Intraarticular Sprifermin (Recombinant Human Fibroblast Growth Factor 18) in Knee Osteoarthritis

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Objective. To evaluate the efficacy and safety of intraarticular sprifermin (recombinant human fibroblast growth factor 18) in the treatment of symptomatic knee osteoarthritis (OA).

Methods. The study was a randomized, double-blind, placebo-controlled, proof-of-concept trial. Intraarticular sprifermin was evaluated at doses of 10 μg, 30 μg, and 100 μg. The primary efficacy end point was change in central medial femorotibial compartment cartilage thickness at 6 months and 12 months as determined using quantitative magnetic resonance imaging (qMRI). The primary safety end points were nature, incidence, and severity of local and systemic treatment-emergent adverse events (AEs) and acute inflammatory reactions, as well as results of laboratory assessments. Secondary end points included changes in total and compartment femorotibial cartilage thickness and volume as assessed by qMRI, changes in joint space width (JSW) seen on radiographs, and pain scores on the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC).

Results. One hundred ninety-two patients were randomized and evaluated for safety, 180 completed the trial, and 168 were evaluated for the primary efficacy end point. We found no statistically significant dose response in change in central medial femorotibial compartment cartilage thickness. Sprifermin was associated with statistically significant, dose-dependent reductions in loss of total and lateral femorotibial cartilage thickness and volume and in JSW narrowing in the lateral femorotibial compartment. All groups had improved WOMAC pain scores, with statistically significantly less improvement at 12 months in patients receiving the 100-μg dose of sprifermin as compared with those receiving placebo. There was no significant difference in serious AEs, treatment-emergent AEs, or acute inflammatory reactions between sprifermin and placebo groups.

Conclusion. No statistically significant relation-
ship between treatment group and reduction in central medial femorotibial compartment cartilage thickness was observed; however, prespecified structural secondary end points showed statistically significant dose-dependent reductions after sprifermin treatment. Sprifermin was not associated with any local or systemic safety concerns.

Osteoarthritis (OA) causes a huge burden of disability-adjusted life years and years lived with disability (1). The disease is estimated to affect >150 million people worldwide, and it accounts for more physical disability among the elderly than any other medical condition (2). Commonly perceived as a disease only of the elderly, the estimated mean age at diagnosis of OA is actually 55 years (3). Current nonsurgical treatments target symptoms and function, with low-to-moderate efficacy (4,5). The potential of a combined beneficial effect on joint structure and symptoms in OA as a result of treatment with diacerein, glucosamine, doxycycline, risedronate, chondroitin sulfate, strontium ranelate, or cindunikast has been investigated (6–13). However, no pharmacologic treatment or other treatment has been shown to have unequivocally beneficial effects on the structural characteristics of joint damage in OA that translate into clinical benefit (14). Accordingly, no structure-modifying treatment has yet been approved by regulatory agencies in the US or European Union.

Many studies have focused on use of antacatabolic agents to delay progression of cartilage breakdown (14). An alternative approach is to stimulate cartilage development and repair. Sprifermin (recombinant human fibroblast growth factor 18; rhFGF18) binds to and specifically activates fibroblast growth factor receptor 3 (FGFR-3) in cartilage to promote chondrogenesis and cartilage matrix production in vitro (15). Preclinical data have shown that sprifermin stimulates chondrocyte proliferation, cartilage matrix formation, and cartilage repair in vitro and in vivo (15–18). These results suggest that sprifermin may also have beneficial effects on joint structure in human OA joints. In a study of patients with knee OA who were scheduled for total joint replacement, no concerns regarding short-term safety at the local or systemic level were noted among those who received intraarticular injections of sprifermin in single and multiple doses (19).

The primary objectives of the present proof-of-concept study were to evaluate the effects of sprifermin on femorotibial cartilage thickness using magnetic resonance imaging (MRI) in patients with symptomatic knee OA and to assess the local and systemic safety of sprifermin. We tested the hypothesis that sprifermin could reduce the loss of joint cartilage that characterizes the natural course of OA (20).

