A Phase 3, 56-Week, Multicenter, Randomized, Double-Blind, Vehicle-Controlled Study Utilizing Patient Reported and Radiographic Outcomes to Evaluate the Efficacy and Safety of a Single Injection of SM04690 Injected in the Target Knee Joint of Moderately to Severely Symptomatic Osteoarthritis Subjects

Study Number: SM04690-OA-11

IND Sponsor: Samumed, LLC

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PROTOCOL SUMMARY

Title: A Phase 3, 56-Week, Multicenter, Randomized, Double-Blind, Vehicle-Controlled Study Utilizing Patient Reported and Radiographic Outcomes to Evaluate the Efficacy and Safety of a Single Injection of SM04690 Injected in the Target Knee Joint of Moderately to Severely Symptomatic Osteoarthritis Subjects

Objective: The objective of this study is to determine the efficacy, safety, and tolerability of the SM04690 Injectable Suspension 0.07 mg dose in the treatment of knee osteoarthritis (OA).

Endpoints:

Primary:
Change from baseline OA pain in the target knee as assessed by the weekly averages of daily pain Numeric Rating Scale (NRS) at Week 12

Secondary:

1. Change from baseline OA pain in the target knee as assessed by the weekly averages of daily pain NRS at Week 24 and Week 52
2. Change from baseline in medial joint space width (mJSW) as documented by radiograph of the target knee at Week 24 and Week 52
3. Change from baseline OA function in the target knee as assessed by Western Ontario and McMaster Universities Arthritis Index physical function subscore (WOMAC Function) at Week 12, Week 24, and Week 52
4. Change from baseline OA disease activity as assessed by Patient Global Assessment at Week 12, Week 24, and Week 52

Safety:
Safety of SM04690 Injectable Suspension as measured by:

1. Adverse events (AEs)
2. Change in bone mineral density from baseline by dual-energy X-ray absorptiometry (DXA) of the spine and hips at Week 56
3. Change in serum bone biomarkers (N-terminal propeptides of procollagen type I [PINP] and β-C-terminal telopeptide [β-CTX]) from baseline, and change in a serum cartilage biomarker (cartilage oligomeric matrix protein [COMP]) from baseline at Week 56

Other Endpoints:

1. Change from baseline health-related quality of life as assessed by the 36-Item Short Form Health Survey (SF-36) at Week 52
2. Change from baseline OA pain in the target knee as assessed by WOMAC Pain subscore at Weeks 12, 24, and 52
3. Change from baseline OA pain, function and stiffness as a composite outcome measure as assessed by WOMAC Total score at Weeks 12, 24, and 52

Methodology:

This study will be a multicenter, randomized, double-blind, vehicle-controlled, parallel group study of a single concentration of SM04690 injected into the target knee joint of moderately to severely symptomatic osteoarthritis subjects at Day 1.

Approximately 725 subjects will be enrolled and randomized at a ratio of 1:1 (0.07 mg active per 2 mL injection: 2 mL vehicle). Subjects will participate in a 10- to 22-day screening period followed by a single injection and a 56-week evaluation period. Clinic visits will be scheduled at Screening Visit 1, Screening Visit 2, Day 1, and Weeks 4, 12, 24, 36, 52, and 56 [End of study (EOS)]/Early Termination (ET).

Radiographic images of the knees will be performed at Screening Visit 1, Week 24, and Week 52 or ET. DXA will be performed at Screening Visit 2 and at Week 56 or ET. Bone and cartilage biomarkers will be assessed at Screening Visit 2 and at Week 56 or ET.

Subjects will be required to complete an electronic diary for the following:

- Daily pain NRS (for target knee OA pain) through Week 56 (EOS)
- Patient Global Assessment at Baseline and Weeks 4, 12, 24, 36, 52, and 56 (EOS)
- WOMAC at Baseline and Weeks 4, 12, 24, 36, 52, and 56 (EOS)
- SF-36 at Baseline and Week 56 (EOS)

Inclusion/ Exclusion Criteria:

Criteria for Inclusion:

