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A novel Wnt pathway inhibitor, SM04690, for the treatment of moderate to severe osteoarthritis of the knee: results of a 24-week, randomized, controlled, phase 1 study

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SUMMARY

Objective: To assess the safety, pharmacokinetics, and exploratory efficacy of SM04690, a novel Wnt pathway inhibitor, as a potential disease modifying treatment for knee osteoarthritis (OA).
Design: Subjects with Kellgren-Lawrence grade 2–3 knee OA were randomized in successive dose-escalation cohorts to receive a knee intra-articular (IA) injection with 0.03, 0.07, or 0.23 mg SM04690, or placebo (PBO) (4:1 ratio). Safety, pharmacokinetics, efficacy (WOMAC Total/Function/Pain, Pain VAS, Physician Global Assessment [MDGA], and OMERACT-OARSI Response), OA-related biomarker (P1NP, ß-CTX, and cartilage oligomeric matrix protein [COMP]), and radiographic/imaging data were collected at baseline and during 24-week follow-up.
Results: 61 subjects (SM04690 $n = 50$; PBO $n = 11$) enrolled. Two dose limiting toxicities (DLTs), increased pain following injection and paroxysmal tachycardia (also the single serious AE), were reported in the 0.07 mg cohort. A total of 72 AEs were reported; Sixteen (occurring in eight subjects) were considered related to study medication. There were three discontinuations; one due to an AE (0.03 mg cohort). Bone marrow edema (BME) remained constant for most subjects. No doses were excluded from further study due to DLT criteria. Plasma levels of SM04690 were below the limit of detection at all time points. At Week 24, improvements from baseline were seen in all cohorts for the exploratory measures WOMAC Total, WOMAC Function, WOMAC Pain, MDGA, Pain VAS, and OMERACT-OARSI response. Joint space width (JSW) improvement was observed in the 0.07 mg cohort ($P = 0.02$ vs PBO).
Conclusion: SM04690 appeared safe and well tolerated, with no evidence of systemic exposure. Exploratory efficacy analyses suggested positive trends for measurements of OA pain, function and disease-modifying osteoarthritis drug (DMOAD) properties.
ClinicalTrials.gov registration: NCT02095548.

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Introduction

Knee osteoarthritis (OA) is a progressive condition, characterized by articular cartilage destruction, subchondral bone remodeling, and varying degrees of synovitis[1]. Many patients experience disability resulting from worsening joint pain and deformity, and this disease increases the risk of developing comorbidities such as cardiovascular disease, metabolic disorders, and obesity[2,3].

Current OA treatments are limited to providing temporary relief from signs and symptoms; there are no approved disease-modifying osteoarthritis drugs (DMOADs). Both the safety and efficacy of available treatments for OA, such as nonsteroidal anti-inflammatory drugs (NSAIDs) and opioids, are important issues[4–6]. While these provide temporary pain relief, many patients are unable to take them due to comorbidities or concern for potential adverse events (AEs). Therefore, there is a need for safer and more effective treatments.

At the cellular level, joint health is partly maintained by mesenchymal stem cells (MSCs) which reside in the synovial space and subchondral bone and are capable of differentiation into cartilage-forming chondrocytes, bone-forming osteoblasts, or adipocytes[7,8]. The synovium of patients with OA is enriched with stem cells[9,10], suggesting that the failure to regenerate articular cartilage is not due to an insufficient supply of stem cells, but rather that the stem cells do not appropriately differentiate to restore healthy cartilage homeostasis of the joint.

The Wnt pathway, a highly conserved and complex cell-signaling pathway, plays a central role in cell differentiation, development, and tissue remodeling[11]. It is subject to modulation at multiple levels, resulting in rheostat-like, rather than binary, responses in most tissues[12,13]. In the joint, the Wnt pathway helps to control tissue homeostasis through regulation of MSC differentiation into chondrocytes and osteoblasts[14,15]. Animal studies have demonstrated that it is associated with cartilage tissue repair and regeneration within joints[16]. In OA, increased Wnt signaling drives MSCs to an osteogenic lineage fate and stimulates metalloproteinase production, leading to cartilage degradation[17,18]. Therefore, pharmacological modulation of Wnt signaling might have beneficial effects on cartilage dysregulation observed in OA[19]. More specifically, local inhibition of Wnt signaling at the site of disease could promote restoration of articular cartilage.

SM04690 is a first-in-class small-molecule Wnt pathway inhibitor in development as a local intra-articular (IA) injection for knee OA. *In vitro* studies have demonstrated that SM04690 potently inhibited the Wnt pathway. Human MSCs treated with SM04690 showed significant downregulation of Wnt gene expression after 48 h. After 21 days, SM04690 induced downregulation of osteogenic gene expression and upregulation of chondrogenic gene expression[20].

Pharmacokinetic (PK) studies conducted in rats (single IA knee injection, analysed at 30, 90, and 180 days) showed SM04690 was retained in the joint above the target concentration of ~30 nM at 180 days post injection[20]. The compound was undetectable in the systemic circulation at all time points as early as 15 min post IA injection, indicative of a low potential for systemic toxicity. Furthermore, systemic exposure to SM04690 following acute intravenous injections up to 1 mg/kg/day did not result in any dose-related adverse effects in rats[20]. *In vivo* studies in rats demonstrated that SM04690 promoted cartilage repair in a surgery-induced OA model[20].

In summary, preclinical studies of SM04690 demonstrated that it inhibited the Wnt pathway, induced chondrogenesis, reduced cartilage degradation, and improved cartilage health[20]. The purpose of this first-in-human phase 1 clinical trial was to assess the safety, tolerability, PK, dose limiting toxicities (DLTs) and recommended phase 2 doses, as well as exploratory efficacy of a single IA knee injection of SM04690 in patients with moderate to severe knee OA.

