

PROTOCOL SM04690-OA-02
(Amendment 04 Version 00, October 13, 2016)

A Phase 2, Multicenter, Randomized, Double-Blind, Placebo-Controlled
Study Evaluating the Safety, Tolerability, and Efficacy of SM04690
Injected in the Target Knee Joint of Moderately to Severely
Symptomatic Osteoarthritis Subjects

NCT02536833

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Study Title: A Phase 2, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Safety, Tolerability, and Efficacy of SM04690 Injected in the Target Knee Joint of Moderately to Severely Symptomatic Osteoarthritis Subjects

Protocol Number: SM04690-OA-02

Investigational Product: SM04690 Injectable Suspension

Clinical Phase: Phase 2

Original Protocol Date: July 14, 2015

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SPONSOR SIGNATURE PAGE

A Phase 2, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Safety, Tolerability, and Efficacy of SM04690 Injected in the Target Knee Joint of Moderately to Severely Symptomatic Osteoarthritis Subjects

Protocol Number: SM04690-OA-02

Date: October 13, 2016

Name & Title	Signature	Date
[REDACTED]		13OCT16
[REDACTED]		13OCT16
[REDACTED]		13OCT2016
[REDACTED]		13OCT2016

Samumed commits to satisfying the requirements of the ICH-GCP Guidelines regarding the responsibilities of the Sponsor, the US Code of Federal Regulations 21 CFR parts 50, 54, 56, 312, and 314 and Good Clinical Practice Guidelines, as applicable.

PRINCIPAL INVESTIGATOR'S SIGNATURE PAGE

Study Title	A Phase 2, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Safety, Tolerability, and Efficacy of SM04690 Injected in the Target Knee Joint of Moderately to Severely Symptomatic Osteoarthritis Subjects		
Protocol Number	SM04690-OA-02		
Protocol Date	October 13, 2016	Protocol Version	AM04 V00

I have read and understand the protocol and agree to implement the study in accordance with the procedures set forth in the protocol and in accordance with the Sponsor's guidelines, all applicable government regulations, and the International Conference on Harmonization Good Clinical Practice Guidelines E6 (ICH-GCP).

I will obtain Institutional Review Board/Ethics Committee (IRB/EC) approval of the protocol and Informed Consent Form prior to enrollment of subjects in the study. I understand that any modifications to the protocol made during the course of the study must first be approved by the IRB/EC prior to implementation except when such modification is made to remove an immediate hazard to the subject.

I will ensure that a fully executed IRB/EC-approved Informed Consent Form is obtained from each subject prior to initiation of any study procedures.

I will allow the Sponsor, Samumed, LLC and its agents, as well as the United States (US) Food and Drug Administration (FDA) and other regulatory agencies, to inspect study facilities and pertinent records at reasonable times and in a reasonable manner, ensuring subject confidentiality. If I am notified that this study is to be inspected by a regulatory agency, I will notify the Sponsor as soon as possible thereafter (no later than 48 hours).

This protocol contains information that is proprietary to Samumed, LLC. The information contained herein is provided for the purpose of conducting a clinical trial for Samumed, LLC.

The contents of this protocol may only be disclosed to study personnel under my supervision and to my IRB/EC. The contents of this protocol may not be disclosed to any other parties (unless such disclosure is required by government regulations or laws) without the prior written approval of Samumed, LLC.

Investigator's Signature

Date

Investigator's Printed Name

SYNOPSIS

Name of Sponsor/Company: Samumed, LLC	
Name of Investigational Product: SM04690 Injectable Suspension	
Name of Active Ingredient: SM04690	
Description of Investigational Product: SM04690 is a small molecule inhibitor of the Wnt pathway important in driving progenitor cells resident in the joint to become chondrocytes, thereby enhancing cartilage formation. SM04690 will be supplied as a single-use injectable formulation containing SM04690 suspended in a sodium carboxymethylcellulose phosphate buffered saline solution. Dose levels will be concentrations of 0.03, 0.07 and 0.23 mg per 2 mL injection.	
Title of Study: A Phase 2, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Safety, Tolerability, and Efficacy of SM04690 Injected in the Target Knee Joint of Moderately to Severely Symptomatic Osteoarthritis Subjects	
Study Center(s): This study will be conducted at up to 40 investigational centers in the United States	
Study period (years): Approximately 20 months Estimated date first subject enrolled: August 2015 Estimated date last subject completed: April 2017	Phase of development: 2
Objectives: Primary: The primary objective of this study will be to evaluate the change from baseline OA pain in the target knee as assessed by the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain subscore at Week 13. Secondary: <ul style="list-style-type: none">• Evaluate change from baseline OA pain in the target knee as assessed by the WOMAC pain subscore at Week 26• Evaluate change from baseline OA function in the target knee as assessed by the WOMAC function subscore at Weeks 13 and 26• Evaluate change from baseline OA disease activity as assessed by the Patient Global Assessment at Weeks 13 and 26• Evaluate change from baseline in medial joint space width (JSW) as documented by X-ray of the target knee at Week 26• Evaluate the safety and tolerability of SM04690 by monitoring for treatment-emergent adverse events (TEAEs) Exploratory: <ul style="list-style-type: none">• Evaluate change from baseline in WOMAC total score for the target knee at Weeks 4, 13, 26, 39 and 52	

- Evaluate change from baseline OA pain in the target knee as assessed by the WOMAC pain subscore at Weeks 4, 39 and 52
- Evaluate change from baseline OA function in the target knee as assessed by the WOMAC function subscore at Weeks 4, 39 and 52
- Evaluate change from baseline OA disease activity as assessed by the Patient Global Assessment at Weeks 4, 39 and 52
- Evaluate change from baseline in medial JSW as documented by X-ray of the target knee at Week 52
- Evaluate change from baseline in lateral JSW as documented by X-ray of the target knee at Weeks 26 and 52
- Determine the percentage of Outcome Measures in Rheumatology Clinical Trials (OMERACT)-Osteoarthritis Research Society International (OARSI) responders and “strict” responders at Weeks 13, 26, and 52
- Evaluate change from baseline health-related quality of life (HRQOL) as assessed by the 36-Item Short Form Health Survey (SF-36) at Weeks 4, 13, 26, 39 and 52
- Evaluate change from baseline OA disease activity as assessed by the Physician Global Assessment at Weeks 4, 13, 26, 39 and 52

Methodology:

This study will be a multicenter, randomized, double-blind, placebo-controlled, parallel group study of three different strengths of SM04690 injected into the target knee joint of moderately to severely symptomatic osteoarthritis subjects.

Approximately 445 subjects will be enrolled and randomized at a ratio of 1:1:1:1 (0.03 mg active per 2 mL injection: 0.07 mg active per 2 mL injection: 0.23 mg active per 2 mL injection: placebo). Subjects will participate in a screening period of up to 21 days and a 52 week follow-up period. Clinic visits will be scheduled at Screening, Treatment Visit Day 1 and Follow-up Weeks 4, 13, 26, 39 and 52 [End of study (EOS) or Early Termination (ET)]. An interim analysis will be performed after all subjects have completed their Week 26 visit; however, clinical study sites and subjects will remain blinded throughout the study.

Number of subjects (planned):

Approximately 445 subjects

Main criteria for inclusion:

1. Males and females between 40 and 80 years of age, inclusive, in general good health
2. Ambulatory (single assistive devices such as canes allowed if needed less than 50% of the time, subjects requiring a walker are excluded)
3. Established diagnosis of primary femorotibial OA in the target knee by standard American College of Rheumatology (ACR) criteria for at least 6 months (clinical AND radiographic criteria); if bilateral knee OA is present, the target knee is defined as the knee with greater pain at screening based on the subject’s evaluation and the Investigator’s clinical judgment
4. Radiographic disease Stage 2 or 3 in the target knee according to the Kellgren-Lawrence grading of knee OA as assessed by independent central readers
5. Screening pain visual analog scale (VAS) score of 30-80 mm (on a scale of 0-100 mm) for the target knee while on symptomatic oral treatment at screening (if the subject requires oral treatment)

6. Total WOMAC score of 72-192 (out of 240) for the target knee while on symptomatic oral treatment at screening (if the subject requires oral treatment)
7. Willingness to omit the following for 24 hours prior to all Study Visits, excluding the Screening Visit:
 - a. Pain medications
 - b. Medications or supplements for the treatment of OA
 - c. Participation in a formalized in-office and/or supervised OA disease program (e.g., a prescribed patient education program, physiotherapy, etc.)
8. Full understanding of the requirements of the study and willingness to comply with all study visits and assessments
9. Subjects must have read and understood the informed consent form, and must have signed it prior to any study-related procedure being performed
10. Subject's Day 1 visit must occur while enrollment into the study is open

Main criteria for exclusion:

1. Women who are pregnant or lactating
2. Women of childbearing potential (i.e., who are not surgically sterile or postmenopausal as defined by no menstrual periods for 12 consecutive months and no other biological or physiological cause for amenorrhea can be identified); males who are sexually active and have a partner who is capable of becoming pregnant, neither of which have had surgery to become sterilized, who are not using an effective method of birth control (e.g., surgically-implanted hormonal therapy, intrauterine devices or oral birth control with barrier method)
3. Body mass index (BMI) >40
4. Partial or complete joint replacement in the target knee
5. Previous exposure to SM04690
6. Major surgery (e.g., interventional arthroscopy) in the target knee within 52 weeks prior to any study injection
7. Any planned or elective surgery during the study period
8. Significant and clinically evident misalignment of the target knee that would impact subject function, as determined by the Investigator
9. History of malignancy within the last 5 years; however, subjects with prior history of in situ cancer or basal or squamous cell skin cancer are eligible. Subjects with other malignancies are eligible if they have been continuously disease free for at least 5 years prior to any study injection
10. Clinically significant abnormal Screening Visit hematology values, blood chemistry values, HbA1c, or urinalysis values as determined by the investigator
11. Any condition, including laboratory findings (not included in the Screening Visit 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
12. Comorbid conditions that could affect pain assessment of the target knee, including, but not limited to, inflammatory rheumatic conditions such as rheumatoid arthritis, psoriatic arthritis, systemic lupus erythematosus, diabetic neuropathy, pseudogout, gout, and fibromyalgia

13. Other conditions that, in the opinion of the Investigator, could affect pain assessment of the target knee, including, but not limited to, symptomatic hip osteoarthritis and symptomatic degenerative disc disease
14. Any diagnosed psychiatric condition that includes, but is not limited to, a history of mania, bipolar disorder, psychotic disorder, schizophrenia, major depressive disorder, or generalized anxiety disorder
15. Participation in a clinical research trial that included the receipt of an investigational product or any experimental therapeutic procedure within 12 weeks prior to any study injection; the last date of participation in the trial, not the last date of receipt of investigational product, must be at least 12 weeks prior to Study Visit Day 1
16. Treatment of the target knee with systemic or intra-articular corticosteroids (e.g., methylprednisolone) within 8 weeks prior to Study Visit Day 1
17. Viscosupplementation (e.g., hyaluronic acid) in the target knee within 24 weeks prior to Study Visit Day 1
18. Effusion of the target knee clinically requiring aspiration within 12 weeks prior to Study Visit Day 1
19. Use of electrotherapy, acupuncture, and/or chiropractic treatments for knee OA within 4 weeks prior to Study Visit Day 1
20. Any known active infections, including 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)
21. Subjects taking prescription medications for OA who have not maintained a stable therapeutic regimen for a minimum of 12 weeks prior to Study Visit Day 1
22. Subjects requiring the chronic use (i.e., regular and consistent use for ≥ 12 weeks) of the medications listed below within 12 weeks prior to Study Visit Day 1.
 - a. Opioids, both oral (e.g., tramadol) or transdermal (e.g., fentanyl patches) formulations
 - b. Centrally acting analgesics (e.g., duloxetine)
 - c. Glucocorticoids (e.g., methylprednisolone) administered by any route, with exception of inhaled, intranasal, and ophthalmic solutions
23. 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 for a minimum of 12 weeks prior to Study Visit Day 1. In addition, the following subjects will be excluded:
 - a. Subjects with a baseline HbA1c >9
 - b. Subjects with uncontrolled hypertension in the opinion of the investigator
 - c. Subjects with symptomatic coronary artery disease in the opinion of the investigator
24. Subjects who have a current or pending disability claim, workers' compensation, or litigation(s) that may compromise response to treatment
25. Subjects who are immediate family members (spouse, parent, child, or sibling; biological or legally adopted) of personnel directly affiliated with the study at the investigative site, or are directly affiliated with the study at the investigative site
26. 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

<p>Investigational product dosage and mode of administration: Three strengths of intra-articularly injected SM04690 suspension will be used in this study:</p> <ul style="list-style-type: none">• SM04690 0.03 mg in 2 mL Injectable Suspension• SM04690 0.07 mg in 2 mL Injectable Suspension• SM04690 0.23 mg in 2 mL Injectable Suspension <p>The study medication will be prepared by trained study staff and administered as a single intra-articular injection.</p>
<p>Reference therapy dosage and mode of administration: The placebo therapy will be an intra-articular injection of 2 mL of phosphate buffered saline (PBS).</p>
<p>Duration of treatment: 1 day; single-dose injection</p>
<p>Duration of subject participation: Approximately 52 weeks following a screening period of up to 21 days</p>
<p>Criteria for evaluation: Efficacy: Efficacy will be assessed by:</p> <ul style="list-style-type: none">• WOMAC pain and function subscores as well as WOMAC total score for the target knee• Patient Global Assessment• Percentage of OMERACT-OARSI responders and “strict” responders• HRQOL as assessed by SF-36• Physician Global Assessment• JSW as evaluated by X-ray <p>Safety: The overall safety and tolerability of SM04690 will be determined by the incidence, severity and relationship of adverse events (AE) and clinically significant changes in clinical laboratory measures and vital signs.</p>
<p>Statistical methods: A sample size of approximately 445 subjects will be randomized across four treatment groups (0.03 mg active per 2 mL injection: 0.07 mg active per 2 mL injection: 0.23 mg active per 2 mL injection: placebo) based on a 1:1:1:1 ratio. The sample size for this study was based upon accepted statistical practice and not on a formal efficacy hypothesis test and corresponding power analysis.</p> <p>The Safety Analysis Set will comprise all subjects who were randomized and received SM04690 or placebo. The Intent-to-Treat Analysis Set (ITT) will comprise subjects who were randomized. The Modified Intent-to-Treat Analysis Set (mITT) will comprise all randomized subjects who received a protocol specified dose of SM04690 or placebo. The Per Protocol Analysis Set (PP) will comprise ITT subjects who complied with all study procedures and evaluations, and did not have major protocol deviations.</p> <p>The incidence of AEs and proportion of subjects experiencing AEs will be summarized by</p>

seriousness and relatedness to study product for each treatment group; severity of the AEs will be assessed by the Investigator according to the “Guidance for Industry: Toxicity Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Trials”. Safety summaries will also include listings of clinical laboratory findings, vital signs, and concomitant medications.

