Efficacy and Safety from a Phase 2b Trial of SM04690, a Novel, Intra-articular, Wnt Pathway Inhibitor, in Development as a Potential DMOAD, for the Treatment of Osteoarthritis of the Knee

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Poster #L03

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 previous phase 2a study of SM04690 demonstrated positive effects on knee OA pain, physical function, and medial joint space width (mJSW) at 52 weeks in key subgroups compared with placebo (PBO).[1]
- A 24 week phase 2b study was performed to refine patient reported outcome (PRO) measures, target population, and dose, and to evaluate safety. **PRO results are presented**.

Methods

- Subjects had ACR-defined knee OA, Kellgren-Lawrence (KL) grades 2-3, Pain Numeric Rating Scale (NRS) ≥4 and ≤8 in target knee, <4 in contralateral knee. A single IA injection of 2 mL SM04690 (0.03, 0.07, 0.15 or 0.23 mg), or vehicle PBO, was given in the target knee at baseline.
- Study subjects were stratified 50% unilateral symptomatic, 50% bilateral symptomatic, 80% Widespread Pain Index (WPI) ≤4, Symptom Severity Score ≤2, and 20% WPI >4 and Symptom Severity Score >2.
- PRO endpoints included change from baseline in weekly average of daily OA target knee pain by numerical rating scale diary (NRS, [0-10]), Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) Pain [0-100], WOMAC Physical Function [0-100], and Patient Global Assessment (PTGA) (VAS [0-100]).
- Radiographic endpoint of change from baseline in mJSW was measured at Week 24.
- The sample size for this study was based upon accepted dose finding statistical practice.[2]

Results and Discussion

Figure 1. PROs: Change from Baseline compared to PBO Over Time

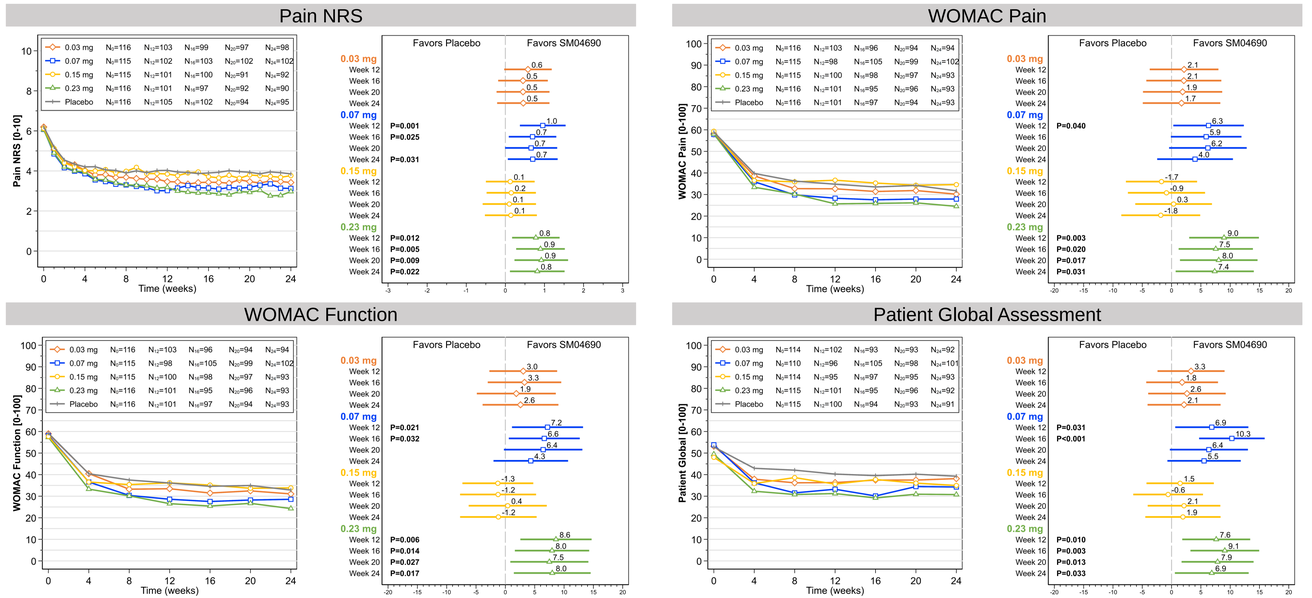

**Figure 1. Actual observations over time and ladder plots depicting mean improvement (± 95% CI) of SM04690 compared with baseline-adjusted ANCOVA versus placebo.*

- 695 subjects (mean age 59.0 [±8.5] years, BMI 29.0 [±4.0] kg/m^2, female 58.4%, KL3 57.3%) were enrolled and dosed; 635 (91.4%) completed the study.
- Positive responses were seen in 0.03, 0.07, and 0.23 mg dose groups compared with PBO, with statistical significance achieved in 0.07 mg at most and 0.23 mg groups at all timepoints (Fig. 1).
- 0.15 mg group showed positive responses compared to baseline, similar in magnitude to PBO.
- No significant differences between PBO and treatment mJSWs were observed at 24 weeks.
- SM04690 appeared safe and well tolerated. Arthralgia was the most common adverse event (AE). All AE rates were comparable between treatment and control groups. Six serious AEs were reported in 6 patients, all deemed unrelated by study physician.

Conclusions

- **In this phase 2b trial, SM04690 showed statistically significant improvements from baseline in pain and function compared with PBO.**
  - **All doses appeared safe and well tolerated**
  - **0.07 mg and 0.23 mg are potentially efficacious doses**
  - **Further analyses of subject characteristics may refine target population**
- **The improvements seen in pain and function suggested SM04690 has a potential role in the treatment of signs and symptoms of knee OA.**
- **SM04690 is undergoing further investigation as a potential DMOAD with long-term studies evaluating structure and morphology.**
- **Pivotal studies are planned.**

Reference

1. Yazici Y, et al. *Arthritis Rheumatol.* 2017; 69 (suppl 10).
2. Ting N, et al. Phase II Clinical Development of New Drugs. Singapore: Springer; 2017.

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