A Phase 2, 52-Week, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Safety, Tolerability, and Efficacy of Two Injections of SM04690 Injected in the Target Knee Joint of Moderately to Severely Symptomatic Osteoarthritis Subjects

Study Number: SM04690-OA-06

IND Sponsor: Samumed, LLC

Version Number: Amendment 04 Version 00

Date: 21 August 2020

Original Protocol Date: 09 May 2018

Amendment 01 Version 00: 29 June 2018

Amendment 02 Version 00: 17 May 2019

Amendment 03 Version 00: 01 August 2019

SPONSOR SIGNATURE PAGE

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Protocol Number: SM04690-OA-06 AM04V00

Date: 21 August 2020

Name & Title	Signature	Date
Mark Fineman, PhD Sr. Vice President, Clinical Development	*Document has been electronically signed. Please see the final page of the viewable rendition for electronic signatures.*	
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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
AESEV	Severity/Intensity Scale for Adverse Events
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
β-CTX	β-C-terminal telopeptide
BMD	Bone mineral density
BMI	Body mass index
BQL	Below quantitation limit
CDISC	Clinical Data Interchange Standards Consortium
CFR	Code of Federal Regulations
COMP	Cartilage oligomeric matrix protein
CRF	Case report form
CT	Computed tomography
DLT	Dose-limiting toxicity
DXA	Dual-energy X-ray absorptiometry
EC	Ethics Committee
eCOA	Electronic clinical outcomes assessment
eCRF	Electronic case report form
ECG	Electrocardiogram
EDC	Electronic data capture
EOSa	Phase A End of Study
EOSb	Phase B End of Study
ER	Emergency room

Abbreviation	Term
ET	Early termination
FAS	Full Analysis Set
FDA	(US) Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
IA	Intra-articular
IB	Investigator Brochure
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
LDH	Lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
mFAS	Modified Full Analysis Set
mg	Milligram
MI	Myocardial infarction
mJSW	Medial joint space width
mL	Milliliter
mm	Millimeter
mSv	Millisievert
NCS	Not clinically significant
NRS	Numeric rating scale
NSAID	Nonsteroidal anti-inflammatory drug
OA	Osteoarthritis

Abbreviation	Term
PINP	N-terminal propeptide of procollagen type I
PA	Posterior-anterior
PCP	Phencyclidine
PI	Principal Investigator
PRO	Patient reported outcomes
PRP	Platelet-rich plasma
PT	Preferred term
qCT	Quantitative computed tomography
RBC	Red blood cell
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Safety Analysis Set
SD	Standard deviation
SOP	Standard operating procedure
SRC	Safety Review Committee
SS	Symptom Severity
SSQ2	Symptom Severity Question 2
ULN	Upper limit of the normal range
UP	Unanticipated problem
US	United States
WBC	White blood cell
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, 52-Week, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Safety, Tolerability, and Efficacy of Two Injections of SM04690 Injected in the Target Knee Joint of Moderately to Severely Symptomatic Osteoarthritis Subjects		
Protocol Number	SM04690-OA-06		
Protocol Date	21 August 2020	Protocol Version	AM04V00

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

Objectives:

Primary:

The primary objective of this study is to evaluate the safety and tolerability of SM04690 Injectable Suspension administered every 6 months through 52 weeks for the treatment of knee osteoarthritis (OA).

Secondary:

The secondary objectives of this study are:

1. To evaluate the effectiveness of SM04690 Injectable Suspension administered every 6 months through 52 weeks for the treatment of knee OA
2. To evaluate the use of quantitative computed tomography (qCT) to assess knee bone mineral density (BMD)
3. To evaluate the safety, tolerability, and effectiveness of SM04690 Injectable Suspension from 52 weeks through 104 weeks

Endpoints:

Phase A General Safety Endpoints:

1. Adverse events (AEs), serious adverse events (SAEs), vital signs, and clinical laboratory measures through Week 52

Phase A Bone Imaging Endpoints:

1. Actual BMD and change from baseline in BMD in the target knee as assessed by qCT through Week 52 compared to placebo
2. Within-subject difference in BMD from baseline through Week 52 between the target and non-target knee by qCT for SM04690
3. Within-subject difference in BMD from baseline through Week 52 between the target and non-target knee by qCT for placebo
4. Change from baseline in BMD in the spine and hips as assessed by dual-energy X-ray absorptiometry (DXA) at Week 24 and 52

Phase A Efficacy Endpoints:

