UNIVERSITY of MARYLAND
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Sprifermin Case Study

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Sprifermin

- Sprifermin is a novel recombinant human fibroblast growth factor-18 (rhFGF-18) that is being developed as a potential disease-modifying OA drug (DMOAD).
- Sprifermin induces hyaline cartilage formation in vitro by increasing chondrocyte proliferation, resulting in increased overall extracellular matrix production.[1]
- A 1-year, placebo-controlled, Proof of Concept (PoC) phase Ib study reported statistically significant, dose-dependent effects on total and lateral cartilage thickness in patients treated with intra-articular sprifermin.[2]
- A 5-year, placebo-controlled phase II study (FORWARD) reported statistically significant, dose-dependent effects on total cartilage thickness in patients treated with intra-articular sprifermin after 2 years.[3]

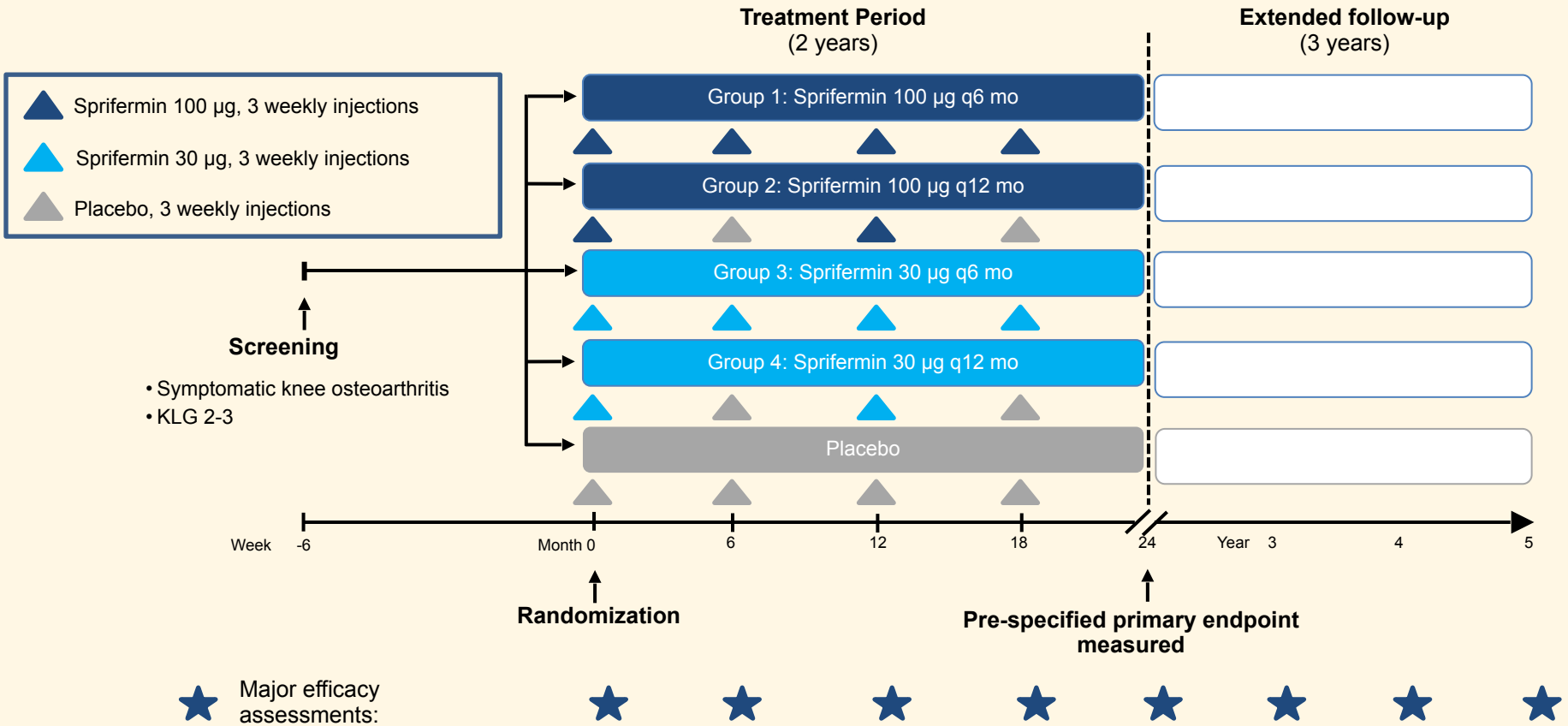
1. Gigout A, et al. Osteoarthritis Cartilage. 2017 pii: S1063-4584(17)31146-9 [Epub ahead of print].
2. Lohmander LS, et al. Arthritis Rheumatol. 2014;66:1820–31. 3. Hochberg MC, et al. JAMA 2019;322(14):1360-70.

