

Radiographic Outcomes Were Concordant with Pain and Function Response: Post-Hoc Analysis from a Phase 2 Study of SM04690, a Wnt Pathway Inhibitor for Knee Osteoarthritis Treatment

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Disclosures

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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 to placebo (PBO), in subgroup analyses¹
- Evidence has suggested decreased JSW is associated with worsening pain and function in knee OA²
 - 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 mJSW change with SM04690 clinical responders

SM04690 Phase 2 study summary

- 455 knee OA subjects 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 recorded to Week 52¹
- 91% subjects had radiographic bilateral knee OA, Kellgren-Lawrence 2-3
- Improvements in WOMAC Pain and Function vs PBO were observed for SM04690 (significant for 0.07 mg dose) in two subgroups at Week 52:
 - Pre-specified subjects with unilateral symptomatic knee OA (UNI, n=164)
 - Post-hoc UNI subjects with non-specific pain excluded (UNI WP, Widespread Pain Index ≤ 4 and Symptom Severity Score ≤ 2 , n=128)
- Significant improvements in mJSW vs PBO were observed for SM04690 0.07 mg UNI and UNI WP at Week 52

Concordance analysis methodology

- Clinical responders defined as subjects who achieved both WOMAC Pain *and* Function improvements of >50% and >20 [scaled to 100] points, similar to an OMERACT-OARSI response¹, but with both pain and function criteria met
- Receiver operator characteristic (ROC) curves were generated following logistic regression analyses between baseline adjusted mJSW change and responders
- Areas Under the Curve (AUC) were calculated to establish concordance. AUC > 0.7 defined as “acceptable” and AUC > 0.8 as “excellent” discrimination² (concordance) between change in mJSW and responders

1. Pham T, et al. (2004) OAC.

2. Hosmer DW and Lemeshow S. (2000) *App Logistic Regression* (2nd ed).

What does 'concordance' mean?

- Also known as C-statistic
- This analysis estimated the predicted probability of a subject having improved mJSW and clinical response, compared to a subject who did not, for PBO, 0.03 mg, 0.07 mg, and 0.23 mg doses of SM04690
- AUC of 0.5 means the model is no better at predicting an outcome than random chance. AUC of 1 means the model perfectly predicts a subject's outcome
- AUC > 0.7 is defined as "acceptable" and AUC > 0.8 as "excellent"^{1,2} concordance between change in mJSW and clinical response

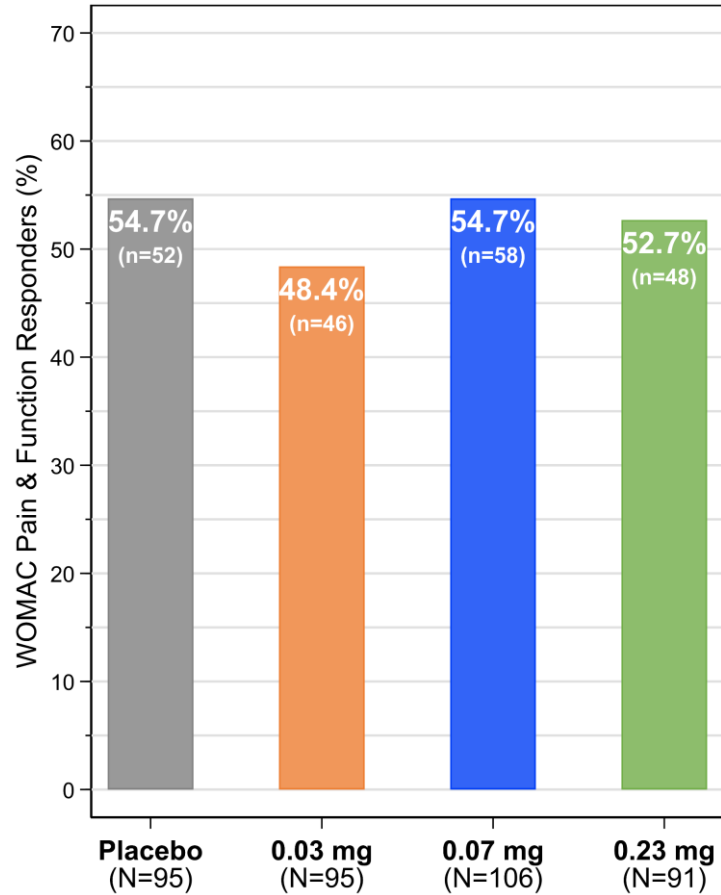
1. Harrell FE Jr. (2001) *Regression modeling strategies*.

