Radiographic Outcomes from a Randomized, Double-Blind, Placebo-Controlled, Phase 1 Study of a Novel, Intra-Articular, Injectable, Wnt Inhibitor (SM04690) in the Treatment of Osteoarthritis of the Knee

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Background

- Osteoarthritis (OA) is a major cause of activity limitation and physical disability in adults. OA accounts for 6.3% of all years of life lost to disability in the U.S., making its disease burden the third greatest in the nation and more than dementia and other degenerative and hereditary CNS disorders (5.0%), diabetes (3.3%), HIV (1.6%), and rheumatoid arthritis (1.3%).[1]
- Loss of cartilage is a hallmark of OA and measurement of joint space width (JSW) provides a surrogate measure of cartilage loss.
- The Wnt signaling pathway is known to play a central role in the formation of joint tissues, and altered Wnt signaling has been associated with cartilage loss in preclinical and clinical studies.[2]
- Samumed is developing a small molecule inhibitor of the Wnt pathway, SM04690, as a potential OA therapeutic to be administered in the form of an intra-articular (IA) injection into the affected joint.
- A Phase 1, dose escalation study evaluating the safety, tolerability, pharmacokinetics and pharmacodynamics of SM04690 in subjects with moderate to severe knee OA was conducted. The primary objective of this study was to evaluate the safety of SM04690, reported previously.[3]
- The purpose of the exploratory analysis presented here was to evaluate radiographic outcomes to further assess proof of concept of efficacy of this molecule.

Methods

- This was a phase 1, first-in-human, multicenter, placebo-controlled, single-dose, dose-escalation study of a Wnt pathway inhibitor in subjects suffering from moderate to severe symptomatic knee OA.
  - *Select inclusion criteria* – Age, 50-75 years; Western Ontario and McMaster Universities Arthritis Index (WOMAC) Total score, 36-72 (out of 96); Kellgren-Lawrence (KL) grade 2 or 3
  - A full list of the inclusion and exclusion criteria for this study can be found on www.clinicaltrials.gov (NCT02095548).
  - Dosing sequence included the following concentration levels: 0.03 mg, 0.07 mg, and 0.23 mg SM04690 per 2 mL injection.
  - Placebo was diluent containing 0.5% carboxymethylcellulose sodium and 0.05% polysorbate 80 in pH 7.4 phosphate buffered saline.
  - Sample size: 20 subjects (randomized 4:1, 16 active: 4 placebo) per dosing cohort was selected for this exploratory study.
  - Subjects were given a single IA injection in the target knee on Treatment Day 1 and participated in a follow-up period of 24 weeks.
- Radiographs of the target knee were taken using lateral and posterior-anterior view of the target knee in full extension, weight-bearing position during the screening period and at Week 24 to document change from baseline in JSW.
- An exploratory analysis of change in JSW was conducted using repeated measures analysis of covariance (ANCOVA) adjusting for baseline JSW in the modified Intention-to-treat (mITT) population. The mITT population included all subjects *as treated*.

Results

- A total of 30/61 (49%) subjects had a KL score of 2 and 31/61 (51%) subjects had a KL score of 3. Notably, in the 0.23 mg treatment group, there were 69% (11/16) subjects with a KL score of 3 compared to 41% (7/17) in 0.03 mg and 47% (8/17) in 0.07 mg cohorts (Table 1).
- No change in medial JSW by radiography from Baseline to Week 24 was observed in the 0.03 mg cohort. The 0.07 mg cohort showed a greater mean increase in medial JSW than the other active treatment cohorts (P=0.02 versus placebo), while there was a mean decrease in medial JSW in the 0.23 mg and placebo cohorts (Table 2).
- Individual subject results demonstrate consistent within treatment group responses, with results not driven by outliers (Figure 1).
- Subjects were defined as responders if their JSW change from baseline to 24-weeks was ≥0. Responders in active treatment cohorts had greater median increases in medial JSW than placebo (Figure 1):
  - 0.03 mg: N=9 (60%), median 0.45 mm
  - 0.07 mg: N=12 (80%), median 0.65 mm
  - 0.23 mg: N=7 (44%), median 0.59 mm
  - Placebo: N=6 (55%), median 0.28 mm

Table 1. Subject Characteristics [mITT]