PATIENTS AND METHODS

Trial conduct. The study was conducted at 30 sites in Europe, South Africa, and North America in accordance with study protocol (see Supplementary Document 1, available on the Arthritis & Rheumatology web site at http://onlinelibrary.wiley.com/doi/10.1002/art.38614/abstract), the International Conference on Harmonisation Guidelines for Good Clinical Practice, applicable local regulations, and the Declaration of Helsinki. The relevant institutional review boards or independent ethics committees and health authorities approved the trial protocol and all amendments according to country-specific laws. The study investigators are listed in Appendix A.

Patient enrollment. Patients age ≥40 years were included if they had an established (≥6 months) diagnosis of primary femorotibial knee OA according to American College of Rheumatology clinical and radiologic criteria (21), with radiographic stage 2 or stage 3 disease in the target knee as determined by Kellgren/Lawrence (K/L) scale scores from weight-bearing fixed flexion radiographs (22). No attempt was made to select patients on the basis of primarily medial or lateral femorotibial involvement. Other inclusion criteria were symptomatic treatment of OA with systemic nonsteroidal antiinflammatory drugs or other analgesics, total Western Ontario and McMaster Universities OA Index (WOMAC) (23) scores of 24–72 (mild to severe, but not extreme, symptoms on a scale of 0–96), and no planned knee surgery for ≥12 months after the first injection of study medication. Exclusion criteria were treatment with intraarticular steroids or a hyaluronic acid derivative within 3 months of baseline and treatment with glucosamine, diacerein, or chondroitin sulfate, unless a stable dose had been taken for ≥4 weeks. Written informed consent was obtained prior to study enrollment.

Study design. In this multicenter, randomized, double-blind, placebo-controlled trial, sprifermin was evaluated as a single treatment and as a multiple-dose regimen (3 doses of either 10 μg, 30 μg, or 100 μg) in 6 cohorts (Figure 1). Safety was reviewed at each new single-dose level before progression to the next level: a safety review board reviewed data that included ≥2 weeks of follow-up after the last injection in all cohorts.

Patients were screened for eligibility within 28 days before receiving the first dose of medication. At week 0, eligible patients were randomized 3:1 within each cohort to receive sprifermin or placebo (Figure 1). After completion of each single-dose cohort assessment, the respective multiple-dose regimen was applied. The intraarticular injections were administered under aseptic conditions, using the lateral patellar route, following each study center’s normal procedures and in accordance with the drug preparation and injection manual. Study investigators (or a qualified designee) administered study medication, witnessed by a qualified second person. No pain medication washout period was required; patients were allowed to continue their pain medication as needed during the course of the trial.
Randomization and blinding. Patients were enrolled into specific cohorts depending on the timing of enrollment, the trial site, and the cohorts already treated. Within each cohort, an interactive voice response system randomized patients sequentially according to a central randomization list, with a block size of 4. Blinded conditions were maintained by provision of visually identical containers of sprifermin and placebo. Unblinding could be performed by authorized staff using the interactive voice response system, if deemed essential to the patient’s health.

Primary end points and assessments. The primary efficacy end point was the longitudinal change from baseline in central medial femorotibial compartment cartilage thickness at 6 months and 12 months, as assessed using quantitative MRI (qMRI). This end point was chosen since it has been shown to be the most sensitive to change (highest ratio of the mean change divided by the SD of change across participants) (24–26). Supplementary Table 1 (available on the Arthritis & Rheumatology web site at http://onlinelibrary.wiley.com/doi/10.1002/art.38614/abstract) provides a list of primary and secondary efficacy and safety end points.

The primary safety end points were local and systemic treatment-emergent adverse events (AEs), acute inflammatory reactions, laboratory findings (blood chemistry, hematology, urinalysis), vital signs, and electrocardiographic results (Supplementary Table 1). Treatment-emergent AEs were defined as any AEs with start dates on or after the date of the first injection of study medication and up to 30 days after the last injection, or AEs classified as possibly or probably related to study medication, with start dates on or after the date of the first injection of study medication and up to 30 days after the trial termination visit. Acute inflammatory reactions were defined as an increase in pain by 30 mm on a 100-mm visual analog scale (VAS), associated with self-reported synovial fluid effusion within 3 days of injection of study medication.

