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The effects of sprifermin on symptoms and structure in a subgroup at risk of progression in the FORWARD knee osteoarthritis trial

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ABSTRACT

Objective: To assess pain outcomes and cartilage thickness change in a subgroup at risk (SAR) of further progression in the FORWARD trial of knee osteoarthritis patients treated with sprifermin.
Methods: Patients were randomised 1:1:1:1:1 to: sprifermin 100 μg every 6 months (q6mo), 100 μg q12mo, 30 μg q6mo, 30 μg q12mo, or placebo for 18 months. SAR was defined as baseline medial or lateral minimum joint-space width (mJSW) 1.5–3.5 mm and Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain score 40–90 units. Follow-up to 3 years was included in the analysis. Treatment benefit was explored by repeated measures, linear dose-effect trends by timepoint.
Results: The SAR comprised 161 (29%) of 549 patients. Mean difference (95% CI) in WOMAC pain at year 3 for sprifermin 100 μg q6mo vs placebo SAR was -8.75 (-22.42, 4.92) for SAR vs 0.97 (-6.22, 8.16) for the intent-to-treat population. SAR placebo patients lost more cartilage over 2 years than the modified ITT (mITT) placebo arm (mean change from baseline, mm [SD]: -0.05 [0.10] vs -0.02 [0.07]). Net total femorotibial joint thickness gain with sprifermin 100 μg q6mo (adjusted mean difference from placebo [95% CI] was similar in the SAR and in the mITT group: 0.06 [0.01, 0.11] vs 0.05 [0.03, 0.07]).
Conclusions: Selection for low mJSW and moderate-to-high pain at baseline resulted in more rapid disease progression and demonstrated translation of structure modification (with maintained net benefit on total cartilage thickness) into symptomatic benefit. This subgroup may represent a target population for future trials.
Clinical trial registration: : NCT01919164.

Introduction

Osteoarthritis (OA) is a prevalent disease associated with pain, reduced joint function, diminished quality of life, and a substantial healthcare burden [1,2]. OA is characterised by structural alterations, particularly progressive loss of articular cartilage [1]. Current OA drugs alleviate symptoms but do not prevent structural disease progression [2,3]. Most symptom-targeting agents have short-term benefits [4] and substantial safety considerations [5]. There is, therefore, an unmet need for disease-modifying OA drugs (DMOADs) that offer structural improvements and consequent symptomatic benefit in pain or function [6–8].

Sprifermin is a recombinant human fibroblast growth factor 18 investigated as a possible anabolic intra-articular (i.a.) DMOAD. Preclinical studies indicate that the mode of action of sprifermin is to stimulate chondrocytes and hyaline extracellular matrix synthesis [9–12]. The phase II FORWARD trial demonstrated differences in longitudinal cartilage thickness change with sprifermin versus placebo

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in people with symptomatic radiographic knee OA; [13] at Year 2 and 3, significant dose-dependent effects on total femorotibial joint (TFTJ) cartilage thickness (primary endpoint) were demonstrated. Two- and 3-year improvements in Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scores and sub-scale scores were seen in all treatment groups [13].

Recent literature supports selection of patients with moderate–high WOMAC scores and low joint space width to improve detection of a pain response while enriching for structural progression [14–17] Such patients display greater cartilage loss than those without joint space narrowing [18,19] and low pain frequency [20].

Insights from FORWARD suggest a floor effect due to the relatively high proportion of patients with low pain (32% with WOMAC pain sub-scale score <40/100) and relatively high minimum joint space width (mJSW; 50% >3.7 mm) at baseline.

The post-hoc analysis described herein tested the hypothesis that selection of a more homogenous OA patient subgroup from FORWARD (subgroup at risk [SAR]) would show symptomatic benefit over placebo in addition to structural modification. Sensitivity analyses explored whether a mJSW- and pain-defined subgroup would better differentiate from the intention-to-treat (ITT)/modified ITT (mITT) cohort than a definition based on either mJSW or pain alone.