1. Characterization of change in OA pain in the target knee as measured by the weekly averages of daily pain numeric rating scale (NRS) from baseline through Week 52 accounting for repeated injections
2. Characterization of change durability of treatment response in OA pain in the target knee as measured by the weekly averages of daily

pain NRS through Week 52 elapsed from prior injection to repeat injection
3. Characterization of change in OA function in the target knee as measured by WOMAC physical function subscore (WOMAC Function) from baseline through Week 52 accounting for repeated injections
4. Characterization of change durability of treatment response in OA function in the target knee as measured by WOMAC Function through Week 52 elapsed from prior injection to repeat injection
5. Characterization of change in medial joint space width (mJSW) as measured by radiograph of the target knee from baseline through Week 52 accounting for repeated injections
6. Characterization of change durability of treatment response in mJSW as measured by radiograph of the target knee through Week 52 elapsed from prior injection to repeat injection
7. Characterization of change in OA pain in the target knee as measured by WOMAC pain subscore (WOMAC Pain) from baseline through Week 52 accounting for repeated injections
8. Characterization of change durability of treatment response in OA pain in the target knee as measured by WOMAC Pain through Week 52 elapsed from prior injection to repeat injection
9. Characterization of change in OA disease activity as measured by Patient Global Assessment from baseline through Week 52 accounting for repeated injections
10. Characterization of change durability of treatment response in OA disease activity as measured by Patient Global Assessment through Week 52 elapsed from prior injection to repeat injection

Phase A Exploratory Biomarker Endpoints:

1. Change from baseline in serum bone biomarkers (e.g., N-terminal propeptide of procollagen type I [PINP] and β-C-terminal telopeptide [β-CTX]) and a serum cartilage biomarker (e.g., cartilage oligomeric matrix protein [COMP]) through Week 52 compared to placebo

Phase B General Safety Endpoints:

1. AEs, SAEs, vital signs, and clinical laboratory measures from Week 52 through Week 104

Phase B Bone Imaging Endpoints:

1. Actual BMD and change from baseline in BMD in the target knee as assessed by qCT through Week 104 compared to placebo
2. Within-subject difference in BMD from baseline through Week 104 between the target and non-target knee by qCT for SM04690
3. Within-subject difference in BMD from baseline through Week

104 between the target and non-target knee by qCT for placebo
4. Change from baseline in BMD in the spine and hips as assessed by DXA through Week 104

Phase B Efficacy Endpoints:

1. Characterization of change in OA pain in the target knee as measured by the weekly averages of daily pain NRS from baseline through Week 104 accounting for repeated injections
2. Characterization of change durability of treatment response in OA pain in the target knee as measured by the weekly averages of daily pain NRS through Week 104 elapsed from prior injection to repeat injection
3. Characterization of change in OA function in the target knee as measured by WOMAC Function from baseline through Week 104 accounting for repeated injections
4. Characterization of change durability of treatment response in OA function in the target knee as measured by WOMAC Function through Week 104 elapsed from prior injection to repeat injection
5. Characterization of change in mJSW as measured by radiograph of the target knee from baseline through Week 104 accounting for repeated injections
6. Characterization of change durability of treatment response in mJSW as measured by radiograph of the target knee through Week 104 elapsed from prior injection to repeat injection
7. Characterization of change in OA pain in the target knee as measured by WOMAC Pain from baseline through Week 104 accounting for repeated injections
8. Characterization of change durability of treatment response in OA pain in the target knee as measured by WOMAC Pain through Week 104 elapsed from prior injection to repeat injection
9. Characterization of change in OA disease activity as measured by Patient Global Assessment from baseline through Week 104 accounting for repeated injections
10. Characterization of change durability of treatment response in OA disease activity as measured by Patient Global Assessment through Week 104 elapsed from prior injection to repeat injection

Phase B Exploratory Biomarker Endpoints:

1. Change from Week 52 in serum bone biomarkers (e.g., PINP and β-CTX) and a serum cartilage biomarker (e.g., COMP) through Week 104

Methodology: This study will be a multicenter, randomized, double-blind, placebo-controlled, parallel group study of a single concentration of SM04690

injected into the target knee joint of moderately to severely symptomatic OA subjects. In this study, "placebo" refers to vehicle product.

Approximately 100 subjects will be enrolled and randomized at a ratio of 1:1 (0.07 mg active per 2 mL injection: 2 mL placebo).

Core Phase (Phase A)

Subjects will participate in a screening period of a minimum of 10 days and up to 19 days and a 52-week evaluation period. Each subject will receive an injection on Day 1 and Week 24 (same dose for each injection) and will be observed for one year after first injection. Clinic visits will be scheduled at Screening Visit 1, Screening Visit 2, Day 1, and Weeks 4, 12, 24, 36, and 52 [Phase A End of Study (EOSa)] or Early Termination (ET).

Phase A Study Assessments

qCT will be performed at Screening Visit 2 and at Weeks 12, 24, 36, and 52 (EOSa) or ET. DXA will be performed at Screening Visit 2 and at Weeks 24 and 52 (EOSa) or ET. Bone and cartilage biomarkers will be assessed at Screening Visit 2 and at Weeks 4, 12, 24, 36, and 52 (EOSa) or ET. Radiographic images of the knees will be performed at Screening Visit 1 and at Weeks 24 and 52 (EOSa) or ET.

