Clinical Outcomes from a Randomized, Double-Blind, Placebo-Controlled, Phase 2 Study of a Novel, Intra-Articular, Injectable, Wnt Pathway Inhibitor (SM04690) for the Treatment of Knee Osteoarthritis: Interim Analysis

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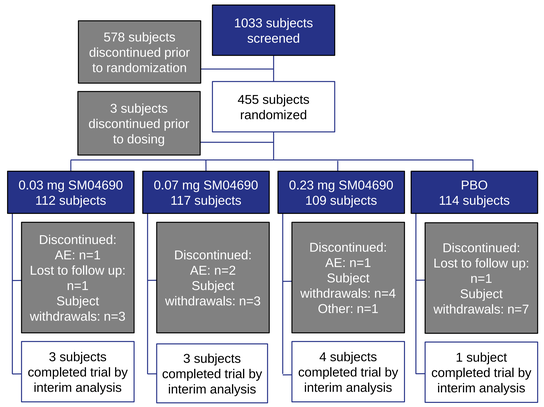
Background

- Knee osteoarthritis (OA) is characterized by pain, disability and joint deformity due to degradation of articular cartilage and bone remodeling.
- The Wnt signaling pathway has a role in tissue regeneration and has been linked to inflammatory processes.[1]
- SM04690, a small molecule Wnt pathway inhibitor in development as a potential disease modifying OA drug (DMOAD), was evaluated in a phase 2, multicenter, 52-week, randomized controlled trial in subjects with moderate to severe knee OA (NCT02536833).
- The primary objective was to evaluate change from baseline at Week 13 in Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain subscore. Secondary objectives included WOMAC Pain & Function, Physician Global Assessment of Disease Activity (MDGA) (Weeks 13 and 26), change in radiographic medial joint space width (reported in OP0166), and safety. An interim analysis at week 26 with additional outcomes from week 39 are reported.

Methods

- Subjects (N=455) with OA meeting American College of Rheumatology (ACR) criteria, Kellgren-Lawrence (KL) grade 2 or 3, and baseline pain 30-80 mm on a 0-100 mm pain visual analog scale (VAS) in the target knee were enrolled.
- Subjects were randomized to receive a single IA injection (2 mL) of 0.03 mg, 0.07 mg, or 0.23 mg SM04690, or placebo (PBO; phosphate buffered saline).
- WOMAC (NR3.1) Pain & Function, and MDGA were collected at Weeks 0, 4, 13, 26, 39, 52.
- Exploratory efficacy analyses were conducted using a baseline-adjusted repeated measures analysis of covariance (ANCOVA) in the Intention-to-Treat (ITT) population. Additional *a priori* defined subgroup analyses included subjects with investigator-determined Unilateral OA with or without widespread chronic pain (WP, defined as Widespread Pain Index score ≥ 4 and Symptom Severity score ≥ 2).[2]

SM04690-OA-02 Subject Disposition



Summary

- SM04690 appeared to be well tolerated (Table 2).
- In the ITT population, clinically meaningful improvements (MCID ≥10%) vs. baseline were seen for all groups and PBO at all timepoints in WOMAC Pain (Figure 1), WOMAC Function (Figure 2), and MDGA.
- In Unilateral symptomatic patients, significant improvements vs. PBO were observed at Week 39 in WOMAC Pain and Function for the all-SM04690 cohort (Figures 1 and 2). Significant improvements in MDGA were observed at Week 13 (0.03 mg, all-SM04690), Week 26 (0.07 mg, all-SM04690), and Week 39 (0.07 mg, 0.23 mg, all-SM04690) in this subgroup (*P*<0.05 vs PBO).
- In Unilateral symptomatic patients without WP, significant improvements vs. PBO were observed in WOMAC Pain at Week 26 (0.07 mg) and Week 39 (0.07 mg, all-SM04690), and in WOMAC Function at Week 26, (0.07 mg) and Week 39 (0.07 mg, all-SM04690) (Figures 1 and 2). Significant improvements in MDGA were observed at Week 13 (0.03 mg, 0.07 mg, all-SM04690), Week 26 (0.07 mg, all-SM04690), and Week 39 (0.07 mg, all-SM04690) in this subgroup (*P*<0.05 vs PBO).