Differences in efficacy outcomes between groups will be estimated at time points using parametric regression methods adjusting for baseline.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
AE	Adverse event
ALT	Alanine aminotransferase
ALP	Alkaline phosphatase
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
CFR	Code of Federal Regulations
CRF	Case report form
DLT	Dose-limiting toxicity
EC	Ethics Committee
EOS	End of study
FDA	(US) Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
HRQOL	Health-related Quality of Life
IB	Investigator Brochure
ICF	Informed consent form
ICH	International Conference on Harmonization
IRB	Institutional Review Board
ITT	Intent-to-treat
LDH	Lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
mL	Milliliter
OA	Osteoarthritis
OARSI	Osteoarthritis Research Society International
OMERACT	Outcome Measures in Rheumatology Clinical Trials
OTC	Over the counter
PD	Pharmacodynamics

Abbreviation	Term
PI	Principal investigator
PK	Pharmacokinetics
PP	Per protocol
RBC	Red blood cell
SAE	Serious adverse event
SAP	Statistical analysis plan
SF-36	36-Item Short Form Healthy Survey
SRC	Safety Review Committee
SOP	Standard operating procedure
US	United States
VAS	Visual Analog Scale
WBC	White blood cell
WOMAC	Western Ontario and McMaster Universities Arthritis Index

1. INTRODUCTION

1.1. Summary

Osteoarthritis (OA) is the most common form of arthritis and the major cause of activity limitation and physical disability in older people. Today, 35 million people (13% of the US population) are 65 and older, and more than half of them have radiological evidence of OA in at least 1 joint. By 2030, 20% of Americans (about 70 million people) will have passed their 65th birthday and will be at risk for OA (Nevitt et al. 2006).

Therapies available to treat OA are limited. Most current treatments are designed only to relieve pain and reduce or prevent the disability caused by bone and cartilage degeneration. Drug therapies target the symptoms but not the cause of this disease; no treatment inhibits or reverses the degenerative structural changes that are responsible for its progression (Nevitt et al. 2006).

Samumed, LLC (Samumed) is developing SM04690 for the treatment of OA. SM04690 is a small molecule inhibitor of the Wnt pathway.

1.2. Nonclinical Assessments

SM04690 has been tested in a number of appropriate nonclinical studies. The results of those studies are included in the Investigator Brochure (IB).

1.3. Study Rationale

Osteoarthritis is the most common form of arthritis and chronic joint disorder in man (Dougados and Hochberg 2011). The exact cause of OA is unknown, but it is associated with aging and normal wear on a joint. Osteoarthritis is characterized by the destruction of the articular cartilage, subchondral bone alterations, and synovitis. Patients present with pain and stiffness in the joints, with the joints becoming more stiff and immobile over time (Dougados and Hochberg 2011). Osteoarthritis is a leading cause of physical disability in the US (Lawrence et al. 2008).

The Wnt pathway plays a central role in the initiation and progression of OA pathology and is crucial in normal joint metabolism (Hochberg et al. 2012). Wnt is a major regulator of joint development and is involved in the formation of bone, cartilage, and synovium. The transcription of Wnt target genes causes an increase in catabolic processes during the development of OA, and increased Wnt signaling may contribute to cartilage loss (Gelse et al. 2012). Polymorphisms in genes involved in Wnt signaling are associated with an increased susceptibility to OA development (Wu et al. 2012). Established research suggests that modulation of Wnt signaling is an attractive target for treatment of OA.

In order to address the need for effective pharmaceutical agents to treat OA, Samumed has used structure-based drug design to synthesize a small molecule inhibitor of the Wnt pathway, SM04690, as a potential OA therapeutic to be administered in the form of a local injection in the affected joint.

SM04690 is currently being tested in a single Phase 1 clinical trial in subjects with moderately to severely symptomatic osteoarthritis of the knee. The trial was a placebo-controlled, double-blind, dose-escalation study conducted in the US of three concentrations of SM04690 (0.03, 0.07, and

0.23 mg per 2 mL injection). In each dose cohort, subjects were randomized to active or vehicle at a ratio of 16 active: 4 vehicle. Subject clinic visits occurred on Day 1 and 2 and Weeks 1, 2, 4, 8, 12, and 24. Each successively higher concentration cohort was enrolled after completion of treatment and review of safety data from the previous cohort by a Safety Review Committee. The Safety Review Committee was comprised of the Samumed medical monitor, the site Investigators, and an independent rheumatologist. As of 07 July 2015, 61 subjects have been enrolled in 3 ascending dose cohorts of approximately 20 subjects per cohort. Per protocol, data from cohort 1 and 2 were unblinded following the safety review of all subjects enrolled in the cohort (observed for a minimum of 12 weeks). Cohort 3 data remains blinded.

As of 07 July 2015, following dosing in all three cohorts, there have been two dose-limiting toxicities (DLTs) and 1 serious adverse event (SAE) reported on the trial. A DLT of increased knee pain was reported and met the DLT criteria of increased pain at the target joint of greater than 30 mm increase on the pain visual analog scale (VAS); this DLT was due to a procedural error and considered unrelated to study drug. A DLT of tachycardia paroxysmal was also reported and met the DLT criteria of an AE deemed by the investigator to be a severe or serious AE. This DLT also met SAE criteria. The event was a report of tachycardia paroxysmal in a 72 year old white male, with previous medical history of tachycardia. This event was considered unrelated to study drug administration by the reporting investigator. Nevertheless, as the FDA requested that all adverse events in this initial OA study be considered related to study drug, this event was reported in an expedited manner. No other DLTs or SAEs have been reported. This data provided justification to move forward with a Phase 2 dosing trial.

2. STUDY OBJECTIVES AND PURPOSE

2.1. Purpose

The purpose of this study is to assess the efficacy, safety, and tolerability of three different strengths of SM04690 (0.03 mg, 0.07 mg, and 0.23 mg per 2 mL injection) injected in the target knee joint of moderately to severely symptomatic osteoarthritis subjects.

2.2. Study Objectives

Primary:

The primary objective of this study will be to evaluate the change from baseline OA pain in the target knee as assessed by the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain subscore at Week 13.

Secondary:

- Evaluate change from baseline OA pain in the target knee as assessed by the WOMAC pain subscore at Week 26
- Evaluate change from baseline OA function in the target knee as assessed by the WOMAC function subscore at Weeks 13 and 26
- Evaluate change from baseline OA disease activity as assessed by the Patient Global Assessment at Weeks 13 and 26

- Evaluate change from baseline in medial joint space width (JSW) as documented by X-ray of the target knee at Week 26
- Evaluate the safety and tolerability of SM04690 by monitoring for treatment-emergent adverse events (TEAEs)

Exploratory:

- Evaluate change from baseline in WOMAC total score for the target knee at Weeks 4, 13, 26, 39 and 52
- Evaluate change from baseline OA pain in the target knee as assessed by the WOMAC pain subscore at Weeks 4, 39 and 52
- Evaluate change from baseline OA function in the target knee as assessed by the WOMAC function subscore at Weeks 4, 39 and 52
- Evaluate change from baseline OA disease activity as assessed by the Patient Global Assessment at Weeks 4, 39 and 52
- Evaluate change from baseline in medial JSW as documented by X-ray of the target knee at Week 52
- Evaluate change from baseline in lateral JSW as documented by X-ray of the target knee at Weeks 26 and 52
- Determine the percentage of Outcome Measures in Rheumatology Clinical Trials (OMERACT)-Osteoarthritis Research Society International (OARSI) responders and “strict” responders at Weeks 13, 26, and 52
- Evaluate change from baseline health-related quality of life (HRQOL) as assessed by the 36-Item Short Form Health Survey (SF-36) at Weeks 4, 13, 26, 39 and 52
- Evaluate change from baseline OA disease activity as assessed by the Physician Global Assessment at Weeks 4, 13, 26, 39 and 52

3. DESCRIPTION OF STUDY DESIGN

This study will be a multicenter, randomized, double-blind, placebo-controlled, parallel group study of three different strengths of SM04690 injected into the target knee joint of moderately to severely symptomatic osteoarthritis subjects.

Approximately 445 subjects will be enrolled and randomized at a ratio of 1:1:1:1 (0.03 mg active per 2 mL injection: 0.07 mg active per 2 mL injection: 0.23 mg active per 2 mL injection: placebo). Subjects will participate in a screening period of up to 21 days and a 52 week follow-up period. Clinic visits will be scheduled at Screening, Treatment Visit Day 1 and Follow-up Weeks 4, 13, 26, 39 and 52 [End of study (EOS) or Early Termination (ET)].

The study schedule is as follows:

- Day -21 to -1: Screening Visit
- Day 1: Treatment visit
- Week 4: Follow-up visit
- Week 13: Follow-up visit
- Week 26: Follow-up visit

- Week 39: Follow-up visit
- Week 52: End of Study (EOS) or Early Termination (ET): Follow-up visit

Specific timing of protocol procedures are described in [Appendix 1](#).

This study will be conducted at up to 40 investigational centers in the US. Potential subjects will attend a Screening Visit and participate in a screening period of no longer than 21 days.

In this study, general medical evaluations and recording of vital signs will be performed at all visits. A pain VAS will be administered at the Screening Visit. X-ray imaging of the target knee joint will be performed at screening and at Weeks 26 and 52 (EOS)/Early Termination. A Widespread Pain Index and Symptom Severity Score assessment will be conducted at the Screening Visit only. Physical examinations will be performed at the Screening Visit (including knee examination), Day 1, Week 13, Week 26, Week 39 and Week 52 (EOS)/Early Termination. Clinical laboratory evaluations will be performed at the Screening Visit, Week 13, Week 26, Week 39 and Week 52 (EOS)/Early Termination. The subject will complete the WOMAC questionnaire, Patient Global Assessment, and SF-36 at all visits; the investigator or designated study staff will complete the Physician Global Assessment at all visits. Recording of signs and symptoms of study medication intolerability and adverse event reporting will start following the injection of the study medication and continue until the subject completes follow-up visit Week 52 (EOS)/Early Termination. All AEs, whether volunteered, elicited, or noted during examination, will be recorded throughout the study.

An interim analysis will be performed after all subjects have completed their Week 26 visit; however clinical study sites and subjects will remain blinded throughout the study.

3.1. Study Endpoints

3.1.1. Primary Endpoints

The efficacy of treatment with SM04690 Injectable Suspension will be assessed by evaluating changes from baseline WOMAC pain subscore for the target knee at Week 13.

3.1.2. Secondary Endpoints

Efficacy will be assessed by evaluating changes from baseline WOMAC pain (Week 26) and function (Weeks 13 and 26) subscores and Patient Global Assessment at Weeks 13 and 26, as well as by evaluating change in JSW as evaluated by X-ray at Week 26.

Safety assessments will be performed on all subjects who are administered study treatments. Safety assessments include vital signs, clinical laboratory sampling, solicitation of adverse events and concomitant medications, as well as general medical evaluations.

Safety analyses will be conducted on data collected from all subjects who are administered study treatment.

3.1.3. Exploratory Endpoints

Exploratory efficacy will be assessed by evaluating changes from baseline WOMAC total score, HRQOL as assessed by SF-36, and Physician Global Assessment at all timepoints, as well as by

evaluating the percentage of OMERACT-OARSI responders and “strict” responders at Weeks 13, 26, and 52 (Pham et al. 2003) and change in lateral JSW as evaluated by X-ray at Week 26 and 52 and medial JSW at Week 52. Additionally, efficacy will be assessed by evaluating changes from baseline WOMAC pain and function subscores and Patient Global Assessment at Weeks 4, 39, and 52.

