Imaging Outcomes Using an Intra-Articular Injection (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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Poster# 313

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 are 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]
  - 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 in the affected joint.
- To assess the safety and efficacy of SM04690, Samumed used magnetic resonance imaging (MRI):
  - Safety evaluations included assessment of bone marrow edema by MRI.
  - MRI was used to document changes from baseline in total cartilage volume and thickness in the compartments of the target knee joint.
- Imaging results (safety and exploratory outcomes) of a Phase 1 study 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 are presented.

Methods

- This is a first-in-human, multicenter, 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 (K-L) 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 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.
- Knee MRIs were obtained with a 16 channel knee coil on a 3.0T MRI machine using a standard diagnostic protocol (resolution 0.1 – 0.4 mm). MRI scans were collected at the baseline visit (which could occur ≤28 days prior to study injection) and again at Weeks 12 and 24.
- As a safety assessment, MRI scans were used to monitor the presence of focal or diffuse bone marrow edema (BME) in all subjects.
- Average cartilage thickness over covered subchrondral bone was reported for 4 compartments:
  - Medial femoral condyles
  - Lateral femoral condyles
  - Medial tibial plateaus
  - Lateral tibial plateaus
- To determine average cartilage thickness, the cartilage thickness between the subchondral bone area (green contour, shown in the example below) and the articular cartilage surface (magenta) was measured at numerous (~400-2000) locations in both directions in the parts covered by cartilage (cAB) and averaged. Measurements were performed in 3D.

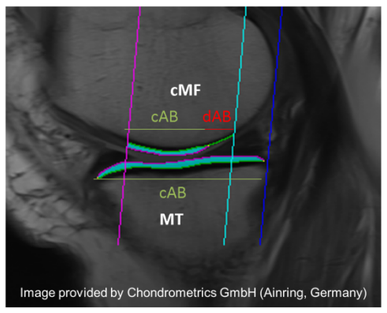

Image provided by Chondrometrics GmbH (Ainring, Germany)

cAB – Subchondral Bone covered by Cartilage

dAB – Denuded Subchondral Bone

cMF – Medial Femur Condyle

MT – Medial Tibia

- Additionally, the average of the lowest 1% of cartilage thickness was reported for all 4 compartments.
- The total for both average thickness and lowest thickness were derived by summing each of the 4 compartments' observations.
- Radiographs of the target knee were taken during the screening period and at Week 24 to document change from baseline in joint space width (JSW).
- Sponsor was unblinded after Week 12 for each cohort; site investigators remained blinded.
- An exploratory analysis of change in imaging outcomes was conducted using repeated measures analysis of covariance (ANCOVA) adjusting for baseline in the Intention-to-Treat (ITT) population.

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 (0%)	1 (6%)	0(0%)
Kellgren-Lawrence Grade 3 [N(%)]	7 (41%)	8 (50%)	11 (69%)	5 (42%)

Bone Marrow Edema (BME)

Edema		0.03 mg (N=17)	0.07 mg (N=16)	0.23 mg (N=16)	Placebo (N=12)
Baseline	**Week 12**				
None [N(%)]					
	None	9 (57%)	11 (69%)	4 (25%)	5 (42%)
	Focal	1 (6%)	2 (13%)	1 (6%)	3 (25%)
	Diffuse	0	0	0	0
Focal [N(%)]					
	None	0	1 (6%)	1 (6%)	0
	Focal	4 (25%)	1 (6%)	8 (50%)	3 (25%)
	Diffuse	0	0	0	0
Diffuse [N(%)]					
	None	0	0	0	0
	Focal	1 (6%)	1 (6%)	0	0
	Diffuse	1 (6%)	0	2 (13%)	1 (8%)

Mean Cartilage Thickness by MRI at Week 12

	0.03 mg	0.07 mg	0.23 mg	Placebo
N	16	16	15	12
Baseline (mm) [Mean (SD)]	5.43 (1.10)	5.38 (0.70)	5.36 (0.94)	5.84 (0.65)
Week 12 (mm) [Mean (SD)]				
Actual	5.38 (1.19)	5.37 (0.71)	5.32 (1.03)	5.84 (0.63)
Change from baseline	-0.06 (0.39)	-0.02 (0.25)	-0.04 (0.24)	0.01 (0.20)

Mean Thinnest Cartilage by MRI at Week 12

	0.03 mg	0.07 mg	0.23 mg	Placebo
N	16	16	15	12
Baseline (mm) [Mean (SD)]	3.75 (1.38)	3.78 (1.37)	3.14 (1.17)	4.24 (1.45)
Week 12 (mm) [Mean (SD)]				
Actual	3.84 (1.57)	3.88 (1.39)	3.01 (1.27)	4.18 (1.26)
Change from baseline	0.11 (0.37)	0.10 (0.55)	-0.13 (0.30)	-0.06 (0.43)

Joint Space Width by Radiograph at Week 24

	0.03 mg	0.07 mg	0.23 mg	Placebo
N	15	14	16	12
Baseline (mm) [Mean (SD)]	4.50 (1.70)	3.57 (1.63)	3.62 (1.75)	3.91 (1.62)
Week 24 (mm) [Mean (SD)]				
Actual	4.50 (1.72)	4.16 (1.64)	3.47 (1.68)	3.53 (1.98)
Change from baseline	0.00 (0.69)	0.59 (0.66)*	-0.15 (1.07)	-0.38 (0.85)

** p=0.006 versus Placebo*

Discussion

- MRI was the primary method utilized to examine BME, which the FDA defined as a safety outcome in this phase 1 trial.
  - BME stayed the same for most subjects from baseline to Week 12. For some subjects in both treatment (N=4) and Placebo (N=3) groups, BME worsened (none to focal). 4 subjects in the treatment groups showed improved BME results (focal to none and diffuse to focal). These interim BME imaging data suggest that a single intra-articular injection of SM04690 into the knee of OA subjects appeared to have no appreciable effect on BME compared to Placebo.
- Although exploratory imaging results in this phase 1 trial suggest that the 0.23 mg dose is less effective than the 0.03 mg and 0.07 mg doses, it should be noted that the 0.23 mg cohort consisted of the highest percentage of K-L Grade 3 subjects.
- Radiography is currently the "gold standard" for knee OA trials. However, while MRI is still considered by regulatory agencies as exploratory, it can provide more comprehensive information on articular tissue pathology than radiography.[7] Although overall sample size was small and measurements were at limits of scan resolution, exploratory analyses of MRI outcomes suggest:
  - *Mean cartilage thickness* – Treated subjects appeared to show no substantial degradation in mean cartilage thickness at Week 12.
  - *Mean thinnest cartilage* – Subjects in the 0.03 mg and 0.07 mg cohorts showed a trend towards increase in the area of mean thinnest cartilage at Week 12.
- Radiographs measuring the change from baseline at Week 24 in JSW show 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, with the Placebo group also exhibiting a decrease.
- MRI efficacy outcome data require further evaluation to determine the utility of this imaging technique for OA. However, the MRI safety outcomes from this interim analysis demonstrated no worsening of bone edema in knee OA subjects treated with SM04690.
- Preliminary safety outcomes observed from MRI analyses, and efficacy outcomes from radiographic and clinical data (reported in Poster 312), support the ongoing development program for SM04690 (NCT02536833; currently enrolling).

References

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