PROTOCOL SM04690-OA-04
(Amendment 03 Version 00, 23 April 2018)

A Phase 2, 24-Week, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Safety and Efficacy of SM04690 for the Treatment of Moderately to Severely Symptomatic Knee Osteoarthritis

NCT03122860

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Study Number: SM04690-OA-04

IND Sponsor: Samumed, LLC

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Date: 23 April 2018

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SPONSOR SIGNATURE PAGE

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Protocol Number: SM04690-OA-04 AM03V00

Date: 23 April 2018

Name & Title	Signature	Date
[redacted]		23APR2018
[redacted]		23 APR 2018
[redacted]		23APR2018
[redacted]		23APR2018

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

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LIST OF ABBREVIATIONS

Abbreviation	Term
ACR	American College of Rheumatology
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
BMI	Body mass index
CFR	Code of Federal Regulations
CRF	Case report form
DLT	Dose-limiting toxicity
EC	Ethics Committee
eCRF	Electronic case report form
ECG	Electrocardiogram
EDC	Electronic data capture
EOS	End of study
ePRO	Electronic patient reported outcomes
ER	Emergency room
ET	Early termination
FAS	Full Analysis Set
FDA	(US) Food and Drug Administration
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
IA	Intra-articular
IB	Investigator Brochure

Abbreviation	Term
ICF	Informed consent form
ICH	International Conference on Harmonization
IND	Investigational new drug
IP	Investigational product
IQRMP	Integrated Quality and Risk Management Plan
IRB	Institutional Review Board
IUD	Intrauterine device
JSW	Joint space width
KOOS	Knee injury and Osteoarthritis Outcome Score
KOOS-PS	Knee injury and Osteoarthritis Outcome Score Physical function Short form
LDH	Lactate dehydrogenase
MCP-Mod	Multiple Comparison Procedure Modelling
MedDRA	Medical Dictionary for Regulatory Activities
mFAS	Modified Full Analysis Set
mg	Milligram
mL	Milliliter
mm	Millimeter
mSv	Millisievert
NCS	Not clinically significant
NRS	Numeric rating scale
NSAID	Nonsteroidal anti-inflammatory drug
OA	Osteoarthritis
OTC	Over the counter
PA	Posterior-anterior
PI	Principal Investigator
PP	Per-protocol
PPAS	Per-Protocol Analysis Set

Abbreviation	Term
PRO	Patient reported outcomes
RBC	Red blood cell
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SAS	Safety Analysis Set
SD	Standard deviation
SOP	Standard operating procedure
SS	Symptom Severity
SSQ	Symptom Severity Question
TEAE	Treatment-emergent adverse event
ULN	Upper limit of the normal range
UP	Unanticipated problem
US	United States
VAS	Visual Analog Scale
WBC	White blood cell
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 2, 24-Week, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Safety and Efficacy of SM04690 for the Treatment of Moderately to Severely Symptomatic Knee Osteoarthritis		
Protocol Number	SM04690-OA-04		
Protocol Date	23 April 2018	Protocol Version	AM03 V00

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

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

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

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

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

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

_____ _____

Investigator’s Signature Date

_____

Investigator’s Printed Name

PROTOCOL SUMMARY

Title: A Phase 2, 24-Week, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Safety and Efficacy of SM04690 for the Treatment of Moderately to Severely Symptomatic Knee Osteoarthritis

Objectives:

Primary:

The primary objective of this study is to determine the effective dose(s) of SM04690 for the treatment of knee OA.

Secondary:

The secondary objective of this study is to evaluate the safety and tolerability of SM04690.

Endpoints:

Primary:

1. Evaluate change from baseline OA pain in the target knee as assessed by the weekly averages of daily pain Numeric Rating Scale (NRS) at Week 24
2. Evaluate change from baseline OA pain in the target knee as assessed by Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain subscore at Week 24
3. Evaluate change from baseline OA function in the target knee as assessed by WOMAC physical function subscore at Week 24
4. Evaluate change from baseline in medial joint space width (JSW) as documented by radiograph of the target knee at Week 24

Secondary:

1. Evaluate the safety of SM04690 as measured by treatment-emergent adverse events (TEAEs)
2. Evaluate change from baseline OA disease activity as assessed by Patient Global Assessment at Week 24

Exploratory:

1. Evaluate change from baseline OA pain in the target knee as assessed by WOMAC pain subscore at Week 4, 8, 12, 16, and 20
2. Evaluate change from baseline OA function in the target knee as assessed by WOMAC physical function subscore at Week 4, 8, 12, 16, and 20
3. Evaluate change from baseline symptoms of OA in the target knee as assessed by WOMAC total score at Week 4, 8, 12, 16, 20, and 24
4. Evaluate change from baseline OA pain in the target knee at each week (aside from Week 24) as assessed by weekly averages of daily pain NRS

5. Evaluate change from baseline OA disease activity as assessed by Patient Global Assessment at Week 4, 8, 12, 16, and 20
6. Evaluate change from baseline OA function in the target knee as assessed by Knee Injury and Osteoarthritis Outcome Score (KOOS) at Week 4, 8, 12, 16, 20, and 24
7. Evaluate change from baseline OA function in the target knee at each week as assessed by KOOS Physical Function Short Form (KOOS-PS)
8. Evaluate change from baseline OA disease activity as assessed by Physician Global Assessment at Week 4, 12, and 24
9. Evaluate change over time in NSAID usage as assessed by weekly averages of daily pain medication electronic diary responses at every week
10. Evaluate subject perception of study treatment received at Week 24
11. Evaluate outcome differences between treatment with sham or placebo injections at Week 4, 8, 12, 16, 20, and 24

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

Approximately 630 subjects will be consented and randomized using a permuted block design to 6 treatment arms (0.03 mg active per 2 mL injection : 0.07 mg active per 2 mL injection : 0.15 mg active per 2 mL injection : 0.23 mg active per 2 mL injection : 0.0 mL vehicle : 2.0 mL vehicle). Subjects will participate in a screening period of a minimum of 10 days and up to 22 days and a 24-week follow-up period. Clinic visits will be scheduled at Screening Visit 1, Screening Visit 2, Day 1, and Weeks 4, 12, and 24 [End of study (EOS)]/Early Termination (ET).

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

- Daily pain NRS (for target knee OA pain)
- Daily monitoring of usage of NSAIDs
- Weekly completion of the KOOS-PS
- Monthly completion of the WOMAC
- Monthly completion of KOOS
- Monthly completion of Patient Global Assessment

Inclusion/ Exclusion Criteria:

Criteria for Inclusion:

1. Males and females between 40 and 80 years of age, inclusive, in general good health
2. Ambulatory
3. Diagnosis of femorotibial OA in the target knee by standard American College of Rheumatology (ACR) criteria at Screening

Visit 1 (clinical AND radiographic criteria); OA of the knee is not to be secondary to any rheumatologic conditions (e.g., rheumatoid arthritis)

4. Pain compatible with OA of the knee(s) for at least 26 weeks prior to Screening Visit 1
5. Primary source of pain throughout the body is due to OA in the target knee
6. Daily OA knee pain diary average NRS intensity score ≥4 and ≤8 in the target knee on the 11-point (0-10) NRS scale for the 7 days immediately preceding Day 1
7. Pain NRS scores recorded for the target knee on at least 4 out of the 7 days immediately preceding Day 1
8. Daily OA knee pain diary average NRS intensity score <4 in the non-target knee on the 11-point (0-10) NRS scale for the 7 days immediately preceding Day 1
9. Pain NRS scores recorded for the non-target knee on at least 4 out of the 7 days immediately preceding Day 1
10. Total WOMAC score of 96-192 (out of 240) for the target knee at baseline regardless of if the subject is on symptomatic oral treatment (baseline questionnaire completed during the screening period prior to randomization)
11. Willingness to use an electronic diary on a daily basis in the evening for the screening period and 24-week study duration
12. Negative drug test for opioids and drugs of abuse, except alcohol and marijuana, at Screening Visit 1
13. Subjects with depression or anxiety must be clinically stable for 12 weeks prior to Screening Visit 1 and, if on treatment for depression or anxiety, be on 12 weeks of stable therapy
14. Full understanding of the requirements of the study and willingness to comply with all study visits and assessments
15. Subjects must have read and understood the informed consent form, and must have signed it prior to any study-related procedure being performed
16. Subject's Screening Visit 1 visit must occur while enrollment into the randomization cohort for which they are eligible is open

Criteria for Exclusion:

1. Women who are pregnant, lactating, or have a positive pregnancy result at Screening Visit 1
2. Women of child bearing potential who are sexually active and are not willing to use a highly effective method of birth control during the study period that includes double barrier, IUD, hormonal

contraceptive combined with single barrier, or abstinence

3. Males who are sexually active and have a partner who is capable of becoming pregnant, neither of whom have had surgery to become sterilized or whom are not using a highly effective method of birth control
4. Body mass index (BMI) > 35
5. Partial or complete joint replacement in either knee
6. Currently requires:
    a. regular use of ambulatory assistive devices (e.g., wheelchair, parallel bars, walker, canes, or crutches), or
    b. use of a lower extremity prosthesis, and/or a structural knee brace (i.e., a knee brace that contains hardware)
7. Radiographic disease Stage 0, 1, or 4 in the target knee at Screening Visit 1 according to the Kellgren-Lawrence grading of knee OA as assessed by independent central readers
8. Previous participation in a Samumed clinical trial investigating SM04690
9. Any surgery (e.g., arthroscopy) in either knee within 26 weeks prior to Screening Visit 1
10. Any planned surgery during the study period. Non-surgical invasive procedures conducted for a diagnostic or therapeutic purpose scheduled during the study period are not prohibited (refer to Section 7.6).
11. Significant and clinically evident misalignment of either knee that would impact subject function, as determined by the Investigator
12. History of malignancy within the last 5 years; however, subjects with prior history of in situ cancer or basal or squamous cell skin cancer are eligible if completely excised. Subjects with other malignancies are eligible if they have been continuously disease free for at least 5 years prior to any study injection
13. Clinically significant abnormal screening hematology values, blood chemistry values, or urinalysis values as determined by the Investigator
14. Any condition, including laboratory findings (not included in the Screening Visit 1 laboratory tests) and findings in the medical history or in the pre-study assessments, that, in the opinion of the Investigator, constitutes a risk or contraindication for participation in the study or that could interfere with the study objectives, conduct, or evaluation
15. 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

16. 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
17. Any diagnosed psychiatric condition that includes, but is not limited to, a history of mania, bipolar disorder, psychotic disorder, schizophrenia, schizoaffective disorder, major depressive disorder, or generalized anxiety disorder
18. Participation in a clinical research trial that included the receipt of an investigational product or any experimental therapeutic procedure, or an observational research trial related to osteoarthritis within 8 weeks prior to any study injection, or planned participation in any such trial; the last date of participation in the trial, not the last date of receipt of investigational product, must be at least 8 weeks prior to Screening Visit 1
19. Treatment of the target knee with intra-articular glucocorticoids (e.g., methylprednisolone) within 12 weeks prior to Screening Visit 1
20. Any intra-articular injection into the target knee with a therapeutic aim including, but not limited to, viscosupplementation (e.g., hyaluronic acid), PRP, and stem cell therapies within 24 weeks prior to Screening Visit 1; treatment of the target knee with intra-articular glucocorticoids greater than 12 weeks prior to Screening Visit 1 is allowed
21. Treatment with systemic glucocorticoids greater than 10 mg prednisone or the equivalent per day within 4 weeks prior to Screening Visit 1
22. Effusion of the target knee clinically requiring aspiration within 12 weeks prior to Screening Visit 1
23. Use of electrotherapy, acupuncture, and/or chiropractic treatments for knee OA within 4 weeks prior to Screening Visit 1 (refer to Appendix 2)
24. Any known active infections, including urinary tract infection, upper respiratory tract infection, sinusitis, suspicion of intra-articular infection, hepatitis B or hepatitis C infection, and/or infections that may compromise the immune system such as human immunodeficiency virus (HIV) at Day 1
25. Use of centrally acting analgesics (e.g., duloxetine) (refer to Appendix 2) within 12 weeks prior to Screening Visit 1
26. Use of anticonvulsants not listed in Appendix 2 within 12 weeks prior to Screening Visit 1, unless used for seizure or migraine prophylaxis

27. Subjects requiring the usage of opioids >1x per week within 12 weeks prior to Screening Visit 1
28. Topical local anesthetic agents (gels, creams, or patches such as the Lidoderm patch) used for the treatment of knee OA within 7 days of Screening Visit 1
29. Any chronic condition that has not been well controlled or subjects with a chronic condition who have not maintained a stable therapeutic regimen of a prescription therapy in the opinion of the investigator. In addition, subjects with a baseline HbA1c >9 will be excluded.
30. If on NSAIDs for the treatment of OA pain, subjects who have not maintained a stable regimen in the opinion of the Investigator at Screening Visit 1
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 630 subjects with moderately to severely symptomatic osteoarthritis of the knee
Phase:	2
Number of Sites enrolling participants:	This study will be conducted at approximately 80 investigational centers in the United States
Description of Study Agent:	SM04690 is a small molecule inhibitor of the Wnt pathway important in driving progenitor cells resident in the joint to become chondrocytes, potentially enhancing cartilage formation
Study Duration:	Approximately 11 months Estimated date first subject consented: April 2017 Estimated date last subject completed: March 2018

Participant Duration: Up to approximately 27 weeks

Criteria for evaluation:

Efficacy:

