Safety, Clinical, and Imaging Outcomes of a Novel, Intra-Articular, Injectable, Wnt Inhibitor (SM04690) in the Treatment of Osteoarthritis of the Knee: Exploratory Analysis of Results From a 24 Week, Randomized, Double-Blind, Placebo-Controlled, Phase 1 Study

samumed

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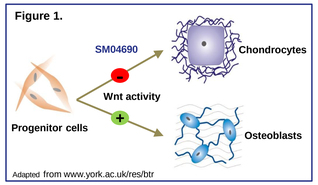
Background

- Osteoarthritis (OA) is a major cause of activity limitation and physical disability in adults, and it has a significant effect on healthcare costs and productivity. The global disease burden of hip and knee OA ranks 11th of 291 conditions, and knee OA has a global prevalence of 3.8%.[1]
- To date, there are no approved disease modifying agents for knee OA.
- 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]
- In osteoarthritic joints, increased Wnt signaling stimulates cartilage-destroying metalloprotease production and directs resident stem cells to become bone-forming osteoblasts instead of cartilage-forming chondrocytes (Figure 1).[2]
- *In vitro* studies have demonstrated that SM04690, a small molecule Wnt inhibitor, induced human mesenchymal stem cells to form chondrocytes, inhibited protease production, and suppressed inflammatory cytokine production.[3]
- *In vivo* studies demonstrated that a single intra-articular (IA) injection of SM04690 into the knee resulted in cartilage regeneration and improved joint health.[3]

Figure 1.



Adapted from www.york.ac.uk/res/btr

- The purpose of this phase 1 study was to evaluate the safety and tolerability of SM04690 administered by IA injection into a target knee joint of subjects with moderate to severe symptomatic OA. Exploratory efficacy analyses were also performed.

Methods

- This was a first-in-human, multicenter, placebo-controlled, single-dose, dose-escalation safety study of a Wnt pathway inhibitor in subjects with moderate to severe symptomatic knee OA:
  - Subjects aged 50-75 years with Western Ontario and McMaster Universities Arthritis Index (WOMAC) Total score 36-72, Kellgren-Lawrence grade 2 or 3, willing to omit pain medication for 24 hours prior to pain assessments, BMI <40, and no treatment with IA steroids within 2 months or hyaluronic acid derivatives within 6 months prior to injection were eligible for the study.
  - The dosing sequence included the following concentration levels: 0.03 mg, 0.07 mg, and 0.23 mg SM04690 per 2 mL injection.
  - A sample size of ~20 subjects (randomized 4:1, 16 active: 4 placebo) per dosing cohort was selected for this exploratory study.
  - Placebo was a vehicle 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 pre-specified 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, knee bone density via qCT, and evaluation of bone marrow lesions via MRI
  - *PK*: Samples collected 0, 4, and 24 hours post dose, and at Weeks 4 and 12
  - Biomarkers: Cartilage oligomeric protein (COMP), N-terminal propeptides of procollagen type 1 (P1NP), and β-C-terminal telopeptide of type 1 collagen (βCTX)
  - *Efficacy*: WOMAC Total score, WOMAC Function and Pain subscores, pain VAS, Physician Global Assessment of Disease Activity, MRI, and radiographs of joint space width
- All AEs reported in this study were considered related to study medication. Investigator opinion regarding the relatedness of AEs was also collected for informational purposes and is presented here.
- Efficacy assessments were used to determine the percentage of OMERACT-OARSI "strict" responders.[4] "Strict" responders were defined as subjects exhibiting either: WOMAC Function subscore improvement of ≥50% with a corresponding WOMAC Function subscore improvement of ≥20 points (scaled to [0-100]); or WOMAC Pain subscore improvement of ≥50% with a corresponding WOMAC Pain subscore improvement of ≥20 points (scaled to [0-100]).
- Exploratory analyses of efficacy outcomes were conducted using a baseline-adjusted repeated measures analysis of covariance (ANCOVA) in the modified Intention-to-Treat (mITT) population. The mITT population includes all patients as treated, including a single patient randomized to placebo who received 0.07 mg due to site error.