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

- Daily pain NRS
- Monthly completion of the WOMAC
- Monthly completion of Patient Global Assessment

Extension Phase (Phase B)

Subjects who complete Phase A will be eligible to enter the extension phase, Phase B, for an additional 52 weeks of treatment. Subjects will remain on their randomized treatment (SM04690 or placebo) for the additional year. Each subject will receive an injection at Week 52 (EOSa) and Week 76 with follow-up clinic visits scheduled at Weeks 64, 76, 88, and 104 [Phase B End of Study (EOSb)] or ET.

Primary analysis of Phase A data will be completed after the last subject completes Week 52 (EOSa). While the Sponsor will be unblinded to study treatment after the Phase A analysis (after the last subject completes Week 52 [EOSa]), the Investigator and the subject will remain blinded.

Phase B Study Assessments

qCT will be performed at Weeks 64, 76, 88, and 104 (EOSb) or ET. DXA will be performed at Weeks 76 and 104 (EOSb) or ET. Bone and cartilage biomarkers will be assessed at Weeks 64, 76, 88, and 104 (EOSb) or ET. Radiographic images of the knees will be performed at Weeks 76 and 104 (EOSb) or ET. Subjects will be required to complete the following:

- Daily pain NRS
- Monthly completion of the WOMAC
- 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. WOMAC pain subscore of 20-40 (out of 50) *and* WOMAC physical function subscore of 68-136 (out of 170) for the target knee at baseline, regardless of if the subject is on symptomatic oral treatment (baseline questionnaire completed during the screening period prior to randomization)
11. Widespread Pain Index (WPI) score of ≤ 4 and a Symptom Severity Question 2 (SSQ2) score of ≤ 2 at Screening Visit 1
12. Willingness to use an electronic diary on a daily basis in the evening for the screening period and 104-week study duration
13. Negative drug test for amphetamine, buprenorphine, cocaine, methadone, opiates, phencyclidine (PCP), propoxyphene, barbiturates, benzodiazepine, methaqualone, and tricyclic antidepressants, except if any such drugs are clinically indicated and allowed by the protocol, at Screening Visit 1
14. Subjects with depression or anxiety must be clinically stable for 12

weeks prior to Screening Visit 1 in the opinion of the Investigator and, if on treatment for depression or anxiety, be on 12 weeks of stable therapy

15. Full understanding of the requirements of the study and willingness to comply with all study visits and assessments
16. Subjects must have read and understood the Informed Consent Form (ICF), and must have signed and dated it prior to any study-related procedure being performed
17. Subject's Screening Visit 1 visit must occur while enrollment into the study is open
18. Subject is able to have a Screening Visit 2 qCT image acquired that does not require a re-scan as determined by the central imaging vendor

Criteria for Exclusion:

1. Pregnant and breastfeeding women, and women who are not post-menopausal (defined as 12 months with no menses without an alternative medical cause) or permanently surgically sterile (includes hysterectomy, bilateral salpingectomy, and bilateral oophorectomy) and have a positive or indeterminate pregnancy result at Screening Visit 2 or Day 1
2. Women who are not post-menopausal or permanently surgically sterile, who are sexually active, and who are not willing to use birth control (as outlined in Section 5.3.1) during the study period
3. Males who are sexually active and have a partner who is capable of becoming pregnant, neither of whom have had surgery to become sterilized or who are not using birth control as outlined in Section 5.3.1
4. Body mass index (BMI) > 35
5. Partial or complete joint replacement in either knee
6. Currently requires:
    a. regular use (in the opinion of the Investigator) 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 enrollment 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 bone fracture(s) within 26 weeks prior to Screening Visit 1
11. Any surgery scheduled 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).
12. Significant and clinically evident misalignment of either knee that would impact subject function, as determined by the Investigator
13. History of malignancy within the last 5 years; however, subjects with prior history of in situ basal or squamous cell skin cancer are eligible if completely excised. Subjects with other malignancies are eligible if they have been continuously disease free for at least 5 years prior to Screening Visit 1
14. Clinically significant abnormal screening hematology values, blood chemistry values, or urinalysis values as determined by the Investigator
15. Any condition, including laboratory findings not included in the Screening Visit 2 laboratory tests and findings in the medical history or in the pre-study assessments, that, in the opinion of the Investigator, constitutes a risk or contraindication for participation in the study or that could interfere with the study objectives, conduct, or evaluation
16. 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
17. 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
18. History of mania, bipolar disorder, psychotic disorder, schizophrenia, schizoaffective disorder, major depressive disorder, or generalized anxiety disorder
19. Participation in a clinical research trial that included the receipt of an investigational product (IP) or any experimental therapeutic procedure within 26 weeks prior to Screening Visit 1, or planned participation in any such trial
20. Treatment of the target knee with intra-articular glucocorticoids (e.g., methylprednisolone) within 12 weeks prior to Screening Visit 1
21. Any intra-articular injection into the target knee with a therapeutic aim including, but not limited to, viscosupplementation (e.g., hyaluronic acid), platelet-rich plasma (PRP), and stem cell therapies within 24 weeks prior to Screening Visit 1; treatment of

the target knee with intra-articular glucocorticoids greater than 12 weeks prior to Screening Visit 1 is allowed

