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## **Loxecivint (SM04690), a Potential Disease-Modifying Treatment for Knee Osteoarthritis, Demonstrated Cartilage-Protective Effects on Human Osteoarthritic Explants**

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**Background:** Wnt pathway upregulation contributes to cartilage thinning in knee osteoarthritis (OA). Lorcivint (LOR; SM04690), a novel, small-molecule CLK/DYRK1A inhibitor that modulates the Wnt pathway, demonstrated disease-modifying potential for knee OA in preclinical studies.<sup>1</sup> This study evaluated the cartilage-protective effects of LOR on human OA explants from total knee replacement (TKR) donors.

**Methods:** Knee joint tissue from 22 TKR donors was collected after IRB approval was obtained from Scripps Health. Cartilage was scored using the Outerbridge classification system based on gross appearance (grade 1=least-damaged tissue, grade 4=most-damaged tissue). Cartilage explants (4 mm in diameter) with Outerbridge grades 2–3 were harvested and cultured for 48 hours to reach metabolic stability. They were then treated with LOR (10 nM, 30 nM) or DMSO and stimulated with either IL-1 $\beta$  (10 ng/ml) or TNF- $\alpha$  (20 ng/ml)+oncostatin M (OM) (10 ng/ml) or left unstimulated. After 72 hours, supernatants and explants were collected. Gene expression of matrix metalloproteinases (MMPs) 1, 3, and 13 was measured by qPCR and protein levels of MMP-1, MMP-3, MMP-13, and thrombospondin-motif-containing disintegrins/metalloproteinases ADAMTS-4 and ADAMTS-5 were measured in supernatants by ELISA. Glycosaminoglycan (GAG) and nitric oxide (NO) levels were measured in supernatants using the dimethylmethylene blue assay and Griess assay, respectively. One-way ANOVA was used for multiple group comparisons.

**Results:** Treatment with IL-1 $\beta$  or TNF- $\alpha$ +OM led to statistically significant increases in gene expression of *MMP1*, *MMP3*, and *MMP13* and increased secretion of GAG, MMP-1, MMP-3, MMP-13, ADAMTS-4, ADAMTS-5, and NO in supernatants compared with unstimulated control. Treatment with LOR decreased both IL-1 $\beta$ -stimulated and TNF- $\alpha$ +OM-stimulated gene expression of all MMPs and secretion of GAG, MMP-1, MMP-3, MMP-13, ADAMTS-4, ADAMTS-5, and NO in supernatants versus treatment with DMSO.

**Conclusion:** LOR demonstrated potent inhibition of cartilage catabolism enzyme production in human OA explants compared with controls. These cartilage-protective effects support the development of LOR as a potential disease-modifying treatment for knee OA. Human trials are ongoing.

**References:** 1. Deshmukh V, et al. *Osteoarthr Cartil.* 2019.