Methods

Study design

This phase 1, multicenter, randomized, placebo (PBO)-controlled, double-blind, dose-escalation safety and tolerability study of SM04690 was conducted at seven US sites between March 2014 and September 2015. Primary objectives were to (1) characterize safety and tolerability of IA administration of SM04690 in individuals with moderate to severe knee OA, (2) determine the maximum tolerated dose (MTD) defined by occurrence of DLTs, and (3) characterize PK of SM04690. Secondary objectives included exploratory measurement of target knee pain and function, and measurement of joint space width (JSW) by radiograph for preliminary evaluation of potential for disease modification.

Eligible subjects were randomized via a central interactive voice response system (IVRS) to receive a single, ultrasound-guided, IA injection into the target knee with 0.03, 0.07, or 0.23 mg SM04690, or PBO (volume 2 ml/injection). These doses correspond to SM04690's lower, middle and upper therapeutic range determined by preclinical studies. The preparation of the study medication and injection was performed by unblinded personnel identified by the study centers, who were required to minimize any contact with the subject following the injection and were not allowed to perform any study assessments. Appropriate measures were taken to conceal the treatment identity from the subject and blinded study staff members. Vehicle, used as PBO, was comprised of 0.5% carboxymethylcellulose/0.05% polysorbate 80 in phosphate buffered saline. The dose of SM04690 was escalated in successive cohorts of 20 subjects (16 active: 4 PBO) (Fig. 1). If <4 subjects in an active group per dose experienced a DLT, then 20 new subjects were randomized by the IVRS and treated at the next higher dose. A DLT was defined as any one of the following: (1) new effusion requiring aspiration that was erythematous and warm on examination, and in investigator's opinion, caused moderate to severe limitation in function; (2) increased target knee pain >30 mm on the pain VAS scale from baseline or subject reaching maximum pain level of 100 mm; (3) evidence of target knee bone loss, measured by computed tomography (CT) of both knee joints, with accompanying symptoms; (4) any AE deemed by the investigator to be severe or a serious AE (SAE) by regulatory definition.

New dose-level cohorts began recruitment when a minimum of 18 subjects at the previous dose level were observed for a minimum of 12 weeks from day of injection, and blinded data from these subjects were reviewed by a Safety Review Committee (SRC) comprising principal investigators, medical monitor, and an independent rheumatologist. DLT stopping rules were applied as defined above. Subject study participation was up to 28 weeks, including a 28-day screening period, 1-day treatment, and 24-week follow-up.

Subjects could remain on existing OA treatments, including NSAIDs, with exceptions of IA steroids and hyaluronates, electrotherapy, and acupuncture. Additionally, subjects refrained from any pain medication 24 h prior to all study visits, excluding screening visit. In cases of study discontinuation, efforts were made to perform all final study day assessments. Subjects withdrawn due to AEs were followed until resolution.

Study population

Subjects aged 50–75 years old with Kellgren-Lawrence (KL) grades 2–3 knee OA, and observed to be in general good health and

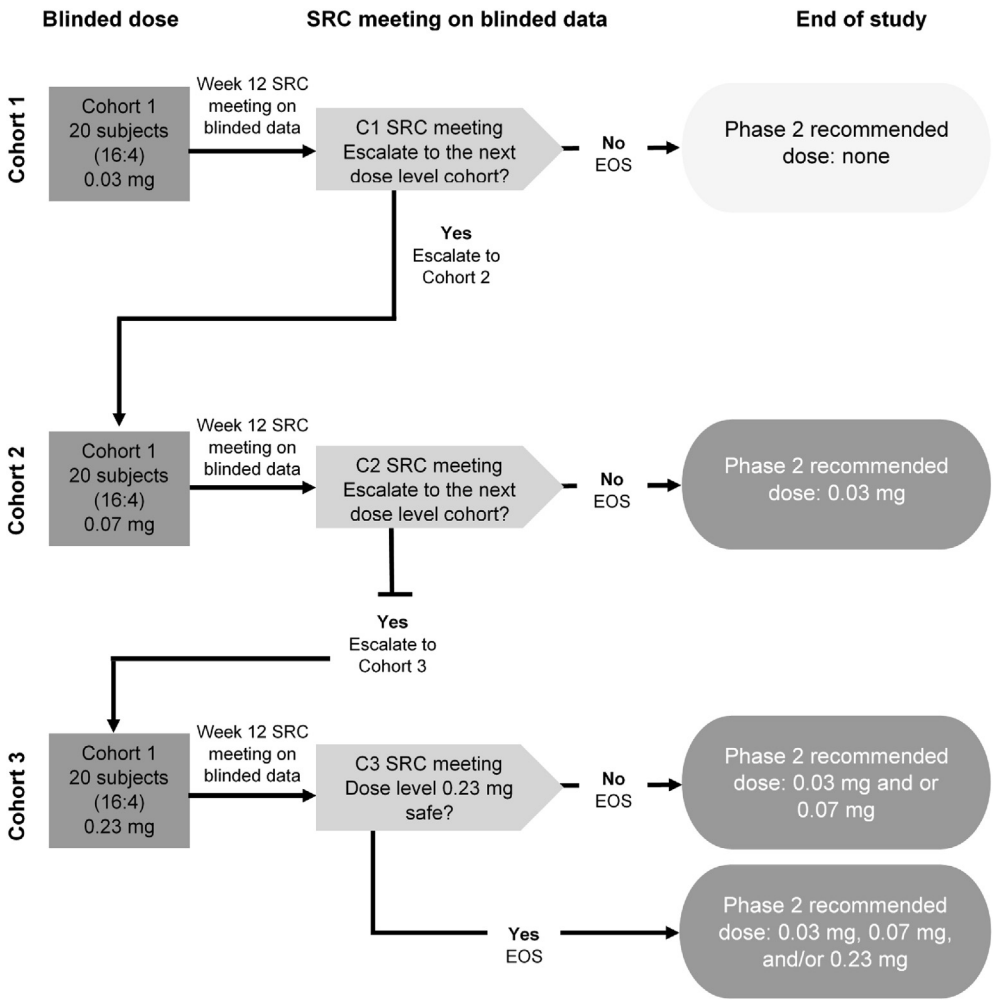

Fig. 1. Flowchart of SM04690 dose escalation. Cohort 1 subjects were randomized at a 16:4 ratio to receive a single IA injection with either 0.03 mg SM04690 or PBO. Recruitment for Cohort 2 (0.07 mg) and Cohort 3 (0.23 mg) began after Week 12 blinded data review by a SRC. C1/2/3, Cohort 1/2/3; EOS, end of study.

