SUPPLEMENTARY MATERIALS

Supplementary Methods

Quantitative MRI assessments

MRI scanning was performed using a high-resolution (1.5 or 3 Tesla), 3-dimensional MRI machine with a commercially available dedicated knee coil. Quantitative MRI analysis focusing on cartilage thickness in the total knee and medial and lateral femorotibial compartments was performed centrally by Chondrometrics GmbH (Ainring, Germany) by experienced MRI analysts, as described previously.[1]

Due to the duration of the study, separate analyses for the primary endpoint and observational follow-up period were conducted and different methodologies (batching and blinding to timepoints) were used at different timepoints. MRI analysis during the double-blind treatment period, from baseline to Year 2, was performed as a single batch (Batch 1), with the readers blinded to timepoint and cohort (treatment), but unblinded to subject, to allow for longitudinal comparisons as well as treatment differences. Year 3 (Batch 2) and 4 (Batch 3) analyses were read in separate batches, unblinded to subject and timepoint, but blinded to cohort, with one random baseline through Year 2 data set as reference. Year 5 MRIs (Batch 4) were read in a similar way, but with reference to the unsegmented Year 2 MRIs (which were re-read) and segmented baseline MRIs. The Year 2 re-reads at Year 5 were performed to allow blinding to timepoint but are not included in the current analysis. Follow-up readings were not intended to represent an unbiased estimate of longitudinal cartilage thickness change, but evaluation of dose-effect and treatment differences to placebo at each timepoint.

Statistical analysis

The intent-to-treat (ITT) population included all randomised patients, and the modified (m)ITT population included all patients with a baseline and ≥1 post-treatment qMRI analysis up to Year 2. qMRI endpoints are presented for the mITT, and all other endpoints presented for the ITT population.

Changes from baseline, and treatment differences versus placebo, were analysed using descriptive statistics (means and 95% confidence intervals [CIs]). Treatment differences compared with placebo were estimated using a repeated measures model that controlled for baseline, treatment, time, pooled country and treatment-by-time interaction, as previously described.[14] CIs were adjusted for multiplicity of treatment using Dunnett's adjustment. Linear dose-effect trend tests were performed exploratively to evaluate the dose response with sprifermin at each timepoint. P-values less than 0.05 were considered statistically significant.

The SAR included all patients with baseline medial or lateral mJSW of 1.5–3.5 mm and a WOMAC pain score of 40–90. Post-hoc exploratory analyses were conducted in the SAR and reported using descriptive statistics (means and 95% CIs).

References

1. Hochberg MC, Guermazi A, Guehring H, et al. Effect of Intra-Articular Sprifermin vs Placebo on Femorotibial Joint Cartilage Thickness in Patients With Osteoarthritis: The FORWARD Randomized Clinical Trial. *Jama* 2019; 322: 1360-1370. 2019/10/09. DOI: 10.1001/jama.2019.14735.

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Supplementary Figures

Figure S1 Study design. JSW, joint space width; KLG, Kellgren-Lawrence grade; MRI, magnetic resonance imaging; q6mo, every 6 months; q12mo, every 12 months; WOMAC, Western Ontaria and McMaster Universities Osetoarthritis Index.