22. Treatment with systemic (oral, intramuscular, or intravenous) glucocorticoids greater than 10 mg prednisone or the equivalent per day within 4 weeks prior to Screening Visit 1
23. Effusion of the target knee clinically requiring aspiration within 12 weeks prior to Screening Visit 1
24. Use of electrotherapy, acupuncture, and/or chiropractic treatments for knee OA within 4 weeks prior to Screening Visit 1 (refer to Appendix 1)
25. Any known active infections, including urinary tract infection, upper respiratory tract infection, sinusitis, suspicion of intra-articular infection, hepatitis B or hepatitis C infection, and/or infections that may compromise the immune system such as human immunodeficiency virus (HIV) at Day 1
26. Subjects requiring the chronic use (i.e., regular and consistent use for ≥ 12 weeks) of centrally acting analgesics (e.g., duloxetine) (refer to Appendix 1) within 12 weeks prior to Screening Visit 1
27. Subjects requiring the chronic use (i.e., regular and consistent use for ≥ 12 weeks) of anticonvulsants not listed in Appendix 1 within 12 weeks prior to Screening Visit 1, unless used for seizure or migraine prophylaxis
28. Subjects requiring the usage of opioids >1x per week within 12 weeks prior to Screening Visit 1
29. Topical local anesthetic agents (gels, creams, or patches such as the Lidoderm patch) used for the treatment of knee OA within 7 days of Screening Visit 1
30. Any chronic condition that has not been well controlled or subjects with a chronic condition who have not maintained a stable therapeutic regimen of a prescription therapy in the opinion of the Investigator. In addition, subjects with an HbA1c >9 at Screening Visit 2 will be excluded.
31. 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
32. Any contraindications for performing DXA scans of the hips or spine including but not limited to:
    a. other radiological investigations using contrast media or radionuclides within 7 days of Screening Visit 2
    b. weight that precludes scanning at these sites
33. Subjects who have had a single or bilateral hip replacement
34. Subjects who have a current or pending disability claim, workers' compensation, or litigation(s) that may compromise response to

treatment

35. 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
36. 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
37. Subject has non-evaluable DXA scans of the hips or spine (i.e., pins, screws, any surgical implant, fracture, or severe degenerative changes in the region of interest), as assessed by the central imaging vendor at the time of screening

Population:	Approximately 100 subjects with moderately to severely symptomatic osteoarthritis of the knee
Phase:	2
Number of Sites enrolling participants:	This study will be conducted at approximately 15 investigational centers in the United States
Description of Study Agent:	SM04690 is a small molecule Wnt pathway inhibitor which potentially (a) reduces signs and symptoms of knee OA via an anti-inflammatory mechanism and (b) inhibits breakdown and enhances formation of cartilage through effects on progenitor cells resident in the joint.
Study Duration:	Approximately 156 weeks Estimated date first subject consented: November 2018 Estimated date last subject completed: October 2021
Participant Duration:	Approximately 55 weeks for Phase A and 52 weeks for Phase B

Criteria for evaluation:

Efficacy:

Efficacy will be assessed by:

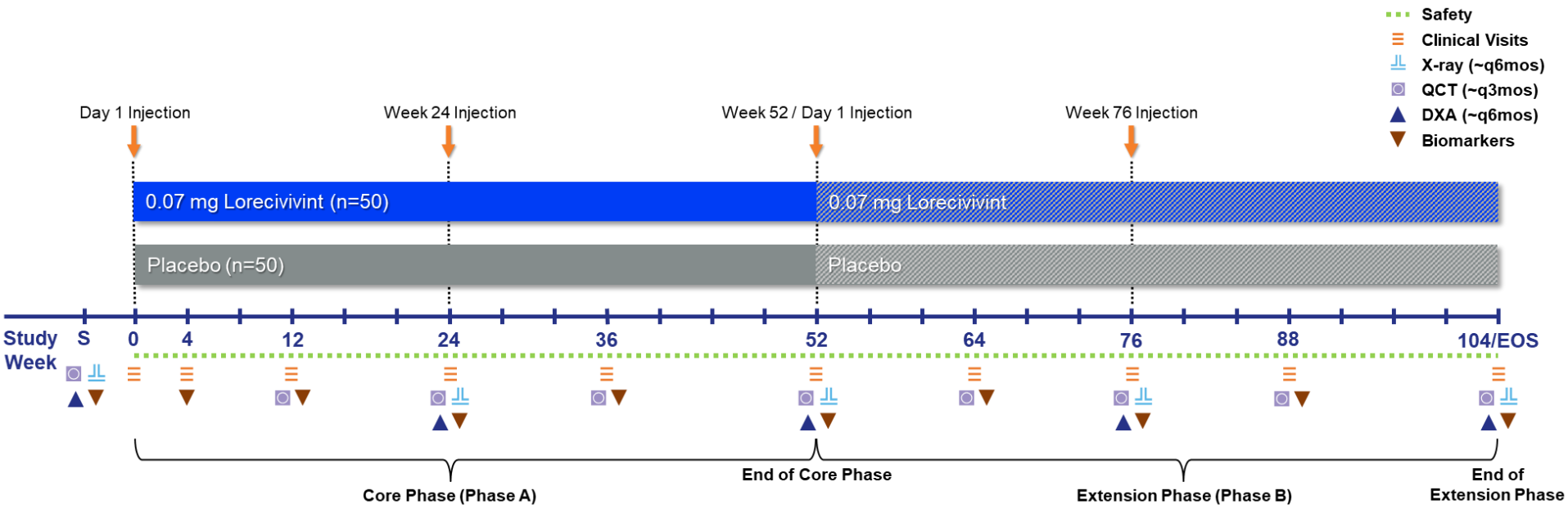
- Weekly averages of daily pain NRS (for target knee OA pain)
- Monthly WOMAC Pain and Function for the target knee
- Monthly Patient Global Assessment
- mJSW by radiograph