Methods

Study design

FORWARD was a multicentre, randomised, double-blind, placebo-controlled, dose-finding, phase II, 5-year trial (NCT01919164). Details of the methods have been reported [13]. Briefly, patients aged 40–85 with symptomatic radiographic knee OA, Kellgren-Lawrence (KL) grade 2 or 3, and medial mJSW ≥2.5 mm in the target knee were randomised (1:1:1:1:1) to receive three once-weekly i.a. injections of: 30 μg sprifermin every 6 months (q6mo) or q12mo; 100 μg sprifermin q6mo or q12mo; or placebo for 18 months (Fig. 1). The primary endpoint was change in TFTJ cartilage thickness from baseline to 2 years. Total WOMAC and pain subscale scores were secondary endpoints. At the time of this analysis, data from the 2-year treatment period plus 1 year of follow-up (at Year 3) were available.

The ITT population (all randomised patients) was used for WOMAC pain analyses; the mITT population (all ITT patients with one baseline and ≥1 post-treatment qMRI assessment) was used for qMRI efficacy analyses; the safety analysis population included all patients who received ≥1 dose of treatment. All patients gave written informed consent. The study was performed in accordance with the Declaration of Helsinki.

Patient SAR

The baseline variables for selecting a subgroup that may potentially benefit in terms of pain and structure modification were mJSW and WOMAC pain [14–18,21]

Based on published measurements for different mJSW strata [17,22,23], mJSW limits of 1.5–3.5 mm (minimum measured medially or laterally, since FORWARD included patients with both medial and lateral compartment disease) were selected.

WOMAC pain score selection of 40–90 was consistent with established study practice [21]. Sub-question A1, referring to pain on walking, was the only protocol-specified pain score (used at screening only, but not at baseline). The current analysis evaluated consistency of treatment effect across all pain endpoints.

Therefore, the subgroup formalised as a post-hoc analysis of a SAR was defined as mJSW >1.5 to ≤3.5 mm, and WOMAC scores of 40–90.

A 'non-SAR' subgroup from the remainder of the ITT population included patients with mJSW >1.5 mm who did not meet the SAR WOMAC criteria and patients with mJSW >3.5 mm, regardless of WOMAC pain score. Patients with mJSW <1.5 mm, missing mJSW or WOMAC data were excluded.

Outcomes

TFTJ cartilage thickness was assessed by qMRI at baseline, before the first injection of each cycle (6, 12 and 18 months) and at follow-up visits (24 and 36 months), using 1.5 or 3 Tesla clinical MRI scanners [13]. Pain was self-assessed as part of the 24-question WOMAC questionnaire [13].

Key structural secondary endpoints included change from baseline in TFTJ cartilage thickness at Year 3 and versus placebo. Key pain secondary endpoints included change from baseline to Year 3 in WOMAC sub-scores for the SAR, non-SAR subgroup, and ITT population, difference in WOMAC sub-score versus placebo in the SAR, and subgroups of patients with different baseline characteristics, as well as percentage of patients with pain improvement scores ≥10 points from baseline over 3 years. Clinically relevant individual improvements in WOMAC pain have been described as ≥10 points from baseline [24]. Also reported were patient-reported outcomes (PROs) at Year 3 with sprifermin 100 μg q6mo versus placebo in the SAR.

Differentiation of responses were evaluated by mJSW and pain individually and together.

Safety, including adverse events (AEs) and serious AEs (SAEs), was assessed up to 3 years.

Statistical analyses are described in the Supplement.

Results

Patients

The ITT population comprised 549 patients, of whom 161 (29%) were classified as the SAR and 339 (62%) as the non-SAR subgroup (Fig. 1). Forty-nine patients (9%) were not classifiable due to missing data (n = 46) or having mJSW <1.5 mm at baseline (n = 3). The mITT included 494 patients.

SAR baseline characteristics were similar to the ITT population in terms of age, sex, race and body mass index (Table 1). More SAR patients had KL grade 3, a lower median mJSW, and higher median WOMAC pain than the ITT population (table S1).