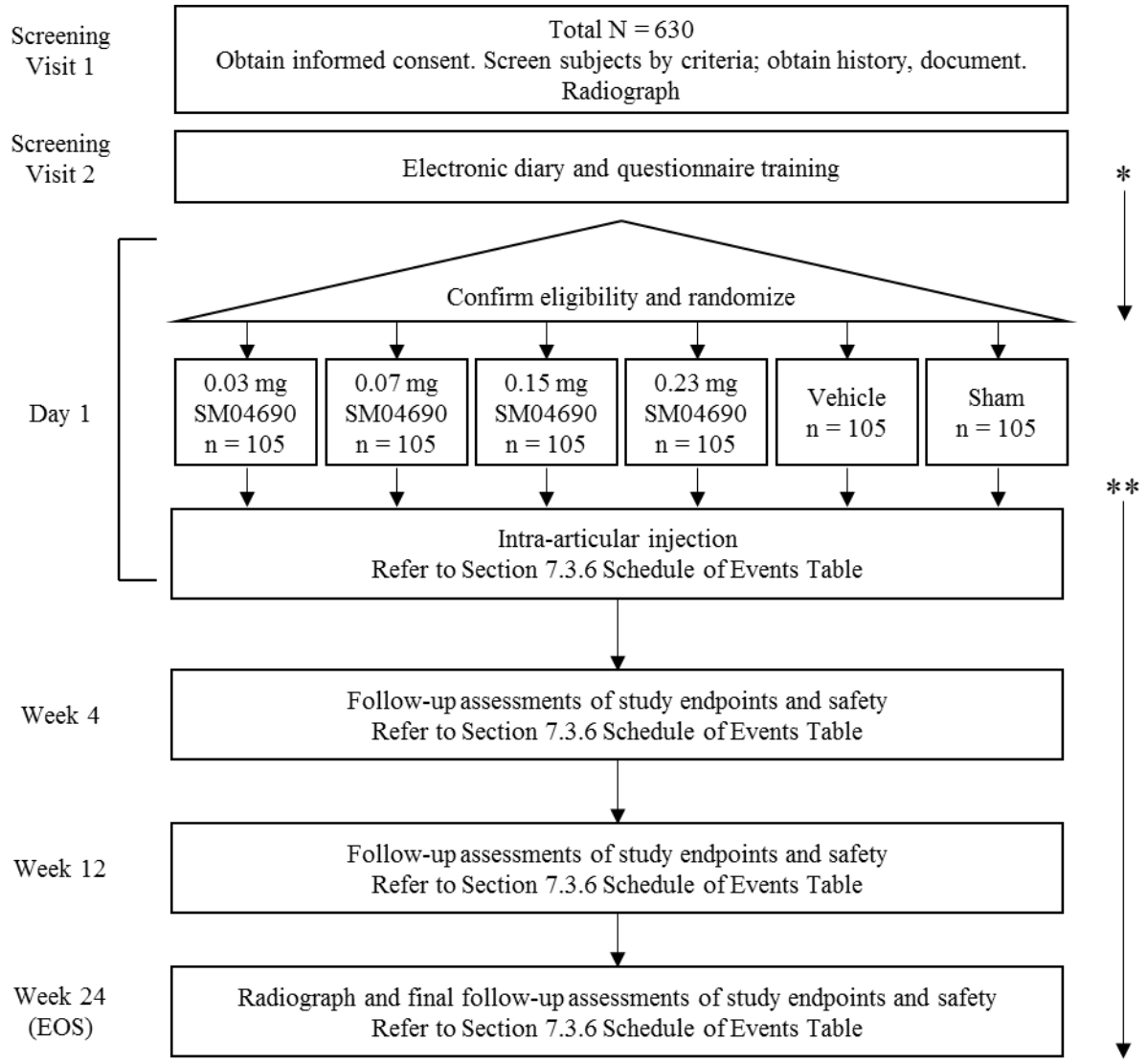
Efficacy will be assessed by:

- Weekly averages of daily pain NRS (for target knee OA pain)
- Monthly WOMAC total score as well as WOMAC pain and function subscores for the target knee
- Weekly KOOS-PS
- Daily collection of NSAID usage
- Monthly KOOS
- Monthly Patient Global Assessment
- Physician Global Assessment at clinic visits
- Medial JSW by radiograph

Safety:

The overall safety and tolerability of SM04690 will be determined by the incidence, seriousness, severity, and relationship of TEAEs and clinically significant changes in clinical laboratory measures and vital signs. Changes from baseline in the amount and duration of NSAID usage will be monitored.

SCHEMATIC OF STUDY DESIGN



* Daily pain NRS and NSAIDs electronic diary, baseline assessments
**Daily pain NRS and NSAIDs electronic diary, weekly KOOS-PS, monthly WOMAC, KOOS, Patient Global Assessment. Refer to Section 7.3.7 Schedule of Electronic Diary and Questionnaire Completion Table.

1. KEY ROLES

Medical monitor	[redacted]
Regulatory specialist	[redacted]
Biostatistician	[redacted]
Data manager	[redacted]
Central radiology reader	[redacted]
Electronic patient reported outcomes (ePRO)	eResearchTechnology, Inc. (ERT) 1818 Market St. Suite 1000 Philadelphia, PA 19103 (215) 972-0420
Central laboratory	ACM Global Central Laboratory 160 Elmgrove Park Rochester, NY 14624 (800) 525-5227

2. INTRODUCTION: BACKGROUND INFORMATION & SCIENTIFIC RATIONALE

2.1 BACKGROUND INFORMATION

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

birthday and will be at risk for OA (Nevitt et al. 2006).

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

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

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

2.2 RATIONALE

Osteoarthritis is the most common form of arthritis and chronic joint disorder in man (Dougados and Hochberg 2011). The exact cause of OA is unknown, but it is associated with aging and normal wear on a joint. 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 US (Lawrence et al. 2008).

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

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

SM04690 was tested in a single phase 1 clinical trial (SM04690-01) in subjects with moderately to severely symptomatic OA of the knee, which was completed on 17Sep2015. The trial was a placebo-controlled, double-blind, dose-escalation study of three concentrations of SM04690 (0.03, 0.07, and 0.23 mg per 2 mL injection), conducted in the US. In each dose cohort, subjects were randomized to active or vehicle at a ratio of 16 active: 4 vehicle. Subject clinic visits occurred on Day 1 and 2, and Weeks 1, 2, 4, 8, 12, and 24. Each successively higher concentration cohort was enrolled after completion of treatment and review of safety data from the previous cohort by a Safety Review Committee. The Safety Review Committee was comprised of the Samumed medical monitor, the site Investigators, and an independent rheumatologist. A total of 33/61 (54.1%) exposed subjects reported no AEs. One SAE (paroxysmal tachycardia) reported was deemed unrelated to study medication by the reporting Investigator. No clinically significant safety concerns or differences among study groups were noted with regard to vital signs, clinical laboratory results, ECGs, or AEs. Based upon these data, a single intra-articular (IA) injection of SM04690 into the knee of OA subjects appeared safe and

well-tolerated.

SM04690 is currently being tested in a phase 2 clinical trial in subjects with moderately to severely symptomatic OA of the knee. The trial is a placebo-controlled, double-blind, parallel group study of three concentrations of SM04690 (0.03, 0.07, and 0.23 mg per 2 mL injection) injected into the target knee joint, conducted in the US. Subjects were randomized at a ratio of 1:1:1:1 (0.03 mg active per 2 mL injection: 0.07 mg active per 2 mL injection: 0.23 mg active per 2 mL injection: placebo). Clinic visits occurred on Treatment Visit Day 1 and Follow-up Weeks 4, 13, 26, 39 and 52 [End of study (EOS)]/Early Termination (ET). As of 30Jun2016, 455 subjects have been randomized. An interim analysis was conducted after all subjects had completed their Week 26 visit. Unblinding in support of the interim analysis occurred on 20Oct2016. As of this date, there has been no obvious dose response or difference from placebo with respect to the most frequently reported AEs, SAEs, or in AEs that led to subject withdrawal.

A phase 3, long-term extension study (SM04690-OA-05) is also being performed to monitor the long-term safety, tolerability, and efficacy of treatment of SM04690 or placebo previously injected in the target knee joints of subjects with moderately to severely symptomatic OA from a Samumed-sponsored SM04690-OA phase 2 or phase 3 study. This study is a multicenter, observational study in subjects that have previously been treated with SM04690 or placebo injected into the target knee joint. Approximately 2000 subjects will be consented and will participate in a 60 month follow-up period. Clinic visits are scheduled at Months 6, 12, 24, 36, 48, and 60 [End of study (EOS)]/Early Termination (ET).

This phase 2 study, SM04690-OA-04, is a placebo-controlled, double-blind, parallel group study of four concentrations of SM04690 (0.03, 0.07, 0.15, and 0.23 mg per 2 mL injection) injected into the target knee joint of subjects with moderately to severely symptomatic OA. Based upon the interim data analysis of SM04690-OA-02, key phenotypes of laterality (unilateral vs bilateral) as well as chronic pain (as measured by the Widespread Pain Index) were identified as confounding variables impacting the overall assessment of both radiologic and clinical efficacy outcomes. The design of SM04690-OA-04 is based upon the SM04690-OA-02 design while assessing strategies to combat the confounding impact of laterality and chronic pain.

Additionally, although many clinical trials with IA therapies commonly use IA saline injections as a placebo comparator arm, there has been growing recognition that the administration of IA saline may have a treatment effect. Several meta-analyses quantifying the effect of IA saline injections on patient-reported outcomes (PRO) such as pain, stiffness, and function in OA clinical trials have found statistically and clinically meaningful improvement in PROs up to 6 months after injection (Zhang et al. 2008, Altman et al. 2016, Saltzman et al. 2016). Clinically noticeable improvements after IA saline injections ultimately call into question the use of such injections as a null control group for comparison to investigative trial arms, as saline may significantly impact clinical symptoms. One hypothesis for this mechanism of action is the dilution of inflammatory mediators within the knee, providing relief of perceived pain, function, as well as stiffness (Zhang et al. 2008, Altman et al. 2016, Saltzman et al. 2016). Determining an adequate control to IA saline injection would remain challenging, while it is suggested that a sham group with a simple needle stick into the joint would remedy some concerns for the potential therapeutic effect of IA saline injections (Saltzman et al. 2016).

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. Potential risks associated with modulation of this pathway include gastrointestinal distress, inhibition of bone formation, and myelosuppression.

SM04690 drug product is a suspension of SM04690 in diluent containing carboxymethylcellulose sodium and polysorbate 80 in phosphate buffered saline. Potential risks associated with carboxymethylcellulose sodium and polysorbate 80 include allergic reaction and hypersensitivity. Serious allergic reactions may be associated with increased risk of death, but serious allergic reactions are rare and, as of 28 June 2017, have not been reported in any subject on human studies testing SM04690. Symptoms of an allergic reaction may include rash, wheezing and difficulty breathing, dizziness and fainting, swelling around the mouth, throat or eyes, a fast pulse, or sweating.

SM04690 has been tested in a single phase 1 clinical trial (SM04690-01) in humans with osteoarthritis (OA) of the knee. In this trial, there was no obvious dose response or difference from placebo with respect to the most frequently reported AEs, regardless of whether or not considered related to study medication. A total of 72 AEs were reported by 28/61 (45.9%) subjects during the study. Sixteen AEs, reported by 8/61 (13.1%) subjects, were considered related to study medication by the reporting investigator. The system organ class with the most reported AEs was Musculoskeletal and connective tissue disorders with 11/61 (18.0%) subjects reporting 19 AEs consisting of 5 preferred terms (arthralgia, back pain, joint swelling, joint stiffness, and musculoskeletal chest pain). Eight of these events comprising three preferred terms (arthralgia, joint swelling, and joint stiffness), reported by 5/61 (8.2%) subjects, were considered related to study medication by the reporting investigator. The AE (preferred term) reported most was Headache, with 7/61 (11.5%) subjects reporting 7 events of mild or moderate headache: 2 reports by 2 (11.8%) subjects in the 0.03 mg treatment group, no reports in the 0.07 mg treatment group, 4 reports by 4 (25.0%) subjects in the 0.23 mg treatment group, and 1 report by 1 (9.1%) subject in the placebo group. One of these events (0.23 mg treatment group) was considered related to study medication by the reporting investigator. Headache was the only AE with an incidence greater than 10%. The AE (preferred term) with the most events considered related to study medication was Arthralgia with 4/61 (6.6%) subjects reporting 4 events which were considered treatment related. 3/61 (4.9%) additional subjects reported 5 events of arthralgia which were considered unrelated to study medication.

A single SAE of “tachycardia paroxysmal” occurred during the study in a subject enrolled in the 0.07 mg treatment group. The event was a report of tachycardia paroxysmal in a 72 year old white male, with previous medical history of tachycardia. This event was considered unrelated to study drug administration by the reporting investigator. Nevertheless, as the FDA requested that all AEs in this initial study of SM04690 be considered related to study drug, this event was reported in an expedited manner to the IND.

Two DLTs were reported on the trial, both occurring in the 0.07 mg treatment group (increased knee pain and tachycardia paroxysmal [also an SAE as noted above]). The DLT of increased knee pain was considered probably related to treatment by the reporting investigator.

Single intra-articular injections of SM04690 at doses of 0.03 mg, 0.07 mg, and 0.23 mg in a 2 mL suspension into the target knee joint appeared to be safe and well-tolerated in subjects with moderately to severely symptomatic OA of the knee. No clinically significant safety concerns or differences between active and placebo treatment groups were noted with regard to AEs, clinical laboratory results, vital signs, ECGs, assessment of bone loss, assessment of bone marrow edema, or assessment of inflammatory cytokines.