ambulatory were included. Assistive devices were allowed if needed <50% of time. A primary diagnosis of femorotibial OA in the target knee by American College of Rheumatology (ACR) clinical and radiological criteria for >6 months was confirmed with radiography at screening. Subjects (on usual oral analgesia) were required to have a screening VAS pain score 30–80, and WOMAC Total score 36–72, for the target knee.

Female subjects were excluded from the study if pregnant, lactating, or of childbearing potential. Male subjects were excluded if they refused to use a barrier method of contraception or practice abstinence through the last visit of the study. Subjects were excluded if they had any condition, including medical history, laboratory findings, or pre-study assessments that constituted a risk or contraindication for participation in the study, or could interfere with study conduct or study objectives evaluations. Further exclusions were body mass index (BMI) > 40 kg/m^2, knee surgery (e.g., arthroscopy) in the target knee <12 months prior to, or any planned surgeries during, the study period. Treatment of the target knee with IA steroids <2 months, or hyaluronates <6 months, or participation in clinical trials of investigational products or experimental procedures <12 weeks, prior to study medication injection were exclusions. History of malignancy <5 years prior to study medication injection also precluded participation, with the exception of subjects with history of *in situ* cancer or basal/squamous cell skin cancer.

Safety assessments

The safety and tolerability of IA SM04690 was assessed by monitoring for treatment-emergent AEs (TEAEs), DLTs, periarticular bone health by knee imaging, measurement of OA-related biomarkers, and PK in blood plasma. Safety imaging included assessment of subchondral bone mineralization by quantitative CT (qCT), and assessment of bone marrow edema (BME) by magnetic resonance imaging (MRI).

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, RadCore/BioTelemetry). Dual-energy X-ray absorptiometry (DXA) of the hips was also completed. MRI and qCT were completed at screening, and weeks 12 and 24. DXA was completed at screening and Week 24. All imaging was standardized by training study sites with study-specific imaging acquisition guidelines.

OA-related biomarkers (cartilage oligomeric matrix protein [COMP], N-terminal propeptides of procollagen type I [PINP], and ß-C-terminal telopeptide [ß-CTX]) were measured at baseline and Weeks 4, 12, and 24. All plasma samples were collected, collated, and shipped to a central lab vendor (PPD Global Central Labs, Highland Heights, KY) for analysis.

Plasma samples for PK analysis were collected from subjects immediately prior to injection, 4 h (±10 min), 24 h (±60 min), 4 weeks, and 12 weeks post-injection. Samples were received by

Agilux Laboratories, (Worcester, MA), via the central lab vendor, frozen and packaged on dry ice, and stored at −80°C. Determination of SM04690 concentration in human plasma was conducted using a validated liquid chromatography with tandem mass spectrometry method (standard curve range of 0.100–25.0 ng/ml).

Additional continually monitored safety assessments included evaluation of incidence, severity, and seriousness of TEAEs, and changes in clinical laboratory parameters, vital signs, and electrocardiograms (ECGs) relative to baseline.

This study was performed in full compliance with International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use and applicable local Good Clinical Practice regulations. This study is registered at www.clinicaltrials.gov (NCT02095548).

Exploratory efficacy assessments

Exploratory efficacy assessments included administration of the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) (v3.1LK scored [0–96]), a subject reported pain visual analog scale (VAS [0–100 mm]), and a physician global assessment (MDGA) of disease activity VAS (0–100 mm). Subject and physician assessments were completed at screening, baseline, and Weeks 1, 2, 4, 8, 12, and 24. WOMAC Function and Pain subscores were further evaluated according to the composite Outcome Measures in Rheumatology-Osteoarthritis Research Society International (OMERACT-OARSI) response[21]. Only a single OMERACT-OARSI response definition (≥50% improvement in WOMAC Pain or Function with corresponding ≥20-point change [100-point scale]) was used in this study as Patient Global Assessment was not collected. Radiographs were obtained using lateral and posterior-anterior views of the target knee in full extension and weight bearing position, with JSW assessments at screening and Week 24.

Statistical methods

The sample size for this study was based on precedent set by other Safety/PK studies of similar nature and was not based on statistical considerations. Safety data analyses were conducted on all subjects (treated and PBO); the Safety Population was defined as any subject receiving SM04690. The general analytical approach for all safety endpoints was descriptive, providing a summary and estimate of the safety profile of SM04690. Analyses consisted of data summaries for clinical, PK, DLT assessment for MTD, biological and pharmacodynamic (PD) parameters, and AEs. The number and percentage of subjects experiencing AEs were summarized by dose-level group and severity. The PK analysis set included all subjects who had blood drawn for PK assessments. Laboratory parameters were summarized using descriptive statistics by post-administration shifts relative to baseline. Clinically significant abnormalities were listed per study participant and time point for safety review. Vital signs and ECGs were summarized by changes from baseline values at each dose level using descriptive statistics.