WOMAC pain sub-score

WOMAC pain changes from baseline in placebo-treated patients of the SAR were consistent with the ITT population (Fig. 2). At Year 3, the placebo WOMAC pain score response from baseline was approximately a 20-point (SAR) and 24-point (ITT population) decrease (Fig. 2).

Compared with the ITT population, a dose-dependent improvement in WOMAC pain in the SAR was observed with sprifermin, which increased to Year 3 (sprifermin 100 μg q6mo versus placebo, p<0.05; Fig. 2). In the non-SAR subgroup, reduction in pain with placebo at Year 3 was numerically greater versus sprifermin 100 μg q6mo (absolute mean difference: 6.45 points [95% CI – 1.76;14.66]; Fig. S1). More than 95% of SAR sprifermin-treated patients (100 μg groups) achieved a clinically relevant observed improvement from baseline of ≥10 in WOMAC pain score at Year 3 (Fig. S2). There was greater differentiation between sprifermin 100 μg q6mo and placebo in WOMAC pain sub-score in the SAR versus either baseline characteristic alone (Fig. 3).

Adjusted mean difference between SAR sprifermin 100 μg q6mo and placebo at Years 2 and 3 were −5.82 (95% CI – 18.87;7.23) and −8.75 (95% CI −22.42;4.92), respectively (Table 2). A sensitivity analysis (unadjusted mean difference in the descriptive results) showed more pronounced differences between sprifermin and placebo. In the

