when compared to an equivalent dose of glucosamine hydrochloride. Whether this difference in synovial levels of glucosamine attained is translated into a therapeutic effect on the joint tissues remains to be elucidated.

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REQUIREMENT FOR TOTAL ARTICULAR REPLACEMENT AFTER DIACEREIN TREATMENT IN HIP
OSTEOARTHRITIS: A 5 YEARS FOLLOW-UP OF THE 3 YEARS PLACEBO-CONTROLLED ECHODIAH TRIAL

M. Dougados1, L. Gossec1, M. Nguyen1, L. Berdah2, B. Mazieres3, E. Vignon1, M. Lequesne5
1René Descartes University, Paris, France; 2Negma Laboratories, Paris, France; 3Paul Sabatier University, Toulouse, France; 4Centre Hospitalier Lyon-Sud, Pierre Bénite, Lyon, France; 5Leopold Bellan Hospital, Paris, France

Purpose: Evaluation of disease modifying osteoarthritis drug (DMOADs) in hip osteoarthritis (OA) is based on effects on both symptoms and structure. Such a beneficial effect might result in a subsequent hard end-point (e.g. requirement to total hip replacement (THR)).

The objective of this study was to evaluate the long term (5 years) effect on requirement for THR of a 3 years intake of diacerein in comparison to placebo in hip OA.

Methods: Two periods: a) 3 years controlled trial evaluating the effects on the structure and the symptoms of 50 mg diacerein b.i.d. versus placebo (Dougados M. et al. Evaluation of the structure modifying effects of diacerein in hip osteoarthritis: ECHODIAH, a three-year, placebo-controlled trial. Arthritis Rheum 2001;44:2539-47); b) 5 years follow-up via an annual phone call contact. Collected data: at baseline demographics and OA characteristics (femoral head migration, radiological joint space width [JSW]). During the 3 years of the therapeutic trial and the 5 years of follow-up: requirement to THR. Analysis: primary analysis: percentage of patients requiring THR with regard to the treatment group in patients completing the 3 years placebo controlled trial (clinical trial completers) using life table analysis technique and log-rank test; secondary analyses: identical end-points and statistical analysis but a) in the whole population entering the trial at year 0; b) in the sub-group of patients with supero-lateral and concentric femoral head migration (excluding the patients with a supero-medial femoral head migration) and a baseline (year 0) JSW of at least 1.5 mm as suggested by the Barcelona consensus meeting (Altman RD, et al. Measurement of structural progression in osteoarthritis of the hip: the Barcelona consensus group. Osteoarthritis Cartilage 2004;12:515-24.).

Results: Of the 507 included patients (255 and 252 in the diacerein and placebo groups, respectively), 262 completed the 3 years of the therapeutic trial (127 in the diacerein group). For these patients, a THR was required during the subsequent 5 years in 40% after diacerein intake versus 43% after placebo (p=0.60). In the whole group of patients entering the trial, a THR was performed at the end of the 8 years follow-up period in 56% whatever the initial treatment group (p=0.94). In the sub-group of 283 patients fulfilling the criteria proposed by the Barcelona consensus group at entry (149 in the diacerein group), a THR was performed at the end of the 8 years follow-up period in 49% after diacerein intake vs 55% after placebo, (p=0.50). In this sub-group, 157 patients (81 in the diacerein group) completed the 3 years of the therapeutic trial. For these patients, a THR was required during the subsequent 5 years in 32% after diacerein intake vs 44% after placebo (p=0.21).

Conclusions: This study failed to demonstrate a statistical significant difference between the two treatment groups with regard to the requirement to THR after a 3 years intake of diacerein in the a priori defined primary analysis. However, the trend in favor of diacerein in different clinically relevant sub-populations suggests that a 3 years intake of diacerein might have a subsequent long term beneficial effect in a sub-group of hip OA patients. Such findings should be evaluated in further clinical trials.

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PHARMACOKINETICS OF GLUCOSAMINE IN MAN AFTER ORAL ADMINISTRATION OF CRISTALLINE
GLUCOSAMINE SULFATE OR GLUCOSAMINE HYDROCHLORIDE ALONE OR IN COMBINATION WITH
CHONDROITIN SULFATE

S. Persiani1, L.C. Rovati1, E. Pastorini2, M. Locatelli2, G. Giacovelli1, D. Paganini1, A. Roda2
1Rottapharm, Monza, Italy; 2Dept. of Pharmaceutical Sciences, University of Bologna, School of Pharmacy, Bologna, Italy

Purpose: Crystalline glucosamine sulfate and glucosamine hydrochloride alone or in combination with chondroitin sulfate have been evaluated as a treatment for knee pain from osteoarthritis (OA) in two recent studies of 6-month duration. The NIH-sponsored GAIT study did not show any effect of treatment with 500 mg glucosamine hydrochloride three times daily (t.i.d.) alone or in combination with 400 mg of chondroitin sulfate t.i.d. Conversely, the GUIDE trial indicated that, at the dose of 1500 mg once-a-day, crystalline glucosamine sulfate soluble powder provided a significant symptomatic effect, thus confirming previous long-term study observations. The pharmacokinetics of crystalline glucosamine sulfate 1500 mg once-a-day were recently investigated and showed glucosamine peak plasma levels in the 10 μM range. These levels were effective in vitro in inhibiting IL-1-induced gene expression, currently regarded as the putative mechanism of action of glucosamine in OA. Conversely, preliminary studies of the pharmacokinetics of glucosamine after administration of the glucosamine hydrochloride capsule formulation used in GAIT, suggested that the peak levels might be much lower. The aim of the present study was therefore to investigate in a direct comparative study, the relative bioavailability of glucosamine following repeated oral administration of the two glucosamine salt formulations and dose regimens, or of the glucosamine hydrochloride/chondroitin sulfate combination, to assess if differences in exposure to the active ingredient and especially in peak plasma levels, might provide a possible explanation for the contrasting clinical results.

Methods: Twelve healthy volunteers (5 males and 7 females) received three consecutive once-daily oral administrations of crystalline glucosamine sulfate soluble powder at the dose of 1500 mg, or glucosamine hydrochloride capsules at the dose of 500 mg t.i.d. for three consecutive days either alone or in combination with chondroitin sulfate 400 mg t.i.d. in an open, randomised, cross-over fashion. Glucosamine was determined after the administration of 500 mg glucosamine hydrochloride alone (Css,max and AUCss averaged 4.5±1.8 μM and 21.4±7.6 μM·h, respectively) or in combination with 400 mg of chondroitin sulfate (Css,max and AUCss averaged 3.3±1.0 μM and 13.8±5.4 μM·h, respectively).

Conclusions: Administration of glucosamine hydrochloride at the dose of 500 mg t.i.d might produce a similar extent of systemic exposure to glucosamine throughout the day, but at significantly lower (less than a half) peak plasma concentrations compared to 1500 mg of crystalline glucosamine sulfate.