

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
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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. cindunistat, strontium ranelate, and oral salmon calcitonin (Hellio Le Graverand 2012, Reginster 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.

The FiH trial is a randomized double-blind placebo-controlled (DBPC) trial that was performed in patients with severe knee OA who were scheduled for total knee replacement (TKR). It evaluated the safety of intra-articular sprifermin (primary); systemic exposure, biomarkers, and explored cartilage histology obtained at the time of TKR.

The Phase 1b trial is a DBPC trial performed in patients with moderate knee OA (Kellgren-Lawrence Grade [KLG] 2–3) who were not scheduled for TKR. It included many endpoints, in-

cluding: cartilage thickness measured by magnetic resonance imaging (MRI) (primary), joint space width by X-ray, symptoms on the Western Ontario McMaster (WOMAC) OA index, and biomarkers. In this trial, dose-dependent reductions in structural changes were observed on sprifermin as compared to placebo. The WOMAC pain score improved in all patients.

Lessons learned: One challenge to designing clinical trials of i.a. DMOADs is the known pain-reducing effect of i.a. placebo. A challenge to the development of all DMOADs in general is that the effects of the drug on multiple joint structures are observed on MRI, but not on X-ray. Another challenge to developing DMOADs in general is that OA is a heterogeneous disease. No one DMOAD may be able to treat all sub-types of OA. In the future, ideally biomarkers may aid in the identification of different OA responder sub-types.

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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