2. Hosmer DW and Lemeshow S. (2000) *App Logistic Regression (2nd ed)*.

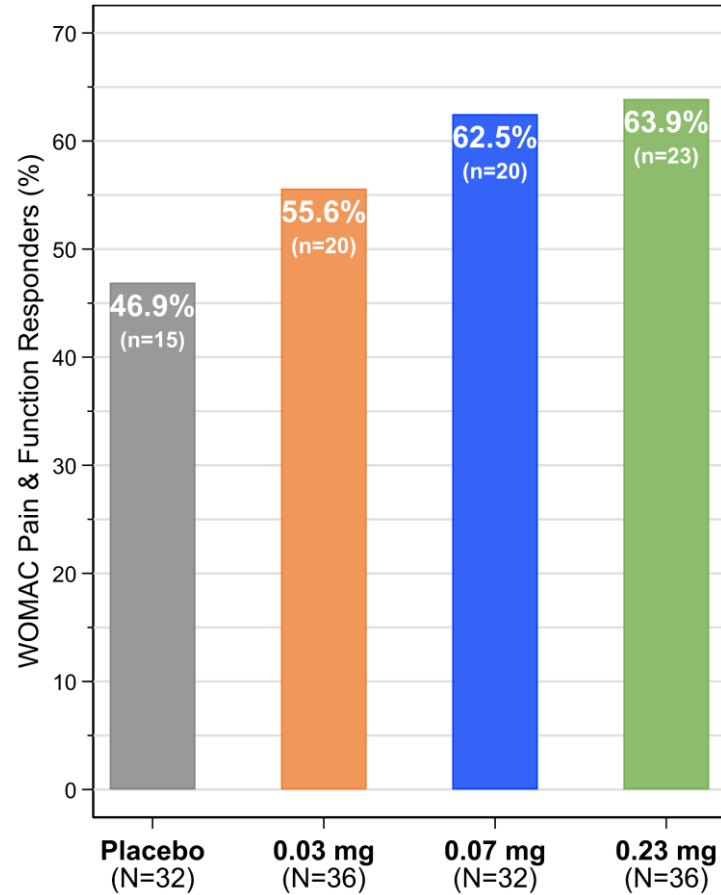
WOMAC Pain and Function Responders to SM04690 & PBO

Outcomes measured at Week 52, post-hoc analysis

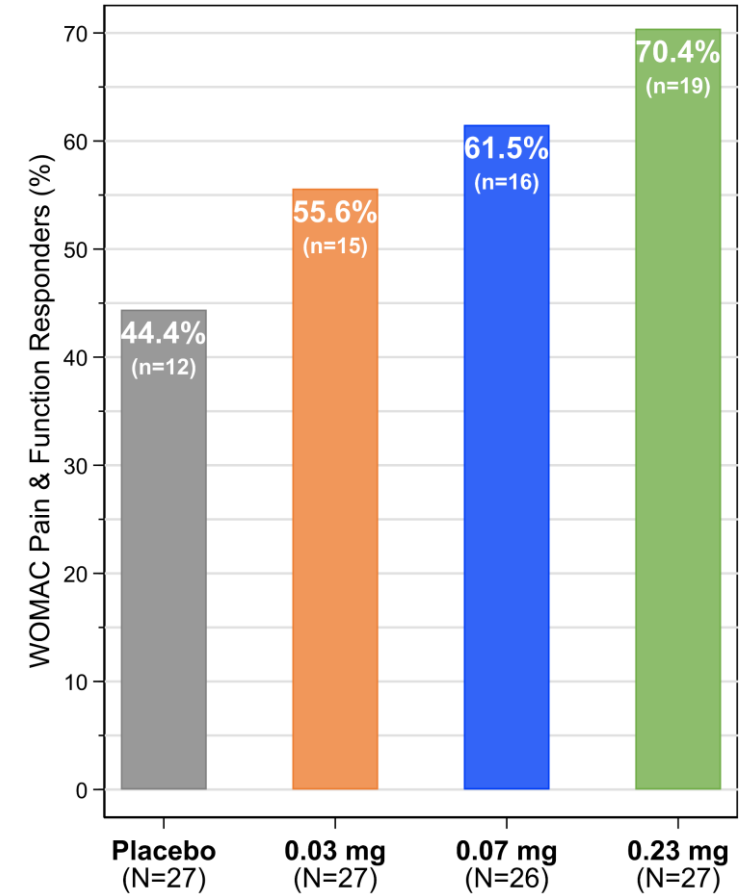
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Unilateral Symptomatic