1. Males and females between 40 and 80 years of age, inclusive, in general good health apart from their knee osteoarthritis
2. Ambulatory (single assistive devices such as canes allowed if needed less than 50% of the time, subjects requiring a walker are excluded)
3. Diagnosis of femorotibial OA in the target knee by standard American College of Rheumatology (ACR) criteria at Screening Visit 1 (clinical AND radiographic criteria); OA of the knee is not to be secondary to any rheumatologic conditions (e.g., rheumatoid arthritis).
4. Baseline medial joint space width by radiograph between 2 and 4 mm, inclusive, in the target knee at Screening Visit 1 as assessed

by independent central readers

5. Pain compatible with OA of the knee(s) for at least 26 weeks prior to Screening Visit 1
6. Primary source of pain throughout the body is due to OA in the target knee
7. Daily OA knee pain diary average NRS intensity score ≥4 and ≤8 in the target knee on the 11-point (0-10) NRS scale for the 7 days immediately preceding Day 1
8. Pain NRS scores recorded for the target knee on at least 4 out of the 7 days immediately preceding Day 1
9. Daily OA knee pain diary average NRS intensity score <4 in the non-target knee on the 11-point (0-10) NRS scale for the 7 days immediately preceding Day 1
10. Pain NRS scores recorded for the non-target knee on at least 4 out of the 7 days immediately preceding Day 1
11. WOMAC Pain score of 20-40 (out of 50) for the target knee at baseline regardless of if the subject is on symptomatic oral treatment (baseline questionnaire completed during the screening period prior to randomization)
12. WOMAC Function score of 68-136 (out of 170) for the target knee at baseline regardless of if the subject is on symptomatic oral treatment (baseline questionnaire completed during the screening period prior to randomization)
13. Willingness to use an electronic diary on a daily basis in the evening for the screening period and 56-Week study duration
14. Widespread Pain Index (WPI) score of ≤ 4 and a Symptom Severity Question 2 (SSQ2) score of ≤ 2 at Screening
15. Negative drug test for amphetamine, methamphetamine, buprenorphine, cocaine, methadone, opiates, phencyclidine (PCP), propoxyphene, barbiturates, benzodiazepine, methaqualone, and tricyclic antidepressants, unless any of these drugs are allowed per protocol and prescribed by a physician to treat a specific condition
16. Subjects with depression or anxiety must be clinically stable for 12 weeks prior to Screening Visit 1 and, if on treatment for depression or anxiety, be on 12 weeks of stable therapy
17. Full understanding of the requirements of the study and willingness to comply with all study visits and assessments
18. Subjects must have read and understood the informed consent form, and must have signed it prior to any study-related procedure being performed

Criteria for Exclusion:

1. Women who are pregnant, lactating, or have a positive or indeterminate pregnancy result at Screening Visit 2 or Day 1
2. Women who are not post-menopausal (defined as 12 months with no menses without an alternative medical cause) or permanently surgically sterile (includes hysterectomy, bilateral salpingectomy, and bilateral oophorectomy, but NOT tubal ligation), who are sexually active, and who are not willing to use birth control (as outlined in Section 5.3.1) during the study period
3. Males who are sexually active and have a partner who is capable of becoming pregnant, neither of whom have had surgery to become sterilized or who are not using birth control as outlined in Section 5.3.1
4. Body mass index (BMI) > 40 kg/m^2
5. Significant malalignment of anatomical axis (medial angle formed by the femur and tibia) of the target knee (varus > 10°, valgus > 10°)
6. Subjects who have had a single or bilateral, partial or complete knee or hip replacement.
7. Currently requires use of a lower extremity prosthesis, and/or a structural knee brace (i.e., a knee brace that contains hardware)
8. Radiographic disease Stage 0, 1, or 4 in the target knee at Screening Visit 1 according to the Kellgren-Lawrence grading of knee OA as assessed by independent central readers
9. Previous treatment with SM04690
10. Subjects who have previously failed screening on this protocol and fail to meet re-screening criteria
11. Any surgery (e.g., arthroscopy) in either knee within 26 weeks prior to Screening Visit 1
12. Any bone fracture(s) within 26 weeks prior to Screening Visit 1
13. Any surgery scheduled during the study period. Non-surgical invasive procedures conducted for a diagnostic or therapeutic purpose scheduled during the study period are allowed (refer to Section 7.6).
14. History of malignancy within the last 5 years; however, subjects with prior history of in situ basal or squamous cell skin cancer are eligible if completely excised. Subjects with other malignancies are eligible if they have been continuously disease free for at least 5 years prior to Screening Visit 1
15. Clinically significant abnormal screening hematology values, blood chemistry values, or urinalysis values as determined by the Investigator