3.2. Measures to Minimize Bias

3.2.1. Blinding

This is a double-blind study. Study medication will be provided to the investigational center. The investigational center must identify unblinded personnel who will be responsible for preparing the appropriate dilution of the study medication and who are able to perform the injection of study medication and/or placebo. Study personnel administering or preparing study medication and reference therapy must minimize any contact with the subject following the injection and may not perform any study assessments throughout the duration of the study. On study visit Day 1, subjects will be randomized via the Medidata database.

3.2.2. Randomization/Assignment to Investigational Product or Placebo

Subjects will be assigned a subject number at their Screening Visit. Eligible subjects will be randomized at their study visit Day 1 to a blinded treatment code within the randomization schema. To be eligible for randomization, the subject must fulfill the following requirements:

- Meet all study inclusion criteria and none of the exclusion criteria
- Have acceptable Screening clinical laboratory test results
- Have signed the Informed Consent form
- Comply with the study instructions

3.2.3. Subject Re-screening

Subjects are allowed to be re-screened once. Re-screens are limited to subjects who did not meet inclusion/exclusion criteria due to a transient reason. Transient refers to self-limiting and predictably resolving conditions or acute events (e.g., seasonal allergies, common cold, or otitis media), reversible medical conditions that are successfully treated (e.g., anemia successfully treated by infusion), and/or being unable to comply with study procedures due to administrative convenience (e.g., family issues or attending to a private matter).

Subjects who failed any entry criteria in which no further treatment or spontaneous resolution is expected are not allowed to be re-screened.

Any re-screened subject must be re-consented and will be issued a new subject number. All screening procedures and assessments must be performed at re-screen; no results or data may be used from the previous screen.

3.2.4. Unblinding During the Study

The blind may be broken by a qualified physician who is an Investigator in this study in the

event of a medical emergency in which knowledge of the identity of the study medication is critical to the management of the subject's immediate course of treatment. Before breaking the blind, the Investigator should determine that the information is necessary (i.e., that it will alter the subject's immediate course of treatment).

If deemed necessary to break the blind for a study subject, the Samumed Medical Monitor is to be contacted to obtain concurrence. If it is not possible to contact the Medical Monitor beforehand, he or she should be contacted as soon as possible after breaking the blind for a subject. Details regarding the emergency unblinding will be documented in Medidata Balance and medical records. Instructions on how to unblind treatment assignment will be provided to each Investigator and kept within a guidance document at each site. No other site users will have access roles to Balance that will allow treatment assignment unblinding.

Any subject whose blind has been broken will continue their follow-up visits as per protocol.

An interim analysis will be performed after all subjects have completed their Week 26 visit; however clinical study sites and subjects will remain blinded throughout the study. Only the study sponsor will be unblinded at this time.

3.3. Investigational Product

3.3.1. Rationale for Dosages and Dosing Regimen

A phase 1 clinical trial was conducted to assess the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of a SM04690 formulation at 3 different dose-level concentrations (0.03, 0.07, and 0.23 mg per 2 mL injection) injected into the intra-articular space of the OA-affected target knee. The initial dose level of SM04690 (0.03 mg) was based on the mammalian species most sensitive to SM04690 in 8-week toxicology studies (the approximate residence time of the drug) in accordance with US Food and Drug Administration (FDA) guidelines. Preclinical studies to date have not demonstrated toxicity or systemic exposure at the biologically efficacious dose, so doses were selected that bracketed the projected biologically efficacious dose based on preclinical studies, hence resulting in the escalation sequence of 0.03, 0.07, and 0.23 mg per 2 mL injection.

As of 07 July 2015, 61 subjects have been enrolled in 3 ascending dose cohorts of approximately 20 subjects per cohort. Per protocol, data from cohort 1 and 2 were unblinded following the safety review of all subjects enrolled in the cohort (observed for a minimum of 12 weeks). Cohort 3 data remains blinded.

A total of 28/61 subjects have reported 68 treatment emergent adverse events (TEAEs) with 35 preferred terms. The system organ class (SOC) most reported was 'Musculoskeletal and connective tissue disorders' with 11/61 subjects reporting 19 TEAEs of 5 preferred terms.

As of 07 July 2015, following dosing in all three cohorts, there have been two dose-limiting toxicities (DLTs) and 1 serious adverse event (SAE) reported on the trial. A DLT of increased knee pain was reported and met the DLT criteria of increased pain at the target joint of greater than 30 mm increase on the pain VAS; this DLT was due to a procedural error and considered unrelated to study drug. A DLT of tachycardia paroxysmal was also reported and met the DLT criteria of an AE deemed by the investigator to be a severe or serious AE. This DLT also met

SAE criteria. The event was a report of tachycardia paroxysmal in a 72 year old white male, with previous medical history of tachycardia. This event was considered unrelated to study drug administration by the reporting investigator. Nevertheless, as the FDA requested that all adverse events in this initial OA study be considered related to study drug, this event was reported in an expedited manner. No other DLTs or SAEs have been reported.

Overall, the data suggest that, at the strengths under evaluation (0.03 mg per 2 mL injection, 0.07 mg per 2 mL injection, and 0.23 mg per 2 mL injection), this Phase 2 clinical trial with SM04690 has the therapeutic potential to safely treat individuals with moderately to severely symptomatic osteoarthritis of the knee.

3.3.2. Dosages and Dosing Regimen

SM04690 will be administered in the following dosage strengths:

- SM04690 0.03 mg in 2 mL Injectable Suspension
- SM04690 0.07 mg in 2 mL Injectable Suspension
- SM04690 0.23 mg in 2 mL Injectable Suspension
- SM04690 0 mg; placebo (PBS) injection only

Each subject will be randomly assigned to a dose at Study Visit Day 1. The injectable investigational product or the placebo (PBS) is to be administered as a 1-time single injection into the target knee joint. Only 1 knee will be treated for each subject in this study.

Only topical anesthetic (absolutely no invasive anesthetic) is allowed for the study injections. Anesthetic is also not allowed to be combined with the study medication for injection.

3.3.3. Dose Modifications

No modification in the specified dose concentration or the volume (2 mL) of the study medication injected into the target knee joint will be allowed.

3.3.4. Prior and Concomitant Medications and Procedures

Prior medications are defined as medications that were taken within 30 days prior to study injection on Day 1. Concomitant medications are defined as medications taken any time after study injection on Day 1 until follow-up visit Week 52 (EOS)/Early Termination. All prior and new or modified concomitant therapy used during the study must be recorded on the "Prior and Concomitant Medications" page of the eCRF.

Procedures that are ongoing, new, or modified at or post-Day 1 must be recorded on the "Procedures and Non-Drug Therapies" page of the eCRF.

Any new or modified concomitant therapy must be considered to determine if it is related to an adverse event (AE).

Subjects will be encouraged to remain on a stable dose of any allowed medications throughout the study. The use of aspirin (325 mg/day) for thrombosis prophylaxis is permitted.

Prohibited Concomitant Medications and Procedures:

- Subjects must not take any pain medication or medications/supplements for the treatment of OA within 24 hours prior to their scheduled visit, excluding the Screening Visit. This includes both OTC and prescription pain medications.
- Subjects must not participate in a formalized in-office and/or supervised OA disease program (e.g., a prescribed patient education program, physiotherapy, etc.) within 24 hours prior to their scheduled visit, excluding the Screening Visit.
- Intra-articular injection of steroids (glucocorticoids/corticosteroids), hyaluronic acid derivatives, or other agents with therapeutic intent into either knee is prohibited while the study subject is on study; intra-articular injection of steroids, hyaluronic acid derivatives, or other therapeutic agents into joints other than the knee are allowed.
- The following medications are prohibited while the subject is on study:
 - Opioids, both oral (e.g., tramadol) or transdermal (e.g., fentanyl patches) formulations
 - Centrally acting analgesics (e.g., duloxetine)
 - Glucocorticoids (also referred to as steroids or corticosteroids such as methylprednisolone,) administered by any route, with exception of inhaled, intranasal or ophthalmic application, or intra-articular injection of a non-knee joint.
- Electrotherapy and acupuncture for knee OA are prohibited while the subject is on study.
- Chiropractic adjustments of the knee are prohibited while the subject is on the study.
- Planned or elective surgery, including arthroscopy, is prohibited while the subject is on the study.

At each visit, excluding the Screening Visit, the study coordinator will ask the subject to confirm that no pain medications and medications/supplements for the treatment of OA were taken within the last 24 hours. The Investigator should notify the Samumed Medical Monitor immediately if any prohibited therapies are required to ensure subject safety.

3.4. Duration of Subject Participation

The duration of study participation for each subject is anticipated to be up to 55 weeks. This duration includes the Screening Visit during a screening period of up to 21 days, a 1-day treatment period occurring at Day 1, and a 52-week follow-up period.

3.5. Procedures for Monitoring Subject Compliance

Subjects will return to the clinic for scheduled visits as specified in [Appendix 1](#). Subjects who do not comply with the visit schedule may be discontinued from the study.

4. SELECTION AND WITHDRAWAL OF SUBJECTS

Eligibility of subjects will be determined by the following inclusion and exclusion criteria. Subjects should meet all the inclusion criteria and none of the exclusion criteria.

4.1. Inclusion Criteria

In order to be eligible for the study, subjects must fulfill all of the following criteria:

1. Males and females between 40 and 80 years of age, inclusive, in general good health
2. Ambulatory (single assistive devices such as canes allowed if needed less than 50% of the time, subjects requiring a walker are excluded)
3. Established diagnosis of primary femorotibial OA in the target knee by standard American College of Rheumatology (ACR) criteria for at least 6 months (clinical AND radiographic criteria); if bilateral knee OA is present, the target knee is defined as the knee with greater pain at screening based on the subject's evaluation and the Investigator's clinical judgment
4. Radiographic disease Stage 2 or 3 in the target knee according to the Kellgren-Lawrence grading of knee OA as assessed by independent central readers
5. Screening pain visual analog scale (VAS) score of 30-80 mm (on a scale of 0-100 mm) for the target knee while on symptomatic oral treatment at screening (if the subject requires oral treatment)
6. Total WOMAC score of 72-192 (out of 240) for the target knee while on symptomatic oral treatment at screening (if the subject requires oral treatment)
7. Willingness to omit the following for 24 hours prior to all Study Visits, excluding the Screening Visit:
 - a. Pain medications
 - b. Medications or supplements for the treatment of OA
 - c. Participation in a formalized in-office and/or supervised OA disease program (e.g., a prescribed patient education program, physiotherapy, etc.)
8. Full understanding of the requirements of the study and willingness to comply with all study visits and assessments
9. Subjects must have read and understood the informed consent form, and must have signed it prior to any study-related procedure being performed
10. Subject's Day 1 visit must occur while enrollment into the study is open

4.2. Exclusion Criteria

Any potential subject who meets one or more of the following criteria will not be included in this study:

1. Women who are pregnant or lactating
2. Women of childbearing potential (i.e., who are not surgically sterile or postmenopausal as defined by no menstrual periods for 12 consecutive months and no other biological or

physiological cause for amenorrhea can be identified); males who are sexually active and have a partner who is capable of becoming pregnant, neither of which have had surgery to become sterilized, who are not using an effective method of birth control (e.g., surgically-implanted hormonal therapy, intrauterine devices or oral birth control with barrier method)

3. Body mass index (BMI) >40
4. Partial or complete joint replacement in the target knee
5. Previous exposure to SM04690
6. Major surgery (e.g., interventional arthroscopy) in the target knee within 52 weeks prior to any study injection
7. Any planned or elective surgery during the study period
8. Significant and clinically evident misalignment of the target knee that would impact subject function, as determined by the Investigator
9. History of malignancy within the last 5 years; however, subjects with prior history of in situ cancer or basal or squamous cell skin cancer are eligible. Subjects with other malignancies are eligible if they have been continuously disease free for at least 5 years prior to any study injection
10. Clinically significant abnormal Screening Visit hematology values, blood chemistry values, HbA1c, or urinalysis values as determined by the investigator
11. Any condition, including laboratory findings (not included in the Screening Visit 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
12. Comorbid conditions that could affect pain assessment of the target knee, including, but not limited to, inflammatory rheumatic conditions such as rheumatoid arthritis, psoriatic arthritis, systemic lupus erythematosus, diabetic neuropathy, pseudogout, gout, and fibromyalgia
13. Other conditions that, in the opinion of the Investigator, could affect pain assessment of the target knee, including, but not limited to, symptomatic hip osteoarthritis and symptomatic degenerative disc disease
14. Any diagnosed psychiatric condition that includes, but is not limited to, a history of mania, bipolar disorder, psychotic disorder, schizophrenia, major depressive disorder, or generalized anxiety disorder
15. Participation in a clinical research trial that included the receipt of an investigational product or any experimental therapeutic procedure within 12 weeks prior to any study injection; the last date of participation in the trial, not the last date of receipt of investigational product, must be at least 12 weeks prior to Study Visit Day 1
16. Treatment of the target knee with systemic or intra-articular corticosteroids (e.g., methylprednisolone) within 8 weeks prior to Study Visit Day 1

17. Viscosupplementation (e.g., hyaluronic acid) in the target knee within 24 weeks prior to Study Visit Day 1
18. Effusion of the target knee clinically requiring aspiration within 12 weeks prior to Study Visit Day 1
19. Use of electrotherapy, acupuncture, and/or chiropractic treatments for knee OA within 4 weeks prior to Study Visit Day 1
20. Any known active infections, including 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)
21. Subjects taking prescription medications for OA who have not maintained a stable therapeutic regimen for a minimum of 12 weeks prior to Study Visit Day 1
22. Subjects requiring the chronic use (i.e., regular and consistent use for ≥ 12 weeks) of the medications listed below within 12 weeks prior to Study Visit Day 1:
 - a. Opioids, both oral (e.g., tramadol) or transdermal (e.g., fentanyl patches) formulations
 - b. Centrally acting analgesics (e.g., duloxetine)
 - c. Glucocorticoids (e.g., methylprednisolone) administered by any route, with exception of inhaled, intranasal, and ophthalmic solutions
23. 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 for a minimum of 12 weeks prior to Study Visit Day 1. In addition, the following subjects will be excluded:
 - a. Subjects with a baseline HbA1c >9
 - b. Subjects with uncontrolled hypertension in the opinion of the investigator
 - c. Subjects with symptomatic coronary artery disease in the opinion of the investigator
24. Subjects who have a current or pending disability claim, workers' compensation, or litigation(s) that may compromise response to treatment
25. Subjects who are immediate family members (spouse, parent, child, or sibling; biological or legally adopted) of personnel directly affiliated with the study at the investigative site, or are directly affiliated with the study at the investigative site
26. 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

4.3. Strategies for Recruitment and Retention

The Investigator is responsible for retention of study subjects at the study site. Specific training regarding retention of study subjects will be provided by the Sponsor to all sites after all subjects have completed the Week 26 visit. This training will include strategies that the sites should

employ to maintain best efforts for subject retention. The Sponsor is responsible for tracking participation to ensure proper retention of study subjects and will work with the site(s) to develop a site-specific action plan if needed.