Unilateral Symptomatic without Widespread Pain

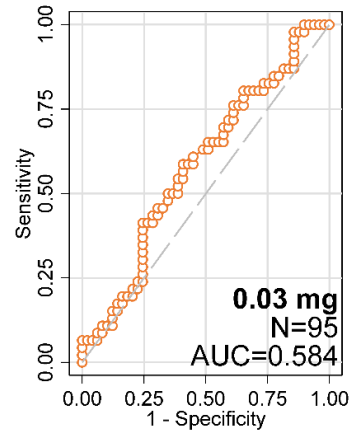
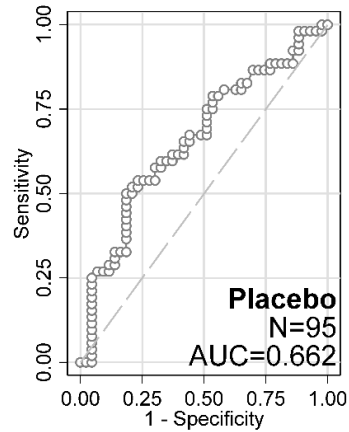


Pain and Function response defined as having both Pain and Function responses separately. No formal statistical comparisons made.

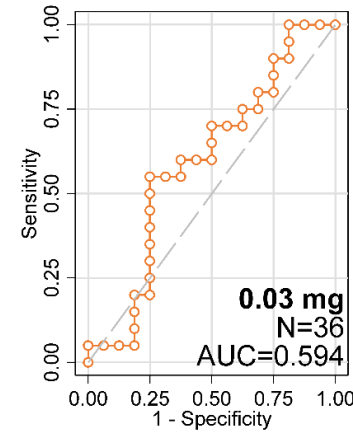
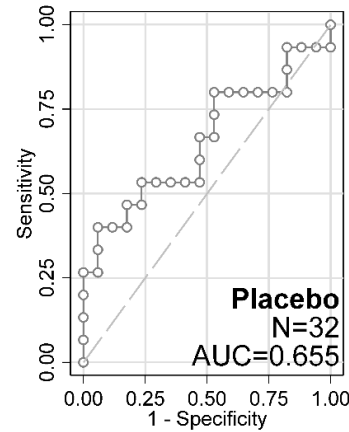
mJSW change concordance with clinical responders

