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Results from a 52-Week Randomized, Double-Blind, Placebo-Controlled, Phase 2 Study of a Novel, Intra-Articular Wnt Pathway Inhibitor (SM04690) for the Treatment of Knee Osteoarthritis

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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 cellular processes and inflammation. SM04690, a small molecule Wnt pathway inhibitor, is in development as a potential disease modifying OA drug (DMOAD) for knee OA. A phase 2, multicenter, 52-week, randomized, double-blind, placebo-controlled (PBO) trial was conducted to identify a target population, determine optimal dose and assess safety of SM04690. The primary endpoint was change from baseline in the target knee in Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) Pain subscore at Week 13.

Methods: Knee OA subjects with Kellgren-Lawrence (KL) grades 2-3, received a single 2 mL injection of 0.03 mg, 0.07 mg, 0.23 mg SM04690 or PBO in target (most painful) knee. WOMAC Pain [0-50] and Function [0-170] were assessed at Weeks 0, 4, 13, 26, 39 and 52, and fixed flexion radiographs (PA, weight-bearing, QuAP™ positioned) were taken at Weeks 0, 26 and 52 for medial joint space width (mJSW). Analysis of covariance adjusted for baseline was conducted with multiple imputation in the intention-to-treat (ITT) population. Two subgroups were explored: 1) unilateral symptomatic knee OA subjects as determined by investigator through history and examination (pre-specified) and 2) unilateral symptomatic knee OA subjects without widespread pain (Widespread Pain Index ≤4 and Symptom Severity ≤2 [WP], post-hoc).

Results: 455 subjects (mean age 60.3 [±8.7] years, BMI 29.9 [±4.6] kg/m^2, female 58.9%, KL grade 3 [64.4%], unilateral symptomatic OA [36.0%]) were enrolled; 91% of patients had bilateral OA on X-ray at Week 0. Serious adverse events, all deemed unrelated to SM04690, were reported in 17 (3.7%) subjects (5 [4.5%, 0.03 mg], 4 [3.5%, 0.07 mg], 4 [3.8%, 0.23 mg], 3 [2.8%, PBO] 1 [6.7%, other]).

The primary endpoint was not met. At all timepoints, in the ITT population, clinically meaningful improvements in WOMAC Pain and Function (>10% full range) compared to baseline were seen

in all groups. At 52 weeks, in the pre-specified unilateral symptomatic subgroup, the 0.07 mg dose group showed significant improvements in WOMAC Pain (P=0.049) and clinically meaningful and significant improvements in WOMAC Function (P=0.035) compared to PBO. In the post-hoc unilateral symptomatic without WP subgroup, the 0.07 mg dose group showed both clinically meaningful and significant improvements in WOMAC Pain (P=0.042; P=0.025) and Function (P=0.035; P=0.017) compared to PBO at Weeks 39 and 52, respectively (Figure 1).

Changes in mJSW by treatment group in the total ITT population and the subgroups are shown in Table 1. At 52 weeks, the 0.07 mg unilateral symptomatic (P=0.021*)* and 0.07 mg unilateral symptomatic without WP (P=0.032) demonstrated significant increase from baseline in mJSW compared to PBO.

Conclusion: A target population of subjects with unilateral symptoms and potential optimal dose (0.07 mg) of SM04690 were identified. These subjects, especially those without WP, reported significant symptomatic improvements compared to PBO subjects. Significant mJSW improvements compared to PBO were also observed at both 26 and 52 weeks with the 0.07 mg dose group in unilateral symptomatic patients without WP. Therefore, clinical and radiographic outcomes suggest that SM04690 has potential as a DMOAD for knee OA treatment, especially in patients with unilateral symptomatic knee OA without WP. Further clinical studies are ongoing.

Table 1. Summary and Analysis of Change in mJSW by Treatment Groups over Subgroups

ITT				
	0.03 mg	**0.07 mg**	**0.23 mg**	**PBO**
N	112	117	110	116
Baseline mJSW (mm) [Mean (SE)]	3.42 (0.12)	3.45 (0.10)	3.06 (0.12)	3.31 (0.13)
Week 52 mJSW Change from Baseline	-0.04 (0.06)	-0.09 (0.06)	-0.16 (0.07)	-0.14 (0.06)
Week 52 mJSW Change compared to Placebo*	0.10 (0.09)	0.06 (0.09)	-0.02 (0.09)	–
P-value	0.259	0.529	0.807	–
Unilateral Symptomatic				
	0.03 mg	**0.07 mg**	**0.23 mg**	**PBO**
N	45	35	45	39
Baseline mJSW (mm) [Mean (SE)]	3.57 (0.20)	3.41 (0.19)	3.01 (0.14)	3.45 (0.24)
Week 52 mJSW Change from Baseline	0.03 (0.10)	0.19 (0.12)	-0.22 (0.11)	-0.21 (0.12)
Week 52 mJSW Change compared to Placebo*	0.24 (0.16)	0.39 (0.17)	-0.04 (0.16)	–
P-value	0.131	**0.021**	0.789	–
Unilateral Symptomatic without Widespread Pain				
	0.03 mg	**0.07 mg**	**0.23 mg**	**PBO**
N	34	29	33	32
Baseline mJSW (mm) [Mean (SE)]	3.55 (0.22)	3.35 (0.21)	3.10 (0.18)	3.43 (0.25)
Week 52 mJSW Change from Baseline	0.07 (0.13)	0.17 (0.14)	-0.16 (0.10)	-0.26 (0.14)
Week 52 mJSW Change compared to Placebo*	0.33 (0.18)	0.42 (0.19)	0.06 (0.17)	–
P-value	0.064	**0.032**	0.701	–

*Reported from imputed Baseline-Adjusted Analysis of Covariance

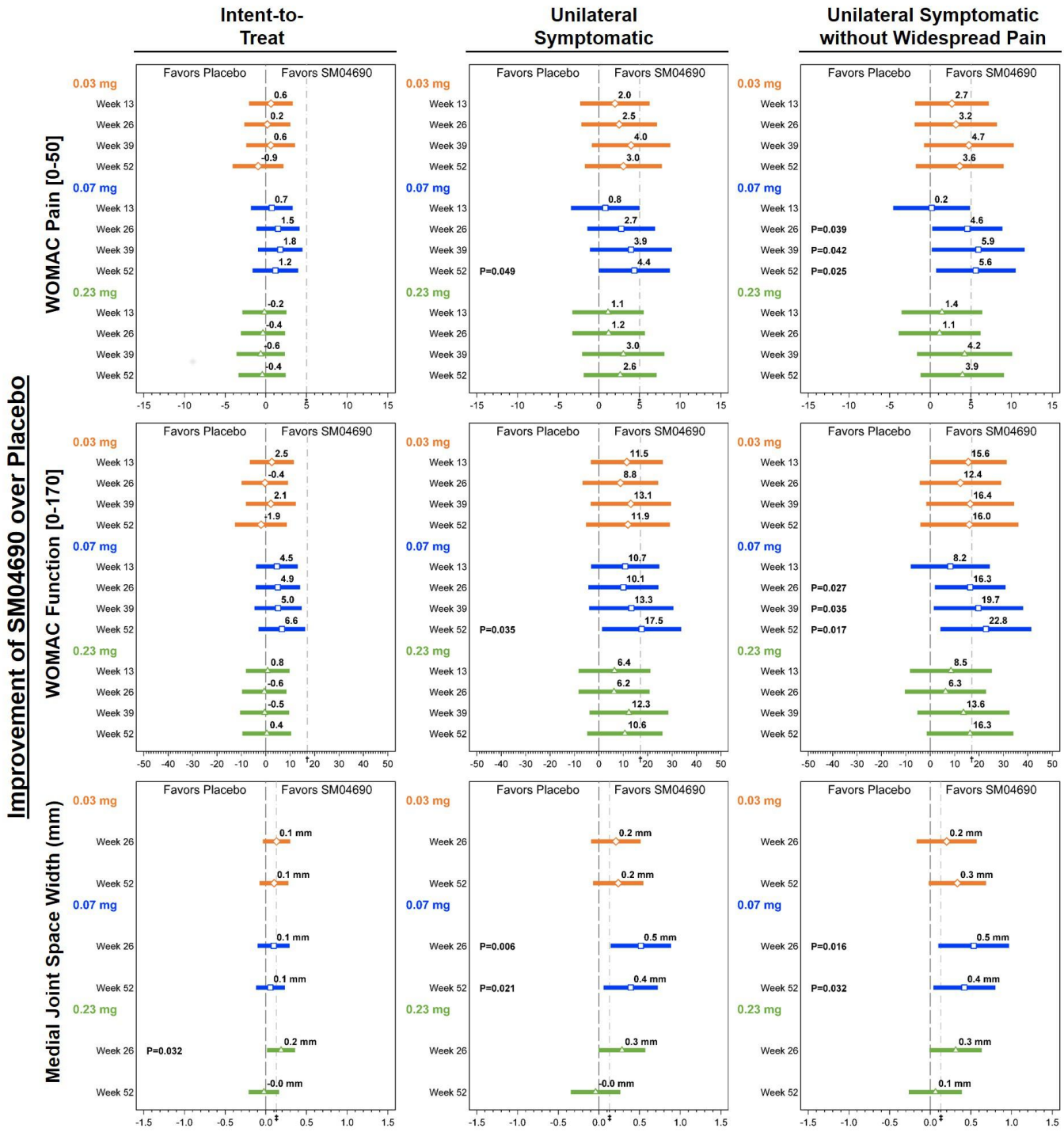

Figure 1. Ladder plots depicting mean improvement (and 95% confidence intervals) of SM04690 over placebo adjusted for baseline.
*Minimal clinically important difference (MCID) defined as 10% of WOMAC Pain scale, or 5 points. †MCID defined as 10% of WOMAC Function scale, or 17 points.
‡Minimum detectable difference (MDD) defined as 0.13 mm of mJSW.