**73 RECOMBINANT HUMAN FIBROBLAST GROWTH FACTOR 18 AS THERAPY FOR OSTEOARTHRITIS: A DOG MENISCECTOMY MODEL STUDY**


**Purpose:** To determine the effects of intra-articular administration of recombinant human fibroblast growth factor 18 (rHGF18, AS92330) in a pilot study of a dog meniscectomy model for established OA.

**Methods:** A unilateral partial medial meniscectomy was performed on the left knee of female beagle dogs 1 month prior to intra-articular administration of 3, 10 or 30 μg/joint of AS92330 or saline (control) as a single dose, or as a once-weekly dose. Long-term treatment effects were observed in a dose-dependent manner at the lower tiw dose (3 μg divided between 3 doses) for 3 weeks. At treatment end (day 22), the dogs were anaesthetized before euthanasia. Left knee joints were collected for gross, microscopic and histopathological evaluation. A scoring system was used for histopathology of the cartilage and for gross pathology; reading was conducted in a blinded manner. Blood serum was collected prior to dosing, on days 7, 14, 18 and 21 and at time of dosing. Microscopic evaluation revealed definite anabolic effects, including increased cloning, cellularity and proteoglycan staining in lesion areas in dogs treated with 30 μg AS92330; these changes were more evident than higher doses. Convincing anabolic effects were observed in a dose-dependent manner at the lowest tiw and once-weekly doses. AS92330-induced effects were found in the upper third to half of the cartilage or matrix adjacent to deeper clefs. Dogs from all treatment groups showed a reduction in histopathological tibial cartilage degeneration; the greatest decrease was in dogs treated once weekly with 30 μg AS92330. Synovitis was minimal or mild with no difference between groups, and subchondral bone sclerosis was highly variable. No treatment-related changes in clinical chemistry parameters or haematology were noted. Additionally, no systemic effects were seen at any dose, as assessed using cartilage thickness in the ear, sternum and tibia. Systemic exposure after intra-articular administration of AS92330 was below the lower limit of quantification (50 pg/mL).

**Conclusions:** Intra-articular treatment with the anabolic agent AS92330 30 μg/joint resulted in definite anabolic effects in all treated knees, with no apparent systemic effects. AS92330 demonstrated efficacy in the improvement of gross pathology and histopathology scoring in a dose-dependent manner in this pilot study involving a dog meniscectomy model, supporting earlier findings in rats.

**74 PHARMACOKINETIC ANALYSIS OF RECOMBINANT LUBRICIN FOLLOWING INTRA-ARTICULAR SUPPLEMENTATION IN RAT KNEE JOINTS**


**Purpose:** We have developed a novel recombinant lubricin construct, LUB-1, which is chondroprotective and prevents cartilage degeneration in a rat meniscal tear model of osteoarthritis (OA). LUB-1 contains a truncated mucin-like domain, and maintains essential properties of cartilage binding and lubrication, and prevention of cell adhesion. The goal of this study was to determine the residence time and tissue localization of radioiodinated LUB-1 following intra-articular administration in the knee joints of rats.

**Methods:** Male Lewis rats were dosed with a single bilateral intra-articular injection of 125I-labeled LUB-1 (1 μCi; 20 μg/knee) and the knee joints were collected at different time points (0.2 hours-672 hours). The retention of 125I-labeled LUB-1 and tissue localization in the knee were assessed by trauma conditioning of whole knees and dissected joint tissues (cartilage, synovium, meniscus) and autoradiography.

**Results:** A fast decline in 125I-LUB-1 concentrations in the whole knee occurred during the first 24 hours (initial phase), indicating rapid clearance from the synovial fluid (i.e. via lymphatic transport) as has been described for other macromolecules such as hyaluronan and albumin. This was followed by a slow decline in 125I-LUB-1 levels, up to 672 hours. The average elimination half-life of intra-articularly injected LUB-1, determined from a one-compartmental fit, was 152 hours. 125I-LUB-1 remained detectable in the knee joint (particularly on the articular cartilage and synovium) even at 672 hours (28 days) after a single injection. 125I-LUB-1 localized onto the surfaces of articular cartilage (tibial plateau, femoral condyle and meniscus), synovium and cruciate ligament as determined by autoradiography.

**Conclusions:** These data indicate that intra-articularly delivered LUB-1 localizes to the surfaces of joint tissues, including articular cartilage, suggesting that at least part of its mechanism of action for slowing OA progression may be by providing a protective coating at cartilage surfaces. The extended residence time of LUB-1 in the joint supports strategies for potential application of recombinant lubricin molecules as therapeutics in the clinic.