An interim analysis of the phase 2 SM04690-OA-02 study was performed in October 2016 after all subjects completed their Week 26 visit. Summarizing the safety events occurring within these 26 weeks and summarized in the interim analysis, 8 SAEs have been reported in 7/452 (1.5%) subjects. The SAEs reported have been Hypertensive crisis, Cholecystitis acute, Gall bladder adenocarcinoma, Uterine prolapse, Diverticulitis, Patella fracture, Osteoarthritis (of the hip), and Non-cardiac chest pain. These events were felt to be either not related or unlikely related to study medication by investigator assessment.

Study Placebos

The 2 possible placebo injections in this study will be either 2 mL of vehicle, which is the inactive substance carboxymethylcellulose sodium and polysorbate 80, or a 0 mL sham injection. The inactive substance carboxymethylcellulose sodium and polysorbate 80 is often used as a food or drug additive. Potential risks associated with carboxymethylcellulose sodium and polysorbate 80 include allergic reaction and hypersensitivity.

The placebo sham injection contains no substance and has the same risks associated with the knee joint injection which include bleeding, bruising, infection, pain at the injection site, swelling of the knee, and/or injury to knee joint.

Risks of Injection

Risks associated with knee joint injection include bleeding, bruising, infection, pain at the injection site, swelling of the knee, and/or injury to knee joint.

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 donating blood.

Knee Radiograph

This study involves radiation exposure from a total of 2 radiographs of the subjects' knees on 2 different days, each approximately 6 months apart. As part of everyday living, everyone is exposed to a small amount of background radiation that comes from soil, rocks, outer space, and within the body itself. The radiation dose for all knee X-rays that the subject will receive in this study is expected to be approximately 0.01 mSv and is less than 1 days' equivalent dose from background radiation. The risk from this dose is small. This radiation exposure may not be necessary for the subjects' medical care, but it is necessary to obtain the research information desired.

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 subjects, even if it may not help the subjects in this study.

3. OBJECTIVES AND PURPOSE

The purpose of this study is to evaluate the safety and efficacy of SM04690 injected in the target knee joint of moderately to severely symptomatic OA subjects.

Primary objective:
The primary objective of this study is to determine the effective dose(s) of SM04690 for the treatment of knee OA.

Secondary objective:
The secondary objective of this study is to evaluate the safety and tolerability of SM04690.

4. STUDY DESIGN AND ENDPOINTS

4.1 DESCRIPTION OF THE STUDY DESIGN

This study is a multicenter, randomized, double-blind, placebo-controlled, parallel group study of four different concentrations of SM04690 injected into the target knee joint of moderately to severely symptomatic OA subjects.

Approximately 630 subjects will be consented and randomized using a permuted block design to 6 treatment arms (0.03 mg active per 2 mL injection : 0.07 mg active per 2 mL injection : 0.15 mg active per 2 mL injection : 0.23 mg active per 2 mL injection : 0.0 mL vehicle : 2.0 mL vehicle). To support the primary objective, active treatment groups will be compared to both vehicle (2.0 mL vehicle) and sham (0.0 mL vehicle). Subjects will participate in a screening period of a minimum of 10 days and up to 22 days and a 24-week follow-up period. Clinic visits will be scheduled at Screening Visit 1, Screening Visit 2, Day 1, and Weeks 4, 12, and 24 (EOS)/ET. Specific timing of protocol procedures is described in the Schedule of Events Table (Section 7.3.6). Specific timing of electronic diary and questionnaire completion is described in the Schedule of Electronic Diary and Questionnaire Completion Table (Section 7.3.7).

This study will be conducted at approximately 80 investigational centers in the US.

In this study, subjects will be required to complete an electronic diary for the following:

- Daily pain NRS
- Daily monitoring of usage of NSAIDs
- Weekly completion of the KOOS-PS
- Monthly completion of the WOMAC
- Monthly completion of KOOS
- Monthly completion of Patient Global Assessment

A Widespread Pain Index and Symptom Severity (WPI&SS) assessment will be administered at Screening Visit 1. Physician Global Assessment will be performed at Day 1 and Weeks 4, 12, and 24 (EOS)/ET. Evaluation of the success of blinding will be performed at Day 1 (post intra-articular injection) and Week 24 (EOS)/ET.

In addition, general medical evaluations including physical examination, knee examination, and recording of vital signs will be performed at Screening Visit 1, Day 1, and Weeks 4, 12, and 24 (EOS)/ET. Height will be measured at Screening Visit 1 and weight will be measured at Screening Visit 1 and Week 24 (EOS)/ET. Clinical laboratory evaluations will be performed at Screening Visit 1 and Weeks 4, 12, and 24 (EOS)/ET. Radiographic imaging of the knees will be performed at Screening Visit 1 and Week 24 (EOS)/ET.

Recording of signs and symptoms of study medication intolerability and TEAE reporting will start following the injection of the study medication and continue until the subject completes Week 24 (EOS)/ET. All TEAEs, whether volunteered, elicited, or noted during examination, will be recorded throughout the study.

Subject Re-Screening

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

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

Any re-screened subject must be re-consented and will be issued a new subject number. All screening procedures and assessments, except for the knee radiograph (if taken at previous screen), must be performed at re-screen; no results or data, except for the knee radiograph, may be used from the previous screen. Target knee selection may not be changed at re-screen.

4.2 STUDY ENDPOINTS

4.2.1 PRIMARY ENDPOINTS

1. Evaluate change from baseline OA pain in the target knee as assessed by the weekly averages of daily pain Numeric Rating Scale (NRS) at Week 24
2. Evaluate change from baseline OA pain in the target knee as assessed by Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain subscore at Week 24
3. Evaluate change from baseline OA function in the target knee as assessed by WOMAC physical function subscore at Week 24
4. Evaluate change from baseline in medial joint space width (JSW) as documented by radiograph of the target knee at Week 24

4.2.2 SECONDARY ENDPOINTS

1. Evaluate the safety of SM04690 as measured by treatment-emergent adverse events (TEAEs)
2. Evaluate change from baseline OA disease activity as assessed by Patient Global Assessment at Week 24

4.2.3 EXPLORATORY ENDPOINTS

1. Evaluate change from baseline OA pain in the target knee as assessed by WOMAC pain subscore at Week 4, 8, 12, 16, and 20
2. Evaluate change from baseline OA function in the target knee as assessed by WOMAC physical function subscore at Week 4, 8, 12, 16, and 20
3. Evaluate change from baseline symptoms of OA in the target knee as assessed by WOMAC total score at Week 4, 8, 12, 16, 20, and 24
4. Evaluate change from baseline OA pain in the target knee at each week (aside from Week 24) as assessed by weekly averages of daily pain NRS
5. Evaluate change from baseline OA disease activity as assessed by Patient Global Assessment at Week 4, 8, 12, 16, and 20
6. Evaluate change from baseline OA function in the target knee as assessed by Knee Injury and Osteoarthritis Outcome Score (KOOS) at Week 4, 8, 12, 16, 20, and 24
7. Evaluate change from baseline OA function in the target knee at each week as assessed by KOOS Physical Function Short Form (KOOS-PS)
8. Evaluate change from baseline OA disease activity as assessed by Physician Global Assessment at Week 4, 12, and 24
9. Evaluate change over time in NSAID usage as assessed by weekly averages of daily pain medication electronic diary responses at every week
10. Evaluate subject perception of study treatment received at Week 24
11. Evaluate outcome differences between treatment with sham or placebo injections at Week 4, 8, 12, 16, 20, and 24

5. STUDY ENROLLMENT AND WITHDRAWAL

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
2. Ambulatory
3. Diagnosis of femorotibial OA in the target knee by standard American College of Rheumatology (ACR) criteria at Screening Visit 1 (clinical AND radiographic criteria); OA of the knee is not to be secondary to any rheumatologic conditions (e.g., rheumatoid arthritis)
4. Pain compatible with OA of the knee(s) for at least 26 weeks prior to Screening Visit 1
5. Primary source of pain throughout the body is due to OA in the target knee
6. Daily OA knee pain diary average NRS intensity score ≥4 and ≤8 in the target knee on the 11-point (0-10) NRS scale for the 7 days immediately preceding Day 1
7. Pain NRS scores recorded for the target knee on at least 4 out of the 7 days immediately preceding Day 1
8. Daily OA knee pain diary average NRS intensity score <4 in the non-target knee on the 11-point (0-10) NRS scale for the 7 days immediately preceding Day 1
9. Pain NRS scores recorded for the non-target knee on at least 4 out of the 7 days immediately preceding Day 1
10. Total WOMAC score of 96-192 (out of 240) for the target knee at baseline regardless of if the subject is on symptomatic oral treatment (baseline questionnaire completed during the screening period prior to randomization)
11. Willingness to use an electronic diary on a daily basis in the evening for the screening period and 24-week study duration
12. Negative drug test for opioids and drugs of abuse, except alcohol and marijuana, at Screening Visit 1
13. Subjects with depression or anxiety must be clinically stable for 12 weeks prior to Screening Visit 1 and, if on treatment for depression or anxiety, be on 12 weeks of stable therapy
14. Full understanding of the requirements of the study and willingness to comply with all study visits and assessments
15. Subjects must have read and understood the informed consent form, and must have signed it prior to any study-related procedure being performed
16. Subject's Screening Visit 1 visit must occur while enrollment into the randomization cohort for which they are eligible is open

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. Women who are pregnant, lactating, or have a positive pregnancy result at Screening Visit 1
2. Women of child bearing potential who are sexually active and are not willing to use a highly effective method of birth control during the study period that includes double barrier, IUD, hormonal contraceptive combined with single barrier, or abstinence
3. Males who are sexually active and have a partner who is capable of becoming pregnant, neither of whom have had surgery to become sterilized or whom are not using a highly effective method of birth control
4. Body mass index (BMI) > 35
5. Partial or complete joint replacement in either knee
6. Currently requires:
    a. regular use of ambulatory assistive devices (e.g., wheelchair, parallel bars, walker, canes, or crutches), or
    b. use of a lower extremity prosthesis, and/or a structural knee brace (i.e., a knee brace that contains hardware)
7. Radiographic disease Stage 0, 1, or 4 in the target knee at Screening Visit 1 according to the Kellgren-Lawrence grading of knee OA as assessed by independent central readers
8. Previous participation in a Samumed clinical trial investigating SM04690
9. Any surgery (e.g., arthroscopy) in either knee within 26 weeks prior to Screening Visit 1
10. Any planned surgery during the study period. Non-surgical invasive procedures conducted for a diagnostic or therapeutic purpose scheduled during the study period are not prohibited (refer to Section 7.6).
11. Significant and clinically evident misalignment of either knee that would impact subject function, as determined by the Investigator
12. History of malignancy within the last 5 years; however, subjects with prior history of in situ cancer or basal or squamous cell skin cancer are eligible if completely excised. Subjects with other malignancies are eligible if they have been continuously disease free for at least 5 years prior to any study injection
13. Clinically significant abnormal screening hematology values, blood chemistry values, or urinalysis values as determined by the Investigator
14. Any condition, including laboratory findings (not included in the Screening Visit 1 laboratory tests) and findings in the medical history or in the pre-study assessments, that, in the opinion of the Investigator, constitutes a risk or contraindication for participation in the study or that could interfere with the study objectives, conduct, or evaluation
15. 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
16. 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

17. Any diagnosed psychiatric condition that includes, but is not limited to, a history of mania, bipolar disorder, psychotic disorder, schizophrenia, schizoaffective disorder, major depressive disorder, or generalized anxiety disorder
18. Participation in a clinical research trial that included the receipt of an investigational product or any experimental therapeutic procedure, or an observational research trial related to osteoarthritis within 8 weeks prior to any study injection, or planned participation in any such trial; the last date of participation in the trial, not the last date of receipt of investigational product, must be at least 8 weeks prior to Screening Visit 1
19. Treatment of the target knee with intra-articular glucocorticoids (e.g., methylprednisolone) within 12 weeks prior to Screening Visit 1
20. Any intra-articular injection into the target knee with a therapeutic aim including, but not limited to, viscosupplementation (e.g., hyaluronic acid), PRP, and stem cell therapies within 24 weeks prior to Screening Visit 1; treatment of the target knee with intra-articular glucocorticoids greater than 12 weeks prior to Screening Visit 1 is allowed
21. Treatment with systemic glucocorticoids greater than 10 mg prednisone or the equivalent per day within 4 weeks prior to Screening Visit 1
22. Effusion of the target knee clinically requiring aspiration within 12 weeks prior to Screening Visit 1
23. Use of electrotherapy, acupuncture, and/or chiropractic treatments for knee OA within 4 weeks prior to Screening Visit 1 (refer to Appendix 2)
24. Any known active infections, including urinary tract infection, upper respiratory tract infection, sinusitis, suspicion of intra-articular infection, hepatitis B or hepatitis C infection, and/or infections that may compromise the immune system such as human immunodeficiency virus (HIV) at Day 1
25. Use of centrally acting analgesics (e.g., duloxetine) (refer to Appendix 2) within 12 weeks prior to Screening Visit 1
26. Use of anticonvulsants not listed in Appendix 2 within 12 weeks prior to Screening Visit 1, unless used for seizure or migraine prophylaxis
27. Subjects requiring the usage of opioids >1x per week within 12 weeks prior to Screening Visit 1
28. Topical local anesthetic agents (gels, creams, or patches such as the Lidoderm patch) used for the treatment of knee OA within 7 days of Screening Visit 1
29. Any chronic condition that has not been well controlled or subjects with a chronic condition who have not maintained a stable therapeutic regimen of a prescription therapy in the opinion of the investigator. In addition, subjects with a baseline HbA1c >9 will be excluded.
30. If on NSAIDs for the treatment of OA pain, subjects who have not maintained a stable regimen in the opinion of the Investigator at Screening Visit 1
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

From Screening Visit 1 until Week 24 (EOS)/ET, all subjects must agree to be strictly abstinent from sexual intercourse or use an acceptable form of contraception as defined by this protocol if the subject or their partner is capable of becoming pregnant.

