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PHARMACOLOGICAL CHARACTERIZATION OF THE ADAMTS-5 INHIBITOR GLPG1972: AN ORAL ANTI-CATABOLIC AGENT FOR THE TREATMENT OF OSTEOARTHRITIS

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Background: Degradation of articular cartilage and alterations of the underlying subchondral bone are hallmarks of osteoarthritis (OA)[1]. A disintegrin and metalloproteinase with thrombospondin motifs-5 (ADAMTS-5) is a key aggrecan-cleaving enzyme involved in this pathogenic process from the earliest stages of cartilage degradation[2] and as such, is an attractive drug target for the development of a disease-modifying OA drug (DMOAD)[3].

Objectives: In this report we describe the *in vitro* and *in vivo* characterization of the small molecule GLPG1972, an inhibitor of ADAMTS-5. GLPG1972 anti-catabolic activity was evaluated in murine and human cartilage explants and DMOAD activity was investigated in the destabilization of the medial meniscus (DMM) mouse model[4].

Methods: The ADAMTS-5 biochemical assay is based on the cleavage of a fluorescent substrate by recombinant ADAMTS-5. Mouse femoral head cartilage explants were stimulated by interleukin-1a (IL-1a) for 3 days and GAG release quantified[2b]. Human articular cartilage explants were stimulated with IL-1β for 12 or 19 days and the NITEGE epitope quantified using the AGNx1 assay. Unilateral OA was induced in C57BL6 mice by DMM[4]. Mice were treated with vehicle or GLPG1972 at 30, 60 or 120 mg/kg, b.i.d. for 8 weeks. Medial femorotibial joint sections were scored by an evaluator blinded to treatment.

Results: GLPG1972 showed potent inhibition of human ADAMTS-5 (IC_{50}=20 nM). Inhibition of ADAMTS-4 was moderate (IC_{50} = 157 nM), and selectivity over 100-fold was observed against a large panel of zinc metalloproteinases. GLPG1972 displayed potent anti-catabolic activity in cartilage explants, with IC_{50} values being 2 μM and < 1 μM in mouse and human, respectively. In the DMM mouse model, GLPG1972 demonstrated DMOAD activity, as shown by significant reduction of femorotibial cartilage proteoglycan loss and cartilage damage score, as well as significant impact on subchondral bone sclerosis.

Conclusions: GLPG1972 is an orally bioavailable, potent and selective ADAMTS-5 inhibitor showing significant anti-catabolic activity in cartilage explants. In the DMM model, treatment with GLPG1972 resulted in significant

protective effects on both cartilage and subchondral bone pathology. Taken together these results provide support to progress GLPG1972 into the clinic as an oral treatment for OA.

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