STRIDES–1

SM04690 Trial Evaluating a Randomized Injection for Determination of Efficacy and Safety

A Phase 3, 28-Week, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of a Single Injection of SM04690 Injected in the Target Knee Joint of Moderately to Severely Symptomatic Osteoarthritis Subjects

Study Number: SM04690-OA-10

IND Sponsor: Samumed, LLC

Version Number: Amendment 03 Version 00

Date: 12 May 2020

Original Protocol Date: 28 November 2018

Amendment 01 Version 00: 01 April 2019

Amendment 02 Version 00: 07 November 2019

SPONSOR SIGNATURE PAGE

A Phase 3, 28-Week, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of a Single Injection of SM04690 Injected in the Target Knee Joint of Moderately to Severely Symptomatic Osteoarthritis Subjects

Protocol Number: SM04690-OA-10 AM03V00

Date: 12 May 2020

Name & Title	Signature Date
Mark Fineman, PhD Senior Vice President, Clinical Development	*Document has been electronically signed. Please see the final page of the viewable rendition for electronic signature(s).*
Christopher Swearingen, PhD Vice President, Clinical Outcomes and Analytics	*Document has been electronically signed. Please see the final page of the viewable rendition for electronic signature(s).*
Ismail Simsek, MD Medical Director	*Document has been electronically signed. Please see the final page of the viewable rendition for electronic signature(s).*

Samumed commits to satisfying the requirements of the International Council for Harmonisation guideline for Good Clinical Practice (ICH-GCP) E6 (R2) regarding the responsibilities of the Sponsor, the United States (US) Code of Federal Regulations (CFR) 21 Title CFR Parts 50, 54, 56, 312, and 314, and GCP Guidelines, as applicable.

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

Abbreviation	Term
ACR	American College of Rheumatology
AE	Adverse event
AESEV	Severity/Intensity Scale for Adverse Events
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
BMI	Body mass index
°C	(degrees) Celsius
CDISC	Clinical Data Interchange Standards Consortium
CFR	Code of Federal Regulations
CRF	Case report form
EC	Ethics Committee
eCOA	Electronic clinical outcomes assessment
eCRF	Electronic case report form
EDC	Electronic data capture
EOS	End of study
ER	Emergency room
ET	Early termination
°F	(degrees) Fahrenheit
FAS	Full analysis set
FDA	(US) Food and Drug Administration
G	Gram
GCP	Good Clinical Practice

Abbreviation	Term
HbA1c	Hemoglobin A1c
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
IA	Intra-articular
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
IP	Investigational product
IQRMP	Integrated Quality and Risk Management Plan
IRB	Institutional Review Board
IUD	Intrauterine device
KL	Kellgren-Lawrence
L	Liter
LDH	Lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
mJSW	Medial joint space width
mL	Milliliter
mm	Millimeter
MMI	Medical Metrics, Inc.
MMRM	Mixed-effects model for repeated measures
mSv	Millisievert
NCS	Not clinically significant
NRS	Numeric rating scale
NSAID	Nonsteroidal anti-inflammatory drug

Abbreviation	Term
OA	Osteoarthritis
PA	Posterior-anterior
PCP	Phencyclidine
PPAS	Per-protocol analysis set
PRBC	Packed red blood cells
PRP	Platelet rich plasma
RBC	Red blood cell
RTSM	Randomization and Trial Supply Management
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Safety analysis set
SD	Standard deviation
SOP	Standard operating procedure
SS	Symptom Severity
SSQ2	Symptom Severity Question 2
ULN	Upper limit of the normal range
UP	Unanticipated problem
US	United States
WBC	White blood cell
WOCBP	Women of childbearing potential
WOMAC	Western Ontario and McMaster Universities Arthritis Index
WPI	Widespread Pain Index
WPI&SS	Widespread Pain Index and Symptom Severity Form

STATEMENT OF COMPLIANCE

Study Title	A Phase 3, 28-Week, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of a Single Injection of SM04690 Injected in the Target Knee Joint of Moderately to Severely Symptomatic Osteoarthritis Subjects		
Protocol Number	SM04690-OA-10		
Protocol Date	12 May 2020	Protocol Version	AM03V00

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 Council for Harmonisation Guideline for Good Clinical Practice (ICH-GCP) E6 (R2).

I will obtain Institutional Review Board/Ethics Committee (IRB/EC) approval of the protocol and Informed Consent Form (ICF) 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 ICF 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

1. PROTOCOL SUMMARY

1.1 SYNOPSIS

Title: A Phase 3, 28-Week, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of a Single Injection of SM04690 Injected in the Target Knee Joint of Moderately to Severely Symptomatic Osteoarthritis Subjects

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

Endpoints:

Primary:
Change from baseline OA pain in the target knee as assessed by the weekly average of daily pain numeric rating scale (NRS) at Week 12

Secondary:

1. Change from baseline OA pain in the target knee as assessed by the weekly average of daily pain NRS at Week 24
2. Change from baseline OA function in the target knee as assessed by Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) physical function subscore (WOMAC Function) at Weeks 12 and 24
3. Change from baseline OA disease activity as assessed by Patient Global Assessment at Weeks 12 and 24
4. Change from baseline in usage of nonsteroidal anti-inflammatory drugs (NSAIDs) and acetaminophen for target knee OA pain

Safety:

Safety of SM04690 Injectable Suspension as measured by adverse events (AEs), serious adverse events (SAEs), vital signs, and clinical laboratory measures for the duration of the study.

Other Endpoints:

1. Change from baseline OA pain in the target knee as assessed by WOMAC pain subscore (WOMAC Pain) at Weeks 12 and 24
2. Change from baseline symptoms of OA in the target knee as assessed by WOMAC total score (WOMAC Total) at Weeks 12 and 24

Methodology: This study is a multicenter, randomized, double-blind, placebo-controlled, parallel group study of a single dose of SM04690 injected into the target knee joint of moderately to severely symptomatic OA subjects at Day 1.

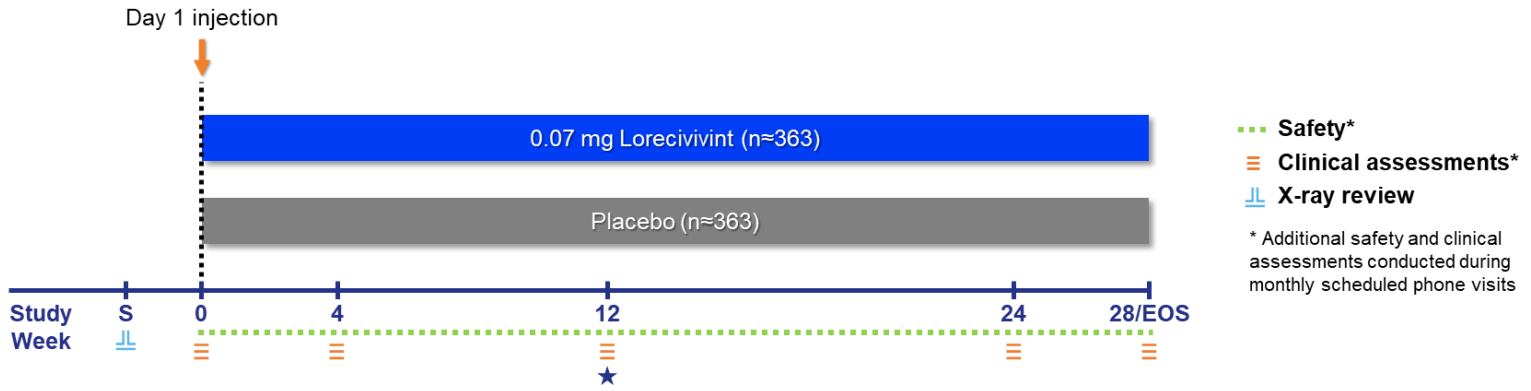
Approximately 726 subjects will be randomized at a ratio of 1:1 (0.07 mg SM04690 per 2 mL injection: 2 mL placebo). Subjects will participate in a 7- to 11-day screening period followed by a single injection and a 28-week evaluation period. Clinic visits will be scheduled at the Screening Visit, Day 1, and Weeks 4, 12, 24, and 28 [End of study (EOS)] / Early Termination (ET). Phone visits will be scheduled at Weeks 8, 16, and 20. Refer to Figure 1 for an overview of study design and endpoints.

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

- Daily pain NRS (for target knee OA pain) through Week 28 (EOS)
- WOMAC at baseline and Weeks 4, 12, 24, and 28 (EOS)
- Patient Global Assessment at baseline and Weeks 4, 12, 24, and 28 (EOS)

Investigator assessment of NSAID/acetaminophen usage will be performed at all in-person and phone visits starting at Day 1. Specific timing of protocol procedures is described in the Schedule of Events Table (Section 7.3.7).

Figure 1. Overview of study design and endpoints



Primary endpoint ★

- Change from baseline in weekly average of daily pain NRS at Week 12

Secondary endpoints

- Change from baseline in weekly average of daily pain NRS at Week 24
- Change from baseline in WOMAC Function at Weeks 12, 24
- Change from baseline in PtGA at Weeks 12, 24
- Change from baseline in usage of NSAIDs and acetaminophen

Safety endpoints

- Safety of lorecivivint injectable suspension as measured by:
  - AEs, serious AEs, vital signs, and clinical laboratory measures for the duration of the study

NRS = Numeric rating scale, WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index, PtGA = Patient global assessment, NSAIDs = Nonsteroidal anti-inflammatory drugs, S = Screening, EOS = End of study, AEs = Adverse events

Inclusion/ Exclusion Criteria:

Criteria for Inclusion:

1. Males and females between 40 and 80 years of age, inclusive, in general good health apart from their knee OA
2. Ambulatory (single assistive devices such as canes allowed if needed less than 50% of the time, subjects requiring a walker are excluded)
3. Diagnosis of femorotibial OA in the target knee by standard American College of Rheumatology (ACR) criteria at the Screening Visit (clinical AND radiographic criteria) (Appendix 1); OA of the knee is not to be secondary to any rheumatologic conditions (e.g., rheumatoid arthritis).
4. Radiographic disease Stage 2 or 3 in target knee within 24 weeks of the Screening Visit according to the Kellgren-Lawrence (KL) grading of knee OA as assessed by independent central readers
5. Pain compatible with OA of the knee(s) for at least 26 weeks prior to the Screening Visit
6. Primary source of pain throughout the body is due to OA in the target knee
7. Body mass index (BMI) $\leq$ 35 kg/m^2 at the Screening Visit
8. Widespread Pain Index (WPI) score of $\leq$ 4 and a Symptom Severity Question 2 (SSQ2) score of $\leq$ 2 at the Screening Visit and Day 1
9. Pain NRS scores recorded for the target knee on at least 4 out of the 7 days immediately preceding Day 1
10. Pain NRS scores recorded for the non-target knee on at least 4 out of the 7 days immediately preceding Day 1
11. Daily OA knee pain diary average NRS intensity score $\geq$ 4 and $\leq$ 8 in the target knee on the 11-point (0–10) NRS scale for the 7 days immediately preceding Day 1
12. Daily OA knee pain diary average NRS intensity score < 4 in the nontarget knee on the 11-point (0–10) NRS scale for the 7 days immediately preceding Day 1
13. WOMAC Function of 68–136 (out of 170) for the target knee at baseline regardless of if the subject is on symptomatic oral treatment
14. Willingness to use an electronic diary daily in the evening for the screening period and 28-week study duration
15. Negative drug test for amphetamine, buprenorphine, cocaine, methadone, opiates, phencyclidine (PCP), propoxyphene, barbiturates, benzodiazepine, methaqualone, and tricyclic antidepressants, unless any of these drugs are allowed per protocol and prescribed by a physician to treat a specific condition

16. Subjects with depression or anxiety must be clinically stable for at least 12 weeks prior to the Screening Visit and, if on treatment for depression or anxiety, be on at least 12 weeks of stable therapy
17. Full understanding of the requirements of the study and willingness to comply with all study visits and assessments
18. Subjects must have read and understood the informed consent form (ICF), and must have signed and dated it prior to any study-related procedure being performed

Criteria for Exclusion:

1. Pregnant women, breastfeeding women, and women who are not post-menopausal (defined as 12 months with no menses without an alternative medical cause) or permanently surgically sterile (includes hysterectomy, bilateral salpingectomy, and bilateral oophorectomy) who have a positive or indeterminate pregnancy test result at the Screening Visit or Day 1
2. Women who are not post-menopausal or permanently surgically sterile who are sexually active, and who are not willing to use birth control (as outlined in Section 5.3.1) during the study period
3. Men who are sexually active and of reproductive potential, who have partners who are capable of becoming pregnant, and who are not willing to use birth control as outlined in Section 5.3.1 during the study period
4. Significant malalignment of anatomical axis (medial angle formed by the femur and tibia) of the target knee (varus > 10°, valgus > 10°) by radiograph within 24 weeks of the Screening Visit as assessed by independent central readers
5. Partial or complete joint replacement in either knee
6. Currently requires use of a lower extremity prosthesis, and/or a structural knee brace (i.e., a knee brace that contains hardware)
7. Any surgery (e.g., arthroscopy) in either knee within 26 weeks prior to Day 1
8. Intra-articular (IA) injection into the target knee with a therapeutic aim including, but not limited to, hyaluronic acid, platelet-rich plasma (PRP), and stem cell therapies within 26 weeks prior to Day 1 or IA glucocorticoids within 12 weeks prior to Day 1
9. Effusion of the target knee clinically requiring aspiration within 12 weeks prior to Day 1
10. Use of electrotherapy (refer to Appendix 2), acupuncture, formalized physical therapy (i.e., prescribed by a medical professional), therapeutic ultrasound, and/or chiropractic treatments for knee OA within 4 weeks prior to Day 1
11. Previous treatment with SM04690

12. Subjects who have previously failed screening on this protocol and fail to meet rescreening criteria (see Section 5.4.2)
13. Participation in a clinical research trial that included the receipt of an investigational product (IP) or any experimental therapeutic procedure within 26 weeks prior to the Screening Visit, or planned participation in any such trial
14. Treatment with systemic (oral, intramuscular, or intravenous) glucocorticoids ≥ 10 mg prednisone or the equivalent per day within 4 weeks prior to Day 1; or subjects on < 10 mg prednisone or the equivalent per day who have not maintained a stable regimen for at least 2 weeks prior to Day 1 in the opinion of the Investigator
15. Use of centrally acting analgesics (refer to Appendix 2) within 12 weeks prior to Day 1
16. Use of anticonvulsants (refer to Appendix 2) within 12 weeks prior to Day 1
17. Subjects requiring the use of opioids > 1x per week within 12 weeks prior to Day 1
18. Topical local anesthetic agents (gels, creams, or patches such as the Lidoderm patch) used for the treatment of knee OA within 7 days of Day 1
19. Planned surgery scheduled during the study period, not including non-surgical invasive procedures conducted for a diagnostic or therapeutic purpose scheduled during the study period (refer to Section 7.6).
20. History of malignancy within the last 5 years, not including subjects with prior history of adequately treated in situ cervical cancer or basal or squamous cell skin cancer
21. Clinically significant abnormal screening hematology values, blood chemistry values, or urinalysis values as determined by the Investigator
22. Any condition 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
23. Other conditions that, in the opinion of the Investigator, could affect study endpoint assessments of either knee, including, but not limited to, peripheral neuropathy (e.g., diabetic neuropathy), symptomatic hip osteoarthritis, symptomatic degenerative disc disease, and patellofemoral syndrome
24. Comorbid conditions that could affect study endpoint assessments of the target knee, including, but not limited to, rheumatoid arthritis, psoriatic arthritis, systemic lupus erythematosus, gout or pseudogout, and fibromyalgia
25. History of mania, bipolar disorder, psychotic disorder,

schizophrenia, or schizoaffective disorder

26. Any known active infections, including urinary tract infection, upper respiratory tract infection, sinusitis, suspicion of IA infection, hepatitis B or hepatitis C infection, and/or infections that may compromise the immune system such as human immunodeficiency virus (HIV) at Day 1
27. Any chronic condition that has not been well controlled or subjects with a chronic condition who have not maintained a stable therapeutic regimen of a prescription therapy in the opinion of the Investigator
28. Hemoglobin A1c (HbA1c) > 9 at the Screening Visit
29. If using NSAIDs and/or acetaminophen, subjects who have not maintained a stable regimen in the opinion of the Investigator for at least 4 weeks prior to Day 1
30. Any contraindications for an IA injection in the target knee in the opinion of the Investigator
31. Subjects who have a current or pending disability claim, workers' compensation, or litigation(s) that may compromise response to treatment
32. Subjects who are immediate family members (spouse, parent, child, or sibling; biological or legally adopted) of personnel directly affiliated with the study at any investigative site, or are directly affiliated with the study at any investigative site
33. 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, or who are immediate family members (spouse, parent, child, or sibling; biological or legally adopted) of said employees responsible for the conduct of the study

Population:	Approximately 726 subjects with moderately to severely symptomatic osteoarthritis of the knee
Phase:	3
Number of Sites enrolling participants:	This study will be conducted at approximately 100 investigational centers
Description of Study Agent:	SM04690 is a small-molecule Wnt pathway modulator that inhibits CLK2 and DYRK1A intranuclear kinases and thereby potentially (a) reduces signs and symptoms of knee OA via an anti-inflammatory mechanism and (b) inhibits breakdown and enhances formation of cartilage through effects on progenitor cells and chondrocytes resident in the joint.

