A 52-Week, Randomized, Double-Blind, Phase 2 Study of an Intra-articular Wnt Pathway Inhibitor (SM04690) for Osteoarthritis

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Background

- The Wnt pathway regulates bone and cartilage stem cell differentiation in joints and has been implicated in osteoarthritis (OA) pathogenesis[1]
- SM04690 is a Wnt pathway inhibitor in development as a potential disease-modifying OA drug for knee OA
- A phase 2a study was conducted to identify target population and dose
- Primary endpoint was change from baseline in WOMAC Pain at Week 13
- Secondary endpoints included change in WOMAC Pain, Function, and radiographic medial joint space width (mJSW) at Week 52

Methods

- Knee OA subjects with Kellgren-Lawrence (KL) grades 2-3 received a single 2 mL injection of SM04690 (0.03, 0.07, 0.23 mg) or saline (PBO) in the most painful knee
- WOMAC Pain and Function subscores were measured (Weeks 0, 4, 13, 26, 39, 52)
- Knee radiographs (PA, weight-bearing, positioned in 10 degrees fixed-flexion) were taken (Weeks 0, 26, 52)
- Analysis of covariance adjusted for baseline with multiple imputation in the intent-to-treat (ITT) population was performed
- An additional pre-specified subgroup analysis of subjects with unilateral symptoms (UNI), defined by investigator by history and physical exam, was studied

Results

- 455 subjects (mean age 60.3 [±8.7] years, BMI 29.9 [±4.6] kg/m2, KL 3 [64.4%], UNI [36.0%]) were enrolled **(Table 1)**
- In ITT, all subjects in all treatment groups achieved >20 point improvement over baseline from Week 13 - 52, beyond the minimal clinically important differences (MCID, defined as 10 points), but differences were not significant compared to PBO
- In the UNI subgroup (n=164), 0.07 mg SM04690 showed statistically significant improvements in WOMAC Pain (-8.73, P=0.049), Function (-10.26, P=0.036), and mJSW (0.39 mm, P=0.021) at Week 52 compared to PBO (**Figure**)
- At Week 26 in ITT, the 0.23 mg SM04690 group showed maintenance in mJSW compared to PBO (*P*=0.032). At Weeks 26 and 52, mJSW in UNI 0.07 mg subjects was statistically significantly different and beyond 0.13 mm, the minimum detectable difference[2], compared to PBO (*P*=0.006 and *P*=0.021, respectively)
- Rates of adverse events (AEs) were not different between SM04690 and PBO subjects (Table 2)

Discussion

- The primary endpoint of WOMAC Pain change from baseline compared to PBO at Week 13 in ITT was not achieved
- UNI 0.07 mg and 0.03 mg subgroups showed trends in WOMAC Pain and Function improvement compared to PBO from 13 through 52 weeks, potentially due to better pain discrimination than subjects with bilateral symptoms
- At 52 weeks, mJSW was improved in UNI subjects beyond 0.13 mm, the minimum detectable difference[2], for the 0.03 mg and 0.07 mg dose groups and significantly greater than PBO for the 0.07 mg dose group
- UNI 0.07 mg dose group appeared to demonstrate the most consistent improvements of all dose groups over PBO in both symptoms and radiography at 52 weeks
- SM04690 appeared safe and well tolerated

Conclusions

- **Clinical and radiographic outcomes in a key subgroup suggested that SM04690 has potential as a disease-modifying osteoarthritis drug for knee OA treatment**
- **A target population of knee OA subjects with unilateral symptoms and a potential optimal dose of 0.07 mg were identified**
- **SM04690 appeared safe and well tolerated**
- **Phase 3 trials will begin in 2019**