Safety:

The overall safety and tolerability of SM04690 will be assessed by the incidence, severity, and relatedness of AEs, SAEs, and clinically significant changes in clinical laboratory measures and vital signs, as assessed by the Investigator.

Safety will also be assessed by evaluating BMD in the knee joints by qCT and evaluating DXA scans of the spine and hips.

SCHEMATIC OF STUDY DESIGN



DXA = dual-energy X-ray absorptiometry; EOS = End of study; qCT = quantitative computed tomography; S = Screening.

1. KEY ROLES

Medical monitor	Ismail Simsek, MD - Medical Director Samumed, LLC 9360 Towne Centre Drive San Diego, CA 92121 (858) 926-2968 ismail@samumed.com
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Central radiology reader	Medical Metrics, Inc. (MMI) 2121 Sage Road, Suite 300 Houston, Texas 77056 (713) 850-7500
Central qCT and DXA reader	Bioclinica 211 Carnegie Center Drive Princeton, NJ 08540 (877) 632-9432
Electronic clinical outcomes assessment (eCOA)	YPrime 263 Great Valley Parkway Malvern, PA 19355 (888) 201-7988
Central laboratory	Medpace Central Laboratories 5365 Medpace Way Cincinnati, Ohio 45227 (800) 749-1737

2. INTRODUCTION: BACKGROUND INFORMATION & SCIENTIFIC RATIONALE

2.1 BACKGROUND INFORMATION

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

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

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

Based on WOMAC Pain and Function results for the 0.07 mg dose group observed in completed clinical studies (SM04690-01 and SM04690-OA-02), the 0.07 mg SM04690 dose was selected for further investigation in this study. This phase 2 study, SM04690-OA-06, is a multicenter, randomized, double-blind, placebo-controlled, parallel group study of a single concentration of

0.07 mg SM04690 per 2 mL injection injected into the target knee joint of moderately to severely symptomatic OA subjects at Day 1 and Week 24 (Phase A). Subjects who complete Phase A will be eligible to enter the extension phase, Phase B, for an additional 52 weeks of treatment. The study is designed to assess the safety and tolerability of repeated SM04690 injections, focusing not only on AEs but also several assessments of bone density.

The control to be used in this study is a placebo concurrent control. The placebo consists of a vehicle containing all components of the SM04690 injectable suspension with the exception of the active ingredient. Vehicle is considered the appropriate control in this study as it allows for evaluation of the safety and tolerability of the SM04690 molecule alone through comparison of the active and placebo arms.

2.3 POTENTIAL RISKS AND BENEFITS

2.3.1 KNOWN POTENTIAL RISKS

Study Medication SM04690

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

Study Placebo

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

Risks of Injection

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

Risks of Topical Anesthetics

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

Blood Sampling

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

Radiographs (X-ray) and Dual-Energy X-ray Absorptiometry (DXA)

This study involves radiation exposure from 5 radiographs and 5 DXA scans of the hips and spine, 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 radiographs that the subject will receive in this study is expected to be about 0.025 mSv or equivalent to approximately 3 days of background radiation in the US. The radiation dose for all DXA scans that the subject will receive in this study is expected to be about 0.03 mSv or equivalent to approximately 4 days of background radiation in the US. The risks from these doses are small. This radiation exposure may not be necessary for the subjects' medical care, but it is necessary to obtain the research information desired.

Computed Tomography (CT) Scans

As part of this study, 9 CT scans will be performed. 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 CT scans that the subject will receive in this study is expected to be about 1.8 mSv or equivalent to approximately 7 months of background radiation in the US dose from background radiation. The risk from this dose is small but may cause a slightly increased risk of cancer over a lifetime. This radiation exposure is not necessary for the subject's medical care but 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, tolerability, and efficacy of two injections 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 evaluate the safety and tolerability of SM04690 Injectable Suspension administered every 6 months through 52 weeks for the treatment of knee OA.