Secondary end points and assessments. Secondary imaging end points included total and compartment (both medial and lateral) femorotibial cartilage thickness and volume as assessed by qMRI at 3, 6, and 12 months after the first injection, quantitative measurement of joint space width (JSW) by fixed-flexion weight-bearing radiography at 12 months (27), and assessment of bone marrow lesions, cartilage, menisci, effusion, and synovitis by semiquantitative MRI using the modified Whole-Organ Magnetic Resonance Imaging Score (WORMS) at 3, 6, and 12 months (28,29). Secondary safety end points included pharmacokinetic measures, serum biomarkers of cartilage and bone metabolism, and formation of antibodies to sprifermin/rhFGF18 (see Supplementary Table 1, available on the Arthritis & Rheumatology web site at http://onlinelibrary.wiley.com/doi/10.1002/art.38614/abstract).

Symptom efficacy, a secondary end point, was evaluated as change at 3, 6, and 12 months from baseline in the WOMAC LK3.1 total score, the WOMAC LK3.1 function and pain subscales (23), and a 0–100-mm VAS for target knee pain. Efficacy end points (including cartilage thickness, volume, JSW, and others) and WOMAC scores, were assessed in multiple-dose cohorts only, since single-dose cohorts provided insufficient statistical power. Safety data were assessed in single- and multiple-dose cohorts, and pharmacokinetic data were assessed in single-dose cohorts.

MRI acquisition and measurement. MRIs were acquired using 1.5T or 3T magnets and validated double-oblique coronal spoiled gradient-recalled sequences with fat suppression (30) or water excitation (31), a reliable method for longitudinal cartilage quantification in multicenter studies (32). An identical scanner and knee coil were used for baseline and followup measurements of each participant. Acquisition parameters were as follows: contiguous slice thickness 1.5 mm, in-plane resolutions 0.23 × 0.23 mm to 0.32 × 0.32 mm, repetition time 18–50 msec, echo time 6.5–14 msec, flip angle...
The area of subchondral bone, and the cartilage surface area of the medial and lateral tibia, and medial and lateral weight-bearing central femoral condyles were segmented manually, excluding osteophytes and osteophyte cartilage. Quantitative measures of cartilage, including mean cartilage thickness, were derived using Chondrometrics software. Mean cartilage thickness over the total area of subchondral bone, cartilage surface area, and cartilage volume were computed for the medial femorotibial compartment by adding values of the medial tibia and those of the weight-bearing femoral condyle, and for the lateral femorotibial compartment by adding values of the lateral tibia and those of the lateral weight-bearing femoral condyle. Cartilage surface area and cartilage volume in the total femorotibial joint were computed as medial femorotibial compartment plus lateral femorotibial compartment, while mean cartilage thickness over the total area of subchondral bone in the total femorotibial joint was computed as total femorotibial joint minus cartilage volume divided by total femorotibial joint minus cartilage surface area. Mean cartilage thickness over the total area of subchondral bone was also determined in 5 tibial and 3 femoral subregions, and in combined central tibial and central femoral subregions (central medial femorotibial compartment and central lateral femorotibial compartment) (34).

Test–retest precision and sensitivity to change for these measures using the same technology have been reported (24,32,34,35). The test–retest precision error using a 1.5T scanner was 3.0% and 2.6% for femorotibial cartilage volume and thickness, respectively, and was 2.6% and 2.5% using a 3T scanner in the same subjects (1.5-mm slice thickness). Errors for central subregions were similar (34). Sensitivity to change, expressed as the standardized response mean (mean change divided by the SD of the change) ranged from 0.35 to 0.50 in the medial femorotibial cartilage plates and (central) sub-regions using a 1.5T scanner, and was similar using a 3T scanner (35). Segmentation of femorotibial cartilage was performed at one expert center (Chondrometrics) by 7 operators with formal training and >5 years of experience in cartilage segmentation; each of the operators was blinded with regard to the time sequence of the acquisitions and to the clinical characteristics and treatment of the study participants. Segmentation by the readers of baseline and all followup images, and quality control readings of the segmentations by 1 expert, were performed after the last measure for a given patient was acquired.

