ACL changes the biomechanical properties of articular cartilage more than cartilage thickness although it seems that three months after ACLT, cartilage thickness is less than control group. On the other hand, in both femur and tibia cartilage seems to become thicker following LPLT; however, none of these changes is statistically significant. Apparently, destructive effects of ACLT are more pronounced on tibial cartilage. 12 weeks after ACLT, tibial cartilage strength and young modulus decreased significantly, although 10 sessions of LPT reversed this process completely. Same trend was observed in femoral cartilage but these changes were not statistically significant.

**Conclusions:** Following ACLT articular cartilage softens and its strength decreases. It seems that therapeutic laser can help cartilage to resume its original characteristics.

**Table 1.**

<table>
<thead>
<tr>
<th>Group</th>
<th>Bone</th>
<th>Right Meniscus</th>
<th>Left Meniscus</th>
<th>Tibia</th>
<th>Left Femur</th>
<th>Right Femur</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sham</td>
<td>0.94±0.06</td>
<td>0.94±0.06</td>
<td>0.94±0.06</td>
<td>0.94±0.06</td>
<td>0.94±0.06</td>
<td>0.94±0.06</td>
</tr>
<tr>
<td>U0126</td>
<td>0.8±0.06</td>
<td>0.8±0.06</td>
<td>0.8±0.06</td>
<td>0.8±0.06</td>
<td>0.8±0.06</td>
<td>0.8±0.06</td>
</tr>
<tr>
<td>MSX</td>
<td>0.94±0.10</td>
<td>0.94±0.10</td>
<td>0.94±0.10</td>
<td>0.94±0.10</td>
<td>0.94±0.10</td>
<td>0.94±0.10</td>
</tr>
<tr>
<td>Laser</td>
<td>0.94±0.10</td>
<td>0.94±0.10</td>
<td>0.94±0.10</td>
<td>0.94±0.10</td>
<td>0.94±0.10</td>
<td>0.94±0.10</td>
</tr>
</tbody>
</table>

**Thick Width**

**Maximal Force**

**Young Modulus**

**Fig. 1.**

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**Therapy – Pharmacologic**

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**MODULATING MAPK SIGNALING CAN ATTENUATE THE SEVERITY OF OSTEOARTHRITIS**

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**Purpose:** Osteoarthritis (OA) is the most common musculoskeletal disorder and represents a major health burden to society. OA is associated with the irreversible degeneration of articular cartilage. Notably, in this condition, articular cartilage chondrocytes undergo phenotypic and gene expression changes that are reminiscent of their hypertrophic differentiation in the growth plate during skeletal development. Also, the adjacent subchondral bone shows signs of abnormal mineral density and enhanced production of bone turnover markers, indicative of osteoblast dysfunction. Our previous study findings suggest that Extracellular signal-regulated kinases (ERK) signaling is activated in both in OA subchondral bone and cartilage. The present study is a follow up of our previous findings to identify whether the pharmacological inhibition ERK signaling pathway slows down the progression of OA.

**Methods:** We developed three different types of OA rat models: Menisectomy (MSX) induced OA, Anterior cruciate ligament transaction (ACL) induced OA and Mono-ido-acetate (MIA) induced OA to test whether U0126, a MAPK-ERK1/2 pathway inhibitor shows any protective effects towards OA cartilage degeneration and subchondral bone changes. The cause of disease occurrence is different in the above models; therefore the obtained data will show how the drug is acting in different types of OA conditions. From day 7 post-surgery treatment groups were given an intra-articular injection of ERK1/2 inhibitor (UO126) every 2 days at a concentration of 0.5 mM in 50μl using 30G needle for 8 weeks. The control group received same volume of vehicle alone (saline + DMSO) without administration drug. At the end of each time point rats were euthanized and knee joints were paraffin embedded. Serial 5μm sections obtained at 100μm intervals from the non weight bearing region and weight-bearing region of each knee joint were stained with safranin O-fast green, Type 10 collagen (COL10), runt-related transcription factor-2 (RUNX2) and a disintegrin and metalloproteinase with thrombospondin type 1 motif-5 (ADAMTS5). OA severity in the tibial plateau was evaluated according to Mankin’s histologic grading system (Mankin’s score: 0 to 14), and a cartilage destruction score was assigned for each knee sample (n = 10). Micro-Ct was performed to see the protective effects of U0126 on subchondral bone. Cartilage and subchondral bone tissue lysate was extracted from drug treated vs. untreated animals and western blotting technique was applied to see the molecular differences.

**Results:** pERK-1/2 was significantly increased in the cartilage and subchondral bone of all three OA models compared to sham confirming the pathological relevance of this signaling pathway in OA. U0126 down regulated the pERK-1/2 expression in treatment group confirming the efficacy of U0126 in inhibiting ERK at in vivo level. Furthermore, U0126 treated animal models showed significantly reduced Mankin score (up to 40–50%), less proteoglycan depletion, decreased expression of COL0, RUNX2 and ADAMTS5 proteins in all three OA models compared to untreated controls (Figure 1). OA knees showed increase in BV and BV/TV compared to shams at week 8. The increased BV and BV/TV were partially reversed when the animals were treated with the U0126, indicating the therapeutic benefits of U0126 on OA subchondral bone changes.

**Conclusions:** Together, these findings raise the possibility that ERK blockade can be used as a therapeutic approach to inhibit OA articular cartilage degeneration and subchondral bone changes.