Results

Subject Characteristics [mITT]

	0.03 mg	0.07 mg	0.23 mg	Placebo
n	17	17	16	11
Age at Consent (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 (77%)	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
Kellgren-Lawrence Grade 3 [n(%)]	7 (41%)	8 (47%)	11 (69%)	5 (46%)

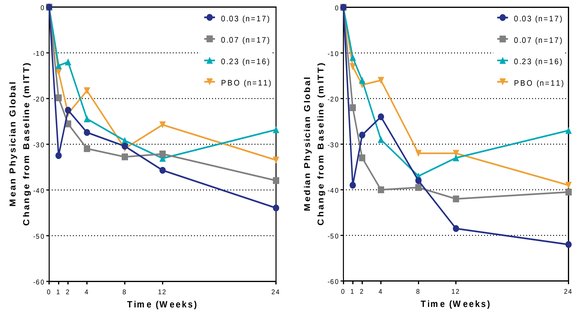
Safety

	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	13	25	19
AE(s) Reported – Target Knee				
Arthralgia	2	1	1	5
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	1	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 Reporting AE(s) [n(%)]	9 (53%)	6 (35%)	7 (44%)	6 (55%)
Subjects Reporting No AE(s) [n(%)]	8 (47%)	11 (65%)	9 (56%)	5 (45%)

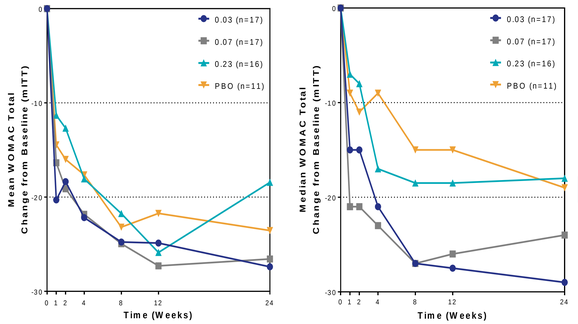
Physician Global Assessment of Disease Activity [0-100]



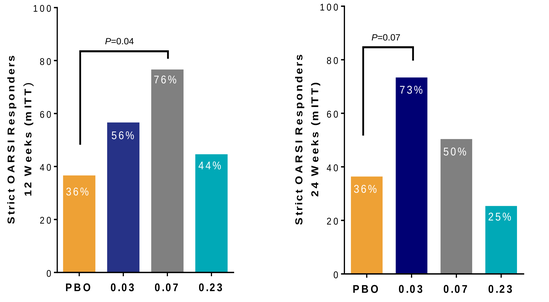
WOMAC Function [0-68] and Pain [0-20]

	0.03 mg	0.07 mg	0.23 mg	Placebo
n	17	17	16	11
WOMAC Function [0-68]				
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]				
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)

WOMAC Total [0-100]



OMERACT-OARSI Responders – Weeks 12 and 24



Medial Joint Space Width

	0.03 mg	0.07 mg	0.23 mg	Placebo
n	15	15	16	11
Baseline (mm) [Mean (SD)]	4.50 (1.70)	3.72 (1.66)	3.62 (1.75)	3.74 (1.58)
Week 24 (mm) [Mean (SD)]				
Actual	4.50 (1.72)	4.20 (1.59)	3.47 (1.68)	3.41 (2.03)
Change from baseline	0.00 (0.69)	0.49* (0.75)	-0.15 (1.07)	-0.33 (0.87)

*0.07 mg vs placebo, *P*=0.02

Safety

- No appreciable effects on bone marrow lesions compared to placebo were observed by MRI.
- All laboratory values, knee qCT, and hip DXA showed no remarkable changes.

Pharmacokinetics

- Samples were collected at 0, 4, and 24 hours post dose, and at weeks 4 and 12.
- Serum levels of SM04690 in all subjects were below limits of detection (BQL<0.100 ng/mL) at all time points.

Biomarkers

- Significant reduction in COMP in the 0.07 mg cohort at Week 12 compared to placebo (difference 130.13 ng/mL, *P*=0.001).
- No significant changes in βCTX or P1NP in any treatment group or with placebo.

Discussion

- These data from the phase 1 study suggested that a single intra-articular injection with the novel Wnt inhibitor SM04690 into the knee of OA subjects appeared safe, well-tolerated, and potentially effective in improving function, pain, and joint space width.
- Serum PK levels in all subjects were below the limit of quantitation at all time points.
- DLTs were observed in two patients, including 1 SAE of paroxysmal tachycardia. No AEs were reported in 28 of 50 exposed subjects (56%).
- This phase 1 study was not powered to detect any statistically significant differences between treatment groups and placebo. However, the data suggested that subjects treated with SM04690 were more likely to achieve an OMERACT-OARSI strict response than placebo. Strict OARSI response was achieved by 76% of 0.07 mg cohort vs. 36% of placebo cohort at week 12 (OR=5.7, *P*=0.04), and by 73% of 0.03 mg cohort vs. 36% of placebo cohort at week 24 (OR=4.8, *P*=0.07). Additionally, comparison of the mean and median changes from baseline for Physician Global Assessment of Disease Activity and WOMAC Total showed consistent improvement in the 0.3 mg and 0.7 mg cohorts, suggesting a uniform effect not driven by outliers.
- A statistically significant change in joint space width from baseline was seen in the 0.07 mg cohort (0.49 mm) vs. placebo (-0.33 mm) at week 24 (*P*=0.02).
- These study data supported 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

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