%), aged 62.8 (sd = 6.8) years and suffering from symptomatic knee osteoarthritis. The number of withdrawn patients and completers are displayed hereafter.

| | **Placebo n=255** | | **L0023 n=253** | | **Total n=508** | |
|---|---|---|---|---|---|---|
| **Number of withdrawn patients** | 40 | ( 15.7%) | 35 | ( 13.8%) | 75 | ( 14.8%) |
| Non serious/serious adverse event | 7 | ( 2.7%) | 7 | ( 2.8%) | 14 | ( 2.8%) |
| Insufficient response | 12 | ( 4.7%) | 5 | ( 2.0%) | 17 | ( 3.3%) |
| Other reason | 25 | ( 9.8%) | 25 | ( 9.9%) | 50 | ( 9.8%) |
| **Completers patients** | 215 | ( 84.3%) | 218 | ( 86.2%) | 433 | ( 85.2%) |

**Efficacy results**

Concerning the efficacy of chondroitin sulphate 1000 mg twice daily in patients with symptomatic knee osteoarthritis, results of the main criteria, *i.e.* the percentages of pain responders (defined by a decrease of at least 30% of the WOMAC Pain score, mean of the 5 pain related-activities items, between baseline and Month 6) and of function responders (defined by a decrease of at least 20% of the WOMAC Function score, mean of the 17 functional activity items, between baseline and Month 6), did not show any statistically significant difference between patients on L0023 (pain 63.6%, function 63.5%) and patients on placebo (pain 61.6%, function 63.5%).

This percentage of responders increased in both treatment groups over the period from Month 6 to Month 12. Therefore no difference in the percentage of responders was showed between both treatments at Month 12: on L0023 (pain responders 71.5%, function responders 72.6%) and on placebo (pain responders 72.2%, function responders 67.8%).

These results have shown a high and unexpected pain and function response on placebo over the 12-month period of treatment. This high placebo effect could mask any potential effect of chondroitin sulphate over the 12-month treatment period on the percentage of both pain and function responders.

A decrease in the WOMAC scores, i.e. pain scores, as well as functional score, was observed over time up to Month 12 whatever the treatment, but no statistically significant difference was observed between both treatments.

For all other efficacy parameters, including the joint space analysis, no clinically relevant difference was observed between both treatments over the 12-month period of treatment.

**Safety results**

Twenty (20) SAE were notified in 18 patients (1 during the screening period, 7 on placebo and 12 on L0023), none of them were considered as drug related apart from a case of angina pectoris with insufficient data for the relationship assessment by the investigator and considered not related by the sponsor. Fourteen (14/508) patients (7/255 on placebo, 7/253 on L0023) prematurely discontinued the study treatment due to an adverse event, 5 of them reported 7 adverse events considered as related to the study drug: 2 AE in 2 patients on placebo (abnormal faeces and rash) and 5 AE in 3 patients on L0023 (2 diarrhoea, nausea, oesophagitis and urticaria).

Respectively 162/255 (63.5%) patients on placebo and 166/253 (65.6%) patients on L0023 had at least one adverse event on study drug during the whole study period of 12 months

The most common SOC over the whole study treatment period were Nervous system disorders [86 (33.7%) on placebo, 91 (36.0%) on L0023], Musculoskeletal & connective tissue disorders [78 (30.6%) on placebo, 75 (29.6%) on L0023], Infections & infestations [53 (20.8%) on placebo, 55 (21.7%) on L0023] and Gastro-intestinal disorders [30 (11.8%) on placebo, 35 (13.8%) on L0023]. The most common TEAE (whatever the study treatment) were headache, back pain, arthralgia, nasopharyngitis, pain in extremity, musculoskeletal pain and bronchitis.

No clinically relevant difference was observed between placebo and L0023 for any of the haematology or biochemistry parameters. Overall 23 patients presented CNALV, respectively 15 on placebo and 8 on L0023. On L0023 they concerned 5 low values of neutrophils (5 patients), a low value of haemoglobin, a low value of platelets and a high value of SGPT (1 patient each).

Slight changes in vital signs (blood pressure or heart rate) were observed on both treatments, but were without any clinical relevance. Overall 28 patients presented significant values and/or changes in vital signs (10 on placebo and 18 on L0023). None of them was considered clinically relevant by the investigator.

No unexpected adverse event was observed in this study according to the "Summary of Product Characteristics".

**Conclusion:** In conclusion, pain and function responses were not statistically significant between chondroitin sulphate 1000 mg twice daily and placebo over both 6 and 12 months of treatment. This absence of difference could be due to a very high and unexpected placebo effect. Chondroitin sulphate 1000 mg twice daily can be considered as safe and well tolerated over 12 months.

**Date of report: July 25, 2012**