16. Any condition, including laboratory findings not included in the Screening Visit 2 laboratory tests and findings in the medical history or in the pre-study assessments, that, in the opinion of the Investigator, constitutes a risk or contraindication for participation in the study or that could interfere with the study objectives, conduct, or evaluation
17. Comorbid conditions that could affect study endpoint assessments of the target knee, including, but not limited to, rheumatoid arthritis, psoriatic arthritis, systemic lupus erythematosus, gout or pseudogout, and fibromyalgia
18. Other conditions that, in the opinion of the Investigator, could affect study endpoint assessments of either knee, including, but not limited to, peripheral neuropathy (e.g., diabetic neuropathy), symptomatic hip osteoarthritis, symptomatic degenerative disc disease, and patellofemoral syndrome
19. Any diagnosed psychiatric condition that includes, but is not limited to, a history of mania, bipolar disorder, psychotic disorder, schizophrenia, schizoaffective disorder, major depressive disorder, or generalized anxiety disorder
20. Participation in a clinical research trial that included the receipt of an investigational product or any experimental therapeutic procedure, or an observational research trial related to osteoarthritis within 8 weeks prior to Screening Visit 1, or planned participation in any such trial; the last date of participation in the trial, not the last date of receipt of investigational product, must be at least 8 weeks prior to Screening Visit 1
21. Any intra-articular injection into the target knee with a therapeutic aim including, but not limited to, viscosupplementation (e.g., hyaluronic acid), platelet-rich plasma (PRP), and stem cell therapies within 24 weeks prior to Screening Visit 1; treatment of the target knee with intra-articular glucocorticoids more than 12 weeks prior to Screening Visit 1 is allowed
22. Treatment with systemic glucocorticoids greater than 10 mg prednisone or the equivalent per day within 4 weeks prior to Screening Visit 1
23. Effusion of the target knee clinically requiring aspiration within 12 weeks prior to Screening Visit 1
24. Use of electrotherapy, acupuncture, and/or chiropractic treatments for knee OA within 4 weeks prior to Screening Visit 1 (refer to Appendix 2)
25. Any known active infections, including urinary tract infection, upper respiratory tract infection, sinusitis, suspicion of intra-articular infection, hepatitis B or hepatitis C infection, and/or infections that may compromise the immune system such as human

immunodeficiency virus (HIV) at Day 1

26. Current use, or use within 12 weeks prior to Screening Visit 1, of centrally acting analgesics (refer to Appendix 2)
27. Current use, or use within 12 weeks prior to Screening Visit 1, of anticonvulsants (refer to Appendix 2)
28. Subjects requiring the use of opioids >1x per week within 12 weeks prior to Screening Visit 1
29. Topical local anesthetic agents (gels, creams, or patches such as the Lidoderm patch) used for the treatment of knee OA within 7 days of Screening Visit 1
30. Any chronic condition that has not been well controlled or subjects with a chronic condition who have not maintained a stable therapeutic regimen of a prescription therapy in the opinion of the Investigator. In addition, subjects with an HbA1c >8 at Screening Visit 2 will be excluded.
31. If using NSAIDs for the treatment of OA pain, subjects who have not maintained a stable regimen in the opinion of the Investigator at Screening Visit 1
32. Any contraindications for performing DXA scans of the hips or spine including but not limited to:
    a. pins, screws, or any surgical implant, either in the spine or any hip that preclude scanning at these sites
    b. severe degenerative changes or fracture deformity in the measurement area
    c. other radiological investigations using contrast media or radionuclides within 7 days prior to Screening Visit 2
    d. weight that precludes scanning at these sites
33. Subjects who have a current or pending disability claim, workers' compensation, or litigation(s) that may compromise response to treatment
34. Subjects who are immediate family members (spouse, parent, child, or sibling; biological or legally adopted) of personnel directly affiliated with the study at any investigative site, or are directly affiliated with the study at any investigative site
35. Subjects employed by Samumed, LLC, or any of its affiliates or development partners (that is, an employee, temporary contract worker, or designee) responsible for the conduct of the study

Population: Approximately 725 subjects with moderately to severely symptomatic osteoarthritis of the knee

