

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

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Background

- Kellgren-Lawrence (KL) radiographic grading is used to classify knee osteoarthritis (OA) but may not accurately reflect disease progression.¹
- Classifying subjects by baseline medial joint space width (mJSW) instead may be more specific and identify a more homogeneous clinical trial population.² This hypothesis was assessed in a post-hoc analysis of a phase 2, 52-week, randomized controlled trial of SM04690, a small molecule Wnt pathway inhibitor and potential disease modifying knee OA drug (DMOAD; clinicaltrials.gov identifier NCT02536833). A subgroup (n=258) with baseline mJSW of 2-4 mm was compared with the intent-to-treat (ITT) population.

Methods

- 455 subjects with KL grades 2-3 knee OA 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 their target (most painful) knee at Day 0.
- Radiographs (PA, QuAP™ positioned) were taken at Weeks 0 and 52. A blind read, fixed, landmark-based methodology was used to measure mJSW.
- Baseline heterogeneity was assessed with 'box and whisker' plots.
- A post-hoc, exploratory analysis of a subgroup (n=258) with baseline mJSW [2-4] mm was compared between groups (ITT, KL 2, KL 3, mJSW [2-4] mm).
- Standardized response means (SRMs) were calculated by dividing mJSW mean change from baseline by standard error.
- Baseline-adjusted ANCOVA with multiple imputation was used to compare treatment with PBO.

Results

Table 1. Demographic characteristics among the ITT Population

	0.03 mg	0.07 mg	0.23 mg	PBO	All subjects
N	112	117	110	116	455
Age at consent (years) [mean (SD)]	59.0 (9.0)	60.0 (8.2)	61.3 (8.7)	60.7 (8.9)	60.3 (8.7)
BMI (kg/m ²) [mean (SD)]	29.8 (4.8)	30.8 (4.7)	29.6 (4.5)	29.2 (4.4)	29.9 (4.6)
Female [n(%)]	68 (60.7%)	60 (51.3%)	68 (61.8%)	72 (62.1%)	268 (58.9%)
Race [n(%)]					
White	92 (82.1%)	102 (87.2%)	96 (87.3%)	102 (87.9%)	392 (86.2%)
African-American	18 (16.1%)	14 (12.0%)	12 (10.9%)	10 (8.6%)	54 (11.9%)
Asian	1 (0.9%)	0	2 (1.8%)	0	3 (0.7%)
Kellgren-Lawrence grade 3 [n(%)]	74 (66.1%)	74 (63.2%)	70 (63.6%)	74 (63.8%)	292 (64.2%)
Unilateral symptomatic OA [n(%)]	45 (40.2%)	35 (29.9%)	45 (40.9%)	39 (33.6%)	164 (36.0%)

Table 2. Baseline and change in mJSW by treatment and analysis group

	ITT mJSW			
	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 with PBO	0.10 (0.09)	0.06 (0.09)	-0.02 (0.09)	-
	Kellgren-Lawrence grade 2 mJSW			
	0.03 mg	0.07 mg	0.23 mg	PBO
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	0.09 (0.11)	-0.12 (0.09)	-0.08 (0.09)	-0.14 (0.11)
Week 52 compared with PBO	0.22 (0.16)	0.02 (0.15)	0.05 (0.14)	-
	Kellgren-Lawrence grade 3 mJSW			
	0.03 mg	0.07 mg	0.23 mg	PBO
N	74	74	70	74
Baseline (mm) [mean (SE)]	3.15 (0.14)	3.09 (0.12)	2.68 (0.15)	3.00 (0.16)
Week 52 change from baseline	-0.10 (0.08)	-0.07 (0.09)	-0.22 (0.09)	-0.14 (0.08)
Week 52 compared with PBO	0.04 (0.12)	0.08 (0.12)	-0.08 (0.13)	-
	mJSW [2-4] 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 with PBO	0.19 (0.13)	0.19 (0.12)	0.06 (0.13)	-

*Group classification based upon observed, non-imputed baseline mJSW

Results

Figure 1. Selecting mJSW [2-4] mm group resulted in reduced heterogeneity compared with other groups

