Treatment of Knee Osteoarthritis with Intra-Articular SM04690, in Development as a Potential DMOAD, Improved WOMAC A1 "Pain on Walking" – Results from a Phase 2 Study of a Wnt Pathway Inhibitor

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Background

SM04690 is an intra-articular (IA), small molecule, Wnt Pathway inhibitor, in development as a potential disease modifying knee OA drug (DMOAD).

- Preclinical studies demonstrated inhibition of inflammation and cartilage degradation compared with vehicle.[1]
- A phase 2a study demonstrated improvements in WOMAC Pain, Function and radiographic medial joint space width (mJSW) compared with placebo (PBO) in clinically relevant subgroups at 52 weeks.[1]

WOMAC Question A1: 'How much pain have you had when walking on a flat surface?

- Major symptom of tibio-femoral OA and differentiates from patella-femoral OA.[3,4]
- Multi-dimensional question incorporating pain and function scored 0-10 on visual-analog scale (VAS).
- Onset usually earlier than rest pain.[5]
- Used as a knee OA clinical trial endpoint for IA hyaluronic acid and oral NSAIDs.

A post-hoc analysis of responses to SM04690 measured by WOMAC A1 from this phase 2a study was performed.

Methods

Knee OA subjects met ACR criteria, Kellgren-Lawrence (KL) grades 2 or 3, pain 30-80 mm (0-100 mm VAS) in target (most painful) knee.

- Subjects received 2 mL, IA SM04690 0.03 mg, 0.07 mg, 0.23 mg, or PBO.
- WOMAC Pain & Function scores collected at Weeks 0, 4, 13, 26, 39, and 52.
- Two clinically relevant subgroups were identified which demonstrated significant improvements compared with PBO for 0.07 mg group at 52 weeks:

  1) Unilateral symptomatic (UNI; pre-specified) and 2) Unilateral symptomatic w/o widespread pain (UNI WP-; post-hoc): Widespread Pain Index ≤ 4, Symptom Severity score ≤ 2)[6]
- WOMAC A1 response effect sizes in 0.07 mg dose group were compared to WOMAC Pain and Function effect sizes in UNI and UNI WP-.

Results

Figure 1. WOMAC Function, Pain, and A1 Subscores Showed Similar Responses Over Time in UNI WP- Subjects

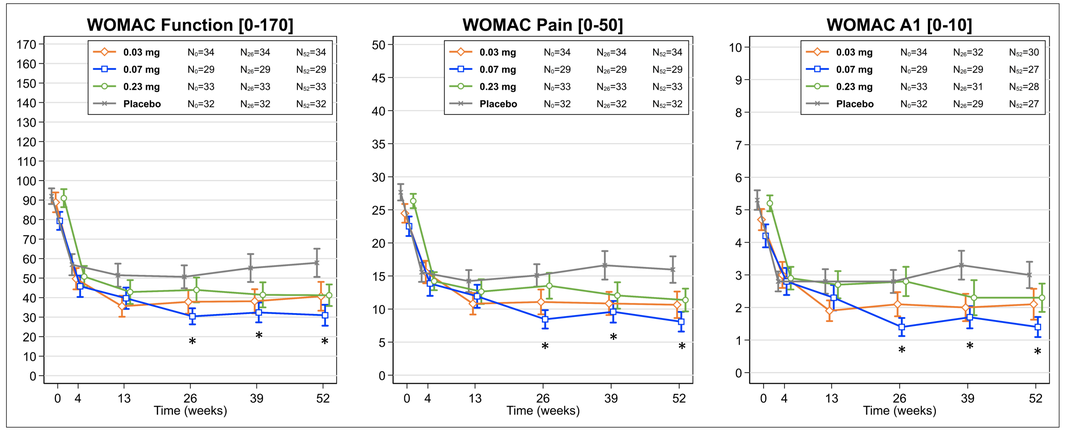

Table 1. Week 52 Effect Size: UNI WP- Subjects

	0.07 mg SM04690 vs. Placebo		
Outcome	**Difference**	**Mean Squared Error**	**Effect Size**
WOMAC A1	-1.40	3.36	0.764
WOMAC Pain	-5.93	81.74	0.655
WOMAC Physical Function	-24.65	1061.00	0.757

- 455 subjects were enrolled, mean age 60.3 [±8.7], BMI 29.9 [±4.6] kg/m^2, female 58.9%, KL 3 64.2%, UNI 36.0% and UNI WP- 28.1%.
- WOMAC A1, Pain and Function treatment effect from 0.07 mg dose in UNI WP- subgroup showed statistically significant improvement over PBO at Weeks 26, 39, and 52.
- WOMAC A1, Pain and Function effect sizes from 0.07 mg dose in UNI WP- subgroup were all numerically similar.

Conclusions

- In this post-hoc analysis of phase 2a data, in UNI WP- subgroup, SM04690 0.07 mg dose demonstrated the following responses at Week 26 persisting through Week 52:
  - Significant WOMAC A1 pain improvements compared with PBO, which mirrored changes seen in full composite WOMAC Pain and Function scores.
  - WOMAC A1 effect size was also similar to those demonstrated by WOMAC Pain and Function subscores at Week 52; therefore supporting the responsiveness of the A1 question.
- The improvements seen in pain and function suggested SM04690, a potential DMOAD, has a role in the treatment of signs and symptoms of knee OA.

References

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