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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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Objective: Wnt signaling is involved in knee osteoarthritis (KOA) pathogenesis. SM04690 is a small molecule Wnt pathway inhibitor in development as a disease-modifying osteoarthritis drug (DMOAD). A phase 2, 52-week trial was conducted to identify a target population, optimize dose, and assess safety of SM04690.

Methods: KOA subjects (Kellgren-Lawrence [KL] grades 2-3) received a single 2-mL injection of SM04690 (0.03 mg, 0.07 mg, 0.23 mg) or placebo (PBO) in the most painful (target) knee. WOMAC Pain and Function were assessed (Weeks 0, 4, 13, 26, 39, 52) and fixed flexion radiographs (QuAP™ positioned; Weeks 0, 26, 52) assessed medial joint space width (mJSW). Analysis of covariance adjusted for baseline was conducted using multiple imputation for missing data. Subgroups explored included 1) unilateral symptomatic subjects (pre-specified; investigator determined) and 2) unilateral symptomatic subjects without comorbid pain (post-hoc; Widespread Pain Index ≤4, Symptom Severity ≤2 [WP-]).

Results: 455 KOA subjects (female 58.9%, KL 3 64.4%, unilateral symptomatic 36.0%) were enrolled.

No safety signals were seen. In ITT, clinically meaningful improvements (>10% full range) were seen in WOMAC Pain and Function compared to baseline in all groups at all timepoints. In 0.07 mg unilateral symptomatic subjects at Week 52 and 0.07 mg unilateral symptomatic WP- at Weeks 26, 39 and 52, significant improvements in WOMAC Pain and Function were seen compared to PBO (**Figure 1**). The primary endpoint (Week 13 WOMAC Pain change from baseline compared to PBO) was not met.

At weeks 26 and 52, unilateral symptomatic and unilateral symptomatic WP- 0.07 mg subjects had significant mJSW increases from baseline compared to PBO (**Table 1**).

Conclusion: A target SM04690 dose (0.07 mg) and population (unilateral symptomatic) were identified, with significant symptomatic and mJSW improvements compared to PBO. Studies of SM04690 as a potential knee DMOAD are ongoing.

Table 1. Change in mJSW by treatment groups

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 PBO	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 PBO	0.24 (0.16)	0.39 (0.17)	-0.04 (0.16)	-
P-value	0.131	**0.021**	0.789	-
Unilateral Symptomatic WP-				
	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 PBO	0.33 (0.18)	0.42 (0.19)	0.06 (0.17)	-
P-value	0.064	**0.032**	0.701	-

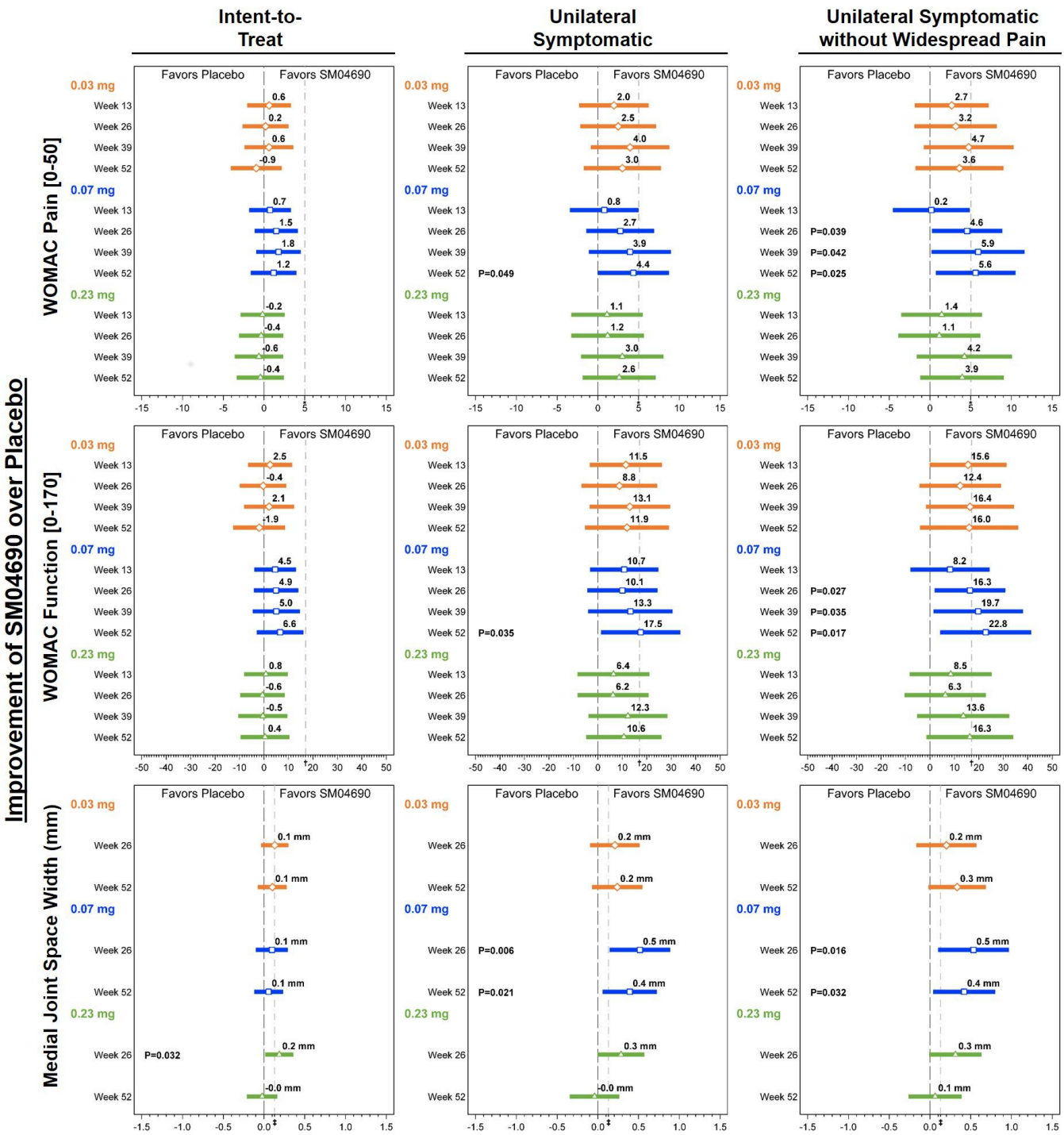

Figure 1. Ladder plots depicting mean improvement (and 95% confidence intervals) of SM04690 over placebo adjusted for baseline.
*Minimal clinically important difference (MCID) defined as 10% of WOMAC Pain scale, or 5 points. †MCID defined as 10% of WOMAC Function scale, or 17 points.
‡Minimum detectable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