Secondary objectives:

The secondary objectives of this study are:

1. To evaluate the effectiveness of SM04690 Injectable Suspension administered every 6 months through 52 weeks for the treatment of knee OA
2. To evaluate the use of quantitative computed tomography (qCT) to assess knee bone mineral density (BMD)
3. To evaluate the safety, tolerability, and effectiveness of SM04690 Injectable Suspension from 52 weeks through 104 weeks

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 a single concentration of SM04690 injected into the target knee joint of moderately to severely symptomatic OA subjects. In this study, "placebo" refers to vehicle.

Approximately 100 subjects will be enrolled and randomized at a ratio of 1:1 (0.07 mg active per 2 mL injection: 2 mL placebo).

This study will be conducted at approximately 15 investigational centers in the US.

Core Phase (Phase A)

Subjects will participate in a screening period of a minimum of 10 days and up to 19 days and a 52-week evaluation period. Each subject will receive an injection on Day 1 and Week 24 (same dose for each injection) and will be observed for one year after first injection. Clinic visits will be scheduled at Screening Visit 1, Screening Visit 2, Day 1, and Weeks 4, 12, 24, 36, and 52 (EOSa) or ET. Specific timing of protocol procedures is described in the Schedule of Events Table (Section 7.3.7). Specific timing of electronic diary and questionnaire completion is described in the Schedule of Electronic Diary and Questionnaire Completion Table (Section 7.3.8).

A Widespread Pain Index and Symptom Severity (WPI&SS) assessment will be administered at Screening Visit 1. qCT will be performed at Screening Visit 2 and Weeks 12, 24, 36, and 52 (EOSa) or ET. DXA will be performed at Screening Visit 2 and Weeks 24 and 52 (EOSa) or ET. Bone and cartilage biomarkers will be assessed at Screening Visit 2 and Weeks 4, 12, 24, 36, and 52 (EOSa) or ET. Radiographic images of the knees will be performed at Screening Visit 1, Week 24, and Week 52 (EOSa) or ET.

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

- Daily pain NRS
- Monthly completion of the WOMAC
- Monthly completion of Patient Global Assessment

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 at Weeks 4, 12, 24, 36, and 52 (EOSa) or ET. Height will be measured at Screening Visit 1 and weight will be measured at Screening Visit 1 and at Weeks 24 and 52 (EOSa) or ET. Clinical laboratory evaluations will be performed at Screening Visit 2 and at Weeks 4, 12, 24, 36, and 52 (EOSa) or ET.

Extension Phase (Phase B)

Subjects who complete Phase A will be eligible to enter the extension phase, Phase B, for an additional 52 weeks of treatment. Subjects will remain on their randomized treatment (SM04690 or placebo) for the additional year. Each subject that consents to enter Phase B will receive an injection at Week 52 (EOSa) and Week 76 with follow-up clinic visits scheduled at Weeks 64, 76, 88, and 104 (EOSb) or ET. Specific timing of protocol procedures is described in the Schedule of Events Table (Section 7.3.7). Specific timing of electronic diary and questionnaire

completion is described in the Schedule of Electronic Diary and Questionnaire Completion Table (Section 7.3.8).

Primary analysis of Phase A data will be completed after the last subject completes Week 52 (EOSa). While the Sponsor will be unblinded to study treatment after the Phase A analysis (after the last subject completes Week 52 [EOSa]), the Investigator and the subject will remain blinded.

In Phase B, qCT will be performed at Weeks 64, 76, 88, and 104 (EOSb) or ET. DXA will be performed at Weeks 76 and 104 (EOSb) or ET. Bone and cartilage biomarkers will be assessed at Weeks 64, 76, 88, and 104 (EOSb) or ET. Radiographic images of the knees will be performed at Weeks 76 and 104 (EOSb) or ET.

Subjects will be required to complete the following:

- Daily pain NRS
- Monthly completion of the WOMAC
- Monthly completion of Patient Global Assessment

Recording of signs and symptoms of study medication intolerability and AE reporting will start following the first injection of the study medication and continue until the subjects complete their last study visit. All AEs, 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 an acceptable image was acquired within the previous 6 weeks), and qCT and DXA (if acceptable images were acquired within the previous 3 months), must be performed at re-screen; no results or data, except for the knee radiograph, qCT, and DXA, may be used from the previous screen. Target knee selection may not be changed at re-screen.

