subjects attending all assessment visits. There was one treat-
ment protocol termination; this subject discontinued HLXL Dan
after week 1 because of a rise in serum transaminase levels.
According to pill counts, overall compliance with study drug was
94 percent. There were no serious adverse events reported.
Overall, there was a significant reduction in VAS knee pain that
was evident by week 3 and continued through the end of the
study (see Tables). While there was no significant change in the
patient global assessment of disease during the intervention (P
= 0.37), 3 patients reported that they were markedly improved, 2
were moderately improved, and 1 each was slightly improved or
had no change at the final visit.

Mean (SE) VAS Knee Pain

<table>
<thead>
<tr>
<th>Period</th>
<th>Mean (SE)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BL to WK 1</td>
<td>-3.9 (3.9)</td>
<td>0.34</td>
</tr>
<tr>
<td>BL to WK 3</td>
<td>-11.0 (4.2)</td>
<td>0.02</td>
</tr>
<tr>
<td>BL to WK 6</td>
<td>-19.2 (4.2)</td>
<td>0.0003</td>
</tr>
</tbody>
</table>

Conclusions: HLXL Dan at a single daily dose of 5,180 mgs
for six weeks was safe and efficacious in this phase I study in
patients with symptomatic knee OA. A Phase II dose-ranging
placebo-controlled clinical trial of this herbal compound, sup-
ported by a grant from NCCAM, is currently being conducted.

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A COMPARISON OF TWO PHYSICAL THERAPY
PROGRAMS ON FUNCTIONAL CAPACITY,
PROPRIOCEPTION, AND BALANCE IN WOMEN WITH
KNEE OSTEOARTHRITIS

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Purpose: Primary finding in knee osteoarthritis (OA) is gait
abnormalities. Also, decrease in muscle strength and range of
motion reduced functional capacity, impaired balance and
proprioception together with resultant increased risk of falling
have been reported. The purpose of this study was to investiga-
te the effects of two physical therapy and rehabilitation programs
on functional capacity, proprioception, and balance in women with
knee OA.

Methods: Forty female patients with knee OA participated in
this study. Patients were randomly and equally divided into two
groups. Group I underwent a physical therapy and rehabilitation
program consisting of hotpack, ultrasound, and proprioceptive
neuromuscular facilitation (PNF) exercises for a total 10 sessions,
5 days per week for 2 weeks. They continued PNF exercises for
3 days per week for additional 4 weeks. Group II underwent
hotpack, ultrasound, and isokinetic exercises for 5 days per
week, for 2 weeks (a total of 10 sessions). Similar to Group I,
they continued isokinetics exercises for 3 days per week for
additional 4 weeks. Patients were evaluated at baseline at the
second and the sixth weeks of treatment. Functional capacity
was evaluated using 15- meter walking distance, time up and go
test and 12- step up and down test. Proprioception was eval-
uated using 15-meter walking distance, time up and go

Results: Functional capacity, proprioception, and balance im-
proved significantly in both groups (p<0.05). There were no
significant differences between the groups in any of the variables
both at the second and the sixth week of treatment in any of the
groups (p>0.05).

Conclusions: Two different physical therapy and rehabilitation
programs had favorable effects on functional capacity, proprio-
ception and balance in women with knee OA. Therefore, both
programs can be used to improve these parameters in patients
with knee OA.

Therapy – Pharmacologic

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COMPARISON OF PHARMACOKINETICS OF
GLUCOSAMINE AND SYNOVIAL FLUID LEVELS
FOLLOWING ADMINISTRATION OF GLUCOSAMINE
SULPHATE OR GLUCOSAMINE HYDROCHLORIDE

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Purpose: To compare the pharmacokinetics of glucosamine
following treatment with glucosamine sulphate or glucosamine
hydrochloride in a large animal model and to compare the syn-
ovial fluid levels attained following the administration of each
formulation at clinically relevant doses.

Methods: Eight adult female horses were used. After an
overnight fast, crystalline glucosamine sulphate (Dona®) or glu-
cosamine hydrochloride were administered at a dose of 20 mg/kg
by either intravenous (IV) injection or nasogastric (NG) intuba-
tion. Plasma samples were collected before dosing and at 5,
15, 30, 60, 120, 360, 480 and 720 minutes after dosing. Syn-
ovial fluid samples were collected from the radio-carpal joints
within 48 hours before dosing and at 1, 6 and 12 hours post
dosing. Glucosamine was measured in both plasma and syn-
ovial fluid by Liquid Chromatography Electrospray Tandem Mass
Spectrometry (LC-ESI/MS/MS).

Results: Endogenous plasma and synovial glucosamine con-
centrations were not significantly different and ranged between
< 10 ng/mL (LOQ) and 39.1 ng/mL. Following IV injection of
either compound, plasma concentrations reached ~ 50 µg/mL
and declined in a similar multi-exponential fashion. After NG ad-
ministration, plasma concentrations attained ~ 1 µg/mL for both
types of glucosamine with no significant difference in attained
median maximal plasma concentrations. The median elimination
half-life of glucosamine after oral glucosamine sulphate admin-
istration was 4.0 hours and 3.0 hours after oral glucosamine
hydrochloride administration. The median oral bioavailability was
marginally but not significantly higher for glucosamine sulphate
than for glucosamine hydrochloride and reached 9.4 % and 6.1 %
respectively. The AUC0-12hr and the AUC0-inf were significantly
higher and the relative clearance was significantly lower after
oral glucosamine sulphate treatment compared to glucosamine
hydrochloride treatment. The median maximal synovial fluid con-
centrations were significantly higher following oral treatment with
glucosamine sulphate (158.3 ng/mL) compared to oral adminis-
tration of glucosamine hydrochloride (88.9 ng/mL). The difference
in synovial fluid concentrations attained following NG adminis-
tration was statistically significant at 1 and 6 hours, but not at
12 hours post treatment. Twelve hours after oral treatment with
glucosamine hydrochloride, plasma and synovial glucosamine
levels had returned to baseline levels. Following oral adminis-
tration of glucosamine sulphate, glucosamine levels in plasma and
the synovial fluid were still significantly higher than baseline
twelve hours post-treatment. The difference in synovial fluid
glucosamine concentrations attained between treatment groups
was not statistically significant following IV treatment.

Conclusions: Following oral administration of a clinically rec-
ommended dose of glucosamine sulphate (Dona®), significantly
higher synovial fluid concentrations of glucosamine are attained,
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 DIAZEPAME TREATMENT IN HIP OSTEOARTHRITIS: A 5 YEARS FOLLOW-UP OF THE 3 YEARS PLACEBO-CONTROLLED ECHODIAH TRIAL

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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 (Dougdos 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 Cartilagge 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 subgroup, 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 CRYSTALLINE GLUCOSAMINE SULFATE OR GLUCOSAMINE HYDROCHLORIDE ALONE OR IN COMBINATION WITH CHONDROITIN SULFATE

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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 thee 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 at steady state in plasma collected up to 48 h after the last dose by a validated LC-MS/MS method.

Results: Glucosamine was bioavailable after administration of the three products. After crystalline glucosamine sulfate 1500 mg once-daily, peak concentrations (Cmax) and extent of exposure (AUCt) averaged 9.1±6.3 µM and 76.5±23.0 µM.h, respectively. Significantly (p<0.005) lower plasma concentrations were determined after the administration of 500 mg glucosamine hydrochloride alone (Cmax and AUCt averaged 4.5±1.8 µM and 21.4±7.6 µM.h, respectively) or in combination with 400 mg of chondroitin sulfate (Cmax and AUCt 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.