4.4. Procedures for Subject Discontinuation from the Study

As the study treatment requires only a single injection, best efforts will be made to encourage subjects to attend all follow-up visits. Nevertheless, subjects will be informed that they are free to withdraw from the study at any time and for any reason.

The Investigator may remove a subject from the study if, in the Investigator's opinion, it is not in the best interest of the subject to continue in the study; refer to [Section 7](#) for further details. Notification of discontinuation will immediately be made to the Sponsor's medical monitor. In case of premature discontinuation of study participation, efforts will be made to perform all final study day [Week 52 (EOS)/Early Termination] assessments within 14 days of subject discontinuation. The date the subject is withdrawn from the study and the reason for discontinuation will be recorded on the subject's case report form (CRF).

The study may be discontinued at the discretion of the Investigator or the Sponsor.

5. CLINICAL ASSESSMENTS

5.1. Collection of Adverse Events Data

Data regarding treatment-emergent adverse events (TEAEs) will be collected in this study. TEAEs are events that occur during the course of the study that are not present prior to Day 1 study medication injection, or, if present at the time of study medication injection, have worsened in severity during the course of the study. Adverse events will be assessed at each study visit from the time of study medication injection on study visit Day 1 through Week 52 (EOS)/Early Termination.

Each subject will be observed and queried by the Investigator or the Investigator's designee at each study visit for any continuing AEs or new AEs since the previous visit. The subject will be asked to return to the site for an unscheduled visit if an AE occurs between study visits, and if, in the opinion of the Investigator, the AE requires a study visit for full evaluation. Any AE reported by the subject or noted by the Investigator or the Investigator's designee will be recorded within the eCRF. The following information will be recorded for each adverse event: description of the event, date of onset and resolution, severity as assessed by the Investigator according to the "Guidance for Industry: Toxicity Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Trials" ([Appendix 2](#)), causal relationship to study medication, outcome, and any treatment given.

Adverse events that are not serious and are ongoing at the subject's last visit will be followed for a maximum of 30 days. Serious adverse events that are not resolved or stabilized during this time period will be followed until resolution or stabilization.

5.2. Clinical Laboratory Sampling

Non-fasting samples for clinical laboratory analysis will be collected by a qualified staff member

at the Screening Visit and follow-up visit Weeks 13, 26, 39, and 52 (EOS)/Early Termination. At a minimum, the following tests will be conducted:

- **Chemistry panel:** Albumin, alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen, bicarbonate, calcium (corrected total), chloride, creatinine, glucose, lactate dehydrogenase (LDH), potassium, sodium, bilirubin (total)
- **Hematology:** Hemoglobin, hematocrit, red blood cell (RBC) count, white blood cell (WBC) count with differential, and platelet count
- **Urinalysis:** Clarity, specific gravity, pH, protein, glucose, ketones, nitrite, leukocytes, and occult blood

A urine-based pregnancy test will be performed on female subjects at the Screening Visit and at study visit Day 1, prior to study medication injection.

An HbA1c test will be performed on all subjects at the Screening Visit.

Urine microscopy will be performed if urinalysis values are out of range and the Investigator deems that the microscopy is clinically warranted.

The Investigator or the Investigator's designee must review the results of each subject's Screening Visit clinical laboratory test results prior to the Day 1 visit. The subject must not be randomized on Day 1 if any of the Screening Visit results are outside the normal range for the laboratory AND, in the opinion of the Investigator, are clinically significant.

The results of the clinical laboratory tests will be reported on the laboratory's standard reports. The Investigator must review all laboratory reports in a timely manner, noting "not clinically significant" (NCS) or comment on the clinical significance (clinically significant: yes/no) of any result that is outside the normal range for the laboratory or has a toxicity grade of 1 or greater, then date and initial the report. The Investigator must report all laboratory results that are BOTH outside the normal range for the laboratory or has a toxicity grade of 1 or greater AND, in the opinion of the Investigator, are clinically significant. If any abnormal, clinically significant laboratory measure is found prior to study medication injection, the subject is to be excluded. If it is found after study medication injection, it should be reported as an AE (see [Section 9](#)).

5.3. Medical History

A medical history will be obtained at screening with a follow-up at end of study or Early Termination. Medical history will include demographic data (e.g., age, race/ethnicity). In addition, medical information will also be recorded, including all (1) medical conditions and disease states that require current or ongoing therapy and (2) other medical conditions and disease states that, in the opinion of the Investigator, are relevant to the subject's study participation. Review of medical history at the Week 52 (EOS)/Early Termination visit will only be to capture End Dates of any ongoing medical history collected at screening.

5.4. Physical Examination

A general physical examination will be conducted at the Screening Visit, Day 1, and Weeks 13, 26, 39, and 52 (EOS)/Early Termination. Results of the physical examination will be noted in the

source documents. Any clinically significant finding noted prior to study medication injection should be recorded as medical history. If it is found after study medication injection, it should be reported as an AE (see [Section 9](#)).

5.4.1. Knee Examination

A knee examination will be conducted at the Screening Visit. Results of the knee examination will be noted in the source documents. Presence of bilateral knee OA (yes/no) will be recorded in the eCRF. If the subject has osteoarthritis in both knees, the site is to establish the target knee as the knee with greater pain at screening based on the subject's evaluation and the Investigator's clinical judgment.

Misalignment of the target knee will be assessed by the Investigator during the knee examination at the Screening Visit. Presence of significant misalignment of the target knee (yes/no) will be recorded in the eCRF. In the opinion of the Investigator, subjects with significant and clinically evident misalignment of the target knee that would impact subject function must be excluded from the study.

5.4.2. Vital Signs

Vital signs will be measured by a qualified staff member at all visits.

At each time point, the following vital signs will be measured:

- Body temperature
- Pulse rate
- Respiration rate
- Blood pressure (systolic and diastolic) after the subject sits for at least 5 minutes

Any measurement that is, in the opinion of the Investigator, abnormal AND clinically significant must be recorded as medical history if found prior to study medication injection or as an AE if found after study medication injection (see [Section 9](#)).

5.4.3. Height and Weight

Height measurements will be taken at the Screening Visit only. Weight measurements will be taken at the Screening Visit and follow-up visit Week 52 (EOS)/Early Termination.

5.5. Pregnancy Tests

A urine-based pregnancy test will be performed on female subjects at the Screening Visit and at study visit Day 1, prior to study medication injection.

5.6. X-Ray of Knee Joints

X-ray of the knee joints will be taken during the screening period and follow-up visit Weeks 26 and 52 (EOS)/Early Termination. The screening X-ray is to be taken within 21 days before study visit Day 1 and must be taken according to the guidance provided by the independent radiologist.

Detailed instructions for obtaining and managing the X-rays will be provided to the

investigational center prior to the initiation of subject enrollment. The intent (and included in the Image Review Charter – Image Acquisition guidelines) is that X-rays should be obtained in the posterior-anterior (PA) view, whenever possible. The Image Acquisition Protocol allows for anteroposterior (AP) view when PA view X-ray cannot be acquired.

All radiographs will be submitted to an independent radiologist who will document disease stage according to the Kellgren-Lawrence grading scale for compliance with enrollment criteria, as well as joint space width for efficacy assessments.

5.7. Widespread Pain Index and Symptom Severity Score

A Widespread Pain Index and Symptom Severity Score assessment will be performed at the Screening Visit only. This assessment consists of a set of questionnaires that determine a subject's areas of pain or tenderness and the severity of specified symptoms (Clauw 2014).

Upon completion of the Widespread Pain Index and Symptom Severity Score assessment, both the subject and the study staff member will sign/initial and date the source document to indicate that the assessments are reported accurately.

The Widespread Pain Index and Symptom Severity Score assessment sheets will be provided by the Sponsor and may not be reproduced.

5.8. Western Ontario and McMaster Universities Arthritis Index (WOMAC)

The subject will complete the WOMAC Version NR3.1 questionnaire at all visits; at the Day 1 visit, the subject will complete the questionnaire prior to study injection. The WOMAC is a widely-used, proprietary outcome measurement tool used by health professionals to evaluate the condition of patients with OA of the knee and hip, including pain, stiffness, and physical functioning of the joints.

Upon completion of the WOMAC, both the subject and the study staff member will sign/initial and date the source document to indicate that the activity and pain assessments are reported accurately.

The WOMAC questionnaires will be provided by the Sponsor and may not be reproduced.

5.9. Pain Visual Analog Scale (VAS)

A pain VAS for the target knee will be administered at the Screening Visit. The VAS is a psychometric response scale. The subject will be asked on a 100 mm scale to rate their knee arthritis pain from “No pain” (left anchor) to “Pain as bad as it could be” (right anchor), considering the last 48 hours.

Upon completion of the pain VAS, both the subject and the study staff member will sign/initial and date the source document to indicate that the pain assessment is reported accurately. The study staff member will record the pain VAS score in the eCRF. The score is determined by

measuring the distance (mm) between the “No pain” anchor and the subject’s mark, providing a range of scores from 0 to 100.

The VAS questionnaires will be provided by the Sponsor and may not be reproduced.

5.10. Patient Global Assessment of Disease Activity

The Patient Global Assessment will be performed at all visits; at the Day 1 visit, the subject will complete the assessment prior to study injection. The Patient Global Assessment will be a 100 mm VAS scale on which the subject will rate how well they are doing, considering all the ways in which illness and health conditions may affect him/her. The VAS scale will be anchored by descriptors at each end (“Very Well” on the left and “Very Poorly” on the right).

Upon completion of the Patient Global Assessment, both the subject and the study staff member will sign/initial and date the source document to indicate that the activity assessments are reported accurately. The study staff member will record the Patient Global Assessment score in the eCRF. The score is determined by measuring the distance (mm) between the “Very Well” anchor and the subject’s mark, providing a range of scores from 0 to 100.

The Patient Global Assessment of Disease Activity questionnaires will be provided by the Sponsor and may not be reproduced.

5.11. Physician Global Assessment of Disease Activity

The Physician Global Assessment will be performed at all visits; at the Day 1 visit, the assessment will be performed prior to study injection. The Physician Global Assessment will be a 100 mm VAS scale on which the investigator will rate the subject’s disease activity independent of the patient’s self-assessment. The VAS scale will be anchored by descriptors at each end (“Very Good” on the left and “Very Bad” on the right).

The investigator completing the Physician Global Assessment must sign/initial and date the source document to indicate that the assessment is reported accurately. A study staff member will record the Physician Global Assessment score in the eCRF. The score is determined by measuring the distance (mm) between the “Very Good” anchor and the Investigator’s mark, providing a range of scores from 0 to 100.

The Physician Global Assessment of Disease Activity questionnaires will be provided by the Sponsor and may not be reproduced.

5.12. 36-Item Short Form Health Survey (SF-36)

The SF-36 will be administered at all visits; at the Day 1 visit, the assessment will be performed prior to study injection. The SF-36 is a widely-used questionnaire which relies upon subject self-reporting and measures the subject’s health-related quality of life.

Upon completion of the SF-36, both the subject and the study staff member will sign/initial and date the source document to indicate that the quality of life assessments are reported accurately.

The SF-36 questionnaires will be provided by the Sponsor and may not be reproduced.

5.13. Documentation of Prior and Concomitant Medications

Details regarding the name, indication, route of administration, dose, and frequency of all medications taken within 30 days prior to study injection on Day 1 will be recorded in the eCRF. Details regarding the name, indication, route of administration, dose, and frequency of all medications taken after study injection will be recorded in the eCRF at study visit Day 1, Week 4, 13, 26, 39, and 52 (EOS)/Early Termination. “All medications” should include prescription, over the counter, supplements, as well as herbal or alternative medications.