Outcomes measured at Week 52, post-hoc analysis

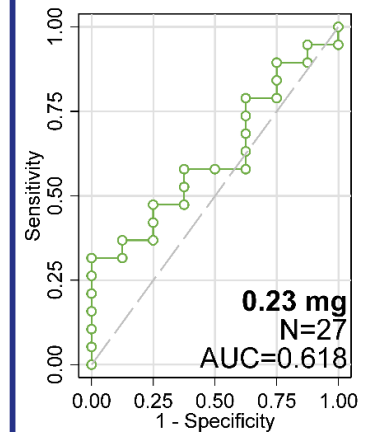
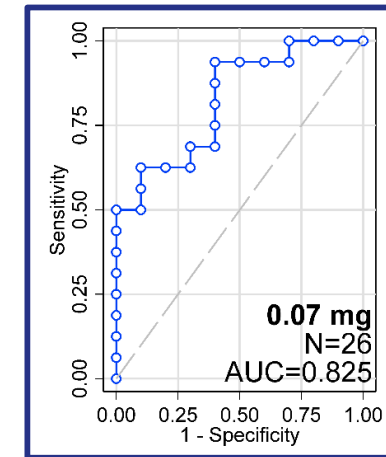
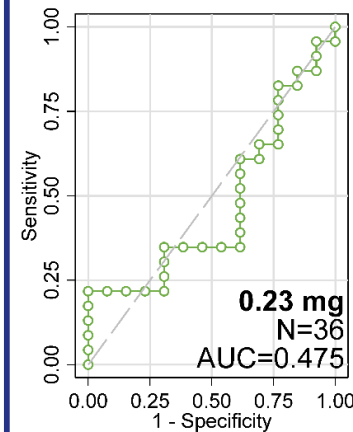
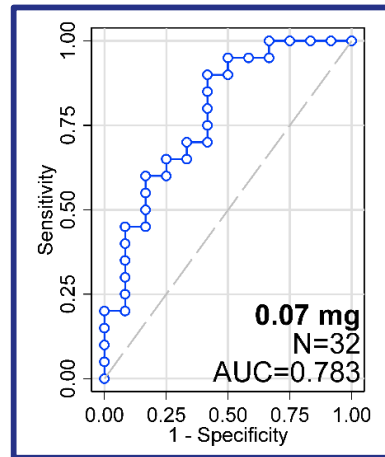
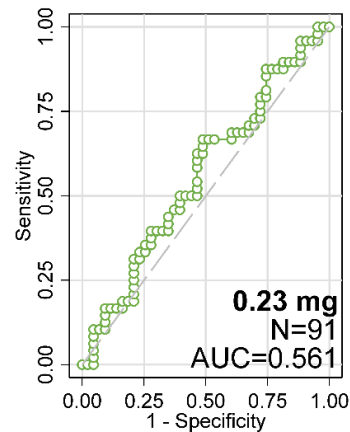
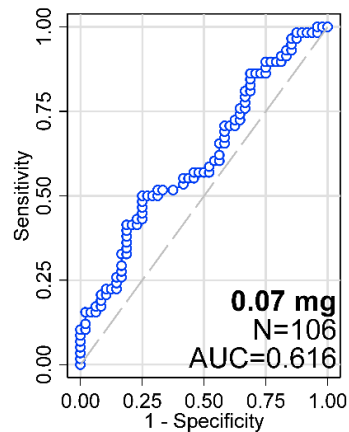
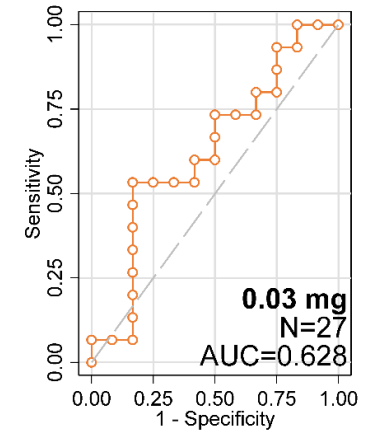
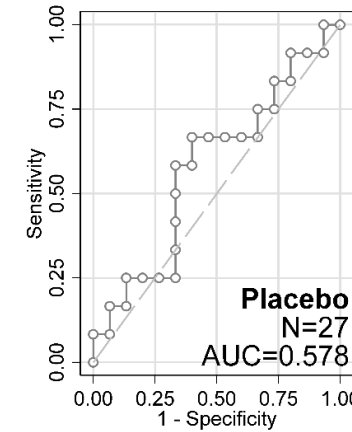
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Unilateral Symptomatic



Unilateral Symptomatic without Widespread Pain



Pain and Function response defined as having both Pain and Function responses separately. Baseline mJSW-adjusted logistic regression used to estimate concordance.

Conclusions

In this post-hoc analysis:

- In Unilateral Symptomatic knee OA subjects treated with SM04690 0.07 mg, 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

Thank you