Study Duration:	Approximately 11 months Estimated date first subject consented: First quarter 2020 Estimated date last subject completed: First quarter 2021
Participant Duration:	Up to approximately 30 weeks
Criteria for evaluation:	**Efficacy:** Efficacy will be assessed by: • Weekly averages of daily pain NRS (for target knee OA pain) • WOMAC questionnaire for WOMAC Pain, Function, and Total score for the target knee • Patient Global Assessment • NSAID/acetaminophen usage **Safety:** The overall safety and tolerability of SM04690 will be assessed by the incidence, seriousness, severity, and relationship of AEs, SAEs, and clinically significant changes in clinical laboratory measures and vital signs, as assessed by the Investigator.

2. INTRODUCTION

2.1 STUDY RATIONALE

Osteoarthritis (OA) is the most common form of arthritis and chronic joint disorder in humans (Dougados and Hochberg 2011). The exact cause of OA is unknown, but it is associated with aging and normal wear on a joint. OA 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). OA is a leading cause of physical disability in the United States (US) (Lawrence, Felson 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, Altman 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, Ekici et al. 2012). Polymorphisms in genes involved in Wnt signaling are associated with an increased susceptibility to OA development (Wu, Huang 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. This study is being conducted to assess the effect of a single-dose SM04690 injection on knee OA pain and function over a 28-week period.

2.2 BACKGROUND INFORMATION

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, Felson 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, Felson et al. 2006).

Samumed, LLC (Samumed) is developing SM04690 for the treatment of OA. SM04690 is a small-molecule Wnt pathway modulator that inhibits CLK2 and DYRK1A intranuclear kinases and thereby potentially (a) reduces signs and symptoms of knee OA via an anti-inflammatory mechanism and (b) inhibits breakdown and enhances formation of cartilage through effects on progenitor cells and chondrocytes resident in the joint.

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

2.3 POTENTIAL RISKS AND BENEFITS

2.3.1 KNOWN POTENTIAL RISKS

Study Medication SM04690

The study drug SM04690 and procedures have risks and discomforts. The study drug SM04690 modulates the Wnt pathway. Refer to the IB for the known potential risks associated with SM04690.

Study Placebo

The placebo injection in this study will be 2 mL of vehicle, which is carboxymethylcellulose sodium and polysorbate 80 in phosphate buffered saline. Carboxymethylcellulose sodium and polysorbate 80 are inactive substances often used as food or drug excipients. There is a small risk of allergic reaction or hypersensitivity to these components.

Risks of Injection

Risks associated with knee joint injection include infection and local site reactions such as erythema, irritation, and edema.

Risks of Topical Anesthetics

Reactions to the topical anesthetic drug that may be applied to the subjects' skin are rare and may consist of cutaneous lesions (patches of skin that contrast with surrounding skin due to differences in texture, thickness, and color), or urticaria (red, raised itchy bumps). In addition to the local reactions, systemic reactions, although much rarer than the local ones, can be seen and include edema, bradycardia, dizziness, drowsiness, paresthesia, nausea, vomiting, or anaphylactoid reactions (generalized itching and hives, swelling, wheezing and difficulty breathing, fainting, and/or other allergy symptoms).

Blood Sampling

There is some risk of pain or local bruising and infection at the site where blood is drawn for laboratory tests. There is also a small risk of a fainting episode, which can occur as a reaction to giving blood.

2.3.2 KNOWN POTENTIAL BENEFITS

Taking part in this study may or may not provide any benefit to the subject. Information from this study may help doctors learn more about treatments for OA and this information may help future patients, even if it may not help the subjects in this study.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

SM04690 is being considered as a new option for the treatment of knee OA. The safety assessments of SM04690 rely on data from product development and previous clinical trials. Based on nonclinical and clinical data, the conduct of the trial is regarded as justifiable at the planned dose and duration. Previous clinical trials (SM04690-01, SM04690-OA-02, SM04690-OA-04) involving over 1000 subjects identified no SAEs that were considered related

to study medication. In previous trials, SM04690 was safe and well tolerated at single doses of 0.23 mg per injection, exceeding the 0.07 mg single dose used in the current study. Additional information about safety data from nonclinical and clinical studies of SM04690 is in the IB.

Risks to subjects will be minimized by clinical safety oversight performed by centralized review and conducted by Medical Monitors per the Medical Monitoring Plan. In addition, on-site review will be conducted by Clinical Research Associates.

Taking the above information into account, an assessment of risks and benefits supports the current study designed to investigate SM04690 as a potential therapy for patients with knee OA.

3. OBJECTIVES AND ENDPOINTS

3.1 OBJECTIVE

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

3.2 STUDY ENDPOINTS

3.2.1 PRIMARY ENDPOINT

Change from baseline OA pain in the target knee as assessed by the weekly average of daily pain numeric rating scale (NRS) at Week 12

3.2.2 SECONDARY ENDPOINTS

1. Change from baseline OA pain in the target knee as assessed by the weekly average of daily pain NRS at Week 24
2. Change from baseline OA function in the target knee as assessed by Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) physical function subscore (WOMAC Function) at Weeks 12 and 24
3. Change from baseline OA disease activity as assessed by Patient Global Assessment at Weeks 12 and 24
4. Change from baseline in usage of nonsteroidal anti-inflammatory drugs (NSAIDs) and acetaminophen for target knee OA pain

3.2.3 SAFETY ENDPOINT

Safety of SM04690 Injectable Suspension as measured by adverse events (AEs), serious adverse events (SAEs), vital signs, and clinical laboratory measures for the duration of the study.

3.2.4 OTHER ENDPOINTS

1. Change from baseline OA pain in the target knee as assessed by WOMAC pain subscore (WOMAC Pain) at Weeks 12 and 24
2. Change from baseline symptoms of OA in the target knee as assessed by WOMAC total score (WOMAC Total) at Weeks 12 and 24

4. STUDY DESIGN

4.1 DESCRIPTION OF THE STUDY DESIGN

This study is a multicenter, randomized, double-blind, placebo-controlled, parallel group study of a single dose of SM04690 injected into the target knee joint of moderately to severely symptomatic OA subjects at Day 1.

Approximately 726 subjects will be enrolled and randomized at a ratio of 1:1 (0.07 mg active per 2 mL injection: 2 mL Placebo). Subjects will participate in a 7- to 11-day screening period followed by a single injection and a 28-week evaluation period. Clinic visits will be scheduled at the Screening Visit, Day 1, and Weeks 4, 12, 24, and 28 (EOS)/ET. Phone visits will be scheduled at Weeks 8, 16, and 20. Specific timing of protocol procedures is described in the Schedule of Events Table (Section 7.3.7). Specific timing of electronic diary and questionnaire completion is described in the Schedule of Electronic Diary and Questionnaire Completion Table (Section 7.3.8).

This study will be conducted at approximately 100 investigational centers.

A Widespread Pain Index and Symptom Severity (WPI&SS) assessment will be administered at the Screening Visit and Day 1.

Subjects will be required to complete an electronic diary for the following (Section 7.3.8):

- Daily pain NRS from the Screening Visit through Week 28 (EOS)
- WOMAC at baseline and Weeks 4, 12, 24, and 28 (EOS)
- Patient Global Assessment at baseline and Weeks 4, 12, 24, and 28 (EOS)

In addition, general medical evaluations including physical examination, knee examination, and recording of vital signs will be performed at the Screening Visit, Day 1, and Weeks 4, 12, 24, and 28 (EOS)/ET. Height will be measured at the Screening Visit and weight will be measured at the Screening Visit and Weeks 28 (EOS)/ET. Clinical laboratory evaluations will be performed at the Screening Visit and Weeks 4, 12, 24, and 28 (EOS)/ET. Investigator assessment of NSAID/acetaminophen usage will be performed at all in-person and phone visits starting at Day 1.

Recording of signs and symptoms of study medication intolerability and AE reporting will start following the injection of the study medication and continue at all subsequent in-person and phone visits until the subject completes Week 28 (EOS)/ET. All AEs, whether volunteered, elicited, or noted during examination, will be recorded throughout the study.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

This phase 3 study, SM04690-OA-10, is a multicenter, randomized, double-blind, placebo-controlled, parallel group study of a single concentration of 0.07 mg SM04690 per 2 mL injection injected into the target knee joint of moderately to severely symptomatic OA subjects at Day 1. The placebo to be used in this study is a vehicle-concurrent control. The vehicle-only injection contains all components of the SM04690 injectable suspension with the exception of the active ingredient. Vehicle is considered the appropriate control in this study as it allows for evaluation of the efficacy, safety, and tolerability of the SM04690 molecule alone through comparison of the active and vehicle arms.

4.3 JUSTIFICATION FOR DOSE

The dose of 0.07 mg SM04690 was selected for this study based on evidence available from nonclinical studies and 3 completed clinical studies (SM04690-01, SM04690-OA-02, and SM04690-OA-04). Administration of the 0.07 mg dose resulted in the most consistently positive responses compared to control when the outcome measures of Pain NRS, WOMAC Function, and medial joint space width (mJSW) were assessed.

4.4 END OF STUDY DEFINITION

A participant is considered to have completed the study if he or she has completed all phases of the study including the last visit shown in the Schedule of Events Table (Section 7.3.7).

5. STUDY POPULATION

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.

5.1 PARTICIPANT 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 apart from their knee OA
2. Ambulatory (single assistive devices such as canes allowed if needed less than 50% of the time, subjects requiring a walker are excluded)
3. Diagnosis of femorotibial OA in the target knee by standard American College of Rheumatology (ACR) criteria at the Screening Visit (clinical AND radiographic criteria) (Appendix 1); OA of the knee is not to be secondary to any rheumatologic conditions (e.g., rheumatoid arthritis).
4. Radiographic disease Stage 2 or 3 in target knee within 24 weeks of the Screening Visit according to the Kellgren-Lawrence (KL) grading of knee OA as assessed by independent central readers
5. Pain compatible with OA of the knee(s) for at least 26 weeks prior to the Screening Visit
6. Primary source of pain throughout the body is due to OA in the target knee
7. Body mass index (BMI) $\leq$ 35 kg/m^2 at the Screening Visit
8. Widespread Pain Index (WPI) score of $\leq$ 4 and a Symptom Severity Question 2 (SSQ2) score of $\leq$ 2 at the Screening Visit and Day 1
9. Pain NRS scores recorded for the target knee on at least 4 out of the 7 days immediately preceding Day 1
10. Pain NRS scores recorded for the non-target knee on at least 4 out of the 7 days immediately preceding Day 1
11. Daily OA knee pain diary average NRS intensity score $\geq$ 4 and $\leq$ 8 in the target knee on the 11-point (0–10) NRS scale for the 7 days immediately preceding Day 1
12. Daily OA knee pain diary average NRS intensity score < 4 in the nontarget knee on the 11-point (0–10) NRS scale for the 7 days immediately preceding Day 1

13. WOMAC Function of 68–136 (out of 170) for the target knee at baseline regardless of if the subject is on symptomatic oral treatment
14. Willingness to use an electronic diary daily in the evening for the screening period and 28-week study duration
15. Negative drug test for amphetamine, buprenorphine, cocaine, methadone, opiates, phencyclidine (PCP), propoxyphene, barbiturates, benzodiazepine, methaqualone, and tricyclic antidepressants, unless any of these drugs are allowed per protocol and prescribed by a physician to treat a specific condition
16. Subjects with depression or anxiety must be clinically stable for at least 12 weeks prior to the Screening Visit and, if on treatment for depression or anxiety, be on at least 12 weeks of stable therapy
17. Full understanding of the requirements of the study and willingness to comply with all study visits and assessments
18. Subjects must have read and understood the informed consent form (ICF), and must have signed and dated it prior to any study-related procedure being performed

5.2 PARTICIPANT EXCLUSION CRITERIA

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

1. Pregnant women, breastfeeding women, and women who are not post-menopausal (defined as 12 months with no menses without an alternative medical cause) or permanently surgically sterile (includes hysterectomy, bilateral salpingectomy, and bilateral oophorectomy) who have a positive or indeterminate pregnancy test result at the Screening Visit or Day 1
2. Women who are not post-menopausal or permanently surgically sterile who are sexually active, and who are not willing to use birth control (as outlined in Section 5.3.1) during the study period
3. Men who are sexually active and of reproductive potential, who have partners who are capable of becoming pregnant, and who are not willing to use birth control as outlined in Section 5.3.1 during the study period
4. Significant malalignment of anatomical axis (medial angle formed by the femur and tibia) of the target knee (varus > 10°, valgus > 10°) by radiograph within 24 weeks of the Screening Visit as assessed by independent central readers
5. Partial or complete joint replacement in either knee
6. Currently requires use of a lower extremity prosthesis, and/or a structural knee brace (i.e., a knee brace that contains hardware)
7. Any surgery (e.g., arthroscopy) in either knee within 26 weeks prior to Day 1
8. Intra-articular (IA) injection into the target knee with a therapeutic aim including, but not limited to, hyaluronic acid, platelet-rich plasma (PRP), and stem cell therapies within 26 weeks prior to Day 1 or IA glucocorticoids within 12 weeks prior to Day 1
9. Effusion of the target knee clinically requiring aspiration within 12 weeks prior to Day 1
10. Use of electrotherapy (refer to Appendix 2), acupuncture, formalized physical therapy

(i.e., prescribed by a medical professional), therapeutic ultrasound, and/or chiropractic treatments for knee OA within 4 weeks prior to Day 1