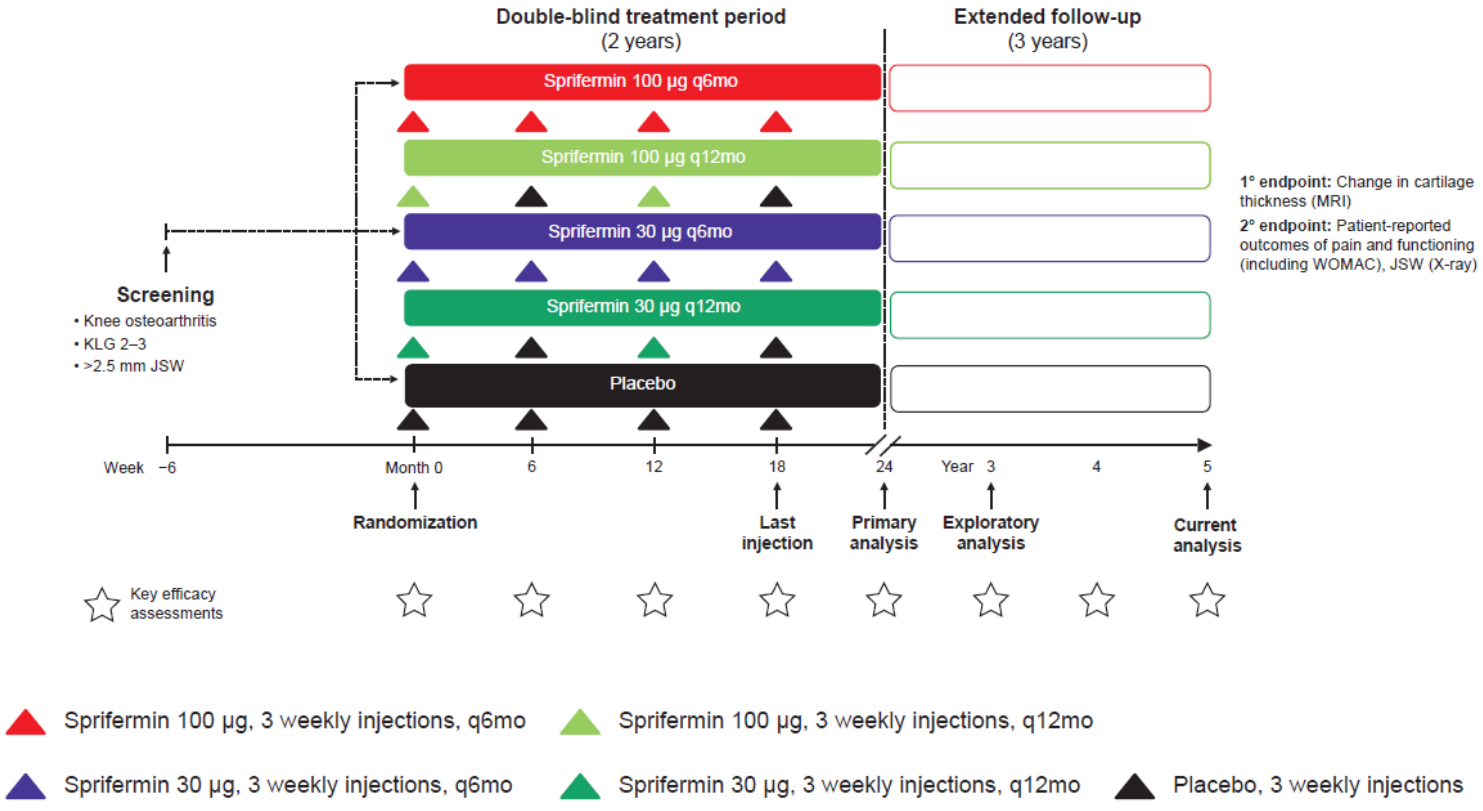