4.2 STUDY ENDPOINTS

4.2.1 PHASE A GENERAL SAFETY ENDPOINTS

1. Adverse events (AEs), serious adverse events (SAEs), vital signs, and clinical laboratory measures through Week 52

4.2.2 PHASE A BONE IMAGING ENDPOINTS

1. Actual BMD and change from baseline in BMD in the target knee as assessed by qCT through Week 52 compared to placebo
2. Within-subject difference in BMD from baseline through Week 52 between the target and non-target knee by qCT for SM04690
3. Within-subject difference in BMD from baseline through Week 52 between the target and non-target knee by qCT for placebo
4. Change from baseline in BMD in the spine and hips as assessed by dual-energy X-ray absorptiometry (DXA) at Week 24 and 52

4.2.3 PHASE A EFFICACY ENDPOINTS

1. Characterization of change in OA pain in the target knee as measured by the weekly averages of daily pain numeric rating scale (NRS) from baseline through Week 52 accounting for repeated injections
2. Characterization of change durability of treatment response in OA pain in the target knee as measured by the weekly averages of daily pain NRS through Week 52 elapsed from prior injection to repeat injection
3. Characterization of change in OA function in the target knee as measured by WOMAC physical function subscore (WOMAC Function) from baseline through Week 52 accounting for repeated injections
4. Characterization of change durability of treatment response in OA function in the target knee as measured by WOMAC Function through Week 52 elapsed from prior injection to repeat injection
5. Characterization of change in medial joint space width (mJSW) as measured by radiograph of the target knee from baseline through Week 52 accounting for repeated injections
6. Characterization of change durability of treatment response in mJSW as measured by radiograph of the target knee through Week 52 elapsed from prior injection to repeat injection
7. Characterization of change in OA pain in the target knee as measured by WOMAC pain subscore (WOMAC Pain) from baseline through Week 52 accounting for repeated injections
8. Characterization of change durability of treatment response in OA pain in the target knee as measured by WOMAC Pain through Week 52 elapsed from prior injection to repeat injection
9. Characterization of change in OA disease activity as measured by Patient Global Assessment from baseline through Week 52 accounting for repeated injections
10. Characterization of change durability of treatment response in OA disease activity as measured by Patient Global Assessment through Week 52 elapsed from prior injection to repeat injection

4.2.4 PHASE A EXPLORATORY BIOMARKER ENDPOINTS

1. Change from baseline in serum bone biomarkers (e.g., N-terminal propeptide of procollagen type I [PINP] and β-C-terminal telopeptide [β-CTX]) and a serum cartilage

biomarker (e.g., cartilage oligomeric matrix protein [COMP]) through Week 52 compared to placebo

4.2.5 PHASE B GENERAL SAFETY ENDPOINTS

1. AEs, SAEs, vital signs, and clinical laboratory measures from Week 52 through Week 104

4.2.6 PHASE B BONE IMAGING ENDPOINTS

1. Actual BMD and change from baseline in BMD in the target knee as assessed by qCT through Week 104 compared to placebo
2. Within-subject difference in BMD from baseline through Week 104 between the target and non-target knee by qCT for SM04690
3. Within-subject difference in BMD from baseline through Week 104 between the target and non-target knee by qCT for placebo
4. Change from baseline in BMD in the spine and hips as assessed by DXA through Week 104

4.2.7 PHASE B EFFICACY ENDPOINTS

1. Characterization of change in OA pain in the target knee as measured by the weekly averages of daily pain NRS from baseline through Week 104 accounting for repeated injections
2. Characterization of change durability of treatment response in OA pain in the target knee as measured by the weekly averages of daily pain NRS through Week 104 elapsed from prior injection to repeat injection
3. Characterization of change in OA function in the target knee as measured by WOMAC Function from baseline through Week 104 accounting for repeated injections
4. Characterization of change durability of treatment response in OA function in the target knee as measured by WOMAC Function through Week 104 elapsed from prior injection to repeat injection
5. Characterization of change in mJSW as measured by radiograph of the target knee from baseline through Week 104 accounting for repeated injections
6. Characterization of change durability of treatment response in mJSW as measured by radiograph of the target knee through Week 104 elapsed from prior injection to repeat injection
7. Characterization of change in OA pain in the target knee as measured by WOMAC Pain from baseline through Week 104 accounting for repeated injections
8. Characterization of change durability of treatment response in OA pain in the target knee as measured by WOMAC Pain through Week 104 elapsed from prior injection to repeat injection
9. Characterization of change in OA disease activity as measured by Patient Global Assessment from baseline through Week 104 accounting for repeated injections
10. Characterization of change durability of treatment response in OA disease activity as measured by Patient Global Assessment through Week 104 elapsed from prior injection to repeat injection

4.2.8 PHASE B EXPLORATORY BIOMARKER ENDPOINTS

1. Change from Week 52 in serum bone biomarkers (e.g., PINP and β-CTX) and a serum cartilage biomarker (e.g., COMP) through Week 104