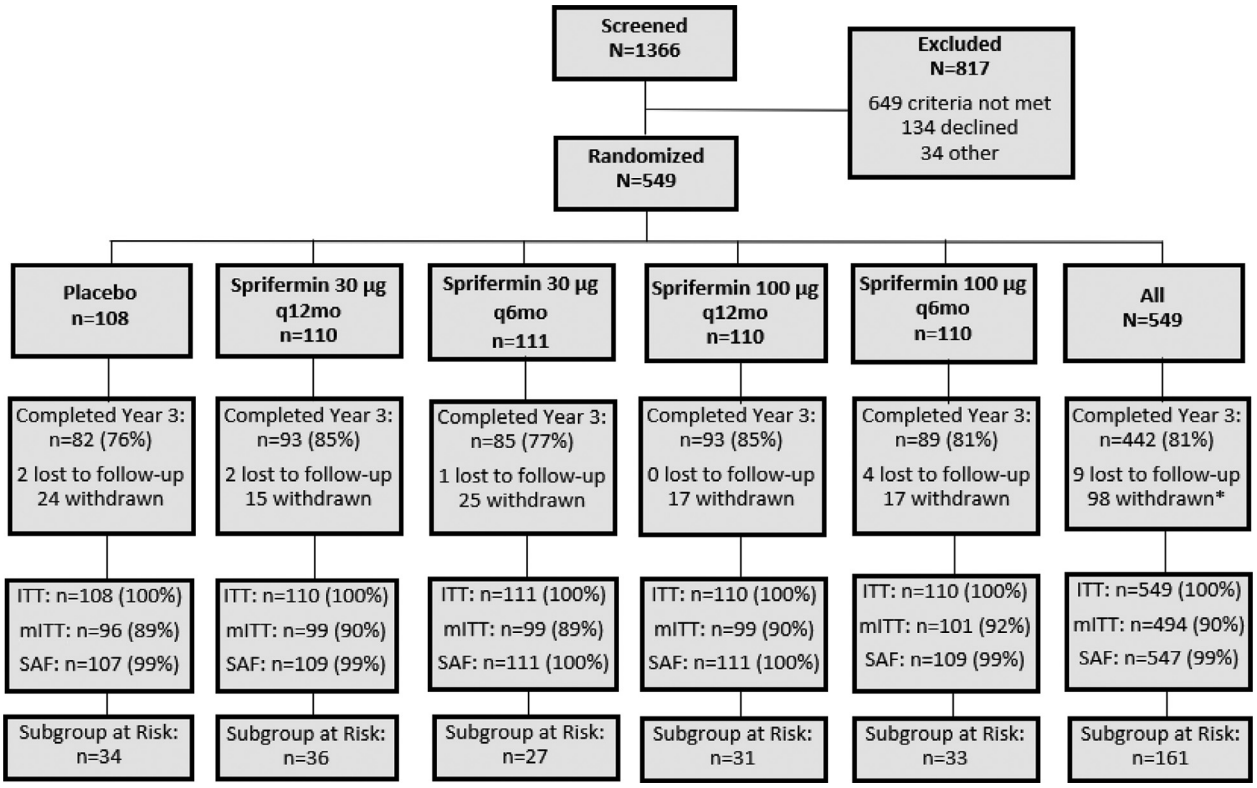

Fig. 1. Study disposition.
* Reasons for withdrawal: adverse event (17), protocol non-compliance (12), withdrew consent (42), disease progression (3), death (1), other (23).

Table 1
Overall baseline characteristics in the ITT, SAR, and non-SAR populations.

	ITT (n = 549)	SAR (n = 161)	Non-SAR subgroup (n = 339)
Median age, years	65.0	66.0	65.0
Predominantly medial disease,%	68.3	83.5	62.0
Female,%	69.0	78.9	63.4
White race,%	80.0	78.9	79.1
Median BMI, kg/m^2	28.6	29.6	27.8
KL grade 2,%*	69.0	47.2	78.2
KL grade 3,%*	31.0	52.8	21.8
Median mJSW, mm (min, max)*	3.6 (1.0, 6.6)	2.8 (1.5, 3.5)	4.1 (1.7, 6.6)
Median WOMAC pain (min, max)*	46.0 (10.0, 88.0)	54 (40.0, 86.0)	40.0 (10.0, 88.0)

*In the target knee. BMI, body mass index; ITT, intention-to-treat; KL, Kellgren-Lawrence; mJSW, minimum joint space width; SAR, subgroup at risk; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

ITT population, change from baseline in WOMAC pain was not different between sprifermin 100 μg q6mo and placebo (adjusted mean difference at Year 3: 0.97 [95% CI −6.22;8.16]). The absolute mean change from baseline in WOMAC sub-score at Year 3 in the non-SAR subgroup was 6.45 (95% CI − 1.76;14.66).

TFTJ cartilage thickness

SAR placebo-treated patients had numerically greater TFTJ cartilage loss between baseline and 2 years than the mITT population (observed mean loss 0.05 vs 0.02 mm; Fig. 4). A similar difference was observed between the SAR and non-SAR subgroup (Fig. S3). In the SAR and mITT population, a nominally significant dose-dependent effect of sprifermin on observed change in total cartilage thickness was seen from Year 1 (Fig. 4). Increased cartilage thickness with sprifermin 100 μg q6mo versus placebo at Year 2 was slightly greater in the SAR (adjusted mean difference 0.06 mm [95% CI 0.01;0.11]; Table 3) versus the mITT population (0.05 mm [95% CI 0.02;0.08]).

While mean cartilage thickness decreased in all treatment groups between Years 2 and 3 in both the SAR and mITT population, the mean difference versus placebo at Year 2 remained similar up to Year 3 (Fig. 4). This was also true of the SAR and non-SAR subgroup (Table 3, Fig. S3).

Other PROs

Three-year findings for other PROs with sprifermin 100 μg q6mo were consistent with WOMAC pain, including total WOMAC score, WOMAC stiffness and function, total weight bearing, WOMAC pain Q3 and Q4 score, knee pain on numerical rating scale, and patient global assessment score (Fig. S4).

Safety

The proportion of patients with AEs with sprifermin versus placebo in the SAR (99.2% vs 100.0%) was comparable to the safety analysis population (96.8% vs 98.1%), as were local AEs (table S2). More placebo-treated patients in the SAR had SAEs versus the safety analysis population (47.1% vs 33.6%) but SAEs were comparable for sprifermin-treated patients in the two groups (21.3% vs 23.6%). The proportion of placebo-treated patients with musculoskeletal and connective tissue disorder SAEs was 29.4% (SAR) and 13.1% (safety analysis population). All SAEs were unrelated to sprifermin. There was one patient death, due to gastric cancer, in the SAR placebo group.