Results

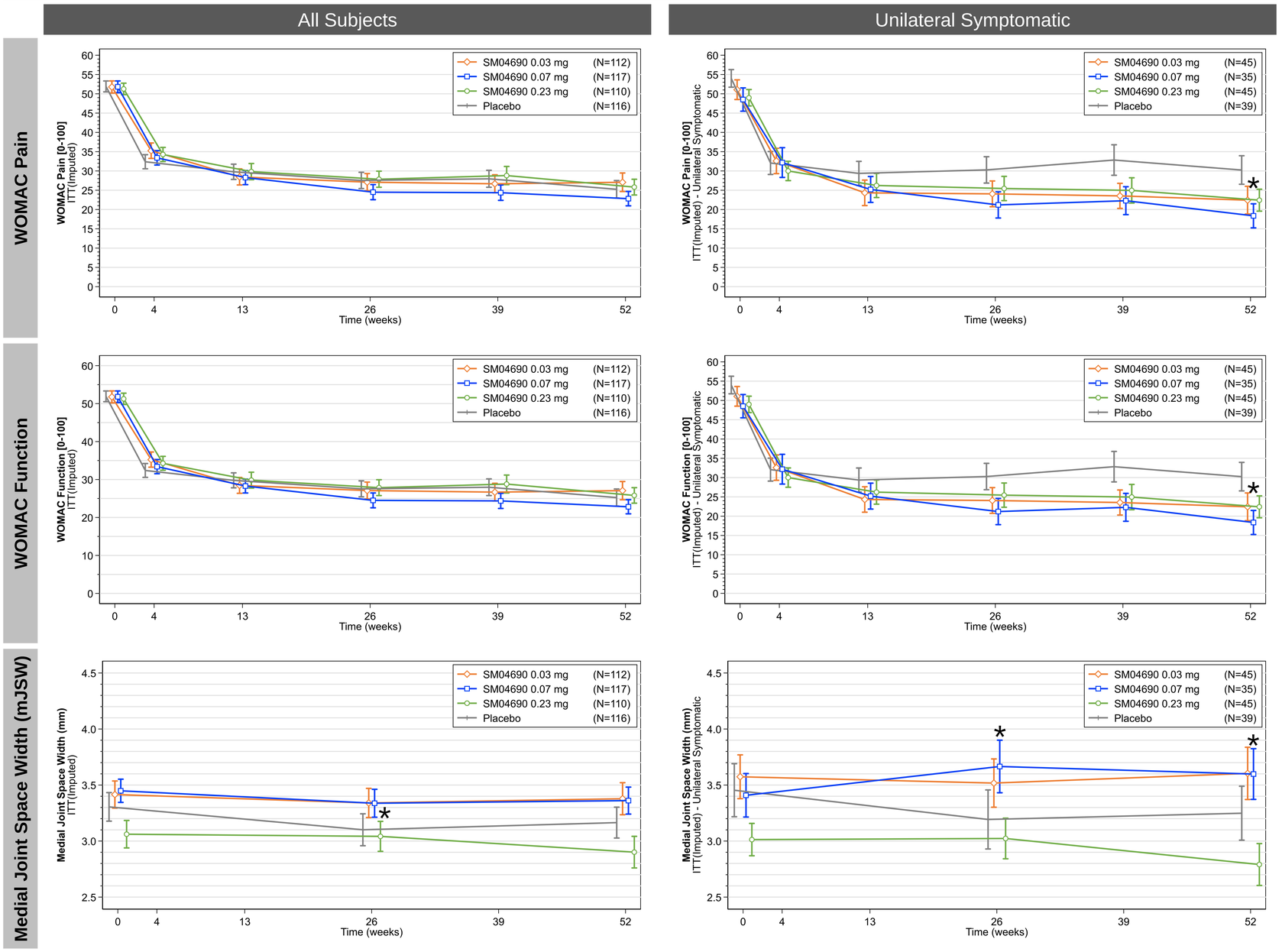

Figure. Actual observations over time depicting mean change from baseline (± standard error). *P<0.05 compared to PBO

Table 1. Subject demographics (ITT population)

	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 (4.8)	30.8 (4.7)	29.6 (4.5)	29.2 (4.4)	29.9 (4.6)
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%)	70 (63.6%)	74 (63.8%)	292 (64.2%)
Unilateral symptomatic OA [n(%)]	45 (40.2%)	35 (29.9%)	45 (40.9%)	39 (33.6%)	164 (36.0%)

Table 2. Incidence of adverse events

AE(s) reported >2% [#AE / N(%)]	0.03 mg	0.07 mg	0.23 mg	Placebo	All subjects
Arthralgia†	16 / 13 (11.7)	14 / 13 (11.4)	13 / 9 (8.7)	12 / 10 (9.3)	61 / 49 (10.8)
Joint swelling	5 / 3 (2.7)	4 / 4 (3.5)	2 / 2 (1.9)	6 / 5 (4.6)	17 / 14 (3.1)
Upper respiratory tract infection	5 / 5 (4.5)	2 / 2 (1.8)	1 / 1 (1.0)	3 / 3 (2.8)	12 / 12 (2.7)
Hypertension	0 / 0 (0.0)	4 / 4 (3.5)	4 / 4 (3.8)	3 / 3 (2.8)	11 / 11 (2.4)
Nasopharyngitis	4 / 4 (3.6)	3 / 3 (2.6)	3 / 3 (2.9)	0 / 0 (0.0)	11 / 11 (2.4)
Osteoarthritis†, ‡	4 / 3 (2.7)	2 / 2 (1.8)	3 / 3 (2.9)	5 / 3 (2.8)	14 / 11 (2.4)
Headache	0 / 0 (0.0)	6 / 3 (2.6)	2 / 2 (1.9)	4 / 4 (3.7)	13 / 10 (2.2)
Joint effusion	5 / 4 (3.6)	2 / 2 (1.8)	1 / 1 (1.0)	2 / 2 (1.9)	10 / 9 (2.0)
Sinusitis	1 / 1 (0.9)	2 / 2 (1.8)	1 / 1 (1.0)	5 / 5 (4.6)	9 / 9 (2.0)
Urinary tract infection	2 / 2 (1.8)	2 / 2 (1.8)	3 / 2 (1.9)	3 / 3 (2.8)	10 / 9 (2.0)

† Noted as an AE when presented as an exacerbation (increase in frequency, severity, or specificity) of preexisting condition(s)
‡ Osteoarthritis in index joint or joint(s) other than index knee

References:
1. Zhu M, et al. *J Bone Miner Res.* 2009;24:12-21.
2. Dupuis DE, et al. *Osteoarthritis Cartilage.* 2003;11:716-24.

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