11. Previous treatment with SM04690
12. Subjects who have previously failed screening on this protocol and fail to meet rescreening criteria (see Section 5.4.2)
13. Participation in a clinical research trial that included the receipt of an investigational product (IP) or any experimental therapeutic procedure within 26 weeks prior to the Screening Visit, or planned participation in any such trial
14. Treatment with systemic (oral, intramuscular, or intravenous) glucocorticoids ≥ 10 mg prednisone or the equivalent per day within 4 weeks prior to Day 1; or subjects on < 10 mg prednisone or the equivalent per day who have not maintained a stable regimen for at least 2 weeks prior to Day 1 in the opinion of the Investigator
15. Use of centrally acting analgesics (refer to Appendix 2) within 12 weeks prior to Day 1
16. Use of anticonvulsants (refer to Appendix 2) within 12 weeks prior to Day 1
17. Subjects requiring the use of opioids > 1x per week within 12 weeks prior to Day 1
18. Topical local anesthetic agents (gels, creams, or patches such as the Lidoderm patch) used for the treatment of knee OA within 7 days of Day 1
19. Planned surgery scheduled during the study period, not including non-surgical invasive procedures conducted for a diagnostic or therapeutic purpose scheduled during the study period (refer to Section 7.6).
20. History of malignancy within the last 5 years, not including subjects with prior history of adequately treated in situ cervical cancer or basal or squamous cell skin cancer
21. Clinically significant abnormal screening hematology values, blood chemistry values, or urinalysis values as determined by the Investigator
22. Any condition 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
23. Other conditions that, in the opinion of the Investigator, could affect study endpoint assessments of either knee, including, but not limited to, peripheral neuropathy (e.g., diabetic neuropathy), symptomatic hip osteoarthritis, symptomatic degenerative disc disease, and patellofemoral syndrome
24. Comorbid conditions that could affect study endpoint assessments of the target knee, including, but not limited to, rheumatoid arthritis, psoriatic arthritis, systemic lupus erythematosus, gout or pseudogout, and fibromyalgia
25. History of mania, bipolar disorder, psychotic disorder, schizophrenia, or schizoaffective disorder
26. Any known active infections, including urinary tract infection, upper respiratory tract infection, sinusitis, suspicion of IA infection, hepatitis B or hepatitis C infection, and/or infections that may compromise the immune system such as human immunodeficiency virus (HIV) at Day 1
27. Any chronic condition that has not been well controlled or subjects with a chronic condition who have not maintained a stable therapeutic regimen of a prescription therapy

in the opinion of the Investigator

28. Hemoglobin A1c (HbA1c) > 9 at the Screening Visit
29. If using NSAIDs and/or acetaminophen, subjects who have not maintained a stable regimen in the opinion of the Investigator for at least 4 weeks prior to Day 1
30. Any contraindications for an IA injection in the target knee in the opinion of the Investigator
31. Subjects who have a current or pending disability claim, workers' compensation, or litigation(s) that may compromise response to treatment
32. Subjects who are immediate family members (spouse, parent, child, or sibling; biological or legally adopted) of personnel directly affiliated with the study at any investigative site, or are directly affiliated with the study at any investigative site
33. 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, or who are immediate family members (spouse, parent, child, or sibling; biological or legally adopted) of said employees responsible for the conduct of the study

5.3 LIFESTYLE GUIDELINES

5.3.1 CONTRACEPTION

WOMEN OF CHILDBEARING POTENTIAL

Women of childbearing potential (WOCBP) refers to women who are not post-menopausal (defined as 12 months with no menses without an alternative medical cause) or permanently surgically sterile (includes hysterectomy, bilateral salpingectomy, and bilateral oophorectomy).

From the Screening Visit until Week 28 (EOS), sexually active WOCBP must agree to use an acceptable form of contraception. Acceptable forms of contraception are:

1. Intrauterine device (IUD)
2. Implantable rod
3. Established hormonal contraceptive methods in combination with a barrier method. This includes injectable, oral, patch, and vaginal ring hormonal contraception. Females who are using hormonal contraceptives must have had consistent use of the same hormonal contraceptive product for at least 4 weeks. Barrier methods include male or female condom, diaphragm with spermicide, sponge with spermicide, or cervical cap with spermicide.
4. Bilateral tubal ligation/occlusion/division
5. Male partner who had a vasectomy provided that the partner is the sole sexual partner of the WOCBP, and that the vasectomized partner has received medical assessment of the success of the surgical procedure or had the vasectomy for at least 6 months

Sexually active WOCBP who withdraw from the study after receiving study medication should remain on an acceptable form of contraception for 28 weeks after Day 1.

MEN

For men who are sexually active with a female partner of childbearing potential, both partners must agree to use an acceptable form of contraception, as outlined below, from the Screening Visit until Week 28 (EOS):

- A condom and one additional acceptable form of birth control:
  a. IUD
  b. Implantable rod
  c. Established hormonal contraceptive methods. This includes injectable, oral, patch, and vaginal ring hormonal contraception. Females who are using hormonal contraceptives must have had consistent use of the same hormonal contraceptive product for at least 4 weeks
  d. Bilateral tubal ligation/occlusion/division
  e. Vasectomy in the male partner for at least 6 months or demonstrated success of the surgical procedure

Men who are sexually active with a female partner of childbearing potential who withdraw from the study after receiving study medication should continue to use an acceptable form of contraception with their partners for 28 weeks after Day 1.

5.4 SCREEN FAILURES

5.4.1 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently randomized or entered in the study.

5.4.2 SUBJECT RESCREENING

Subjects are allowed to be rescreened once for this protocol and, if the subject is affected by an amendment(s) that changes the inclusion/exclusion criteria, they are additionally allowed to rescreen. Rescreens are limited to subjects who did not meet inclusion/exclusion criteria due to a transient reason or if the inclusion/exclusion criteria have changed. Transient refers to self-limiting and predictably resolving conditions or acute events (e.g., common cold or otitis media), reversible medical conditions that are successfully treated (e.g., resolved anemia), being unable to comply with study procedures due to administrative convenience (e.g., family issues or attending to a private matter), and/or being within the exclusion window for past medications and/or procedures, as outlined in Section 5.2.

Subjects who failed any entry criteria for which no further treatment or spontaneous resolution is expected are not allowed to be rescreened. Daily OA knee pain diary noncompliance is not a transient event and subjects with knee pain diary noncompliance may not be rescreened.

Any rescreened subject must be reconsented and will be issued a new subject number. All screening procedures and assessments must be performed at rescreen; no results or data may be used from the previous screen. Target knee selection may not be changed at rescreen without the permission of the Medical Monitor.

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

A detailed recruitment and retention plan will be maintained by the Sponsor.

5.6 PARTICIPANT WITHDRAWAL OR TERMINATION

5.6.1 REASONS FOR WITHDRAWAL OR TERMINATION

Because the study treatment requires only one injection, best efforts will be made to encourage subjects to attend all follow-up visits. Subjects will be informed they are free to withdraw from the study at any time and for any reason. A premature discontinuation from the 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:

- AE
- Total or partial knee replacement of the target knee
- Lost to follow-up after a minimum of 3 attempts have been made to contact the subject, including sending a registered letter
- Withdrawal by subject for reason other than lack of efficacy
- Subject non-compliance
- Physician decision for reason other than lack of efficacy
- Study terminated by Sponsor
- Site terminated by Sponsor
- Request by regulatory authority
- Lack of efficacy
- Pregnancy
- Death
- Randomized by mistake without study treatment
- Other

5.6.2 HANDLING OF PARTICIPANT WITHDRAWALS OR TERMINATION

In case of premature discontinuation of study participation, ET procedures should be conducted within 14 days of discontinuation for any subject who was randomized at the Day 1 visit, if possible. The date the subject is withdrawn from the study and the reason for the discontinuation should be recorded on the electronic case report form (eCRF). The Investigator or designee must complete all applicable eCRF pages for subjects who discontinue from the study prematurely.

Replacement of subjects who withdraw or discontinue prematurely is not allowed.

5.7 PREMATURE TERMINATION OR SUSPENSION OF STUDY

The Sponsor reserves the right to prematurely terminate the study at any time for administrative or safety reasons. Written notification, documenting the reason for study suspension or termination, will be provided to the Investigator, Sponsor, and regulatory authorities as

appropriate. If the study is prematurely terminated or suspended, the Investigator will promptly inform the IRB and will provide the reason(s) for the termination or suspension.

6. STUDY AGENT

6.1 STUDY AGENT(S) AND CONTROL DESCRIPTION

6.1.1 ACQUISITION

The Sponsor will be responsible for the manufacturing, labeling, packaging, distribution, reconciliation of study medication, and ultimate destruction of unused study medication (both SM04690 drug product and placebo product).

6.1.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

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 and placebo products are supplied as vials of 2.4 mL of formulated suspension. Placebo product contains 0.5% carboxymethylcellulose sodium and 0.05% polysorbate 80 in pH 7.4 phosphate buffered saline.

Study medication will be supplied as single-use vials. SM04690 drug and placebo products will be supplied to the study pharmacist and labeled according to the applicable local and country regulations. For dispensing, dose preparation, and labeling instructions, refer to the Pharmacy Manual.

6.1.3 PRODUCT STORAGE AND STABILITY

The study medication should be stored at the appropriate temperature (15°C–30°C [59°F–86°F]) and in a restricted area with limited access. Temperature excursions are to be evaluated on a case-by-case basis by the Sponsor.

6.1.4 PREPARATION

Each dose of study medication should be well mixed (the drug product is a suspension) prior to injecting 2 mL intra-articularly into the target knee. Refer to the Pharmacy Manual for detailed instructions on study medication preparation.

6.1.5 DOSING AND ADMINISTRATION

SM04690 will be administered in the following dosage strengths:

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

The injectable drug product or placebo product is to be administered by the Unblinded Investigator as a single injection into the target knee joint once at Day 1. The Unblinded Investigator must minimize any contact with the subject following the injection and may not

perform any study assessments throughout the duration of the study. All subject contact for the remainder of the study is limited to the Blinded Investigator and other appropriate blinded study personnel.

Only 1 knee will be treated for each subject in this study. The injection can be done either through lateral or medial (including superior/suprapatellar, midpatellar, and inferior/anterior) approaches, based on the standard practice of the Unblinded Investigator or the knee examination of the subject. Although not required, the injections may be guided by ultrasound or fluoroscopy without contrast if it is the standard practice of the Unblinded Investigator.

Only topical anesthetics are allowed prior to study injection. Local anesthetic injections are prohibited.

Prior to administration of the IA knee injection, the subject should be blinded to observation of the study medication and injection procedure according to the processes specified in the Site-Specific Blinding Plan.

The Unblinded Investigator (injector) should place the needle into the joint and the total volume contained in the syringe is to be injected into the joint space. Because SM04690 drug product is a suspension, prior aspiration of synovial fluid into the syringe containing the injectate should be avoided to prevent trapping of particles within synovial aspirate/cellular content residues. If it is the standard practice of the injector to aspirate a small amount (0.3-0.5 mL) of joint fluid to confirm correct needle placement, this will have to be done with an empty sterile syringe. Using the same needle, the study medication should then be injected with a separate syringe.

The Sponsor will provide sterile needles and syringes that should be used for the injection of study medication.

6.1.6 ROUTE OF ADMINISTRATION

Injectable SM04690 drug product or placebo product is to be administered as a single IA injection into the target knee joint once at Day 1.

6.1.7 STARTING DOSE AND DOSE ESCALATION SCHEDULE

Not applicable to this study. Each subject will be randomly assigned to SM04690 or placebo on Day 1.

6.1.8 DOSE ADJUSTMENTS/MODIFICATIONS/DELAYS

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

6.1.9 DURATION OF THERAPY

Study medication is to be administered as a single IA injection into the target knee joint once at Day 1.

6.1.10 STUDY INTERVENTION COMPLIANCE

Not applicable to this study.

6.1.11 DEVICE SPECIFIC CONSIDERATIONS

Not applicable to this study.

6.2 STUDY AGENT ACCOUNTABILITY PROCEDURES

All used and unused vials of the study medication 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 injected
- Quantity dispensed (drug product vial and placebo vial)
- Quantity returned/used (drug product vial and placebo vial)

All study medication dispensed by the Unblinded Investigator and/or unblinded designee will be inventoried and accounted for throughout the study. 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 medications supplied for this study are for use only in subjects properly consented and randomized 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. Procedures for return or destruction of used and unused vials of the study medication will be provided in the Pharmacy Manual.

7. STUDY PROCEDURES AND SCHEDULE

7.1 STUDY PROCEDURES/EVALUATIONS

7.1.1 STUDY SPECIFIC PROCEDURES

Collection of Adverse Events Data

Data regarding AEs will be collected in this study. AEs are events that occur during 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 study. AEs will be assessed at each in-person and phone visit from the time of study medication injection on Day 1 through Week 28 (EOS)/ET.

Each subject will be observed and queried by the Investigator or designee at each study visit for any continuing AEs or new AEs since the previous visit. The subject may 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. The following information will be recorded within the eCRF for each AE: Description of the event, date of onset and resolution, etiology, and severity as assessed by the Investigator according to the Clinical Data Interchange Standards Consortium (CDISC) Severity/Intensity Scale for Adverse Events (AESEV) (Table 1), causal relationship to study medication, outcome, and any action taken.

In this protocol, signs and symptoms of exacerbation or worsening of target knee OA will be captured in the context of efficacy assessments and recorded on specific pages of the eCRF or electronic diary. Anticipated fluctuations or anticipated deterioration (in the opinion of the Investigator) of the underlying disease (target knee OA) will not be considered as AEs nor captured on the AE page of the eCRF.

Whenever possible, it is preferable to record a diagnosis as the AE term rather than a series of symptoms relating to a diagnosis. Fluctuations of pre-existing conditions that do not represent a clinically significant exacerbation or worsening need not be considered AEs.

AEs will be followed until the subject's last visit or resolution, whichever comes first. For subjects who discontinue from the study within 30 days of their dose of study medication, AEs that are ongoing at the subject's last visit will be followed for 30 days after administration of the dose or until resolution, whichever comes first. Resolution is defined as the return to baseline status or stabilization of the condition. SAEs and selected AEs identified by the Investigator or the Sponsor to warrant further follow-up that are ongoing at a subject's last visit will be followed until resolution.

Medical History

A medical history will be obtained at the Screening Visit and Day 1 with a follow-up at Week 28 (EOS)/ET to capture End Dates of any ongoing medical history collected at the Screening Visit and Day 1. Medical history at the Screening Visit will include demographic data (e.g., age, race, ethnicity) and use of assistive devices. 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. Examples of medical conditions and disease states that should be considered relevant to the subject's study participation include history of current disease, medical history that confirms the eligibility criteria of the subject, and asymptomatic medical history that could become symptomatic while on the study.

Past Treatments for Knee OA Pain

Subjects will be asked at the Screening Visit about their previous use, at any time in the past, of the following treatments for their knee OA pain: NSAIDs, acetaminophen, opioids, IA steroids, and IA hyaluronic acid. Responses will be recorded on the eCRF as Yes/No/Unknown.

Physical Examination

A general physical examination will be conducted at the Screening Visit, Day 1, and at Weeks 4, 12, 24, and 28 (EOS)/ET. 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.

Knee Examination

A knee examination of both knees will be conducted at the Screening Visit, Day 1, and at Weeks 4, 12, 24, and 28 (EOS)/ET. Results of the knee 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.

Presence of unilateral or bilateral symptomatic knee OA will be recorded in the eCRF at the Screening Visit. If the subject has OA in both knees, the site is to establish the target knee as the knee with greater pain at the Screening Visit based on the subject's evaluation and the Investigator's clinical judgment. If the Investigator's clinical judgement of the target knee differs from the subject-reported target knee (as reported during prescreen), sites should contact the Sponsor for further guidance.

Vital Signs

Vital signs will be measured by a qualified staff member at the Screening Visit, Day 1, and Weeks 4, 12, 24, and 28 (EOS)/ET.

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

- Body temperature
- Pulse rate
- Respiratory rate
- Blood pressure (systolic and diastolic) after the subject rests (sitting or supine) 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.

Height and Weight

Height measurements will be taken at the Screening Visit only. Weight measurements will be taken at the Screening Visit and Week 28 (EOS)/ET.

Review of Prescreen Radiograph Report

Prior to entry into a Samumed study for OA of the knee, subjects must have a radiograph taken and read by the Sponsor-specified central reader. Prior to the Screening Visit, the subject's prescreen radiograph report must be reviewed to confirm eligibility for this study. At the Screening Visit, after confirmation of the target knee by the Investigator, the subject's prescreen radiograph report must be reviewed for the target knee to confirm compliance with inclusion/exclusion criteria.