For exploratory efficacy analyses, two different analysis sets were defined. The Intention-to-Treat (ITT) analysis set was defined as all randomized subjects according to their randomized treatment cohort assignment. The modified Intention-to-Treat (mITT) analysis set included all randomized subjects according to their actual treatment received; one subject randomized to PBO was given 0.07 mg SM04690 in error. For brevity, only exploratory efficacy analyses using the mITT analysis set are presented here.

Analysis of covariance (ANCOVA) models were used to evaluate exploratory efficacy outcome measures. Two ANCOVA models were estimated using the efficacy outcomes: (1) a repeated measure ANCOVA model estimating change within each treatment group and PBO while adjusting for baseline value, and (2) an ANCOVA model at Week 12 and Week 24 separately estimating change in outcome between each treatment group and PBO adjusting for baseline value.

Fisher's Exact Test was used to explore the proportion of OMERACT-OARSI responders within each treatment group versus PBO at Weeks 12 and 24. Logistic regression was used to estimate the odds of achieving an OMERACT-OARSI response between treatment cohorts and PBO.

Missing data were reported as missing, and no imputation of missing data was conducted. If a subject discontinued the study, early termination assessments were performed according to the protocol. If these assessments occurred within the window of a scheduled visit (±1 day for Weeks 1 and 2, ±3 days for Weeks 4 and 8, ±7 days for Weeks 12 and 24), they were associated with that visit for the purposes of mITT analysis.

All data processing, summarization and analyses used SAS® Version 9.4.

Results

Patient population

A total of 133 subjects were screened. Of these, 61 (45.9%) met eligibility criteria and were enrolled. All subjects that were enrolled received treatment. Three subjects discontinued after receiving treatment (described in detail below). Nineteen subjects (90.5%) in Cohort 1, 19 subjects (95%) in Cohort 2, and 20 subjects (100%) in Cohort 3 completed the study (Fig. 2). Subject demographics and key baseline characteristics are shown in Table I.

Safety and toxicity outcomes

AEs and DLTs

No deaths were reported during the study. A total of 72 AEs were reported by 28 (45.9%) subjects during the study. Sixteen AEs, reported by 8 (13.1%) subjects, were considered related to study medication by the reporting investigator (Supplemental Table A). The AE with most events considered related to study medication was arthralgia (all knee related), with 4 (6.6%) subjects reporting four events. Across all three active treatment cohorts, there were two DLTs and one serious adverse event (SAE). A DLT of increased knee pain (>30 mm increase on the pain VAS), which was considered 'probably related' to the study medication by the investigator, was observed in a subject (0.07 mg SM04690 group) who received multiple injection attempts during Visit Day 1. A DLT of paroxysmal tachycardia occurred in a 72-year-old man (0.07 mg SM04690 group) with a medical history of tachycardia and was reported at the Week 8 visit. This DLT, requiring hospitalization, met the criteria of an SAE, but was considered unrelated to the study medication by the investigator. There were 71 incidences of non-serious AEs in 27 subjects (44.3%); 62 were mild, eight moderate and one severe. None were considered life threatening. There were three incidences of treatment discontinuations; one due to an AE of joint pain classified unrelated to study medication by the investigator (Table II). AEs occurring in >5% of subjects in the Safety Analysis Set are presented in Table II. There were no clinically significant safety concerns or differences among cohorts with regard to vital signs, clinical laboratory results, ECGs or AEs.

There were three major protocol deviations. These included one patient who was mistakenly injected with 0.07 mg SM04690 instead of PBO on his Day 1 visit; one patient who participated in another IA injection trial; and one patient assessed by an unblinded physician.

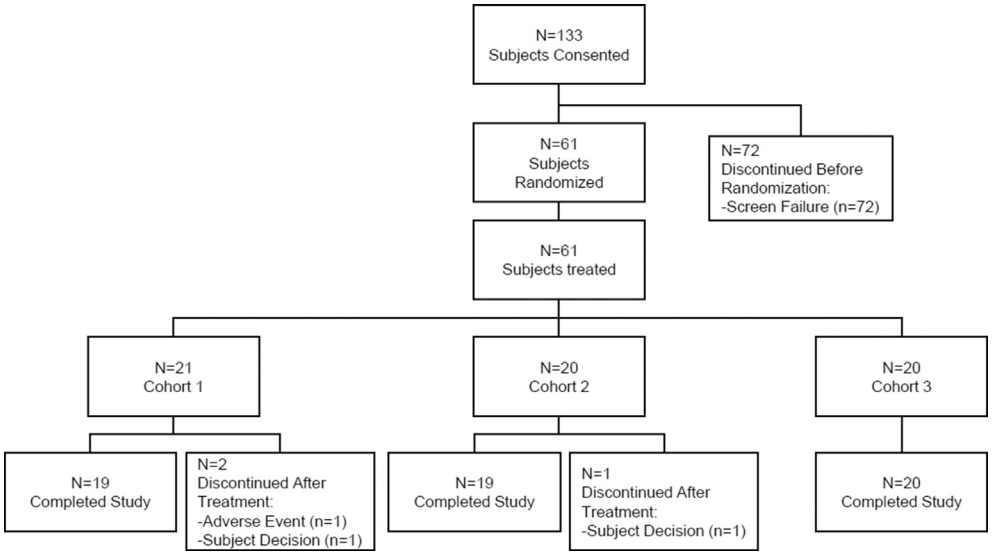

Fig. 2. Flow chart of patient disposition.