FORWARD Trial

- 5-year randomized placebo-controlled phase II dose-finding study of IA sprifermin in persons aged 40-85 with symptomatic knee OA
  - KL grade 2 or 3, medial mJSW >= 2.5 mm
  - Score of 4-9 on WOMAC A1
- Pre-specified primary analysis at 2 years
- Primary endpoint: Change in total femorotibial joint cartilage thickness in the index knee from baseline to 2 years measured by qMRI.
  - Change in WOMAC total and subscale scores was a secondary endpoint

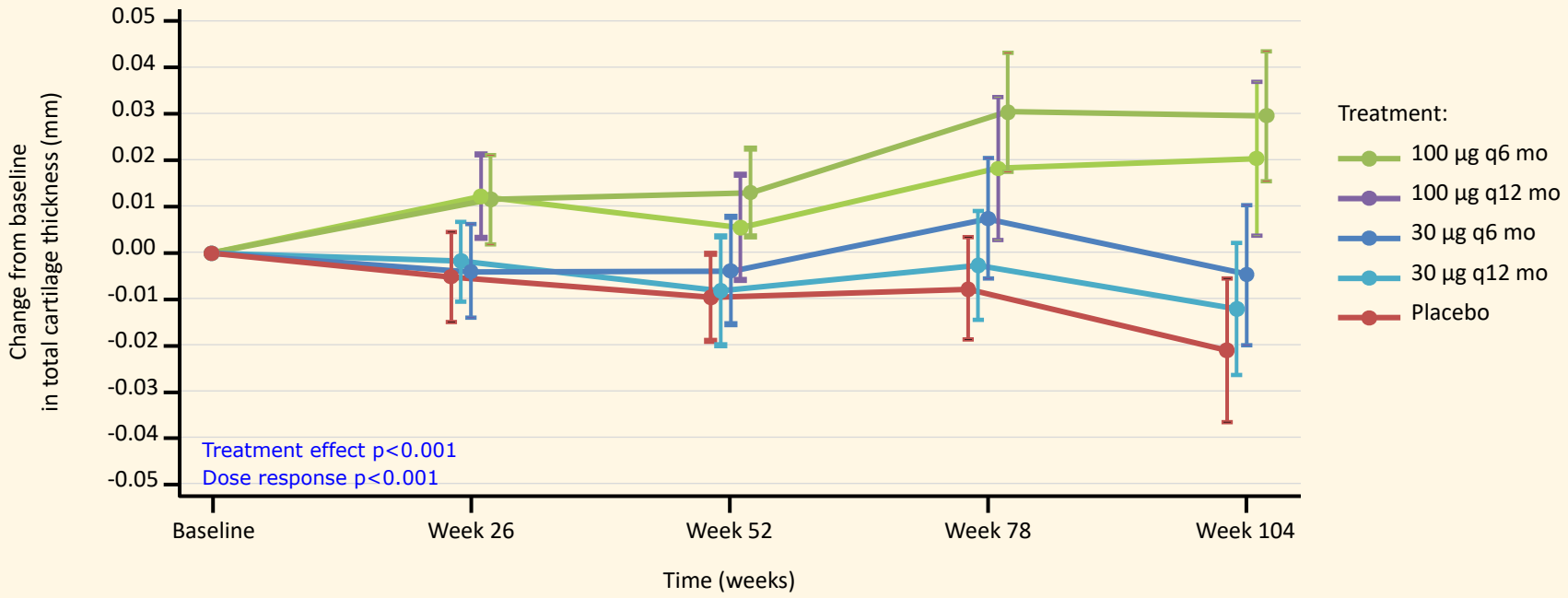
Hochberg MC, et al: JAMA 2019;322(14):1360-70 and Eckstein F, et al: Ann Rheum Dis 2021 May 7.