Table 1. SM04690-OA-02 Demographics (ITT)

	0.03 mg	0.07 mg	0.23 mg	Placebo	All subjects
N	**112**	**117**	**110**	**116**	**455**
Age at Consent (Years) [Mean (SD)]	59.0 (9.0)	60.0 (8.2)	61.3 (8.7)	60.7 (8.9)	60.3 (8.7)
BMI (kg/m²) [Mean (SD)]	29.8 (4.82)	30.84 (4.75)	29.68 (4.46)	29.20 (4.41)	29.89 (4.64)
Female [n(%)]	68 (60.7%)	60 (51.3%)	68 (61.8%)	72 (62.1%)	268 (58.9%)
Race [n(%)]					
White	92 (82.1%)	102 (87.2%)	96 (87.3%)	102 (87.9%)	392 (86.2%)
African-American	18 (16.1%)	14 (12.0%)	12 (10.9%)	10 (8.6%)	54 (11.9%)
Asian	1 (0.9%)	0	2 (1.8%)	0	3 (0.7%)
Kellgren-Lawrence Grade 3 [n(%)]	74 (66.1%)	74 (63.2%)	71 (64.5%)	74 (63.8%)	193 (64.4%)
Unilateral Osteoarthritis [n(%)]	45 (40.2%)	35 (29.9%)	45 (40.9%)	39 (33.6%)	164 (36.0%)

Table 2. SM04690-OA-02 Safety (Safety Population - Interim Analysis)

	0.03 mg	0.07 mg	0.23 mg	Placebo	All Subjects
SAE(s) Reported* [n(%)]	1/1 (0.9)	2/1 (0.9)	2/2 (1.9)	2/2 (1.8)	8/7 (1.5)
AE(s) Reported >1% *[n(%)]*					
Arthralgia	7/7 (6.4)	10/10 (8.8)	8/6 (5.8)	4/4 (3.7)	35/31 (6.9)
Upper respiratory tract infection	3/3 (2.7)	0/0 (0.0)	1/1 (1.0)	3/3 (2.8)	8/8 (1.8)
Headache	0/0 (0.0)	2/2 (1.8)	1/1 (1.0)	4/4 (3.7)	7/7 (1.5)
Hypertension	0/0 (0.0)	3/3 (2.6)	3/3 (2.9)	1/1 (0.9)	7/7 (1.5)
Nasopharyngitis	3/3 (2.7)	2/2 (1.8)	1/1 (1.0)	0/0 (0.0)	7/7 (1.5)
Urinary tract infection	2/2 (1.8)	1/1 (0.9)	3/2 (1.9)	2/2 (1.8)	8/7 (1.5)
Osteoarthritis	2/2 (1.8)	1/1 (0.9)	1/1 (0.9)	4/2 (1.8)	8/6 (1.3)
Bursitis	1/1 (0.9)	3/2 (1.8)	2/2 (1.9)	0/0 (0.0)	6/5 (1.1)
Fall	2/2 (1.8)	2/2 (1.8)	0/0 (0.0)	1/1 (0.9)	5/5 (1.1)
Joint Effusion	1/1 (0.9)	2/2 (1.8)	1/1 (1.0)	1/1 (0.9)	5/5 (1.1)

SAEs Reported: Hypertensive crisis, Cholecystitis acute, Gall bladder adenocarcinoma, Diverticulitis, Uterine prolapse, Patella fracture, Osteoarthritis, and Non-cardiac chest pain. All SAEs deemed unrelated to study medication by Investigator.

	0.03 mg	0.07 mg	0.23 mg	Placebo
Subjects Reporting AE(s) [N(%)]	40 (36.4)	43 (37.7)	35 (33.7)	35 (32.1)