Sexually active subjects must use one of the following methods of contraception from Screening Visit 1 until Week 24 (EOS)/ET:

1. Use of a condom for males with a vasectomy (vasectomy must have been performed at least 6 months prior to Screening Visit 1)
2. Males without a vasectomy or a vasectomy performed within 6 months prior to Screening Visit 1 must use a condom and be instructed that their female partner(s), if any, must be of nonchildbearing potential or use another form of highly effective birth control which includes the following:
    a. Double barrier methods of contraception such as condom plus diaphragm or cervical/vault cap with spermicide (i.e., physical plus chemical)
    b. Established hormonal contraceptive methods. Females who are using hormonal contraceptives must have had consistent use of the same hormonal contraceptive product for at least 4 weeks prior to dosing and must continue to use the same contraceptive during the study
    c. Intrauterine device (IUD)
    d. Surgically sterile (e.g., bilateral tubal ligation/occlusion, hysterectomy)
    e. Postmenopausal
3. Women of childbearing potential must agree to use a highly effective method of contraception (as described in #2 above) and be instructed that their male partner(s), if any, must use a condom

5.4 STRATEGIES FOR RECRUITMENT AND RETENTION

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

5.5 PARTICIPANT WITHDRAWAL OR TERMINATION

5.5.1 REASONS FOR WITHDRAWAL OR TERMINATION

As the study treatment requires only a single injection, best efforts will be made to encourage subjects to attend all follow-up visits. Subjects will be informed that they are free to withdraw

from the study at any time and for any reason. A premature discontinuation from study will occur when a subject who signed informed consent ceases participation in this study, regardless of circumstances, prior to completion of the defined study period. Subjects can be prematurely discontinued from the study for one of the following reasons:

- Death
- Lost to follow-up after a minimum of 3 attempts have been made to contact the subject, including sending a registered letter
- Subject withdraws consent
- TEAE
- Subject non-compliance
- Request by regulatory authority
- Study terminated by Sponsor

The Investigator may remove a subject from the study if, in the Investigator's opinion, it is not in the best interest of the subject to continue in the study.

5.5.2 HANDLING OF PARTICIPANT WITHDRAWALS OR TERMINATION

In case of premature discontinuation of study participation, Week 24 (EOS)/ET procedures should be conducted within 14 days of discontinuation for any subject who discontinues after 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 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.

5.6 PREMATURE TERMINATION OR SUSPENSION OF STUDY

The Investigator and the Institutional Review Board/Ethics Committee (IRB/EC) reserve the right to prematurely terminate the study in the interest of subject safety and welfare. The Sponsor reserves the right to prematurely terminate the study at any time for administrative or safety reasons. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party 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

Samumed will be responsible for the manufacturing, labeling, packaging, distribution, reconciliation, and destruction of study medication product and vehicle product related to the study.

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 product is supplied as 2.4 mL of formulated suspension in a 3 mL Type I glass vial. A separate 3 mL Type I glass vial contains 2.4 mL of vehicle to be used as a diluent. SM04690 vehicle product contains 0.5% carboxymethylcellulose sodium and 0.05% polysorbate 80 in pH 7.4 phosphate buffered saline. The placebo will be vehicle only or a sham injection.

SM04690 and vehicle are manufactured by PrimaPharma, Inc. (San Diego, CA) and will be supplied as single-use injections. SM04690 and vehicle 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 and vehicle must be stored at the appropriate temperature (15°-30°C or 59°-86°F) and in a restricted area with limited access. Temperature excursions are allowed between 2°-60°C (36°-140°F) for a time period not to exceed a cumulative of 72 hours.

6.1.4 PREPARATION

Each dose will be prepared by taking a known volume of SM04690 drug product and adding to a vehicle (diluent) vial, mixing well to re-suspend the product, then injecting 2 mL 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 0.03 mg in 2 mL Injectable Suspension
- SM04690 0.07 mg in 2 mL Injectable Suspension
- SM04690 0.15 mg in 2 mL Injectable Suspension
- SM04690 0.23 mg in 2 mL Injectable Suspension
- SM04690 0 mg; 2 mL vehicle injection only
- SM04690 0 mg; 0 mL sham injection (intra-articular injection procedure is performed identically to all other treatment groups but without the injection of any liquid)

Each subject will be consented and randomized using a permuted block design to 1 of 6 treatment arms at Day 1. The injectable investigational product or vehicle, or the sham injection is to be administered by the unblinded Investigator as a 1-time single injection into the target knee joint. Only 1 knee will be treated for each subject in this study. Although not required, the injection may be guided by ultrasound if it is the standard practice of the Investigator.

Only topical anesthetic (absolutely no invasive anesthetic) is allowed for the study injections.

Anesthetic, if used, may not be combined with the study medication prior to injection.

Prior to administration of the intra-articular 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, while not required, if it is the standard practice of the Investigator, a small amount (0.3-0.5 mL) of joint fluid can be aspirated (if present) in order to confirm correct needle placement; the aspirated fluid does not need to be re-injected. Thereafter, the total volume contained in the syringe is to be injected into the joint space of subjects that were randomized to either active or vehicle arms. In subjects randomized to sham injection (only intra-articular positioning of the needle without volume application), while not required, if it is the standard practice of the Investigator, a small amount (0.3-0.5 mL) of joint fluid can be aspirated (if present) in order to confirm correct needle placement. The duration that the needle remains inside the joint as well as the pressure that is applied should be similar to the active and vehicle injections in order to minimize subject awareness that they are receiving a sham injection. Unblinded Investigators (injectors) participating in the trial should also inform subjects that they may or may not feel any sensation related to the injection.

6.1.6 ROUTE OF ADMINISTRATION

The injectable investigational product or vehicle, or the sham injection is to be administered as a 1-time single intra-articular injection into the target knee joint.

6.1.7 STARTING DOSE AND DOSE ESCALATION SCHEDULE

Not applicable to this study. Each subject will be randomly assigned to a dose on Day 1.

6.1.8 DOSE ADJUSTMENTS/MODIFICATIONS/DELAYS

No modification in the specified dose concentration or the volume (2 mL, or 0 mL for sham) of the study medication or vehicle injected into the target knee joint will be allowed.

6.1.9 DURATION OF THERAPY

The injectable investigational product or vehicle, or the sham injection is to be administered as a 1-time single intra-articular injection into the target knee joint.

6.1.10 TRACKING OF DOSE

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

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

All study medication and vehicle prepared and 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 and vehicle 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 Investigator return or destruction of used and unused vials of the study medication and vehicle 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 treatment-emergent adverse events (TEAEs) will be collected in this study. TEAEs are events that occur during the course of the study that are not present prior to Day 1 study medication injection, or, if present at the time of study medication injection, have worsened in severity during the course of the study. TEAEs will be assessed at each study visit from the time of study medication injection on study visit Day 1 through Week 24 (EOS)/ET.

Each subject will be observed and queried by the Investigator or the Investigator's designee at each study visit for any continuing TEAEs or new TEAEs since the previous visit. The subject may be asked to return to the site for an unscheduled visit if a TEAE occurs between study visits, and if, in the opinion of the Investigator, the TEAE requires a study visit for full evaluation. Any TEAE reported by the subject or noted by the Investigator or the Investigator's designee will be recorded within the eCRF. The following information will be recorded for each TEAE: description of the event, date of onset and resolution, etiology, and severity as assessed by the Investigator according to the "Guidance for Industry: Toxicity Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Trials" (Appendix 1), causal relationship

to study medication, outcome, and any treatment given.

TEAEs that are not serious and are ongoing at the subject's last visit will be followed until the study close-out visit, if requested. Serious adverse events that are not resolved or stabilized during this time period will be followed until resolution or stabilization.

Medical History

A medical history will be obtained at Screening Visit 1 and Day 1 with a follow-up at Week 24 (EOS)/ET. Medical history at Screening Visit 1 will include demographic data (e.g., age, race, ethnicity) and usage 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. Review of medical history at the Week 24 (EOS)/ET visit will only be to capture End Dates of any ongoing medical history collected at screening.

Physical Examination

A general physical examination will be conducted at Screening Visit 1, Day 1, and Weeks 4, 12, and 24 (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 a TEAE.

Knee Examination

A knee examination of both knees will be conducted at Screening Visit 1, Day 1, and Weeks 4, 12, and 24 (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 a TEAE.

Presence of bilateral knee OA (yes/no) will be recorded in the eCRF at Screening Visit 1. If the subject has OA in both knees, the site is to establish the target knee as the knee with greater pain at Screening Visit 1 based on the subject's evaluation and the Investigator's clinical judgment.

Misalignment of both knees will be assessed by the Investigator during the knee examination at Screening Visit 1. In the opinion of the Investigator, subjects with significant and clinically evident misalignment in either knee that would impact subject function must be excluded from the study.

Vital Signs

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

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

- Body temperature
- Pulse rate
- Respiration rate
- Blood pressure (systolic and diastolic) after the subject rests (sitting or supine) for at least 5 minutes; same resting position should be used for all blood pressure

measurements throughout the study

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 a TEAE if found after study medication injection.

Height and Weight

Height measurements will be taken at Screening Visit 1 only. Weight measurements will be taken at Screening Visit 1 and Week 24 (EOS)/ET.

Radiograph of Knee Joints

Radiograph of the knee joints will be taken at Screening Visit 1 and Week 24 (EOS)/ET.

Detailed instructions for obtaining and managing the radiographs will be provided to the investigational center prior to the initiation of subject enrollment. The intent (as described in the Image Review Charter – Image Acquisition Guidelines) is that radiographs should be obtained in the posterior-anterior (PA) view, whenever possible.

All radiographs will be submitted to an independent radiologist who will document disease stage according to the Kellgren-Lawrence grading scale for compliance with inclusion/exclusion criteria, as well as JSW for efficacy assessments.

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 [Widespread Pain Index (WPI)] and symptom severity (SS) questions (Clauw 2014). A WPI&SS assessment will be completed by the subject at Screening Visit 1 on paper.

Upon completion of the WPI&SS assessment, the subject will sign/initial and date the source document to indicate that the assessments are reported accurately.

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

Electronic Diary Device Provision and Training

Electronic diary device provision will occur at Screening Visit 2. Subjects will be trained on electronic diary and questionnaire completion at Screening Visit 2. Subject training will include details on what medications are NSAIDs. Detailed instructions for subject training and electronic questionnaire completion will be provided to the investigational center. Electronic devices are to be returned to the site at Week 24 (EOS)/ET.

Electronic devices will store completed questionnaire data for up to 30 days. Therefore, it is recommended that site personnel review study subject ePRO data and compliance reports in the ePRO vendor web portal (StudyWorks) at least once a week or more frequently as needed to ensure timely subject completion and transmission of questionnaire data between study visits.

Pain Numeric Rating Scale (NRS)

The pain NRS is an 11-point scale (0-10) for subject self-reporting of average knee pain in the last 24 hours. A pain NRS for each knee will be completed daily by the subject during the screening period from Screening Visit 2 until Day 1 to assess subject ability to be compliant with a daily pain assessment. 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 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. Refer to Section 7.3.7 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. If a subject does not complete the electronic dairy for pain NRS for at least 4 out of 7 days in a given week, this will be considered a protocol deviation due to subject non-compliance, but the subject should not be removed from the study unless the Investigator determines it is in the best interest of the subject.

Increases in pain should only be considered TEAEs if reported by the subject, regardless of pain NRS scores.

Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) Electronic Diary

The daily electronic diary of NSAID usage will document subject usage of any NSAID medication as “yes” or “no” in response to the following question, “Did you take any medication that is an NSAID in the last 24 hours?”. Starting on the day of Screening Visit 2 after the site visit, daily electronic diary of NSAID usage is to be completed by subjects in the evening (between 5:00 pm and 11:59 pm) remotely on their electronic devices. Refer to Section 7.3.7 for a schedule of electronic diary and questionnaire completion.

Subjects will complete electronic diary of NSAID usage on the Sponsor-provided electronic device. Subjects will receive notifications reminding them to complete the electronic diary of NSAID usage. If a subject does not complete the electronic diary of NSAID usage for at least 4 out of 7 days in a given week, this will be considered a protocol deviation due to subject non-compliance, but the subject should not be removed from the study unless the Investigator determines it is in the best interest of the subject.

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 devices on Screening Visit 2 + 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. After Day 1, monthly (every 4 weeks) WOMAC assessments will be completed by the subjects for their target knee in the evening (between 5:00 pm and 11:59 pm) remotely on their electronic devices. Refer to Section 7.3.7 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 monthly WOMAC assessment.

Knee Injury and Osteoarthritis Outcome Score (KOOS)

KOOS is a widely-used, non-proprietary tool used by health professionals to assess a subject's opinion about their knee and associated problems. KOOS evaluates pain, symptoms, 2 types of physical function, and knee-related quality of life. The KOOS 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 devices on Screening Visit 2 + 5 days (or up until the day before the Day 1 visit). After Day 1, monthly (every 4 weeks) KOOS questionnaires will be completed by the subjects in the evening (between 5:00 pm and 11:59 pm) remotely on their electronic devices. Refer to Section 7.3.7 for a schedule of electronic diary and questionnaire completion.

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

KOOS Physical Function Short Form (KOOS-PS)

KOOS-PS is derived from the KOOS and is used to assess a subject's opinion about the difficulties they experience with activity due to problems with their knee. The KOOS-PS 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 devices on Screening Visit 2 + 5 days (or up until the day before the Day 1 visit). After Day 1, weekly (every 7 days) KOOS-PS questionnaires will be completed by the subjects in the evening (between 5:00 pm and 11:59 pm) remotely on their electronic devices. Refer to Section 7.3.7 for a schedule of electronic diary and questionnaire completion.