Axial, coronal, and sagittal intermediate-weighted turbo or fast spin–echo fat-suppressed sequences were used for semiquantitative scoring of synovial tissue pathology (28,29), with identical parameters at baseline and followup. Acquisition parameters were as follows: slice thickness 3.0 mm, in-plane resolution 0.55 × 0.55 mm, repetition time 3,600–4,000 msec, and echo time 30–40 msec.


Radiographic assessment. Fixed-flexion radiographs of the weight-bearing target knee were acquired at baseline and at 12 months, using a standard positioning device (27). Baseline scoring of medial and lateral osteophytes and grading of joint space narrowing were performed by a single musculoskeletal radiologist (AG) who was blinded with regard to clinical characteristics and treatment and who had 13 years of experience in OA imaging research using the Osteoarthritis Research Society International atlas (36). Intrareader reliability was 0.91. Minimum medial JSW was determined using semiautomated software (KneeTool; Optasia), under blinded conditions with regard to clinical characteristics, acquisition order, and treatment.

Statistical analysis. Statistical analyses were performed using SAS software (version 9.1, SAS Institute). Statistical methodology and assumptions were applied to calculate sample size based on central medical femorotibial compartment data from a subsample of the Osteoarthritis Initiative cohort (37). Because these data were skewed toward negative values, the effects of study medication on MRI data (not normally distributed) and WOMAC end point data (normally distributed) were analyzed with nonparametric statistical tests. Repeated-measures analysis of variance was used on absolute change values from baseline, transformed as ranked data, to investigate a possible dose-response relationship using a linear trend test, followed by pairwise comparisons using an adjusted Dunnett’s test. This methodology allowed both an overall analysis of the 12-month trial period and time point–specific analyses. The SAS Mixed procedure was used, including a Repeated statement on the time, taking into account baseline value, treatment group, and time as factors, and treatment time, age, body mass index, sex, and radiographic severity as interaction. P values less than 0.05 were considered significant. Demographic and baseline characteristics, as well as safety end points, were described using summary statistics.

This analysis was performed by the Global Biostatistics Department of Merck Serono. Before locking the database, the following actions were performed under conditions blinded for the type of intervention: the database was cleaned, all queries were resolved, a review meeting regarding blinded data was conducted, protocol deviations were identified and the per-protocol population was defined, the statistical analysis plan was developed, and signed approval was obtained. Following the final database lock, investigators were unblinded with regard to treatments, and the statistical analysis was performed.

Sample size calculations were based on the assumption that there would be a 0.1-mm decrease in central medial femorotibial compartment cartilage thickness per annum (~3%) in untreated patients, and that sprifermin would cause a 75% reduction in loss to ~0.025 mm/year. A sample size of 144 patients in the multiple-dose cohorts provided 75–82% power to detect a significant linear trend, and 71–79% power to detect a significant pairwise difference. Assuming that the 1-year study duration would result in a dropout of ~15% of patients in the multiple-dose cohorts, the number of patients was set at 168. All single-dose cohorts were to include 8 patients, to allow for detection of a true incidence of acute inflammatory reaction events of 5%.

