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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 Lorecivivint (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 Numerical 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 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.

Reference:

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

Figure:

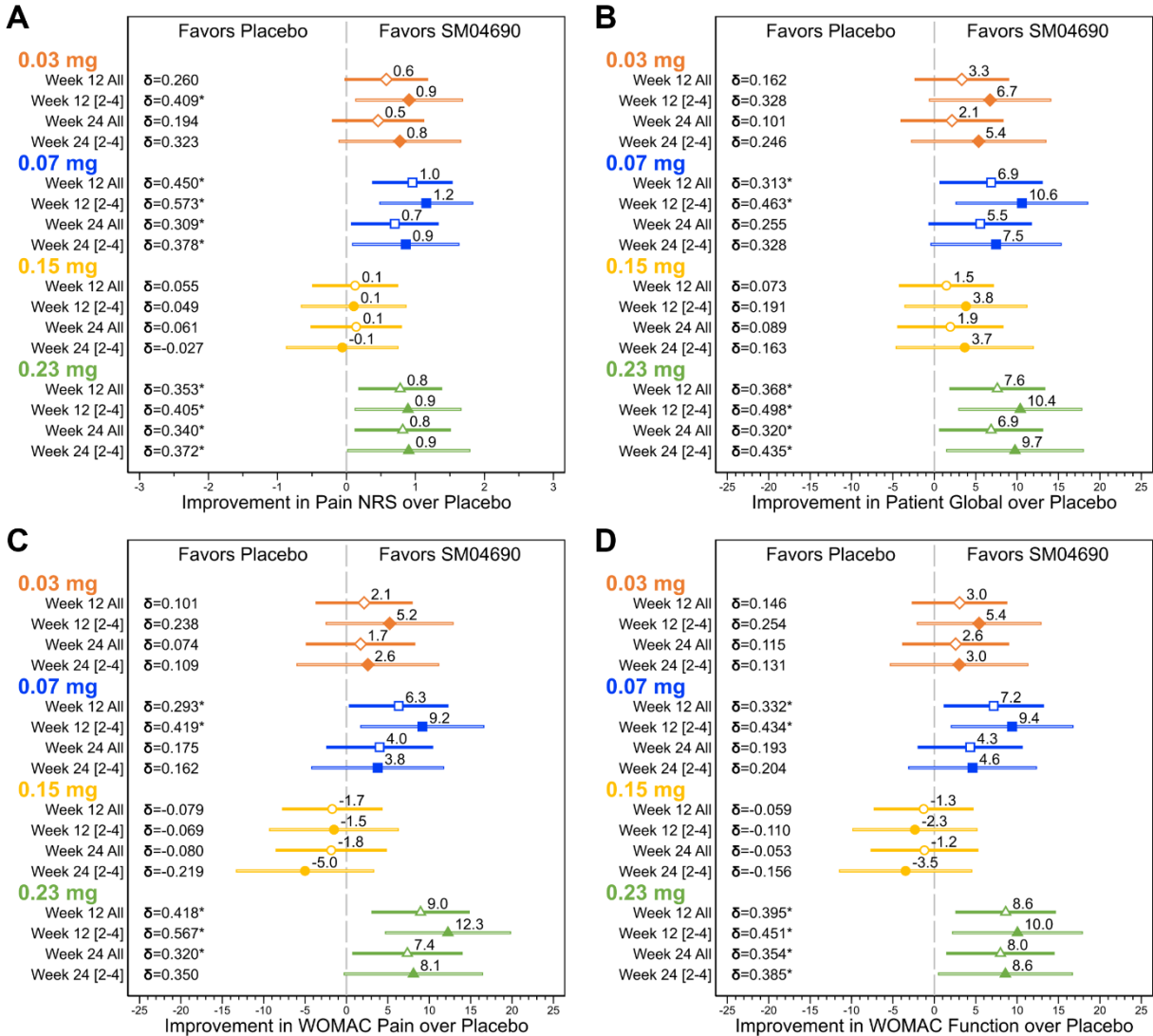


Figure. Ladder Plots of Effect Sizes and Treatment Estimates (with 95% confidence intervals) of Improvement over Placebo from Baseline-Adjusted ANCOVAs for All Subjects as well as All Subjects with baseline mJSW between 2 and 4 mm ([2-4]).

A) Pain NRS B) Patient Global C) WOMAC Pain D) WOMAC Function δ : Effect Size * $P < 0.05$