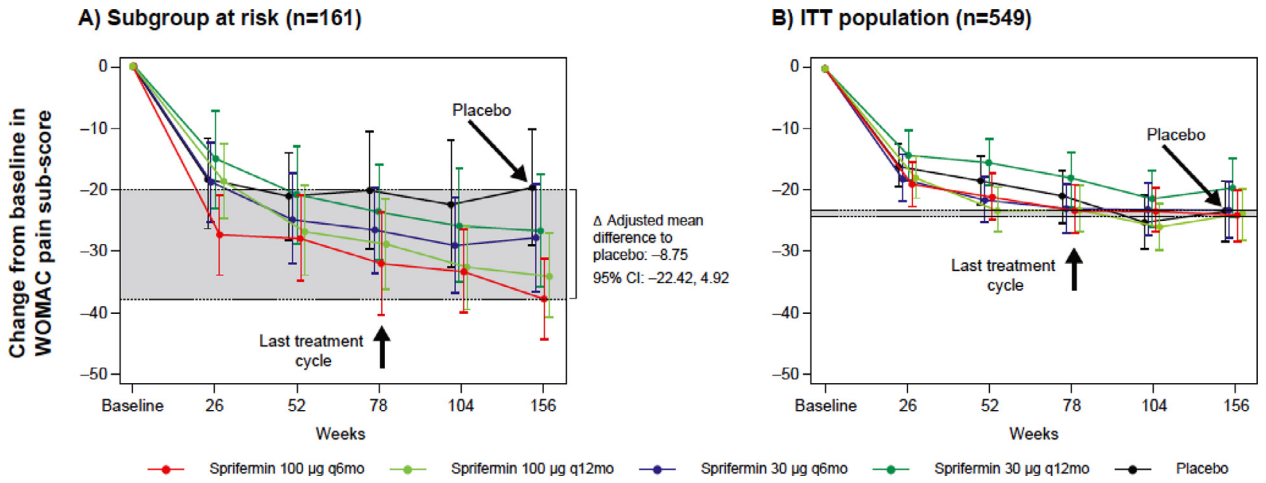

Fig. 2. Observed change in WOMAC pain sub-score at Year 3. CI, confidence interval; ITT, intention-to-treat; q6mo, every 6 months; q12mo, every 12 months; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