Study Design



q6mo, every 6 months active cycles; q12 mo, every 12 months active cycles

Primary Endpoint: Total TFJ Cartilage Thickness
Mean Change from Baseline Over 2 Years (mITT)



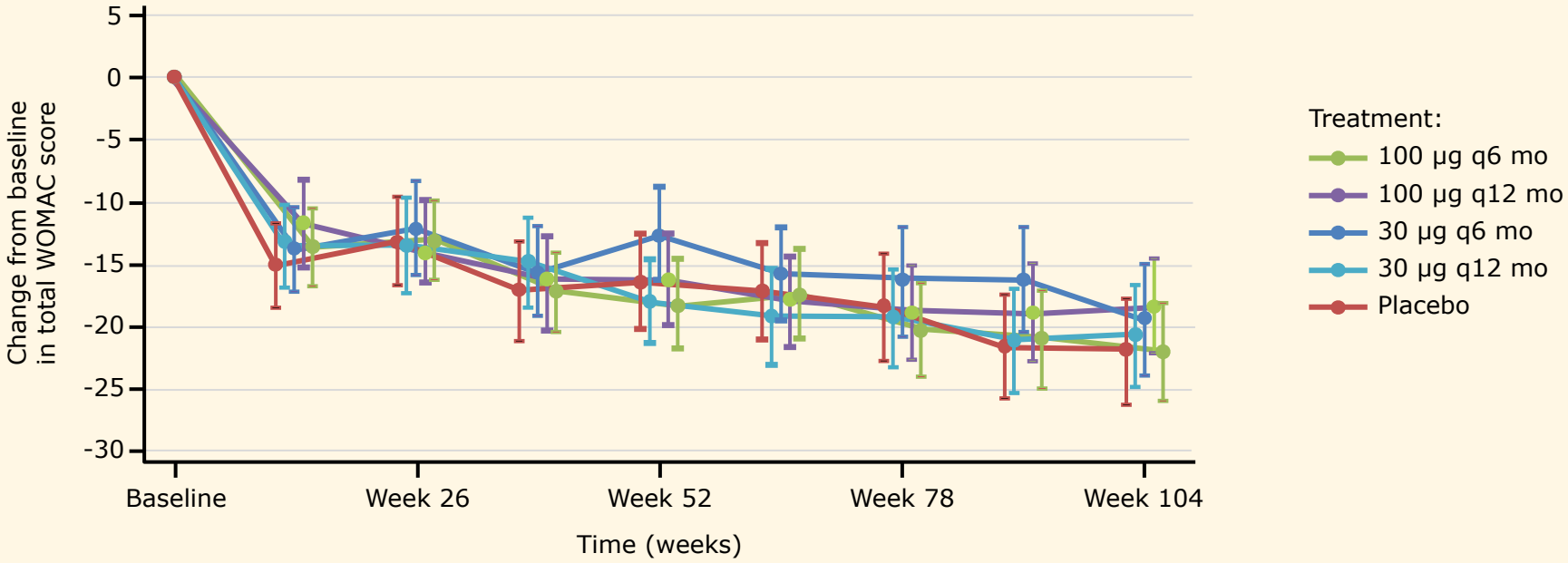
At baseline, total cartilage thickness was similar in all treatment arms and averaged ~1.8 mm.
TFJ, total femorotibial joint.

Secondary Imaging Endpoints

- Results consistent for both Medial and Lateral TFJ cartilage thickness as well as both the central medial and central lateral TFJ subregions
  - Eckstein F et al: Ann Rheum Dis 2020;79(4):525-8.
  - Roemer FW et al: OAC 2020;28(9):1229-34.
- Significant dose-response and treatment effect for lateral but not medial mJSW.