Biomarker outcomes

Assessment of bone loss and cartilage degradation by measurement of OA-related biomarkers revealed unremarkable changes from baseline in ß-CTX or PINP in any treatment group (Supplemental Table B). For COMP, there was no statistically significant change in mean plasma concentrations compared to baseline in the 0.03 mg group, but reductions were seen in the 0.07 mg dose group at Weeks 12 (−130.0 ng/ml; 95% CI [−167.8,−92.2]; $P < 0.001$) and 24 (−89.3 ng/ml; 95% CI [−132.4,−46.1]; $P < 0.001$), and in the 0.23 mg group at Week 24 (−53.6 ng/ml; 95% CI [−83.0,−24.2]; $P < 0.001$); a significant change from baseline was also observed in the PBO group at Week 24 (−105.3; 95% CI [−177.9,−32.7]; $P = 0.005$). Compared to PBO, change in COMP for the 0.07 mg group at Week 12 was statistically significant (difference −108.5 ng/ml; 95% CI [−170.2, −46.8]; $P = 0.001$); at Week 24 this was not statistically significant (difference 48.3 ng/ml; 95% CI [−20.8, 117.4]; $P = 0.162$).

Bone health

No significant changes were seen in bone mineral density in treated vs untreated knees or hip as measured by qCT and DXA. BME remained constant for most subjects from baseline through Week 24 (Supplemental Table C). At Week 12, five treated (0.03 mg = 1; 0.07 mg = 3; 0.23 mg = 1) and two PBO subjects showed progression of BME, from 'none' to 'focal'. At Week 24, five treated (0.03 mg = 0; 0.07 mg = 4; 0.23 mg = 1) and one PBO subject showed progression from 'none' to 'focal' or 'focal' to 'diffuse'. BME improvement, from 'focal' to 'none' or from 'diffuse' to 'focal', was seen in four treated subjects at Week 12 (0.03 mg = 1; 0.07 mg = 2; 0.23 mg = 1), and three treated subjects at Week 24 (0.03 mg = 1; 0.07 mg = 1; 0.23 mg = 1). No improvements in BME were observed in PBO subjects.

Dose determination

No MTD was established as a result of this study due to the low incidence of DLTs. Therefore, all three doses were eligible for further investigation in a phase 2 study.

Pharmacokinetics analysis

All plasma concentration measurements were below quantifiable limits (<0.100 ng/ml) at all recorded time points (0, 4 and 24 h; 4 and 12 weeks post-injection) for all subjects.

Clinical outcomes

Observations from exploratory analyses conducted using WOMAC Total, WOMAC Function and WOMAC Pain subscale scores are shown in Table III. At Week 12, within-cohort mean

Table I
Patient demographics and baseline characteristics (safety analysis set)

Parameter	SM04690			PBO ($n = 11$)	All subjects ($n = 61$)
	0.03 mg ($n = 17$)	0.07 mg ($n = 17$)	0.23 mg ($n = 16$)		
Mean age (SD)	63.2 (6.55)	60.5 (5.32)	63.1 (4.90)	64.1 (5.92)	62.6 (5.72)
Mean BMI, kg/m^2 (SD)	31.42 (4.79)	30.60 (4.86)	28.71 (5.00)	31.16 (3.37)	30.43 (4.66)
Female sex, n (%)	10 (58.8)	13 (76.5)	12 (75.0)	6 (54.5)	41 (67.2)
Race n (%)					
White	14 (82.4)	14 (82.4)	14 (87.5)	9 (81.8)	51 (83.6)
Black or African American	2 (11.8)	3 (17.6)	1 (6.3)	2 (18.2)	8 (13.1)
Asian	1 (5.9)	0	1 (6.3)	0	2 (3.3)
Kellgren-Lawrence Grade, n (%)					
Grade 2	10 (58.8)	9 (52.9)	5 (31.3)	6 (54.5)	30 (49.2)
Grade 3	7 (41.2)	8 (47.1)	11 (68.8)	5 (45.5)	31 (50.8)

Table II
Summary of adverse eventAEs (safety analysis set)

	SM04690			PBO ($n = 11$)	All subjects ($n = 61$)
	0.03 mg ($n = 17$)	0.07 mg ($n = 17$)	0.23 mg ($n = 16$)		
Total AEs	15 (52.9)	13 (35.3)	25 (43.8)	19 (54.5)	72 (45.9)
Serious AEs	0	1 (5.9)*	0	0	1 (1.6)
Treatment discontinuations					
Adverse eventAE	1 (5.9)	0	0	NA	1 (1.6)
Patient decision	1 (5.9)	1 (5.9)	0	NA	2 (3.3)
All Reported Adverse EventAEs					
Headache	2/2 (11.8)	0	4/4 (25.0)	1/1 (9.1)	7/7 (11.5)
Arthralgia	2/1 (5.9)	1/1 (5.9)	1/1 (6.3)	5/3 (27.3)	9/6 (9.8)
Back pain	1/1 (5.9)	1/1 (5.9)	0	2/2 (18.2)	4/4 (6.6)
Joint swelling	1/1 (5.9)	1/1 (5.9)	1/1 (6.3)	1/1 (9.1)	4/4 (6.6)
Nasopharyngitis	1/1 (5.9)	1/1 (5.9)	0	2/2 (18.2)	4/4 (6.6)
Upper respiratory tract infection	2/2 (11.8)	0	1/1 (6.3)	0	3/3 (4.9)
Urinary tract infection	1/1 (5.9)	1/1 (5.9)	0	1/1 (9.1)	3/3 (4.9)
DiarrhoeaDiarrhea	0	0	1/1 (6.3)	1/1 (9.1)	2/2 (3.3)
Injection site pain	0	2/1 (5.9)	1/1 (6.3)	0	3/3 (4.9)
Nausea	1/1 (5.9)	0	1/1 (6.3)	0	2/2 (3.3)
Abdominal discomfort	0	0	1/1 (6.3)	0	1/1 (1.6)
Acne	0	1/1 (5.9)	0	0	1/1 (1.6)
Arthropod bite	0	0	1/1 (6.3)	0	1/1 (1.6)
Blister	0	0	2/1 (6.3)	0	2/1 (1.6)
Blood uric acid increase	0	0	1/1 (6.3)	0	1/1 (1.6)
Confusion	0	0	0	1/1 (9.1)	1/1 (1.6)
Cough	0	0	0	1/1 (9.1)	1/1 (1.6)
Dehydration	0	0	0	1/1 (9.1)	1/1 (1.6)
Diverticulitis	0	0	1/1 (6.3)	0	1/1 (1.6)
Electrocardiogram ECG change	0	1/1 (5.9)	0	0	1/1 (1.6)
Excoriation	1/1 (5.9)	0	0	0	1/1 (1.6)
Gingival pain	0	0	0	1/1 (9.1)	1/1 (1.6)
Hypertension	0	0	0	1/1 (9.1)	1/1 (1.6)
Injection site bruising	0	0	1/1 (6.3)	0	1/1 (1.6)
Joint injury	1/1 (5.9)	0	0	0	1/1 (1.6)
Joint stiffness	0	0	1/1 (6.3)	0	1/1 (1.6)
Limb injuring	0	0	0	1/1 (9.1)	1/1 (1.6)
Meniscus injury	0	0	1/1 (6.3)	0	1/1 (1.6)
Menstruation irregular	0	1/1 (5.9)	0	0	1/1 (1.6)
Musculoskeletal chest pain	1/1 (5.9)	0	0	0	1/1 (1.6)
Neutrophil count increased	0	1/1 (5.9)	0	0	1/1 (1.6)
ParaesthesiaParesthesia	0	0	1/1 (6.3)	0	1/1 (1.6)
Pruritis	0	0	1/1 (6.3)	0	1/1 (1.6)
Rash	0	0	1/1 (6.3)	0	1/1 (1.6)
Seasonal allergy	1/1 (5.9)	0	0	0	1/1 (1.6)
Tachycardia paroxysmal	0	1/1 (5.9)	0	0	1/1 (1.6)
Tremor	0	0	1/1 (6.3)	0	1/1 (1.6)
Upper-airway cough syndrome	0	0	1/1 (6.3)	0	1/1 (1.6)
Vomiting	0	0	1/1 (6.3)	0	1/1 (1.6)
White blood cell count increased	0	1/1 (5.9)	0	0	1/1 (1.6)
Total	**15/9 (52.9)**	**13/6 (35.3)**	**25/7 (43.8)**	**19/6 (54.5)**	**72/28 (45.9)**

