OMERACT-OARSI 'Strict Responders' Analysis from Results of 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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Poster #315

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, 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]
- The Wnt signaling pathway is known to play a central role in the formation of joint tissues. 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. Additionally, altered Wnt signaling has been associated with cartilage loss in preclinical and clinical studies.[5]
- 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 injection into the affected joint.[6]
- Outcome Measures in Rheumatology Clinical Trials (OMERACT)-Osteoarthritis Research Society International (OARSI) strict responder criteria form a clinically relevant composite score incorporating both OA pain and function.[7]
- OMERACT-OARSI strict responders are defined as subjects with:
  - 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])[7]
- The purpose of this pre-specified analysis was to evaluate OMERACT-OARSI strict responses from the SM04690 study, "Phase 1, Dose Escalation Study Evaluating the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of SM04690 in Moderate to Severe Knee Osteoarthritis (OA)," to further assess proof of concept of efficacy of this molecule.

Methods

- This was 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 (KL grade 2-3) symptomatic knee OA.
  - 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.
  - Placebo was 2 ml vehicle for API: a diluent containing 0.5% polysorbate 80 and 0.05% carboxymethylcellulose sodium 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, intra-articular injection in the target knee on Treatment Day 1 and participated in a follow-up period of 24 weeks.
  - Primary study outcomes were reported previously.[8]
- Exploratory analyses of efficacy outcomes were conducted using a baseline-adjusted repeated measures analysis of covariance (ANCOVA) and logistic regression in the Modified Intention-to-Treat (mITT) population. The mITT population includes all subjects *as treated*.
- Efficacy assessments were used to determine the percentage of OMERACT-OARSI strict responders.

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%)

Safety [mITT]

	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	13	25	19
AE(s) Reported – Target knee	2	4	5	5

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

Results

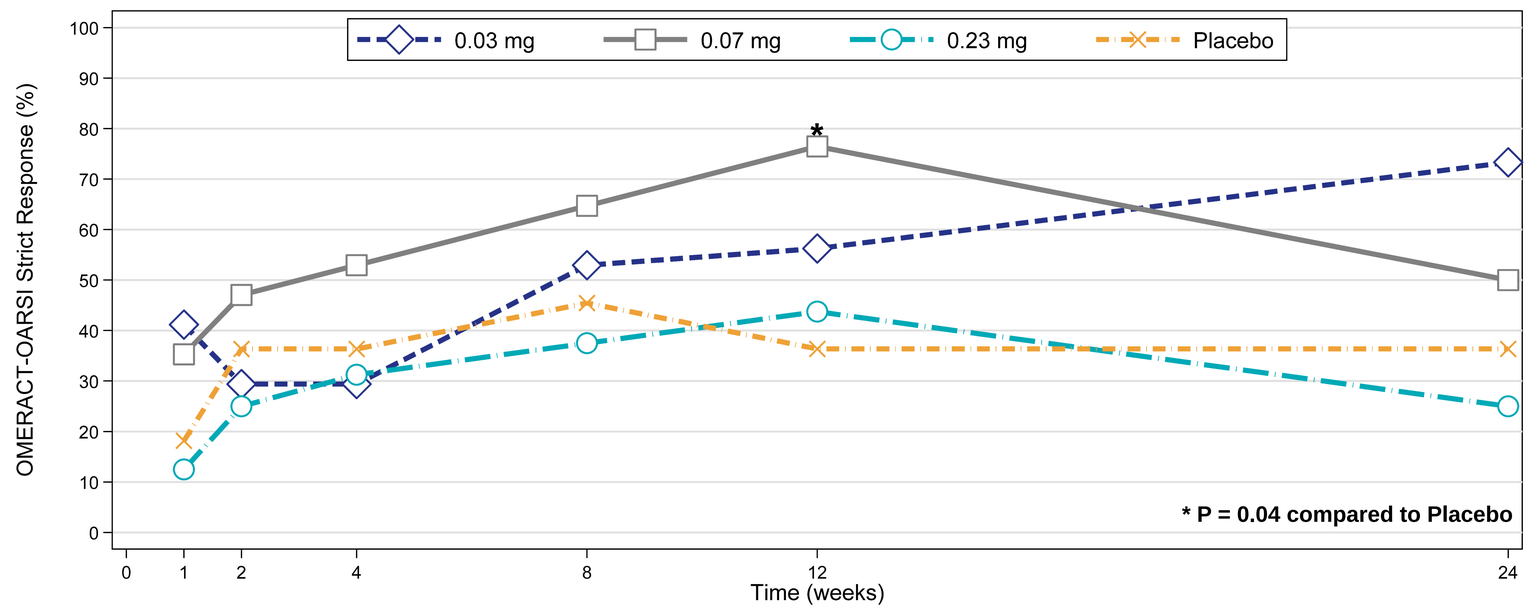
WOMAC Function [0-68] [mITT]