The main efficacy analyses were conducted in the
modified intent-to-treat population, which comprised all randomized patients in the multiple-dose cohorts who received ≥1 dose of study medication and had ≥1 post-baseline efficacy measurement available. Imputation of missing data was not performed because we wanted to provide an exact measure of the response observed. No adjustment for multiplicity was made when analyzing secondary end points. Qualitative safety analyses were performed in the safety population (comprising

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<th>Table 1. Baseline characteristics of patients with OA in the sprifermin single-dose and multiple-dose cohorts (safety population)*</th>
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<td><strong>Characteristic</strong></td>
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<td>Age, mean ± SD years</td>
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<td>K/L grade 3, no. (%)</td>
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<td>cMFTC cartilage thickness, mean ± SD mm</td>
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<td>Total femorotibial cartilage thickness, mean ± SD mm</td>
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<td>Bilateral knee OA, no. (%)</td>
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*OA = osteoarthritis; BMI = body mass index; K/L = Kellgren/Lawrence; cMFTC = central medial femorotibial compartment; JSW = joint space width; LFTC = lateral femorotibial compartment; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

Figure 2. Disposition of patients in the multiple-dose (MAD) cohorts. AE = adverse event; FU = followup.
all patients who received ≥1 dose of study medication and had ≥1 post-dose safety assessment available). A post hoc analysis using formal statistical testing for all treatment-emergent AEs, serious AEs (SAEs), and acute inflammatory reactions was performed using Fisher’s exact test to compare all doses of sprifermin combined versus placebo. To further evaluate the dose-response relationship as it pertains to acute inflammatory reactions, the Cochran-Armitage exact trend test was used to assess whether increasing occurrence of acute inflammatory reactions was associated with increasing doses of sprifermin.

RESULTS

Patient disposition and baseline demographics. The study was conducted between October 2008 and December 2010: 477 patients were screened and 192 were randomized to 1 of 2 groups (24 to the single-dose cohorts and 168 to the multiple-dose cohorts) (Table 1 and Figure 2). All patients in the single-dose cohorts received treatment with the study drug and completed the trial. All patients in the multiple-dose cohorts received ≥1 dose of study medication, with 168 forming the modified intent-to-treat population; 156 (92.9%) completed the trial. Four patients were withdrawn because of AEs (as well as other reasons), and 3 patients were lost to followup. One patient who received the 100-μg dose of sprifermin was withdrawn from the study due to a protocol violation after undergoing diagnostic arthroscopy of the target knee. A further 4 patients withdrew for other reasons (e.g., relocation). A baseline K/L grade of 3 in the target knee was reported in 87 of 168 patients (51.8%) in the multiple-dose cohorts.

Primary efficacy end point. At 6 months, the mean change from baseline in cartilage thickness of the central medial femorotibial compartment was −0.06 mm (95% confidence interval [95% CI] −0.14, 0.02) for the placebo group, 0.03 mm (95% CI −0.18, 0.24) for the 10-μg sprifermin group, −0.09 mm (95% CI −0.16, −0.03) for the 30-μg sprifermin group, and −0.01 mm (95% CI −0.06, 0.03) for the 100-μg sprifermin group (Figure 3). At 12 months, the mean change was −0.11 mm (95% CI −0.20, −0.02) for the placebo group, 0.02

![Figure 3](image-url). Mean change in central medial femorotibial compartment cartilage thickness of the target knee in patients with osteoarthritis who were administered multiple doses of sprifermin (10–100 μg) or placebo (PBO) (modified intent-to-treat population). The change from baseline in cartilage thickness was measured using quantitative magnetic resonance imaging. 95% CI = 95% confidence interval.
mm (95% CI −0.18, 0.23) for the 10-μg sprifermin group, −0.11 mm (95% CI −0.18, −0.03) for the 30-μg sprifermin group, and −0.03 mm (95% CI −0.11, 0.04) for the 100-μg sprifermin group (Figure 3). There was no statistically significant dose response in central medial femorotibial compartment cartilage thickness change (Figure 3) (P = 0.74 at 12 months, P = 0.89 at 6 months, and P = 0.41 at 12 months for overall linear trend).

Secondary efficacy end points. No clear dose-response relationship was observed for mean change in cartilage thickness of the central medial femorotibial compartment from baseline to 3 months (see Supplementary Table 2, available on the Arthritis & Rheumatology web site at http://onlinelibrary.wiley.com/doi/10.1002/art.38614/abstract).