Phase: 3

Number of Sites enrolling participants:	This study will be conducted at approximately 65 investigational centers in the United States
Description of Study Agent:	SM04690 is a small molecule Wnt pathway inhibitor which potentially (a) reduces signs and symptoms of knee OA via an anti-inflammatory mechanism and (b) inhibits breakdown and enhances formation of cartilage through effects on progenitor cells resident in the joint.
Study Duration:	Approximately 64 weeks Estimated date first subject consented: March 2019 Estimated date last subject completed: July 2020
Participant Duration:	Up to approximately 60 weeks
Criteria for evaluation:	**Efficacy:** Efficacy will be assessed by: • Weekly averages of daily pain NRS (for target knee OA pain) • mJSW by radiograph • WOMAC questionnaire for WOMAC pain and function subscores for the target knee • Patient Global Assessment **Safety:** The overall safety and tolerability of SM04690 will be assessed by the incidence, seriousness, severity, and relationship of AEs and clinically significant changes in clinical laboratory measures and vital signs. Safety will also be assessed by evaluating concentrations of biomarkers in the serum (COMP, PINP, β-CTX), and evaluating DXA scans of the spine and hips.

SCHEDULE OF EVENTS TABLE

Procedure	**Screening Period**[a] (Days -22 to -1)		**Day 1**[b]	**Week 4** (Day 29 +3 days)	**Week 12** (Day 85 ±3 days)	**Week 24** (Day 169 +3 days)	**Week 36** (Day 253 -3 to + 7 days)	**Week 52** (Day 365 - 3 to +7 days)	**Week 56 (EOS)** (Day 393 - 3 to +7 days) / **ET**
	Screening Visit 1 (Days -22 to -10)	**Screening Visit 2** (Days -11 to -7)							
Informed consent	X								
Inclusion & exclusion criteria	X		X						
Demographics	X								
Medical history	X		X						X[c]
Current and prior procedures/medications	X		X						
Serum pregnancy test		X							
Urine pregnancy test			X						
Urine drug test	X								
WPI & SS	X								
Radiograph	X					X		X[h]	
DXA		X							X
Physical examination	X		X	X	X	X	X	X	X
Knee examination	X		X	X	X	X	X	X	X
Selection of target knee	X								
Height	X								
Weight	X					X		X	X
Vital signs	X		X	X	X	X	X	X	X
Clinical laboratory sampling		X		X	X	X	X	X	X
Biomarkers[d]		X							X[i]
Electronic diary and questionnaire training		X[e] (eDiary device provision and training)							
Pain NRS			X[f] (Review)						
WOMAC			X[g] (Review)						
SF-36			X (Review)						
Randomization			X						
Intra-articular injection			X						

Procedure	**Screening Period**[a] (Days -22 to -1)		**Day 1**[b]	**Week 4** (Day 29 +3 days)	**Week 12** (Day 85 ±3 days)	**Week 24** (Day 169 +3 days)	**Week 36** (Day 253 -3 to + 7 days)	**Week 52** (Day 365 - 3 to +7 days)	**Week 56 (EOS)** (Day 393 - 3 to +7 days) / **ET**
	Screening Visit 1 (Days -22 to -10)	**Screening Visit 2** (Days -11 to -7)							
AEs and concomitant procedures/medications			X	X	X	X	X	X	X

[a] The screening period is a minimum of 10 days and a maximum of 22 days and includes Screening Visit 1 and Screening Visit 2; Screening Visit 2 should occur at least 3 days after Screening Visit 1, at least 7 days prior to Day 1, and after confirmation of eligible radiograph and urine drug test report results.
[b] At Day 1, all procedures should be performed prior to study medication injection except for collection of AE and concomitant procedures/medication data.
[c] Review medical history to capture End Date(s), if applicable, of any ongoing medical history(ies) collected at screening.
[d] Concentrations of bone and cartilage biomarkers are analyzed in the serum
[e] Electronic diary devices will be provided to subjects at Screening Visit 2; subject electronic diary and questionnaire training will be conducted at Screening Visit 2.
[f] Electronic diary compliance and assessment of target and contralateral knee pain scores for daily pain NRS over the screening period will be reviewed at Day 1 prior to randomization to determine subject eligibility.
[g] WOMAC questionnaire will be reviewed at Day 1 prior to randomization to determine subject eligibility.
[h] Radiographic images of the knees will be performed at Week 52 or ET.
[i] Collection of serum for biomarker analysis will be performed at Week 56 or ET.