Radiographic Outcomes Were Associated with Pain and Function Responses: Post-Hoc Analysis of Results from a Phase 2 Study of a Small Molecule Wnt Pathway Inhibitor, SM04690, for Knee Osteoarthritis Treatment

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Background

- Osteoarthritis (OA) is characterized by pain, disability, and joint deformity due to articular cartilage degradation and bone remodeling.
- The Wnt pathway is a major family of signaling molecules that regulates cell development and tissue regeneration.[1]
- Wnt signaling affects OA by modulating inflammation, cartilage breakdown, and bone/cartilage formation. Increased Wnt signaling induces differentiation of mesenchymal stem cells into osteoblasts, whereas inhibition induces chondrogenesis.[2]
- Evidence suggests that joint space narrowing (JSN) is associated with pain and loss of function in knee OA.[3]
- SM04690 is a small molecule, intra-articular Wnt pathway inhibitor in development as a potential disease modifying OA drug (DMOAD). Results of a randomized, double-blind, phase 2 trial are presented elsewhere (abstract 935). This post-hoc analysis evaluated associations of JSN with changes in pain and function.

Methods

- 455 subjects received a 2 mL SM04690 injection (0.03, 0.07, 0.23 mg) or saline placebo (PBO) in the target (most painful) knee at Week 0.
- 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).
- JSN was assessed by analysis of covariance adjusted for baseline medial joint space width (mJSW) with multiple imputation.
- A pre-specified unilateral symptomatic knee OA subgroup was investigator defined by history and examination.
- An examination of the impact of widespread pain as measured at baseline by the Widespread Pain Index[4] was also pre-specified.
- A post-hoc subgroup, unilateral symptomatic subjects without widespread pain, was identified to exclude non-discriminatory pain [Widespread Pain Index ≤4 and Symptom Severity Score ≤2].
- Responders were defined as subjects who achieved both WOMAC Pain and Function improvement of >50% and >20 [scaled to 100 points], similar to an OMERACT-OARSI response[5], but with both pain and function criteria met.
- Receiver operator characteristic curves (ROC) were generated following logistic regression analyses to assess statistical concordance between baseline adjusted mJSW change and responders.
- Area Under the Curve (AUC) was calculated to establish concordance. AUC > 0.7 was defined as "acceptable" and AUC > 0.8 as "excellent" discrimination [6] (concordance) between change in mJSW and responders.

Results

Table 1. SM04690-OA-02 Demographics (ITT)

	0.03 mg	0.07 mg	0.23 mg	Placebo	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. Clinical Outcomes by Treatment Group

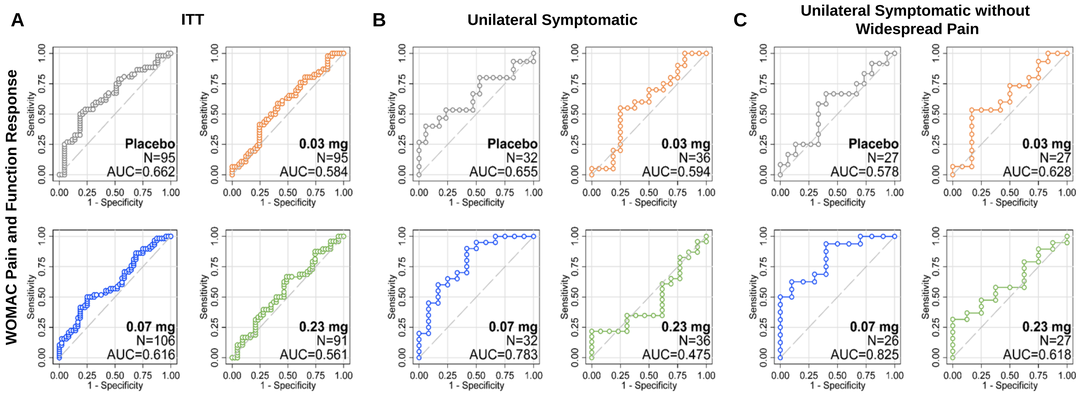
ITT				
	0.03 mg	**0.07 mg**	**0.23 mg**	**PBO**
N	112	117	110	116
WOMAC Pain and Function Response [N(%)]	46 (48%)	58 (55%)	48 (53%)	52 (55%)
Baseline mJSW (mm) [Mean (SE)]	3.42 (0.12)	3.45 (0.10)	3.06 (0.12)	3.31 (0.13)
Week 52 mJSW Change from Baseline	-0.04 (0.06)	-0.09 (0.06)	-0.16 (0.07)	-0.14 (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
WOMAC Pain and Function Response [N(%)]	20 (56%)	20 (63%)	23 (64%)	15 (47%)
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
WOMAC Pain and Function Response [N(%)]	15 (56%)	16 (62%)	19 (70%)	12 (44%)
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

Concordance between change in mJSW and Clinical Response

- No group achieved acceptable concordance as all AUC<0.7 in ITT (**Fig. 1A**).
- Acceptable concordance (AUC=0.78) was observed in unilateral symptomatic subjects treated with SM04690 0.07 mg (**Fig. 1B**).
- Excellent concordance (AUC=0.83) was seen in unilateral symptomatic subjects without widespread pain treated with SM04690 0.07 mg (**Fig. 1C**).

Figure 1. ROC Curves of mJSW Changes Concordance with WOMAC Pain and Function Response



Discussion

- Radiographic outcomes from this study demonstrated that treatment with all doses of SM04690 maintained or increased mJSW compared to PBO at Week 52 (**Table 2).**
- Unilateral symptomatic subjects were pre-specified to investigate subject discrimination of symptoms between target and non-target knees. In addition to this, the unilateral symptomatic without widespread pain subgroup further excluded chronic pain syndromes.
- In unilateral symptomatic subjects treated with SM04690 0.07 mg, changes in mJSW were concordant (AUC=0.78) with WOMAC Pain and Function response at Week 52 (**Fig. 1B**).
- In unilateral symptomatic subjects without widespread pain, PBO, SM04690 0.03 mg and 0.23 mg doses showed no concordance between mJSW and WOMAC Pain and Function response at Week 52 (AUC < 0.7, **Fig. 1C**). However, subjects treated with SM04690 0.07 mg showed excellent concordance between change in mJSW and WOMAC Pain and Function response (AUC=0.83).

Conclusions

- In a targeted population of unilateral symptomatic knee OA subjects without widespread pain, change in mJSW was concordant with a pain and function response in a post-hoc analysis.
- This post-hoc analysis demonstrated concordance can be established between radiographic mJSW change and clinical outcomes when investigating potential DMOAD treatments in knee OA.

References

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