Although we observed no statistically significant effect in the overall analysis (during the 12-month trial period), at the 12-month time point there was a statistically significant dose-dependent reduction in loss of total femorotibial cartilage thickness in patients receiving sprifermin (−0.03 mm [95% CI −0.04, 0.01] for the placebo group, 0.00 mm [95% CI −0.08, 0.08] for the 10-μg group, −0.01 mm [95% CI −0.02, 0.01] for the 30-μg group, and 0.01 mm [95% CI 0.00, 0.03] for the 100-μg group; P = 0.0318), and a statistically significant difference in the same measure between the 100-μg sprifermin group and the placebo group (P = 0.0394) (Figure 4A). At 12 months, no statistically significant effect of sprifermin on cartilage thickness change in the medial femorotibial compartment was observed (Figure 4B). In contrast, there was a statistically significant dose-dependent effect on cartilage thickness change in the lateral femorotibial compartment in the overall analysis (P = 0.0311) and at 12 months (−0.04 mm [95% CI −0.10, 0.02] for the placebo group, −0.02 mm [95% CI −0.19, 0.15] for the 10-μg group, 0.02 mm [95% CI −0.02, 0.05] for the 30-μg group, and 0.04 mm [95% CI 0.01, 0.07] for the 100-μg group; P = 0.0072). There was also a statistically significant difference in lateral femorotibial compartment thickness change between the 100-μg sprifermin group and the placebo group at 12 months (P = 0.0326) (Figure 4C).

Changes in cartilage volume followed a similar pattern as those in cartilage thickness, with similar statistically significant differences in corresponding compartments (see Supplementary Table 2, available on

There was no trend in change in JSW of the medial femorotibial compartment in patients receiving sprifermin; however, in the lateral femorotibial compartment a dose-dependent reduction in JSW narrowing was observed, with a statistically significant difference between the 100-µg sprifermin group and the placebo group at 12 months (−0.18 mm [95% CI −0.42, 0.06] for the placebo group and 0.34 mm [95% CI 0.11, 0.57] for the 100-µg group; P = 0.0118) (Supplementary Table 2).

No meaningful changes in semiquantitative MRI (WORMS) parameters were observed over the course of the study in either the placebo group or the active treatment group (Supplementary Table 2).

There was an improvement from baseline in the WOMAC pain index score in all groups. At 12 months, a lesser improvement in patients receiving sprifermin compared with placebo was noted; this was statistically significant for the 100-µg cohort versus the placebo group (−5.56 [95% CI −6.84, −4.28] for the placebo group and −2.87 [95% CI −4.07, −1.66] for the 100-µg group; P = 0.0013, by adjusted Dunnett’s test). The total WOMAC score and WOMAC function score were consistent with these findings (Supplementary Table 2). No increase from baseline in pain VAS scores was observed in any treatment group at any time point.

**Primary safety end points.** Sprifermin was not associated with any major local or systemic safety concerns. No deaths were reported. Overall, there was no significant difference in the occurrence of SAEs, treatment-emergent AEs, or acute inflammatory reactions between the combined sprifermin group and the placebo group (by post hoc Fisher’s exact test). There was no statistically significant dose-response relationship between increasing occurrences of acute inflammatory reactions and increasing doses (by post hoc Cochran-Armitage exact trend test).

No SAEs were observed in single-dose cohorts; 19 SAEs (3 local and 16 systemic) were reported in 16 patients in the multiple-dose cohorts. All SAEs were considered unrelated or unlikely to be related to the study medication, with the exception of 1 case of bacterial arthritis in the placebo group that was considered possibly related.

