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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Poster# 466

Background

- Knee osteoarthritis (OA) is characterized by pain, loss of function, and disability due to articular cartilage degradation and bone remodeling.[1]
- Wnt signaling affects OA by modulating inflammation, cartilage breakdown, and bone/cartilage formation.[2]
- Evidence suggests radiographic features are associated with pain and loss of function in knee OA.[3]
- SM04690 is a small molecule Wnt pathway inhibitor in development as a potential disease-modifying OA drug (DMOAD). Results of a 52-week, randomized, double-blind, phase 2 trial are presented: **poster# 550**. In this post-hoc analysis, associations of medial joint space width (mJSW) with changes in pain and function were evaluated.

Methods

- 455 subjects received a 2 mL, intraarticular injection of SM04690 (0.03, 0.07, or 0.23 mg) or saline placebo (PBO) in the target (most painful) knee at baseline.
- A pre-specified unilateral symptomatic knee OA subgroup was investigator designated at baseline by history and examination.
- A post-hoc subgroup of unilateral symptomatic subjects without widespread pain (WP) was identified to exclude non-discriminatory pain (Widespread Pain Index ≤4 and Symptom Severity Score ≤2).[4]
- Western Ontario and McMaster Universities Arthritis Index (WOMAC) Pain [0-50] and Function [0-170] subscores were assessed (Weeks 0, 4, 13, 26, 39, 52) and target knee radiographs taken (Weeks 0, 26, 52).
- OMERACT-OARSI "strict response" was defined as achieving either a WOMAC Pain or Function improvement of ≥50% and ≥20 (scaled to 100) units from baseline.[5]
- Analysis of covariance adjusted for baseline mJSW with multiple imputation for missing outcomes was used to determine differences in mJSW changes from baseline at Week 52 between SM04690 and PBO.
- Receiver operating characteristic (ROC) curves were generated following as-observed logistic regression to assess statistical concordance between baseline-adjusted mJSW change and strict response.
- Areas under the curve (AUC) were calculated to establish concordance. AUC >0.7 was defined as "acceptable" and AUC >0.8 as "excellent" concordance.[6]

Results

Table 1. Demographic characteristics among the ITT population

	0.03 mg	0.07 mg	0.23 mg	PBO	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. 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 with PBO (mm) [mean (SE)]	0.10 (0.09)	0.06 (0.09)	-0.02 (0.09)	–
P-value	0.259	0.529	0.807	–

