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

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Disclosures

Jeyanesh Tambiah	Samumed, LLC, employee and shareholder
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Christopher Swearingen	Samumed, LLC, employee and shareholder
Sarah Kennedy	Samumed, LLC, employee and shareholder
Alan Brett	Imorphics, subsidiary of Stryker
Mike Bowes	Imorphics, subsidiary of Stryker
Philip Conaghan	Flexion Therapeutics, AbbVie, Infirst, Medivir, Merck Serono, Novartis, ONO Pharmaceutical Co., Samumed, LLC

Background and purpose

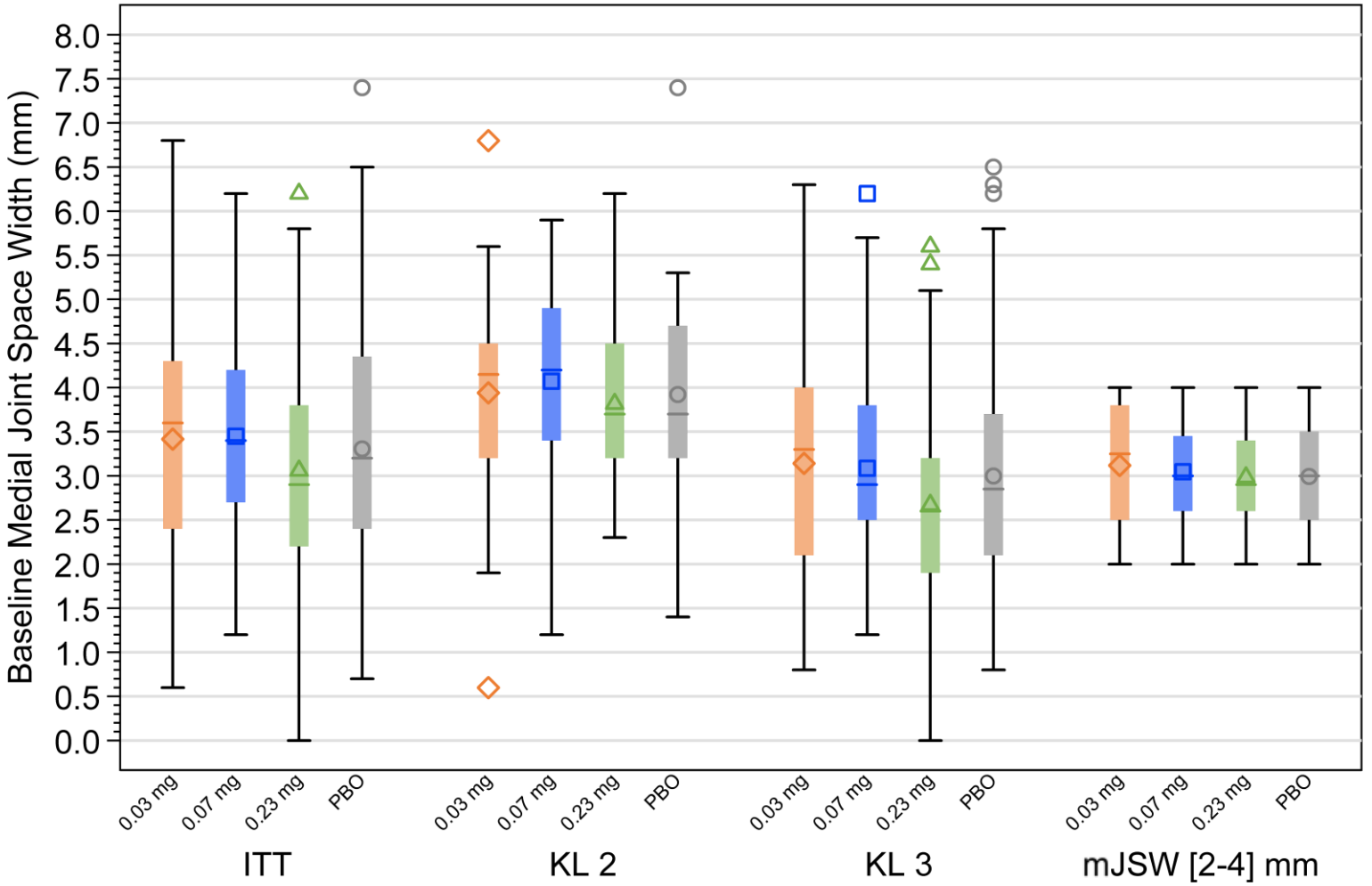
- Kellgren-Lawrence (KL) radiographic grading of knee osteoarthritis (OA) subjects:
  - Standard baseline knee OA disease classification in trials
  - Subjective evaluation of joint space narrowing and osteophyte formation
  - Leads to trial population with varied baseline joint space width (JSW), reducing structural measurement responsiveness and ability to detect change
- A more objective baseline measure may reduce JSW heterogeneity compared with KL grading and increase measurement responsiveness
  - Previous Osteoarthritis Initiative analysis suggested improved responsiveness for structural measurement in subjects with baseline medial JSW 2-4 mm[1]
- This hypothesis was further tested in a post-hoc analysis of phase 2 data for SM04690, a Wnt pathway inhibitor and potential disease modifying knee OA treatment