Widespread Pain Index and Symptom Severity (WPI&SS) Form

The WPI&SS assessment consists of a body map that determines a subject's areas of pain or tenderness (WPI) and symptom severity (SS) questions. The WPI&SS assessment used in this study is modified from that described in (Clauw 2014). A WPI&SS assessment will be

completed by the subject at the Screening Visit and Day 1.

Upon completion of the WPI&SS assessment, the subject will sign or initial the source document and date it to indicate that the assessment is reported accurately.

The WPI&SS assessment sheets will be provided by the Sponsor and may not be reproduced.

Electronic Diary Device Provision and Training

Detailed instructions and site training regarding subject electronic questionnaire completion will be provided to the investigational center. Electronic diary device provisioning to the subject will occur at the Screening Visit and electronic diary devices are to be returned to the site at Week 28 (EOS)/ET.

Subject training for electronic diary and questionnaire completion on the electronic diary device is required at the Screening Visit prior to subject completion of the pain NRS, WOMAC, and Patient Global Assessment questionnaires. Training will remain available on the electronic diary device throughout the study in case subject retraining is needed.

Additionally, at the Screening Visit, subjects will have training on accurate pain reporting and placebo response reduction prior to subject completion of the pain NRS, WOMAC, and Patient Global Assessment questionnaires. It is recommended that subjects complete the training on accurate pain reporting and placebo response reduction at Day 1 and Weeks 4, 12, and 24.

Pain Numeric Rating Scale

The pain NRS is an 11-point scale [0–10] for subject self-reporting of average knee pain in the last 24 hours. The NRS will be anchored by descriptors at each end (“No Pain” on the left and “Pain as bad as you can imagine” on the right). A pain NRS for each knee will be completed daily by the subject during the screening period from the Screening Visit until Day 1 to assess subject ability to be compliant with a daily pain assessment and to determine subject eligibility. During the screening period, daily pain NRS assessments will be completed by subjects in the evening (between 5:00 pm and 11:59 pm) remotely on their electronic devices for each knee to collect average knee pain in the last 24 hours. Subject eligibility and electronic diary compliance for daily pain NRS over the screening period will be reviewed at Day 1 prior to randomization. After screening, starting on Day 1, daily pain NRS assessments are to be completed by subjects in the evening (between 5:00 pm and 11:59 pm) remotely on their electronic devices for the target knee only. Electronic diary compliance for daily pain NRS will be reviewed at all clinic visits from Day 1 to Week 24. It is recommended that the site re-train the subject if the site determines it is necessary after review. Refer to Section 7.3.8 for a schedule of electronic diary and questionnaire completion.

Subjects will complete the pain NRS on the Sponsor-provided electronic device. Subjects will receive notifications reminding them to complete the daily pain NRS assessment.

Western Ontario and McMaster Universities Arthritis Index (WOMAC)

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 a target joint. The WOMAC Version NRS 3.1 questionnaire will be completed by the subject for their target knee in the evening (between

5:00 pm and 11:59 pm) remotely on their electronic device 5 days after their Screening Visit (i.e., Screening Visit + 5 days) or up until the day before the Day 1 visit. WOMAC questionnaire completion will be reviewed at Day 1 prior to randomization to determine subject eligibility. Baseline WOMAC questionnaire should be completed within 9 days prior to Day 1. After Day 1, WOMAC assessments will be completed by the subject for their target knee in the evening (between 5:00 pm and 11:59 pm) remotely on their electronic device at Week 4 (with a window of ± 3 days) and Weeks 12, 24, and 28 (with windows of ± 7 days). Electronic diary compliance for WOMAC questionnaire completion will be reviewed at all clinic visits from Day 1 to Week 24. It is recommended that the site re-train the subject if the site determines it is necessary after review. Refer to Section 7.3.8 for a schedule of electronic diary and questionnaire completion.

Subjects will complete the WOMAC on the Sponsor-provided electronic device. Subjects will receive notifications reminding them to complete the WOMAC assessment.

Patient Global Assessment of Disease Activity

The Patient Global Assessment is an 11-point [0–10] NRS on which the subjects will rate how they feel their target knee OA is doing, considering all the ways in which their target knee OA may affect them. The NRS will be anchored by descriptors at each end (“Very Good” on the left and “Very Bad” on the right). The Patient Global Assessment will be completed by the subject in the evening (between 5:00 pm and 11:59 pm) remotely on their electronic device 5 days after their Screening Visit (i.e., Screening Visit + 5 days) or up until the day before the Day 1 visit. Baseline Patient Global Assessment of Disease Activity questionnaire should be completed within 9 days prior to Day 1. After Day 1, Patient Global Assessments will be completed by the subject in the evening (between 5:00 pm and 11:59 pm) remotely on their electronic device at Week 4 (with a window of ± 3 days) and Weeks 12, 24, and 28 (with windows of ± 7 days). Electronic diary compliance for Patient Global Assessment questionnaire completion will be reviewed at all clinic visits from Day 1 to Week 24. It is recommended that the site re-train the subject if the site determines it is necessary after review. Refer to Section 7.3.8 for a schedule of electronic diary and questionnaire completion.

Subjects will complete the Patient Global Assessment on the Sponsor-provided electronic device. Subjects will receive notifications reminding them to complete the Patient Global Assessment.

Assessment of NSAID/Acetaminophen Usage

Information about NSAID and acetaminophen usage will be collected as part of concomitant medications at all visits. Subjects will be asked to recall the name, usual total daily dose, and usual number of days taken per week of any oral NSAID or acetaminophen medications during the previous 4 weeks. Subjects will be trained on what medications are NSAIDs at the Screening Visit. Assessment of NSAID/acetaminophen usage on Day 1 prior to study medication administration will be used to establish the subject’s baseline 4-week NSAID/acetaminophen usage and will be documented on the “NSAID/Acetaminophen usage – Day 1” eCRF.

Starting at Week 4 and at all subsequent in-person and phone visits until Week 28 (EOS)/ET, subjects will be asked about their NSAID/acetaminophen usage during the previous 4 weeks. This information (name, usual total daily dose, usual number of days taken per week) will be documented as concomitant medications. The Investigator will then compare the data with the

baseline information obtained on Day 1. If there is a change from baseline, the Investigator will first assess whether the change was clinically relevant and, if clinically relevant, whether it was due to the subject's target knee OA pain. Assessments will be documented on the "NSAID/Acetaminophen Usage (Clinical Visits or Telephone Visits)" eCRF.

7.1.2 STANDARD OF CARE STUDY PROCEDURES

All Investigators are to provide appropriate care to their subjects as they deem necessary; however, additional standard of care study procedures are not required by this protocol.

7.2 LABORATORY PROCEDURES/EVALUATIONS

7.2.1 CLINICAL LABORATORY EVALUATIONS

Samples for clinical laboratory analysis by Medpace Central Laboratories will be collected by a qualified staff member at the Screening Visit and Weeks 4, 12, 24, and 28 (EOS)/ET. Refer to the Laboratory Manual for details about collection of specimens. 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, 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, leukocyte esterase, and occult blood

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

Urine microscopy will be performed if urinalysis urine protein, leukocyte esterase (WBC esterase), occult blood, or nitrite values are out of range, or if the Investigator deems that the microscopy is clinically warranted.

The Investigator or 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 of any result that is outside the normal range for the laboratory, then date and initial the report. The Investigator must report all laboratory results that are BOTH outside the normal range for the laboratory 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.

7.2.2 OTHER ASSAYS OR PROCEDURES

Pregnancy Test

A serum-based pregnancy test will be performed on WOCBP at the Screening Visit and a urine-based pregnancy test will be performed on WOCBP at Day 1. Results from the pregnancy test will be utilized to determine subject eligibility.

WOCBP are women who are not post-menopausal (defined as 12 months with no menses without an alternative medical cause) or permanently surgically sterile (includes hysterectomy, bilateral salpingectomy, and bilateral oophorectomy).

Drug Test

A urine sample for drug testing will be collected at the Screening Visit. The urine drug test will include amphetamine, buprenorphine, cocaine, methadone, opiates, PCP, propoxyphene, barbiturates, benzodiazepine, methaqualone, and tricyclic antidepressants. Results from the drug test will be utilized to determine subject eligibility.

7.2.3 SPECIMEN PREPARATION, HANDLING, AND STORAGE

Refer to the Laboratory Manual for Medpace Central Laboratories.

7.2.4 SPECIMEN SHIPMENT

Refer to the Laboratory Manual for Medpace Central Laboratories.

7.3 STUDY SCHEDULE

7.3.1 PRESCREENING

Prior to entry into a Samumed study for OA of the knee, subjects must have a radiograph taken and read by the Sponsor-specified central reader. This radiograph may qualify the subject for one or more Samumed studies.

Prior to the Screening Visit, the subject's prescreen radiograph report must be reviewed to confirm eligibility for this study.

7.3.2 SCREENING

Screening Visit

The Screening Visit must occur within 7 to 11 days prior to Day 1.

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 and date the ICF. Written informed consent must be provided, signed, and dated 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. After written informed consent is obtained, the subject will be assigned a subject number.

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.

The following procedures and assessments will be performed initially during the Screening Visit:

- Physical examination, including knee examination of both knees and confirmation of target knee
- Review of prescreen radiograph report for target knee
- Documentation of demographic information, including date of birth, sex, race, and ethnicity
- Subject NSAID training
- Documentation of current and past medical history including prior procedures and non-drug therapies, assistive device usage, documentation of current medications, and review of prior medication excluded by the protocol
- Documentation of past treatments for knee OA
- WPI&SS assessment
- Height and weight measurements
- Vital sign measurements (pulse rate, blood pressure, respiratory rate, and temperature)

It is recommended that the results from these evaluations will be compared with inclusion/exclusion criteria to determine subject eligibility. If the subject is confirmed eligible, the following procedures and assessments will be performed:

- Pregnancy test (serum-based) for WOCBP
- Urine drug test
- Venipuncture and collection of samples for clinical laboratory tests
- Electronic diary device provision and subject training for electronic diary and questionnaire completion on the electronic device
- Training on accurate pain reporting and placebo response reduction

Starting on the day of the Screening Visit, after the site visit, subjects will begin completion of daily pain NRS assessments remotely on their electronic devices in the evening (between 5:00 pm and 11:59 pm).

Note: Five days after the Screening Visit (or up until the day before the Day 1 visit), subjects will complete the WOMAC and Patient Global Assessment, in addition to the pain NRS assessment, in the evening (between 5:00 pm and 11:59 pm) remotely on their electronic devices. Refer to Section 7.3.8 for a schedule of electronic diary and questionnaire completion.

7.3.3 RANDOMIZATION

Day 1

This visit must occur within 7 to 11 days of the Screening Visit.

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

- Review of current and past medical history, documentation of current medications, and review of prior medication excluded by the protocol
- WPI&SS assessment
- Review of pain NRS electronic diary compliance from the Screening Visit to Day 1
- Electronic questionnaire review (WOMAC and Patient Global Assessment)
- Assessment of NSAID/acetaminophen pain medication usage to establish/document baseline usage
- Physical examination, including knee examination of both knees
- Vital sign measurements (pulse rate, blood pressure, respiratory rate, and temperature)
- Pregnancy test (urine-based) for WOCBP

Results from the Screening Visit and Day 1 evaluations will be compared with inclusion/exclusion criteria to determine subject eligibility.

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

- IA injection of randomized study medication by the Unblinded Investigator (injector)
- Collection of AE and concomitant procedures/medication data

Note: After the Day 1 site visit, subjects will complete the following in the evening (between 5:00 pm and 11:59 pm) remotely on their electronic devices:

- Daily pain NRS assessments
- WOMAC and Patient Global Assessment questionnaires at Week 4 (with a window of ± 3 days) and Weeks 12, 24, and 28 (with windows of ± 7 days)

Refer to Section 7.3.8 for a schedule of electronic diary and questionnaire completion.

7.3.4 FOLLOW-UP

Week 4

The Week 4 visit should occur on Day 29 (with a window of ± 3 days).

The following procedures and assessments will be performed at these visits:

- Collection of AE and concomitant procedures/therapies/medication data
- Assessment of NSAID/acetaminophen usage
- Review of pain NRS, WOMAC, and Patient Global Assessment electronic diary compliance
- Physical examination, including knee examination of both knees
- Vital sign measurements (pulse rate, blood pressure, respiratory rate, and temperature)
- Venipuncture and collection of samples for clinical laboratory tests

Weeks 8, 16, and 20 (Phone Visits)

Sites will contact subjects for phone visits on Days 57, 113, and 141 (with windows of ± 7 days). The following assessments will be performed at each visit:

- Collection of AE and concomitant procedures/therapies/medication data
- Assessment of NSAID/acetaminophen usage

Weeks 12 and 24

The Week 12 visit should occur on Day 85 (with a window of ± 7 days) and the Week 24 visit should occur on Day 169 (with a window of ± 7 days).

The following procedures and assessments will be performed at these visits:

- Collection of AE and concomitant procedures/therapies/medication data
- Assessment of NSAID/acetaminophen usage
- Review of pain NRS, WOMAC, and Patient Global Assessment electronic diary compliance
- Physical examination, including knee examination of both knees
- Vital sign measurements (pulse rate, blood pressure, respiratory rate, and temperature)
- Venipuncture and collection of samples for clinical laboratory tests

7.3.5 FINAL STUDY VISIT

Week 28 End of Study

This final study visit should occur on Day 197 with a window of ± 7 days.

The following procedures and assessments will be performed at Week 28 (EOS):

- Collection of AE and concomitant procedures/therapies/medication data
- Review of medical history
- Assessment of NSAID/acetaminophen usage
- Physical examination, including knee examination of both knees
- Weight measurement
- Vital sign measurements (pulse rate, blood pressure, respiratory rate, and temperature)
- Venipuncture and collection of samples for clinical laboratory tests

7.3.6 EARLY TERMINATION VISIT

If possible, the following procedures and assessments should be performed within 14 days of subject premature withdrawal or termination.

- Collection of AE and concomitant procedures/therapies/medication data

- Review of medical history
- Assessment of NSAID/acetaminophen usage
- Physical examination, including knee examination of both knees
- Weight measurement
- Vital sign measurements (pulse rate, blood pressure, respiratory rate, and temperature)
- Venipuncture and collection of samples for clinical laboratory tests

7.3.7 SCHEDULE OF EVENTS TABLE

Procedure	**Screening Visit**[a] (Days -11 to -7)	**Day 1**[b]	**Week 4** (Day 29 ±3 days)	**Weeks 8, 16, 20**[c] (±7 days) (Phone Visits)	**Week 12** (Day 85 ±7 days)	**Week 24** (Day 169 ±7 days)	**Week 28 (EOS)** (Day 197 ±7 days) / **ET**
Informed consent	X						
Inclusion & exclusion criteria	X	X					
Demographics	X						
Medical history	X	X					X[d]
Current and prior procedures/medications	X	X					
Past treatments for knee OA pain	X						
Subject NSAID training	X						
Investigator assessment of NSAID/ Acetaminophen usage		X	X	X	X	X	X
Serum pregnancy test[e]	X						
Urine pregnancy test[e]		X					
Urine drug test	X						
WPI&SS	X	X					
Review prescreen radiograph report	X						
Physical examination	X	X	X		X	X	X
Knee examination	X	X	X		X	X	X
Selection of target knee	X						
Height	X						
Weight	X						X
Vital signs	X	X	X		X	X	X
Clinical laboratory sampling	X		X		X	X	X
Electronic diary provision and questionnaire training	X[f]						
Review Pain NRS compliance		X[g]	X		X	X	
Review WOMAC compliance		X[h]	X		X	X	
Review Patient Global Assessment compliance		X	X		X	X	
Randomization		X					
Intra-articular injection		X					
AEs and concomitant procedures/medications		X	X	X	X	X	X

[a] The screening period is a minimum of 7 days and a maximum of 11 days. The Screening Visit should only occur after review of the prescreen radiograph report for eligibility in this study.
[b] At Day 1, all procedures should be performed prior to study medication injection except for collection of AE and concomitant procedures/medication data.
[c] Phone visits should take place on Days 57, 113, and 141 (± 7 days for all visits).
[d] Review medical history to capture End Date(s), if applicable, of any ongoing medical history(ies) collected at the Screening Visit and Day 1.
[e] Serum and urine pregnancy tests are to be performed on WOCBP only.
[f] Electronic diary devices will be provided to subjects at the Screening Visit; subject electronic diary and questionnaire training including accurate pain reporting and placebo response reduction training will be conducted at the Screening Visit. Accurate pain reporting and placebo response reduction training is recommended at Day 1 and Weeks 4, 12, and 24.
[g] Electronic diary compliance and assessment of target and non-target knee pain scores for daily pain NRS over the screening period will be reviewed at Day 1 prior to randomization to determine subject eligibility.
[h] WOMAC questionnaire will be reviewed at Day 1 prior to randomization to determine subject eligibility.

