

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

Philip Conaghan¹, Jeyanesh R.S. Tambiah², Christopher J. Swearingen², Sarah Kennedy², Mike Bowes³, Alan Brett³, and Christian Lattermann⁴

¹University of Leeds, Leeds, United Kingdom, ²Samumed, LLC, San Diego, CA, USA, ³Imorphics, Manchester, United Kingdom, ⁴University of Kentucky, Lexington, KY, USA

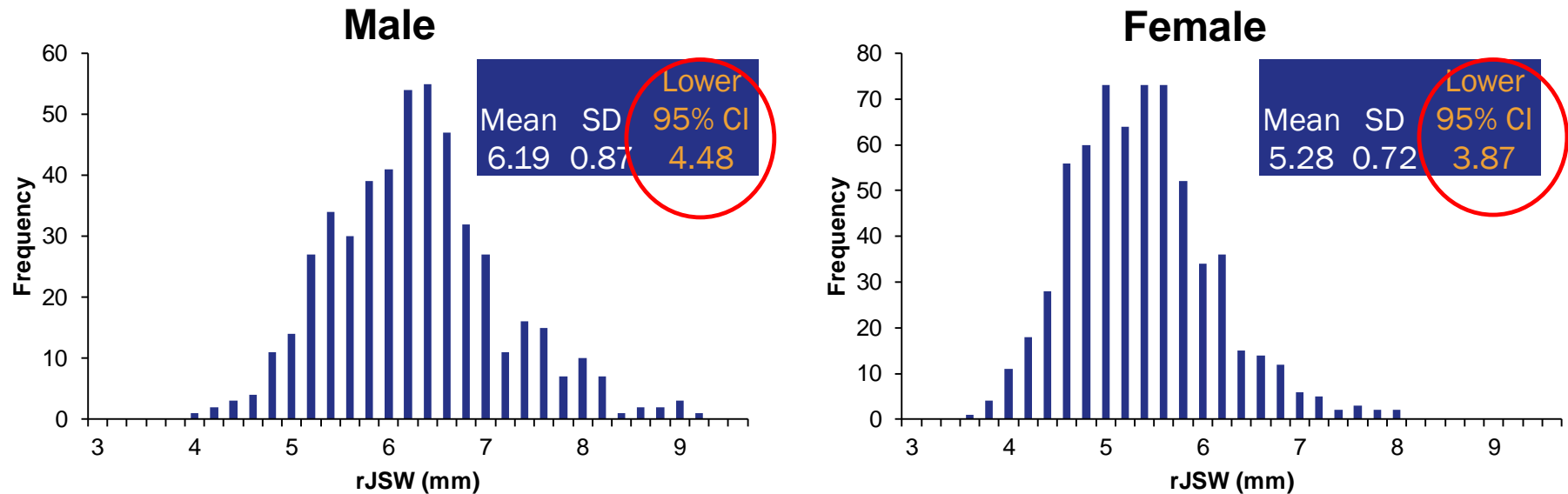
Disclosures

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

Background

- 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 (OAI) analysis suggested improved responsiveness for structural measurement in subjects with baseline medial JSW 2-4 mm¹

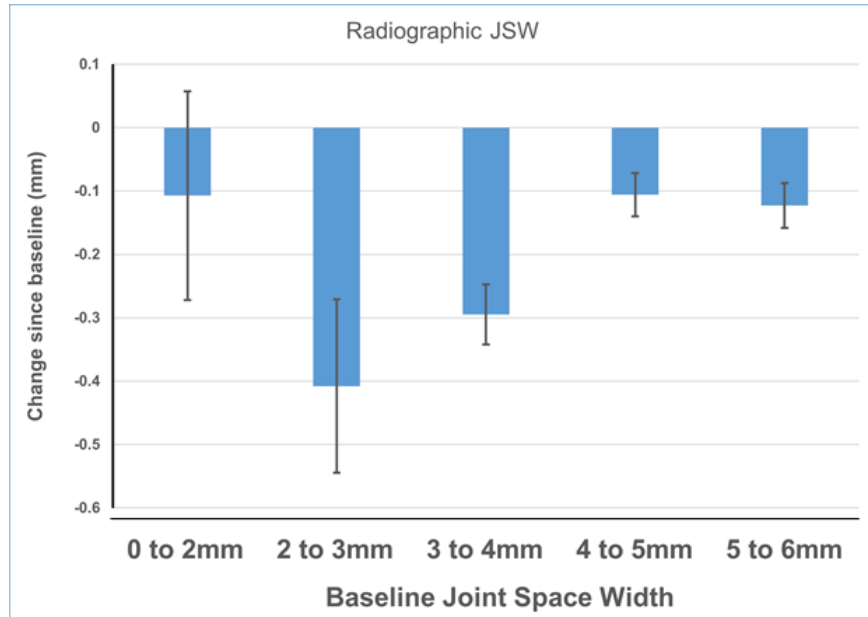
Radiographic joint space width distribution in KL 0 males and females in the OAI



