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Radiographic Outcomes Were Associated with Pain and Function Responses: Post-Hoc Analysis of Results from a Phase 2 Study of a Small Molecule Wnt Pathway Inhibitor, SM04690, for Knee Osteoarthritis Treatment

Program Book Publication:

Yusuf Yazici, Samumed, LLC

Abstract Supplement and Online Publication:

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Abstract Text

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Background/Purpose: Knee osteoarthritis (OA) is characterized by pain, disability and joint deformity due to articular cartilage degradation and bone remodeling. Wnt signaling is involved in these processes. SM04690, a potential disease modifying knee OA drug (DMOAD) is a small molecule, intra-articular Wnt pathway inhibitor. A phase 2, multicenter, 52-week, single-dose, randomized, placebo-controlled (PBO) trial was conducted, and a post-hoc analysis evaluated associations of radiographic changes with changes in pain and function.

Methods: Subjects were randomized to receive a 2 mL injection of 0.03 mg, 0.07 mg, 0.23 mg SM04690 or PBO in target (most painful) knees at Week 0. Western Ontario and McMaster Universities Arthritis Index (WOMAC) Pain [0-50] and Function [0-170] were assessed at Weeks 0, 4, 13, 26, 39 and 52 and target knee radiographs taken at Weeks 0, 26 and 52. Joint space narrowing was assessed by analysis of covariance adjusted for baseline medial joint space width (mJSW) with multiple imputation. A unilateral symptomatic knee subgroup was pre-specified and investigator defined by patient history and examination. Logistic regression analysis estimated associations between mJSW changes and pain and function changes for

subjects who achieved combined WOMAC Pain and Function improvement of >50% and >20 [scaled to 100] points.

Results: 455 subjects were enrolled (mean age 60.3 [±8.7] years, BMI 29.9 [±4.6] kg/m^2, 268 [58.9%] female, 293 [64.4%] Kellgren-Lawrence (KL) Grade 3, 164 [36.0%] unilateral symptomatic knee OA). Contralateral knee KL grade was equal / worse in 91% of intention to treat (ITT) population. Subjects who achieved a combined WOMAC Pain and Function improvement as defined above were: a) in ITT: 46 (48%) in 0.03 mg, 58 (55%) in 0.07 mg, 48 (53%) in 0.23 mg and 52 (55%) in PBO; and b) in unilateral symptomatic: 20 (56%) in 0.03 mg, 20 (63%) in 0.07 mg, 23 (64%) in 0.23 mg and 15 (47%) in PBO.

At Week 52, in ITT, PBO mean mJSW change was -0.14 [SE 0.06] mm. Mean mJSW changes in dose groups were 0.10 [SE 0.09] mm (0.03 mg), 0.06 [SE 0.09] mm (0.07 mg), and -0.02 [SE 0.09] mm (0.23 mg). In the unilateral symptomatic group, PBO mJSW change was -0.26 [SE 0.11] mm. Mean mJSW changes in dose groups were 0.24 [SE 0.16] mm (0.03 mg), 0.39 [SE 0.17] mm (0.07 mg, p=0.02), and -0.04 [SE 0.16] mm (0.23 mg) (**Figure 1**). Logistic regression for ITT showed area under the curve (AUC) > 0.7 was not achieved by any SM04690 dose. In the unilateral symptomatic group, 0.07 mg AUC = 0.78, indicating baseline-adjusted increase in mJSW was concordant with improvement in pain and function (**Figure 2**).

Conclusion: Radiographic outcomes from this study demonstrated treatment with SM04690 potentially maintained or increased mJSW compared to PBO. In unilateral symptomatic knee OA 0.07 mg subjects, changes in mJSW were predictive of WOMAC pain and function improvement. These data support potential of SM04690 as a DMOAD for treatment of knee OA.