6. STUDY VISITS (SEE [APPENDIX 1](#))

The following procedures are to be performed at each study visit.

6.1. Screening Visit

The Investigator or designee must explain the nature of the study protocol and associated risks to the potential study participant. The potential participant must be allowed to review the study information and to ask questions before being asked to sign the informed consent form. Written informed consent must be provided by the potential study participant prior to initiation of any screening evaluations or other study-related procedures. The signature, date, and the name of the individual at the site who obtained the informed consent will be recorded in the subject’s source record. After written informed consent is obtained, the subject will be assigned a subject number.

The following procedures and assessments will be performed within 21 days prior to study visit Day 1:

- Documentation of demographic information, including date of birth, gender, race, and ethnicity
- Documentation of current and past medical history, documentation of current medications, and review of prior medication excluded by the protocol
- Physical examination, including knee examination
- Vital signs measurements (pulse, blood pressure, respiration rate, and temperature)
- Height and weight measurements
- Venipuncture and collection of samples for clinical laboratory tests
- Pregnancy test (urine-based)
- X-ray – bilateral in weight bearing fixed flexion position, posterior-anterior view
- Widespread Pain Index and Symptom Severity Score assessment
- WOMAC and pain VAS assessments
- Patient Global Assessment and Physician Global Assessment
- SF-36

Results from these evaluations will be compared with inclusion/exclusion criteria to determine subject eligibility. Investigators will maintain a confidential log of all subjects who have been screened for participation in the study whether or not the subject was eligible for study participation.

6.2. Day 1

This visit must occur within 21 days of the Screening Visit.

The following procedures and assessments will be performed at Day 1 prior to randomization:

- Physical examination
- Vital signs measurements (pulse, blood pressure, respiration rate, and temperature)
- Pregnancy test (urine-based)

Results from these evaluations will be compared with inclusion/exclusion criteria to determine subject eligibility.

The following procedures and assessments are also to be performed prior to randomization; however, results from the following evaluations do not determine eligibility.

- WOMAC assessment, Patient Global Assessment, and Physician Global Assessment
- SF-36

The following procedures and assessments will be performed at Day 1 following randomization:

- Intra-articular study medication injection (or placebo)
- Collection of AE and concomitant medication data

6.3. Week 4

This follow-up visit should occur 28 days after study medication injection with a window of ± 3 days.

The following procedures and assessments will be performed at follow-up visit Week 4:

- Collection of AE and concomitant medication data
- Vital signs measurements (pulse, blood pressure, respiration rate, and temperature)
- WOMAC assessment, Patient Global Assessment, and Physician Global Assessment
- SF-36

6.4. Week 13

This follow-up visit should occur 91 days after study medication injection with a window of ± 3 days.

The following procedures and assessments will be performed at follow-up visit Week 13:

- Collection of AE and concomitant medication data
- Vital signs measurements (pulse, blood pressure, respiration rate, and temperature)
- Physical examination
- Venipuncture and collection of samples for clinical laboratory tests
- WOMAC assessment, Patient Global Assessment, and Physician Global Assessment

- SF-36

6.5. Week 26

This follow-up visit should occur 182 days after study medication injection with a window of - 10 days.

The following procedures and assessments will be performed at follow-up visit Week 26:

- Collection of AE and concomitant medication data
- Vital signs measurements (pulse, blood pressure, respiration rate, and temperature)
- Physical examination
- Venipuncture and collection of samples for clinical laboratory tests
- WOMAC assessment, Patient Global Assessment, and Physician Global Assessment
- SF-36
- X-ray – bilateral in weight bearing fixed flexion position, posterior-anterior view

6.6. Week 39

This follow-up visit should occur 273 days after study medication injection with a window of ± 3 days.

The following procedures and assessments will be performed at follow-up visit Week 39:

- Collection of AE and concomitant medication data
- Vital signs measurements (pulse, blood pressure, respiration rate, and temperature)
- Physical examination
- Venipuncture and collection of samples for clinical laboratory tests
- WOMAC assessment, Patient Global Assessment, and Physician Global Assessment
- SF-36

6.7. Week 52 End of Study (EOS)/Early Termination (ET)

This follow-up visit should occur 365 days after study medication injection with a window of ± 7 days, or within 14 days of subject premature discontinuation.

The following procedures and assessments will be performed at follow-up visit Week 52 (EOS)/Early Termination:

- Collection of AE and concomitant medication data
- Physical examination
- Review of medical history
- Vital signs measurements (pulse, blood pressure, respiration rate, and temperature)
- Weight measurement
- Venipuncture and collection of samples for clinical laboratory tests

- WOMAC assessment, Patient Global Assessment, and Physician Global Assessment
- SF-36
- X-ray– bilateral in weight bearing fixed flexion position, posterior-anterior view

7. PREMATURE DISCONTINUATION FROM STUDY

As the study treatment requires only a single injection, best efforts will be made to encourage subjects to attend all follow-up visits. A premature discontinuation from study will occur when a subject who signed informed consent ceases participation in this study, regardless of circumstances, prior to completion of the defined study period. Subjects can be prematurely discontinued from the study for one of the following reasons:

- Death
- Lost to follow-up after a minimum of 2 attempts have been made to contact the subject, including sending a registered letter
- Subject withdraws consent

The reason for the discontinuation should be recorded on the eCRF. The Investigator or designee must complete all applicable eCRF pages for subjects who discontinue from the study prematurely. Week 52 (EOS)/Early Termination procedures should be conducted within 14 days of discontinuation for any subject who discontinues after study injection on Day 1.

The principal Investigator and the Institutional Review Board/Ethics Committee (IRB/EC) reserve the right to prematurely terminate the study in the interest of subject safety and welfare. The Sponsor reserves the right to prematurely terminate the study at any time for administrative reasons.

8. PRODUCT SPECIFICATIONS

8.1. Description

SM04690 drug substance is an off-white powder. SM04690 drug product is a sterile suspension in diluent containing 0.5% carboxymethylcellulose sodium and 0.05% polysorbate 80 in pH 7.4 phosphate buffered saline. SM04690 drug product is 2 mL in a 3 mL Type I glass vial. A separate 3 mL Type I glass vial contains 2 mL of vehicle to be used as a diluent. The placebo will be phosphate buffered saline and is provided in a different container.

8.2. Formulation, Packaging, and Labeling

SM04690 and vehicle will be supplied as single-use injections. SM04690, vehicle, and placebo will be supplied to the study pharmacist and labeled according to the applicable local and country regulations. For dispensing and labeling instructions, refer to the [Pharmacy Manual](#).

8.3. Preparation of Study Medication

Each dose will be prepared by taking a known volume of SM04690 drug product and adding to a vehicle (diluent) vial, mixing well to re-suspend the product, then injecting 2 mL intrarticularly. Each placebo will be prepared by taking a known volume of PBS and adding to a

saline vial, mixing well, and then injecting 2 mL intra-articularly. Refer to the [Pharmacy Manual](#) for detailed instructions on study medication preparation.

8.4. Accountability of Study Medications

All study medication vials received must be returned and accounted for. All injections prepared and dispensed must also be logged. The log includes the following:

- Subject number and initials
- Date that study medication was prepared/injected
- Quantity dispensed (active vial, vehicle vial, PBS vial, and saline vial)
- Quantity returned (active vial, vehicle vial, PBS vial, and saline vial)

All study medication received, prepared, and dispensed by the unblinded Investigator and/or unblinded designee will be inventoried and accounted for throughout the study. The study medication must be stored at the appropriate temperature (15°-30°C or 59°-86°F) and in a restricted area with limited access. Temperature excursions are allowed between 2°-60°C (36°-140°F) for a time period not to exceed 72 hours and only during study medication shipment. The unblinded Investigator and/or unblinded designee must maintain an accurate, up-to-date dispensing log for all study medications supplied by the Sponsor. Study medication dispensed for all subjects must be recorded on the drug accountability forms. The study medication dispensing log and remaining drug inventory will be reviewed by the Sponsor-designated unblinded clinical monitor.

The study medication supplied for this study is for use only in subjects properly consented and enrolled into this protocol. Used and unused study medications must be kept in a secure, blinded location physically separated from standard clinic or office drug supplies and with access limited to the unblinded Investigator and/or unblinded designee.

9. SAFETY MONITORING AND ADVERSE EVENTS

9.1. Treatment-Emergent Adverse Events (TEAEs)

Data regarding TEAEs will be collected in this study. TEAEs are events that are not present prior to study medication injection or, if present prior to study medication injection, have worsened in severity.

The reporting period for AEs starts after the injection of study medication on Day 1 and ends after the final study visit.

Definition of Adverse Events:

Adverse events in the eCRF will be classified according to the most recent US FDA definitions and in a manner consistent with ICH guidelines. As such the following definitions will be used:

An adverse event (AE) is any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an investigational (medicinal) product (IP) or other protocol-imposed intervention, regardless of attribution. An AE may include intercurrent illnesses or injuries that represent an exacerbation (increase in frequency, severity, or specificity) of preexisting conditions (e.g., worsening of asthma).

The Investigator must report all laboratory results that are BOTH outside the normal range for the laboratory or has a toxicity grade of 1 or greater AND, in the opinion of the Investigator, are clinically significant. If any abnormal, clinically significant laboratory measure is found after informed consent but prior to study medication injection, the subject is to be excluded. If it is found after study medication injection, it should be reported as an AE.

Whenever possible, it is preferable to record a diagnosis as the AE term rather than a series of symptoms relating to a diagnosis. In order to classify AEs and diseases, preferred terms will be assigned by the Sponsor to the original terms entered on the eCRF, using the Medical Dictionary for Regulatory Activities (MedDRA).

The Investigator will assess AEs for severity utilizing the “Guidance for Industry: Toxicity Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Trials”. This toxicity scale is presented in [Appendix 2](#). Laboratory values not listed on the toxicity scale will be assessed for severity by the clinical Investigator.

All adverse events that occur during this trial will be considered related to the study treatment.

For future planning and informational purposes, the investigator opinion regarding the relatedness of the adverse event is to be collected for all adverse events. All adverse events that occur within the trial will continue to be reported to all regulatory authorities as well as summarized in the final clinical study report as related to study medication. The Investigator will determine the relationship of an AE to study treatment and will record it on the source documents and eCRF using the categories defined below.

The relationship of the study treatment to an AE will be determined by the investigator based on the following definitions:

1. Not Related

The AE is not related if (1) exposure to the investigational product (or placebo) or administration of the study injection has not occurred **or** (2) the occurrence of the AE is not reasonably related in time **or** (3) the AE is considered related to another event or product not associated with the investigational product (or placebo) or the study injection.

2. Unlikely Related

The AE is unlikely related if (1) the AE is unlikely related in time **or** (2) the AE is considered unlikely to be related to use of the investigational product (or placebo) or study injection (i.e., there are no facts [evidence] or arguments to suggest a causal relationship).

3. Possibly Related

The AE is possibly related if (1) the investigational product (or placebo) or the study injection and AE are considered reasonably related in time **and** (2) the AE could be explained by causes other than exposure to the investigational product (or placebo) or administration of the study injection.

4. Probably Related

Exposure to the investigational product (or placebo) or administration of the study injection and AE are probably related if (1) the investigational product (or placebo) or study injection and AE are considered reasonably related in time **and** (2) the investigational product (or placebo) or

study injection is more likely than other causes to be responsible for the AE **or** is the most likely cause of the AE.

Adverse events must be followed until resolution by the PI. Resolution is defined as the return to baseline status or stabilization of the condition with the expectation that it will remain chronic. Adverse events that are not serious and are ongoing at the subject's last visit will be followed for a maximum of 30 days. Serious adverse events that are not resolved or stabilized during this time period will be followed until resolution or stabilization.

9.2. Serious Adverse Events

According to the ICH Guidelines for Good Clinical Practice (E6), an SAE is any untoward medical occurrence during the course of a clinical investigation that is characterized by 1 or more of the following:

- Results in death
- Is life threatening
- Requires nonscheduled (not routine or planned) subject hospitalization or prolongation of existing hospitalization for ≥ 24 hours and admission to the hospital
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is an important medical event, defined as an event that does not fit one of the other outcomes, but may jeopardize the subject and may require medical or surgical intervention (treatment) to prevent one of the other outcomes. Examples include allergic bronchospasm (a serious problem with breathing) requiring treatment in an emergency room, serious blood dyscrasias (blood disorders), or seizure/convulsion that does not result in hospitalization. The development of drug dependence or drug abuse would be other examples of important medical events.

Although pregnancy is not a formal SAE, if a study participant or the partner of a study participant becomes pregnant while the study participant is on study, the pregnancy is to be reported via the SAE reporting process.

9.2.1. Investigator Reporting Requirements for Serious Adverse Events

All SAEs must be reported as described in the study manual at sae@samumed.com or by FAX by the Investigator, study coordinator, other designated study personnel, or clinical research associate within 24 hours of notification of the SAE. Follow-up information must be reported to the medical monitor as it becomes available. The Investigator also must report all SAEs promptly to the appropriate IRB/EC as required by the institution. Sponsor contact information for SAE reporting if needed is provided in [Table 1](#).

