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

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Poster #29

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 to vehicle[1]
- A previous phase 2a study demonstrated positive effects on Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) Pain, Function, and medial joint space width (mJSW) at 52 weeks in key subgroups compared to placebo (PBO)[1]
- A 24-week phase 2b study was performed to refine target population, dose, and to evaluate patient reported outcomes (PROs) and safety
- **PRO results are presented**

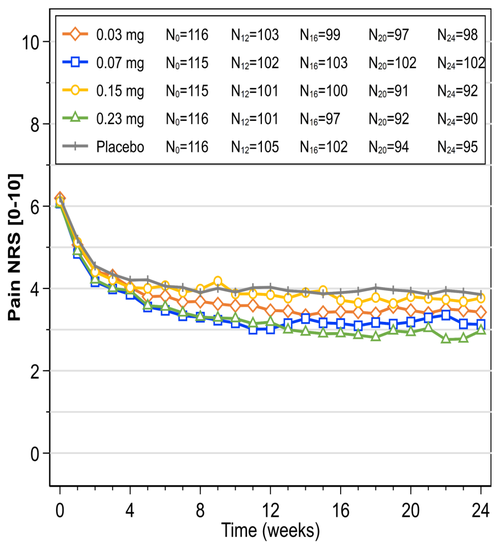
Methods

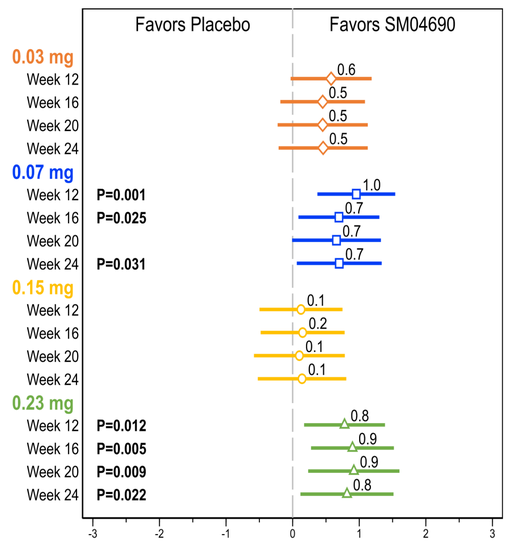
- Subjects had ACR-defined knee OA, Kellgren-Lawrence (KL) grade 2 or 3, Pain Numeric Rating Scale (NRS) scores ≥4 and ≤8 in target knee, and <4 in contralateral knee
- A single IA injection of 2 mL SM04690 (0.03, 0.07, 0.15, or 0.23 mg) or vehicle PBO was given in the target knee at baseline
- Study subjects were stratified 50% unilateral symptomatic, 50% bilateral symptomatic, 80% Widespread Pain Index (WPI) ≤4, Symptom Severity Score ≤2, and 20% WPI >4, 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], 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

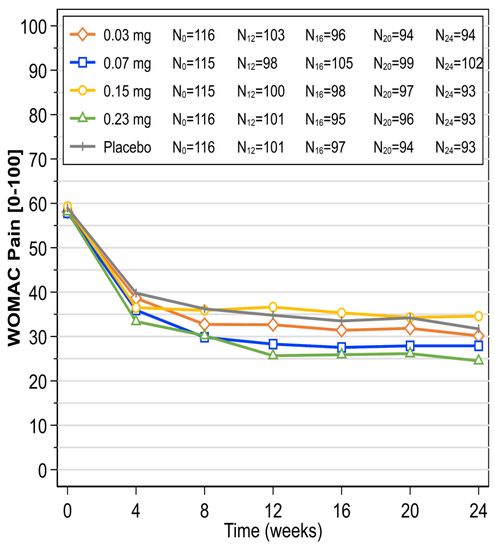
Figure 1. PROs: Change from baseline compared to PBO over time

