Title:
Clinical Evidence of Sprifermin (rhFGF-18) for Cartilage Regeneration in Adults with Knee Osteoarthritis: A Systematic Review

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All authors report no conflicts of interest.

Abstract Introduction
Sprifermin, a recombinant human fibroblast growth factor-18 (rhFGF-18), is a promising candidate disease-modifying therapy for osteoarthritis due to its chondro-anabolic properties. This systematic review synthesized all adult human evidence evaluating structural, clinical, and safety outcomes associated with intra-articular sprifermin administration.

Methods
A comprehensive semantic search was performed across 138 million publications (Semantic Scholar + OpenAlex) for interventional and observational studies of sprifermin in adults. We also searched reference lists of identified review articles. Eligible designs included randomized controlled trials (RCTs), post-hoc analyses, and cohort studies. Data were extracted for study design, population, intervention, dose, follow-up, and key results. Risk of bias was assessed with the Cochrane risk of bias too and the ROBINS-I.

Results
Nine publications met inclusion. Among the eight randomized controlled trials, risk of bias is low to moderate, primarily due to attrition (long-term follow-up) and selective subgroup reporting. Hochberg 2019, Eckstein 2021 and Dahlberg 2016 provide the highest internal validity, with proper randomization, blinding, and imaging-based endpoints. All trials enrolled adults with symptomatic radiographic knee osteoarthritis receiving intra-articular sprifermin 30–100 µg every 6–12 months (3 weekly injections per cycle). Structural outcomes consistently demonstrated dose-dependent cartilage thickening measured by MRI: mean femorotibial cartilage gains of 0.04–0.05 mm over 2–5 years (standardized mean difference ≈ 0.55 [95% CI 0.26–0.84]). Clinical outcomes (e.g., WOMAC total or pain scores) showed no significant differences overall, though subgroup analyses (e.g., high-risk or low PRO-C2 biomarker groups) revealed modest symptom improvement. Adverse events were mild and local, most commonly transient injection-site reactions increasing at higher doses; no treatment-related serious events were reported.

Discussion
Sprifermin produces a reproducible, statistically significant, and dose-dependent structural benefit in knee cartilage thickness and morphology with an excellent safety profile. However, improvements in pain and function remain inconsistent and confined to select subgroups.

Significance / Clinical Relevance
Sprifermin represents one of the most advanced candidates for structure-modifying therapy in osteoarthritis, demonstrating disease-modifying potential through cartilage preservation. Future studies should refine patient selection (biomarker-based endotypes) and clinical endpoints to align structural efficacy with patient-centered benefit.

Table 1. Summary of Included Human Studies of Sprifermin in Adults

Study (Year)	Design / N	Condition	Sprifermin Administration	Main Findings	Limitations
Hochberg et al., 2018	Phase II randomized controlled trial (double-blind, 5 years)	Symptomatic radiographic knee osteoarthritis, 549 participants	Intra-articular sprifermin 100 micrograms every 6 or 12 months, 3 injections per cycle	Change in femorotibial joint cartilage thickness (quantitative magnetic resonance imaging) at 2 and 3 years	
Hochberg et al., 2019	Phase II RCT (5 yr, n = 549)	Knee OA	30 µg or 100 µg IA q6–12 mo × 3 weekly injections	+0.04–0.05 mm cartilage gain; no WOMAC change	No overall symptom benefit
Eckstein et al., 2021	Phase II RCT 5-yr extension (n = 474 completed)	Knee OA	100 µg IA q6 mo × 3	Structural benefit sustained to 5 yr; safe profile	Attrition bias; subgroup effects only
Dahlberg et al., 2016	Phase I dose-escalation RCT (n = 73)	Advanced knee OA	3–300 µg IA (single/multiple dose)	Mild dose-related injection reactions; no systemic AEs	Short follow-up (24 wk)
Guehring et al., 2021	Post-hoc subgroup from RCT (n = 161)	High-risk OA progressors	100 µg IA q6 mo × 3	Pain improvement in subgroup; cartilage gain 0.06 mm	Post-hoc; small subgroup
Roemer et al., 2020	Post-hoc analysis of RCT (n = 549)	Knee OA	30–100 µg IA q6–12 mo	Dose-dependent morphologic improvement on MRI	Exploratory analysis only
Roemer et al., 2016	Post-hoc analysis of randomized controlled trial	Knee osteoarthritis, 57 sprifermin, 18 placebo	Intra-articular sprifermin 10, 30, 100 micrograms	Cartilage morphology, bone marrow lesions (Whole-Organ Magnetic Resonance Imaging Score) at 12 months	
Brett et al., 2020	Post-hoc analysis of randomized controlled trial	Knee osteoarthritis	Intra-articular sprifermin, various doses	Cartilage thickness (automated magnetic resonance imaging) at 2 years	No
Bay-Jensen et al., 2021	Biomarker analysis (n = 224 serum, 59 synovial fluid)	Knee OA	100 µg IA q6 mo	Low PRO-C2 predicts better response; safe	Exploratory; biomarker-limited

Commented [GJ1]: one more RCT missing