Table 1: Sponsor Contact Information for SAE Reporting

Primary Contact	Alternative Contact
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Medical Monitor: [REDACTED]	Vice President of Clinical Development: [REDACTED]
Office Tel: [REDACTED]	Office Tel: [REDACTED]
Office Fax: [REDACTED]	Office Fax: [REDACTED]
Cellular: [REDACTED]	Cellular: [REDACTED]
Email: [REDACTED]	Email: [REDACTED]

9.2.2. Recording of SAEs

All SAE information must be recorded on the SAE form approved by the Sponsor. Additional follow-up information (e.g., test results, autopsy, and discharge summary) may be requested to supplement the SAE report form and can be attached as de-identified records.

10. STATISTICAL CONSIDERATIONS

This section describes the planned statistical analyses in general terms. A complete description of the statistical analyses will be specified in a statistical analysis plan (SAP), finalized prior to completion of the study. The study assesses the efficacy, safety, and tolerability of SM04690.

Approximately 445 subjects will be enrolled and randomized in this study.

10.1. Sample Size Determination

A sample size of approximately 445 randomized subjects is selected for this exploratory study. The sample size for this study was based upon accepted statistical practice ([Piantadosi 1997](#)).

10.2. Randomization

Subjects will be randomized 1:1:1:1 (0.03 mg active per 2 mL injection: 0.07 mg active per 2 mL injection: 0.23 mg active per 2 mL injection: placebo) to each dose group using a permuted block design stratified by each site. Specific information regarding the use of Medidata Balance to store and implement the permuted block design will be detailed within the statistical analysis plan.

10.3. Study Medication Dosing

Three strengths of SM04690 injectable suspension and placebo will be used in this study:

- SM04690 0.03 mg in 2 mL Injectable Suspension
- SM04690 0.07 mg in 2 mL Injectable Suspension
- SM04690 0.23 mg in 2 mL Injectable Suspension
- SM04690 0 mg; placebo (PBS) injection only

10.4. Analysis Data Sets

Intent-to-Treat (ITT) Analysis Set: All subjects who were randomized (SM04690 or placebo).

Modified Intent-to-Treat (mITT) Analysis Set: ITT subjects who received a protocol specified dose of SM04690 or placebo, analyzed as treated. Subjects incorrectly receiving doses not prescribed by the protocol are excluded from this analysis set.

Per-Protocol Analysis Set: ITT subjects who complied with all study procedures and evaluations, and did not have any major protocol deviations

Safety Analysis Set: Subjects who were randomized and received SM04690 or placebo will be included in the safety analyses.

10.5. Data Analyses

10.5.1. Global Parameters

For all analyses detailed here, the following global parameters will be used. For continuous variables, number of subjects in the analysis, mean, standard deviation (SD), median, minimum, and maximum will be reported. All categorical endpoints will be summarized using frequencies and percentages.

10.5.2. Baseline

For comparisons with baseline within each analysis population, baseline is defined as the last value recorded for any given parameter prior to study medication injection at Day 1.

10.5.3. Safety analysis

Safety assessments will be performed on all subjects who were randomized and received the study medication injection (SM04690 or placebo). Safety assessments include physical examinations, vital signs, clinical laboratory tests, solicitation of AEs and concomitant medications, and general medical evaluations. No formal statistical analyses are planned. Safety will be evaluated based on the incidence, severity, and seriousness of treatment-emergent AEs and by changes in clinical laboratory parameters and vital signs, relative to baseline.

10.5.4. Interim Analysis

An interim analysis will be performed after all subjects have completed their Week 26 visit; however clinical study sites and subjects will remain blinded throughout the study. The aim of this interim analysis is to assess safety and efficacy objectives at Weeks 13 and 26. No trial adaptation(s) will be made based upon these results.

10.5.5. Efficacy Analysis

Efficacy analysis will be performed on the ITT, mITT, and PP Analysis Sets. Change in primary and secondary efficacy endpoints from baseline will be estimated at specified time points using parametric analysis of covariance (ANCOVA) models. Formal hypothesis testing between treatment groups will be conducted using a strategy to control the familywise error rate; the error rate strategy is detailed in the study's SAP.

Exploratory efficacy analysis will be performed on the ITT, mITT, and PP analysis sets. Change in WOMAC total, WOMAC pain subscore, WOMAC function subscore, Patient Global Assessment, Physician Global Assessment, JSW and HRQOL from baseline will be estimated at specified time points using parametric analysis of covariance (ANCOVA) models. Logistic regression will be used to analyze the proportion of OARSI responders within each treatment group compared to placebo at specified time points. Exploratory subgroup analyses may also be performed.

11. DATA COLLECTION, STUDY MONITORING, AND DATA DISCLOSURE

11.1. Data Collection and Reporting

The Investigator must maintain required records for all study subjects. Data for this study will be recorded in the subject's source document and on the eCRFs. All data on these eCRFs should be recorded completely and promptly. A copy of the completed eCRFs for each subject will be retained by the investigational center.

The Investigator must maintain adequate and accurate source documents upon which eCRFs for each subject are based. They are to be separate and distinct from eCRFs, except for cases in which the Sponsor has predetermined that direct data entry into specified pages of the subject's eCRF is appropriate. The source documents should include detailed notes on the following:

- The oral and written communication with the subject regarding the study treatment (including the risks and benefits of the study); the date and time of informed consent(s) must be recorded in the source documentation
- The subject's medical and disease history before participation in the study
- The subject's basic identifying information, such as subject number, that links the subject's source documents with the eCRFs
- The results of all diagnostic tests performed, diagnoses made, therapy provided, and any other data on the condition of the subject
- The subject's exposure to study medication
- All AEs
- The subject's exposure to any concomitant therapy (including start and stop dates, route of administration, and dosage)

11.2. Study Monitoring

All aspects of the study will be monitored by the Sponsor or the Sponsor's designees with respect to current Good Clinical Practice (GCP) and Standard Operating Procedures (SOPs) for compliance with applicable government regulations. It is the responsibility of the Investigator to provide all study records, including eCRFs and source documents among other records, for review and inspection by the clinical monitor.

All eCRFs will be 100% source verified against corresponding source documentation (e.g.,

office and clinical laboratory records) for each subject. Clinical monitors will periodically evaluate the progress of the study, including the verification of appropriate consent form procedures, review of drug accountability and preparation procedures, adherence to dosing procedures, and the verification of the accuracy and completeness of eCRFs. Clinical monitors will also ensure that all protocol requirements, applicable US FDA regulations, other Regulatory requirements, and the Investigator's obligations are being fulfilled.

11.3. Records Retention

During this study, an Investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated with the investigational product or entered as a control in the investigation. Case report forms will be provided for each subject by the Sponsor. Data reported on the eCRFs and derived from source documents must be consistent with the source documents or the discrepancies must be explained. The completed eCRFs must be promptly reviewed, signed, and dated by a qualified physician who is an Investigator on the study. During this study, the Investigator must retain study medication (investigational product and placebo) disposition records, copies of eCRFs (or electronic files), and source documents for the maximum period required by (1) applicable regulations and guidelines or institution procedures **or** (2) for the period specified by the Sponsor, whichever is longer. The Investigator must contact the Sponsor prior to destroying any records associated with the study.

The Sponsor will notify the Investigator when the study records are no longer needed.

In the event the Investigator withdraws from the study (e.g., relocation, retirement), the records shall be transferred to a mutually agreed-upon designee (e.g., another Investigator). Notice of such transfer will be given in writing to the Sponsor.

The Investigator must ensure that clinical study records are retained according to national regulations, as documented in the Clinical Trial Agreement entered into with the Sponsor in connection with this study. For example, US federal laws require that an Investigator maintain all study records for the indication under investigation for 2 years following the date of a New Drug Application approval or, if no application is filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and the FDA is notified.

The Sponsor will maintain correspondence with the Investigator after study closeout to ensure that study documentation is retained for the appropriate amount of time. Subject files and other source data must be kept for the maximum period of time permitted by the hospital, institution, or private practice and should be retained in accordance with applicable legislation. The Investigator must inform the Sponsor immediately if any documents are to be destroyed, to be transferred to a different facility, or to be transferred to a different owner.

11.4. Data Disclosure and Subject Confidentiality

The Investigator(s) and the Sponsor or its authorized representative will preserve the confidentiality of all subjects participating in a study, in accordance with GCP, federal, state, and local regulations, including, to the extent applicable, the Health Insurance Portability and Accountability Act of 1996 ("HIPAA").

In order to maintain subject confidentiality, all eCRFs, study reports, and communications relating to the study will identify subjects by initials and assigned subject numbers; subjects should not be identified by name. If a subject name appears on any document, it must be obliterated before a copy of the document is supplied to the Sponsor or its authorized representative. Study findings stored on a computer will be stored in accordance with federal, state, and local data protection laws. Subjects will be told that representatives of the Sponsor, its authorized representative, IRB or EC, or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information will be held in strict confidence and in accordance with applicable data protection laws. The Investigator will maintain a personal subject identification list (subject numbers with the corresponding subject names) to make it possible for records to be identified.

Clinical information will not be released without written permission from the subject, except as necessary for monitoring by the IRB/EC, the FDA, or the study Sponsor.

Any information, inventions, or discoveries (whether patentable or not), innovations, suggestions, ideas, and reports made or developed by the Investigator(s) as a result of conducting this study shall be promptly disclosed to the Sponsor and shall be the sole property of the Sponsor. The Investigator agrees, upon the Sponsor's request and at the Sponsor's expense, to execute such documents and to take such other actions, as the Sponsor deems necessary or appropriate, to obtain patents in the Sponsor's name covering any of the foregoing.

11.5. Policy for Publication and Presentation of Data

The Sponsor encourages the scientific publication of data from clinical research studies. Investigators, however, may not present or publish partial or complete study results individually without the participation of the Sponsor. The PI(s) and the Sponsor may propose appropriate scientific manuscripts or abstracts from the study data. All proposed publications must be reviewed and commented on by the Sponsor before submission for publication. The detailed procedures for the review of publications are set out in the Clinical Trial Agreement entered into with the Sponsor in connection with this study. These procedures are in place to ensure coordination of study data publication and adequate review of data for publication against the validated study database for accuracy. Names of all Investigators and Sponsor representatives responsible for designing the study and analyzing the results will be included in the publication(s).

12. PROTECTION OF HUMAN SUBJECTS

12.1. Declaration of Helsinki

The study will be conducted in accordance with the Declaration of Helsinki (1964), including all amendments up to and including the South Africa revision (2008).

12.2. Institutional Review Board/Ethics Committee

The Investigator agrees to provide the IRB/EC with all appropriate material, including a copy of the informed consent form (ICF). The study will not be initiated until the Investigator obtains

written approval of the research plan and the ICF from the appropriate IRB/EC and copies of these documents are received by the Sponsor. Appropriate reports on the progress of this study will be made by the Investigator to the IRB/EC and Sponsor in accordance with applicable government regulations and in agreement with the policies established by the Sponsor and the IRB/EC. The Sponsor ensures that the IRB/EC complies with the requirements set forth in US 21 Code of Federal Regulations Part 56.

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APPENDIX 1. SCHEDULE OF STUDY PROCEDURES

Procedure	Screen (Days -21 to -1)	Day 1^a	Week 4 (Day 29 ± 3 days)	Week 13 (Day 92 ± 3 days)	Week 26 (Day 183 -10 days)	Week 39 (Day 274 ± 3 days)	Week 52(EOS) (Day 366 ± 7 days) / ET
Informed consent	X						
Inclusion & exclusion criteria	X	X					
Demographics	X						
Medical history	X						X ^b
Pregnancy test	X	X					
X-ray	X				X		X
Physical examination	X	X		X	X	X	X
Knee examination	X						
Height	X						
Weight	X						X
Vital signs	X	X	X	X	X	X	X
Clinical laboratory sampling	X			X	X	X	X
Widespread Pain Index and Symptom Severity Score Assessment	X						
Pain VAS	X						
Intra-articular injection		X					
Randomization		X					
WOMAC	X	X	X	X	X	X	X
Patient Global Assessment	X	X	X	X	X	X	X
Physician Global Assessment	X	X	X	X	X	X	X
SF-36	X	X	X	X	X	X	X
AEs and concomitant procedures/medications		X	X	X	X	X	X

Abbreviations: ACR, American College of Rheumatology; VAS, Visual Analog Scale; WOMAC, Western Ontario and McMaster Universities Arthritis Index; SF-36, 36-Item Short Form Healthy Survey; AEs, Adverse Events.

^a At Study Visit Day 1, all procedures should be performed prior to study medication injection except for collection of AE and concomitant procedures/medication data.

^b Review medical history to capture End Date(s), if applicable, of any ongoing medical history(ies) collected at screening.

APPENDIX 2. GUIDANCE FOR INDUSTRY: TOXICITY SCALE FOR HEALTHY ADULT AND ADOLESCENT VOLUNTEERS ENROLLED IN PREVENTIVE VACCINE TRIALS

Table A1: Tables for Clinical Abnormalities

Local Reaction to Injectable Product	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Pain	Does not interfere with activity	Repeated use of non-narcotic pain reliever > 24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	Emergency room (ER) visit or hospitalization
Tenderness	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	ER visit or hospitalization
Erythema/Redness *	2.5 – 5 cm	5.1 – 10 cm	> 10 cm	Necrosis or exfoliative dermatitis
Induration/Swelling **	2.5 – 5 cm and does not interfere with activity	5.1 – 10 cm or interferes with activity	> 10 cm or prevents daily activity	Necrosis

* In addition to grading the measured local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable.

