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## **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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**Purpose:** Limitations of Kellgen-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 radiographic JSW, MRI cartilage thickness and MRI bone area OA biomarkers over 12 months (Bowes et al. *EULAR* 2017). 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, 0.23 mg SM04690 or placebo (PBO) into the target (most painful) knee at Day 0. Radiographs (PA, weight-bearing, QuAP™ positioned), were taken at Weeks 0, 26 and 52 and centrally read by two blinded technicians to measure mJSW using a landmark-based methodology identifying the narrowest portion of the joint. A post-hoc comparison assessed the effect of baseline mJSW heterogeneity between groups (ITT, KL 2, KL 3, mJSW 2-4 mm) using box-and-whisker plots; changes in mJSW at Week 52 between groups were also compared using baseline-adjusted analysis of covariance; multiple imputation was used to account for missing mJSW measurements.

**Results:** Of 455 subjects, 161 were graded KL 2, 292 graded KL 3, and 258 had baseline 2-4 mm mJSW. Baseline mJSW heterogeneity was reduced in the 2-4 mm group compared to ITT, KL2, and KL3 groups (Figure 1). At Week 52, observed mJSW changes from baseline compared to PBO were beyond measurement error (>0.13 mm; Depuis et al. *OAC* 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 1).

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

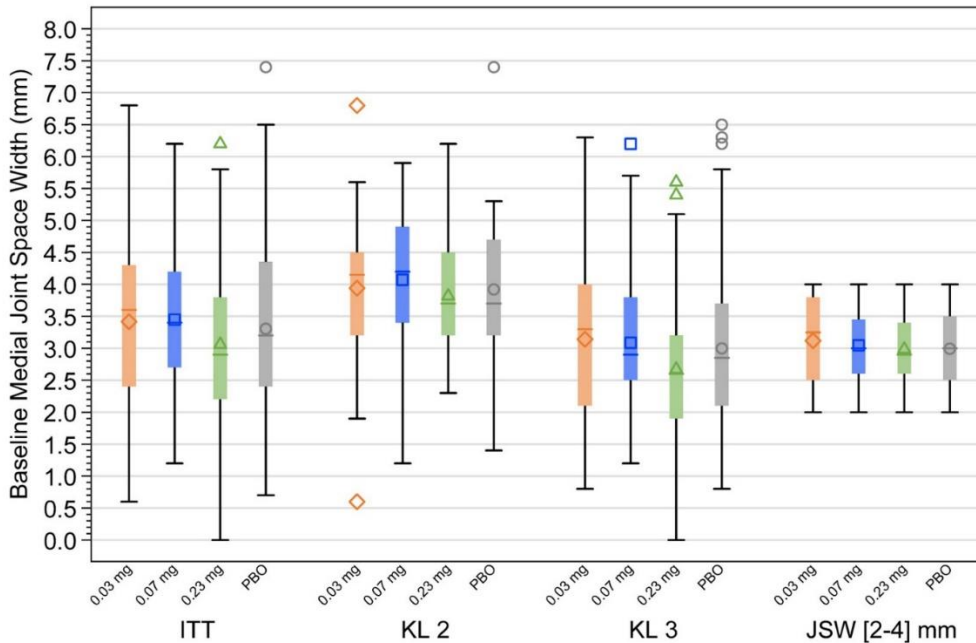


Figure 1. Box and Whisker plot of Baseline JSW in ITT, by KL 2, KL 3 and ITT restricted within 2-4 mm.  
 Interior Bar: Median; Box: Interquartile [25<sup>th</sup>-75<sup>th</sup>] range; Whisker: 1.5x Interquartile Range; Interior Symbol: Mean; Exterior Symbol: Outlier

**Table 1. Baseline and Change in mJSW by Treatment over Analysis Group**

	Intent-to-Treat Baseline mJSW			
	0.03 mg	0.07 mg	0.23 mg	PBO
<b>N</b>	112	117	110	116
<b>Baseline (mm) [Mean (SE)]</b>	3.42 (0.12)	3.45 (0.10)	3.06 (0.12)	3.31 (0.13)
<b>Week 52 Change from Baseline</b>	-0.04 (0.06)	-0.09 (0.06)	-0.16 (0.07)	-0.14 (0.06)
<b>Week 52 Compared to PBO</b>	0.10 (0.09)	0.06 (0.09)	-0.02 (0.09)	—

	Kellgren-Lawrence Grade 2 Baseline mJSW			
	0.03 mg	0.07 mg	0.23 mg	Placebo
<b>N</b>	38	43	39	41
<b>Baseline (mm) [Mean (SE)]</b>	3.94 (0.20)	4.07 (0.16)	3.82 (0.14)	3.92 (0.17)
<b>Week 52 Change from Baseline</b>	0.09 (0.11)	-0.12 (0.09)	-0.08 (0.09)	-0.14 (0.11)
<b>Week 52 Compared to PBO</b>	0.22 (0.16)	0.02 (0.15)	0.05 (0.14)	—

	Kellgren-Lawrence Grade 3 Baseline mJSW			
	0.03 mg	0.07 mg	0.23 mg	Placebo
<b>N</b>	74	74	70	74
<b>Baseline (mm) [Mean (SE)]</b>	3.15 (0.14)	3.09 (0.12)	2.68 (0.15)	3.00 (0.16)
<b>Week 52 Change from Baseline</b>	-0.10 (0.08)	-0.07 (0.09)	-0.22 (0.09)	-0.14 (0.08)
<b>Week 52 Compared to PBO</b>	0.04 (0.12)	0.08 (0.12)	-0.08 (0.13)	—

	Baseline mJSW between 2 to 4 mm*			
	0.03 mg	0.07 mg	0.23 mg	PBO
<b>N</b>	56	72	65	65
<b>Baseline (mm) [Mean (SE)]</b>	3.12 (0.09)	3.05 (0.06)	2.98 (0.07)	2.99 (0.07)
<b>Week 52 Change from Baseline</b>	-0.03 (0.08)	-0.03 (0.08)	-0.16 (0.09)	-0.22 (0.09)
<b>Week 52 Compared to PBO</b>	0.19 (0.13)	0.19 (0.12)	0.06 (0.13)	—

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