Subjects will complete the KOOS-PS questionnaire on the Sponsor-provided electronic device. Subjects will receive notifications reminding them to complete the weekly KOOS-PS assessment.

Patient Global Assessment of Disease Activity

The Patient Global Assessment is a 50 mm visual analog scale (VAS) on which the subjects will rate how well they are doing, considering all the ways in which illness and health conditions may affect them. The VAS will be anchored by descriptors at each end ("Very Well" on the left and "Very Poorly" 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 devices on Screening Visit 2 + 5 days (or up until the day before the Day 1 visit). After Day 1, monthly (every 4 weeks) Patient Global Assessments will be completed by the subjects in the evening (between 5:00 pm and 11:59 pm) remotely on their electronic devices. Refer to Section 7.3.7 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 monthly Patient Global Assessment.

Physician Global Assessment of Disease Activity

The Physician Global Assessment is a 100 mm VAS on which the Investigator will rate the subject's disease activity independent of the patient's self-assessment. The VAS will be anchored by descriptors at each end ("Very Good" on the left and "Very Bad" on the right). The Physician Global Assessment will be performed on paper at Day 1 and Weeks 4, 12, and 24

(EOS)/ET.

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

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

Evaluation of Success of Blinding

At Day 1 (post intra-articular injection) and Week 24 (EOS)/ET, subjects will complete a questionnaire on paper as to which treatment arm of the study they believe they were assigned to in order to evaluate the effectiveness of blinding. The questionnaire will capture responses of "Study drug injection," "Injection of 2 mL inactive vehicle substance," "Needle insertion into the knee with no vehicle substance injected," and "Do not know."

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

Non-fasting samples for clinical laboratory analysis by ACM Global Central Laboratory will be collected by a qualified staff member at Screening Visit 1 and Weeks 4, 12, and 24 (EOS)/ET. At a minimum, the following tests will be conducted:

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

An HbA1c test will be performed on all subjects at Screening Visit 1.

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

The Investigator or the Investigator's designee must review the results of each subject's Screening Visit 1 clinical laboratory test results prior to the Day 1 visit. The subject must not be randomized on Day 1 and, if results are available for review prior to Screening Visit 2, is not

recommended to proceed to Screening Visit 2 if any of the Screening Visit 1 results are outside the normal range for the laboratory AND, in the opinion of the Investigator, are clinically significant.

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

7.2.2 OTHER ASSAYS OR PROCEDURES

Pregnancy Test

A serum-based pregnancy test will be performed on female subjects at Screening Visit 1. Results from the pregnancy test will be utilized to determine subject eligibility.

Drug Test

A urine sample for drug testing will be collected at Screening Visit 1. The urine drug test will include: cocaine, opioids, methamphetamine, amphetamine, phencyclidine, barbiturates, methadone, oxycodone, and ecstasy. 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 ACM Global Laboratory.

7.2.4 SPECIMEN SHIPMENT

Refer to the Laboratory Manual for ACM Global Laboratory.

7.3 STUDY SCHEDULE

7.3.1 SCREENING

Screening Visit 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 the informed consent form. Written informed consent must be provided by the potential study participant prior to initiation of any screening evaluations or other study-related procedures. The signature, date, and the name of the individual at the site who obtained the informed consent will be recorded in the subject's source record. After written informed consent is obtained, the subject will be assigned a subject number.

The following procedures and assessments will be performed 10-22 days prior to Day 1:

- Documentation of demographic information, including date of birth, gender, race, and ethnicity
- Documentation of current and past medical history including assistive device usage, documentation of current medications, and review of prior medication excluded by the protocol
- Physical examination, including knee examination of both knees and selection of target knee
- Vital signs measurements (pulse, blood pressure, respiration rate, and temperature)
- Height and weight measurements
- Venipuncture and collection of samples for clinical laboratory tests
- Pregnancy test (serum-based)
- Urine drug test
- WPI&SS assessment
- Radiograph – bilateral in weight-bearing fixed flexion position, posterior-anterior (PA) view X-ray

Results from these evaluations will be compared with inclusion/exclusion criteria to determine subject eligibility. In order to complete randomization, WPI&SS scores and subject bilateral/unilateral OA of the knee status from Screening Visit 1 must be entered into EDC prior to the study reaching the enrollment caps described in Section 7.3.2.

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.

Screening Visit 2

This visit must occur at least 3 days after Screening Visit 1 and between 7 to 12 days (inclusive) prior to Day 1.

This visit should occur after confirmation of eligible pregnancy test (if applicable), radiograph, clinical laboratory, and urine drug test report results.

The following procedures and assessments will be performed at Screening Visit 2:

- Electronic diary device provision and subject training for electronic diary and questionnaire completion

Starting on the day of Screening Visit 2, after the site visit, subjects will begin completion of daily pain NRS assessments and NSAIDs electronic diary completion remotely on their electronic devices in the evening (between 5:00 pm and 11:59 pm).

Note: On Screening Visit 2 + 5 days (or up until the day before the Day 1 visit), subjects will complete the WOMAC, KOOS, KOOS-PS, and Patient Global Assessment, in addition to the pain NRS assessment and NSAIDs electronic diary, in the evening (between 5:00 pm and 11:59

pm) remotely on their electronic devices. Refer to Section 7.3.7 for a schedule of electronic diary and questionnaire completion.

7.3.2 RANDOMIZATION

Day 1

This visit must occur within 10 to 22 days of Screening Visit 1. Subjects with a period of more than 12 days between Screening Visit 2 and Day 1 are to be screen failed due to the lengthened time between baseline questionnaires and study medication injection.

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

- Review and/or documentation of current and past medical history, documentation of current medications, and review of prior medication excluded by the protocol
- Physical examination, including knee examination of both knees
- Vital signs measurements (pulse, blood pressure, respiration rate, and temperature)
- Review of pain NRS electronic diary compliance from Screening Visit 2 to Day 1
- Electronic questionnaire review (WOMAC)

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

Physician Global Assessment will also be performed prior to randomization; however, results from this assessment do not determine eligibility.

The following randomization cohorts will be available until the associated subject counts are reached:

- Unilateral OA with WPI ≤ 4 and SSQ2 ≤ 2 – 240 subjects
- Bilateral OA with WPI ≤ 4 and SSQ2 ≤ 2 – 240 subjects
- Unilateral OA with WPI > 4 and/or SSQ2 > 2 – 60 subjects
- Bilateral OA with WPI > 4 and/or SSQ2 > 2 – 60 subjects

In order for a subject to be eligible for randomization, WPI&SS scores and subject bilateral/unilateral OA of the knee status from Screening Visit 1 must be entered into EDC prior to the study reaching the enrollment caps described above.

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

- Intra-articular study medication injection (or placebo)
- Collection of TEAE and concomitant procedures/medication data
- Evaluation of success of blinding

Note: After the Day 1 site visit, subjects will complete monthly (every 4 weeks) WOMAC, KOOS, and Patient Global Assessment, weekly (every 7 days) KOOS-PS, and daily pain NRS and NSAIDs electronic diary completion in the evening (between 5:00 pm and 11:59 pm) remotely on their electronic devices. Refer to Section 7.3.7 for a schedule of electronic diary and

questionnaire completion.

7.3.3 FOLLOW-UP

Week 4 and Week 12

The Week 4 and Week 12 visits should occur on Day 29 (with a window of + 3 days) and Day 85 (with a window of + 3 days), respectively.

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

- Collection of TEAE and concomitant procedures/medication data
- Physical examination, including knee examination of both knees
- Vital signs measurements (pulse, blood pressure, respiration rate, and temperature)
- Venipuncture and collection of samples for clinical laboratory tests
- Physician Global Assessment

7.3.4 FINAL STUDY VISIT

Week 24 End of Study (EOS)

This final study visit should occur on Day 169 with a window of + 7 days.

The following procedures and assessments will be performed at Week 24 (EOS):

- Collection of TEAE and concomitant procedures/therapies/medication data
- Review of medical history
- Vital signs measurements (pulse, blood pressure, respiration rate, and temperature)
- Physical examination, including knee examination of both knees
- Weight measurement
- Venipuncture and collection of samples for clinical laboratory tests
- Radiograph – bilateral in weight-bearing fixed flexion position, posterior-anterior (PA) view X-ray
- Physician Global Assessment
- Evaluation of success of blinding
- Return of electronic device

7.3.5 EARLY TERMINATION VISIT

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

- Collection of TEAE and concomitant procedures/therapies/medication data
- Review of medical history
- Vital signs measurements (pulse, blood pressure, respiration rate, and temperature)

- Physical examination, including knee examination of both knees
- Weight measurement
- Venipuncture and collection of samples for clinical laboratory tests
- Radiograph – bilateral in weight-bearing fixed flexion position, posterior-anterior (PA) view X-ray
- Physician Global Assessment
- Evaluation of success of blinding
- Return of electronic device

7.3.6 SCHEDULE OF EVENTS TABLE

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

Procedure	Screening Period[a] (Days -22 to -1)		Day 1[b]	Week 4 (Day 29 +3 days)	Week 12 (Day 85 +3 days)	Week 24 (EOS) (Day 169 +7 days) / ET
	Screening Visit 1 (Days -22 to -10)	Screening Visit 2 Days (-12 to -7)				
Physician Global Assessment			X	X	X	X
Randomization			X			
Intra-articular injection			X			
TEAEs and concomitant procedures/medications			X	X	X	X
Evaluation of success of blinding			X			X
Return of electronic device						X

[a] The screening period is a minimum of 10 days and a maximum of 22 days and includes Screening Visit 1 and Screening Visit 2; Screening Visit 2 should occur at least 3 days after Screening Visit 1, at between 7 to 12 days prior to Day 1, and after confirmation of eligible pregnancy test (if applicable), radiograph, clinical laboratory, and urine drug test report results.

[b] At Day 1, all procedures should be performed prior to study medication injection except for collection of TEAE and concomitant procedures/medication data and the evaluation of success of blinding.

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

[d] Electronic diary devices will be provided to subjects at Screening Visit 2; subject electronic diary and questionnaire training will be conducted at Screening Visit 2.

[e] WPI&SS will be administered on site at Screening Visit 1.

[f] Electronic diary compliance for daily pain NRS over the screening period will be reviewed at Day 1 prior to randomization to determine subject eligibility.

[g] WOMAC questionnaire will be reviewed at Day 1 prior to randomization to determine subject eligibility.

7.3.7 SCHEDULE OF ELECTRONIC DIARY AND QUESTIONNAIRE COMPLETION TABLE

	Monthly WOMAC, KOOS, and Patient Global Assessment	**Weekly KOOS-PS**	**Daily pain NRS and NSAIDs electronic diary**
Study Visit or Day	WOMAC, KOOS, and Patient Global Assessment will be completed by subjects on Screening Visit 2 + 5 days (or up until the day before the Day 1 visit) and monthly in the evening (between 5:00 pm and 11:59 pm) remotely on their electronic devices. Monthly questionnaires should be performed in the 2 days prior to each month (4 weeks) as outlined below.	KOOS-PS will be completed by subjects on Screening Visit 2 + 5 days (or up until the day before the Day 1 visit) and weekly in the evening (between 5:00 pm and 11:59 pm) remotely on their electronic devices. KOOS-PS should be performed in the 2 days prior to each week as outlined below.	Pain NRS and NSAIDs electronic diary should be completed daily starting after Screening Visit 2. Subjects will complete the diary in the evening (between 5:00 pm and 11:59 pm) remotely on their electronic devices. Diary completion should occur every day including on study visit days.
Screening Visit 1			
Screening Visit 2			
			Complete daily starting on the same day of Screening Visit 2 (after the visit); pain NRS assessments are to be completed for each knee.
Screening Visit 2 + 5 days	Baseline monthly questionnaires (or up until the day before the Day 1 visit)	Baseline weekly questionnaire (or up until the day before the Day 1 visit)	
Day 1			
		Complete on Day 6 or 7	Starting on the same day of Day 1 (after the visit), pain NRS assessments are to be completed for the target knee only.
Week 1 (Day 8)			
		Complete on Day 13 or 14	
Week 2 (Day 15)			
		Complete on Day 20 or 21	

	Monthly WOMAC, KOOS, and Patient Global Assessment	Weekly KOOS-PS	Daily pain NRS and NSAIDs electronic diary
Week 3 (Day 22)			Complete daily
	Complete on Day 27 or 28	Complete on Day 27 or 28	
Week 4 (Day 29)	*Questionnaires should NOT be completed on same day as a study visit.*		
		Complete on Day 34 or 35	
Week 5 (Day 36)			
		Complete on Day 41 or 42	
Week 6 (Day 43)			
		Complete on Day 48 or 49	
Week 7 (Day 50)			
	Complete on Day 55 or 56	Complete on Day 55 or 56	
Week 8 (Day 57)			
		Complete on Day 62 or 63	
Week 9 (Day 64)			
		Complete on Day 69 or 70	
Week 10 (Day 71)			
		Complete on Day 76 or 77	
Week 11 (Day 78)			
	Complete on Day 83 or 84	Complete on Day 83 or 84	
Week 12 (Day 85)	*Questionnaires should NOT be completed on same day as a study visit.*		
		Complete on Day 90 or 91	
Week 13 (Day 92)			
		Complete on Day 97 or 98	
Week 14 (Day 99)			
		Complete on Day 104 or 105	
Week 15 (Day 106)			
	Complete on Day 111 or 112	Complete on Day 111 or 112	
Week 16 (Day 113)			

	Monthly WOMAC, KOOS, and Patient Global Assessment	Weekly KOOS-PS	Daily pain NRS and NSAIDs electronic diary
		Complete on Day 118 or 119	Complete daily
Week 17 (Day 120)			
		Complete on Day 125 or 126	
Week 18 (Day 127)			
		Complete on Day 132 or 133	
Week 19 (Day 134)			
	Complete on Day 139 or 140	Complete on Day 139 or 140	
Week 20 (Day 141)			
		Complete on Day 146 or 147	
Week 21 (Day 148)			
		Complete on Day 153 or 154	
Week 22 (Day 155)			
		Complete on Day 160 or 161	
Week 23 (Day 162)			
	Complete on Day 167 or 168	Complete on Day 167 or 168	
Week 24 (Day 169)	*Questionnaires should NOT be completed on same day as a study visit.*		

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 Screening Visit 1 through Week 24 (EOS)/ET will be recorded in the eCRF. "All medications" should include prescription, over the counter, supplements, as well as herbal or alternative medications. Subjects with a "yes" response for daily NSAID usage in their electronic diary should have a corresponding NSAID recorded in the eCRF.