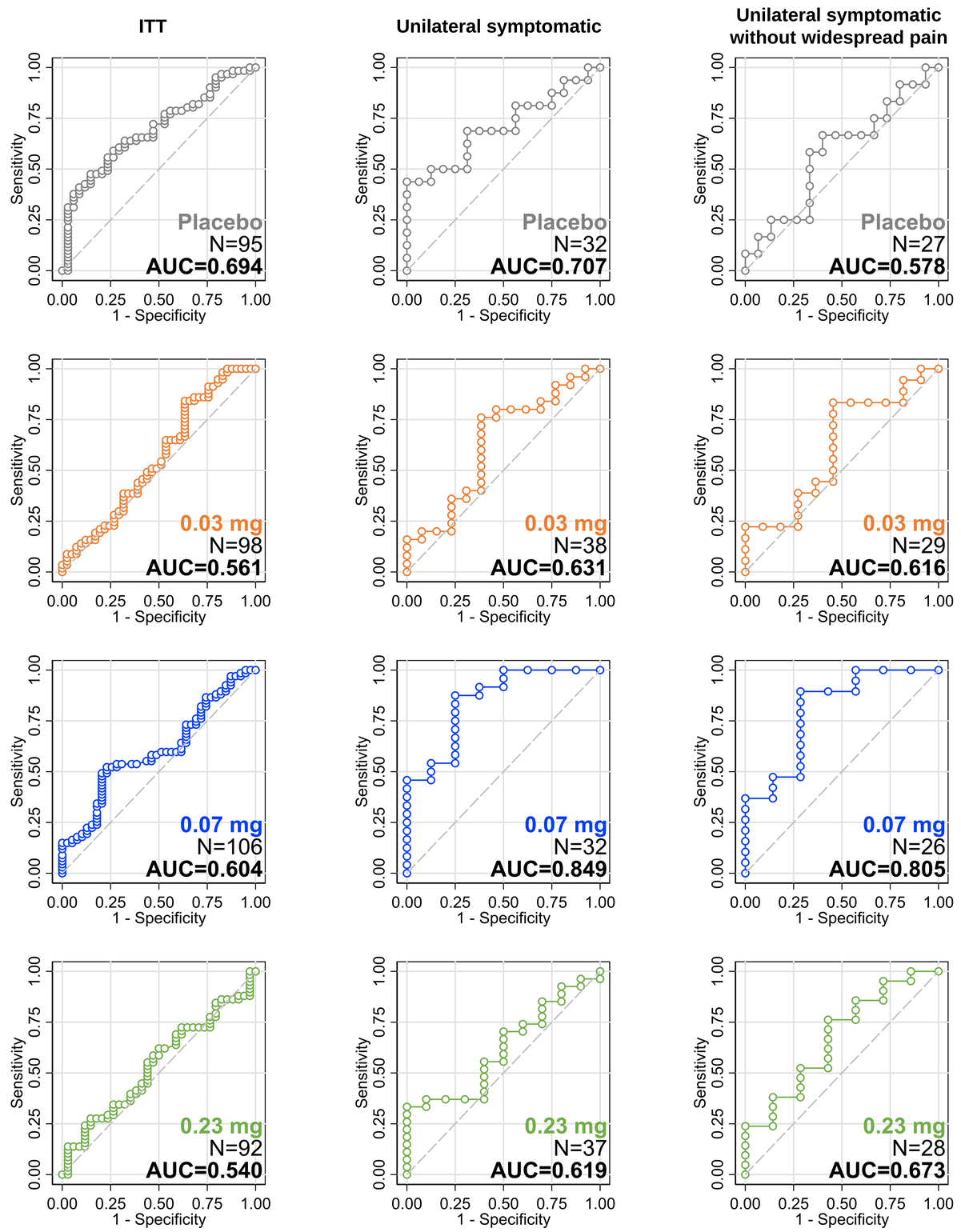
Unilateral symptomatic	0.03 mg	0.07 mg	0.23 mg	PBO
N	45	35	45	39
OMERACT-OARSI strict response [n(%)]*	26 (65%)	24 (73%)	27 (71%)	17 (52%)
Baseline mJSW (mm) [mean (SE)]	3.57 (0.20)	3.41 (0.19)	3.01 (0.14)	3.45 (0.24)
mJSW change from baseline (mm) [mean (SE)]	0.03 (0.10)	0.19 (0.12)	-0.22 (0.11)	-0.21 (0.12)
mJSW change compared with 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	PBO
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 with 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 calculated from as-observed data.

Results

Figure 1. ROC curves evaluating concordance between OMERACT-OARSI strict response and mJSW change by treatment group and analysis group



Conclusions

- In this post-hoc analysis, treatment with SM04690 maintained or increased mJSW in 0.03 and 0.07 mg dose groups compared with PBO at 52 weeks in ITT and unilateral symptomatic subjects (with or without WP).
- No group achieved acceptable concordance among the ITT population.
- Among unilateral symptomatic subjects, changes in mJSW were concordant with OMERACT-OARSI strict response in the 0.07 mg (AUC=0.849) and PBO (AUC=0.707) groups.
- Among unilateral symptomatic subjects without WP, only the 0.07 mg group achieved excellent concordance (AUC=0.805).
- Findings support further study of SM04690 at a dose of 0.07 mg as a potential DMOAD for knee OA.

References

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