Medical or Research Professionals/Clinicians

Topic area: Clinical topics by disease

Topic: 23. Osteoarthritis

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SAFETY, CLINICAL AND IMAGING OUTCOMES OF A NOVEL, INTRA-ARTICULAR, INJECTABLE, WNT INHIBITOR (SM04690) IN THE TREATMENT OF OSTEOARTHRITIS OF THE KNEE: EXPLORATORY ANALYSIS OF RESULTS FROM A 24 WEEK, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED PHASE 1 STUDY

Y. Yazici[*1], T. E. McAlindon[2], R. M. Fleischmann[3], A. Gibofsky[4], N. E. Lane[5], A. J. Kivitz[6], S. Majumdar[7], V. Strand[8], C. J. Swearingen[1], A. DiFrancesco[1], J. Tambiah[1], J. Hood[1], M. C. Hochberg[9]
[1]Samumed, LLC, San Diego, [2]Tufts Medical Center, Boston MA, [3]Metroplex Clinical Research Center, Dallas TX, [4] Hospital for Special Surgery, New York NY, [5]University of California Davis, Davis CA, [6]Altoona Arthritis and Osteoporosis Center, Altoona PA, [7]University of California San Francisco, San Francisco CA, [8]Stanford University, Palo Alto CA, [9] University of Maryland Medical Center, Baltimore MD, United States

My abstract has been or will be presented at a scientific meeting during a 12 months period prior to EULAR 2016: No

Is the first author applying for a travel bursary and/or an award for undergraduate medical students?: No

Background: Wnt signaling pathway plays a central role in joint tissue formation and altered Wnt signaling has been associated with cartilage loss in preclinical/clinical studies.[1] SM04690 is an IA small molecule inhibitor of the Wnt pathway.

Objectives: To report safety, clinical and imaging efficacy results from a 24 week phase 1 randomized, double-blind, placebo-controlled, dose-escalation clinical trial of a small molecule Wnt pathway inhibitor, SM04690, in knee OA.

Methods: Subjects with symptomatic, radiographic knee OA were randomized to receive a single IA injection in the target knee with either 0.03, 0.07, 0.23 mg SM04690 or vehicle (volume 2mLs) in a 4:1 SM04690 (N=16): vehicle (N=4) ratio. Safety, pharmacokinetics, WOMAC Total, Function, Pain subscales and strict OARSI responses[2], and radiographs were collected at baseline and during the 24 week trial. Analyses of efficacy outcomes were conducted using a modified Intention-To-Treat (mITT) baseline-adjusted analysis of covariance (ANCOVA) and logistic regression.

Results: A total of 61 subjects (female N=41, mean age 62.6 yrs, BMI 30.4 kg/m^2) were enrolled. Serum levels of SM04690 in all subjects were below limits of detection at all time points. Two dose limiting toxicities (DLTs), paroxysmal tachycardia, (also an SAE), and increased pain were reported in 0.07 mg cohort. A total of 72 AEs were reported in 28 (46%) subjects; 16 AEs in 8 subjects were considered possibly or probably related to study drug.

At Week 24, improved WOMAC Total Score was seen for both 0.03 mg and 0.07 mg cohorts (change from baseline, -27.4 and -26.6 respectively) compared to placebo (-21.7). (**Figure 1**). Odds of having an OMERACT-OARSI strict response in 0.07 mg cohort were higher than in the placebo cohort at week 12 (odds ratio=5.7, 95% CI: 1.1, 30.0, P=0.04); odds of an OMERACT-OARSI strict response in 0.03 mg cohort were higher than in the placebo cohort at week 24 (odds ratio=4.8, 95% CI: 0.9, 25.8, P=0.07) (**Figure 2**). Joint space width by radiographs showed no change from baseline to Week 24 in the 0.03 mg cohort (0.00 mm), an increase in the 0.07 mg cohort (0.49 mm), and a decrease in the 0.23 mg cohort (-0.15 mm), with the placebo cohort exhibiting a larger decrease (-0.33 mm). Compared to placebo, the change in joint space width seen in 0.07 mg cohort was statistically significant (P=0.02).

Image/graph:

Figure 1. Change from Baseline in WOMAC Total over time by Cohort

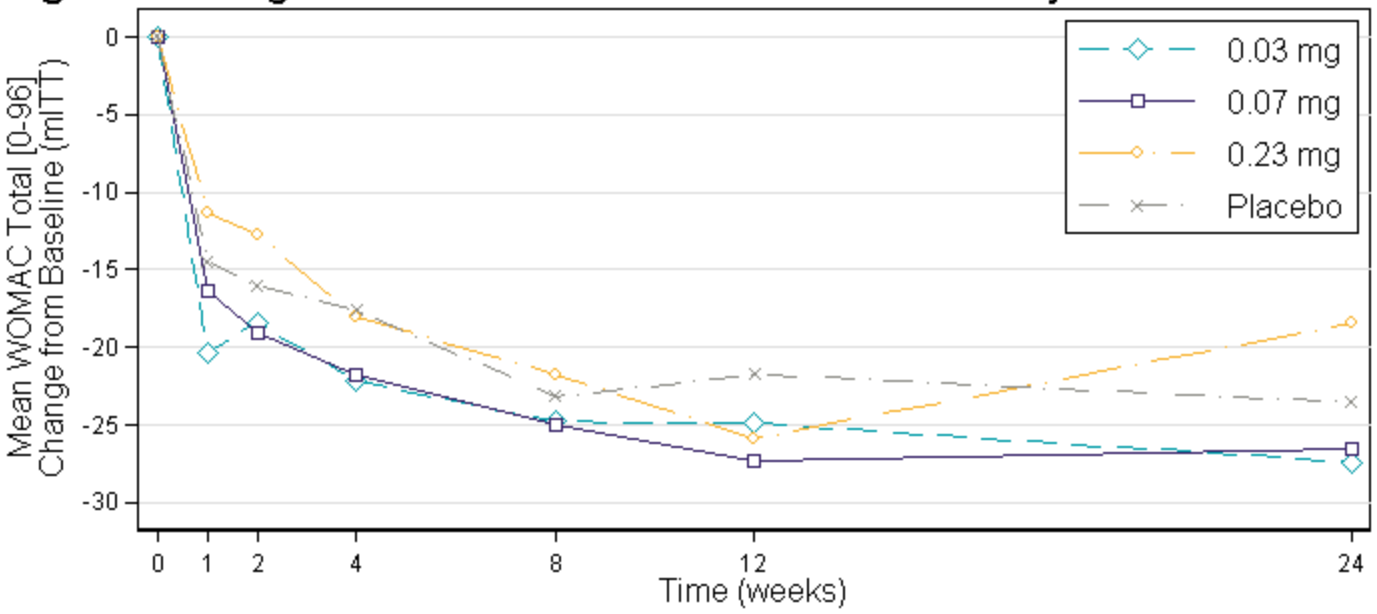
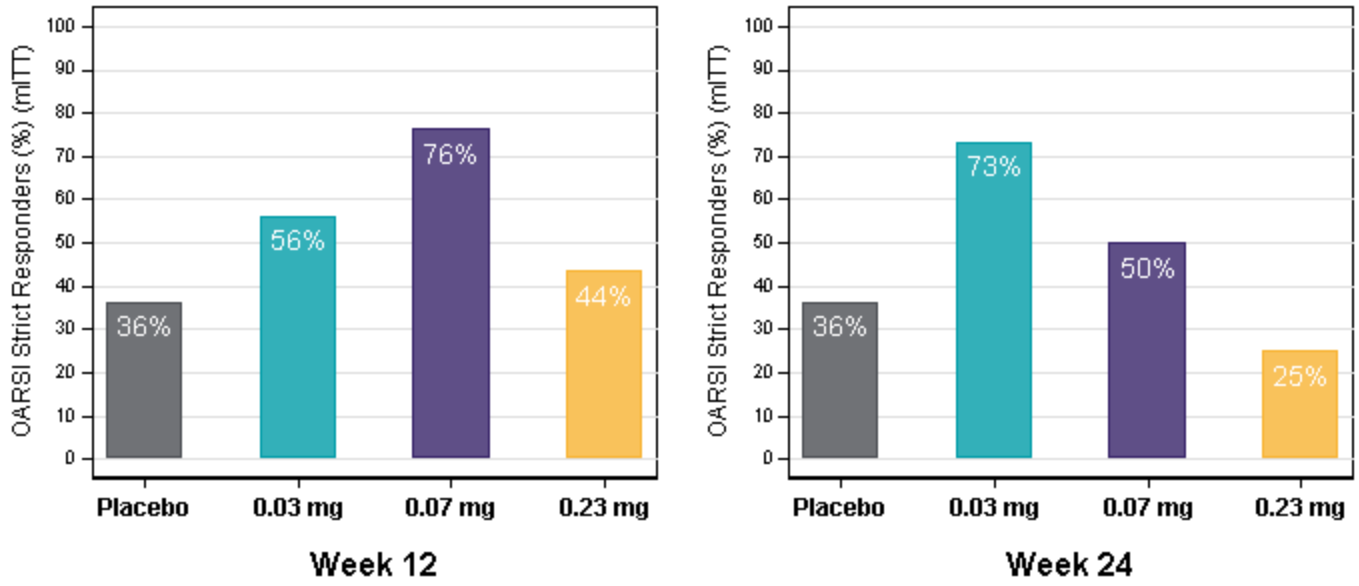


Figure 2. Strict OARSI Response by Cohort at Weeks 12 and 24



Conclusions: These phase 1 data suggested that an intra-articular injection with a novel Wnt inhibitor SM04690 into the knee of OA patients was safe and well-tolerated. SM04690 appeared to potentially improve function, pain and knee joint space width. Additional studies are underway to further evaluate safety, tolerability, efficacy and potential DMOAD properties.

References: 1. Gelse K. *Osteoarthr Cartil* 2002; 20(2): 162-71. 2. Pham T, et al. *J Rheumatol.* 2003;30(7):1648-1654

Disclosure of Interest: Y. Yazici Employee of: Samumed, LLC, T. McAlindon Consultant for: Pfizer, Regeneron, Flexion, Fidia, R. Fleischmann Grant/research support from: Samumed, LLC, A. Gibofsky Shareholder of: AbbVie, Amgen, J&J, GSK, Regeneron, Consultant for: AbbVie, Pfizer, Horizon, Iroko, Celgene, Novartis/Sandoz, Speakers bureau: AbbVie, Amgen, Celgene, Pfizer, N. Lane Consultant for: Samumed, LLC, A. Kivitz Grant/research support from: Samumed, LLC, Consultant for: Samumed, LLC, S. Majumdar Consultant for: Samumed, LLC, V. Strand Consultant for: Abbvie, Afferent, Bioventus, Carbylan, Eupraxia, Iroko, Pfizer, Regeneron, SKK, C. Swearingen Employee of: Samumed, LLC, A. DiFrancesco Employee of: Samumed, LLC, J. Tambiah Employee of: Samumed, LLC, J. Hood Employee of: Samumed, LLC, M. Hochberg Consultant for: Bioiberica, EMD Serono, Novartis Pharma AG, Plexxikon, Regeneron, Samumed, Theralogix LLC