Secondary Endpoint: Total WOMAC Score

Mean (95% CI) Change from Baseline Over 2 Years (ITT)

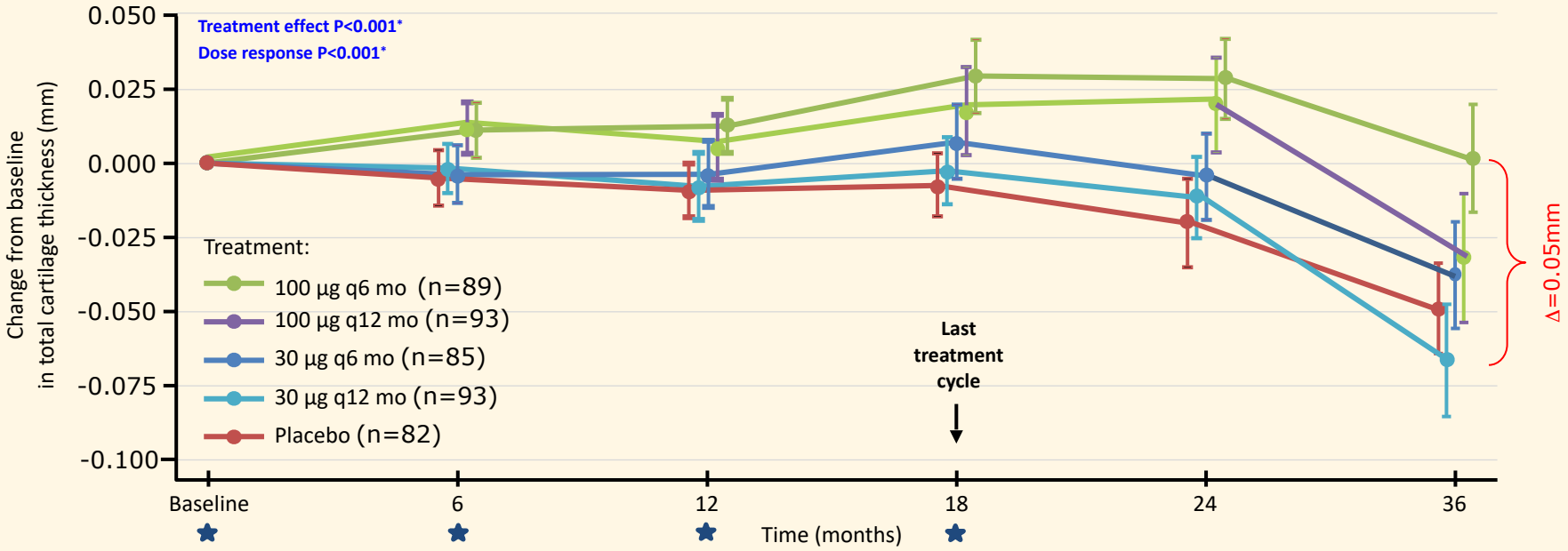


All treatment groups had a mean decrease of ~50% in total WOMAC score (baseline total WOMAC score ~40)

No significant differences between treatment groups for WOMAC Pain, Physical Function and Stiffness subscale scores.

Main 3-year Exploratory Endpoint: TFTJ Cartilage Thickness

Mean Change from Baseline Over 2 Years (mITT)



*P values represent baseline to 36 months
Difference from placebo in mean [95% CI] and P-value† absolute change from baseline:
0.05 mm [0.03–0.07] 100 µg q6mo; P<0.001
0.02 mm [-0.01–0.04] 100 µg q12mo; P=0.193
0.01 mm [-0.01–0.03] 30 µg q6mo; P=0.330
-0.02 mm [-0.04–0.01] 30 µg q12mo; P=0.160
†The 95% CI and t-test P value are calculated by considering unequal variance