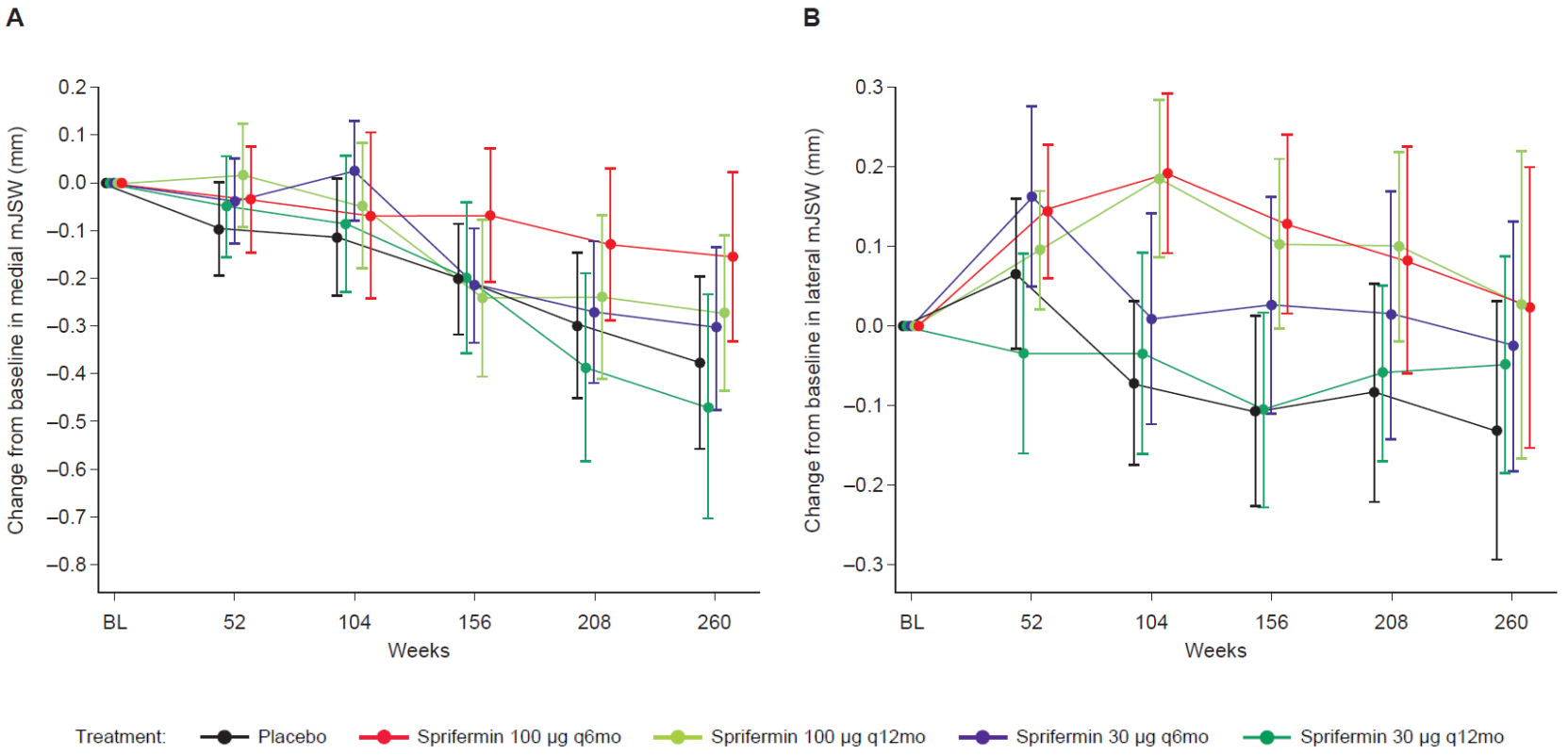