	0.03 mg	0.07 mg	0.23 mg	Placebo
N	17	17	16	11
Baseline [Mean (SD)]	39.1 (7.2)	37.5 (7.5)	40.4 (8.6)	34.4 (10.1)
Change from Baseline				
Week 12 [Mean (SD)]	-18.4 (13.5)	-19.5 (15.9)	-17.8 (15.1)	-14.9 (13.4)
Week 24 [Mean (SD)]	-20.1 (10.8)	-18.9 (10.9)	-12.4 (14.2)	-16.0 (14.1)

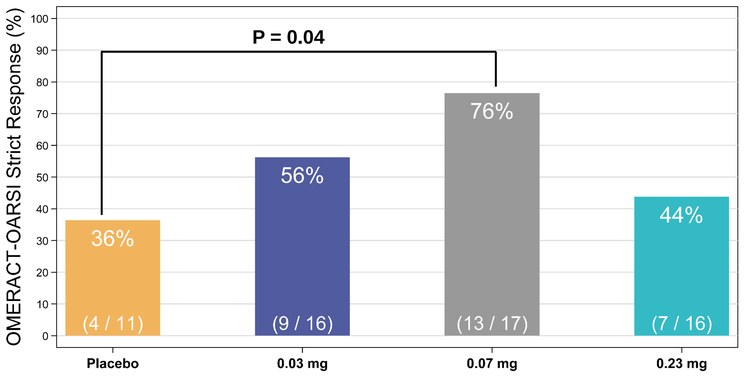
WOMAC Pain [0-20] [mITT]

	0.03 mg	0.07 mg	0.23 mg	Placebo
N	17	17	16	11
Baseline [Mean (SD)]	10.8 (2.0)	10.8 (2.9)	11.4 (2.7)	9.9 (2.1)
Change from Baseline				
Week 12 [Mean (SD)]	-4.4 (3.0)	-5.8 (4.6)	-5.7 (4.4)	-4.2 (4.1)
Week 24 [Mean (SD)]	-5.6 (3.1)	-5.3 (4.0)	-4.3 (4.7)	-4.8 (4.2)

OMERACT-OARSI Strict Responders over Time [mITT]

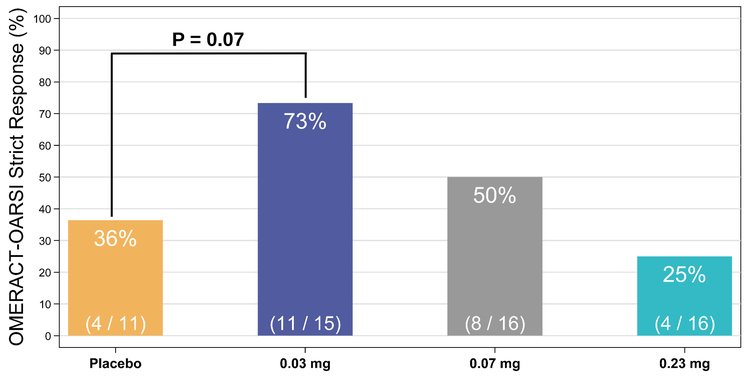


OMERACT-OARSI Strict Responders at Week 12 [mITT]



- At Week 12, 76% of 0.07 mg cohort achieved strict OMERACT-OARSI response compared to 36% of Placebo (OR = 5.7, P = 0.04).

OMERACT-OARSI Strict Responders at Week 24 [mITT]



- At Week 24, 73% of 0.03 mg cohort achieved strict OMERACT-OARSI response compared to 36% of Placebo (OR = 4.8, P = 0.07).

Discussion

- This phase 1 study suggested that a single intra-articular injection with the novel Wnt inhibitor SM04690 into the knee of OA subjects appeared well-tolerated and potentially effective in reducing pain and improving function.
- Although this phase 1 study was not powered to see any statistically significant differences between treatment groups and placebo, these data suggested that subjects treated with SM04690 (0.03 and 0.07 mg doses) were more likely to achieve an OMERACT-OARSI strict response than placebo.
- The changes observed in OMERACT-OARSI strict response over time for the 0.03 and 0.07 mg SM04690 cohorts suggest that further investigation into optimal dosing is also needed.
- These study data support the development of an ongoing phase 2 study (NCT02536833) designed to formally further investigate additional safety, dose response, and efficacy in subjects with OA.

References

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