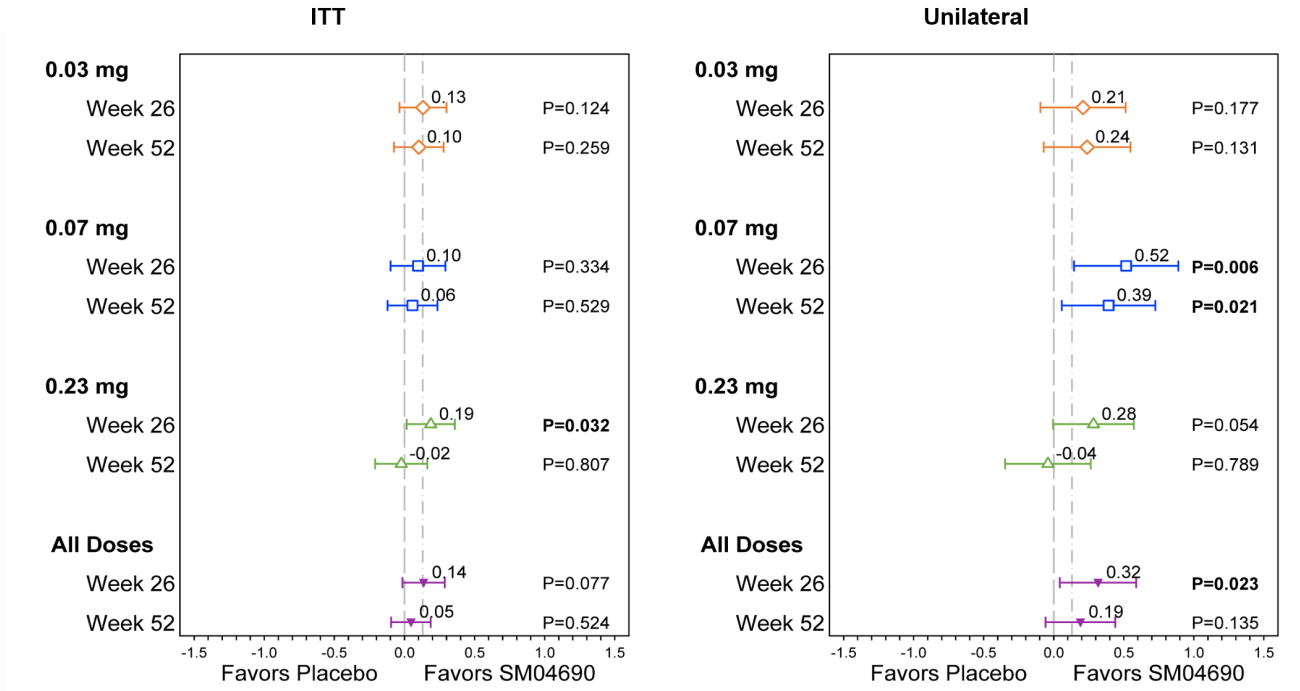

Figure 1. Ladder plots depicting change from baseline in medial joint space width between treatment groups to placebo adjusting for baseline. The x-axis represents change in mJSW of treatment vs. placebo; the long dashed line represents no difference between treatment and placebo, while a minimal clinical important difference is represented by the short dash line. Error bars represent 95% confidence interval.

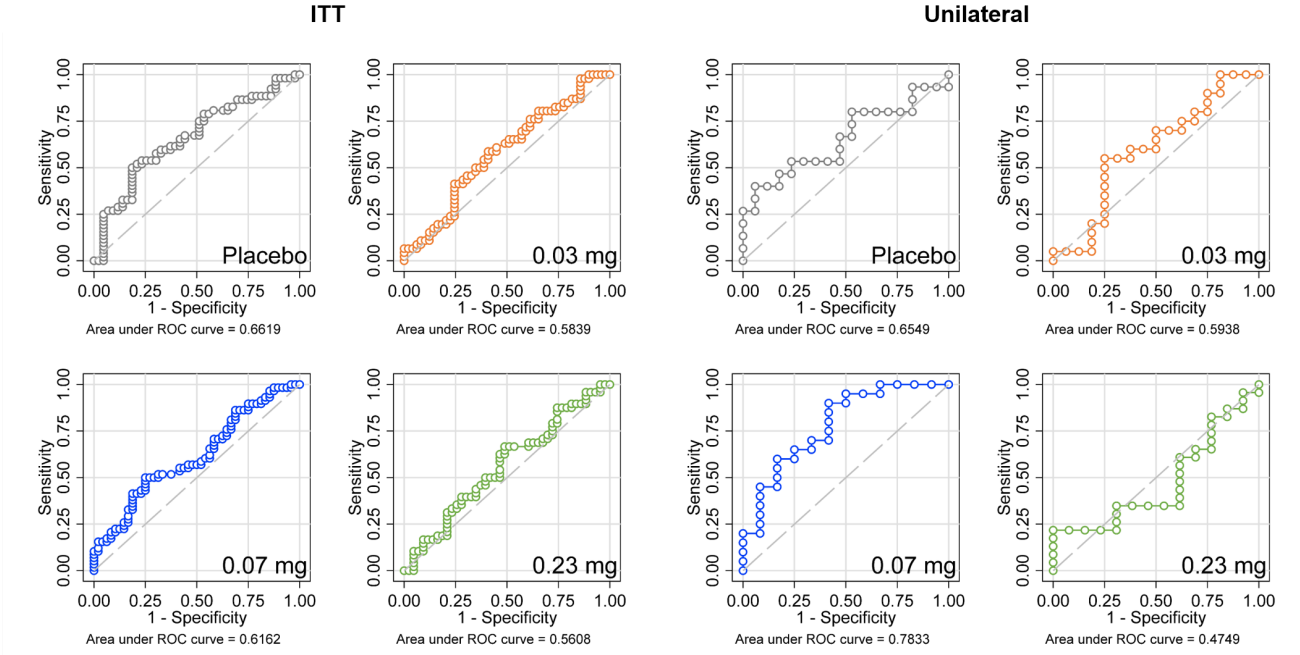

Figure 2. Receiver-Operator Characteristic (ROC) curves depicting prediction of WOMAC Pain and Function response by baseline-adjusted mJSW change.

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Submitter's E-mail Address:
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WNT Signaling, clinical trials, osteoarthritis, radiography and small molecules

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Additional Information:

Research Method:
Clinical

Trial Type:
Treatment

This abstract reports the results of a clinical trial not yet approved by a regulatory agency.

Trial Phase:
Phase II

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