Radiographic outcomes were associated with pain and function responses: Post-hoc analysis from a phase 2 study of a Wnt pathway inhibitor, SM04690, for knee osteoarthritis treatment

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Background

- SM04690 is a small-molecule Wnt pathway inhibitor in development as a potential disease-modifying knee OA drug (DMOAD).
- A phase 2 trial demonstrated pain, function, and radiographic improvements at 52 weeks, compared with placebo (PBO), in subgroup analyses.[1]
- Evidence has suggested decreased joint space width (JSW) is associated with worsening pain and function in knee OA.[2]
- Therefore, does increased JSW predict improvements in pain and function?
- To test this hypothesis, a post-hoc analysis was performed on phase 2 data, evaluating concordance of medial JSW (mJSW) change with SM04690 clinical response.

Methods

- 455 knee OA subjects were administered SM04690 injection (0.03, 0.07, 0.23 mg) or saline PBO. Western Ontario and McMaster Universities Arthritis Index (WOMAC) scores and mJSW from radiographs were recorded to Week 52.[1]
- Subgroups included: 1) pre-specified unilateral symptomatic knee OA (UNI) subjects, investigator designated at baseline by history and examination and 2) post-hoc unilateral symptomatic subjects with comorbid pain excluded (Widespread Pain Index ≤4 and Symptom Severity Score ≤2; UNI WP-).[3]
- Clinical responders were defined as subjects who achieved both WOMAC Pain and Function improvements of ≥50% and ≥20 (scaled to 100) points, similar to OMERACT-OARSI response[4], but with both pain and function criteria met.
- Receiver operating characteristic (ROC) curves were generated following logistic regression analyses between baseline-adjusted mJSW change and clinical response. Areas under the curve (AUC) were calculated to establish concordance.
- C-statistic analysis estimated the predicted probability of a subject having improved mJSW and clinical response, compared with a subject who did not achieve improved mJSW and clinical response, for PBO and 0.03 mg, 0.07 mg, and 0.23 mg doses of SM04690.
- AUC of 0.5 meant the model was no better at predicting an outcome than random chance. AUC of 1 meant the model perfectly predicted a subject's outcome.
- AUC >0.7 was defined as "acceptable" and AUC >0.8 as "excellent" concordance between change in mJSW and clinical response.[5]

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%)
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	Placebo
N	112	117	110	116
Baseline mJSW (mm)*	3.42 (0.12)	3.45 (0.10)	3.06 (0.12)	3.31 (0.13)
mJSW change from baseline (mm)*	-0.04 (0.06)	-0.09 (0.06)	-0.16 (0.07)	-0.14 (0.06)
mJSW change compared with PBO (mm)*	0.10 (0.09)	0.06 (0.09)	-0.02 (0.09)	–
***P*-value**	0.259	0.529	0.807	–

UNI	0.03 mg	0.07 mg	0.23 mg	Placebo
N	45	35	45	39
Baseline mJSW (mm)*	3.57 (0.20)	3.41 (0.19)	3.01 (0.14)	3.45 (0.24)
mJSW change from baseline (mm)*	0.03 (0.10)	0.19 (0.12)	-0.22 (0.11)	-0.21 (0.12)
mJSW change compared with PBO (mm)*	0.24 (0.16)	0.39 (0.17)	-0.04 (0.16)	–
***P*-value**	0.131	**0.021**	0.789	–

UNI WP-	0.03 mg	0.07 mg	0.23 mg	Placebo
N	34	29	33	32
Baseline mJSW (mm)*	3.55 (0.22)	3.35 (0.21)	3.10 (0.18)	3.43 (0.25)
mJSW change from baseline (mm)*	0.07 (0.13)	0.17 (0.14)	-0.16 (0.10)	-0.26 (0.14)
mJSW change compared with PBO (mm)*	0.33 (0.18)	0.42 (0.19)	0.06 (0.17)	–
***P*-value**	0.064	**0.032**	0.701	–

*Mean (SD) from multiple imputation analysis of covariance reported.

