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:

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Abstract Supplement and Online Publication:

These authors will be published in a supplement of the *Arthritis & Rheumatology* journal as well as the abstracts section of the ACR/ARHP Meeting Abstract website (acrabstracts.org).

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Abstract Text

*Character count for abstract text: 2717 (33 Characters Remaining)*

**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/m², 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.
Disclosure: Y. Yazici, Samumed, LLC, 3, Samumed, LLC, 1; T. E. McAlindon, None; A. Gibofsky, Pfizer Inc, 1, AbbVie, 1, Amgen, 1, Bristol-Myers Squibb, 1, Johnson & Johnson, 1, Regeneron, 1, AbbVie, 5, AbbVie, 8, Pfizer Inc, 5, Pfizer Inc, 8, Celgene, 8, Novartis Pharmaceutical Corporation, 8, Takeda, 5, Horizon, 5, Relburn, 5, Samumed, 5; N. E. Lane, LLP2A-Ale, 4; N. Skrepnik, Orthofix, 5,

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**Topic Selection:**  
Osteoarthritis – Clinical Aspects

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**Preferred Presentation Format:**  
No Preference

**Study Sponsors:**
- Samumed: Samumed, LLC designed, funded and monitored the study. Samumed also conducted data management, and statistical analysis.

**Keywords:**  
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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