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Joint Space Width Criteria Can Reduce Knee Osteoarthritis Trial Heterogeneity: Phase 2 Post-Hoc Data from Wnt Pathway Inhibitor SM04690

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Problem statement: Limitations of Kellgren-Lawrence (KL) grading in osteoarthritis (OA) trials include inconsistent interpretation leading to study population heterogeneity. Knees with radiographic 2-4 mm medial joint space width (mJSW) showed improved responsiveness for OA biomarkers during a 12-month follow-up period. This criterion was applied post-hoc to data from a phase 2 trial of SM04690, a small molecule Wnt pathway inhibitor in development as a potential disease-modifying drug in knee OA (DMOAD).

Methods: Knee OA subjects, KL grades 2-3 were randomized to receive a single 2 mL intra-articular injection of 0.03 mg, 0.07 mg, or 0.23 mg SM04690 or placebo (PBO) into the target (most painful) knee at Day 0. Radiographs (posteroanterior, weight-bearing, QuAP™ positioned), were taken at Weeks 0 and 52. Two blinded, centralized readers measured mJSWs, which were compared qualitatively, post-hoc, between groups (intent-to-treat [ITT], KL 2, KL 3, mJSW 2-4 mm). Heterogeneity was assessed with mJSW box-and-whisker plots. Finally, to assess effects of baseline heterogeneity, Week 52 in-group changes in mJSW were compared.

Results: Of 453 subjects, 161 were graded as KL 2 and 290 as KL 3, and 258 had baseline mJSW 2-4 mm. Baseline heterogeneity was reduced in the 2-4 mm group compared with ITT, KL 2, and KL 3 groups (Figure). Observed mJSW changes at Week 52 compared with PBO were beyond measurement error (>0.13 mm; Dupuis et al., *Osteoarthritis and Cartilage* 2003) for 0.03 mg and 0.07 mg SM04690 doses in the 2-4 mm group, and 0.03 mg dose in the KL 2 group (Table).

Conclusion: A less heterogenous baseline reduces measurement variability, which may reduce the required population size in a clinical trial while maintaining statistical power to detect change beyond radiographic measurement error. Specific mJSW inclusion criteria should be considered in knee DMOAD trials.

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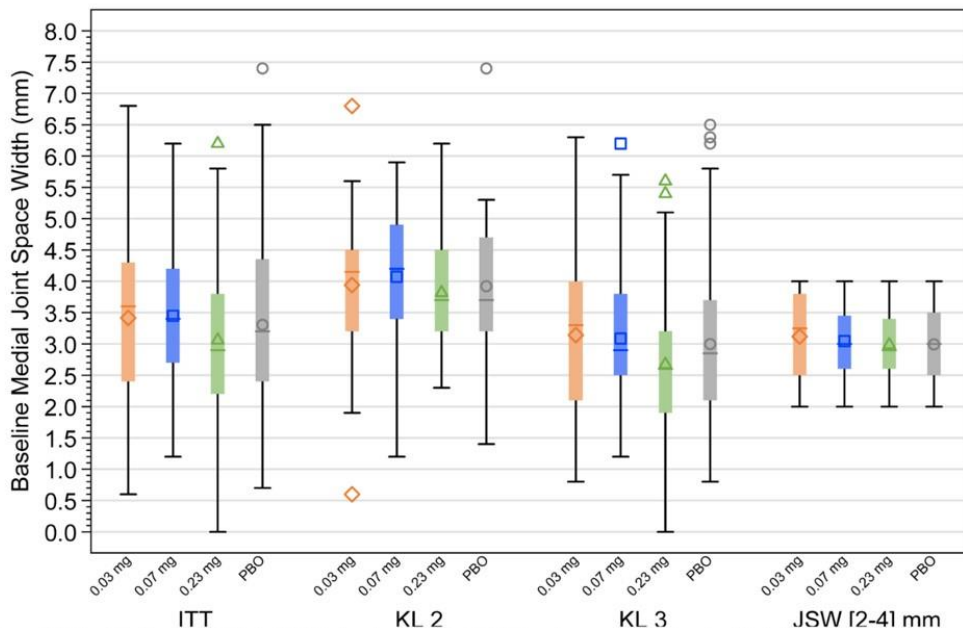
Table. mJSW measurements by group

ITT				
	0.03 mg	0.07 mg	0.23 mg	PBO
N	112	117	110	116
Baseline (mm) [Mean (SE)]	3.42 (0.12)	3.45 (0.10)	3.06 (0.12)	3.31 (0.13)
Week 52 Change from Baseline	-0.04 (0.06)	-0.09 (0.06)	-0.16 (0.07)	-0.14 (0.06)
Week 52 Compared to PBO	0.10 (0.09)	0.06 (0.09)	-0.02 (0.09)	—
P-value	0.259	0.529	0.807	—

Baseline Kellgren-Lawrence Grade 2				
	0.03 mg	0.07 mg	0.23 mg	Placebo
N	38	43	39	41
Baseline (mm) [Mean (SE)]	3.94 (0.20)	4.07 (0.16)	3.82 (0.14)	3.92 (0.17)
Week 52 Change from Baseline	0.10 (0.10)	-0.13 (0.09)	-0.08 (0.07)	-0.13 (0.11)
Week 52 Compared to PBO	0.23 (0.15)	0.02 (0.14)	0.06 (0.14)	—
P-value	0.129	0.891	0.681	—

Baseline Kellgren-Lawrence Grade 3				
	0.03 mg	0.07 mg	0.23 mg	Placebo
N	73	74	69	74
Baseline (mm) [Mean (SE)]	3.14 (0.14)	3.09 (0.12)	2.67 (0.15)	3.00 (0.16)
Week 52 Change from Baseline	-0.12 (0.07)	-0.07 (0.09)	-0.24 (0.09)	-0.16 (0.09)
Week 52 Compared to PBO	0.03 (0.11)	0.09 (0.12)	-0.09 (0.13)	—
P-value	0.774	0.473	0.502	—

Baseline JSW between 2 to 4 mm				
	0.03 mg	0.07 mg	0.23 mg	PBO
N	56	72	65	65
Baseline (mm) [Mean (SE)]	3.12 (0.09)	3.05 (0.06)	2.98 (0.07)	2.99 (0.07)
Week 52 Change from Baseline	-0.03 (0.08)	-0.03 (0.08)	-0.16 (0.09)	-0.22 (0.09)
Week 52 Compared to PBO	0.19 (0.13)	0.19 (0.12)	0.06 (0.13)	—
P-value	0.144	0.121	0.624	—



Box and Whisker plot of Baseline JSW in the ITT, in Kellgren-Lawrence Grade 2, Kellgren-Lawrence Grade 3, and restricted within 2-4 mm. Interior Bar: Median; Box: Interquartile [25th-75th] range; Whisker: 1.5x Interquartile Range; Interior Symbol: Mean; Exterior Symbol: Outlier