Treatment of Knee Osteoarthritis with Intra-Articular SM04690, in Development as a Potential DMOAD, Improved Health-Related Quality of Life – Results from a Phase 2 Study of a Novel Wnt Pathway Inhibitor

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Background
Short Form Survey (SF-36) is a measure of health-related quality of life (HRQoL):
- OA patients report significant loss of HRQoL.
- SF-36 is a multi-dimensional instrument with 8 domains. It is validated for assessing health status outcomes in randomized controlled trials (RCTs) in patients.2,3
- SM04690 is an intra-articular (IA), small molecule, Wnt Pathway inhibitor, in development as a potential disease modifying knee OA drug (DMOAD).
- In preclinical studies it inhibited inflammation and cartilage degradation compared with vehicle.4
- A phase 2a RCT demonstrated improvements in WOMAC Pain, Function and radiographic medial joint space width compared with placebo (PBO) in clinically relevant subgroups at 52 weeks.4

Methods
Subjects and study design
- Knee OA subjects (N=455) meeting ACR criteria, Kellgren-Lawrence (KL) grade 2 / 3, pain 30-80 mm (0-100 mm visual analog scale) in target knees were enrolled.
- Subjects were randomized to receive a single IA 2 mL, 0.03 mg, 0.07 mg, 0.23 mg SM04690, or PBO (phosphate buffered saline).
- Baseline-adjusted ANCOVA analyses were conducted in the intent-to-treat (ITT) population, with SF-36 improvements ≥ minimum clinically important differences (MCID - 5 points for domain scores; 2.5 points for summary component scores5) noted.
- Two subgroups were explored: 1) unilateral symptomatic (UNI) knee OA (pre-specified) and 2) unilateral symptomatic knee OA without widespread pain or comorbid symptoms (Widespread Pain Index ≤4 and Symptom Severity ≤2, post-hoc: UNI WP).

Results
Figure 1. SF-36 Scores at 52 Weeks

- **455 subjects enrolled, mean age 60.3 [±8.7], BMI 29.9 [±4.6] kg/m²), female 58.9%, KL 3 64.2%, UNI 36.0% and UNI WP -28.1%.
- 0.07 mg UNI subjects showed significant improvements (p<0.05) in 3 of 8 domains compared with PBO at 52 weeks and exceeded AG norms (Fig. 1).
- 0.07 mg UNI WP- subjects showed significant improvements in 7 of 8 domains and exceeded AG norms (Fig 1.)

Conclusions
- In this phase 2a trial at 52 weeks, IA SM04690 0.07 mg dose UNI and UNI WP- demonstrated:
  - Statistically significant and clinically meaningful HRQoL improvements compared with PBO
  - Improvements beyond age and gender normative scores
- These data, along with phase 2a clinical outcomes that showed improvements in pain and function, support further investigation of SM04690, as a potential DMOAD, for treatment of knee OA.

References

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