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**SINGLE ORAL DOSE OF (1200 MG) SACHET OF CHONDROTIN 4&6 SULFATE (CS4&6 – CHONDROSULF®) RELIEVES PAIN AND IMPROVES FUNCTION. RESULTS OF A DOUBLE BLIND STUDY, VERSUS PLACEBO AND AN ACTIVE TREATMENT IN KNEE OA PATIENTS**

J. Regimenter1, E. Tajana2. 1Univ. of Liège, Liège 1, Belgium; 2IBSA – Inst. Biochimique SA, Pambio-Noranco, Switzerland

**Objective:** Efficacy, safety and tolerability evaluation of a single oral dose, 1200 mg sachet of chondroitin 4&6 sulfate (Chondrosulf® 1200) versus placebo (superiority study) and versus 3 daily capsules of chondroitin 4&6 sulfate 400 mg (Chondrosulf® 400), during 91 days, in patients with knee OA (non inferiority study).

**Methods:** Comparative, double-blind, randomized, multicenter study, in parallel groups, including 353 patients of both genders, over 45 years, with knee OA for at least 6 months. Minimum inclusion criteria was a
Lequesne index (LI) ≥7 and pain ≥40 mm on a visual analogical scale (VAS). LI and VAS were assessed after 30, 60 and 91 days. Global efficacy evaluation and general product tolerability was also performed.

**Results:** Results were confirmed both in per protocol (PP) and intent to treat (ITT) population.

Non-inferiority was demonstrated after 3 month treatment between the oral daily single dose of CS 1200 formulation and the 3 daily capsules of CS 400 (delta=0.13, [−0.81;1.08]).

Patients treated with CS 1200 or CS 3*400 were significantly improved compared to placebo in terms of LI (p < 0.0001). LI score of patients treated with Chondrosulf® was significantly improved in both groups of CS4&6 at D60 and D91 (p < 0.01 and <0.001 respectively).

Pain scores were significantly improved in both treatment groups at D91 (p=0.0052) compared to baseline and placebo. The global efficacy evaluation by patients and investigators showed a statistically significant superiority of both CS 1200 and CS 400 groups compared to placebo after 60 and 91 days.

No significant difference in terms of tolerance and tolerability was observed between the 3 groups.

No serious AE were reported. No AE were related to study drug.

<table>
<thead>
<tr>
<th>LI score of patients treated with Chondrosulf®</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CS 1200</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CS 3*400</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Control</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

**Conclusion:** This study suggests that daily administration of an oral sachet of 1200 mg of chondroitin 4&6 sulphate (Chondrosulf®) allows a significant clinical improvement compared to placebo. A similar clinical improvement was observed between the oral daily single dose of CS 1200 formulation and the 3 daily capsules of CS 400. No significant difference in tolerance and tolerability was observed across the two chondroitin sulphate groups as compared to placebo.

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**TERIPARATIDE AS A CHONDRO-REGENERATIVE THERAPY FOR INJURY-INDUCED KNEE OSTEOARTHRITIS**


**Purpose:** Currently, there are no disease-modifying therapeutic strategies for osteoarthritis (OA), a degenerative joint disease projected to affect more than 67 million Americans by 2030. In OA, the cells responsible for maintenance of joint cartilage, articular chondrocytes (AC) inappropriately undergo a maturational program normally only associated with endochondral ossification. Therefore, signaling pathways that govern chondrocyte maturation represent candidate therapeutic targets. Parathyroid hormone (PTH) induces chondrocyte matrix synthesis and suppresses maturation via the PTH receptor 1 (PTH1R), which we found to be up-regulated in ACs following meniscal injury and during OA in humans and in injury-induced knee OA in mice. Thus, we hypothesized that recombinant human PTH(1–34) (teriparatide) would inhibit aberrant chondrocyte maturation and associated articular cartilage degeneration.

**Methods:** PTH1R levels were analyzed in injured and arthritic human and mouse cartilage samples via immunogorading and qPCR. We administered systemic teriparatide, an FDA-approved treatment for osteoporosis (Forteo), either immediately or beginning 8 weeks after meniscal/ligamentous injury (MLI) in mice. Knee joints were harvested at 4, 8, or 12 weeks post-MLI to examine the effects of teriparatide on OA bone and cartilage phenotypes using microCT, histologic scoring, morphometric methods and immunostaining. Bone phenotypes assessed included subchondral bone volume and osteophyte formation. Cartilage phenotypes examined included articular cartilage integrity and area, as well as molecular assessment of AC maturation.

**Results:** Human cartilage samples harvested from non-OA patients undergoing meniscal repair surgery or end-stage OA patients undergoing total-knee arthroplasty displayed increased PTH1R levels as assessed by immunostaining. Similarly, mice with progressing OA induced by MLI surgery displayed increased PTH1R levels as determined by immunostaining and qPCR. Micro-computed tomography revealed increased bone volume in knee joints following MLI. Teriparatide treatment increased bone volume in both sham-operated and MLI joints, confirming the bone anabolic effect of the systemic therapy. However, osteophyte formation initiated by MLI surgery was not exacerbated by teriparatide treatment and no osteophytes were evident in sham-operated joints from teriparatide-treated mice. Furthermore, targeted activation of the PTH1R in ACs by systemic teriparatide treatment was demonstrated by increased expression of Jagged-1, a direct transcriptional target of the receptor’s downstream signaling pathway. Immediate systemic administration of teriparatide increased proteoglycan abundance and decelerated articular cartilage degeneration. Strikingly, delayed teriparatide treatment beginning 8 weeks post-injury induced a chondro-regenerative effect. Overall, these effects correlated with up-regulation of proteoglycan-4 and decreased levels of matrix metalloproteinase-13, type X collagen and Runx2 in ACs.

**Conclusions:** These preclinical findings provide proof-of-concept for the use of teriparatide (Forteo) to decelerate cartilage degeneration in OA patients and to delay the onset of morbidity associated with end-stage disease.