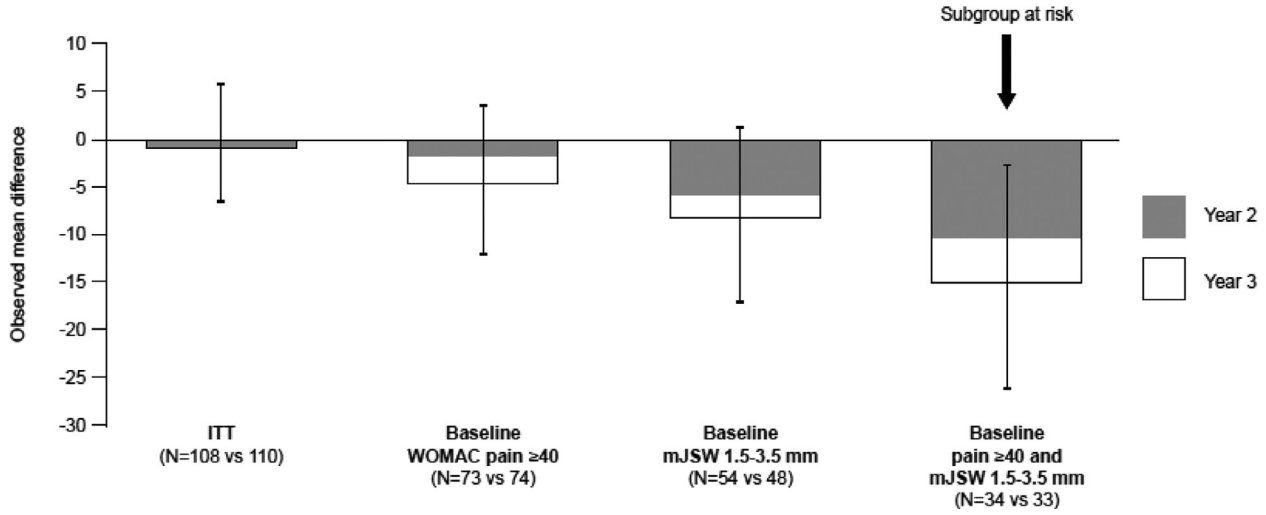

Fig. 3. Observed mean difference in change from baseline to Year 3 in WOMAC pain sub-score (95% CI) with sprifermin 100 μg q6mo vs placebo* for subgroups of patients with different baseline characteristics. *N = number of participants receiving placebo vs sprifermin 100 μg q6mo. BL, baseline; ITT, intention-to-treat; mJSW, minimum joint space width; q6mo, every 6 months; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

Discussion

Both structural and symptomatic benefit are needed for an agent to be considered a DMOAD [25], and clinical trials have previously failed to demonstrate concomitant improvements in both outcomes [7,26–28]. This may be because patient populations were too heterogeneous, typically including patients whose structural degradation and associated pain symptoms may progress at different rates or not at all [7,14,29]. In addition, patients without cartilage loss at baseline may not be expected to benefit

Table 2
Adjusted mean difference in WOMAC pain sub-score with sprifermin 100 μg q6mo (n = 34) vs placebo (n = 33) in the SAR.

	Number of non-missing values (n)		Adjusted* mean difference with sprifermin 100 μg q6mo vs placebo (95% CI)†	Trend test‡
	Sprifermin 100 μg q6mo	Placebo		
Year 1	31	31	−3.65 (−15.73–8.43)	0.435
Year 1.5	31	28	−4.88 (−17.73–7.97)	0.307
Year 2	31	28	−5.82 (−18.87–7.23)	0.246
Year 3	28	27	−8.75 (−22.42–4.92)	0.037

* Repeated measure model with adjustment on baseline and pooled country to account for potential baseline difference generated by the creation of the subgroup and missing data.
† CIs are adjusted for multiplicity of treatment groups.
‡ Dose-effect trend test across all treatment groups for adjusted values.
CI, confidence interval; n, number of participants with change from baseline available; q6mo, every 6 months; SAR, subgroup at risk; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

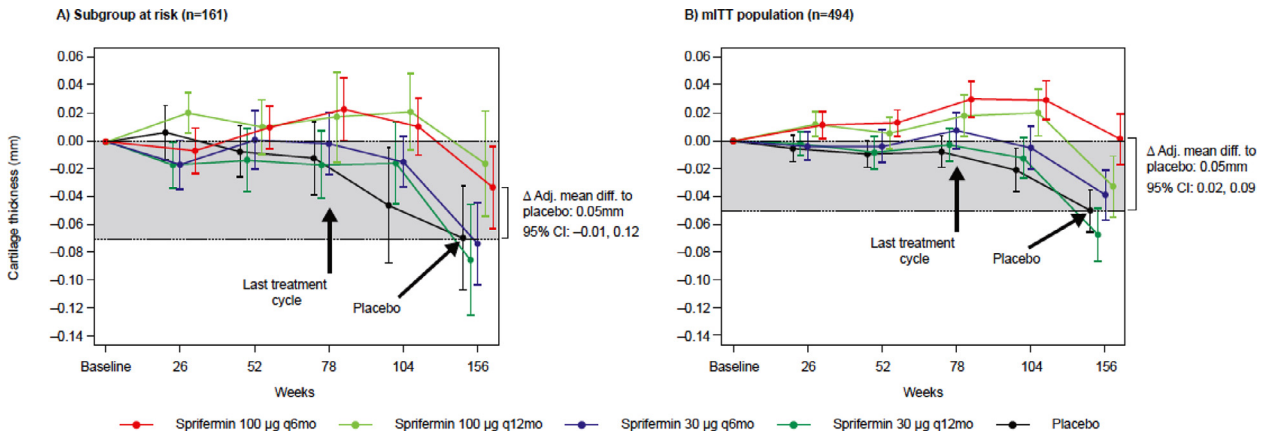

Fig. 4. Observed change in total femorotibial joint cartilage thickness at Year 3. CI, confidence interval; mITT, modified intention-to-treat; q6mo, every 6 months; q12mo, every 12 months.