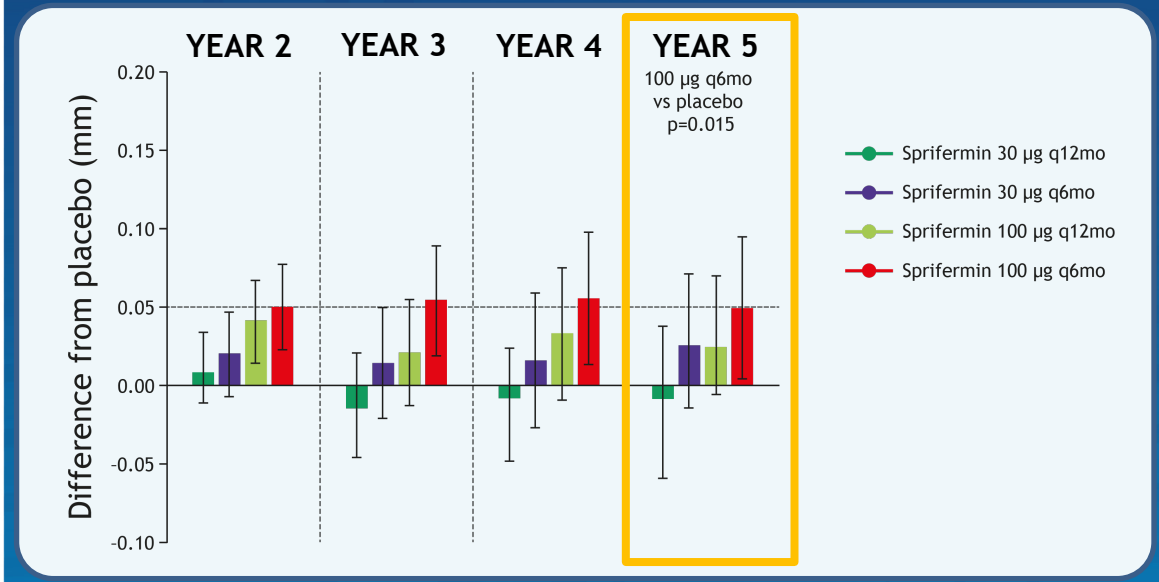
5-YEAR CHANGE IN TOTAL CARTILAGE THICKNESS

Mean (95% CI) Difference from Placebo at Year 2 and in the Follow-up Period

- The significant 0.05 mm mean increase in TFTJ cartilage thickness with sprifermin 100 µg q6mo vs placebo at Year 2 was sustained to Year 5
  - 0.05 mm (95% CI: 0.00, 0.10)