Higher percentages of patients receiving sprifermin as compared to placebo experienced ≥1 treatment-emergent AE (Table 2). However, differences were not statistically significant, and the highest percentages were observed in the groups receiving the lowest doses. The most common treatment-emergent AEs were musculoskeletal/connective tissue disorders (arthralgia and joint swelling), infections and infestations (nasopharyngitis), and nervous system disorders (headache). A greater proportion of “mild” treatment-emergent AEs was observed in the sprifermin cohorts. In single-dose cohorts, no AEs led to treatment discontinuation or trial withdrawal. In multiple-dose cohorts, 3 patients discontin-
treated patients was 19.0%, 10.3%, and 18.3% in the 10-
incidence of acute inflammatory reactions in sprifermin-
(diverticulitis) between treatment cycles. One further patient in the
the target knee in 1 and pain during injection of study
medication in the other). One further patient in the
combined placebo group withdrew due to an SAE
(directive) between treatment cycles.

No acute inflammatory reactions were observed
in single-dose cohorts. In multiple-dose cohorts, the
incidence of acute inflammatory reactions in sprifermin-
treated patients was 19.0%, 10.3%, and 18.3% in the 10-
µg, 30-µg, and 100-µg dose cohorts, respectively, versus
7.7% in the placebo cohort. None of these acute inflam-
matory reactions required specific treatment or inter-
ruption of study medication. There was no evidence of a
dose-response relationship (P = 0.1296). In addition, no
statistically significant differences were found when comparing all sprifermin treatment groups combined to
placebo.

Safety laboratory tests, vital signs, and electrocardiograms indicated no local or systemic safety concerns. No detectable levels of antibodies to rhFGF18 were
found in any patient.

Secondary safety end points. Results of assess-
ments for secondary safety end points also did not reveal
any concerns. Serum sprifermin levels in single-dose
cohorts were below the lower limit of quantitation (100
pg/ml) at all time points in all patients. There were no
meaningful changes over time or between treatment
groups in systemic levels of serum markers of cartilage
or bone formation or degradation (Supplementary Ta-
ble 1, available on the Arthritis & Rheumatology web site
abstract) in single- or multiple-dose cohorts (Supple-
mentary Figures 1–7 and Supplementary Document 3).

DISCUSSION
In this 1-year, randomized, double-blind,
placebo-controlled, proof-of-concept study of intraartic-
ular sprifermin treatment in patients with knee OA, we
identified no local or systemic safety concerns associated
with any of the doses tested, and systemic levels of
sprifermin were below detectable levels. We found no
statistically significant relationship between treatment
group and the primary efficacy end point of reduction in
central medial femorotibial compartment cartilage
thickness. In contrast, prespecified secondary structural
efficacy MRI end points, such as loss of total femorotib-
ial and lateral femorotibial cartilage thickness and loss
of radiographically evident lateral JSW, showed statistically
significant dose-dependent reductions.

Our study has several limitations. Patients did not
know whether they received an active drug or placebo,
but, due to the study design, they were aware of the dose
cohort (single or multiple) to which they had been
recruited. Further, the study was not designed or pow-
ered to analyze symptom outcomes, and the study
duration may have been too short to detect the full effect
of treatment on either cartilage structure or symptoms.
The power analysis preceding the study assumed a 75%
treatment effect for the subregion that was selected as
the primary end point (central medial femorotibial
compartment), and more moderate treatment effects
may have been missed, given the limited number of
participants.

We tested a novel, chondrocyte-driven principle of
cartilage growth stimulation. Sprifermin specifically
activates FGFR-3 in cartilage to promote chondrogen-
esis, cartilage matrix formation, and cartilage repair in
vitro and in vivo (15–18); thus, it may also have beneficial
effects in human OA. In a first-in-humans study in
patients scheduled for knee joint replacement, tissue
samples obtained during surgery suggested that intra-
articular sprifermin stimulated chondrocyte prolifera-
tion and had a positive influence on histologic and
biomechanical cartilage properties (19).