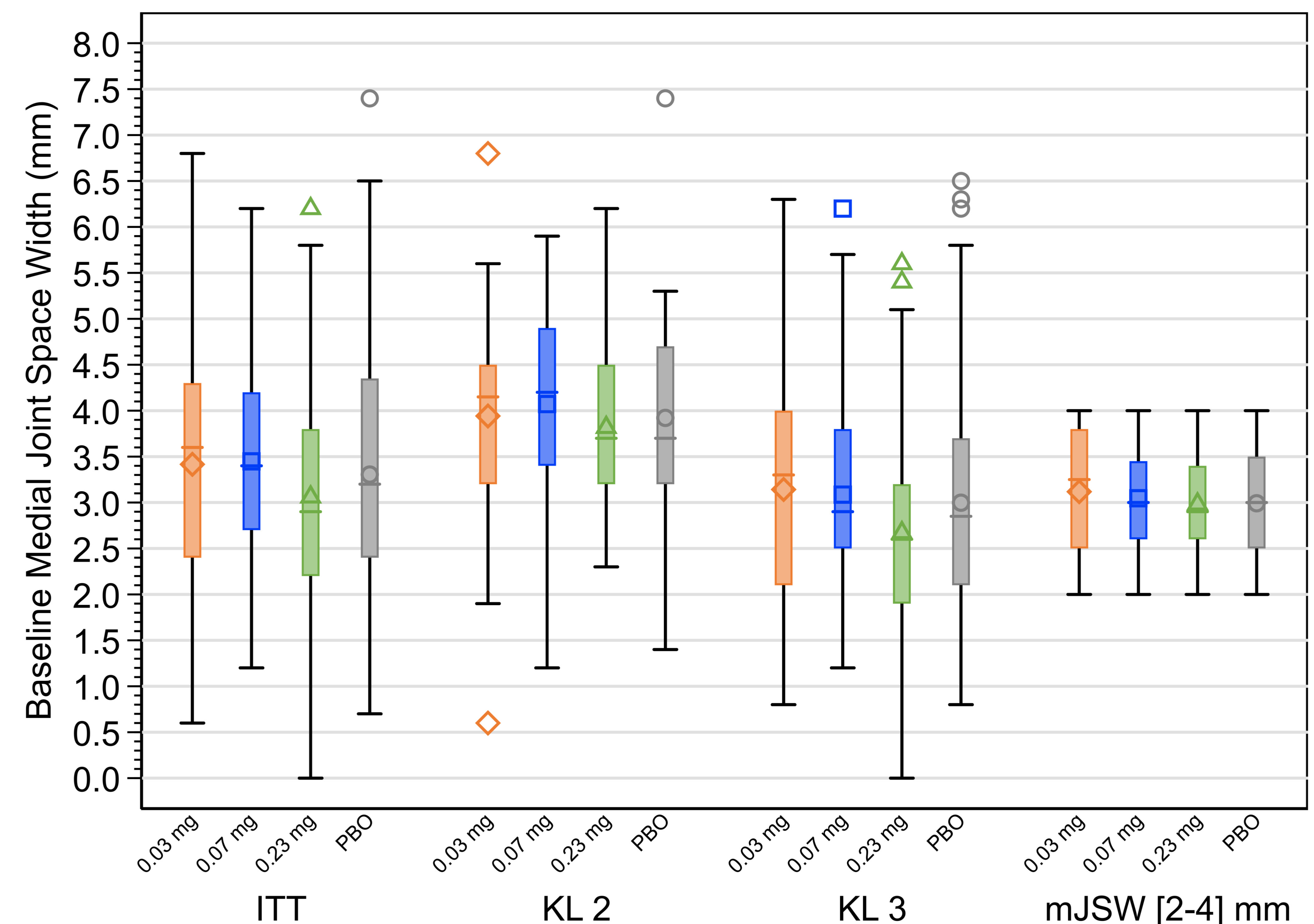


Figure 1. Box and whisker plot of baseline mJSW in ITT, by KL 2, KL 3, and ITT restricted within 2-4 mm. Interior bar: Median; Box: Interquartile [25th-75th] range; Whisker: 1.5x interquartile range. Interior symbol: Mean; Exterior symbol: Outlier.

