Analysis of Pain and Function Components in OMERACT-OARSI Strict Responders 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]
- 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]
- OA is characterized by increases in inflammatory cytokines and cartilage degrading metalloproteases.[3]
- 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.
- Preclinical studies show that SM04690 suppressed inflammatory cytokines and inhibited protease production.[4]
- 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.[5]
- OMERACT-OARSI strict responders are defined as subjects who report:
  - WOMAC Function subscore improvements ≥50% with a corresponding Function score improvement of ≥20 points (scaled to [0-100]), OR
  - WOMAC Pain subscore improvements ≥50% with a corresponding Pain score improvement of ≥20 points (scaled to [0-100])[5]
- The purpose of this exploratory analysis was to evaluate OMERACT-OARSI strict responders 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 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 / exclusion criteria for this study can be found on www.clinicaltrials.gov (NCT02095548).
  - Concentration levels included in dosing sequence: 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.
  - 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 safety outcomes were reported previously.[6]
- 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 included all subjects *as treated*.
- The percentage of OMERACT-OARSI strict responders was assessed by determining the number of subjects who reported improvements defined above based on WOMAC function criteria only, pain criteria only, or both function and pain criteria.
- Dropouts were not imputed for OMERACT-OARSI strict responders grouped by dose at Weeks 12 and 24 (Figures 1 and 2).

Results

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. 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)
Week 12 [Mean (SD)]				
Actual	20.3 (10.5)	17.9 (15.5)	22.8 (10.3)	19.5 (12.1)
Change from baseline	-18.4 (13.5)	-19.5 (15.9)	-17.8 (15.1)	-14.9 (13.4)
Week 24 [Mean (SD)]				
Actual	19.9 (11.7)	18.6 (11.0)	28.0 (11.0)	18.4 (12.3)
Change from baseline	-20.1 (10.8)	-18.9 (10.9)	-12.4 (14.2)	-16.0 (14.1)

Table 3. 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)
Week 12 [Mean (SD)]				
Actual	6.3 (2.7)	5.0 (4.4)	5.8 (2.7)	5.7 (3.8)
Change from baseline	-4.4 (3.0)	-5.8 (4.6)	-5.7 (4.4)	-4.2 (4.1)
Week 24 [Mean (SD)]				
Actual	5.2 (3.2)	5.4 (3.0)	7.1 (3.7)	5.1 (3.1)
Change from baseline	-5.6 (3.1)	-5.3 (4.0)	-4.3 (4.7)	-4.8 (4.2)

Figure 1. OMERACT-OARSI Strict Responders Grouped by Dose at Week 12 [mITT]

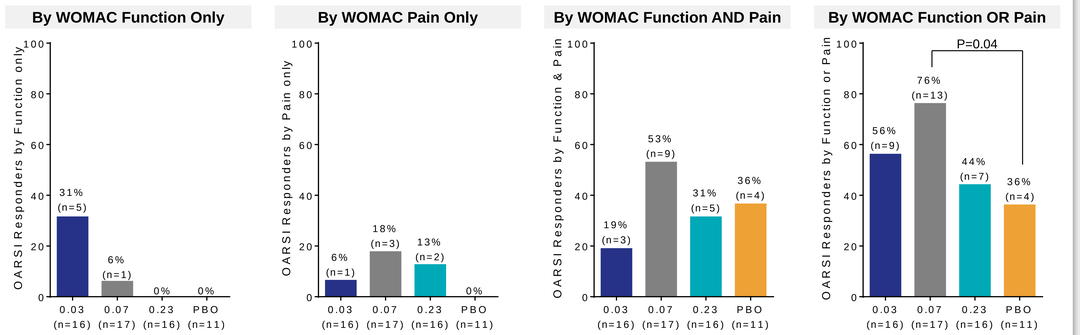
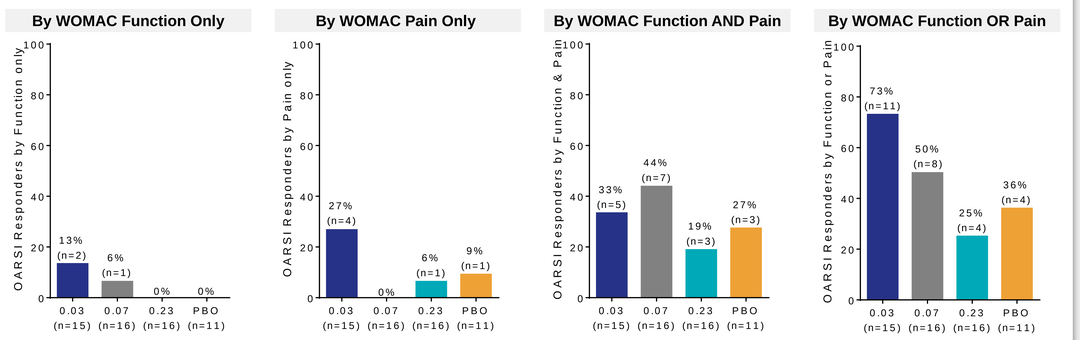


Figure 2. OMERACT-OARSI Strict Responders Grouped by Dose at Week 24 [mITT]



- 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).
- The 0.07 mg treatment group reported generally more favorable reductions in WOMAC function and pain subscores from Baseline to Week 12, while the 0.03 mg treatment group reported more favorable reductions in WOMAC function and pain subscores from Baseline to Week 24 (Tables 2 and 3).
- The 0.03 mg group included more OMERACT-OARSI strict responders fulfilled by WOMAC function criteria than any other group at Week 12 and Week 24 (Figures 1 and 2).
- The 0.07 mg group included more OMERACT-OARSI strict responders fulfilled by both WOMAC function and pain criteria than any other group at Weeks 12 and 24 (Figures 1 and 2).
- 76% of subjects in the 0.07 mg group reported OMERACT-OARSI strict responses by either WOMAC function or pain criteria compared with 36% in placebo at Week 12 (P=0.04) and 73% in the 0.03 mg group compared with 36% in placebo at Week 24 (Figures 1 and 2).

Discussion

- This phase 1 study was not powered to show statistically significant differences between treatment groups and placebo. However, these data demonstrate that more subjects treated with SM04690 [0.03 and 0.07 mg (P=0.04 at Week 12)] were OMERACT-OARSI strict responders than placebo (Figures 1 and 2).
- OMERACT-OARSI strict responses were not driven by either WOMAC function or pain criteria as most strict OMERACT-OARSI responders fulfilled both WOMAC function and pain criteria (Figures 1 and 2).
- These data support the development of an ongoing phase 2 study (NCT02536833) designed to further investigate additional efficacy, safety, and dose responses in subjects with OA.

References

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