Safety, Efficacy, and Biomarker Outcomes of a Novel, Intra-Articular, Injectable, Wnt Inhibitor (SM04690) in the Treatment of Osteoarthritis of the Knee: Interim, Exploratory Analysis of Results from a Randomized, Double-Blind, Placebo-Controlled Phase 1 Study

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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]
- Patients with OA experience significant risk of developing comorbidities and have an association with increased mortality compared to the general population.[2-4]
- Knee OA is characterized by the destruction of articular cartilage, subchrondral bone alterations and varying degrees of synovitis.
- 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.[5]
  - In osteoarthritic joints, increased Wnt signaling stimulates cartilage destroying metalloprotease production and drives resident stem cells to become bone-forming osteoblasts instead of cartilage-forming chondrocytes.[5]
  - In an animal model of OA, inhibition of the Wnt pathway reverses both of these processes leading to increased cartilage stability and formation.[6]
  - Therefore, a drug which inhibits the Wnt pathway in knee OA is potentially disease modifying, compared to current treatments which only relieve the signs and symptoms of OA.
- Samumed is developing a small molecule inhibitor of the Wnt pathway, SM04690, as a potential OA therapeutic to be administered in the form of a local injection into the affected joint.
- The purpose of this Phase 1 study was to evaluate the safety and tolerability of SM04690 administered by intra-articular injection into a target knee joint of moderate to severe symptomatic OA subjects.

Methods

- This is a first-in-human, multicenter, 24-week, placebo-controlled, single-dose, dose-escalation safety study of a Wnt pathway inhibitor in subjects suffering from moderate to severe symptomatic knee OA.
  - *Inclusion criteria* – Age, 50-75 years; Western Ontario and McMaster Universities Arthritis Index (WOMAC) Total score, 36-72 (out of 96); Kellgren-Lawrence grade, 2 or 3; willingness to omit pain medication for 24 hours prior to pain assessments
  - *Exclusion criteria* – BMI >40; treatment with IA steroids within 2 months or HA derivatives within 6 months prior to injection
  - A full list of the inclusion and exclusion criteria for this study can be found on 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.
  - Sample size: 20 subjects (randomized 4:1, 16 active: 4 placebo) per dosing cohort was selected for this exploratory study.
  - Placebo was a diluent containing 0.5% carboxymethylcellulose sodium and 0.05% polysorbate 80 in pH 7.4 phosphate buffered saline.
  - Subjects were given a single, intra-articular injection in the target knee on Treatment Day 1 and participated in a follow-up period of 24 weeks.
- Safety, pharmacokinetics (PK), biomarker, and efficacy data were collected at baseline and during the 24-week follow-up period:
  - *Safety*: Adverse events (AEs), concomitant medications, clinical laboratory sampling, medical history, vital signs, ECGs, hip bone density (DXA) analysis, qCT of the target knee, evaluation of bone edema via MRI[7]
  - *PK*: Samples collected 0, 4, and 24 hours post dose, and at Weeks 4 and 12
  - *Biomarkers:* Procollagen type 1 N-propeptide (P1NP), beta C-terminal telopeptide of type 1 collagen (βCTX), and cartilage oligomeric matrix protein (COMP)
  - *Efficacy*: WOMAC Total score, WOMAC Function and Pain subscores, pain VAS, Physician Global Assessment of Disease Activity, MRI[7], radiographs
- Efficacy assessments were used to determine the percentage of OMERACT-OARSI "strict" responders.[8]
- Exploratory analyses of efficacy outcomes were conducted using a baseline-adjusted repeated measures analysis of covariance (ANCOVA) in the Intention-to-Treat (ITT) population.
- Sponsor was unblinded after Week 12 for each cohort; site investigators remained blinded.
- All AEs reported in this study were considered related to study medication. Investigator opinion regarding whether AEs were related to SM04690 was also collected for informational purposes.

Results

Subject Characteristics

	0.03 mg	0.07 mg	0.23 mg	Placebo
N	17	16	16	12
Age at Consent (Years) [Mean (SD)]	63.2 (6.6)	60.6 (5.5)	63.1 (4.9)	63.7 (5.8)
BMI (kg/m²) [Mean (SD)]	31.4 (4.8)	31.3 (4.1)	28.7 (5.0)	30.2 (4.6)
Female [N(%)]	10 (59%)	12 (75%)	12 (75%)	7 (58%)
Race [N(%)]				
White	14 (82%)	13 (81%)	14 (88%)	10 (83%)
African-American	2 (12%)	3 (19%)	1 (6%)	2 (17%)
Asian	1 (6%)	0	1 (6%)	0
Kellgren-Lawrence Grade 3 [N(%)]	7 (41%)	8 (50%)	11 (69%)	5 (42%)

Safety

	0.03 mg	0.07 mg	0.23 mg	Placebo
SAE(s) Reported	0	1*	0	0
DLT(s) Reported	0	2*	0	0
AE(s) Reported – All	15	11	25	19
AE(s) Reported – Target knee				
Arthralgia	1	1	1	4
Injection site bruising	0	0	1	0
Injection site pain	0	2	1	0
Joint injury	1	0	0	0
Joint stiffness	0	0	1	0
Joint swelling	0	1	1	1
Meniscus injury	0	0	1	0