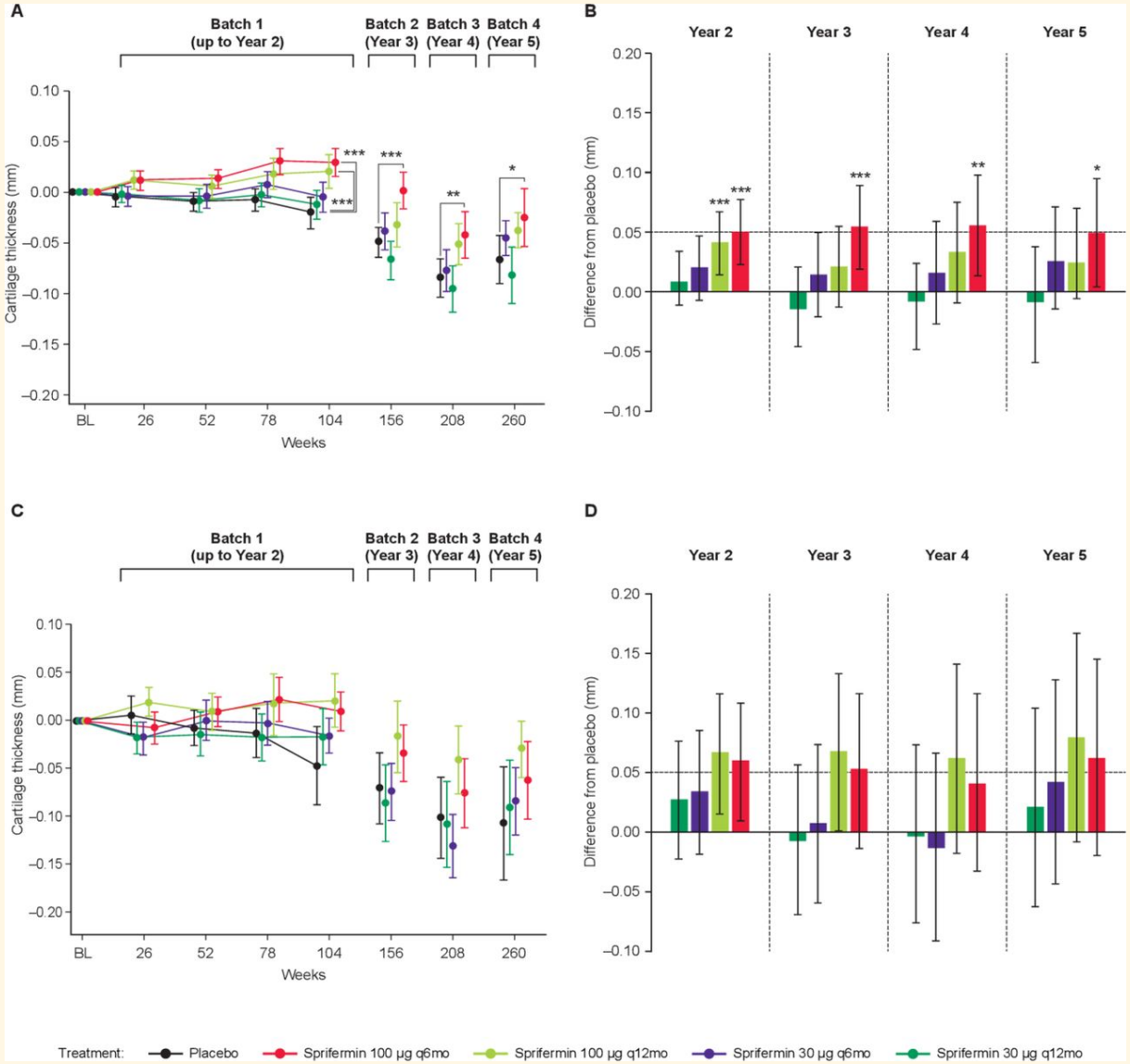
mITT POPULATION (n=494)

Dose response at Year 5, *P* <0.001



CI, confidence interval; mITT, modified intent-to-treat; TFTJ, total femorotibial joint; q6mo, every 6 months; q12mo, every 12 months

Change in TFTJ cartilage thickness up to year 5 in the (A) mITT population (n=494) and (B) SAR (n=161)