7.3.8 SCHEDULE OF ELECTRONIC DIARY AND QUESTIONNAIRE COMPLETION TABLE

	WOMAC and Patient Global Assessment	**Daily pain NRS**
Study Week/Day	WOMAC and Patient Global Assessment will be completed by subjects 5 days after the Screening Visit (or up until the day before the Day 1 visit), at Week 4 (with a window of ± 3 days), and at Weeks 12, 24, and 28 (with a window of ± 7 days) in the evening (between 5:00 pm and 11:59 pm local time) remotely on their electronic devices, as outlined below; ranges shown are inclusive.	Pain NRS should be completed daily starting after the Screening Visit. Subjects will complete the diary in the evening (between 5:00 pm and 11:59 pm local time) remotely on their electronic devices. Diary completion should occur every day including on study visit days.
Screening Visit		
		Complete daily starting on the same day of the Screening Visit (after the visit); pain NRS assessments are to be completed for each knee.
5 days after the Screening	Baseline WOMAC and Patient Global Assessment questionnaires (or up until the day before the Day 1 visit)	
Day 1	N/A	Starting on the same day of Day 1 (after the visit), pain NRS assessments are to be completed for the target knee only. Complete daily.
Week 4 (Day 29)	Complete between Day 26 and 32	
Week 12 (Day 85)	Complete between Day 78 and 92	
Week 24 (Day 169)	Complete between Day 162 and 176	
Week 28 (Day 197)	Complete between Day 190 and 204	

7.4 JUSTIFICATION FOR SENSITIVE PROCEDURES

Not applicable for this study.

7.5 CONCOMITANT MEDICATIONS, TREATMENTS, AND PROCEDURES

Details regarding the name, indication, route of administration, dose, and frequency of all medications taken within 30 days prior to the Screening Visit through Week 28 (EOS)/ET will be recorded in the "Prior and Concomitant Medications" eCRF. "All medications" should include prescription, over-the-counter, supplements, as well as herbal or alternative medications.

Procedures or non-drug therapies that are ongoing, new, or modified at or after the Screening Visits must be recorded on the "Procedures and Non-Drug Therapies" eCRF.

AE assessments should include consideration of any new or modified concomitant therapies administered to the subject.

7.5.1 PRECAUTIONARY MEDICATIONS, TREATMENTS, AND PROCEDURES

Not applicable to this study.

7.6 PROHIBITED MEDICATIONS, TREATMENTS, AND PROCEDURES

Prohibited Concomitant Medications and Procedures:

- Any IA injection, including glucocorticoids, hyaluronic acid derivatives, PRP, stem cell therapies, or other agents with therapeutic intent, into either knee is prohibited while the subject is on study; IA injection of glucocorticoids, hyaluronic acid derivatives, PRP, stem cells, or other therapeutic agents into joints other than the knee is allowed.
- The following medications are prohibited while the subject is on study:
  - Opioids; short-term use of opioids as part of anesthesia or procedural sedation during the study period is permitted
  - Centrally acting analgesics (e.g., duloxetine) (refer to Appendix 2)
  - Topical local anesthetic agents; short-term use as part of anesthesia, including for study injections during the study period is permitted
  - Other anticonvulsants not listed in Appendix 2
  - Systemic glucocorticoids ≥ 10 mg of prednisone per day or the equivalent; epidural, inhaled, intranasal, and topical glucocorticoids are permitted
  - Drugs screened to assess eligibility, unless clinically indicated and allowed by the protocol: amphetamine, buprenorphine, cocaine, methadone, opiates, PCP, propoxyphene, barbiturates, benzodiazepine, methaqualone, and tricyclic antidepressants
- Electrotherapy (refer to Appendix 2), acupuncture, formalized physical therapy (i.e., prescribed by a medical professional), therapeutic ultrasound, and/or chiropractic treatments for knee OA are prohibited while the subject is on study.

- Elective surgery, including arthroscopy, is prohibited while the subject is on the study. Non-surgical invasive procedures conducted for a diagnostic or therapeutic purpose that are scheduled during the study period are not prohibited. Examples include, but are not limited to endoscopy, colonoscopy, bronchoscopy, cystoscopy, radiologic procedures such as coronary artery catheterization with or without intervention, and non-surgical cosmetic procedures such as Botox or other cosmetic injections.
- Subjects are prohibited from participating in any other clinical research trial that includes the receipt of an IP or any experimental therapeutic procedure. Subjects are also prohibited from participating in any observational research trial while on study.

The Investigator should notify the Samumed Medical Monitor immediately if any prohibited therapies are required to ensure subject safety.

7.7 PROPHYLACTIC MEDICATIONS, TREATMENTS, AND PROCEDURES

Not applicable to this study.

7.8 RESCUE MEDICATIONS, TREATMENTS, AND PROCEDURES

Subjects are allowed to remain on their stable regimen of NSAIDs/acetaminophen during this study and may change their usage as needed for pain management, including for the rescue of knee pain.

7.9 PARTICIPANT ACCESS TO STUDY AGENT AT STUDY CLOSURE

Not applicable to this study.

8. ASSESSMENT OF SAFETY

8.1 SPECIFICATION OF SAFETY PARAMETERS

Safety assessments include physical examinations, vital signs, clinical laboratory tests, collection of AEs and SAEs, concomitant medications, and general medical evaluations.

8.1.1 DEFINITION OF ADVERSE EVENTS (AE)

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

An AE is any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an 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).

Whenever possible, it is preferable to record a diagnosis as the AE term rather than a series of symptoms relating to a diagnosis. Fluctuations of pre-existing conditions, including the disease under study that does not represent a clinically significant exacerbation or worsening, need not be considered AEs. 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).

In this protocol, signs and symptoms of exacerbation or worsening of target knee OA will be captured in the context of efficacy assessments and recorded on specific pages of the eCRF or electronic diary. Anticipated fluctuations or anticipated deterioration (in the opinion of the Investigator) of the underlying disease (target knee OA) will not be considered as AEs nor captured on the AE page of the eCRF.

8.1.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

According to the ICH-GCP Guidelines (E6), an SAE is any untoward medical occurrence during the course of a clinical investigation that is characterized by one or more of the following:

- Results in death
- Is life threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- 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 (ER), 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.

The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.

“Inpatient hospitalization” is clarified as hospitalization lasting ≥ 24 hours. Admission to the hospital or prolongation of hospitalization qualifies as an SAE only if it is the result of an AE.

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.

8.1.3 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

An AE observed during the conduct of a study should be considered an Unanticipated Problem (UP) involving risk to human subjects, and be reported to the IRB, only if it was unexpected, serious, and would have implications for the conduct of the study (e.g., requiring a significant, and usually safety-related, change in the protocol, such as revising inclusion/exclusion criteria or including a new monitoring requirement, informed consent, or IB). The occurrence of such an event would suggest that the research places study participants or others at a greater risk of harm.

FDA recommends that there be careful consideration of whether an AE is a UP that must be reported to IRBs. In summary, FDA believes that only the following AEs should be considered

as UPs that must be reported to the IRB:

- A single occurrence of a serious, unexpected event that is uncommon and strongly associated with drug exposure (such as angioedema, agranulocytosis, hepatic injury, or Stevens-Johnson syndrome)
- A single occurrence, or more often a small number of occurrences, of a serious, unexpected event that is not commonly associated with drug exposure, but uncommon in the study population (e.g., tendon rupture, progressive multifocal leukoencephalopathy)
- An AE that is described or addressed in the IB, protocol, or informed consent documents, but occurs at a specificity or severity that is inconsistent with prior observations
- An SAE that is described or addressed in the IB, protocol, or informed consent documents, but for which the rate of occurrence in the study represents a clinically significant increase in the expected rate of occurrence (ordinarily, reporting would only be triggered if there were a credible baseline rate for comparison)
- Any other AE or safety finding (e.g., based on animal or epidemiologic data) that would cause the sponsor to modify the IB, study protocol, or informed consent documents, or would prompt other action by the IRB to ensure the protection of human subjects

8.2 CLASSIFICATION OF AN ADVERSE EVENT

8.2.1 SEVERITY OF EVENT

The Investigator will assess AEs for severity utilizing the CDISC AESEV, which classifies AEs as mild, moderate, or severe (Table 1).

Table 1: CDISC Definitions of Adverse Event Severity

CDISC Submission Value	CDISC Definition
MILD	A type of adverse event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
MODERATE	A type of adverse event that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
SEVERE	A type of adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

8.2.2 RELATIONSHIP TO STUDY AGENT

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

Not Related

The AE is not related if (1) exposure to the study medication 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, medical condition, or product not associated with the study medication or the study injection.

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 study medication or study injection (i.e., there are no facts [evidence] or arguments to suggest a causal relationship), or the AE is considered possibly related to another event, medical condition, or product not associated with the study medication.

Possibly Related

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

Probably Related

Exposure to study medication or administration of the study injection and AE are probably related if (1) the study medication or study injection and AE are considered reasonably related in time **and** (2) the study medication or study injection is more likely than other causes to be responsible for the AE **or** is the most likely cause of the AE.

8.2.3 EXPECTEDNESS

The Sponsor will be responsible for determining whether an AE/SAE is expected or unexpected. An AE/SAE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study agent in the IB or is not listed in the IB at the specificity or severity that has been observed.

8.3 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

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

AEs will be followed until the subject's last visit or resolution, whichever comes first. For subjects who discontinue from the study within 30 days of their dose of study medication, AEs that are ongoing at the subject's last visit will be followed for 30 days after administration of the dose or until resolution, whichever comes first. Resolution is defined as the return to baseline status or stabilization of the condition. SAEs and selected AEs identified by the Investigator or the Sponsor to warrant further follow-up that are ongoing at a subject's last visit will be followed until resolution.

8.4 REPORTING PROCEDURES

8.4.1 ADVERSE EVENT REPORTING

The Investigator is responsible for reporting AEs to the Sponsor via the eCRF and to the IRB according to the protocol and 21 Code of Federal Regulations (CFR) Parts 50, 56, and 312. The Investigator is responsible for ensuring accurate AE information is reviewed and recorded in the

subject source and the AE eCRF in a timely manner. The Sponsor is responsible for submitting reports of AEs associated with the use of study medication that are both serious and unexpected to the FDA according to 21 CFR 312.32. All Investigators participating in ongoing studies with the study medication will receive copies of these reports from the Sponsor for prompt submission to their IRB/EC according to their institution's requirements.

8.4.2 SERIOUS ADVERSE EVENT REPORTING

The Investigator is responsible for reporting SAEs to the Sponsor and IRB according to 21 CFR Parts 50, 56, and 312.

Using the SAE Report Form, SAEs must be reported within 24 hours of study site personnel's knowledge of the event, regardless of the Investigator assessment of the relationship of the event to study drug. The Investigator should review the SAE information and sign the SAE report, and the Investigator or designee should submit the SAE report to the Samumed Study SAE email address: sae@samumed.com or FAX: +1 858 408 4470.

The initial report should include, at a minimum, the following:

- Investigator name
- Subject number, sex, and age
- Details of study drug administration
- The date of the report
- A description of the SAE (including event term and serious criteria)
- Causal relationship to the study drug
- If the subject died, the report should include the cause of death as the event term (with fatal outcome) and whether or not the death was related to study drug, as well as the autopsy findings if available

Follow-up information must be detailed in a follow-up SAE report and reported to the Samumed Study SAE email address or fax number 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 questions regarding SAE reporting is provided in Table 2.

Table 2: Sponsor Contact Information for Questions on SAE Reporting

Primary Contact	**Alternative Contact**
Roza Amin, MD, Medical Reviewer, Drug Safety and Pharmacovigilance	Sherry Beckman, Scientist, Drug Safety and Pharmacovigilance
Cellular: (858) 732-2386	Cellular: (858) 500-6021
Email: roza@samumed.com	Email: sherryb@samumed.com

8.4.3 UNANTICIPATED PROBLEM REPORTING

Incidents or events that meet the criteria for UP (see Section 8.1.3) require the creation and completion of an UP report. It is the site Investigator's responsibility to report UPs to their IRB and to the Sponsor. The UP report will include the following information:

- Protocol identifying information: protocol title and number, Investigator's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome; and
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are SAEs will be reported to the Sponsor and the IRB within 24 hours of the Investigator becoming aware of the event on the SAE report form.
- Any other UP will be reported to the IRB and to the Sponsor within the IRB-required reporting timeframe.

8.4.4 EVENTS OF SPECIAL INTEREST

Not applicable to this study.

8.4.5 REPORTING OF PREGNANCY

If the subject or partner of the subject becomes pregnant, the pregnancy is to be followed until the outcome is known. An IRB-approved Pregnant Subject or Pregnant Partner Data Release Form should be completed by the subject or the subject's pregnant partner in order to obtain consent to follow the progress of the pregnancy and birth, and the health of the infant.

Any pregnancy will be collected on a Samumed Pregnancy Report Form. Information will be collected for any pregnancy in a female subject or the pregnant female partner of a male subject (if consenting), which occurs during the study, including perinatal and neonatal outcome. Infants resulting from such pregnancies should be followed for a minimum of 12 weeks.

8.5 STUDY HALTING RULES

Not applicable to this study.

8.6 SAFETY OVERSIGHT

Clinical safety oversight will be performed by centralized review conducted by Medical Monitors per the Medical Monitoring Plan. In addition, on-site review will be conducted by Clinical Research Associates.

9. CLINICAL MONITORING

All aspects of the study will be monitored by the Sponsor or the Sponsor's designees with respect to current 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.

Clinical monitoring will be performed per the Clinical Monitoring Plan. Clinical monitors will periodically evaluate the progress of the study, including the verification of appropriate consent

form 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.

Centralized data monitoring will be performed per the Centralized Data Monitoring Plan in order to periodically evaluate study progress and risks. A regular report of risks will be utilized together with centralized data monitoring to direct overall monitoring focus and activities to the areas of greatest risk which have the most potential to impact subject safety and data quality.

The accuracy of the data will be verified by reviewing the documents described in Section 11.

10. STATISTICAL CONSIDERATIONS

10.1 STATISTICAL AND ANALYTICAL PLANS

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 database lock.