Distribution of rJSW values for all KL0 knees (3,440 knees in total)

Lower 95% threshold is about 0.5 mm thicker for males than females – used 4 mm for both for convenience – a knee below 4 mm rJSW is likely to already fall outside healthy range

2 year change for all 3 measures using bins from baseline rJSW dataset = whole OAI with radiographic measures ~ 6500 knees



- Mean 2 year changes were greatest for the categories of 2-3 and 3-4 mm baseline rJSW
- Notably little change in knees with rJSW <2 mm for rJSW
 - This is why we set the lower boundary to 2 mm (in common with most clinical trials)
- Best pragmatic compromise is that baseline rJSW should be >2 mm, and <4 mm for maximum responsiveness

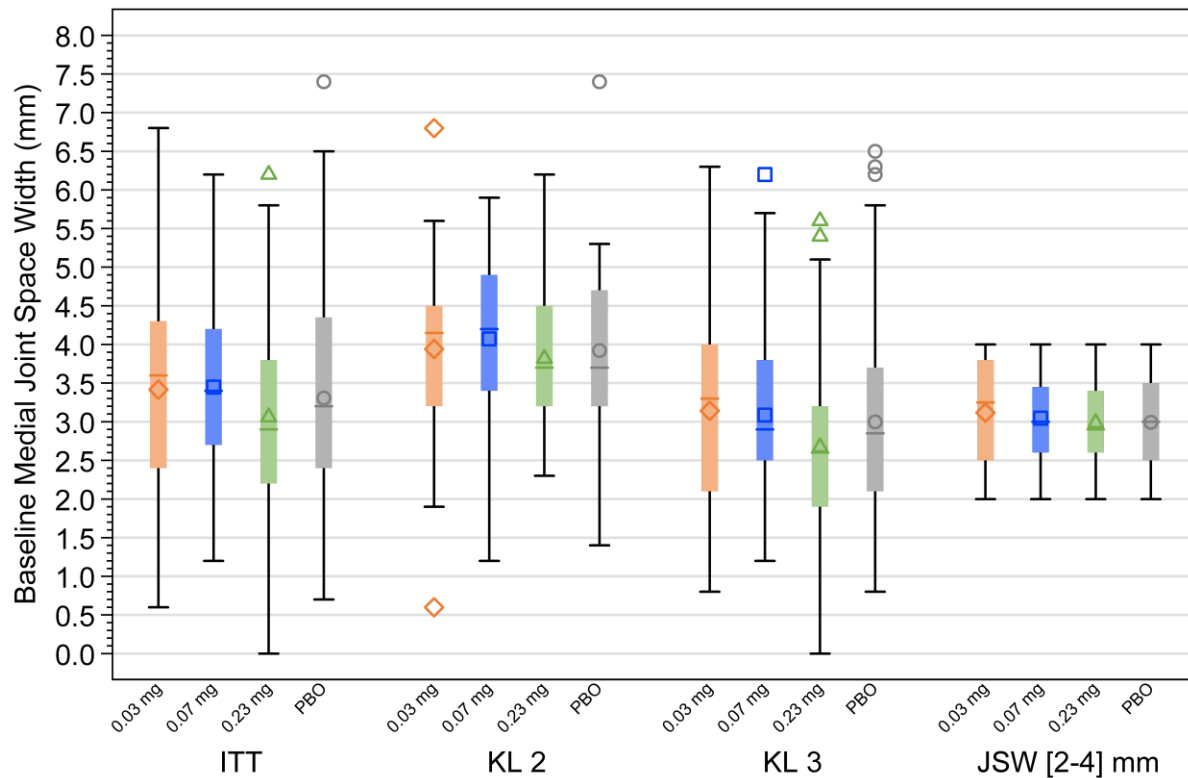
Does selecting subjects with baseline mJSW 2-4 mm improve responsiveness in a clinical trial setting?