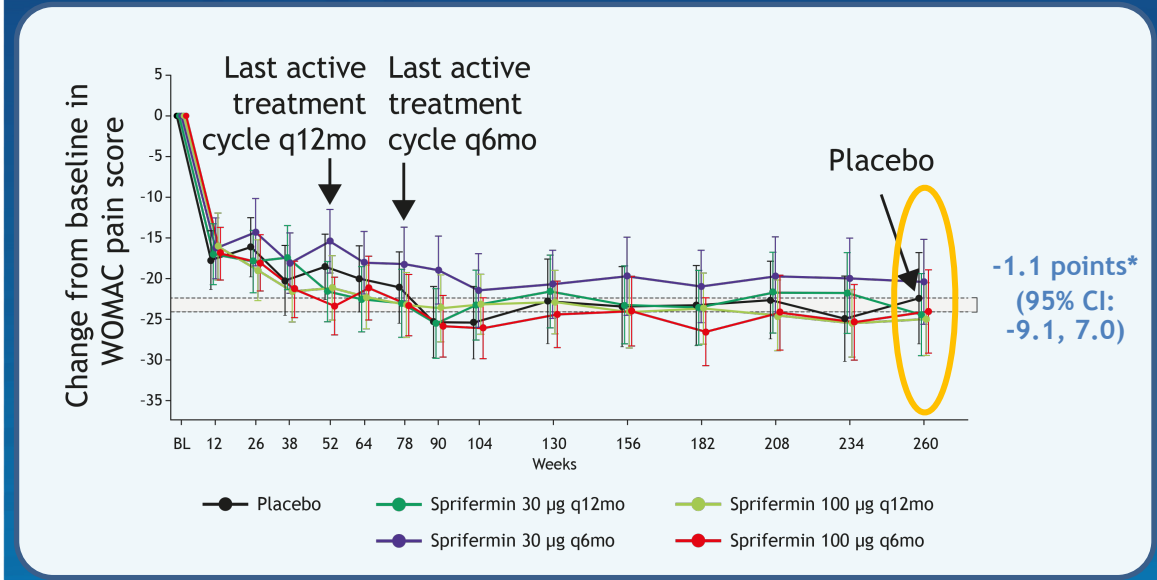
5-YEAR CHANGE IN WOMAC PAIN SCORE

Mean (95% CI) Absolute Change from Baseline at Year 2 and in the Follow-up Period

- The 50% improvement in WOMAC pain at Year 2 was maintained to Year 5 in all cohorts in the ITT population
- No significant treatment effect comparing any dose of sprifermin with placebo

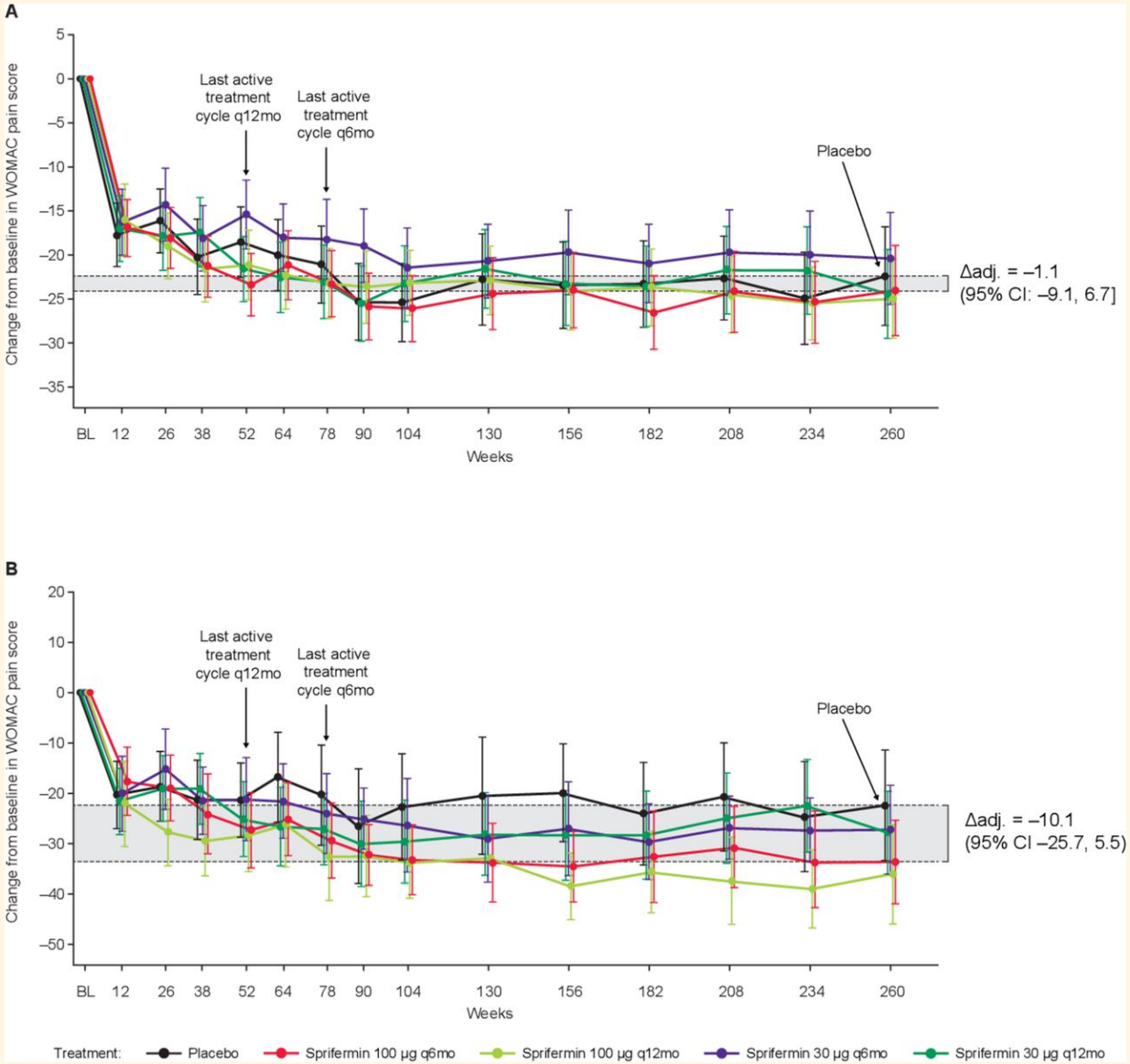
ITT POPULATION (n=549)