10.2 STATISTICAL HYPOTHESES

The statistical hypotheses being tested in this study include:

- The least squares estimate of improvement from baseline in weekly average of daily pain NRS at Week 12 is greater for subjects who received 0.07 mg SM04690 compared to placebo.
- The least squares estimate of improvement from baseline in weekly average of daily pain NRS at Week 24 is greater for subjects who received 0.07 mg SM04690 compared to placebo.
- The least squares estimate of improvement from baseline in WOMAC Function at Week 12 is greater for subjects who received 0.07 mg SM04690 compared to placebo.
- The least squares estimate of improvement from baseline in WOMAC Function at Week 24 is greater for subjects who received 0.07 mg SM04690 compared to placebo.
- The least squares estimate of improvement from baseline in Patient Global Assessment at Week 12 is greater for subjects who received 0.07 mg SM04690 compared to placebo.
- The least squares estimate of improvement from baseline in Patient Global Assessment at Week 24 is greater for subjects who received 0.07 mg SM04690 compared to placebo.

The familywise error rate will be controlled in the strong sense using the closed, fixed sequence testing method (Dmitrienko, Tamhane et al. 2010). All hypothesis tests will be evaluated in a pre-specified sequential order that will be documented in the SAP.

10.3 ANALYSIS DATASETS

Full Analysis Set (FAS): All subjects who are randomized and receive a study injection. The FAS is used to describe the analysis set which is as complete as possible and as close as possible to the intent-to-treat ideal of including all randomized subjects.

Per-Protocol Analysis Set (PPAS): FAS subjects who complete the study and do not have any major protocol deviations.

Safety Analysis Set (SAS): All subjects who receive a study injection.

10.4 DESCRIPTION OF STATISTICAL METHODS

10.4.1 GENERAL APPROACH

For continuous variables, the 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.

10.4.2 ANALYSIS OF THE PRIMARY ENDPOINT

Change over time in weekly average of daily pain NRS will be characterized using a mixed-effects model for repeated measures (MMRM) in order to estimate change from baseline with treatment group, week, treatment × week interaction and baseline value as covariates. The model will be evaluated at Week 12. Unadjusted 95% confidence intervals and *P* values will be reported. The potential confounding effect of change in NSAID/acetaminophen usage on the treatment effect will be considered for sensitivity analysis.

10.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

Change over time in secondary endpoints will be characterized using MMRM in order to estimate change from baseline with treatment group, week, treatment × week interaction and baseline value as covariates. The model will be evaluated for weekly average of daily pain NRS at Week 24 and WOMAC Function and Patient Global Assessment at Weeks 12 and 24, as well as change in NSAID/acetaminophen usage. Unadjusted 95% confidence intervals and *P* values will be reported. The potential confounding effect of change in NSAID/acetaminophen usage on the treatment effect will be considered for sensitivity analysis.

10.4.4 SAFETY ANALYSES

Safety analyses will be performed on subjects who receive a study injection. 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, seriousness, severity, and relationship of AEs and by changes in clinical laboratory parameters and vital signs, relative to baseline.

10.4.5 OTHER ENDPOINTS

Change over time in WOMAC Pain and WOMAC Total will be characterized using MMRM in order to estimate change from baseline with treatment group, week, treatment × week interaction and baseline value as covariates. The models will be evaluated at Weeks 12 and 24. Unadjusted 95% confidence intervals and *P* values will be reported.

10.4.6 BASELINE DESCRIPTIVE STATISTICS

Baseline is defined as the last value recorded for any given parameter prior to study injection unless otherwise specified. If a subject never received a study injection, baseline is defined as the last value recorded prior to study termination.

Baseline descriptive statistics will include age, sex, race, height, weight, BMI, mJSW, KL grade, and the presence of symptomatic and radiographic OA.

10.4.7 PLANNED INTERIM ANALYSES

Not applicable to this study.

10.4.7.1 SAFETY REVIEW

Medical monitoring of study safety assessment data will be performed during periodic safety reviews detailed in the Medical Monitoring Plan.

10.4.7.2 EFFICACY REVIEW

Not applicable to this study.

10.4.8 EXPLORATORY ANALYSES

Not applicable to this study.

10.4.9 SUB-GROUP ANALYSES

Efficacy analyses described in Sections 10.4.2 and 10.4.3 will be further analyzed with subjects having a baseline mJSW within 1.5 to 4 mm inclusive.

10.5 SAMPLE SIZE

A sample size of approximately 726 subjects was selected for this study in order to yield 325 evaluable subjects per treatment group assuming 10% dropout.

One-thousand Monte Carlo simulations generated baseline and follow-up data from a bivariate normal distribution for each treatment group, and estimated the least squares difference between treatment and placebo in an outcome's change using a baseline-adjusted ANCOVA. The proportion of statistically significant results at $\alpha = 0.05$ was estimated as the approximate power for a sample size of 325 subjects per group.

The following assumptions were made based upon observed data in the SM04690-OA-02 and SM04690-OA-04 studies:

- For weekly average of daily pain NRS, assuming a baseline mean (SD) of 6.0 (1.5), follow-up mean (SD) of 3.0 (3.0) for SM04690 and 3.8 (3.0) for placebo (presumed treatment difference -0.8), and a baseline to follow-up correlation of 0.25, power is estimated to be 93.5%.
- For WOMAC Function, assuming a baseline mean (SD) of 60 (14), follow-up mean (SD) of 30 (29) for SM04690 and 37.5 (29) for placebo (presumed treatment difference -7.5), and a baseline to follow-up correlation of 0.25, power is estimated to be 92.0%.
- For Patient Global Assessment, assuming a baseline mean (SD) of 55 (20), follow-up mean (SD) of 35 (27) for SM04690 and 42.5 (27) for placebo (presumed treatment

difference -7.5), and a baseline to follow-up correlation of 0.25, power is estimated to be 95.3%.

10.6 MEASURES TO MINIMIZE BIAS

10.6.1 BLINDING PROCEDURES

This is a double-blind study. Study medication will be provided to the investigational center, which must identify unblinded personnel who are able to prepare and perform the injection of study medication. Study personnel administering or preparing study medication must minimize any contact with the subject following the injection and may not perform any study assessments throughout the duration of the study. Each site will be required to document a blinding plan that identifies the blinded and unblinded personnel at the investigational center and describes how the study blind will be maintained.

Subjects will be assigned a subject number at the Screening Visit. On Day 1, eligible subjects will be randomized via the Medidata Rave database. Upon randomization of a subject, an email with the subject's corresponding kit number will be sent from Medidata (*Medidata-Notification@mdsol.com*) to the investigational staff member designated to dispense study medication. Subjects will be randomized 1:1 (0.07 mg active per 2 mL injection: 2 mL placebo) to each treatment group using a permuted block design. Specific information regarding the use of Medidata Rave Randomization and Trial Supply Management (RTSM) to store and implement the permuted block design will be detailed within the SAP.

10.6.2 EVALUATION OF SUCCESS OF BLINDING

Not applicable to this study.

10.6.3 BREAKING THE STUDY BLIND/PARTICIPANT CODE

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 Rave RTSM 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 blinded site users will have access roles to Medidata Rave RTSM that will allow treatment assignment unblinding.

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

In circumstances when the blind is unintentionally broken at the investigational center, the breaking of the blind should be reported to the designated Sponsor-unblinded Clinical Research

Associate as soon as possible after breaking the blind for a subject.

11. SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

The Investigator must maintain required records for all study subjects. Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data for this study will be recorded in the subject's source documents and on the eCRFs, unless otherwise noted. 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 (e.g., electronic clinical outcomes assessment [eCOA] questionnaires). The source documents should include detailed notes on the following:

- The oral and written communication with the subject regarding the study (including the risks and benefits of the study), both at the site and by phone, and the date 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
- All AEs
- The subject's exposure to any concomitant therapy (including start and stop dates, route of administration, and dosage)

eCOA questionnaire data is considered electronic source data created as subjects enter responses into the electronic device. Once submitted, responses cannot be changed or modified by the subject or any other user. There is no source data verification required for such data as is it directly attributable to the subject once electronically stored. Therefore, eCOA questionnaire results are not transferred to eCRFs.

12. QUALITY ASSURANCE AND QUALITY CONTROL

This study will be organized, performed, and reported in compliance with the protocol, SOPs, site/Investigator training, and applicable regulations and guidelines. Clinical Investigator sites will be trained at the Investigator Meeting and/or individual, on-site visits. All aspects of the study will be monitored carefully by the Sponsor's designees with respect to current GCP and SOPs for compliance with applicable government regulations. It is the responsibility of the Investigator to provide all study records, including case report forms (CRFs) and source documents, among other records, for review and inspection by the clinical monitor and regulatory authorities, as needed.

The Integrated Quality and Risk Management Plan (IQRMP) details the trial specific quality

management plans to indicate how risks are mitigated and data quality is addressed in the clinical trial.

13. ETHICS/PROTECTION OF HUMAN SUBJECTS

13.1 ETHICAL STANDARD

The study will be conducted in accordance with the Declaration of Helsinki (1964), including all amendments up to and including the Brazil revision (2013). The Investigator will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Subjects of Research set forth in US 21 CFR Part 50, 21 CFR Part 56, and/or the ICH-GCP E6 (R2).

13.2 INSTITUTIONAL REVIEW BOARD

The Investigator agrees to provide the IRB/EC with all appropriate material, including a copy of the 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. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether previously consented participants need to be re-consented. The Sponsor ensures that the IRB/EC complies with the requirements set forth in US 21 CFR Part 56.

13.3 INFORMED CONSENT PROCESS

13.3.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms describing in detail the study procedures and risks will be given to the potential participant and written documentation of informed consent is required prior to starting any screening evaluations or other study-related procedures.

13.3.2 CONSENT PROCEDURES AND DOCUMENTATION

The informed consent and consent process should be in accordance with the current Declaration of Helsinki, ICH, GCP, federal, state, and local regulations. 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 and date the ICF. Written informed consent must be provided (signed and dated) by the potential study participant prior to initiation of any screening evaluations or other study-related procedures. A copy of the ICF will be given to the participants for their records. The signature, date, and the name of the individual at the site who obtained the informed consent will be recorded.

13.4 PARTICIPANT AND DATA 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 current 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 or designee 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.

13.4.1 RESEARCH USE OF STORED HUMAN SAMPLES, SPECIMENS, OR DATA

Not applicable to this study.

13.5 FUTURE USE OF STORED SPECIMENS

Not applicable to this study.

14. DATA HANDLING AND RECORD KEEPING

14.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

As defined by ICH guidelines, the CRF is a printed, optical, or electronic document designed to record all protocol-required information to be reported to the Sponsor on each study subject.

Data required by the protocol will either be collected within eCRFs of the study-specific Medidata Rave database or provided directly to the Sponsor via data transfers. Medidata Rave is a validated electronic data capture (EDC) system fully compliant with regulatory expectations for software developers and service providers within the global regulatory environment, including but not limited to ICH-GCP E6 (R2) and US 21 CFR Parts 312, 812, and 11. Data to

be transferred external to Rave may include eCOA questionnaires, central laboratory data, and imaging results.

Data collection on the eCRF will follow the instructions described in the eCRF Completion Guidelines. The Investigator has ultimate responsibility for the collection and reporting of all clinical data entered on the eCRF. The Investigator or designee as identified on Form FDA 1572 will electronically sign the completed eCRF to attest to its accuracy, authenticity, and completeness. Copies of the completed eCRFs will be retained by each investigational center as well as the Sponsor.

Clinical data management activities will be conducted by the Sponsor as described in the study-specific Data Management Plan.

14.2 STUDY RECORDS RETENTION

During this study, the 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 IP or entered as a control in the investigation. CRFs 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, and electronically signed and dated in EDC by a qualified physician who is an Investigator on the study once all data is considered final. During this study, the Investigator must retain 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 regulations. 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.

14.3 PROTOCOL DEVIATIONS

The Investigator and study staff will apply due diligence to avoid protocol deviations. If protocol deviations do occur, the Investigator or study staff must report them to the local IRB/EC per their guidelines.

14.4 PUBLICATION AND DATA SHARING POLICY

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 Investigator(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).

15. STUDY ADMINISTRATION

15.1 STUDY LEADERSHIP

The study will be led and conducted by Samumed, LLC.

15.2 KEY ROLES

Medical monitor	Christian Bulcao, MD - Sr. Study Physician Samumed, LLC 9381 Judicial Dr. San Diego, CA 92121 (858) 365-0238 *christian@samumed.com*
Back-up medical monitor	Ismail Simsek, MD - Medical Director Samumed, LLC 9381 Judicial Dr. San Diego, CA 92121 (858) 926-2968 *ismail@samumed.com*
Central radiology reader	Medical Metrics, Inc. (MMI) 2121 Sage Road, Suite 300 Houston, Texas 77056 (713) 850-7500
Electronic clinical outcomes assessment (eCOA)	Medidata 350 Hudson Street 9th Floor New York, New York 10014 (212) 918-1800
Central laboratory	Medpace Central Laboratories 5365 Medpace Way Cincinnati, Ohio 45227 (800) 749-1737

16. LITERATURE REFERENCES

Altman, R., E. Asch, D. Bloch, G. Bole, D. Borenstein, K. Brandt, W. Christy, T. D. Cooke, R. Greenwald, M. Hochberg and et al. (1986). "Development of criteria for the classification and reporting of osteoarthritis. Classification of osteoarthritis of the knee. Diagnostic and Therapeutic Criteria Committee of the American Rheumatism Association." Arthritis Rheum **29**(8): 1039-1049.

Clauw, D. J. (2014). "Fibromyalgia: a clinical review." JAMA **311**(15): 1547-1555.

Dmitrienko, A., A. C. Tamhane and F. Bretz (2010). Multiple testing problems in pharmaceutical statistics. Boca Raton, FL, Chapman & Hall/CRC.

Dougados, M. and M. C. Hochberg (2011). Management of osteoarthritis. Rheumatology. M. C. Hochberg, A. J. Silman, J. S. Smolen, M. E. Weinblatt and M. H. Weisman. PA, USA, Elsevier**:** 1793-1799.

Gelse, K., A. B. Ekici, F. Cipa, B. Swoboda, H. D. Carl, A. Olk, F. F. Hennig and P. Klinger (2012). "Molecular differentiation between osteophytic and articular cartilage--clues for a transient and permanent chondrocyte phenotype." Osteoarthritis Cartilage **20**(2): 162-171.

Hochberg, M. C., R. D. Altman, K. T. April, M. Benkhalti, G. Guyatt, J. McGowan, T. Towheed, V. Welch, G. Wells, P. Tugwell and R. American College of (2012). "American College of Rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee." Arthritis Care Res (Hoboken) **64**(4): 465-474.

Lawrence, R. C., D. T. Felson, C. G. Helmick, L. M. Arnold, H. Choi, R. A. Deyo, S. Gabriel, R. Hirsch, M. C. Hochberg, G. G. Hunder, J. M. Jordan, J. N. Katz, H. M. Kremers, F. Wolfe and W. National Arthritis Data (2008). "Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part II." Arthritis Rheum **58**(1): 26-35.

Nevitt, M. C., D. T. Felson and G. Lester (2006). " *A Knee Health Study.*" "The Osteoarthritis Initiative.".

Wu, L., X. Huang, L. Li, H. Huang, R. Xu and W. Luyten (2012). "Insights on biology and pathology of HIF-1alpha/-2alpha, TGFbeta/BMP, Wnt/beta-catenin, and NF-kappaB pathways in osteoarthritis." Curr Pharm Des **18**(22): 3293-3312.