- SM04690, a Wnt pathway inhibitor and potential disease modifying knee OA treatment in development was tested in a phase 2a trial (N=455)
- Knee OA subjects (KL grades 2-3) were randomized and received a single intra-articular injection of SM04690 (0.03 mg, 0.07 mg, or 0.23 mg) or placebo (PBO)
- Radiographs (PA, QuAP™ positioned) were taken at Weeks 0 and 52; mJSW was assessed using a blind read, fixed landmark-based technology
- 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) to assess effects on radiographic measurement responsiveness

Post-hoc analysis methodology

- Baseline heterogeneity of each group (ITT, KL 2, KL 3, mJSW [2-4] mm) was assessed with 'box-and-whisker' plots
- Standardized response means (SRMs) were calculated:
 - Week 52 mJSW mean change from baseline compared with PBO divided by standard error
- Baseline-adjusted ANCOVA used to compare SM04690 with PBO for mJSW at Week 52
- Multiple imputation was employed to account for missing data

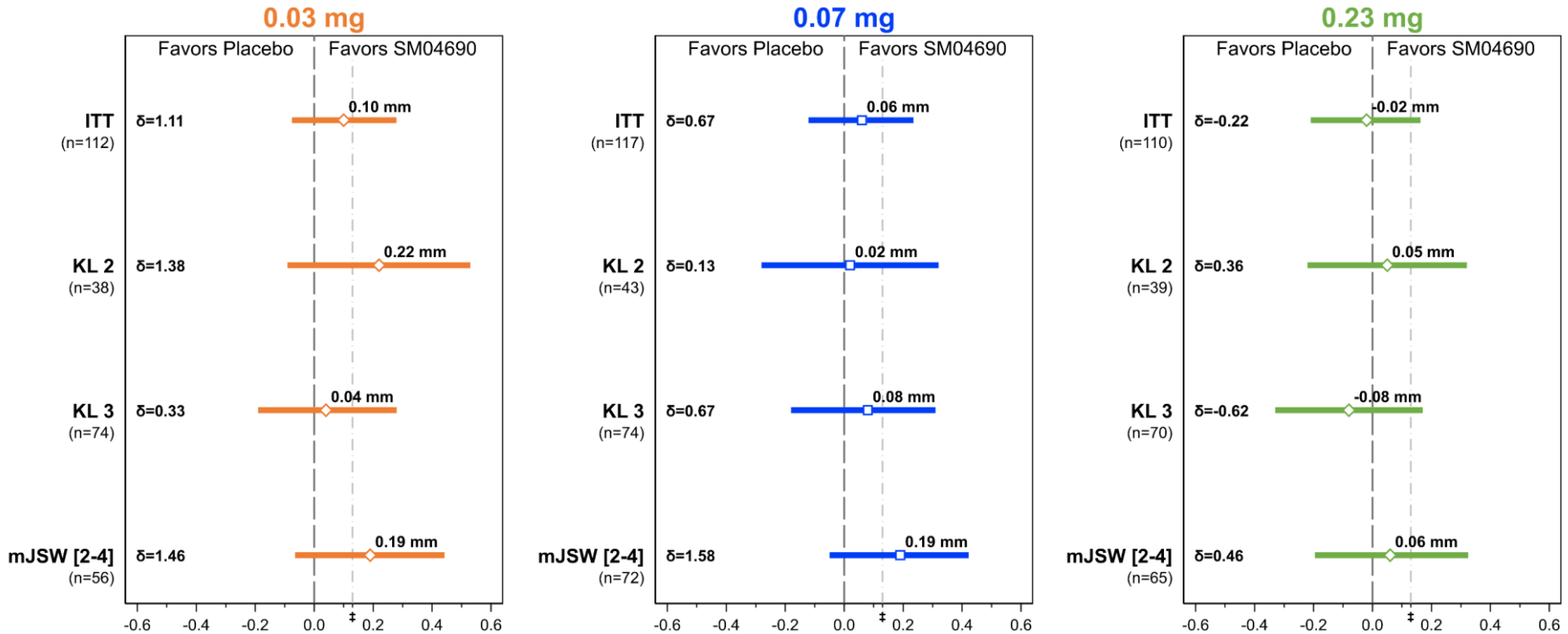
Selecting mJSW [2-4] mm group resulted in reduced heterogeneity compared with other groups



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

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



*Ladder plots from baseline-adjusted ANCOVA comparing treatment with 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

Thank you