** Induration/Swelling should be evaluated and graded using the functional scale as well as the actual measurement.

Vital Signs *	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Fever (°C) ** (°F) **	38.0 – 38.4 100.4 – 101.1	38.5 – 38.9 101.2 – 102.0	39.0 – 40 102.1 – 104	> 40 > 104
Tachycardia - beats per minute	101 – 115	116 – 130	> 130	ER visit or hospitalization for arrhythmia
Bradycardia - beats per minute***	50 – 54	45 – 49	< 45	ER visit or hospitalization for arrhythmia
Hypertension (systolic) - mm Hg	141 – 150	151 – 155	> 155	ER visit or hospitalization for malignant hypertension
Hypertension (diastolic) - mm Hg	91 – 95	96 – 100	> 100	ER visit or hospitalization for malignant hypertension
Hypotension (systolic) - mm Hg	85 – 89	80 – 84	< 80	ER visit or hospitalization for hypotensive shock
Respiratory Rate – breaths per minute	17 – 20	21 – 25	> 25	Intubation

* Subject should be at rest for all vital sign measurements.

** Oral temperature; no recent hot or cold beverages or smoking.

*** When resting heart rate is between 60 – 100 beats per minute. Use clinical judgment when characterizing bradycardia among some healthy subject populations, for example, conditioned athletes.

Systemic (General)	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Nausea/vomiting	No interference with activity or 1 – 2 episodes/24 hours	Some interference with activity or > 2 episodes/24 hours	Prevents daily activity, requires outpatient IV hydration	ER visit or hospitalization for hypotensive shock
Diarrhea	2 – 3 loose stools or < 400 gms/24 hours	4 – 5 stools or 400 – 800 gms/24 hours	6 or more watery stools or >800gms /24 hours or requires outpatient IV hydration	ER visit or hospitalization
Headache	No interference with activity	Repeated use of non-narcotic pain reliever > 24 hours or some interference with activity	Significant; any use of narcotic pain reliever or prevents daily activity	ER visit or hospitalization
Fatigue	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization
Myalgia	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization

Systemic Illness	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Illness or clinical adverse event (as defined according to applicable regulations)	No interference with activity	Some interference with activity not requiring medical intervention	Prevents daily activity and requires medical intervention	ER visit or hospitalization

Table A2: Tables for Laboratory Abnormalities

Serum *	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)**
Sodium – Hyponatremia mEq/L	132 – 134	130 – 131	125 – 129	< 125
Sodium – Hypernatremia mEq/L	144 – 145	146 – 147	148 – 150	> 150
Potassium – Hyperkalemia mEq/L	5.1 – 5.2	5.3 – 5.4	5.5 – 5.6	> 5.6
Potassium – Hypokalemia mEq/L	3.5 – 3.6	3.3 – 3.4	3.1 – 3.2	< 3.1
Glucose – Hypoglycemia mg/dL	65 – 69	55 – 64	45 – 54	< 45
Glucose – Hyperglycemia Fasting – mg/dL Random – mg/dL	100 – 110 110 – 125	111 – 125 126 – 200	>125 >200	Insulin requirements or hyperosmolar coma
Blood Urea Nitrogen BUN mg/dL	23 – 26	27 – 31	> 31	Requires dialysis
Creatinine – mg/dL	1.5 – 1.7	1.8 – 2.0	2.1 – 2.5	> 2.5 or requires dialysis
Calcium – hypocalcemia mg/dL	8.0 – 8.4	7.5 – 7.9	7.0 – 7.4	< 7.0
Calcium – hypercalcemia mg/dL	10.5 – 11.0	11.1 – 11.5	11.6 – 12.0	> 12.0
Magnesium – hypomagnesemia mg/dL	1.3 – 1.5	1.1 – 1.2	0.9 – 1.0	< 0.9
Phosphorous – hypophosphatemia mg/dL	2.3 – 2.5	2.0 – 2.2	1.6 – 1.9	< 1.6
CPK – mg/dL	1.25 – 1.5 x ULN***	1.6 – 3.0 x ULN	3.1 – 10 x ULN	> 10 x ULN
Albumin – Hypoalbuminemia g/dL	2.8 – 3.1	2.5 – 2.7	< 2.5	--
Total Protein – Hypoproteinemia g/dL	5.5 – 6.0	5.0 – 5.4	< 5.0	--
Alkaline phosphate – increase by factor	1.1 – 2.0 x ULN	2.1 – 3.0 x ULN	3.1 – 10 x ULN	> 10 x ULN
Liver Function Tests –ALT, AST increase by factor	1.1 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10 x ULN	> 10 x ULN
Bilirubin – when accompanied by any increase in Liver Function Test increase by factor	1.1 – 1.25 x ULN	1.26 – 1.5 x ULN	1.51 – 1.75 x ULN	> 1.75 x ULN
Bilirubin – when Liver Function Test is normal; increase by factor	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.0 – 3.0 x ULN	> 3.0 x ULN
Cholesterol	201 – 210	211 – 225	> 226	---
Pancreatic enzymes – amylase, lipase	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.1 – 5.0 x ULN	> 5.0 x ULN

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

** The clinical signs or symptoms associated with laboratory abnormalities might result in characterization of the

laboratory abnormalities as Potentially Life Threatening (Grade 4). For example, a low sodium value that falls within a grade 3 parameter (125-129 mE/L) should be recorded as a grade 4 hyponatremia event if the subject had a new seizure associated with the low sodium value.

*** “ULN” is the upper limit of the normal range.

Hematology *	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Hemoglobin (Female) - gm/dL	11.0 – 12.0	9.5 – 10.9	8.0 – 9.4	< 8.0
Hemoglobin (Female) change from baseline value - gm/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
Hemoglobin (Male) - gm/dL	12.5 – 13.5	10.5 – 12.4	8.5 – 10.4	< 8.5
Hemoglobin (Male) change from baseline value – gm/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
WBC Increase - cell/mm ³	10,800 – 15,000	15,001 – 20,000	20,001 – 25,000	> 25,000
WBC Decrease - cell/mm ³	2,500 – 3,500	1,500 – 2,499	1,000 – 1,499	< 1,000
Lymphocytes Decrease - cell/mm ³	750 – 1,000	500 – 749	250 – 499	< 250
Neutrophils Decrease - cell/mm ³	1,500 – 2,000	1,000 – 1,499	500 – 999	< 500
Eosinophils - cell/mm ³	650 – 1500	1501 - 5000	> 5000	Hypereosinophilic
Platelets Decreased - cell/mm ³	125,000 – 140,000	100,000 – 124,000	25,000 – 99,000	< 25,000
PT – increase by factor (prothrombin time)	1.0 – 1.10 x ULN**	1.11 – 1.20 x ULN	1.21 – 1.25 x ULN	> 1.25 ULN
PTT – increase by factor (partial thromboplastin time)	1.0 – 1.2 x ULN	1.21 – 1.4 x ULN	1.41 – 1.5 x ULN	> 1.5 x ULN
Fibrinogen increase - mg/dL	400 – 500	501 – 600	> 600	--
Fibrinogen decrease - mg/dL	150 – 200	125 – 149	100 – 124	< 100 or associated with gross bleeding or disseminated intravascular coagulation (DIC)

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

** “ULN” is the upper limit of the normal range.

Urine *	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Protein	Trace	1+	2+	Hospitalization or dialysis
Glucose	Trace	1+	2+	Hospitalization for hyperglycemia
Blood (microscopic) – red blood cells per high power field (rbc/hpf)	1 - 10	11 – 50	> 50 and/or gross blood	Hospitalization or packed red blood cells (PRBC) transfusion

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

APPENDIX 3. AMENDMENTS

AMENDMENT 04 VERSION 00 SUMMARY OF CHANGES

Study Title: A Phase 2, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Safety, Tolerability, and Efficacy of SM04690 Injected in the Target Knee Joint of Moderately to Severely Symptomatic Osteoarthritis Subjects

Purpose: The purpose of this amendment is to address FDA comments received during the Type C Meeting and to provide additional information regarding subject retention

Summary of Changes: The table below provides a list of changes and their rationale

Change	Sections Affected	Rationale
“Protocol AM04 V00 Date” has been added on the title page.	Title Page	Change was made to capture the dates of all previous and current protocol versions
Protocol date and version have been updated as applicable.	All	Change was made to reflect current protocol amendment
The study objectives were modified and now include exploratory objectives in addition to the primary and secondary objectives.	Synopsis and Section 2.2	Change was made to align with Statistical Analysis Plan and to address FDA comments
Study endpoints were updated and Section 3.1.3 Exploratory Endpoints was added to reflect modification of study objectives described above.	Section 3.1	Changes were made to align with Statistical Analysis Plan and to address FDA comments
A new Section 4.3 Strategies for Recruitment and Retention was added.	Section 4.3	Information was added as it was deemed that Investigator considerations for retention of subjects will be important due to the duration of the study
Section 10.5.5 Efficacy Analysis was updated to reflect modification of study objectives described above.	Section 10.5.5	Changes were made to align with Statistical Analysis Plan and to address FDA comments

AMENDMENT 03 VERSION 00 SUMMARY OF CHANGES

Study Title: A Phase 2, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Safety, Tolerability, and Efficacy of SM04690 Injected in the Target Knee Joint of Moderately to Severely Symptomatic Osteoarthritis Subjects

Purpose: The purpose of this amendment is to update the timing of the planned interim analysis and Week 26 visit window, and to provide clarification to protocol language in areas noted below

Summary of Changes: The table below provides a list of changes and their rationale

Change	Sections Affected	Rationale
“Protocol AM03 V00 Date” has been added on the title page.	Title Page	Change was made to capture the dates of all previous and current protocol versions
Protocol date and version have been updated as applicable.	All	Change was made to reflect current protocol amendment
On Sponsor Signature page, John Hood has been removed as a signatory and Anita DiFrancesco’s title has been updated to “Vice President, Clinical Development.”	Sponsor Signature Page	Change was made to reflect personnel and title change, respectively
The date of last subject completed has been changed from December 2016 to April 2017 and the duration of study was updated to 20 months accordingly.	Synopsis	Change was made to align with new estimate of last subject completed date
Interim analysis will now be performed at Week 26 (previously Week 13).	Synopsis, Section 3, Section 3.2.4, and Section 10.5.4	Change was made to refine study design
The Per-Protocol Analysis Set definition was modified: ITT subjects who complied with all study procedures and evaluations, and did not have any major protocol deviations that may affect efficacy outcomes.	Synopsis and Section 10.4	Change was made for consistency to match Sponsor definition
A new analysis data set was added to the synopsis and Section 10.4: Modified Intent-to-Treat (mITT) Analysis Set: ITT subjects who received a protocol-specified dose of SM04690 or placebo, analyzed as treated. Subjects incorrectly receiving doses not prescribed by the protocol	Synopsis, Section 10.4, and Section 10.5.5	Change was made for consistency as this analysis set was used in SM04690-OA-01

Change	Sections Affected	Rationale
are excluded from this analysis set.		
The following line was deleted from the Statistical Methods section of the synopsis: “If statistical assumptions supporting parametric regression methods cannot be supported, rank-based or semi-parametric methods may be used.”	Synopsis	Change was made to align with Statistical Analysis Plan
In Section 3. Description of Study Design, the following correction was made: “; the physician <i>investigator or designated study staff</i> will complete the Physician Global Assessment...”	Section 3	Change was made to align with updated Physician Global site signatory wording
Aspirin at a dose of 325 mg/day (instead of one to two 81 mg doses/day) is allowed for thrombosis prophylaxis.	Section 3.3.4	Change was made to conform to common clinical practice for thrombosis prophylaxis
IA injection of other agents with therapeutic intent into either knee was added as a prohibited concomitant medication and procedure. IA injection of other therapeutic agents into joints other than the knee are allowed.	Section 3.3.4	Change was made to refine prohibited concomitant medications and procedures
IA injection of glucocorticoids (also referred to as steroids or corticosteroids such as methylprednisolone) in a non-knee joint is allowed.	Section 3.3.4	Change was made to refine prohibited concomitant medications and procedures
A review of medical history has been added to the end of study visit. Review of medical history at the Week 52 (EOS)/Early Termination visit will only be to capture End Dates of any ongoing medical history collected at screening.	Section 5.3, Section 6.7, and Appendix 1	Review of medical history was added to track any status changes
A clarification has been added regarding X-ray view: “The intent (and included in the Image Review Charter – Image Acquisition guidelines) is that X-rays should be obtained in the posterior-anterior (PA) view, whenever possible. The Image Acquisition Protocol allows for anteroposterior (AP) view when	Section 5.6 and Section 6	Clarification was added to align with the Image Acquisition Protocol