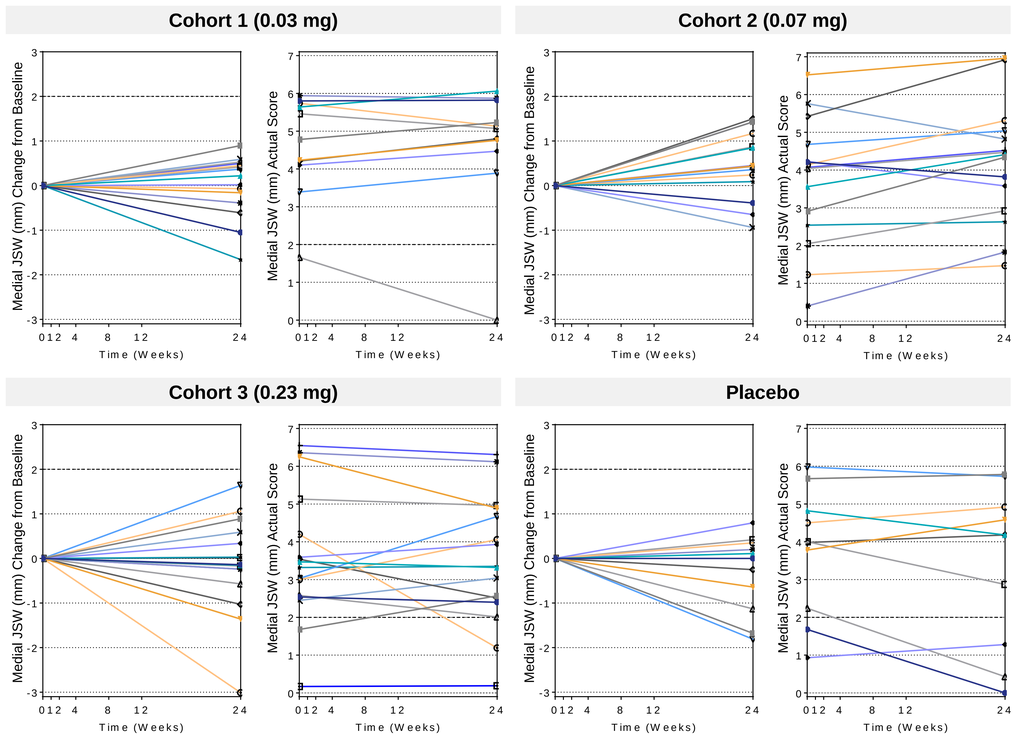
	0.03 mg	0.07 mg	0.23 mg	Placebo
N	**17**	**17**	**16**	**11**
Age (Years) [Mean (SD)]	**63.2 (6.6)**	**60.5 (5.3)**	**63.1 (4.9)**	**64.1 (5.9)**
BMI (kg/m²) [Mean (SD)]	**31.4 (4.8)**	**30.6 (4.9)**	**28.7 (5.0)**	**31.2 (3.4)**
Female [n(%)]	**10 (59%)**	**13 (76%)**	**12 (75%)**	**6 (55%)**
Race [n(%)]				
White	**14 (82%)**	**14 (82%)**	**14 (88%)**	**9 (82%)**
African-American	**2 (12%)**	**3 (18%)**	**1 (6%)**	**2 (18%)**
Asian	**1 (6%)**	**0**	**1 (6%)**	**0**
KL Grade 3 [n(%)]	**7 (41%)**	**8 (47%)**	**11 (69%)**	**5 (45%)**

Table 2. Medial Joint Space Width [mITT]

	0.03 mg	0.07 mg	0.23 mg	Placebo
N	**15**	**15**	**16**	**11**
Baseline (mm) [Mean (SD)]	**4.50 (1.70)**	**3.72 (1.66)**	**3.62 (1.75)**	**3.74 (1.58)**
Week 24 (mm) [Mean (SD)]				
Actual	**4.50 (1.72)**	**4.20 (1.59)**	**3.47 (1.68)**	**3.41 (2.03)**
Change from baseline	**0.00 (0.69)**	**0.49 (0.75)**	**-0.15 (1.07)**	**-0.33 (0.87)**

Results (continued)

Figure 1. Medial Joint Space Width Over Time [mITT]



Discussion

- Exploratory radiographic findings measuring the change from baseline at Week 24 in JSW suggested no change in the 0.03 mg cohort, an increase in the 0.07 mg cohort, and a decrease in the 0.23 mg cohort and the placebo group (Table 2). The analyses suggested that treatment with SM04690 may have potentially maintained or increased JSW in the 0.03 mg and 0.07 mg cohorts compared to placebo.
- Our findings in this study should be interpreted with caution given the small number of subjects enrolled.
- These study data support the development of an ongoing phase 2 study (NCT02536833) designed to further investigate additional safety, dose response, and efficacy in subjects with knee OA.

References

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