Table shows number of AEs/number of unique subjects (percent of unique subjects).
* Investigator-assessed relationship deemed to be 'unrelated to treatment'. Sorted highest to lowest percent of all subjects experiencing the AE preferred term. AEs,: adverse events.

improvements from baseline were seen across all cohorts, including PBO. At Week 24, within-cohort improvement from baseline was maintained for all treatment cohorts (WOMAC Total, −27.4, −26.6, −18.4 and −23.5; WOMAC Function, −20.1, −18.9, −12.4, and −16.0; WOMAC Pain, −5.6, −5.3, −4.3 and −4.8 for the 0.03, 0.07, 0.23 mg, and PBO groups, respectively). Mean and median changes from baseline over time for WOMAC Total are presented in Fig. 3. Positive changes from baseline in MDGA and VAS pain scores were also observed in all groups at 12 and 24 weeks (Table III). While there were clinically relevant[22] changes from baseline within cohorts, no statistically significant differences between treatment cohorts and PBO were observed for any measurements.

OMERACT-OARSI responses

At Weeks 12 and 24, more subjects treated with SM04690 demonstrated an OMERACT-OARSI response than those treated with PBO (Fig. 4). At both 12 and 24 weeks, 4 (36%) PBO subjects showed response. Compared to PBO, 9 (56%) of the 0.03 mg cohort (OR = 2.3, 95% CI: [0.5, 10.9]), 13 (76%) of the 0.07 mg cohort (OR = 5.7, 95% CI: [1.1, 30.0], $P = 0.04$), and 7 (44%) of the 0.23 mg cohort (OR = 1.4, 95% CI: [0.3, 6.6]) achieved OMERACT-OARSI responses at Week 12. At Week 24, 11 (73%) of the 0.03 mg cohort (OR = 4.8, 95% CI: [0.9, 25.8], $P = 0.07$), 8 (50%) of the 0.07 mg cohort (OR = 1.8, 95% CI: [0.4, 8.4]) and 4 (25%) of the 0.23 mg cohort (OR = 0.6, 95% CI: [0.1, 3.1]) achieved an OMERACT-OARSI response compared to PBO.

Radiographic findings

Evaluable radiographs at Week 24 (Table III) exhibited a mean change from baseline in target knee medial JSW of 0.00 mm for the 0.03 mg cohort ($n = 15$), and 0.49 mm for the 0.07 mg cohort ($n = 15$; difference 0.81 mm, 95% CI: [0.14, 1.49], $P = 0.02$ vs PBO). The latter represented a 13% increase from baseline in JSW. At Week 24, JSW declined slightly compared with baseline for both the 0.23 mg cohort ($n = 16$, −0.15 mm) and PBO ($n = 11$, −0.33 mm).

