Efficacy and Safety of Intra-Articular Sprifermin in Symptomatic Radiographic Knee Osteoarthritis: Pre-Specified Analysis of 3-Year Data From a 5-Year Randomised, Placebo-Controlled, Phase II Study

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Background: Sprifermin, a novel recombinant human fibroblast growth factor 18, is currently being investigated as a potential disease-modifying osteoarthritis (OA) drug. Two-year results of the 5 year phase II FORWARD study showed a statistically significant dose-dependent cartilage thickness increase in the total femorotibial joint (TFJ), and in the medial, lateral and central medial sub-region TFJ compartments by quantitative magnetic resonance imaging (qMRI).

Objectives: Here we report the pre-specified 3 year results.

Methods: Patients (pts) aged 40–85 years with symptomatic radiographic knee OA, Kellgren-Lawrence grade (KLO) 2 or 3, and median mJSW ≥2.5 mm in the target knee were randomised (1:1:1:1:1) to receive 3 weekly i.a. injections with double-blinded placebo (PBO) or sprifermin, administered q6mo (0, 6, 12, and 18 months) or q12mo (0 and 12 months). The primary endpoint was the change in TFJ cartilage thickness from baseline (BL) to Year 2 with pre-specified analyses at Year 3. The intent-to-treat (ITT) population (all randomised pts) was used for non-qMRI endpoints; and the modified ITT population (all ITT pts with BL and ≥1 post-treatment MRI up to Year 2) for qMRI endpoints.

Results: 549 pts were randomised (median age 65 years, 69% women, 80% white, 69% KLO2, and ~70% predominantly medial disease); of which 18.4% (sprifermin) and 24.1% (PBO) discontinued the study within 3 years. TFJ cartilage thickness decreased from Year 2 to 3 in all treatment groups; however, the 0.05 mm difference between sprifermin 100 μg q6mo and PBO was maintained (0.00 vs –0.05 mm; p=0.001; figure 1a). Additionally, significant differences in mean cartilage thickness change from BL to Year 2 were maintained up to Year 3 with sprifermin 100 μg vs PBO in both the medial (100 μg q6mo –0.01 vs –0.06 mm; p=0.025) and lateral TFJ compartments (100 μg q6mo and q12mo: +0.01 and 0.00 vs –0.04 mm; p<0.001 and p=0.003, respectively), and central medial (100 μg q6mo:+0.009 vs –0.084 mm; p=0.008; figure 1b) and central lateral (100 μg q6mo and q12mo:+0.038 and +0.017 vs –0.053 mm; p=0.001 and p=0.003, respectively) TFJ sub-regions. The significant mean change from BL to Year 2 in lateral (but not medial) mJSW by X-ray was maintained up to Year 3 with both sprifermin 100 μg groups vs PBO (100 μg q6 and q12mo:+0.13 and +0.10 vs –0.11 mm; p=0.014 and p=0.040, respectively). By Year 2 total WOMAC scores were improved by ~50% in all treatment groups including PBO, and maintained up to Year 3 (18 months after last injection) without a significant difference between treatment groups. AEs and serious AEs remained balanced between groups at Years 2 and 3.
KNEE JOINT DISTRACTION COMPARED WITH HIGH TIBIAL OSTEOTOMY AND TOTAL KNEE ARTHROPLASTY: TWO-YEAR CLINICAL, STRUCTURAL, AND BIOMARKER OUTCOMES

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Background: Knee joint distraction (KJD) is a new joint-preserving surgery technique that, like high tibial osteotomy (HTO), aims to delay total knee arthroplasty (TKA) especially in younger patients with knee osteoarthritis (OA). One year after treatment, KJD demonstrated similar beneficial outcomes compared to HTO and compared to TKA.

Objectives: To compare radiographic joint space width and clinical outcome over two-years for KJD vs TKA and for KJD vs HTO and to additionally study KJD cartilage repair by evaluation of systemic collagen type II markers.

Methods: End-stage knee OA patients considered for TKA were randomised to KJD (n=20; KJDTKA) or TKA (n=40). Medial compartmental knee OA patients with a varus deviation of <10° considered for opening wedge HTO were randomised to KJD (n=23; KJDHTO) or HTO (n=46). Distraction surgery was performed by use of two external fixators with built in springs, placed lateral and medial of the knee joint. The knee was distracted 5 mm for 6 weeks and weight-bearing was encouraged.

WOMAC questionnaires (100 best) and VAS pain scores (0 best) were assessed at baseline (0), 3, 6, 12, 18 and 24 months. In the KJD groups, serum PIAPP and urinary CTXII levels, as markers for collagen type II synthesis and breakdown, were determined over time. Normalised Z-indexes were calculated (Zindex=ZPIAPP/ZCTXII) to express net collagen type II synthesis. The minimum and mean joint space width (JSW) of the most affected compartment (MAC) were measured with KIDA software on standardised radiographs taken at 0, 12 and 24 months.

Results: Of the 129 included patients, 1, 6, 3, and 5 patients were lost in the KJDTKA, TKA, KJDHTO, and HTO group respectively, for various reasons. One-year structural and clinical outcomes were statistically significantly improved as reported before, and these beneficial effects sustained for at least two years after treatment when compared to baseline (figure 1A-C).

At 24 months, there were no significant differences between the KJDHTO and HTO groups (all p>0.25) and between the KJDTKA and TKA group, except for VAS pain scores in favour of TKA at 24 months (p=0.037; figure 1B).

Compared to baseline, the ratio of synthesis over breakdown of collagen type II biomarkers (figure 1D) was significantly decreased at 3 months (-0.45±0.20; p=0.032) after which this reversed towards an increase over time (at 24 months +0.59±0.19; p=0.004).

Conclusions: Sustained improvement of clinical benefit and increase in JSW after KJD is demonstrated for over 2 years of follow-up in case of treatment of patients with medial compartmental knee OA indicated for HTO or patients with end-stage knee OA indicated for TKA. The structural cartilage repair observed on radiographs is supported by a beneficial change in systemic biomarkers for collagen type II. For the HTO-induced population, results of KJD patients were similar to those of HTO. For the TKA-induced patients, TKA appeared to result in a slightly better clinical outcome, however at the expense of the native knee joint.

REFERENCES: