Medical or Research Professionals/Clinicians

Topic area: Clinical topics by disease

Topic: 23. Osteoarthritis

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RADIOGRAPHIC OUTCOMES FROM A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PHASE 2 STUDY OF A NOVEL, INTRA-ARTICULAR, INJECTABLE, WNT PATHWAY INHIBITOR (SM04690) IN THE TREATMENT OF OSTEOARTHRITIS OF THE KNEE: WEEK 26 INTERIM ANALYSIS

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My abstract has been or will be presented at a scientific meeting during a 12 months period prior to EULAR 2017: No

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

Background: Knee osteoarthritis (OA) is characterized by pain, functional impairment, and joint space narrowing due to degradation of articular cartilage and bone remodeling. The Wnt pathway plays a central role in the formation of joint tissues, and altered Wnt signaling has been associated with cartilage loss in preclinical studies. SM04690 is a small molecule Wnt pathway inhibitor in development as a disease modifying OA drug (DMOAD) and administered as an intra-articular (IA) knee injection. A phase 2, multicenter, 52-week, single-dose, randomized controlled trial of SM04690 is ongoing in subjects with moderate to severe knee OA. Radiographic results from an interim analysis at 26 weeks are reported.

Objectives: To evaluate the safety and efficacy of SM04690 IA injection for the treatment of OA.

Methods: Subjects were randomized to receive a single, 2 mL, IA injection of 0.03 mg, 0.07 mg, 0.23 mg SM04690 or placebo into the target knee on Treatment Day 1. Safety, tolerability and efficacy outcomes were assessed at Weeks 4, 13 and 26. Target knee radiographs were taken at baseline and Week 26; change in medial joint space width (mJSW) was analyzed using an intention-to-treat analysis of covariance (ANCOVA) adjusting for baseline mJSW.

Results: 455 subjects (average age 60.3 [±8.7] years, 268 [58.9%] female, mean BMI 29.9 [±4.6] kg/m^2, 293 [64.4%] Kellgren-Lawrence Grade 3, 291 [64.0%] bilateral OA) were enrolled. At Week 26, 8 serious adverse events (SAEs) in 7 subjects were reported; these were deemed unrelated to drug by the investigators. Mean mJSW change from baseline was -0.22 [±0.64] mm in placebo cohort (table 1). Compared to placebo, mean mJSW change from baseline was -0.07 [±0.62] mm in the 0.03 mg (P=0.069), -0.16 [±0.95] mm in 0.07 mg (P=0.489), and -0.03 [±0.59] mm in 0.23 mg (P=0.019) cohorts, respectively. Increase in mean mJSW was observed in 50 (47.6%) subjects in 0.03 mg, 45 (40.5%) subjects in 0.07 mg, 40 (39.6%) subjects in 0.23 mg and 32 (30.5%) subjects in placebo cohorts, respectively (figure 1). Odds of mJSW improvement, defined as change in mJSW > 0, were increased 107% in 0.03 mg cohort compared to placebo (OR=2.1, 95% CI [1.2, 3.7], P=0.011), and odds of mJSW improvement were increased 69% for all SM04690 doses combined compared to placebo (OR=1.7, 95% CI [1.1, 2.7], P=0.029). Additionally, in *a priori* subanalyses, each treatment cohort, and all SM04690 doses combined, had higher probability of improving mJSW in the unilateral OA subgroup, with a 420% increase in odds of JSW response compared to placebo (all SM04690 groups combined OR=5.2, 95% CI [2.1, 12.8], P<0.001).

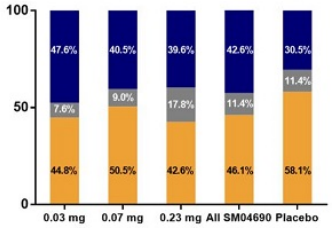
Image/graph:

Table 1. Medial joint space width at baseline and week 26

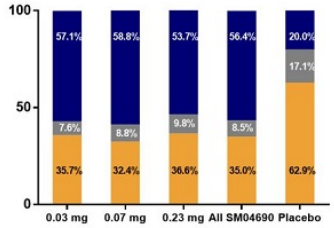
	0.03 mg	0.07 mg	0.23 mg	All SM04690	Placebo
N	**111**	**117**	**109**	**337**	**116**
Baseline (mm) [Mean (SD)]	3.41 (1.28)	3.45 (1.11)	3.08 (1.26)	3.34 (1.24)	3.33 (1.36)
Week 26 (mm) [Mean (SD)]					
Actual	3.38 (1.38)	3.30 (1.40)	3.06 (1.38)	3.25 (1.39)	3.10 (1.52)
Change from baseline	-0.07 (0.62)*	-0.16 (0.95)	-0.03 (0.59)**	-0.09 (0.74)	-0.22 (0.64)

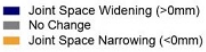
*0.03 mg vs PBO, p=0.069; **0.23 mg vs PBO, p=0.019

Figure 1. JSW Change at 26 weeks: All subjects



JSW Change at 26 weeks: Unilateral subjects





Conclusions: Radiographic outcomes from this interim analysis demonstrated that treatment with SM04690 maintained or increased JSW compared to placebo. These data support the continued development of SM04690 as a potential DMOAD for the treatment of knee OA. Further studies are ongoing.

Disclosure of Interest: Y. Yazici Shareholder of: Samumed, LLC, Employee of: Samumed, LLC, T. McAlindon Grant/research support from: Samumed, Consultant for: Astellas, Flexion, Pfizer, Regeneron, Samumed,and Seikugaku, A. Gibofsky Shareholder of: AbbVie, Amgen, J&J, GSK, Regneron, Consultant for: AbbVie, Pfizer, Horizon, Iroko, Celgene, Novartis/Sandoz, Samumed, Speakers bureau: AbbVie, Amgen, Celgene, Pfizer, N. Lane Consultant for: Samumed, LLC, N. Skrepnik Grant/research support from: Samumed, LLC, Consultant for: Orthofix and Sanofi, E. Armas Grant/research support from: Samumed, LLC, C. Swearingen Shareholder of: Samumed, LLC, Employee of: Samumed, LLC, A. DiFrancesco Shareholder of: Samumed, LLC, Employee of: Samumed, LLC, J. Tambiah Shareholder of: Samumed, LLC, Employee of: Samumed, LLC, M. Hochberg Consultant for: Bioberica, EMD Serono, Novartis Pharma AG, Plexxicon, Pfizer, Proximagen, Regeneron, Samumed, and Theralogix LLC