APPENDIX

Appendix 1. American College of Rheumatology Clinical and Radiographic Criteria for Classification of Osteoarthritis of the Knee

Per American College of Rheumatology (ACR) clinical and radiographic classification criteria (Altman, Asch et al. 1986), the presence of all 3 of the following items classifies knee OA in patients:

1. Knee pain,
2. Osteophytes, AND
3. At least 1 of 3:
    - Age > 50 years
    - Morning stiffness < 30 minutes duration
    - Crepitus on active motion

Appendix 2. Prohibited Concomitant Medications and Procedures (Supplement)

1) Excluded and prohibited centrally acting analgesics include, but are not limited to, the following:
   - Gabapentin (Neurontin, Horizant, Gaberone, Gralise, Fusepaq Fanatrex)
   - Pregabalin (Lyrica)
   - Carbamazepine (Tegretol, Carbatrol, Epitol, Equetrol)
   - Duloxetine (Cymbalta, Irenka)
   - Milnacipran (Savella)
   - Orphenadrine Citrate (Norflex, Orfro, Orphenate, Mio-Rel, Antiflex)
   - Amitriptyline (Elavil, Vanatrip)
   - Clomipramine (Anafranil)
   - Nortriptyline (Aventyl, Pamelor)
   - Desipramine (Norpramin)
   - Imipramine (Tofranil)
   - Doxepin (Prudoxin, Sinequan, Zonalon, Silenor)
   - Ketamine (Ketalar)
   - Sodium Oxybate (Xyrem, GHB)

2) Other non-listed anticonvulsants are also prohibited.

3) Excluded and prohibited electrotherapy treatments include, but are not limited to, the following:
   - Diathermy
   - TENS
   - NMES
   - Interferential therapy
   - Shortwave therapy
   - Iontophoresis
   - LASER

Appendix 3. Amendments

AMENDMENT 03 VERSION 00 SUMMARY OF CHANGES

Study Title: A Phase 3, 28-Week, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of a Single Injection of SM04690 Injected in the Target Knee Joint of Moderately to Severely Symptomatic Osteoarthritis Subjects

Purpose: The purpose of this amendment is to refine the study design, including revising inclusion/exclusion criteria

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

Change	Sections Affected	Rationale
Protocol Amendment 03 Version 00 has been added on the title page.	Title Page	Change was made to capture the dates of previous and current protocol versions
Protocol date and version have been updated as applicable.	All	Change was made to reflect current protocol amendment
Inclusion criterion #4 was revised: "Radiographic disease Stage 2 or 3 in target knee within ~~12~~ *24* weeks of the Screening Visit according to the Kellgren-Lawrence (KL) grading of knee OA as assessed by independent central readers"	Sections 1.1 and 5.15.2	Change was made to refine the study design and allow use of prescreening radiographs from up to 24 weeks before the Screening Visit
Exclusion criterion #4 was revised: "Significant malalignment of anatomical axis (medial angle formed by the femur and tibia) of the target knee (varus > 10°, valgus > 10°) by radiograph within ~~12~~ *24* weeks of the Screening Visit as assessed by independent central readers"	Sections 1.1 and 5.2	Change was made to refine the study design and allow use of prescreening radiographs from up to 24 weeks before the Screening Visit
Edits to exclusion criterion #10 and Section 7.6 Prohibited Medications, Treatments, and Procedures were made to clarify that *formalized* physical therapy (i.e., prescribed by a medical professional) is excluded within 4 weeks prior to Day 1 and is prohibited while the subject is on the study.	Sections 1.1, 5.2, and 7.6	Change was made to clarify an exclusion criterion and prohibited therapy
The following was added in Section 5.4.2 Subject Rescreening: "Target knee selection may not be changed at rescreen *without the permission of the Medical Monitor*."	Section 5.4.2	Change was made to refine study design and allow change in target knee selection at rescreen only with permission of the Medical Monitor
Edits were made to Section 5.7 Premature Termination or Suspension of Study.	Section 5.7	Changes were made to reflect that the Sponsor (not the Investigator or IRB/EC) reserves the right to prematurely terminate the study
Edits were made to Section 6.1.3 Product Storage and Stability. "Study medication should not be frozen" was deleted as this is already described in the storage conditions.	Section 6.1.3	Changes were made for clarity

Change	Sections Affected	Rationale
The following addition was made: "It is the responsibility of the Investigator to provide all study records, including case report forms (CRFs) and source documents, among other records, for review and inspection by the clinical monitor *and regulatory authorities, as needed*."	Section 12	Change was made to align with new standard language and address possible inspection by regulatory authorities
The eCOA vendor was changed from YPrime to Medidata.	Section 15.2	Change was made for administrative reasons

AMENDMENT 02 VERSION 00 SUMMARY OF CHANGES

Study Title: A Phase 3, 28-week, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of a Single Injection of SM04690 Injected in the Target Knee Joint of Moderately to Severely Symptomatic Osteoarthritis Subjects

Purpose: The purpose of this amendment is to refine the study design, including revising the screening process and inclusion/exclusion criteria, updating and clarifying study assessments, etc.

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

Change	Sections Affected	Rationale
Protocol Amendment 02 Version 00 has been added on the title page.	Title Page	Change was made to capture the dates of previous and current protocol versions
Protocol date and version have been updated as applicable.	All	Change was made to reflect current protocol amendment
Sponsor signatory list was revised.	Sponsor Signature Page	Change was made for administrative reasons
List of Abbreviations was updated.	List of Abbreviations	Change was made to align list with current amendment
"Other" endpoint #3 (OMERACT-OARSI responders) was deleted.	Sections 1.1, 3.2.4, 10.4.5	Change was made to refine study endpoints
Screening Visit 1 and Screening Visit 2 were combined into a single Screening Visit. The radiograph will be performed at a prescreening visit outside of this study.	Sections 1.1, 4.1, 7.1, 7.3.1, 7.3.2, 7.3.7, 7.3.8, 7.5	Change was made to refine study design
The following deletion was made: "Investigator assessment of NSAID/acetaminophen usage ~~for target knee OA pain~~ will be performed…"	Sections 1.1 and 4.1	Change was made because any usage of NSAID/acetaminophen will be collected and assessed
Figure 1 was updated.	Figure 1	Change was made for clarity
A new Appendix 1 was added to clarify ACR clinical and radiographic criteria for classification of knee OA.	Sections 1.1 and 5.1, Appendix 1	Change was made to clarify the criteria noted in inclusion criterion #3

Change	Sections Affected	Rationale
Inclusion criterion #4 (mJSW) was deleted. mJSW will be recorded as part of baseline data.	Sections 1.1, 5.1, 7.1.1, 10.4.6	Change was made to refine inclusion criteria and allow for increased enrollment
Inclusion criterion #7 was revised: "Body mass index (BMI) ≤ 35 kg/m^2 *at the Screening Visit.*"	Sections 1.1 and 5.1	Change was made to clarify timing
Inclusion criterion regarding WOMAC Pain score was deleted.	Sections 1.1 and 5.1	Change was made to refine inclusion criteria
Inclusion criterion #18 was edited to include "*at least* 12 weeks…"	Sections 1.1 and 5.1	Change was made to clarify required duration
Exclusion criterion #1 (pregnant and breastfeeding women and positive pregnancy test) was reworded.	Sections 1.1 and 5.2	Changes were made to clarify the exclusion criterion
Definitions of post-menopausal and permanently surgically sterile were removed from exclusion criterion #2.	Sections 1.1 and 5.2	Change was made to remove redundancy with exclusion criterion #1
Exclusion criterion #3 (men of reproductive potential) was reworded.	Sections 1.1 and 5.2	Changes were made to clarify the exclusion criterion
"within 12 weeks of the Screening Visit" was added to exclusion criterion #4 (malalignment).	Sections 1.1 and 5.2	Change was made to allow for use of the prescreen radiograph.
Exclusion criterion #7 (any surgery) was revised from Screening Visit to Day 1.	Sections 1.1 and 5.2	Changes were made to account for any surgery that may occur between the Screening Visit and Day 1
Exclusion criterion #8 (IA injections) was reworded and revised from Screening Visit 1 to Day 1.	Sections 1.1 and 5.2	Changes were made to clarify the exclusion criterion and account for IA injections that may occur between the Screening Visit and Day 1
Exclusion criterion #9 (effusion of the target knee) was revised from Screening Visit 1 to Day 1.	Sections 1.1 and 5.2	Changes were made to refine the exclusion criterion and account for effusion that may occur between the Screening Visit and Day 1
Exclusion criterion #10 (electrotherapy, acupuncture, etc.) was revised to include physical therapy and therapeutic ultrasound and revised from Screening Visit 1 to Day 1.	Sections 1.1 and 5.2	Changes were made to refine the exclusion criterion and account for any electrotherapy, acupuncture, etc. that may occur between the Screening Visit and Day 1
The exclusion criterion regarding bone fractures within 26 weeks of Screening Visit 1 was deleted.	Sections 1.1 and 5.2	Changes were made to refine the exclusion criterion
"for knee OA" was deleted from exclusion criterion #13.	Sections 1.1 and 5.2	Change was made because participation in any clinical research trial described is exclusionary
Systemic was clarified as "oral, intramuscular, or intravenous" in exclusion criterion #14, and the allowed dosage of prednisone was revised. This exclusion criterion was also revised from Screening Visit to Day 1.	Sections 1.1 and 5.2	Change was made to clarify and refine the exclusion criterion
Exclusion criteria #15, 16, 19, and 20 were reworded.	Sections 1.1 and 5.2	Grammatical changes were made to clarify the exclusion criteria
Exclusion criteria #17 (opioids) and #18 (topical local anesthetic agents) were revised from Screening Visit to Day 1.	Sections 1.1 and 5.2	Change was made to account for use of opioids or topical local anesthetic agents that may occur between the Screening Visit and Day 1
The following was deleted from exclusion criterion #22: "including laboratory findings not	Sections 1.1 and 5.2	Change was made because the deleted text was unnecessary/redundant

Change	Sections Affected	Rationale
included in the Screening Visit 2 laboratory tests and findings in the medical history or in the pre-study assessments."		
Exclusion criterion #25 was reworded and "major depressive disorder or generalized anxiety disorder" was deleted.	Sections 1.1 and 5.2	Change was made to clarify and refine the exclusion criterion
"Hemoglobin A1c (HbA1c) > 9 at the Screening Visit" was made into a separate exclusion criterion (#28).	Sections 1.1 and 5.2	Change was made for clarity
Exclusion criterion #30 was added: "Any contraindications for an IA injection in the target knee in the opinion of the Investigator."	Sections 1.1 and 5.2	Change was made to refine exclusion criteria and exclude contraindications for an IA injection in the target knee
Number of sites enrolling participates was changed from 70 to 100, and study duration was updated.	Section 1.1	Changes were made for accuracy
Description of study agent was revised.	Sections 1.1 and 2.2	Change was made to align with the most up-to-date description of SM04690
Schematic of study design was deleted because it was no longer an accurate depiction of the study design.	Section 1.1	Change was made for accuracy
The 36-Item Short Form Health Survey (SF-36) was removed from the assessments for this study.	Sections 4.1, 7.1.1, 7.3.3, 7.3.4, 7.3.6, 7.3.7	Change was made because the SF-36 assessment is included in another SM04690 study and will not be used in current study
Section 5.3.1 Contraception was revised to clarify lifestyle guidelines pertaining to WOCBP and men.	Section 5.3.1	Changes were made to clarify contraception guidelines
Section 5.4.2 Subject Rescreening was revised and subjects affected by a protocol amendment may be rescreened.	Section 5.4.2, 7.1.1, 7.3.1	Changes were made to refine subject rescreening criteria
"Total or partial knee replacement of the target knee" was added as a reason for premature discontinuation.	Section 5.6.1	Change was made to refine reasons for withdrawal or termination
The following edit was made in Section 5.6.2: ET procedures should be conducted for any subject who ~~discontinues after~~ *was randomized at* the Day 1 visit.	Section 5.6.2	Change was made to refine when ET procedures should be conducted
"Ready to use" was removed from the description of the drug and placebo products.	Sections 6.1.2 and 6.1.4	Change was made to avoid confusion; further information is provided in the pharmacy manual
"Study medication should not be frozen." was added to Section 6.1.3 Product Storage and Stability.	Section 6.1.3	Change was made to refine instructions for study medication storage and stability.
Guidance on administration of study medication was updated.	Section 6.1.5	Changes were made to clarify guidance on study medication injections
"Collection of Adverse Events Data" was updated to clarify information recorded and length of follow-up.	Sections 7.1.1 and 8.3	Changes were made to clarify collection of AEs
Information regarding malalignment of the target knee was deleted from the Knee Examination section.	Section 7.1.1	Change was made because malalignment will be assessed as part of the prescreen radiograph.

Change	Sections Affected	Rationale
The following phrase was deleted from the vital signs description: "same resting position should be used for all blood pressure measurements throughout the study".	Section 7.1.1	Change was made because same resting position is not required
Weight will only be measured at the Screening Visit and Week 28 (EOS)/ET, not at Weeks 12 and 24.	Sections 7.1.1 and 7.3.4	Change was made to refine study assessment timepoints
"Review of Prescreen Radiograph Report" section was added.	Section 7.1.1	Change was made to refine study design and align with new screening process
Training on accurate pain reporting and placebo response reduction is recommended at Day 1 and Weeks 4, 12, and 24.	Sections 7.1.1 and 7.3.7 7.3.4	Change was made to refine study assessment timepoints
Electronic diary compliance for questionnaire completion will be conducted at site visits from Day 1 to Week 24.	Sections 7.1.1, 7.3.3, 7.3.4, 7.3.7	Change was made to refine study design; compliance will be reviewed, and sites may re-train subjects as necessary
The names of the NSAID/Acetaminophen usage eCRFs were corrected.	Section 7.1.1	Change was made for alignment with the database
"Calcium" was added to the chemistry panel under Clinical Laboratory Evaluations.	Section 7.2.1	Change was made for completeness
Clarification was added that pregnancy tests will only be performed on WOCBP.	Section 7.3.1, 7.3.3, 7.3.7	Change was made for clarity
Section 7.3.1 Prescreening was added for clarification of study design.	Section 7.3.1	Change was made for to align with new screening process
The Schedule of Events Table in Section 7.3.7 was updated to reflect any and all changes made throughout this amendment.	Section 7.3.7	Changes were made for accuracy
The sentence regarding concomitant therapy in relation to AE assessments was revised.	Section 7.5	Change was made to clarify the meaning of the sentence
Section 7.6 Prohibited Medications, Treatments, and Procedures was updated.	Section 7.6	Change was made to refine and clarify prohibited concomitant medications and procedures
Clarification was added to the "life-threatening" bullet point in the SAE definition.	Section 8.1.2	Change was made to clarify what constitutes "life-threatening" as it pertains to an SAE
Guidance on SAE reporting was updated.	Section 8.4.2	Change was made to refine and clarify SAE reporting procedures
Sponsor contact information for questions on SAE reporting was updated.	Section 8.4.2	Change was made for administrative reasons
Information regarding procedures for pregnancy reporting were added.	Section 8.4.5	Change was made to update pregnancy reporting procedures
Section 10.4 Description of Statistical Methods header was added.	Section 10.4	Header was missing from original protocol
The following was added to Section 10.4.2 and 10.4.3: "Unadjusted 95% confidence intervals and *P* values will be reported."	Sections 10.4.2 and 10.4.3	Addition was made to refine the description of statistical methods
Section 10.4.9 Sub-Group Analysis was updated.	Section 10.4.9	Changes were made to refine statistical methods
Section 14.3 Protocol Deviations was updated.	Section 14.3	Changes were made to provide updated guidance on protocol deviations

Change	Sections Affected	Rationale
The Medical Monitor was changed to Christian Bulcao and Ismail Simsek was included as a backup Medical Monitor. The address for YPrime was updated.	Section 15.2	Change was made for administrative reasons
Appendix 2 Prohibited Concomitant Medications and Procedures was modified.	Appendix 2	Changes were made for clarity and accuracy
Formatting, spelling, and grammar/terminology were refined.	Throughout	Changes were made for clarity and presentation

AMENDMENT 01 VERSION 00 SUMMARY OF CHANGES

Study Title: A Phase 3, 28-week, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of a Single Injection of SM04690 Injected in the Target Knee Joint of Moderately to Severely Symptomatic Osteoarthritis Subjects

Purpose: The purpose of this amendment is to refine the study design following feedback from regulatory authorities.