1. Bowes M, et al. (2017) *Ann Rheum Dis.*

Methods

- Knee OA subjects (KL grades 2-3) were randomized and received an intra-articular injection of SM04690 (0.03 mg, 0.07 mg, or 0.23 mg) or placebo (PBO) at Day 0
- Radiographs (PA, QuAP™ positioned) were taken at Weeks 0 and 52; mJSW was assessed using a blind read, fixed landmark-based technology
- Baseline heterogeneity was assessed with ‘box and whisker’ plots
- A post-hoc, exploratory analysis of subjects 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:
  - mJSW mean change from baseline at Week 52 compared with PBO / standard error
- Baseline-adjusted ANCOVA used to compare treatment with PBO. Multiple imputation was employed to account for missing data

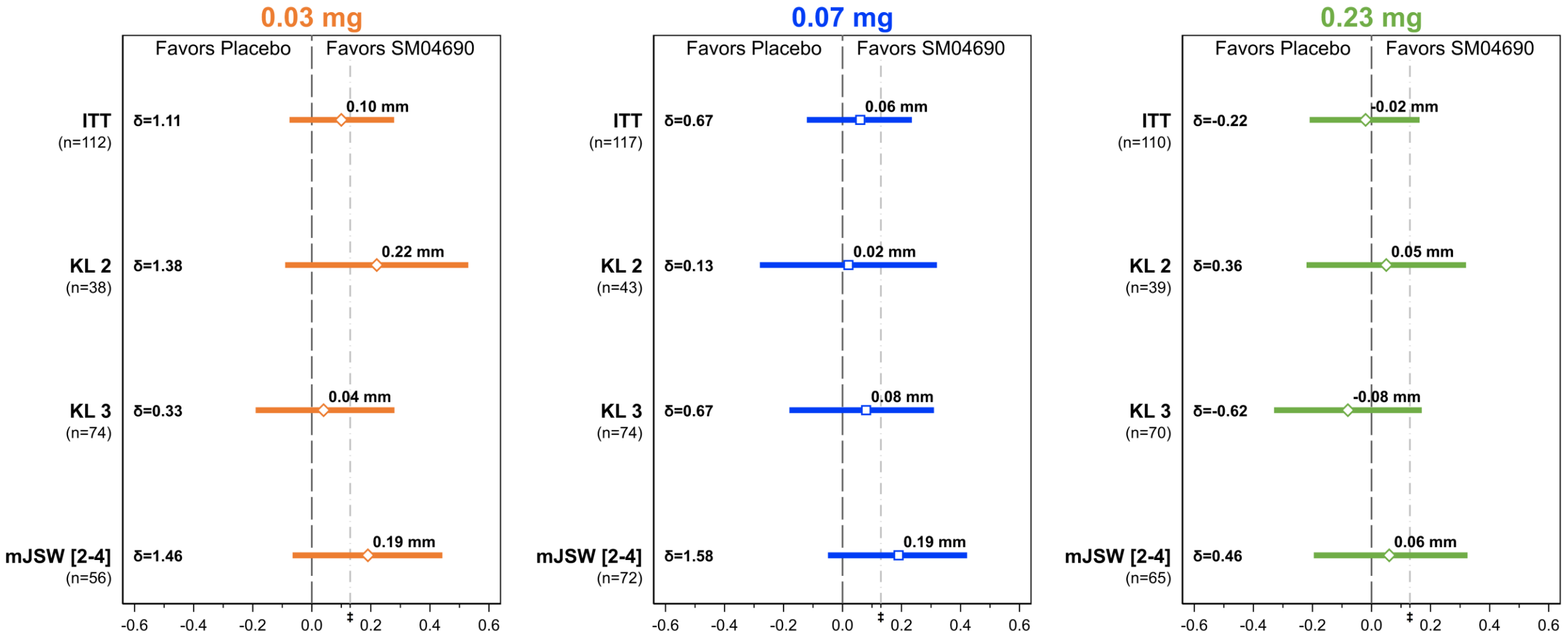
Selecting mJSW [2-4] mm group resulted in reduced heterogeneity compared with other groups



N per group	SM04690			
	0.03 mg	**0.07 mg**	**0.23 mg**	**Placebo**
ITT	112	117	110	116
KL 2	38	43	39	41
KL 3	74	74	70	74
mJSW [2-4] mm	56	72	65	65

Interior Bar: Median
Box: Interquartile [25 -75%] range
Whisker: 1.5x Interquartile Range
Interior Symbol: Mean
Exterior Symbol: Outlier
Post-hoc analysis

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



*Ladder plots from baseline-adjusted ANCOVA comparing treatment to placebo at Week 52 with Standardized Response Means (SRMs) reported as favoring SM04690. ‡0.13mm is radiographic Minimal Detectable Difference. (Dupuis, et al. (2003) *OAC.*) **δ**:SRM

This post-hoc analysis demonstrated:

- Week 52 mJSW changes compared with PBO were beyond minimal detectable difference (>0.13 mm)[1] for 0.03 mg and 0.07 mg SM04690 doses in the mJSW [2-4] mm group, and 0.03 mg dose in the KL 2 group
- mJSW [2-4] mm group increased SRMs for mJSW measurements compared with most other groups, and with reduced subject numbers compared with ITT
- A less heterogenous baseline mJSW can potentially increase responsiveness, reducing the knee OA trial population size needed to detect mJSW changes, while maintaining statistical power
- Radiographic mJSW [2-4] mm should therefore be considered as an inclusion criterion in knee DMOAD trials

1. Dupuis, et al. (2003) *OAC.*

Thank you