The majority of previous clinical trials of treat-
ments aimed at improving symptoms and reducing joint
cartilage loss in OA used standardized acquisition and
assessment of radiographs (14). MRI has the advantage
of providing highly accurate and precise quantitative
data on multiple synovial joint structures (30,31,38,39).
MRI was utilized in 2 recent clinical trials to assess
structure modification (40,41). Interestingly, and similar
to the findings in the present trial, more marked treat-
ment effects were observed on the lateral, as compared
to the medial, compartment cartilage. However, those
trials differed from the current trial in that only partic-
ipants with disease in the medial femorotibial
compartment were included, whereas in the current study no
effort was made to exclude participants with primarily
lateral involvement.

The present clinical trial is the first to use subre-
Gional qMRI end points to evaluate change in cartilage
thickness and to go beyond global measures of plates
and compartments. The primary end point (central
subregions of the medial femorotibial compartment) was
selected because previous results indicated that the
central medial femorotibial compartment shows the
greatest rate of change and sensitivity to change in cartilage thickness (20,24,26,42). In light of the previous trials showing more marked treatment effects on the lateral knee compartment as compared to the medial knee compartment (40,41), it is interesting to note that the primary end point of the present trial was not met, while dose-dependent treatment effects were found for the lateral knee compartment (lateral femorotibial compartment).

The reasons for the seemingly preferential effect on the lateral knee compartment in the present and previous studies are not clear. We may speculate that in OA the status of cartilage differs between the medial and lateral femorotibial compartments, with the medial compartment more commonly severely affected. An anabolic agent acting on cartilage may be less effective in tissue that is severely damaged. Further, in a varus knee with predominantly medial involvement, dynamic loading is greater in the medial compartment as compared to the lateral compartment. It is possible that such pathomechanics overwhelm attempts to slow cartilage loss or the ability to regenerate cartilage tissue (43). This concept is supported by observations of cartilage thinning and JSW increases in knees with end-stage OA that are shielded from load by an external fixator (44). Unfortunately, detailed information on baseline knee alignment or dynamic loading was not available for the present or previous trials. In future trials of disease-modifying therapy for knee OA, investigators may need to consider knee alignment and bone shape (45,46), as well as the choice of compartment and subregion for assessment of tissue changes.

In all treatment groups, including placebo groups, symptoms improved markedly during the first weeks of treatment. At 12 months, but not at other time points, we observed statistically significantly less improvement in WOMAC scores among those in the sprifermin-treatment groups versus those in the placebo groups. However, the difference between placebo groups and sprifermin-treatment groups was less than what is commonly regarded as clinically important (47,48). The interpretation of symptom changes in this trial is further limited because the study was not primarily designed to assess symptom outcomes, and patients were allowed to use pain medication as needed with no washout required.

None of the pharmacologic agents tested to date for OA has convincingly demonstrated the level of disease-modifying activity with concomitant meaningful symptom improvement necessary for approval by regulatory agencies (6–13). Quantitative MRI measures of cartilage thickness loss were shown to contribute to prediction of knee replacement in a 4-year natural history study of OA (26). However, we lack an estimate of the extent of structural modification required to provide patient benefit in the clinical trial setting. Changes in joint structures other than cartilage need to be explored for their value in the same context (14,49). Our understanding of the associations between structural change and symptom change in OA is incomplete; notably, some trials have shown slowing of structural progression without symptom benefit (6,9). Observation times of >12 months in a disease-modifying drug trial are likely needed to clarify any relationship.

In conclusion, the primary end point of this trial, a reduction of cartilage loss in the central medial femorotibial compartment, was not met. However, secondary end points were consistent with a dose-related treatment effect of sprifermin on the cartilage across the total femorotibial joint and in the lateral femorotibial compartment. These results, and the apparent absence of safety issues, suggest that continued clinical and basic studies of this agent in the treatment of OA are warranted.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Lohmander had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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ADDITIONAL DISCLOSURES

Author Dreher is an employee of Totzke & Dreher Scientific. Author Krantz is an employee of Farmovs-Parexel. Author Kruger was an employee of Parexel Early Phase during the time the study was conducted. Author Guermazi is an employee of Boston Imaging Core Lab. Author Eckstein is an employee of Chondrometrics.

REFERENCES


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