Table 3
Adjusted mean difference in total femorotibial cartilage thickness with sprifermin 100 μg q6mo (n = 34) vs placebo (n = 33) in the SAR.

	Number of non-missing values (n)		Adjusted* mean difference with sprifermin 100 μg q6mo vs placebo (95% CI)†	Trend test‡
	Sprifermin 100 μg q6mo	Placebo		
Year 1	29	29	0.02 (−0.01–0.05)	0.049
Year 1.5	29	26	0.03 (−0.01–0.08)	0.012
Year 2	29	27	0.06 (0.01–0.11)	<0.001
Year 3	25	23	0.05 (−0.01–0.12)	0.002

* Repeated measure model with adjustment on baseline and pooled country to account for missing data and potential baseline difference generated by the creation of the subgroup and missing data.
† CIs are adjusted for multiplicity of treatment groups.
‡ Dose-effect trend test across all treatment groups for adjusted values from the repeated measure model.
CI, confidence interval; n, number of participants with change from baseline available; q6mo, every 6 months; SAR, subgroup at risk.

symptomatically from increasing cartilage thickness. Conversely, patients whose disease progresses more rapidly may be more likely to exhibit a symptomatic response to treatment [29]. In this post-hoc analysis, we identified a subgroup of patients at risk of structural and symptomatic progression during the trial, based on baseline characteristics.

Although FORWARD met its primary endpoint on structure, there was no differentiation from placebo regarding the key secondary pain outcome. There are several possible reasons for this. Using i.a. saline injections as a control may act as an active placebo [30], masking symptomatic improvements associated with sprifermin. It is well-documented that placebos can yield a clinically relevant response and it is plausible that i.a. saline injections exert effects through the dilution of inflammatory components [31], making it challenging to demonstrate an effect size between placebo and comparator. Furthermore, FORWARD was primarily designed as a dose-finding, structural effects trial, not a pain trial; modern pain inclusion criteria were not implemented. Routine and rescue pain medications were monitored, but not restricted. The ~90% of patients in each treatment group who took additional pain medications in the first 2 years may have contributed to a greater response with placebo.

While mean pain score differences between sprifermin 100 μg and placebo were observed from 1.5 years, the dose-effect trend test did not reach a nominal p-value <0.05 until Year 3 in the SAR. Compared with the cartilage thickness effect, this time lag may have occurred because the pain response was indirect and secondary to structural modification. The delay could reflect a reduction in symptomatic progression due to the structural modification with sprifermin in patients who would otherwise progress more rapidly if left untreated. This underscores the time it takes for structural improvement to translate into a symptomatic benefit, suggesting that it may not always be measurable within a typical OA clinical trial timeframe in unselected, heterogeneous patient populations. As with the ITT population, a high proportion of SAR placebo-patients demonstrated a WOMAC pain response that was initially comparable to sprifermin.

It is clear that selection of a SAR based on both mJSW and pain criteria was more effective than selection based on either alone, an important message for designers of future trials, although several limitations must be considered. This post-hoc analysis was hypothesis-generating in nature, and results need to be confirmed in independent clinical trials. The SAR had missing data, some baseline imbalances, and small sample sizes with outliers that may have impacted the results. In addition, pain endpoints have large variability. However, sensitivity analyses indicated that the observed mean difference between sprifermin and placebo in WOMAC pain change from baseline was larger than the adjusted mean difference, supporting the main SAR findings. At Year 3, a dose effect trend test gave a nominal p value, <0.05. Finally, it is not known how many patients the medication washout applied to.