Table III
Absolute change from baseline for efficacy outcomes at Weeks 12 and 24

		SM04690			PBO
		0.03 mg	0.07 mg	0.23 mg	
Week 12	*n*	16	17	16	11
	WOMAC total (0–96)				
	Mean (SD)	−24.9 (16.8)	−27.3 (22.2)	−25.9 (20.9)	−21.7 (18.3)
	Median (Min, Max)	−27.5 (−56, 10)	−26.0 (−65, −4)	−18.5 (−68, −3)	−15.0 (−52, 6)
	WOMAC function (0–68)				
	Mean (SD)	−18.4 (13.5)	−19.5 (15.9)	−17.8 (15.1)	−14.9 (13.4)
	Median (Min, Max)	−20.0 (−40, 9)	−21.0 (−44, 31)	−13.0 (−49, −2)	−10.0 (−42, 4)
	WOMAC pain (0–20)				
	Mean (SD)	−4.4 (3.0)	−5.8 (4.6)	−5.7 (4.4)	−4.2 (4.1)
	Median (Min, Max)	−4.0 (−12, 0)	−6.0 (−14, 8)	−3.5 (−14, 0)	−2.0 (−11, 2)
	MDGA (0–100)				
	Mean (SD)	−35.7 (27.8)	−32.1 (27.5)	−33.1 (18.6)	−25.7 (30.2)
	Median (Min, Max)	−48.5 (−77, 14)	−42.0 (−62, 49)	−33.0 (−67, −5)	−32.0 (−80, 26)
	Pain VAS (0–100)				
	Mean (SD)	−34.1 (27.2)	−34.9 (28.4)	−34.6 (20.6)	−34.2 (24.5)
	Median (Min, Max)	−46.0 (−77, 8)	−34.0 (−77, 44)	−34.5 (−80, −6)	−34.0 (−80, 8)
Week 24	*n*	15	16	16	11
	WOMAC total (0–96)				
	Mean (SD)	−27.4 (14.2)	−26.6 (16.2)	−18.4 (20.1)	−23.5 (19.2)
	Median (Min, Max)	−29.0 (−56, 3)	−24.0 (−65, −4)	−18.0 (−57, 15)	−19.0 (−67, 6)
	WOMAC function (0–68)				
	Mean (SD)	−20.1 (10.8)	−18.9 (10.9)	−12.4 (14.2)	−16.0 (14.1)
	Median (Min, Max)	−20.0 (−40, 3)	−18.0 (−44, −2)	−12.5 (−38, 11)	−12.0 (−49, 4)
	WOMAC pain (0–20)				
	Mean (SD)	−5.6 (3.1)	−5.3 (4.0)	−4.3 (4.7)	−4.8 (4.2)
	Median (Min, Max)	−6.0 (−12, 1)	−4.0 (−14, 0)	−3.5 (−14, 3)	−4.0 (−12, 2)
	MDGA (0–100)				
	Mean (SD)	−43.9 (27.2)	−37.9 (19.7)	−26.8 (24.5)	−33.5 (21.8)
	Median (Min, Max)	−52.0 (−77, 24)	−40.5 (−76, 1)	−27.0 (−71, 18)	−39.0 (−72, −2)
	Pain VAS (0–100)				
	Mean (SD)	−42.9 (24.1)	−35.7 (22.6)	−28.2 (21.2)	−39.1 (22.5)
	Median (Min, Max)	−45.0 (−77, 1)	−38.5 (−77, 11)	−30.0 (−69, 8)	−40.0 (−80, −10)
	JSW (mm)				
	Mean (SD)	0.00 (0.69)	0.49 (0.75)*	−0.15 (1.07)	−0.33 (0.87)
	Median (Min, Max)	0.22 (−1.7, 0.9)	0.44 (−0.9, 1.5)	−0.15 (−3.0, 1.6)	0.00 (−1.8, 0.8)

*Least square difference estimate compared to PBO from baseline-adjusted analysis of covariance: 0.81, 95% CI (0.14, 1.49), $P = 0.02$.

Discussion

The findings from this first-in-human phase 1 trial suggested that a single IA injection of SM04690 in knee OA patients appeared safe and well tolerated, with no evidence of systemic exposure. The imaging results suggested that a single IA injection of SM04690 did not have appreciable effects on BME or bone health.

These results represent the first human exposure to SM04690. All AEs were classified as related to study drug, as specified by the study protocol. Investigator assessment of relationship of AEs to

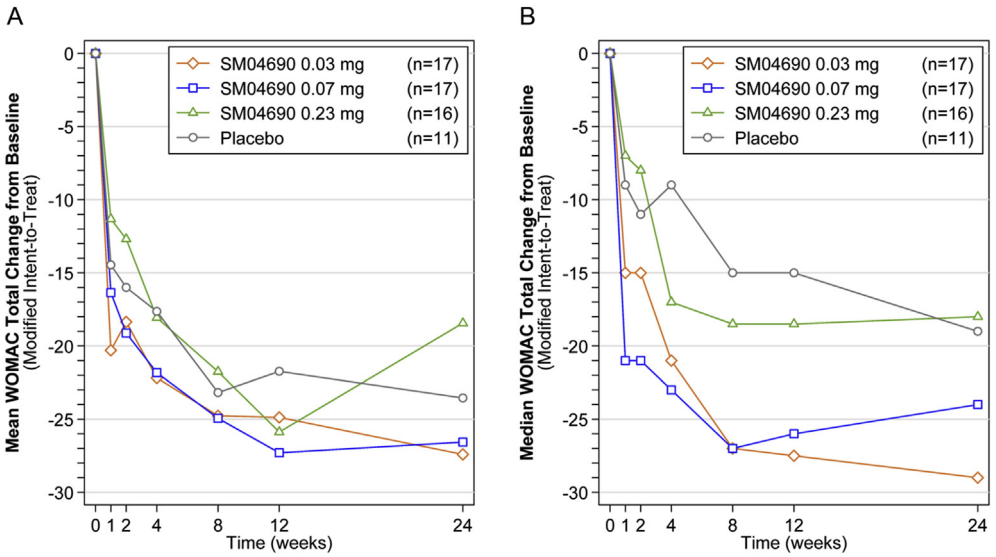

Fig. 3. Mean (A) and median (B) change from baseline in WOMAC Total over time for all cohorts.