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

Change	Sections Affected	Rationale
Protocol Amendment 01 Version 00 has been added on the title page.	Title Page	Change was made to capture the dates of previous and current protocol versions
Protocol date and version have been updated as applicable	All	Change was made to reflect current protocol amendment
Changed from electronic signatures to wet signatures	Sponsor Signature Page	Change was made for administrative reasons
Name of control treatment has changed from “Vehicle” to “Placebo”	All	Change was made to more precisely describe control treatment
Updated titles for Hutch Humphreys and Ismail Simsek; added Cristina Damatarca and Mark Fineman as signatories and removed Anita DiFrancesco	Sponsor Signature Page, Section 15.2	Changes were made for administrative reasons
Updated List of Abbreviations	List of Abbreviations	Change was made due to new abbreviations
Extended the screening period to 22 days (previously 21 days)	Sections 1.1, 4.1 and 7.3	Change was made for consistency with other SM04690 trials
Added Figure 1 as an overview of study design and endpoints	Section 1.1	Change was made to facilitate understanding of the study design
Added “serious adverse events (SAEs), vital signs, and clinical laboratory measures” to the safety endpoint.	Sections 1.1 and 3.2.3	Change was made to refine the safety endpoint
Added usage of NSAIDs and acetaminophen for target knee OA pain as a secondary endpoint	Sections 1.1, 3.2.2, and 10.4.3	Based on guidance from the FDA to capture usage of pain medications as an endpoint during the trial

Change	Sections Affected	Rationale
Usage of NSAIDs and acetaminophen will be assessed at each visit starting at Day 1; subject NSAID training will occur at Screening Visit 1.	Sections 1.1, 4.1, 7.1.1, 7.3	Change was made to collect information on pain medication usage and allow rescue medications
Rearranged inclusion and exclusion criteria	Sections 1.1, 5.1 and 5.2	Similar items were grouped together
Modified inclusion criteria #4: "~~Baseline~~ mJSW by radiograph"	Sections 1.1 and 5.1	"Baseline" is a statistical term that does not fit an inclusion criterion
Modified inclusion criteria #20: "Subjects must have read and understood the informed consent form … signed *and dated* it …"	Sections 1.1 and 5.1	Change was made to be consistent with documentation requirements
Exclusion criterion #1 was modified to apply it only to WOCBP.	Sections 1.1 and 5.2	Change was made to refine exclusion criteria; only WOCBP will undergo pregnancy testing in this study
Revised exclusion criterion #4: "~~Subjects who have had a single or bilateral,~~ Partial or complete *joint replacement in either* knee ~~or hip replacement~~ "	Sections 1.1 and 5.2	The hip replacement portion of the criterion was removed because it was deemed too restrictive given the procedures planned for the study
Changed HbA1c exclusion (#27) from > 8 to > 9	Sections 1.1 and 5.2	Change was made to meet current standards for subject exclusion
Revised exclusion criteria #7 (IA injections) and #13 (different experimental drug or procedure) to 26 weeks exclusion prior to Screening Visit 1	Sections 1.1 and 5.2	Change was made for consistency with other criteria
Revised exclusion criteria #28: If using NSAIDs ~~for the treatment of OA pain~~ *and/or acetaminophen*, subjects who have not maintained a stable regimen in the opinion of the Investigator *for at least 4 weeks prior to* ~~at~~ Screening Visit 1	Sections 1.1 and 5.2	Change was made to establish timeline for stable usage of pain medications prior to trial
Modified exclusion criterion #32: "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, *or who are immediate family members (spouse, parent, child, or sibling; biological or legally adopted) of said employees responsible for the conduct of the study*	Sections 1.1 and 5.2	Change was made to ensure that family members of employees of the Sponsor are excluded
Revised criteria for evaluation: "…measures and vital signs, *as assessed by the Investigator.*"	Section 1.1	Change was made to clarify that these measures will be determined by Investigator assessment
Revised Study Duration information	Section 1.1	Change was made to revise study schedule
Updated Schematic of Study Design	Section 1.2	Change was made to add monthly phone visits
Removed several listings from Key Roles, moved Key Roles to from Section 1 to Section 15; reordered Introduction, Objectives, and Endpoint sections; added sections on "Assessment of Potential Risks and Benefits," "Justification for Dose," "End of Study Definition," "Study Population," and "Screen Failures;" renamed "Tracking of Dose" as "Study Intervention Compliance".	Throughout	Changes were made to align with FDA protocol template v1.0 (April 2017)
Modified description of study placebo risks: "	Section 2.3.1	Changes was made to refine

Change	Sections Affected	Rationale
The ~~control~~ *placebo* injection in this study will be 2 mL of vehicle, which is ~~the inactive substance~~ carboxymethylcellulose sodium and polysorbate 80 in phosphate saline buffer. ~~The inactive substance~~ Carboxymethylcellulose sodium and polysorbate 80 are inactive substances often used as food or drug excipients. *There is a small risk of reaction to these substances.* ~~Refer to the IB for the potential risks associated with the study vehicle.~~		description and to align protocol with current IB.
Modified description of study injection risks: " "Risks associated with knee joint injection include ~~bleeding, bruising,~~ infection, ~~pain at the injection~~ *and local* site ~~swelling of the knee, and/or injury to the knee joint~~ reactions such as erythema, irritation, and edema.	Section 2.3.1	Change was made to refine description and to align protocol with current IB.
Added the SF-36 questionnaire at Day 1 and Week 24.	Sections 4.1, 7.1.1, 7.3.3, 7.3.5, 7.3.6, and 7.3.7	SF-36 was added in order to collected baseline data on subjects who may enroll in future long-term extension studies.
Added the following sentence to contraception guidelines: "WOCBP who withdraw from the study after receiving study medication should remain on an acceptable form of contraception for 28 weeks after Day 1." An identical sentence was added to cover men. Also changed description to "Men of ~~Childbearing~~ *Reproductive* Potential"	Section 5.3.1	Added sentence for situations in which a subject withdraws early, to remind sites that subjects should remain on contraception. Change of "childbearing" to "reproductive" was made for accuracy.
Added following as reason for subject rescreening: "…being unable to comply with study procedures due to administrative convenience (e.g., family issues or attending to a private matter), and/or being within the exclusion window for past medications and procedures, as outlined in Section 5.2. Subjects who were screen failed because of unacceptable knee radiographs as assessed by the central imaging vendor may also be rescreened for this protocol."	Section 5.4.2	Added to cover transient situations in which subjects may be eligible for the study at a later time.
Added following to Reasons for Withdrawal: • Withdrawal by subject *for reason other than lack of efficacy* • Physician decision *for reason other than lack of efficacy*	Section 5.6.1	Phrase was added to distinguish these from the category of "Lack of Efficacy"
Removed "Screen failure" as a Reason for Withdrawal	Section 5.6.1	Subjects who fail screening in this protocol are not enrolled into the trial and as such cannot withdraw
Referred to treatment arms throughout as "study drug" (or "SM04690") and "placebo" and the two together as "study medication".	Section 6	Change was made to clarify language about treatments.
Removed drug product manufacturer and type of vials.	Section 6.1.2	Identity of manufacturer is not necessary in the protocol.
Allowable temperature excursions for study medication was modified to "*evaluated on a case*	Section 6.1.3	Drug product from a new manufacturer is being used in this

Change	Sections Affected	Rationale
by case basis by the Sponsor."		study, and while stability studies for the drug product are ongoing, they have not yet been completed.
Added following information on blinding: "The Unblinded Investigator must minimize any contact with the subject following the injection and may not perform any study assessments throughout the duration of the study. All subject contact for the remainder of the study is limited to the blinded Investigator and other appropriate blinded study personnel."	Section 6.1.5	Drug product and placebo have different appearances; injections therefore must be performed by unblinded personnel. Change was made to inform sites that Unblinded Investigators who administer injections should not participate in any study evaluations.
Added following: "The Sponsor will provide sterile needles and syringes that are to be used for the injection of study medication."	Section 6.1.5	Change was made to help sites by providing needles and syringes to be used with study medication.
Changed scale for collecting adverse events from "Guidance for Industry: Toxicity Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Trials" to "*Clinical Data Interchange Standards Consortium (CDISC) Severity/Intensity Scale for Adverse Events (AESEV)*."	Section 7.1.1, Appendix 1	The Toxicity Scale is applicable for vaccine trials with healthy volunteers, whereas this is a Phase 3 trial of a non-vaccine drug.
Reworded timing of AE reporting: AEs that are ~~not serious and are~~ ongoing at *a* ~~the~~ subject's last visit will be *followed for 30 days after administration of the last dose of study medication or until resolution, whichever comes first. Resolution is defined as the return to baseline status or stabilization of the condition. SAEs that are ongoing at a subject's last visit will be followed until resolution.* ~~until the study close-out visit, if requested by the Sponsor. If not requested, AEs 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 (SAEs) that are not resolved or stabilized during this time period will be followed until resolution or stabilization.~~	Sections 7.1.1 and 8.3	Changes were made to refine definitions and timing of collection
Minor edits were made in the Medical History subsection.	Section 7.1.1	Edits were made for clarity
Added procedures "Past Treatments for Knee OA pain" and "Assessment of NSAID/Acetaminophen Usage"	Sections 7.1.1 and 7.3	Changes were made to capture new information about past history with pain medications, and new secondary endpoint for NSAID/acetaminophen usage
Revised vital sign terminology.	Sections 7.1.1 and 7.3	Changes were made to align with CDISC standard terminology
Clarified number of radiographs to take to get an acceptable image: "Upon receipt of images, the central imaging vendor will assess the image quality as acceptable or unacceptable. It is recommended that the Investigator attempt one additional image capture at Screening Visit 1 in order to obtain an acceptable image. Subjects that do not have an	Section 7.1.1	Change was made to ensure compliance with eligibility criteria and to ensure adequate data collection at the end of trial

Change	Sections Affected	Rationale
acceptable image at Screening Visit 1 will be screen failed."		
Altered wording about WPI&SS questionnaire: "subject will sign~~/~~ *or* initial ~~and date~~ the source document *and date it* to…	Section 7.1.1	Change was made because original wording created confusion
Clarified description of assessment: "The WPI&SS assessment used in this study is modified from that described in (Clauw 2014)"	Section 7.1.1	Change was made to indicate that our assessment is not the same as that in reference
Added additional information about electronic diaries including accurate pain reporting and placebo response.	Section 7.1.1 and 7.3.1	Change was made to clarify study procedures and add new training as procure
Added anchor descriptors to Pain NRS.	Section 7.1.1	Changes were made to clarify procedures
Deleted "Increases in pain should only be considered AEs if reported by the subject, regardless of pain NRS scores." from the Pain NRS subsection.	Section 7.1.1	Change was made to align with updated definition of AEs (see below)
Removed methamphetamine as tested drug	Sections 1.1, 5.2, 7.1.1, 7.6	Drug is included with "Amphetamines" in the list of drugs
Revised language to indicate that pregnancy tests will be performed only on WOCBP.	Section 7.2.2	Change was made to refine study design
Deleted "biomarker analysis" from description of study procedures to be performed at Screening Visit 2	Section 7.3.1	Inclusion of biomarker analysis was made in error and will not be performed in this study
Added phone visits at Weeks 8, 16, and 20	Section 7.3.4	Change was made to allow monthly collection of NSAID usage
Updated Schedule of Events Table	Section 7.3.7	Change was made to update procedures
Clarified which eCRF page prior and concomitant medications will be recorded on.	Section 7.5	Addition was made for clarification
Added sentence to Rescue Medications: "Subjects are allowed to remain on their stable regimen of NSAIDs/acetaminophen during this study and may change their usage as needed for pain management, including for the rescue of knee pain."	Section 7.8	Change was made following FDA feedback to allow subjects to rescue pain during the study.
Added following to Definitions of Adverse Events: "In this protocol, signs and symptoms of exacerbation or worsening of target knee OA will be captured in the context of efficacy assessments and recorded on specific pages of the eCRF or electronic diary. Anticipated fluctuations or anticipated deterioration (in the opinion of the Investigator) of the underlying disease (target knee OA) will not be considered as AEs nor captured on the AE page of the eCRF."	Sections 7.1.1 and 8.1.1	Change was made because knee pain is an endpoint and this information will be captured as part of efficacy measures
The following was added to definitions of SAEs: "Admission to the hospital or prolongation of hospitalization qualifies as an SAE only if it is the result of an AE."	Section 8.1.2	Change was made to align with current ICH definitions of SAEs.
Descriptions for Unanticipated Problems (UPs) changed.	Sections 8.1.3 and 8.4.3	Change was made for clarity and to align with current reporting

Change	Sections Affected	Rationale
		guidelines.
Added following to definition of "Unlikely Related": "…or the AE is considered possibly related to another event, medical condition, or product not associated with the study medication." Also added "medical condition" as other possible explanation of AE	Section 8.2.2	Changes were made to clarify definitions of relatedness to study drug
Added following: "*The Investigator should review the SAE information and sign the SAE report, and the…"*	Section 8.4.2	Change was made to clarity reporting requirements
Added Kathleen Toscano as Alternative Contact for SAE Reporting and to Key Role overseeing Drug Safety and Pharmacovigilance	Section 8.4.2	Changes were made for administrative reasons
Removed text from UP Reporting: 1: ~~"A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP."~~ 2: ~~"All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures) and IRB within the timeframe specified by the institution procedures and IRB."~~	Section 8.4.3	Changes were made because 1) Investigators are not responsible for protocol changes, and 2) This information was already indicated in the section
Removed phrase: ~~"The Investigator and Samumed will manage reporting of pregnancies according to the study document "Guidelines for the Management of Serious Adverse Events (SAEs) and Pregnancies".~~	Section 8.4.5	Change was made because document is no longer used.
The following edit was made in Section 9: "A regular report of risks will be utilized together with ~~on-site and off-site~~ centralized data monitoring…"	Section 9	Change was made for correctness
The statistical hypotheses were re-ordered.	Section 10.2	Change was made to refine hypothesis testing
Added the following to Analysis of Secondary Endpoints: "…as well as change in NSAID/acetaminophen usage. The potential confounding effect of change in NSAID/acetaminophen usage on the treatment effect will be considered for sensitivity analysis."	Section 10.4.3	Change was made because of new endpoint
Baseline descriptive statistics were further refined: "…and the presence of ~~bilateral~~ *symptomatic and radiographic* OA."	Section 10.4.6	Change was made to refine baseline descriptive statistics
Sub-group analyses was revised to: "…analyzed with unilateral symptomatic OA *and bilateral radiographic disease (KL grade 2-3 in both knees)* subjects."	Section 10.4.9	Change was made to refine data analyses
Changed e-mail for Medidata notification to sites	Section 10.6.1	Change was made for administrative reasons

Change	Sections Affected	Rationale
Removed Appendix 1 (Toxicity Vaccine Scale)	Appendix 1	Scale was replaced by CDISC scale for AE collection
Added Table of Changes in Amendment 01	Appendix 3	Change was made to list changes in this version
References and bibliography were updated	Throughout	Changes were made for completeness and presentation
Formatting, spelling, and grammar/terminology were refined	Throughout	Changes were made for clarity and presentation

Signature Page for VV-TMF-135008 v1.0

Reason for signing: Approved	Name: Christopher Swearingen Role: Vice President, Clinical Outcomes and Analytics Date of signature: 12-May-2020 18:32:48 GMT+0000

Reason for signing: Approved	Name: Ismail Simsek Role: Medical Director Date of signature: 12-May-2020 18:40:02 GMT+0000

Reason for signing: Approved	Name: Mark Fineman Role: Vice President, Clinical Development Date of signature: 12-May-2020 22:02:47 GMT+0000

Signature Page for VV-TMF-135008 v1.0