Figure 1. WOMAC Pain and Function responders

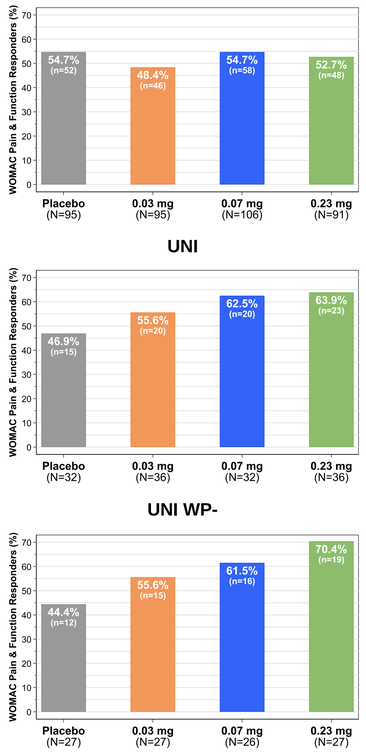
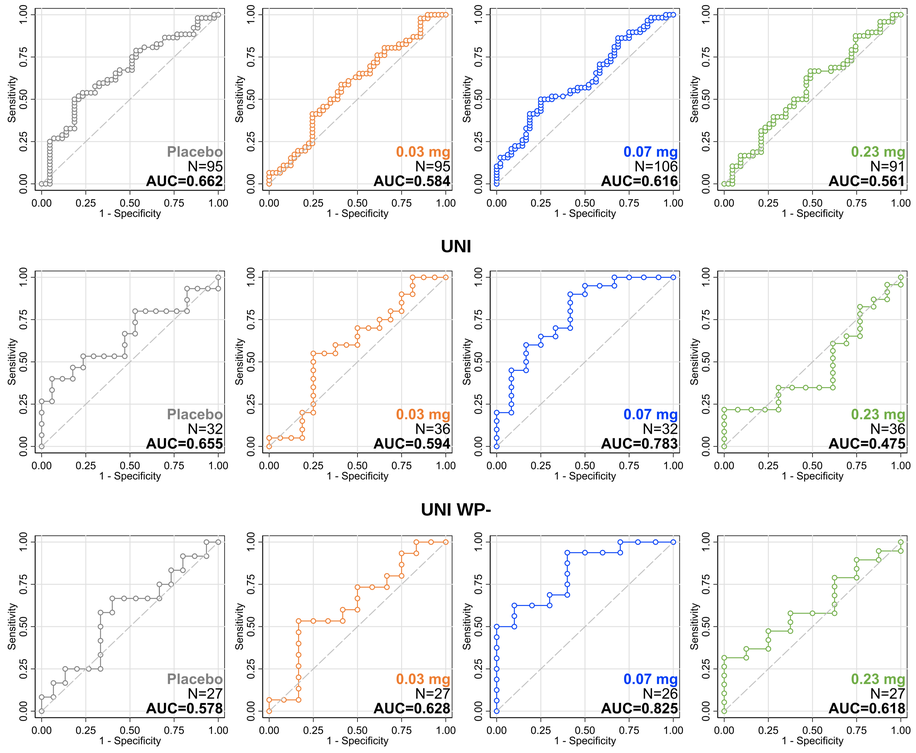


Figure 2. ROC curves evaluating concordance between WOMAC Pain and Function response and mJSW change by treatment group and analysis group



Conclusions

- In this post-hoc analysis, treatment with SM04690 maintained or increased mJSW with the 0.07 mg dose 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.
- In UNI and UNI WP- subjects treated with 0.07 mg SM04690, changes in mJSW were concordant with pain and function responses.
- Concordance analysis can potentially quantify the strength of relationship between radiographic change and clinical outcomes when investigating potential DMOAD treatments in knee OA.
- Findings support further study of SM04690 at a dose of 0.07 mg as a potential DMOAD for knee OA.

References: 1. Yazici Y, et al. *Osteoarthritis Cartilage*. 2017;25:1598-1606. 2. Neogi T, et al. *BMJ*. 2009;339:b2844. 3. Clauw DJ. *JAMA*. 2014;311:1547-55. 4. Pham T, et al. *Osteoarthritis Cartilage*. 2004;12:389-99. 5. Hosmer DW, Lemeshow S. *Applied Logistic Regression (2nd ed)*. 2000. Wiley New York.

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