Figure S2 Change from baseline in medial and lateral mJSW up to Year 5. Absolute change from baseline in (**A**) medial mJSW (mm) and (**B**) lateral mJSW (mm) for the ITT population (n=549), and absolute change from baseline in (**C**) medial mJSW (mm) and (**D**) lateral mJSW (mm) for the SAR (n=161). Means and 95% confidence intervals shown. BL, baseline; ITT, intention to treat; mJSW, minimum joint space width; q6mo, every 6 months; q12mo, every 12 months; SAR, subgroup at risk.



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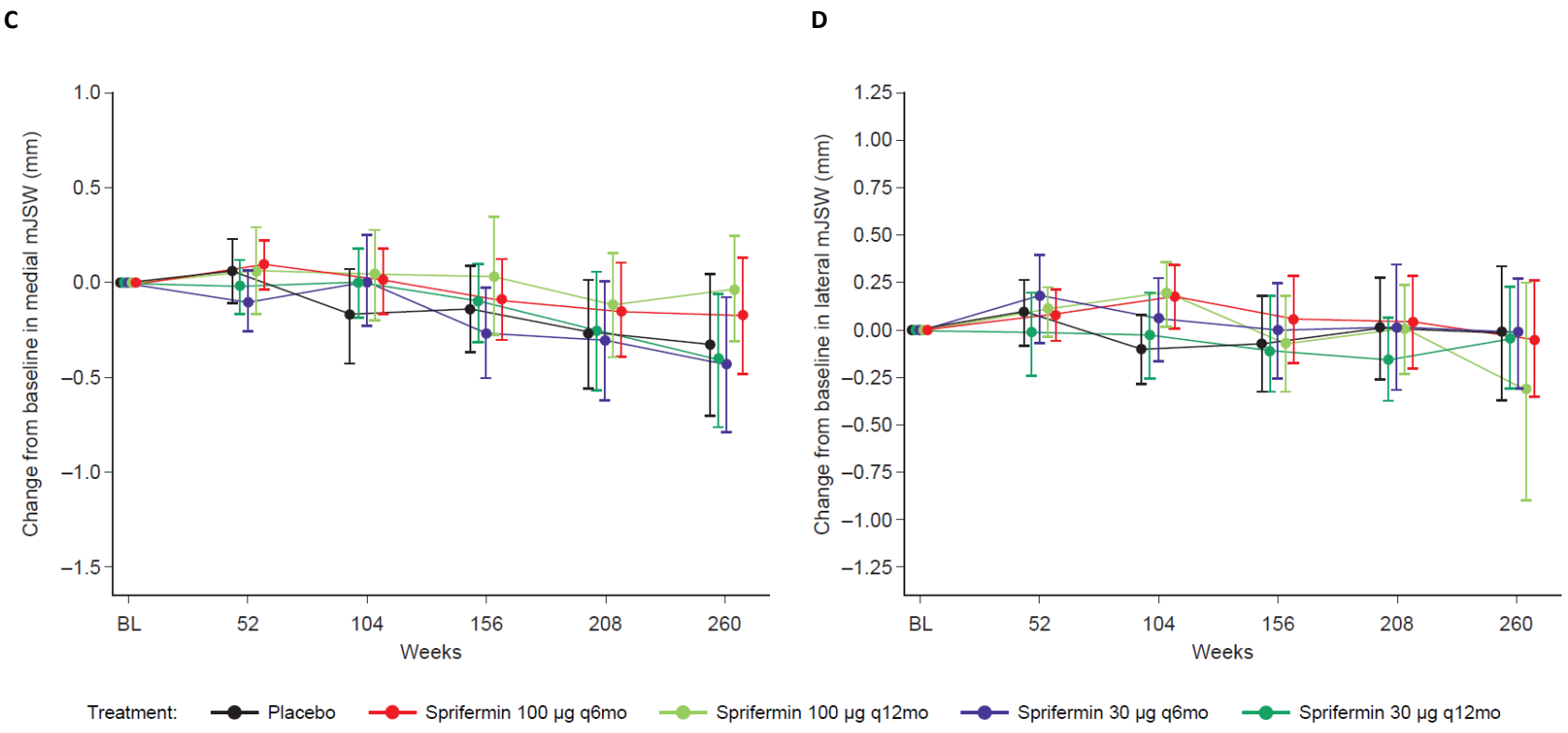
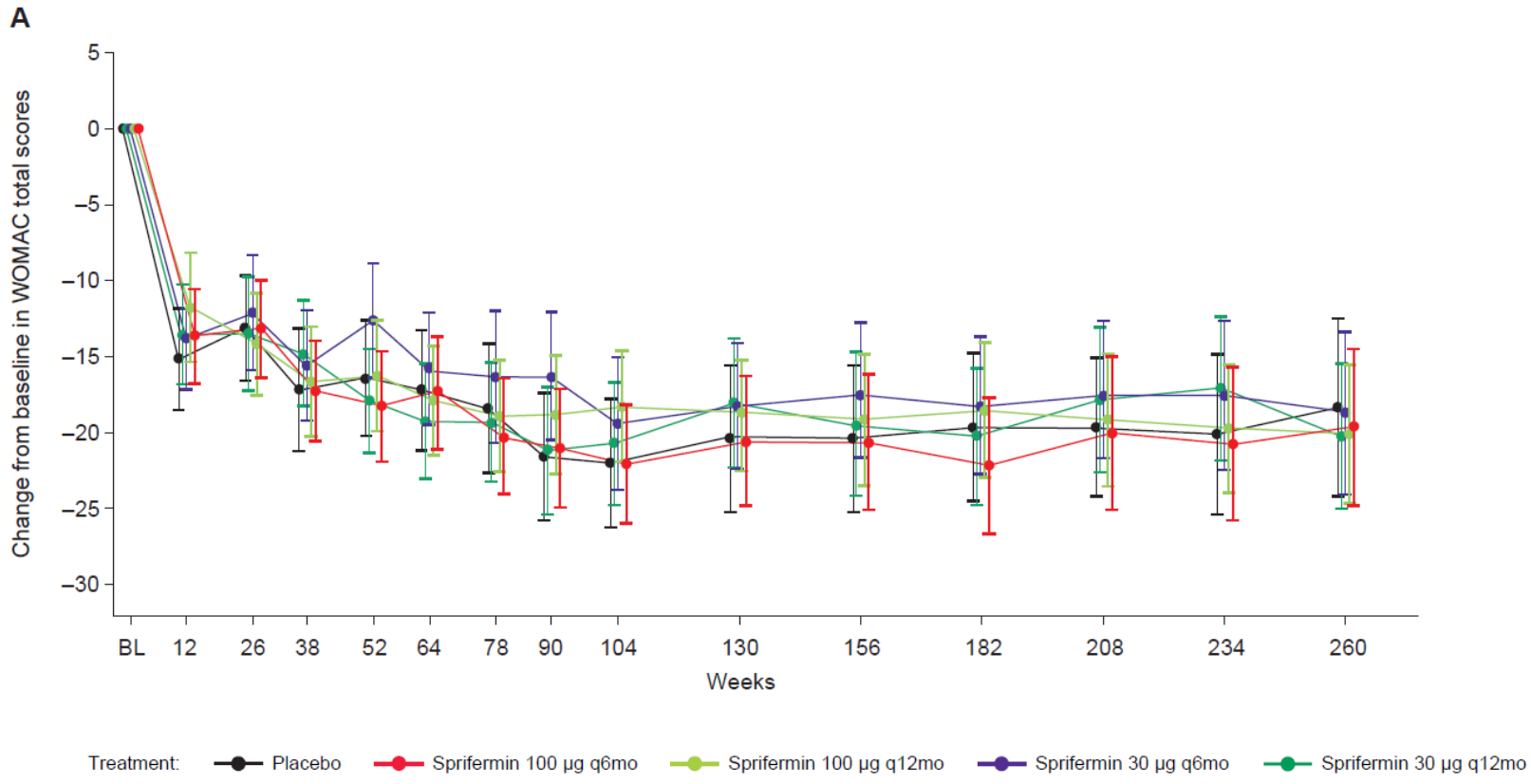