Change	Sections Affected	Rationale
PA view X-ray cannot be acquired.”		
The Week 26 visit window was changed from ±3 days to -10 days.	Section 6.5 and Appendix 1	Change was made to refine study design
The following was added to Section 9.1: “The Investigator must report all laboratory results that are BOTH outside the normal range for the laboratory <i>or has a toxicity grade of 1 or greater</i> AND, in the opinion of the Investigator, are clinically significant.”	Section 9.1	Change was made for consistency with wording in Section 5.2
A pregnancy is not to be reported as an SAE but via the SAE reporting process.	Section 9.2	Change was made for consistency with SM04690-OA-02-SAE-Reporting-Guidelines-2015aug28
The SAE reporting process and contact information were updated.	Section 9.2.1	Change was made for consistency with SM04690-OA-02-SAE-Reporting-Guidelines-2015aug28
The following was deleted from Section 10: “The general analytical approach for all endpoints will be descriptive in nature, providing a summary and estimate of the safety and efficacy profile of SM04690. No formal statistical hypothesis testing will be conducted in this study. All summaries will present the data by dose group.”	Section 10	Change was made to align with Statistical Analysis Plan
Section 10.1 Sample Size Determination was revised with the following deletion: “...the sample size for this study was based upon accepted statistical practice and not on a formal efficacy hypothesis test and corresponding power analysis (Piantadosi 1997). However, based upon this sample size, a treatment response rate of 45% can be estimated with a confidence interval width of 10 percentage points. ”	Section 10.1	Change was made to simplify and clarify sample size determination
The Safety Analysis Set definition was modified: Subjects who were randomized and received SM04690 or placebo will be included in the safety analyses. This population is identical to the ITT Population	Section 10.4	Change was made for accuracy

Change	Sections Affected	Rationale
The following was added to Section 10.5.4: “The aim of this interim analysis is to assess safety and efficacy objectives at Weeks 13 and 26. No trial adaptation(s) will be made based upon these results.”	Section 10.5.4	Change was made to clarify the aim of the interim analysis
The following was deleted from Section 10.5.5: “If parametric assumptions fail to be supported, rank-based or non-parametric methods may be used. The goal of this primary efficacy analysis is to provide a precise estimate of treatment effect.”	Section 10.5.5	Change was made to align with Statistical Analysis Plan

AMENDMENT 02 VERSION 00 SUMMARY OF CHANGES

Study Title: A Phase 2, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Safety, Tolerability, and Efficacy of SM04690 Injected in the Target Knee Joint of Moderately to Severely Symptomatic Osteoarthritis Subjects

Purpose: The purpose of this amendment is to refine the study design and protocol procedures; several amendments were made in response to FDA feedback, as noted below

Summary of Changes: The table below provides a list of changes and their rationale

Change	Sections Affected	Rationale
“Protocol AM02 V00 Date” has been added on the title page.	Title Page	Change was made to capture the dates of all previous and current protocol versions
Protocol date and version have been updated as applicable.	All	Change was made to reflect current protocol amendment
The screening period was expanded to 21 days (originally 14 days).	Synopsis, Section 3, Section 3.4, Section 5.6, Section 6.1, Section 6.2, Appendix 1	Change was made to refine study design
Inclusion criteria #5 and 6 were clarified; “while on symptomatic oral treatment” applies to subjects who require oral treatment.	Synopsis and Section 4.1	Change was made for clarification
Inclusion criteria #1 was updated to: “Males and females between 40 and 7580 years of age, inclusive, in general good health”	Synopsis and Section 4.1	Change was made to refine study design
“Months” were converted to “weeks” in the exclusion criteria for consistency.	Synopsis and Section 4.2	Change was made for consistency
In exclusion criteria #8, significant and clinically evident misalignment of the target knee was clarified as “that would impact subject function.”	Synopsis and Section 4.2	Change was made for clarification
Exclusion criteria #10 was revised to: “Clinically significant abnormal Screening Visit hematology values, blood chemistry values, HbA1c, or urinalysis values as determined by the investigator”	Synopsis and Section 4.2	Change was made to refine study design
A clarification was added to exclusion criteria #11; ‘laboratory	Synopsis and Section 4.2	Change was made for clarification

Change	Sections Affected	Rationale
findings’ refers to those “not included in the Screening Visit laboratory tests.”		
Exclusion criteria #18 was updated to “effusion of the target knee <i>clinically</i> requiring aspiration...”	Synopsis and Section 4.2	Change was made to refine study design
Chiropractic treatments and clarification of “ <i>knee</i> OA” were added to exclusion criteria #19.	Synopsis and Section 4.2	Change was made to refine study design
In exclusion criteria #22, “chronic” was clarified to be “regular and consistent use for ≥ 3 months.”	Synopsis and Section 4.2	Change was made for clarification
Exclusion criteria #22c was revised to: “Glucocorticoids (e.g., methylprednisolone) administered by any route, with exception of <i>inhaled</i> , intranasal, and ophthalmic solution.	Synopsis and Section 4.2	Change was made to refine study design
In exclusion criteria #23, exclusion of subjects with uncontrolled hypertension and/or symptomatic coronary artery disease is to be “in the opinion of the investigator.”	Synopsis and Section 4.2	Change was made to refine study design
Section 3.2.3 Subject Re-screening was added to allow subjects to be re-screened once.	Section 3.2.3	Change was made to refine study design
In Section 3.3.3, the clarification was made that procedures that are ongoing, new, or modified <i>at or post-Day 1</i> must be recorded on the “Procedures and Non-Drug Therapies” page of the eCRF.	Section 3.3.4	Change was made for clarification
<p>Prohibited Concomitant Medications and Procedures were clarified:</p> <ul style="list-style-type: none"> • “Intra-articular injections of steroids or hyaluronic acid derivatives into joints other than the knee are allowed. • Electrotherapy, acupuncture, and chiropractic adjustments <i>of the knee</i> are prohibited. 	Section 3.3.4	Change was made for clarification
Section 5.2 was updated and Section 5.5 Pregnancy Tests was added. Pregnancy tests will be performed on	Section 5.2, Section 5.5, Section 6.1, Section 6.2, and Appendix 1	Change was made per FDA request

Change	Sections Affected	Rationale
female subjects at screening and on Day 1 prior to study medication injection.		
Section 5.4.1 Knee Examination was updated to align with exclusion criteria #8.	Section 5.4.1	Change was made for accuracy
Section 5.6 X-Ray of Knee Joints was revised to reflect the bilateral view of the x-ray as well as to correctly describe assessments being performed with the radiographs.	Section 5.6	Change was made for accuracy
Only one view is required for the knee X-ray (bilateral in weight bearing fixed flexion position, anteroposterior view).	Section 6.1, Section 6.5, and Section 6.7	Change was made to align with vendor requirements
Clarification was added to Section 6.2 regarding which procedures will be evaluated for subject eligibility.	Section 6.2	Change was made for clarification
Temperature correction and excursion clarification was added to Section 8.4: “The study medication must be stored at the appropriate temperature (15°-30°C or 59°-86°F) and in a restricted area with limited access. <i>Temperature excursions are allowed between 2°-60°C (36°-140°F) for a time period not to exceed 72 hours and only during study medication shipment.</i> ”	Section 8.4	Change was made for accuracy
In Section 9.1, the following correction was made: “Definition of Adverse Events and Adverse Drug Reactions ”	Section 9.1	Change was made for accuracy
Per FDA request, all AEs that occur during the trial will be considered related to study treatment. Investigator opinion regarding relatedness will still be collected for future planning and informational purposes.	Section 9.1	Change was made per FDA request
In Section 10.5.5, reference to gatekeeping was removed to align with the SAP.	Section 10.5.5	Change was made to align with SAP

Change	Sections Affected	Rationale
“Week 52(EOS) or ET” was revised to “Week 52 (EOS)/Early Termination” to align with study database.	Throughout	Change was made for accuracy
Grammar and punctuation corrections were made throughout.	Throughout	Changes were made to correct minor errors

AMENDMENT 01 VERSION 00 SUMMARY OF CHANGES

Study Title: A Phase 2, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Safety, Tolerability, and Efficacy of SM04690 Injected in the Target Knee Joint of Moderately to Severely Symptomatic Osteoarthritis Subjects

Purpose: The purpose of this amendment is to refine the study design and protocol procedures

Summary of Changes: The table below provides a list of changes and their rationale

Change	Sections Affected	Rationale
“Protocol AM01 V00 Date” has been added on the title page	Title Page	Change was made to capture the dates of all previous and current protocol versions
Protocol date and version have been updated as applicable	All	Change was made to reflect current protocol amendment
Inclusion criteria #5 was revised to: “Screening pain visual analog scale (VAS) score of 40-30-80 mm”	Synopsis and Section 4.1	Change was made to refine study design
Inclusion criteria #6 was revised to: “Total WOMAC score of 36-77 72-192 (out of 96 240) for the target knee while on symptomatic oral treatment at screening”	Synopsis and Section 4.1	Change was made to reflect updated scaling of WOMAC scores
Exclusion criteria #8 was revised to: “Significant and clinically evident misalignment of the target knee, as assessed by centrally read radiograph [as determined by Investigator]”	Synopsis and Section 4.2	Change was made to refine study design
Exclusion criteria #12 was revised to: “Comorbid conditions that, in the opinion of the Investigator, could affect pain assessment of the target knee...”	Synopsis and Section 4.2	Change was made to refine study design
Symptomatic hip osteoarthritis and symptomatic degenerative disc disease were moved from exclusion criteria #12 to a new exclusion criteria #13.	Synopsis and Section 4.2	Change was made to refine study design
Exclusion criteria #21 was revised to: “Subjects taking [prescription] medications or supplements for OA who have not maintained a stable therapeutic regimen for a minimum of	Synopsis and Section 4.2	Change was made to refine study design

Change	Sections Affected	Rationale
3 months prior to Study Visit Day 1		
<p>Exclusion criteria #22 and Section 3.3.4 was revised to include:</p> <ul style="list-style-type: none"> a. Opioids, both oral (e.g., tramadol) or transdermal (e.g., fentanyl patches) formulations b. Centrally acting analgesics (e.g., duloxetine) c. Glucocorticoids (e.g., methylprednisolone) administered by any route, with exception of intranasal and ophthalmic solutions 	Synopsis, Section 3.3.4, and Section 4.2	Change was made for clarity and to refine study design
Exclusion criteria #23a was revised to: “Subjects with diabetes who have a baseline HbA1c >9”	Synopsis and Section 4.2	Change was made to refine study design
Updates were made to the Phase 1 clinical trial description in Section 1.3 Study Rationale and Section 3.3.1 Rationale for Dosages and Dosing Regimen.	Section 1.3 and Section 3.3.1	Change was made to align with Investigator Brochure
The modified 2010 ACR Fibromyalgia Diagnostic Criteria assessment was replaced with the Widespread Pain Index and Symptom Severity Score assessment in Section 3 Description of Study Design.	Section 3	Change was made to correct an error; the modified 2010 ACR Fibromyalgia Diagnostic Criteria will not be used at the Screening Visit.
The following change was made in Section 3.2.1: “...subjects will be randomized via the Medidata Balance database.”	Section 3.2.1	Change was made to avoid confusion
In Section 3.2.2, an additional requirement was added in order for a subject to be eligible for randomization; the subject must have signed the Informed Consent form.	Section 3.2.2	Change was made for clarity
The following was added to Section 3.3.2 Dosages and Dosing Regimen: “Only topical anesthetic (absolutely no invasive anesthetic) is allowed for the study injections. Anesthetic is also not allowed to be combined with the study medication for injection”	Section 3.3.2	Change was made to refine protocol procedures

Change	Sections Affected	Rationale
“An HbA1c test will be performed on all subjects at the Screening Visit” was added to Section 5.2.	Section 5.2	Change was made for clarity
In Section 5.2 and 9.1, the following correction was made: “If any abnormal, clinically significant laboratory measure is found prior to study medication injection, [the subject is to be excluded.]”	Section 5.2 and Section 9.1	Change was made for consistency with exclusion criteria
Section 5.4.1 Knee Examination was updated with information regarding assessment of misalignment of the target knee.	Section 5.4.1	Change was made for clarity
In Section 5.5 X-ray of Target Knee Joint, the clarification was made that the X-ray taken during the screening period “must be taken according to the guidance provided by the independent radiologist.”	Section 5.5	Change was made for clarity
All questionnaires will be provided by the sponsor and may not be reproduced.	Section 5.7, Section 5.8, Section 5.9, Section 5.10, Section 5.11, and Section 5.12	Change was made to refine protocol procedures
Updates were made to Sections 5.8, 5.9, and 5.10 to align with questionnaires to be used in the study: -No numbers will be included with the anchor descriptors. -Scoring instructions for the site staff were added.	Section 5.9, Section 5.10, and Section 5.11	Changes were made for consistency and clarity
The 2 views of the target knee joint X-ray are to be the lateral and anteroposterior views.	Section 6.1, Section 6.5, and Section 6.7	Change was made for clarity
Placebo preparation instructions were added to Section 8.3 Preparation of Study Medication.	Section 8.3	Change was made to refine protocol procedures
“Quantity dispensed” and “Quantity returned” applies to active vials, vehicle vials, PBS vials, and saline vials.	Section 8.4	Change was made for clarity
Clarifications were made to Section 8.4 Accountability of Study	Section 8.4	Change was made for clarity

Change	Sections Affected	Rationale
Medications; unblinded PI and/or designee are responsible for study medication accountability.		
The Systemic Illness row was added to Table A1: Tables for Clinical Abnormalities.	Appendix 2	Change was made to align with Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials