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Radiographic Outcomes Were Concordant with Outcome Measures in Rheumatology-Osteoarthritis Research Society International (OMERACT-OARSI) Strict Response: Post-Hoc Analysis from a Phase 2 Study of a Wnt Pathway Inhibitor, SM04690, for Knee Osteoarthritis Treatment

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Purpose: Wnt signaling is involved in articular cartilage degradation and bone remodeling in knee osteoarthritis (OA), which is characterized by pain, disability and joint deformity. SM04690, a potential disease modifying knee OA drug (DMOAD) is a small molecule, intra-articular Wnt pathway inhibitor. A phase 2, multicenter, 52-week, single-dose, randomized, placebo-controlled (PBO) trial was conducted. A post-hoc analysis evaluated if radiographic medial joint space width (mJSW) changes were concordant with OMERACT-OARSI pain and function strict responder status.

Methods: Subjects were randomized to receive a 2-mL injection of 0.03 mg, 0.07 mg, 0.23 mg SM04690 or PBO in the target (most painful) knee at Week 0. Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) Pain [0-50] and Function [0-170] were assessed at Weeks 0, 4, 13, 26, 39 and 52, and mJSW was measured in fixed-flexion X-rays at Weeks 0, 26 and 52. Three groups were studied: 1) intent-to-treat (ITT); 2) unilateral symptomatic, a pre-specified subgroup reporting pain in one knee as determined by investigator; 3) unilateral symptomatic without widespread pain (WP), a post-hoc subgroup of unilateral symptomatic subjects with a WP Index score ≤ 4 and Symptom Severity score ≤ 2. Subjects who achieved a WOMAC Pain or Function improvement from baseline of $\geq$50% and $\geq$20 [scaled to 100] units at Week 52 were defined as OMERACT-OARSI strict responders. Differences in Week 52 mJSW changes from baseline between SM04690 and PBO were assessed by analysis of covariance adjusted for baseline mJSW with multiple imputation. Logistic regression was applied between mJSW changes and OMERACT-OARSI strict responders within each treatment group and subgroup. Receiver-operator characteristic (ROC) curves were generated with area under the curve (AUC) to estimate concordance.

Results: 455 subjects were enrolled (mean age 60.3 [SD 8.7] years, body mass index 29.9 [SD 4.6] kg/m^2, 268 (59%) female, 292 (64%) Kellgren-Lawrence Grade 3, 164 (36%) unilateral symptomatic knee OA, 386 (91%) bilateral radiographic OA, 128 (28%) unilateral symptomatic without WP).

OMERACT-OARSI strict responders and changes from baseline in mJSW at Week 52 are summarized in Table 1. In the ITT analysis, approximately 60% of subjects in all treatment groups were strict responders. In both the unilateral symptomatic and unilateral symptomatic without WP subgroup analyses, treatment with SM04690 was associated with higher percentages of strict responders than PBO. The 0.03 mg and 0.07 mg doses within the two subgroups also demonstrated improved mJSW compared to PBO (non-significant and $P<0.05$, respectively).

None of the treatment groups in the ITT population achieved acceptable concordance, defined as an AUC > 0.7 (Figure 1). In the unilateral symptomatic subgroup, PBO demonstrated acceptable concordance, and the 0.07 mg group demonstrated excellent concordance (AUC > 0.8). In the unilateral symptomatic subgroup without WP, only the SM04690 0.07 mg group demonstrated excellent concordance (AUC = 0.81).

Conclusions: In this post-hoc analysis, treatment with SM04690 maintained or increased mJSW in the 0.03 and 0.07 mg dose groups compared to PBO over 52 weeks. In unilateral symptomatic knee OA subgroup, changes in mJSW were concordant with OMERACT-OARSI strict responses in 0.07 mg and PBO cohorts. When WP was further excluded from this subgroup, only the 0.07 mg group showed concordance at a level deemed excellent. These data further support examination of SM04690 at a dose of 0.07 mg as a potential DMOAD for treatment of knee OA.

Table 1. Week 52 Outcomes by Treatment Group and Analysis Group

ITT				
	0.03 mg	**0.07 mg**	**0.23 mg**	**PBO**
N	112	117	110	116
OMERACT-OARSI Strict Response [n(%)]*	59 (57%)	67 (63%)	59 (62%)	62 (64%)
Baseline mJSW (mm) [Mean (SE)]	3.42 (0.12)	3.45 (0.10)	3.06 (0.12)	3.31 (0.13)
mJSW Change from Baseline (mm) [Mean (SE)]	-0.04 (0.06)	-0.09 (0.06)	-0.16 (0.07)	-0.14 (0.06)
mJSW Change compared to PBO (mm) [Mean (SE)]	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**	**Placebo**
N	45	35	45	39
OMERACT-OARSI Strict Response [n(%)]*	26 (65%)	24 (73%)	27 (71%)	17 (52%)
Baseline mJSW (mm) [Mean (SE)]	3.57 (0.20)	3.41 (0.19)	3.01 (0.14)	3.45 (0.24)
mJSW Change from Baseline (mm) [Mean (SE)]	0.03 (0.10)	0.19 (0.12)	-0.22 (0.11)	-0.21 (0.12)
mJSW Change compared to PBO (mm) [Mean (SE)]	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**	**Placebo**
N	34	29	33	32
OMERACT-OARSI Strict Response [n(%)]*	19 (63%)	19 (70%)	21 (75%)	12 (44%)
Baseline mJSW (mm) [Mean (SE)]	3.55 (0.22)	3.35 (0.21)	3.10 (0.18)	3.43 (0.25)
mJSW Change from Baseline (mm) [Mean (SE)]	0.07 (0.13)	0.17 (0.14)	-0.16 (0.10)	-0.26 (0.14)
mJSW Change compared to PBO (mm) [Mean (SE)]	0.33 (0.18)	0.42 (0.19)	0.06 (0.17)	–
P-value	0.064	**0.032**	0.701	–