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" page of the eCRF.

Any new or modified concomitant therapy must be considered to determine if it is related to a TEAE.

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 intra-articular 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; intra-articular 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)
  - Other anticonvulsants not listed in Appendix 2 are also prohibited unless used for seizure or migraine prophylaxis
  - Systemic glucocorticoids greater than 10 mg of prednisone per day or the equivalent
  - Drugs of abuse except alcohol and marijuana
- Electrotherapy (refer to Appendix 2), acupuncture, and/or chiropractic treatments for knee OA are prohibited while the subject is on study.
- Any new formalized (i.e., prescribed by a medical professional) physical therapy exercise programs for knee OA are prohibited while the subject is on study; continuation of formalized physical therapy exercise programs that are already in

progress at the time of screening are allowed.

- Planned or 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 investigational product or any experimental therapeutic procedure. Subjects are also prohibited from participating in any observational research trial related to osteoarthritis 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

Not applicable to this study.

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, solicitation of TEAEs and concomitant medications, and general medical evaluations.

8.1.1 DEFINITION OF ADVERSE EVENTS (AE)

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

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

Whenever possible, it is preferable to record a diagnosis as the TEAE term rather than a series of symptoms relating to a diagnosis. In order to classify TEAEs 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).

8.1.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

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

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

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 unanticipated problem is defined as, in general, any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

8.2 CLASSIFICATION OF AN ADVERSE EVENT

8.2.1 SEVERITY OF EVENT

The Investigator will assess TEAEs for severity utilizing the "Guidance for Industry: Toxicity Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Trials". This

toxicity scale is presented in Appendix 1. Laboratory values not listed on the toxicity scale will be assessed for severity by the clinical Investigator.

8.2.2 RELATIONSHIP TO STUDY AGENT

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

1. Not Related

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

2. Unlikely Related

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

3. Possibly Related

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

4. Probably Related

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

8.2.3 EXPECTEDNESS

The Sponsor will be responsible for determining whether a TEAE/SAE is expected or unexpected. A TEAE/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 TEAEs starts after the injection of study medication on Day 1 and ends after the final study visit.

TEAEs must be followed until resolution by the Investigator. Resolution is defined as the return to baseline status or stabilization of the condition with the expectation that it will remain chronic. TEAEs that are not serious and are ongoing at the subject's last visit will be followed until the

study close-out visit, if requested. Serious adverse events that are not resolved or stabilized during this time period will be followed until resolution or stabilization.

8.4 REPORTING PROCEDURES

8.4.1 ADVERSE EVENT REPORTING

The Investigator is responsible for reporting TEAEs to the Sponsor and IRB according to the protocol as well as 21 Code of Federal Regulations (CFR) part 50, part 56, and part 312. The Investigator is responsible for ensuring accurate TEAE information is reviewed and recorded in the subject source and the TEAE eCRF in a timely manner. The Sponsor is responsible for submitting reports of TEAEs associated with the use of study medication that are both serious and unexpected to the FDA according to 21 Code of Federal Regulations (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 Code of Federal Regulations (CFR) part 50, part 56, and part 312. The Investigator and Samumed will manage SAEs according to the study document "Guidelines For The Management Of Serious Adverse Events (SAEs) And Pregnancies".

All SAEs must be reported as described in the study manual by the Investigator, Study Coordinator, other designated study personnel, or Clinical Research Associate within 24 hours of notification of the SAE. 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. 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 1.

Table 1: Sponsor Contact Information for Questions on SAE Reporting

Primary Contact	Alternative Contact
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

8.4.3 UNANTICIPATED PROBLEM REPORTING

Incidents or events that meet the criteria for unanticipated problem 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, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP; and
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the 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 IRB and to the Sponsor within 24 hours of the investigator becoming aware of the event.
- Any other UP will be reported to the IRB and to the Sponsor within the IRB-required reporting timeframe.
- 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.

8.4.4 EVENTS OF SPECIAL INTEREST

Not applicable to this study.

8.4.5 REPORTING OF PREGNANCY

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

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 Good Clinical Practice (GCP) and Standard Operating Procedures (SOPs) for compliance with applicable government regulations. It is the responsibility of the Investigator to provide all study records, including eCRFs and source documents among other records, for review and inspection by the clinical monitor.

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 on-site and off-site 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

No formal hypotheses are being tested in this study.

10.3 ANALYSIS DATASETS

Full Analysis Set (FAS): All subjects who are randomized and receive a study injection. Full analysis set 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.

Modified Full Analysis Set (mFAS): FAS subjects who receive a protocol specified injection. Subjects who are administered a treatment that is not prescribed by the protocol will be excluded from this analysis set.

Per-Protocol Analysis Set (PPAS): mFAS 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(S)

Analysis of covariance (ANCOVA) will be used to estimate the least squares difference in the change in weekly average of daily pain NRS, WOMAC Pain, WOMAC Function, and medial

JSW adjusting for baseline value. Change will be assessed from baseline between each treatment group and the vehicle placebo group. Unadjusted 95% confidence intervals and P values will be reported.

Multiple Comparison Procedure Modelling (MCP-Mod) will estimate SM04690 dose response compared to vehicle using the results of the primary efficacy endpoint analyses.

As the study is stratified based upon known clinical phenotypes of OA, all primary efficacy analyses will be completed in three subject populations: 1) subjects with unilateral symptomatic OA, 2) subjects with unilateral symptomatic OA and without widespread pain (WPI ≤ 4 and SSQ2 ≤ 2), and 3) all subjects.

10.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

The number and percent of subjects experiencing TEAEs will be summarized by seriousness, severity, and relationship for each treatment group.

ANCOVA will be used to estimate the least squares difference in the change in Patient Global Assessment adjusting for baseline value. Change will be assessed from baseline between each treatment group and the vehicle placebo group. Unadjusted 95% confidence intervals and P values will be reported.

MCP-Mod will estimate SM04690 dose response compared to vehicle using the results of the secondary efficacy endpoint analyses.

As the study is stratified based upon known clinical phenotypes of OA, all secondary efficacy analyses will be completed in three subject populations: 1) subjects with unilateral symptomatic OA, 2) subjects with unilateral symptomatic OA and without widespread pain (WPI ≤ 4 and SSQ2 ≤ 2), and 3) all subjects.

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 TEAEs 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 TEAEs and by changes in clinical laboratory parameters and vital signs, relative to baseline. Changes from baseline in the amount and duration of NSAID usage will be monitored.

10.4.5 BASELINE DESCRIPTIVE STATISTICS

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

10.4.6 PLANNED INTERIM ANALYSES

Not applicable to this study.

10.4.6.1 SAFETY REVIEW

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

10.4.6.2 EFFICACY REVIEW

Not applicable to this study.

10.4.7 EXPLORATORY ANALYSES

Change from baseline will be summarized with descriptive statistics at Weeks 4, 8, 12, 16, and 20 for WOMAC pain subscore, WOMAC function subscore, and Patient Global Assessment; at Weeks 4, 8, 12, 16, 20, and 24 for WOMAC total score, and KOOS (five subscales [Pain, Symptoms, ADL, Sport/Rec and QOL] as well as aggregate scores $KOOS_4$ and $KOOS_5$); and at Weeks 4, 12, and 24 for Physician Global Assessment. Change from baseline will also be statistically described for weekly KOOS-PS and weekly averages of daily pain NRS (aside from Week 24). Change over time in weekly NSAID usage will also be assessed at every week.

ANCOVA will be used to estimate the least squares difference in the change from baseline in exploratory outcomes between each of the four active treatment groups and the vehicle group, adjusted for baseline value. Additionally, ANCOVA will be used to estimate the least squares difference in the change from baseline in all outcomes (including primary and secondary) between the vehicle group and the sham group, adjusted for baseline value. Unadjusted 95% confidence intervals and P values will be reported.

MCP-Mod will estimate SM04690 dose response compared to vehicle using the results of the exploratory efficacy endpoint analyses.

As the study is stratified based upon known clinical phenotypes of OA, all exploratory efficacy analyses will be completed in three subject populations: 1) subjects with unilateral symptomatic OA, 2) subjects with unilateral symptomatic OA and without widespread pain (WPI $\leq$ 4 and SSQ2 $\leq$ 2), and 3) all subjects.

Evaluation of subject awareness of randomized treatment given and the success of blinding in this trial will be estimated using an appropriate categorical analysis. Specifically, the percentage of subjects accurately identifying the assigned treatment group will be estimated.

10.4.8 ADDITIONAL SUB-GROUP ANALYSES

Efficacy analyses described in Section 10.4.2 and Section 10.4.7 will be further analyzed by additional, complementary clinical phenotypes of OA not already defined in the primary analysis. Details on these sub-group analyses will be provided in the SAP.

The additional clinical phenotypes of OA will include, but are not limited to:

- Bilateral Symptomatic OA
- WPI $\leq$ 4 and SSQ2 $\leq$ 2
- WPI > 4 and/or SSQ2 > 2
- Unilateral Symptomatic OA with WPI > 4 and/or SSQ2 > 2

- Bilateral Symptomatic OA with WPI ≤ 4 and SSQ2 ≤ 2
- Bilateral Symptomatic OA with WPI > 4 and/or SSQ2 > 2

10.5 SAMPLE SIZE

A sample size of approximately 630 subjects will be randomized at a ratio of 1:1:1:1:1:1 (0.03 mg active per 2 mL injection : 0.07 mg active per 2 mL injection : 0.15 mg active per 2 mL injection : 0.23 mg active per 2 mL injection : 0.0 mL vehicle : 2.0 mL vehicle). The sample size for this study was based upon accepted dose finding statistical practice (Ting et al. 2017).

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. The investigational center must identify unblinded personnel who will be responsible for preparing the appropriate dilution of the study medication and who are able to perform the injection of study medication and/or vehicle. Study personnel administering or preparing study medication and reference therapy must minimize any contact with the subject following the injection and may not perform any study assessments throughout the duration of the study. 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 their Screening Visit 1. On Day 1, eligible subjects will be randomized via the Medidata database. Upon randomization of a subject, a Treatment Arm Notification email will be sent from *noreply@mdsol.com* to the unblinded investigational staff member designated in the Site-Specific Blinding Plan. Subjects will be randomized 1:1:1:1:1:1 (0.03 mg active per 2 mL injection : 0.07 mg active per 2 mL injection : 0.15 mg active per 2 mL injection : 0.23 mg active per 2 mL injection : 0.0 mL vehicle : 2.0 mL vehicle) to each treatment group using a permuted block design stratified by presence of bilateral knee OA (50% bilateral, 50% unilateral) and WPI&SS (80% WPI ≤ 4 and SSQ2 ≤ 2, 20% WPI > 4 and/or SSQ2 > 2). Specific information regarding the use of Medidata Balance to store and implement the permuted block design will be detailed within the SAP.

10.6.2 EVALUATION OF SUCCESS OF BLINDING

Subjects will be queried regarding the perceived effectiveness of blinding. Details of this analysis will be provided in the SAP.

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 Balance and medical records. Instructions on how to unblind treatment assignment will be provided to each Investigator and kept within a guidance document at each site. No other site users will have access roles to Balance that will allow treatment assignment unblinding.

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

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. 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., ePRO 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); the date and time of informed consent(s) must be recorded in the source documentation
- The subject's medical and disease history before participation in the study
- The subject's basic identifying information, such as subject number, that links the subject's source documents with the eCRFs
- The results of all diagnostic tests performed, diagnoses made, therapy provided, and any other data on the condition of the subject
- All TEAEs (All TEAEs may be documented in the source document but only those defined in the protocol will be transferred to the eCRFs)
- The subject's exposure to any concomitant therapy (including start and stop dates, route of administration, and dosage) (All concomitant therapies may be documented in the source document but only those defined in the protocol will be transferred to the eCRFs)

ePRO 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, ePRO 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 individual, on-site, Site Initiation 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 CRFs and source documents, among other records, for review and inspection by the clinical monitor.

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 Code of Federal Regulations Part 50, 21 Code of Federal Regulations Part 56, and/or the ICH E6.

13.2 INSTITUTIONAL REVIEW BOARD

The Investigator agrees to provide the IRB/EC with all appropriate material, including a copy of the informed consent form (ICF). The study will not be initiated until the Investigator obtains written approval of the research plan and the ICF from the appropriate IRB/EC and copies of these documents are received by the Sponsor. Appropriate reports on the progress of this study will be made by the Investigator to the IRB/EC and Sponsor in accordance with applicable government regulations and in agreement with the policies established by the Sponsor and the IRB/EC. 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 Code of Federal Regulations 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 Investigator or designee must explain the nature of the study protocol and associated risks to the potential study participant. The potential participant must be allowed to review the study information and to ask questions before being asked to sign the ICF. Written informed consent must be provided 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 in the subject's source record.

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 GCP, federal, state, and local regulations, including, to the extent applicable, the Health Insurance Portability and Accountability Act of 1996 ("HIPAA").