Dose response at Year 5, *P* = 0.673



*Δ adjusted mean difference to placebo (scale 0-100)
CI, confidence interval; ITT, intent-to-treat; q6mo, every 6 months; q12mo, every 12 months; WOMAC, Western Ontario and McMaster Universities osteoarthritis index

Change from baseline in WOMAC pain scores up to year 5 in the (A) ITT population (n=549) and (B) SAR (n=161)



SAFETY UP TO YEAR 5

- There were no clear differences in the nature, severity or type of reported AEs or SAEs between sprifermin groups and placebo
- A total of 15 patients had knee replacements, none of whom were in the sprifermin 100 µg q6mo group

Patients, n (%)	ITT POPULATION					SUBGROUP AT RISK				
	Placebo n=108	30 µg q12mo n=110	30 µg q6mo n=111	100 µg q12mo n=110	100 µg q6mo n=110	Placebo n=34	30 µg q12mo n=36	30 µg q6mo n=27	100 µg q12mo n=31	100 µg q6mo n=33
All AEs	105 (98.1)	107 (98.2)	109 (98.2)	107 (96.4)	107 (98.2)	34 (100)	35 (97.2)	27 (100)	31 (100)	33 (100)
Local AEs	52 (48.6)	54 (49.5)	57 (51.4)	54 (48.6)	53 (48.6)	18 (52.9)	17 (47.2)	13 (48.1)	18 (58.1)	12 (36.4)
Systemic AEs	103 (96.3)	104 (95.4)	105 (94.6)	105 (94.6)	106 (97.2)	34 (100.0)	35 (97.2)	27 (100.0)	31 (100.0)	33 (100.0)
All SAEs	39 (36.4)	35 (32.1)	34 (30.6)	32 (28.8)	41 (37.6)	18 (52.9)	11 (30.6)	10 (37.0)	11 (35.5)	12 (36.4)
Local SAEs	5 (4.7)	4 (3.7)	6 (5.4)	3 (2.7)	1 (0.9)	4 (11.8)	1 (2.8)	0 (0.0)	0 (0.0)	0 (0.0)
SAEs leading to death	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Knee replacements	4 (4.6)	4 (4.0)	5 (5.4)	2 (2.0)	0 (0.0)	3 (8.8)	1 (2.8)	1 (3.7)	0 (0.0)	0 (0.0)

AEs, adverse events; ITT, intent-to-treat; SAEs, serious adverse events; q6mo, every 6 months; q12mo, every 12 months

FORWARD Trial: Conclusions

- The longest phase II DMOAD trial reported
  - Hochberg MC et al: JAMA 2019;322(14):1360-70.
  - Eckstein F et al: Ann Rheum Dis 2021 May 7.
- Sprifermin at a dose of 100 ug administered IA weekly for 3 doses every 6 months significantly increased TFJ cartilage thickness but did not significantly reduce symptoms as measured by WOMAC
- Post-hoc analysis of a “subgroup at risk” suggested translation of the structural benefit to clinical benefit
  - Guehring H et al: Semin Arthritis Rheum 2021;51(2):450-6.
- Thus, a target dose and patient population have been identified for future phase III studies.

Thank you for your attention.