*Strict response from all available data; multiple imputation used for mJSW analysis.

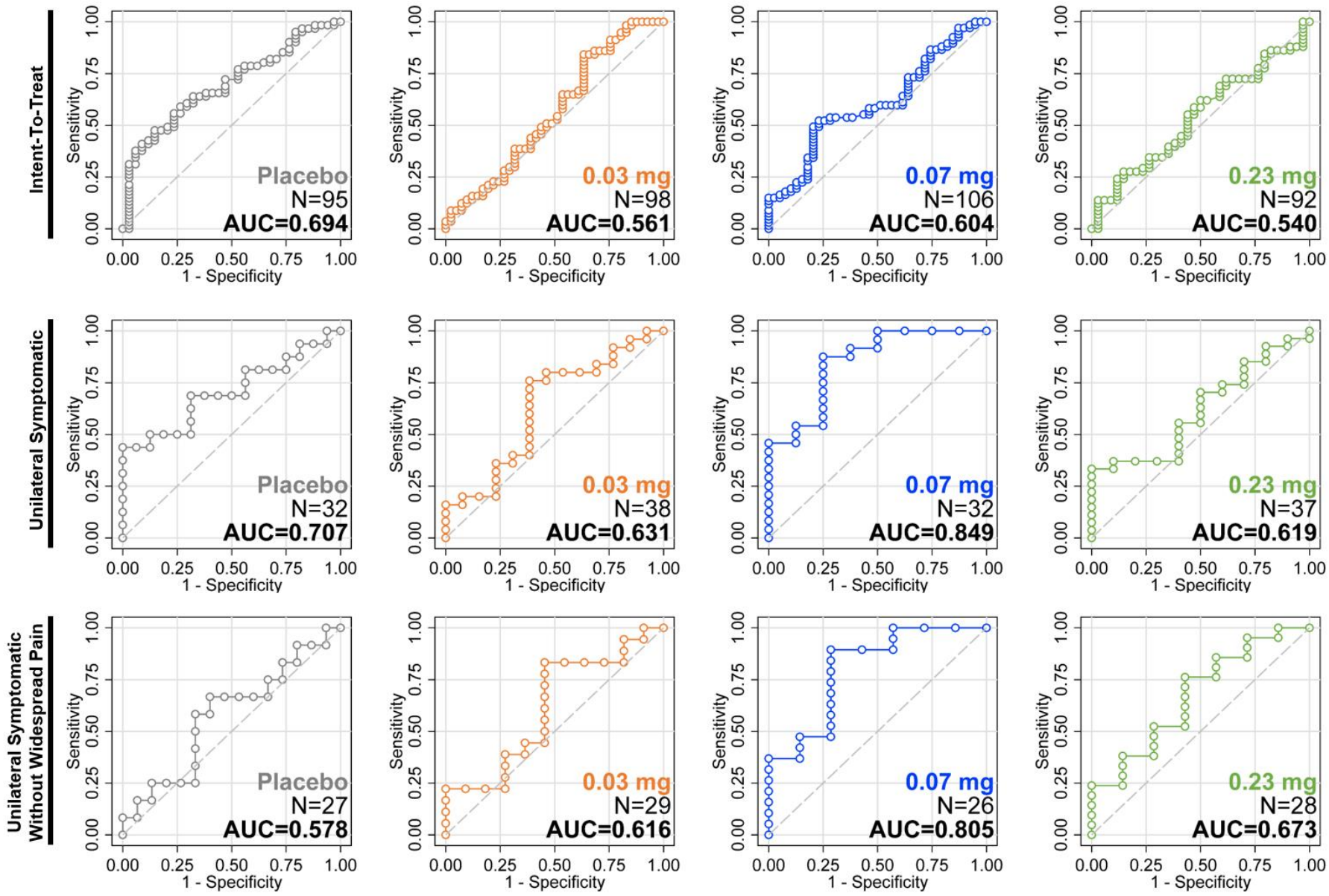

Figure 1. ROC Curves Illustrating Concordance between OMERACT-OARSI Strict Response and mJSW Change by Treatment Group and Analysis Group