Development of a Disease-Modifying OA Drug (DMOAD) in Knee Osteoarthritis: The Example of Sprifermin

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1. Introduction: OA and unmet clinical need for a DMOAD
2. Past DMOAD drug development
3. Sprifermin, its MOA, and clinical development program
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It is estimated that osteoarthritis (OA) affects 150 million people around the world. While OA is the most common cause of physical disability in older adults, the average age at diagnosis is around 55 years. Currently available drugs to treat OA primarily provide symptom relief. Accordingly, there is a strong unmet need for a Disease-Modifying OA Drug (DMOAD), i.e., a drug that will alter OA disease progression by improving joint structure and ameliorating symptoms, either by reducing pain or improving physical function.

In the past, a number of potential DMOADS were investigated – including three compounds recently investigated in large Phase III clinical development programs, i.e. cindinustat, strontium ranelate, and oral salmon calcitonin (Hellio Le Graverand 2012, Register 2012, and Karsdal 2014). Some of these trials measured structure on MRI in subsets of subjects, but none of these obtained MRI results in all subjects. Some drugs showed trends toward improvement on X-ray, but efficacy effects were not statistically significant (Hellio Le Graverand 2012, Brandt 2005). Although there have been many clinical development programs of drugs to treat OA, no DMOAD has yet been approved by European Union regulatory bodies or FDA.

Sprifermin, a truncated form of fibroblast growth factor 18 (rhFGF18), is currently being investigated as a potential DMOAD. Sprifermin induces cartilage formation by increasing chondrocyte proliferation, resulting in increased overall extracellular matrix production by chondrocytes.

Two clinical trials of intra-articularly (i.a.) injected sprifermin vs. placebo have been completed: (1) a Phase 1 First-in-Human (FiH) trial (clinicaltrials.gov NCT00911469) and (2) a Phase 1b trial (NCT01033994). Both trials found no major safety or injection-site issues on sprifermin. A Phase II dose-ranging DBPC trial of sprifermin is currently ongoing (NCT01919164). It will assess structure in all patients both by MRI and X-ray, evaluate symptoms via WOMAC and other patient-reported outcome measures, while also exploring the potential for future biomarker prediction of subjects who are clinical responders to treatment.

Summary and next steps: DMOAD development is challenging. Additional clinical trials are needed to replicate the positive results from early sprifermin trials and to confirm optimal dosing. A Phase II dose-ranging DBPC trial of sprifermin is currently ongoing (NCT01919164). It will assess structure in all patients both by MRI and X-ray, evaluate symptoms via WOMAC and other patient-reported outcome measures, while also exploring the potential for future biomarker prediction of subjects who are clinical responders to treatment.

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