Conclusion

Our findings indicate that, in addition to increasing cartilage thickness, treatment with sprifermin may confer symptomatic benefits, such as decreased pain. This is the first analysis to provide a proof of concept that structure (cartilage thickness) modification in knee OA by an i.a. drug may translate into symptomatic clinical benefit, provided an adequate patient cohort with established disease is selected and followed for a duration long enough to determine potential symptom benefits. Furthermore, this analysis is the first to suggest that enriching a trial population with low mJSW and high WOMAC pain at baseline results in greater differentiation between a

DMOAD and placebo in WOMAC pain. Selecting a more homogenous patient population that is likely to progress within an OA clinical trial timeframe may improve the ability to reach a symptomatic endpoint and ultimately lead to the approval of potential DMOADs. The patient subgroup identified in this analysis may represent a target population for future clinical trials of sprifermin or other potential DMOADs.

Author contributions

Hans Guehring: Data analysis, data interpretation, writing and critical review of the manuscript

Flavie Moreau: Biostatistics, data analysis, data interpretation

Benjamin Daelken: Writing and critical review of the manuscript

Christoph Ladel: Data analysis, data interpretation, writing and critical review of the manuscript

Oliver Guenther: Writing and critical review of the manuscript

Asger Reinstrup Bihlet: Data analysis, data interpretation, writing of manuscript

Wolfgang Wirth: Data interpretation, writing and critical review of the manuscript

Felix Eckstein: Data interpretation, writing and critical review of the manuscript

Marc Hochberg: Data interpretation, writing and critical review of the manuscript

Philip G Conaghan: Analysis design and interpretation, drafting and critical review of manuscript.

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Declaration of Competing Interest

Hans Guehring is an employee of Merck KGaA, Darmstadt, Germany

Flavie Moreau is an employee of EMD Serono, Billerica, MA, USA; a business of Merck KGaA, Darmstadt, Germany

Benjamin Daelken is an employee of Merck KGaA, Darmstadt, Germany

Christoph Ladel was an employee of Merck KGaA, Darmstadt, Germany when the work was conducted and is currently an employee of BioBone BV, Amsterdam, Netherlands

Oliver Guenther is an employee of Merck KGaA, Darmstadt, Germany

Asger Reinstrup Bihlet is an employee and shareholder of Nordic Bioscience Clinical Development (NBCD) A/S, Herlev, Denmark

Wolfgang Wirth is an employee and shareholder of Chondrometrics GmbH, Ainring, Germany; he has provided consulting services to Galapagos

Felix Eckstein is CEO/CMO and co-owner of Chondrometrics GmbH; he has provided consulting services to Merck KGaA, AbbVie, Samumed, Kolon TissueGene Inc, Servier, Galapagos, Roche, Novartis, ICM, and Healthlink

Marc Hochberg reports being the president of Rheumcon Inc and receiving consulting fees from Bone Therapeutics, Bristol-Myers Squibb, Eli Lilly, Galapagos, IBSA Insititut Biotechniq SA, Novartis Pharma AG, Pfizer, Samumed LLC, Theralogix LLC, and Kolon TissueGene Inc.

Philip G Conaghan has done consultancies or speakers bureaus for AbbVie, AstraZeneca, BMS, EMD Serono, a business of Merck KGaA, Darmstadt, Germany, Flexion Therapeutics, Galapagos, Kolon TissueGene Inc, Novartis, Pfizer, Samumed, and Stryker.

Patient consent for publication

Not required.

Ethics approval

The study was conducted in accordance with the Declaration of Helsinki, the International Conference on Harmonisation Guidelines for Good Clinical Practice and local regulations. The study protocol [9] and all major amendments were approved by the relevant Institutional Review Boards or Independent Ethics Committees and by Health Authorities, according to country-specific laws.

Data sharing

Any requests for data by qualified scientific and medical researchers for legitimate research purposes will be subject to Merck KGaA's Data Sharing Policy. All requests should be submitted in writing to Merck KGaA's data sharing portal. When Merck KGaA has a co-research, co-development, or co-marketing or co-promotion agreement, or when the product has been out-licensed, the responsibility for disclosure might be dependent on the agreement between parties. Under these circumstances, Merck KGaA will endeavour to gain agreement to share data in response to requests.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.semarthrit.2021.03.005.

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