*Increased target knee pain (DLT) and paroxysmal tachycardia (DLT and SAE)

	0.03 mg	0.07 mg	0.23 mg	Placebo
Subjects Who Reported AE(s) [N(%)]	9 (53%)	6 (37%)	7 (44%)	6 (50%)
Subjects Who Reported No AE(s) [N(%)]	8 (47%)	10 (63%)	9 (56%)	6 (50%)

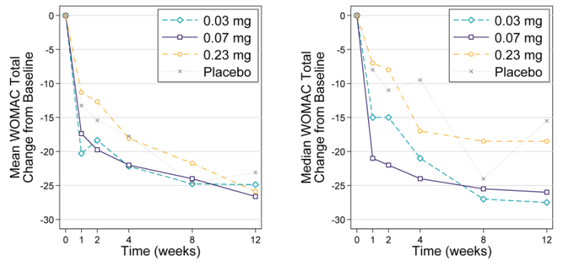
Pharmacokinetics

- PK samples were collected at 0, 4, and 24 hours post dose, and at Weeks 4 and 12.
- All subjects in cohorts 1, 2, and 3 had levels below limits of quantitation (BQL < 0.100 ng/mL) at all recorded timepoints.

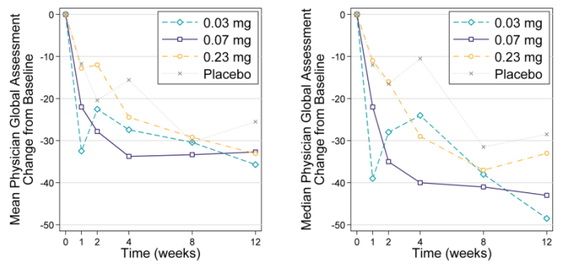
Biomarkers

- Biomarker data showed significant reduction in COMP in the 0.07 mg cohort at Week 12 (130.13 ng/mL, P=0.001).
- There were no significant changes in COMP in the 0.03 mg cohort, 0.23 mg cohort, or the placebo group, or in βCTX or P1NP in any treatment or placebo group.

WOMAC Total [0-96]



Physician Global Assessment of Disease Activity [0-100]



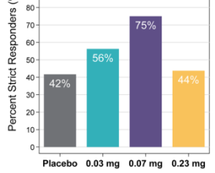
WOMAC Function [0-68]

	0.03 mg	0.07 mg	0.23 mg	Placebo
N	17	16	16	12
Baseline [Mean (SD)]	39.1 (7.2)	37.6 (7.8)	40.4 (8.6)	34.5 (10.6)
Week 12 [Mean (SD)]				
Actual	20.3 (10.5)	18.4 (15.9)	22.6 (10.3)	18.8 (11.8)
Change from baseline	-18.4 (13.5)	-19.2 (16.3)	-17.8 (15.1)	-15.8 (13.1)

WOMAC Pain [0-20]

	0.03 mg	0.07 mg	0.23 mg	Placebo
N	17	16	16	12
Baseline [Mean (SD)]	10.8 (2.0)	10.8 (3.0)	11.4 (2.7)	9.9 (2.0)
Week 12 [Mean (SD)]				
Actual	6.3 (2.7)	5.3 (4.5)	5.8 (2.7)	5.3 (3.9)
Change from baseline	-4.4 (3.0)	-5.6 (4.7)	-5.7 (4.4)	-4.6 (4.1)

OARSI Responders – Week 12



Strict OARSI Responders:

- WOMAC Function subscore improvement of ≥50% with a corresponding Function score improvement of ≥20 points (scaled to [0-100]), OR
- WOMAC Pain subscore improvement of ≥50% with a corresponding Pain score improvement of ≥20 points (scaled to [0-100])

Discussion

- These interim data from the ongoing phase 1 trial suggest that a single intra-articular injection with the novel Wnt inhibitor SM04690 into the knee of OA subjects appears safe, well-tolerated, and potentially effective in reducing pain and improving function.
  - All subjects had PK levels below the limit of quantitation at all recorded time points.
  - 27 of 49 (55%) exposed subjects reported no AEs. One SAE (paroxysmal tachycardia) was considered unrelated to study medication in the opinion of the reporting investigator.
  - All AEs reported in this study were deemed related to study medication. Only 16 of 77 (22%) AEs were considered related to study medication by the reporting investigator.
- This phase 1 study was not powered to see any statistically significant differences between treatment groups and placebo. However, the data suggest that subjects treated with SM04690 were more likely to have a strict OARSI response than placebo. At Week 12, 75% of 0.07 mg cohort achieved strict OARSI response compared to 42% of placebo (OR = 4.2, P = 0.081).
- These study data supported the development of an ongoing phase 2 study (NCT02536833; currently enrolling) designed to formally further investigate additional safety, dose response, and efficacy in subjects with OA.

References

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