Title

Efficacy and safety from a phase 2B trial of SM04690, a novel, intra-articular, WNT pathway inhibitor for the treatment of osteoarthritis of the knee

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Conclusions: In addition to apoptosis of chondrocytes and degradation of the extracellular matrix, inflammation or atrophy are constantly detected in the synovial membrane in OA. Decrease in the synthesis of hyaluronic acid with its anti-inflammatory properties, glucose levels, the accumulation of oxidation products, like free-radical forms of oxygen and lactic acid, in SF are the consequence of degenerative changes in the synovia's vascular bed and directly in the cellular layer. These adverse conditions of energy deficiency significantly reduce the synthetic possibilities of chondrocytes, which lead to the progression of OA. The carried out combined method of treating OA of the knee, consisting of PRP procedures and oral intake of GH and CS, favorably affects not only the synovial environment of the joints, but also general health; is well tolerated and increases the efficacy of treatment, especially in patients with OA Grades 0, I and II K-L.

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EFFICACY AND SAFETY FROM A PHASE 2B TRIAL OF SM04690, A NOVEL, INTRA-ARTICULAR, WNT PATHWAY INHIBITOR FOR THE TREATMENT OF OSTEOARTHRITIS OF THE KNEE

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Purpose: A phase 2a study of SM04690, a small molecule, intra-articular (IA) Wnt pathway inhibitor, demonstrated positive beneficial effects on knee pain, improved physical function, and increased medial joint space width (mJSW) at 52 weeks in key subgroups of subjects with knee osteoarthritis (OA) compared to placebo (PBO). A 24-week phase 2b study was conducted to refine patient reported outcome (PRO) measures, target population, medication dose, and to evaluate safety. PRO results for Weeks 12 and 24 are presented here.
Methods: Subjects had ACR-defined knee OA, Kellgren-Lawrence (KL) grades 2-3, Pain Numeric Rating Scale (NRS) score $\geq$4 and $\leq$8 in the target knee and <4 in the contralateral knee. A single IA injection of 2 mL SM04690 (0.03, 0.07, 0.15 or 0.23 mg), vehicle PBO, or sham (dry needle only) was given in the target knee at baseline. PRO endpoints included change from baseline in weekly average of daily pain in the target knee by NRS diary (NRS [0-10]), Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) Pain [0-100], WOMAC Physical Function [0-100], and Patient Global Assessment (PtGA) (VAS [0-100]). This study was not formally powered, and sample size was based upon accepted dose-finding convention.
Results: 695 subjects (mean age 59.0 [±8.5] years, BMI 29.0 [±4.0] kg/m^2, female 58.4%, KL3 57.3%) were enrolled and dosed; 635 (91.4%) completed the study. No meaningful differences in incidence of adverse events were seen between treatment and control groups. In the 'full analysis set' (all randomized, dosed subjects), significant improvements from baseline compared with PBO were observed in pain NRS for 0.07 mg (Week 12 [*P*=0.001], Week 24 [*P*=0.031]) and 0.23 mg (Week 12 [*P*=0.012], Week 24 [*P*=0.022]) SM04690 dose groups (**Figure**). Similar improvements were observed in WOMAC Pain for 0.07 mg (Week 12 [*P*=0.04]) and 0.23 mg (Week 12 [*P*=0.003], Week 24 [*P*=0.031]) dose groups. For WOMAC Physical Function, improvements were observed for 0.07 mg (Week 12 [p=0.021]) and 0.23 mg (Week 12 [p=0.006], Week 24 [P=0.017]) dose groups. PtGA improvements were observed for 0.07 mg (Week 12 [*P*=0.031]), and 0.23 mg (Week 12 [*P*=0.010], Week 24 [*P*=0.033]) dose groups.
Conclusions: SM04690, in development as a potential disease modifying OA drug, showed in this phase 2b study statistically significant improvements from baseline in both the 0.07 mg and 0.23 mg dose groups compared with PBO for Pain NRS, WOMAC Pain, WOMAC Physical Function, and PtGA. These data support the continued development of SM04690 as a potential treatment for knee OA. Phase 3 studies are being planned.

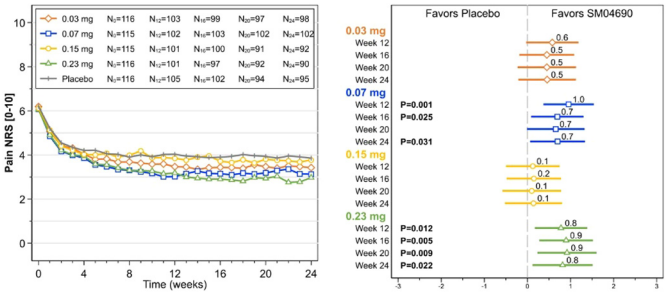

Figure. Actual observations over time and ladder plots depicting mean improvement (± 95% CI) of SM04690 compared with placebo adjusted for baseline for Pain NRS.

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THE EFFECT OF GLUCOSAMINE AND CHONDROITIN SULFATE ON MRI-BASED OSTEOARTHRITIS FEATURES IN THE PATELLOFEMORAL JOINT IN PEOPLE WITH KNEE OSTEOARTHRITIS: A RANDOMISED PLACEBO-CONTROLLED TRIAL OF SINGLE AND COMBINATION REGIMENS

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Purpose: To determine if glucosamine, chondroitin sulfate, or combined supplements taken over two years reduce the progression of cartilage defects and bone marrow lesions (BMLs) in the patellofemoral joint, compared to placebo, in people with knee osteoarthritis.
Methods: We present results from a randomised placebo-controlled trial evaluating 304 participants with chronic knee pain and medial tibiofemoral joint space narrowing, recruited from the general community in New South Wales, Australia and received knee magnetic resonance imaging (MRI) scans from the Longitudinal Evaluation of Glucosamine Sulfate (LEGS) trial. Participants were randomly allocated to receive one of four daily supplements (a) chondroitin, b) glucosamine, c) combined glucosamine and chondroitin, and d) placebo), and were blinded to treatment. Assessments were conducted at baseline, one and two years. Primary outcomes were evaluated using the MRI Osteoarthritis Knee Score (MOAKS) for the size of bone marrow lesions (BMLs), full thickness cartilage loss and osteophytes of the patellofemoral joint. MOAKS subscales were dichotomized into those that structurally improved/remained the same and worsened. One grade difference in MOAKS in either direction indicated structural change. A 3x4 χ^2 test was used to assess difference between treatment groups at follow-up. A p-value of 0.05 indicated differences between treatment groups.
Results: Due to poor response rates at two years, results for one year follow up assessments were reported (69%). For all MRI-based patellofemoral joint features, there were no differences in structural changes over time between treatment groups.
Conclusions: Glucosamine and chondroitin sulfate supplements, used separately and in combination had no significant effect on BMLs, full thickness cartilage loss and osteophytes in the patellofemoral joint over a year compared to placebo.

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HIGH MOLECULAR WEIGHT INTRAARTICULAR HYALURONIC ACID FOR THE TREATMENT OF KNEE OSTEOARTHRITIS: NETWORK META-ANALYSIS

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Purpose: In 2013, the American Academy of Orthopaedic Surgeons (AAOS) clinical practice guideline (CPG) on the treatment of knee osteoarthritis (OA) made a strong recommendation not in favor of the use of intraarticular hyaluronic acid (IAHA) because the improvement in pain, although statistically significant, did not meet the threshold for a minimal clinically important difference. The AAOS CPG, and publications since, suggest there may be clinically important differences in the effectiveness of high versus low molecular weight (MW) IAHA.