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

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

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

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 of the 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 Samumed via data transfers. Medidata Rave is a validated electronic data capture system fully compliant with regulatory expectations for software developers and service providers within the global regulatory environment, including but not limited to ICH E6 and US 21 CFR parts 312, 812, and 11. Data to be transferred external to Rave may include ePRO questionnaires 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 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 Samumed.

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

14.2 STUDY RECORDS RETENTION

During this study, an Investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated with the 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 legislation. The Investigator must inform the Sponsor immediately if any documents are to be destroyed, to be transferred to a different facility, or to be transferred to a different owner.

14.3 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol requirements. The noncompliance may be either on the part of the subject, the Investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly. Protocol deviations must be sent to the site IRB per their guidelines. The site PI/study staff is responsible for knowing and adhering to their IRB requirements.

Refer to the current version of Samumed SOP-300-013 Protocol Deviations for Sponsor procedures related to protocol deviations.

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.

16. LITERATURE REFERENCES

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APPENDIX

Appendix 1. Guidance for Industry: Toxicity Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Trials

Table A1: Tables for Clinical Abnormalities

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

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

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

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

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

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

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

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

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

Table A2: Tables for Laboratory Abnormalities

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

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

** The clinical signs or symptoms associated with laboratory abnormalities might result in characterization of the laboratory abnormalities as Potentially Life Threatening (Grade 4). For example, a low sodium value that falls within a grade 3 parameter (125-129 mE/L) should be recorded as a grade 4 hypernatremia event if the subject had a new seizure associated with the low sodium value.
*** "ULN" is the upper limit of the normal range.

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

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

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

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

Appendix 2. Prohibited Concomitant Medications and Procedures (Supplement)

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)

Tramadol (Ultram, Ryzolt, Conzip, Rybix ODT, Fusepaq Synapryn)

Tapentadol (Nucynta)

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)

Other non-listed anticonvulsants are also prohibited while use for seizure prophylaxis or migraine prophylaxis would be permitted.

Excluded and prohibited electrotherapy treatments include, but are not limited to, the following:

Diathermy

TENS

NMES

Interferential therapy

Shortwave therapy

Iontophoresis

LASER

Ultrasound

Appendix 3. Amendments

AMENDMENT 03 VERSION 00 SUMMARY OF CHANGES

Study Title: A Phase 2, 24-Week, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Safety and Efficacy of SM04690 for the Treatment of Moderately to Severely Symptomatic Knee Osteoarthritis

Purpose: The primary purpose of this amendment is to refine and clarify the analytical design. Additional administrative changes and corrections are also made.

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

Change	Sections Affected	Rationale
"Amendment 03 Version 00" and updated date have been added on the title page.	Title Page	Change was made to capture the dates of all previous and current protocol versions
Protocol date and version have been updated as applicable.	All	Change was made to reflect current protocol amendment
Titles have been updated for Christopher Swearingen and Ismail Simsek.	Sponsor Signature Page and Section 1	Change was made for administrative reasons
List of Abbreviations was updated.	List of Abbreviations	Change was made to capture additions and removal of various abbreviations in this amendment.
The following was added as a Secondary Endpoint: "Evaluate change from baseline OA disease activity as assessed by Patient Global Assessment at Week 24"	Protocol Summary, Section 4.2.2, and Section 10.4.3	Change was made to refine study outcomes in alignment with regulatory labeling requirements.
The following was added as an Exploratory Endpoint: "Evaluate outcome differences between treatment with sham or placebo injections at Week 4, 8, 12, 16, 20, and 24"	Protocol Summary, Section 4.2.3, and Section 10.4.7	Change was made to refine the analytical design to more accurately reflect the investigational rationale for including the sham procedure.
A correction was made in the Primary Endpoints section. #4 erroneously said "Week 2" instead of "Week 24".	Section 4.2.1	Change was made to correct an error and align with the Protocol Summary
A correction was made to Section 7.1.1 which incorrectly noted the WOMAC version as "NR3.1". This was corrected to "NRS 3.1".	Section 7.1.1	Change was made to correct an error
The following edit was made in Section 8.3: "TEAEs that are not serious and are ongoing at the subject's last visit will be followed ~~for a maximum of 30 days~~ *until the study close-out visit, if requested*."	Section 8.3	Change was made to align with update to Section 7.1.1 made in Amendment 02 Version 00.
Analysis dataset definitions were revised.	Section 10.3	Change was made to align with

Change	Sections Affected	Rationale
		accepted statististical practice and ICH guidance.
Details were added regarding the MCP-Mod approach.	Section 10.4.2, Section 10.4.3, and Section 10.4.7	Change was made to clarify the analytical approach.
Subject populations were defined.	Section 10.4.2, Section 10.4.3, and Section 10.4.7	Change was made to refine the analytical design to more accurately reflect the investigational rationale for stratifying by disease phenotype.
Sham was removed from ANCOVA models.	Section 10.4.2	Change was made to refine the analytical design and remove comparison to sham control as part of the analysis of primary endpoints.
Clarification was added regarding the KOOS analysis. Subscales and two aggregate scoring modalities were specified.	Section 10.4.7	Change was made to clarify the outcomes of the instrument.
Sub-group definitions were modified.	Section 10.4.8	Change was made to refine the analytical design to more accurately reflect the investigational rationale for stratifying by disease phenotype.

AMENDMENT 02 VERSION 00 SUMMARY OF CHANGES

Study Title: A Phase 2, 24-Week, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Safety and Efficacy of SM04690 for the Treatment of Moderately to Severely Symptomatic Knee Osteoarthritis

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

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

Change	Sections Affected	Rationale
"Amendment 02 Version 00" and updated date have been added on the title page.	Title Page	Change was made to capture the dates of all previous and current protocol versions
Protocol date and version have been updated as applicable.	All	Change was made to reflect current protocol amendment
The screening window was changed from 21 days to 22 days. Screening Visit 1 must occur between Days -22 to -10 and Screening Visit 2 must occur between Days -12 and -7.	Protocol Summary, Section 4.1, Section 7.3.1, and Section 7.3.6	Change was made to refine study design; baseline questionnaires can be completed up to 7 days prior to Day 1
Approximate number of subjects to be enrolled was updated from 330 to 630.	Protocol Summary, Schematic of Study Design, Section 4.1, and Section 10.5	Change was made to refine study design; sample size is being increased in accord with current dose-finding statistical practice
Subjects will complete a daily electronic diary of NSAID usage generally, not just for the treatment of OA pain.	Protocol Summary, Section 4.1, Section 4.2.3, Section 7.1.1, Section 10.4.4, and Section 10.4.7	Change was made to refine study design; subjects will document any NSAID usage
Edits were made to Exclusion Criterion #6 for clarification; "regular use" applies only to ambulatory assistive devices and "structural knee braces" are braces that contain hardware.	Protocol Summary and Section 5.2	Change was made to clarify the exclusion criterion
"Corticosteroids" was replaced with "glucocorticoids" throughout the protocol.	Protocol Summary, Section 5.2, and Section 7.6	Change was made for clarity and correctness; not all corticosteroids are excluded (e.g., mineralocorticoids are allowed), but all glucocorticoids are excluded
Study duration and estimated date of last subject complection were updated.	Protocol Summary	Change was made for accuracy
Risks and symptoms associated with serious allergic reactions were added to Section 2.3.1.	Section 2.3.1	Change was made to align with the Informed Consent Form
The following edits were made: -Deleted, "Re-screens are limited to subjects who did not meet inclusion/exclusion criteria ~~at Screening Visit 1~~ due to a transient reason." -Added, "*Diary non-compliance is not a*	Section 4.1	Change was made to refine study design; re-screens are allowed if subjects screen fail due to transient reasons at Screening Visit 2 or Day 1

Change	Sections Affected	Rationale
transient event and subjects with diary non-compliance may not be re-screened."		
Additional reasons for withdrawal or early termination were added: •Request by regulatory authority •Study terminated by Sponsor	Section 5.5.1	Change was made for completeness
The following was added in Section 6.1.5: "…if it is the standard practice of the Investigator, a small amount (0.3-0.5 mL) of joint fluid can be aspirated (if present) in order to confirm correct needle placement; *the aspirated fluid does not need to be re-injected.*"	Section 6.1.5	Change was made to clarify the procedure
The following addition was made in Section 6.2: "Quantity returned*/used* (active vial, vehicle vial)"	Section 6.2	Change was made to clarify the study drug accountability procedures
The following addition was made in Section 6.2: "Procedures for Investigator return *or destruction* of used and unused vials of the study medication and vehicle will be provided in the Pharmacy Manual."	Section 6.2	Change was made for completeness as some sites may destroy used and unused vials of medication
The following edit was made in the Collection of Adverse Events Data section: "The subject ~~will~~ *may* be asked to return to the site for an unscheduled visit if a TEAE occurs between study visits…"	Section 7.1.1	Change was made for correctness
The etiology of all TEAEs will be recorded in the eCRF.	Section 7.1.1	Change was made to refine study design
The following edit was made in the Collection of Adverse Events Data section: "TEAEs that are not serious and are ongoing at the subject's last visit will be followed ~~for a maximum of 30 days~~ *until the study site close-out visit, if requested*."	Section 7.1.1	Change was made to refine study design; non-serious TEAEs may be followed until the study site close-out visit
The following was added to the Day 1 Visit description: "Subjects with a period of more than 12 days between Screening Visit 2 and Day 1 are to be screen failed due to the lengthened time between baseline questionnaires and study medication injection."	Section 7.3.2	Change was made to emphasize the importance of the screening visit windows
The following edit was made to Section 10.5: "The sample size for this study was based upon accepted *dose finding* statistical practice *(Ting 2017)*."	Section 10.5, Section 16	Change was made to align with more recent dose finding knowledge
A correction was made to the AM01V00	Appendix 3	Change was made to correct an error

Change	Sections Affected	Rationale
Summary of Changes: "other cosmetic injections are also ~~prohibited~~ *allowed* during the study"		

AMENDMENT 01 VERSION 00 SUMMARY OF CHANGES

Study Title: A Phase 2, 24-Week, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Safety and Efficacy of SM04690 for the Treatment of Moderately to Severely Symptomatic Knee Osteoarthritis

Purpose: The purpose of this amendment is to refine and clarify the study design partially in response to site and IRB feedback

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

Change	Sections Affected	Rationale
"Amendment 01 Version 00" and "Original Protocol Date" have been added on the title page.	Title Page	Change was made to capture the dates of all previous and current protocol versions
Protocol date and version have been updated as applicable.	All	Change was made to reflect current protocol amendment
Additional terms were added to the List of Abbreviations.	List of Abbreviations	Change was made for completeness; new abbreviations were used in the amendment
Primary and secondary objectives were revised.	Summary and Section 3	Change was made to better clarify primary and secondary objectives
The timepoint of the pain NRS primary enpoint was revised to Week 24 instead of Week 12. Evaluation of change from baseline OA pain and OA function at Week 24 and in medial JSW at Week 24 were added as primary endpoints. Analysis of primary endpoints in the Statistical Considerations section was revised accordingly.	Summary, Section 4.2.1, and Section 10.4.2	Change was made to further refine study endpoints
Secondary endpoints were narrowed down to evaluation of safety of SM04690 as measured by TEAEs. Analysis of secondary endpoints in the Statistical Considerations section was revised accordingly.	Summary, Section 4.2.2, and Section 10.4.3	Change was made to further refine study endpoints
Remaining secondary endpoints were added to exploratory endpoints. Exploratory analyses in the Statistical Considerations section were revised accordingly.	Summary, Section 4.2.3, and Section 10.4.7	Change was made to further refine study endpoints
"Evaluate subject perception of study treatment received at Week 24" was added as an exploratory objective. Exploratory analyses in the Statistical Considerations section were revised accordingly.	Summary, Section 4.2.3, and Section 10.4.7	Change was made to further refine study endpoints
"Monthly" and "weekly" descriptors	Summary, Section 4.2.2,	Change was made to further refine

Change	Sections Affected	Rationale
were removed from study endpoints.	and Section 4.2.3	study endpoints
The screening period was increased from 14 days to 21 days. Participant duration was changed to "Up to approximately ~~26~~27 weeks." Screening Visit windows were added.	Summary, Section 4.1, Section 7.3.1, Section 7.3.2, and Section 7.3.6	Change was made per site feedback to allow a larger screening window
The interim analysis has been removed from the study.	Summary, Section 4.1, Section 10	Change was made to align with updated study endpoints; an interim analysis is no longer necessary
The following was deleted from inclusion criterion #2: "(single assistive devices such as canes allowed if needed less than 50% of the time)	Summary and Section 5.1	Change was made to refine inclusion criteria; information regarding assistive devices was added to exclusion criterion #6
The following was added to inclusion criterion #5: "Primary source of pain *throughout the body is* due to OA in the target knee."	Summary and Section 5.1	Change was made to clarify that the primary source of pain throughout the body, not just in the knee, should be due to OA in the target knee
Inclusion criterion #10 was revised: Total WOMAC score of 96-192 (out of 240) for the target knee *at baseline* regardless of if the subject is on symptomatic oral treatment (*baseline questionnaire completed* during the screening period prior to randomization)	Summary and Section 5.1	Change was made for consistency with terminology; baseline WOMAC scores, which will be assessed during the screening period, will be used for eligibility
Inclusion criterion #12 was revised. Amphetamines were deleted. Prohibited concomitant medications were revised accordingly.	Summary, Section 5.1, and Section 7.6	Change was made for accuracy; subjects must test negative for *meth*amphetamines and are prohibited from using *meth*amphetamines while on the study; methamphetamines are already covered under "drugs of abuse"
Inculsion criterion #16 was revised to "Subject's ~~Day 1~~ *Screening Visit 1* visit must occur while…"	Summary and Section 5.1	Change was made as subjects who are screened before the cohort closes will still be allowed to enroll if all other eligibiligy criteria are met
Exclusion criterion #6 was revised: "Currently requires *regular use of ambulatory assistive devices (e.g., wheelchair, parallel bars, walker, canes, or crutches) or* use of a ~~walker,~~ lower extremity prosthesis, and/or a structural ~~patellofemoral~~ knee brace"	Summary and Section 5.2	Change was made to refine exclusion criteria; regular use of ambulatory assistive devices is excluded
The timing of exclusion criteria #9, 18 (previously 19), 19 (previously 20), 22 (previously 23), and 23 (previously 24) were revised to "Screening Visit 1."	Summary and Section 5.2	Change was made for consistency with other exclusion criteria
"Gout or pseudogout" was added to exclusion criterion #15 and exclusion criterion #16 was deleted.	Summary and Section 5.2	Change was made to refine exclusion criteria; gout or pseudogout are excluded altogether