Results

Figure 1. WOMAC Pain Subscore [0-50] Change from Baseline

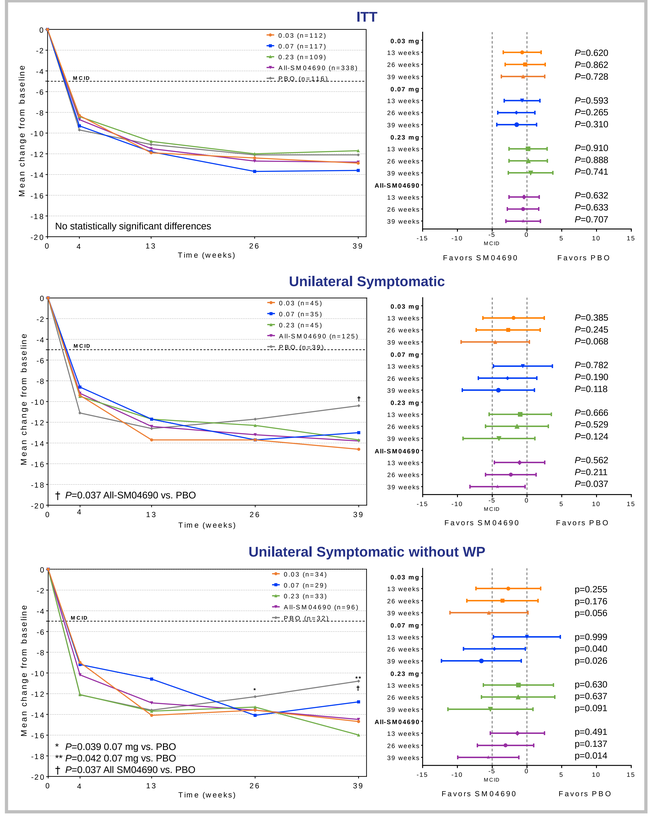
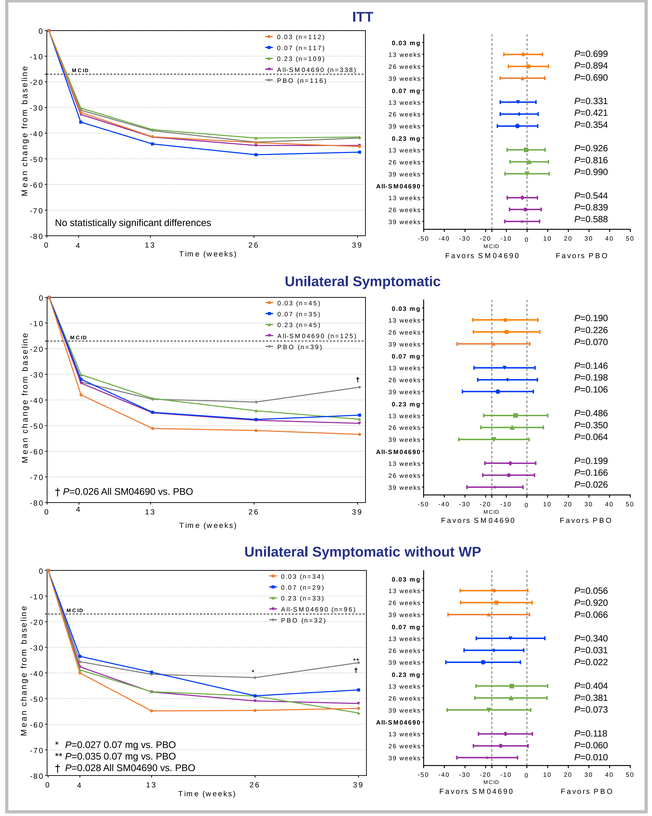


Figure 2. WOMAC Function Subscore [0-170] Change from Baseline



Discussion

- In this phase 2 interim analysis, SM04690 appeared to be well tolerated; SM04690 and PBO (ITT) demonstrated clinically relevant outcome improvements from baseline at all timepoints.
- In Unilateral symptomatic patients, consistent improvements were seen in WOMAC Pain and Function 0.03 mg, 0.07 mg, and all-SM04690 arms vs. PBO.
- Unilateral symptomatic patients without WP may have been better able to discriminate pain responses, as evidenced by increased effect sizes, compared to the heterogenous ITT and Unilateral symptomatic patients.
- These data provided evidence that SM04690 improved clinical outcomes of knee OA subjects, and further studies to evaluate the safety and efficacy of SM04690 as a potential DMOAD for knee OA are ongoing (NCT03122860).

References: 1. Lambert, et al. *Arth & Rheum.* 2014; 66(4): 960-8. 2. Wolfe, et al. *Sem in Arth and Rheum.* 2016; 46: 319-29.

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