Background

- Osteoarthritis (OA) is a major cause of activity limitation and physical disability in adults. OA affects 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%).

- Loss of cartilage is a hallmark of OA and measurement of joint space width (JSW) provides a surrogative 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.

- Samumed is developing a small molecule inhibitor of the Wnt pathway, SM04690.

- 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%).

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.

- The Wnt signaling pathway has been shown to be involved in the development of joint tissues, and altered Wnt signaling has been associated with cartilage loss in preclinical and clinical studies.

- Samumed is developing a small molecule inhibitor of the Wnt pathway, SM04690.

- 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%).

- 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.

- 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 (Table 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

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 median 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 median 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
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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).

- 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