Figure S3 Change from baseline in WOMAC total scores up to Year 5 in the (**A**) ITT population (n=549) and (**B**) SAR (n=161). Means and 95% confidence intervals shown. BL, baseline; ITT, intention-to-treat; q6mo, every 6 months; q12mo, every 12 months; SAR, subgroup at risk; WOMAC, Western Ontaria and McMaster Universities Osetoarthritis Index.



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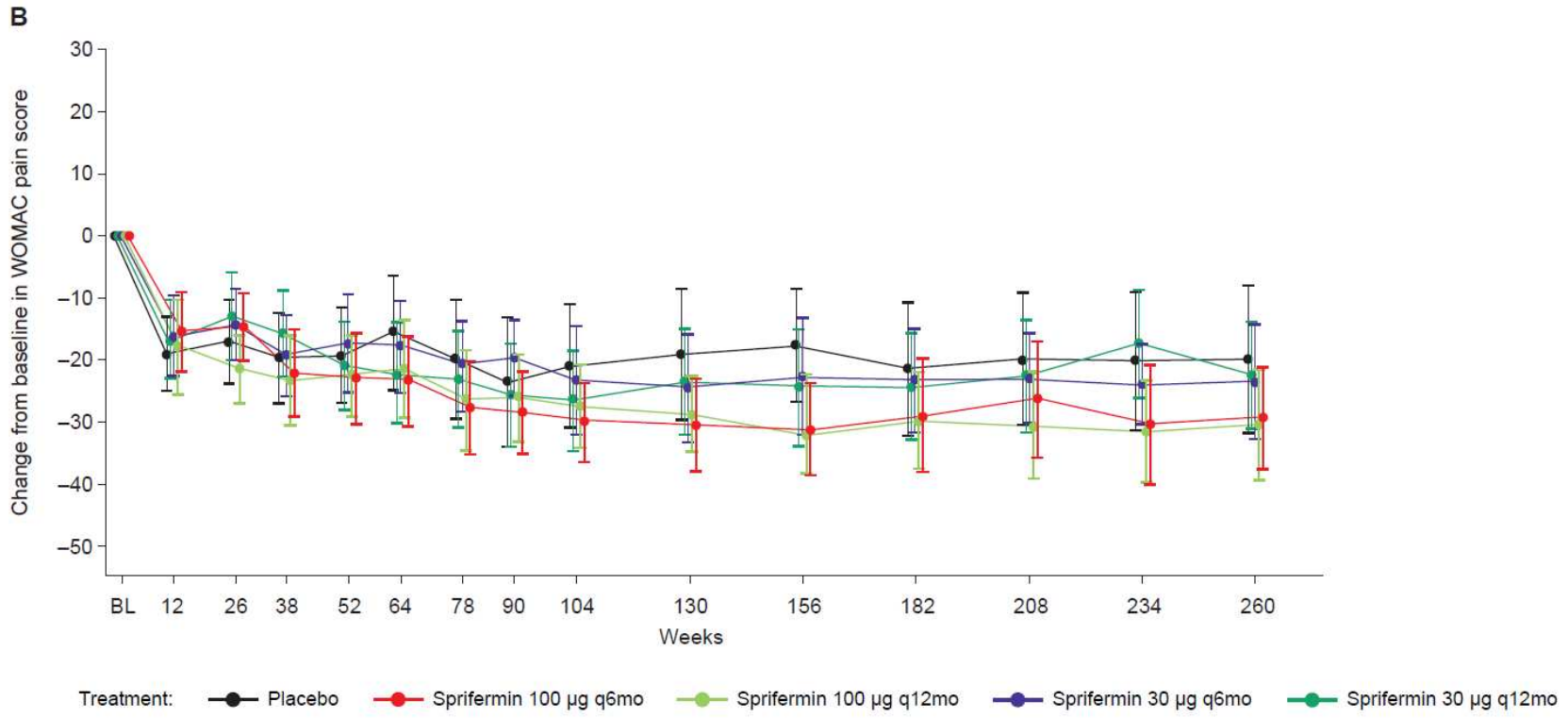

Supplementary Tables

Table S1 Baseline characteristics of the ITT population (n=549) and SAR (n=161).