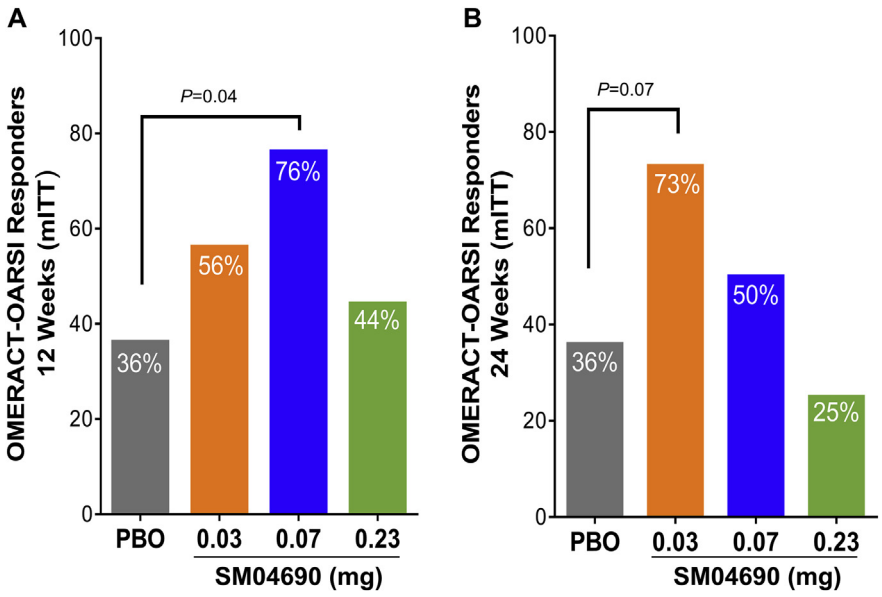

Fig. 4. Percent of OMERACT-OARSI responders at Weeks 12 and 24.

study drug determined that no SM04690-related trends were observed in any dose group with regard to SAEs and significant AEs (DLTs).

OA-related biochemical markers were measured as a safety outcome in this trial. Although some changes from baseline were seen, these were inconclusive and may be reflective of biomarker measurements obtained from serum rather than from the knee joint. These findings need further exploration.

All plasma concentration measurements for SM04690 were below quantifiable limits, and as such, it was not possible to construct concentration–time profiles, estimate PK parameters, or determine associations between systemic exposure and clinical or PD outcomes.

The exploratory WOMAC, MDGA, and VAS pain analyses showed positive trends in regard to SM04690 reducing pain and improving function. Additionally, the consistency of responses observed when comparing mean and median changes in the SM04690 cohorts suggested overall uniform trends rather than results driven by outliers (Table III). The OMERACT-OARSI responder analysis explored the clinical relevance of efficacy observations in this trial, and results suggested that treated subjects were more likely to achieve an OMERACT-OARSI response than those who received PBO (Fig. 3).

Radiography remains the standard for evaluating DMOAD efficacy in OA studies[23]. Radiographic JSW measurements are dependent on accurate positioning; joint space narrowing is not only caused by cartilage loss, but also by meniscal extrusion[24]. Exploratory radiographic findings measuring average JSW change from baseline at Week 24 suggested no change in the 0.03 mg cohort, an increase in the 0.07 mg cohort, and decreases in the 0.23 mg cohort and PBO group. Our findings in this study are interpreted with caution, given the small number of subjects enrolled and resultant statistical measurement error margins. Nevertheless, these early exploratory findings showing a difference from PBO for 0.03 mg and 0.23 mg, and an increase from baseline for 0.07 mg in radiographic JSW beyond the measurement error of 0.13 mm[25] suggested SM04690 may have potential utility as a DMOAD in knee OA.

Limitations for this study included the small number of subjects enrolled. As such, the clinical evaluations and all comparative statistical data relating to treatment arms versus PBO are provided solely to demonstrate potential signals. Further studies with a larger number of subjects are required and are being conducted at this time.

In summary, we present safety and exploratory clinical findings with SM04690 from a phase 1 trial. The compound appeared safe and well tolerated, with no evidence of systemic exposure, in the small numbers studied. This was primarily a safety study, but exploratory efficacy analyses suggested positive trends for measurements of OA pain, function and DMOAD properties. These data, coupled with preclinical results and the novel target pathway of SM04690, support further clinical trials. The phase 2 development program for SM04690 is currently underway, commencing with two studies of safety, tolerability, and efficacy in approximately 445 and 330 subjects with moderate to severe symptomatic knee OA (clinicaltrials.gov identifier NCT02536833 and NCT03122860, respectively).

Author contributions

Conception and design: Y. Yazici, C. Swearingen, A DiFrancesco, J. Tambiah, and J. Hood.

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Critical revisions to manuscript: All authors.

Final approval of manuscript for submission: All authors.

Responsibility for the integrity of the work as a whole: Y. Yazici.

Conflicts of interest

Y. Yazici, C. Swearingen, A. DiFrancesco, J. Tambiah, are employees and stockholders of Samumed. J. Hood is a former employee of Samumed and received equity. R. Fleischmann is a study investigator and reported receiving honoraria and a grant to Metroplex Clinical Research Center from Samumed LLC; and serving as a consultant to Abbvie, Pfizer, UCB, Janssen, BMS, Lilly, Akros, Amgen, and Sanofi-Genzyme. A. Gibofsky reported receiving honoraria

from Samumed; serving as consultant to Lilly; serving as a speaker for Abbvie, Pfizer, UCB, Celgene, and Novartis; and holding stock in Abbvie, Pfizer, Amgen, GSK, J&J, BMS, and Regeneron. N. Lane reported being a consultant to Samumed. E. Armas is a study investigator. N. Skrepnik is a study investigator and reported serving as a consultant to Sanofi and Orthofix. A. Kivitz is a study investigator. T. McAlindon is a study investigator and reported serving as a consultant to Samumed, Flexion, Pfizer, Regeneron, Astellas, and Seikugaku. M. Hochberg reported being a consultant to Bioberica, EMD Serono, Novartis, Pfizer, Plexxikon, Proximagen, Samumed, and Theralogix.

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Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.joca.2017.07.006.

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