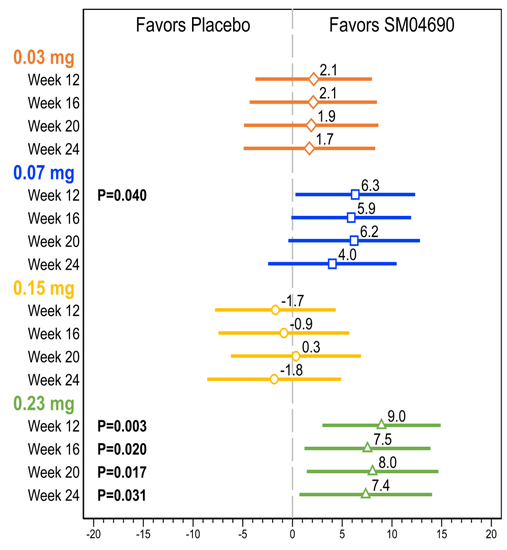
Pain NRS



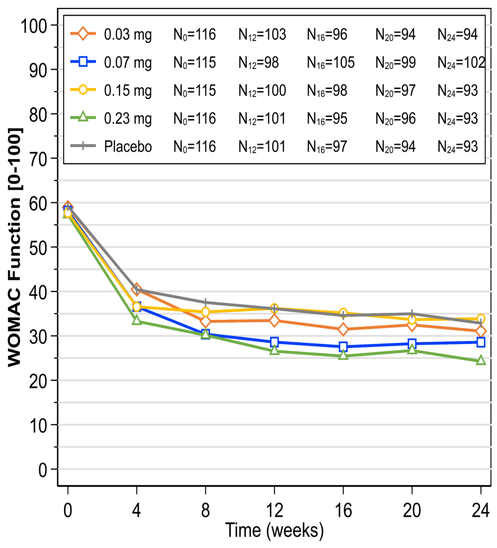


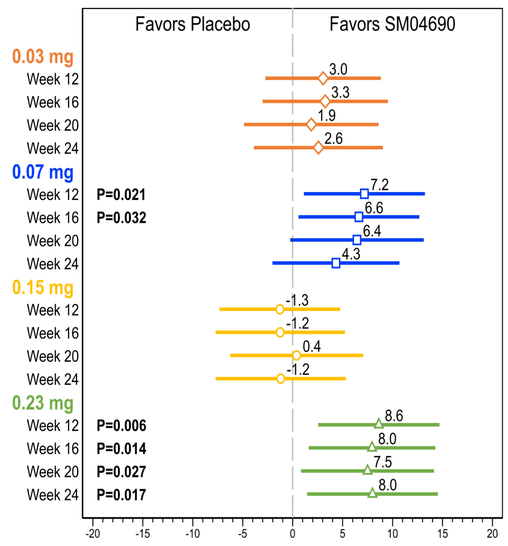
WOMAC Pain



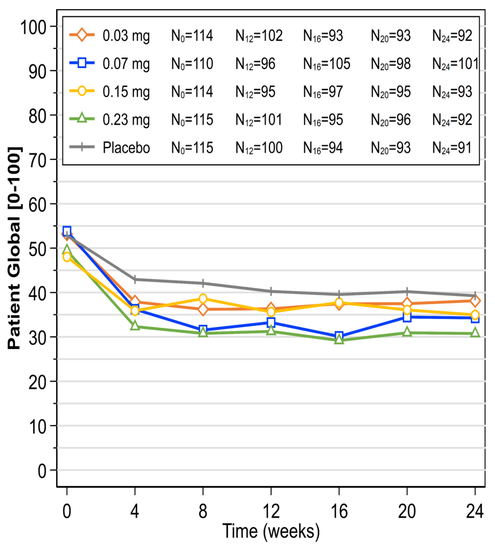


WOMAC Function





Patient Global Assessment



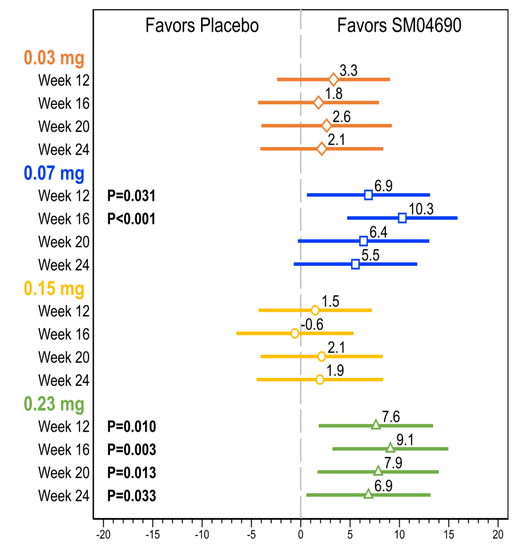


Figure 1. Actual observations over time and ladder plots depicting mean improvement (± 95% CI) of SM04690 compared with baseline-adjusted ANCOVA versus placebo

Conclusions

- **In this study, SM04690 showed statistically significant improvements from baseline in pain and function compared to PBO**
  - **All doses appeared safe and well tolerated**
  - **0.07 mg and 0.23 mg appeared to be potentially efficacious doses**
  - **Further analyses of subject characteristics may refine target population**
- **Improvements seen in pain and function suggest that SM04690 has a potential role in treatment of knee OA signs and symptoms**
- **Further investigation of SM04690 as a potential DMOAD with studies evaluating structure and morphology are underway**
- **Pivotal studies are planned**

Results

- 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; 635 (91.4%) completed the study
- Positive responses were seen in 0.03, 0.07, and 0.23 mg dose groups compared to PBO, with statistical significance achieved in the 0.07 mg group at most timepoints and in the 0.23 mg group at all outcome timepoints (Fig. 1)
- 0.15 mg group showed positive responses compared to baseline, similar in magnitude to PBO
- No significant differences were observed in the change in mJSW from baseline to Week 24 between PBO and treatment groups
- SM04690 appeared safe and well tolerated. All AE rates were comparable between treatment and control groups. Six serious AEs were reported in 6 patients, all deemed unrelated by study physician

References

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.

All authors are employees, shareholders, or consultants of Samumed, LLC. Other disclosures are listed in the published abstract.

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