	ITT					SAR				
	Placebo	Sprifermin				Placebo	Sprifermin			
		30 µg q12mo	30 µg q6mo	100 µg q12mo	100 µg q6mo		30 µg q12mo	30 µg q6mo	100 µg q12mo	100 µg q6mo
	n=108	n=110	n=111	n=110	n=110	n=34	n=36	n=27	n=31	n=33
Median age, years	64.5	66.5	65.0	65.0	66.0	63.0	66.5	66.0	67.0	68.0
Female, %	70.4	66.4	72.1	70.0	66.4	70.6	75.0	81.5	83.9	84.8
Median BMI, kg/m^2	29.2	28.8	28.2	27.9	29.4	29.6	30.1	28.1	27.1	31.1
KLG 2*, %	68.5	66.4	69.4	70.0	70.9	41.2	47.2	44.4	45.2	57.6
KLG 3*, %	31.5	33.6	30.6	30.0	29.1	58.8	52.8	55.6	54.8	42.4
Predominately medial disease, %	63.1	67.4	69.3	69.6	71.9	64.7	69.4	77.8	80.6	69.7
Median (min, max) mJSW*, mm	3.30 (1.5, 6.2)	3.60 (1.6, 6.1)	3.85 (1.5, 6.1)	3.60 (1.8, 6.6)	3.60 (1.5, 6.4)	2.70 (1.5, 3.5)	2.55 (1.6, 3.5)	3.00 (1.5, 3.5)	2.80 (1.8, 3.5)	3.00 (1.5, 3.5)
Median (min, max) WOMAC pain*	45 (16, 82)	46 (10, 86)	44 (18, 88)	46 (10, 86)	48 (12, 84)	52 (40, 82)	54 (40, 80)	50 (40, 84)	54 (44, 86)	60 (40, 74)

***In the target knee

BMI, body mass index; KLG, Kellgren-Lawrence grade; max, maximum; mJSW, minimum joint space width; min, minimum; q6mo, every 6 months; q12mo, every 12 months; SAR, subgroup at risk; SD, standard deviation; TFTJ, total femorotibial joint; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

Table S2 Absolsute medial and lateral mJSW up to Year 5 and absolute change from baseline at Year 5 in the ITT population as assessed by X-ray (n=549).

ITT, intention to treat; mJSW, minimum joint space width; q6mo, every 6 months; q12mo, every 12 months.

Mean (SD)	Placebo n=108	Sprifermin 30 µg q12mo n=110	Sprifermin 30 µg q6mo n=111	Sprifermin 100 µg q12mo n=110	Sprifermin 100 µg q6mo n=110
Medial femorotibial compartment					
Baseline	3.72 (1.16)	3.58 (1.04)	3.82 (1.10)	3.82 (1.08)	3.72 (1.18)
Year 2	3.73 (1.30)	3.46 (1.20)	3.82 (1.24)	3.79 (1.28)	3.64 (1.31)
Year 3	3.65 (1.25)	3.26 (1.16)	3.52 (1.27)	3.58 (1.23)	3.69 (1.25)
Year 4	3.58 (1.44)	3.08 (1.24)	3.51 (1.28)	3.61 (1.29)	3.59 (1.33)
Year 5	3.63 (1.55)	3.01 (1.35)	3.46 (1.38)	3.59 (1.19)	3.53 (1.36)
Change from baseline at Year 5	-0.38 (0.72)	-0.47 (1.02)	-0.31 (0.75)	-0.27 (0.75)	-0.16 (0.77)
Lateral femorotibial compartment					
Baseline	5.43 (1.33)	5.50 (1.16)	5.66 (1.33)	5.72 (1.36)	5.66 (1.17)
Year 2	5.33 (1.43)	5.49 (1.35)	5.65 (1.46)	5.87 (1.36)	5.87 (1.40)
Year 3	5.25 (1.45)	5.40 (1.37)	5.67 (1.42)	5.76 (1.36)	5.79 (1.34)
Year 4	5.37 (1.60)	5.44 (1.33)	5.74 (1.41)	5.68 (1.43)	5.74 (1.44)
Year 5	5.35 (1.62)	5.43 (1.41)	5.72 (1.43)	5.65 (1.56)	5.71 (1.46)
Change from baseline at Year 5	-0.13 (0.65)	-0.05 (0.60)	-0.03 (0.69)	0.03 (0.88)	0.02 (0.76)

Table S3 Change in WOMAC total score and WOMAC subscale scores over 5 years in the ITT population (n=549). ITT, intention-to-treat; q6mo, every 6 months; q12mo, every 12 months; WOMAC, Western Ontaria and McMaster Universities Osetoarthritis Index.

