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Optimizing Subject Selection in Knee Osteoarthritis Clinical Trials by Radiographic Joint Space Width: Post Hoc Clinical Response Analysis from a Phase 2b Trial of Wnt Pathway Inhibitor SM04690

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Background: Knee osteoarthritis (OA) trial radiographic inclusion criteria usually comprises Kellgren-Lawrence (KL) grading, which mixes features such as osteophytes and joint space narrowing and leads to study population heterogeneity. Selecting subjects with baseline medial joint space width (mJSW) 2-4 mm has been shown to reduce heterogeneity and improve responsiveness to radiographic change in comparison to broader knee OA populations.^{1,2} However, effects of baseline fixed mJSW on symptom responsiveness are unknown.

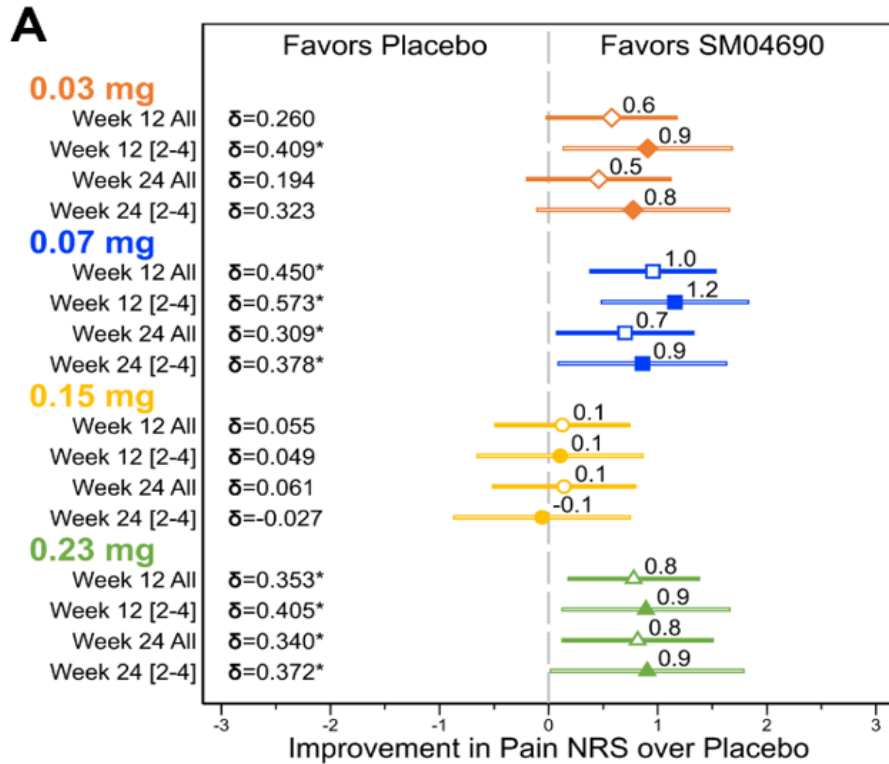
Objective: To evaluate the impact of baseline mJSW 2-4 mm on patient-reported outcomes (PROs) as measured by effect size in a 24-week Phase 2b trial of SM04690, a Wnt pathway inhibitor in development as a potential disease-modifying OA drug (DMOAD).

Methods: Knee OA subjects with KL grades 2-3 and Pain Numeric Rating Scale (NRS, [0-10]) ≥ 4 and ≤ 8 in the target knee and < 4 in the contralateral knee received a single IA 2 mL SM04690 injection (0.03, 0.07, 0.15, 0.23 mg), vehicle placebo (PBO), or sham (dry needle) in the target knee at baseline. PRO 24-week endpoints included change from baseline in weekly average of daily OA target knee pain by NRS, Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) Pain [0-100], WOMAC Physical Function [0-100], and Patient Global Assessment (PtGA) [0-100]. Primary results are presented elsewhere.³ A post hoc completer analysis of subject results with baseline mJSW 2-4 mm is reported.

Results: 635 subjects (91.4%) completed the study (mean age 59.0 [± 8.5] years, BMI 29.0 [± 4.0] kg/m², female 58.4%, KL3 57.3%). In both Full Analysis Set (FAS, all dosed subjects) and mJSW 2-4 mm subjects, significant improvements compared to PBO ($P < 0.05$) were seen in Pain NRS, WOMAC Pain, WOMAC Function, and PtGA for 0.07 mg and 0.23 mg SM04690 dose groups at Week 12 (Figure). The effect sizes were improved in the mJSW 2-4 mm group in comparison to the FAS for most doses at Weeks 12 and 24.

Conclusion: In this post hoc analysis of SM04690-treated knee OA subjects, those with baseline mJSW 2-4 mm showed increased PRO effect sizes compared to those in the FAS. Previous data also demonstrated SM04690-treated subjects with mJSW 2-4 mm had improved radiographic sensitivity to change. Data from SM04690 studies suggest mJSW 2-4 mm should be considered as an inclusion criterion for trials of potential knee DMOADs.

Figure: Ladder plot of effect size and treatment estimates (with 95% confidence intervals) for improvement in Pain NRS over PBO.



δ : Effect size *: $P < 0.05$

References:

1. Bowes M, et al. *ARD*. 2017
2. Yazici Y, et al. *Arthritis Rheumatol*. 2017
3. Yazici Y, et al. *Arthritis Rheumatol*. 2018