Figure 2. mJSW [2-4] mm group showed increased SRMs compared with most other groups

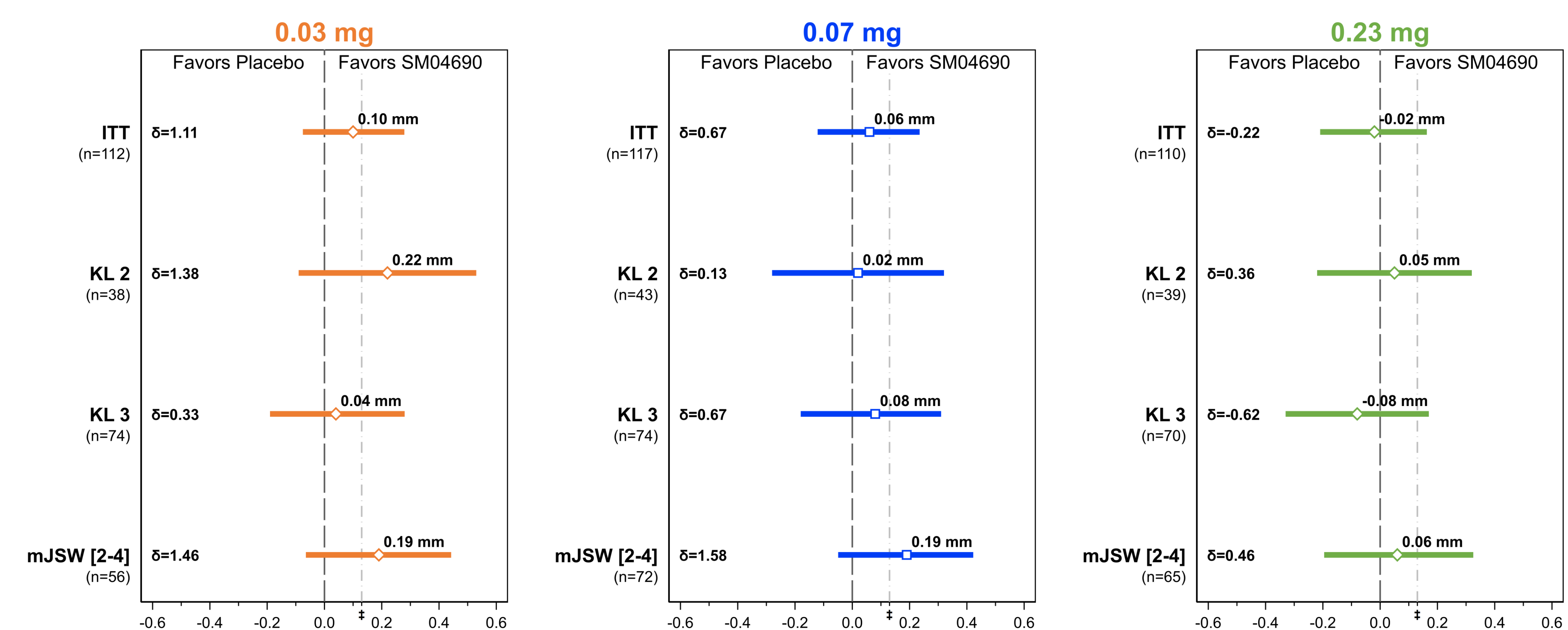


Figure 2. Ladder plots from baseline-adjusted ANCOVA compared treatment with PBO at Week 52 with SRMs reported as favoring SM04690. ±0.13 mm is radiographic minimal detectable difference.³ δ : SRM

Conclusions

- In this post-hoc analysis conducted among a subgroup with 2-4 mm mJSW at baseline, mJSW changes beyond radiographic measurement error (>0.13 mm)³ were observed with 0.03 mg and 0.07 mg SM04690 groups compared with PBO, suggesting baseline cartilage thickness is an important determinant for detection of change.
- A less heterogenous baseline reduces measurement variability, which may reduce the required population size in a clinical trial while maintaining statistical power.
- Future trials using radiography to assess structure modification in knee OA should consider mJSW [2-4] mm as a specific inclusion criterion.

References

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2. Bowes M, et al. *Ann Rheum Dis.* 2017;76:119-20.
3. Dupuis DE, et al. *Osteoarthritis Cartilage.* 2003;11:716-24.