	Placebo n=108	Sprifermin 30 µg q12mo n=110	Sprifermin 30 µg q6mo n=111	Sprifermin 100 µg q12mo n=110	Sprifermin 100 µg q6mo n=110
WOMAC total score					
Baseline, mean (SD)	46.35 (16.10)	45.36 (16.84)	45.29 (15.26)	42.33 (16.31)	46.89 (18.18)
Year 5, mean (SD)	26.92 (22.26)	25.22 (19.12)	24.43 (22.82)	21.26 (17.45)	25.93 (20.62)
Mean (SD) change from baseline at Year 5	-18.35 (23.08)	-20.25 (21.11)	-18.76 (23.06)	-20.12 (20.39)	-19.64 (22.71)
Difference from placebo (95% CI) at Year 5	–	-1.90 (-9.33, 5.53)	-0.41 (-8.23, 7.42)	-1.77 (-9.10, 5.56)	-1.29 (-9.01, 6.43)
WOMAC pain index score					
Baseline, mean (SD)	46.49 (14.37)	46.80 (15.39)	45.87 (15.73)	45.18 (15.45)	48.17 (16.50)
Year 5, mean (SD)	23.24 (20.41)	23.00 (18.59)	22.89 (22.16)	19.44 (16.84)	23.24 (20.45)
Mean (SD) change from baseline at Year 5	-22.38 (22.19)	-24.41 (22.48)	-20.38 (22.49)	-24.94 (19.95)	-24.00 (22.38)
Difference from placebo (95% CI) at Year 5	–	-2.02 (-9.48, 5.43)	2.00 (-5.57, 9.57)	-2.56 (-9.65, 4.54)	-1.62 (-9.13, 5.89)
WOMAC function index score					
Baseline, mean (SD)	46.07 (17.46)	44.96 (18.75)	45.29 (15.98)	41.48 (17.65)	46.65 (19.93)
Year 5, mean (SD)	28.06 (23.37)	26.04 (20.11)	24.71 (23.29)	21.67 (18.12)	26.66 (20.75)
Mean (SD) change from baseline at Year 5	-17.03 (24.15)	-18.74 (21.87)	-18.55 (23.76)	-18.82 (21.62)	-18.56 (23.60)
Difference from placebo (95% CI) at Year 5	–	-1.71 (-9.45, 6.04)	-1.52 (-9.65, 6.61)	-1.78 (-9.49, 5.92)	-1.53 (-9.58, 6.53)

WOMAC stiffness index score					
Baseline, mean (SD)	48.40 (20.80)	45.00 (20.15)	43.76 (20.58)	42.34 (19.65)	45.78 (21.49)
Year 5, mean (SD)	26.51 (23.01)	23.75 (20.17)	25.81 (26.21)	22.32 (18.41)	26.45 (24.45)
Mean (SD) change from baseline at Year 5	-19.44 (27.61)	-22.66 (25.10)	-16.49 (27.28)	-19.05 (22.59)	-17.89 (28.30)
Difference from placebo (95% CI) at Year 5	–	-3.21 (-12.08, 5.65)	2.96 (-6.35, 12.27)	0.39 (-8.14, 8.92)	1.55 (-7.86, 10.96)
WOMAC weight-bearing pain score					
Baseline, mean (SD)	53.96 (14.18)	53.27 (14.18)	53.43 (14.52)	52.18 (14.22)	55.23 (14.21)
Year 5, mean (SD)	27.41 (23.40)	26.67 (19.64)	26.49 (24.29)	22.72 (17.97)	27.28 (21.99)
Mean (SD) change from baseline at Year 5	-25.56 (24.08)	-27.17 (23.08)	-24.91 (23.18)	-28.10 (19.39)	-26.67 (22.35)
Difference from placebo (95% CI) at Year 5	–	-1.62 (-9.52, 6.28)	0.65 (-7.38, 8.67)	-2.55 (-9.95, 4.85)	-1.11 (-8.97, 6.75)