Change	Sections Affected	Rationale
Exclusion criterion #18 (previously 19) was revised. Participation in an observational research trial related to osteoarthritis or planned participation in clinical research trials are excluded. The prohibited medications, treatments, and procedures section was updated accordingly.	Summary, Section 5.2, and Section 7.6	Change was made to refine exclusion criteria and prohibited medications, treatments, and therapies; participation in the noted clinical trials is excluded and prohibited
"Glucocorticosteroids", "corticosteroids", and "glucocorticoids" were revised to only "corticosteroids."	Summary, Section 5.2, and Section 7.6	Change was made for consistency and simplicity
New exclusion criterion #20 was added: Any intra-articular injection into the target knee with a therapeutic aim including but not limited to viscosupplementation (e.g., hyaluronic acid), PRP, and stem cell therapies within 24 weeks prior to Screening Visit 1; treatment of the target knee with intra-articular corticosteroids greater than 12 weeks prior to Screening Visit 1 is allowed. -Exclusion criterion #22 regarding viscosupplementation was deleted as it was merged with the new #20. -The prohibited medications, treatments, and procedures section was updated accordingly.	Summary, Section 5.2, and Section 7.6	Change was made to refine exclusion criteria; any IA injection into the target knee with therapeutic intent is excluded
Exclusion criterion #21 was revised from "equivalent to 10 mg prednisone or more" to "greater than 10 mg prednisone or the equivalent…" The prohibited medications, treatments, and procedures section was updated accordingly.	Summary, Section 5.2, and Section 7.6	Change was made to refine exclusion criteria and prohibited medications; greater than 10 mg prednisone or the equivalent is excluded and prohibited
Exclusion criterion #25 (previously 26) was revised to: "~~Subjects requiring the chronic use (i.e., regular use for ≥ 12 weeks)~~ *Use* of centrally acting analgesics (e.g. duloxetine) *(refer to Appendix 2)* within 12 weeks prior to Screening Visit 1." The prohibited medications, treatments, and procedures section and Appendix 2 was updated accordingly.	Summary, Section 5.2, Section 7.6, and Appendix 2	Change was made to refine the exclusion criterion; any use of centrally acting analgesics within 12 weeks of Screening Visit 1 is excluded/prohibited
New exclusion criterion #26 was added: "Use of anticonvulsants not listed in Appendix 2 within 12 weeks prior to Screening Visit 1, unless used for seizure or migraine prophylaxis"	Summary, Section 5.2, Section 7.6, and Appendix 2	Change was made to refine the exclusion criterion; any use of anticonvulsants not listed in Appendix 2 is excluded/prohibited, unless used for seizure or migraine prophylaxis
Definition of chronic use in exclusion criterion #27 was changed from "regular use for ≥ 12 weeks" to "usage > 1x per	Summary and Section 5.2	Change was made to clarify the definition of chronic opioid usage

Change	Sections Affected	Rationale
week."		
New exclusion criterion #30 was added: If on NSAIDs for the treatment of OA pain, subjects who have not maintained a stable regimen in the opinion of the Investigator at Screening Visit 1.	Summary and Section 5.2	Change was made to refine exclusion criteria; subjects should be on a stable regimen of NSAIDs (if using them for OA pain) prior to the study
Exclusion criterion #32 (previously 31) was revised to state "…*any* investigative site…"	Summary and Section 5.2	Change was made to refine exclusion criteria; subjects who are directly affiliated or are immediate family members of personnel directly affiliated with the study at *any* investigative site are excluded
Exclusion criterion #33 (previously 32) was revised to add immediate family members.	Summary and Section 5.2	Change was made to refine exclusion criteria; subjects employed by Samumed or its affiliates and their immediate family members are excluded
The number of investigational centers was changed from 35 to 80.	Summary and Section 4.1	Change was made for accuracy
Minor corrections were made to the study design schematic.	Schematic of Study Design	Changes were made to ensure the study design schematic accurately represented the study
Job title for Todd Smith was updated.	Section 1	Change was made for administrative reasons
Rationale for the use of a sham injection in this study was added to Section 2.2.	Section 2.2	Change was made per the request of the IRB
Additional information regarding possible risks associated with study vehicle were added to Section 2.3.1 (Study Medication SM04690).	Section 2.3.1	Change was made for completeness; there are some risks associated with study vehicle
Edits were made to the interim analysis description in Section 2.3.1 (Study Medication SM04690).	Section 2.3.1	Change was made for accuracy; the OA-02 safety summary provided is per the interim analysis data (not a locked database). Extra information was deleted for consistency with the IB
Known potential risks related to the study placebos were added to Section 2.3.1.	Section 2.3.1	Change was made for completeness; there are some risks associated with placebo injections
The following was added to Section 4.1: "To support the primary objective, active treatment groups will be compared to both vehicle (2.0 mL vehicle) and sham (0.0 mL vehicle)."	Section 4.1	Change was made to clarify study design
"Seasonal allergies" was deleted from examples of transient reasons for screen failure.	Section 4.1	Change was made because seasonal allergies was not a good example of a transient reason
Details regarding the evaluation of the success of blinding were added to the	Section 4.1, Section 7.1.1, Section 7.3.4, Section	Change was made for completeness; the evaluation was previously

Change	Sections Affected	Rationale
protocol.	7.3.5, and Section 7.3.6, and Section 10.4.7	mentioned in Section 10.6.2 without further details
The following was added to Section 6.1.5: "Although not required, the injection may be guided by ultrasound if it is the standard practice of the investigator."	Section 6.1.5	Change was made per site request; clarification regarding ultrasound guidance was needed
Information regarding how to perform the intra-articular injections (active vs. vehicle vs. sham) was added to Section 6.1.5.	Section 6.1.5	Change was made per the request of the IRB
The following deletion was made in Section 6.2: "All study medication and vehicle ~~received,~~ prepared, and dispensed…"	Section 6.2	Change was made for accuracy; study medication and vehicle may be received by blinded and unblinded staff.
Widespread Pain Index and Symptom Severity Form terminology was updated throughout.	Sections 4.1, 7.1.1, 7.3.1, , 7.3.6, 10.4.8, and 10.6.1	Changes were made for consistency with Sponsor terminology
The WPI&SS assessment will be performed at Screening Visit 1 instead of Screening Visit 2.	Sections 4.1, 7.1.1, 7.3.1, and 7.3.6	Change was made to aid with stratification of cohorts
The following was deleted from the Knee Examination description: "Presence of significant misalignment in either knee (yes/no) will be recorded in the eCRF."	Section 7.1.1	Change was made because this information will not be recorded in the eCRF; this information would be captured via exclusion criterion #11
The Vital Signs description was revised: "Blood pressure (systolic and diastolic) after the subject ~~sits~~*rests (sitting or supine)* for at least 5 minutes; *same resting position should be used for all blood pressure measurements throughout the study"*	Section 7.1.1	Change was made to allow subjects to rest in either sitting or supine position as long as it is used for all BP measurements throughout the study
Regarding the WPI&SS, the following deletions were made: "Upon completion of the WPI&SS assessment, ~~both~~ the subject ~~and the study staff member~~ will sign/initial and date…"	Section 7.1.1	Change was made because study staff are not required to sign the WPI&SS form
Additional detail regarding data storage was added to the Electronic Diary Device Provision and Training section.	Section 7.1.1	Change was made to inform sites of the duration of data storage to ensure data and reports are reviewed in a timely manner
The Pain Numeric Rating Scale (NRS) description was modified to indicate that the subject would be reporting "average knee pain in the last 24 hours."	Section 7.1.1	Change was made to clarify the pain NRS assessment
The description of "just prior to going to bed" was removed throughout the protocol.	Sections 7.1.1, 7.3.1, 7.3.2, and 7.3.7	Change was made to avoid confusion; bedtimes may vary so subjects are just required to complete the questionnaires between 5 pm and

Change	Sections Affected	Rationale
		11:59 pm
The description of "from home" was replaced with "remotely on their electronic devices" throughout the protocol.	Sections 7.1.1, 7.3.1, 7.3.2, and 7.3.7	Change was made to avoid confusion; questionnaires need only be performed remotely
Definitions of non-compliance (missing greater than 3 of 7 entries in a given week) were added to the pain NRS and NSAIDs electronic diary descriptions.	Section 7.1.1	Change was made per site request to clarify the definition of non-compliance and subsequent courses of action
The timeframe to complete baseline questionnaires was updated to Screening Visit 2 + 5 days (or up until the day before the Day 1 visit).	Sections 7.1.1, 7.3.1, and 7.3.7	Change was made per site request to allow for a larger window to complete baseline questionnaires
The Patient Global Assessment description was changed from 100 mm VAS to 50 mm VAS.	Section 7.1.1	Change was made for accuracy; the Patient Global Assessment is a 50 mm VAS
It was clarified that the WPI&SS assessment and the Physician Global Assessment will be performed on paper.	Section 7.1.1	Change was made for clarity; these assessments will not be performed on the electronic device
Section 7.2.1 was revised to state, "Urine microscopy will be performed if urinalysis urine protein, leukocyte esterase (WBC esterase), occult blood, or nitrites values are out of range or if the investigator deems that the microscopy is clinically warranted."	Section 7.2.1	Change was made per site feedback
Section 7.2.1 was revised to state: "The subject must not be randomized on Day 1 and, *if results are available for review prior to Screening Visit 2*, is not recommended to ~~be scheduled for~~ proceed to Screening Visit 2…"	Section 7.2.1	Change was made for clarity; *if* laboratory results are available, it is recommended that they are reviewed prior to the Screening 2 visit
"MDMA" was replaced with "ecstasy" in the urine drug test panel.	Section 7.2.2	Change was made to align with ACM laboratory test description
ACM Global Central Laboratory was changed to ACM Global Laboratory.	Section 7.2.3 and Section 7.2.4	Change was made to align with the laboratory's name change.
The following was added to Screening Visit 1: "In order to complete randomization, WPI&SS scores and subject bilateral/unilateral status from Screening Visit 1 must be entered into EDC prior to the study reaching the enrollment caps described in Section 7.3.2."	Section 7.3.1	Change was made to remind sites to enter WPI&SS scores and subject bilateral/unilateral status into the EDC after Screening Visit 1
The screening window was increased to 21 days: SV1 (Day -21 to -10) and SV2 Day -11 to Day -7).	Section 7.3.1 and Section 7.3.6	Change was made per site request to allow a larger screening window
Section 7.3.2 was renamed	Section 7.3.2	Change was made for accuracy; the Day 1 visit neither qualified as the

Change	Sections Affected	Rationale
"Randomization".		consent or baseline visit (some baseline assessments are to be performed prior to Day 1)
Information regarding randomization cohorts and eligibility for randomization was added to the Day 1 visit.	Section 7.3.2	Change was made for clarity; randomization cohorts were previously mentioned without a description
In Section 7.3.2, "with a window of -2 days" was deleted from the description of monthly and weekly assessments.	Section 7.3.2	Change was made to avoid confusion; details on questionnaire completion are provided in Section 7.3.7
"Return of electronic device" was added to the EOS and ET visits. The study procedures description and schedule of events table were revised accordingly.	Section 7.1.1, Section 7.3.4, Section 7.3.5, and Section 7.3.6	Change was made for completeness; subjects are to return their devices at the EOS or ET visit
The following sentences were deleted from Section 7.6: "Subjects will be encouraged to remain on a stable dose of any allowed medications throughout the study. The use of aspirin (325 mg/day) for thrombosis prophylaxis is permitted."	Section 7.6	Change was made to avoid confusion; NSAIDs are allowed on this study
The first bullet point of the prohibited concomitant medications and procedures list was revised to cover *any* intra-articular injection into either knee.	Section 7.6	Change was made for clarification; any intra-articular injections into either knee are prohibited during the study
New formalized (i.e., prescribed by a medical professional) exercise physical therapy exercise programs for knee OA were added to the list of prohibited concomitant medications and procedures.	Section 7.6	Change was made to refine prohibited therapies; subjects are not allowed to start new physical therapy programs for knee OA while on the study.
The following addition was made to the prohibited concomitant medications and procedures list: "…non-surgical cosmetic procedures such as Botox *or other cosmetic* injections."	Section 7.6	Change was made for clarification; other cosmetic injections are also allowed during the study
A new phone number was provided for the Medical Monitor.	Section 8.4.2	Change was made for administrative reasons
Fax numbers were removed from Table 1.	Section 8.4.2	Change was made to avoid confusion; SAEs should not be reported using the sponsor contact fax numbers
Clarifications were made to the additional sub-group analyses.	Section 10.4.8 and Section 10.6.1	Change was made for clarification of subgroups
References were added due to additions to the rationale section.	Section 16	Change was made for completeness; new references were used in the rationale section
Various spelling, abbreviation, and grammar corrections.	Throughout	Changes were made for correctness and consistency