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. WOMAC pain subscore of 20-40 (out of 50) *and* WOMAC physical function subscore of 68-136 (out of 170) for the target knee at baseline, regardless of if the subject is on symptomatic oral treatment (baseline questionnaire completed during the screening period prior to randomization)
11. Widespread Pain Index (WPI) score of ≤ 4 and a Symptom Severity Question 2 (SSQ2) score of ≤ 2 at Screening Visit 1
12. Willingness to use an electronic diary on a daily basis in the evening for the screening period and 104-week study duration
13. Negative drug test for amphetamine, buprenorphine, cocaine, methadone, opiates, phencyclidine (PCP), propoxyphene, barbiturates, benzodiazepine, methaqualone, and tricyclic antidepressants, except if any such drugs are clinically indicated and allowed by the protocol, at Screening Visit 1.
14. Subjects with depression or anxiety must be clinically stable for 12 weeks prior to Screening Visit 1 in the opinion of the Investigator and, if on treatment for depression or anxiety, be on 12 weeks of stable therapy

15. Full understanding of the requirements of the study and willingness to comply with all study visits and assessments
16. Subjects must have read and understood the Informed Consent Form (ICF), and must have signed and dated it prior to any study-related procedure being performed
17. Subject's Screening Visit 1 visit must occur while enrollment into the study is open
18. Subject is able to have a Screening Visit 2 qCT image acquired that does not require a re-scan as determined by the central imaging vendor

5.2 PARTICIPANT EXCLUSION CRITERIA

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

1. Pregnant and breastfeeding women, and women who are not post-menopausal (defined as 12 months with no menses without an alternative medical cause) or permanently surgically sterile (includes hysterectomy, bilateral salpingectomy, and bilateral oophorectomy) and have a positive or indeterminate pregnancy result at Screening Visit 2 or Day 1
2. Women who are not post-menopausal or permanently surgically sterile, who are sexually active, and who are not willing to use birth control (as outlined in Section 5.3.1) during the study period
3. Males who are sexually active and have a partner who is capable of becoming pregnant, neither of whom have had surgery to become sterilized or who are not using birth control as outlined in Section 5.3.1
4. Body mass index (BMI) > 35
5. Partial or complete joint replacement in either knee
6. Currently requires:
    a. regular use (in the opinion of the Investigator) 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 enrollment 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 bone fracture(s) within 26 weeks prior to Screening Visit 1
11. Any surgery scheduled 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).
12. Significant and clinically evident misalignment of either knee that would impact subject function, as determined by the Investigator
13. History of malignancy within the last 5 years; however, subjects with prior history of in situ basal or squamous cell skin cancer are eligible if completely excised. Subjects with

other malignancies are eligible if they have been continuously disease free for at least 5 years prior to Screening Visit 1

14. Clinically significant abnormal screening hematology values, blood chemistry values, or urinalysis values as determined by the Investigator
15. Any condition, including laboratory findings not included in the Screening Visit 2 laboratory tests and findings in the medical history or in the pre-study assessments, that, in the opinion of the Investigator, constitutes a risk or contraindication for participation in the study or that could interfere with the study objectives, conduct, or evaluation
16. 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
17. 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
18. History of mania, bipolar disorder, psychotic disorder, schizophrenia, schizoaffective disorder, major depressive disorder, or generalized anxiety disorder
19. Participation in a clinical research trial that included the receipt of an investigational product (IP) or any experimental therapeutic procedure within 26 weeks prior to Screening Visit 1, or planned participation in any such trial
20. Treatment of the target knee with intra-articular glucocorticoids (e.g., methylprednisolone) within 12 weeks prior to Screening Visit 1
21. Any intra-articular injection into the target knee with a therapeutic aim including, but not limited to, viscosupplementation (e.g., hyaluronic acid), platelet-rich plasma (PRP), and stem cell therapies within 24 weeks prior to Screening Visit 1; treatment of the target knee with intra-articular glucocorticoids greater than 12 weeks prior to Screening Visit 1 is allowed
22. Treatment with systemic (oral, intramuscular, or intravenous) glucocorticoids greater than 10 mg prednisone or the equivalent per day within 4 weeks prior to Screening Visit 1
23. Effusion of the target knee clinically requiring aspiration within 12 weeks prior to Screening Visit 1
24. Use of electrotherapy, acupuncture, and/or chiropractic treatments for knee OA within 4 weeks prior to Screening Visit 1 (refer to Appendix 1)
25. Any known active infections, including urinary tract infection, upper respiratory tract infection, sinusitis, suspicion of intra-articular infection, hepatitis B or hepatitis C infection, and/or infections that may compromise the immune system such as human immunodeficiency virus (HIV) at Day 1
26. Subjects requiring the chronic use (i.e., regular and consistent use for ≥ 12 weeks) of centrally acting analgesics (e.g., duloxetine) (refer to Appendix 1) within 12 weeks prior to Screening Visit 1
27. Subjects requiring the chronic use (i.e., regular and consistent use for ≥ 12 weeks) of anticonvulsants not listed in Appendix 1 within 12 weeks prior to Screening Visit 1,

unless used for seizure or migraine prophylaxis

28. Subjects requiring the usage of opioids >1x per week within 12 weeks prior to Screening Visit 1
29. Topical local anesthetic agents (gels, creams, or patches such as the Lidoderm patch) used for the treatment of knee OA within 7 days of Screening Visit 1
30. Any chronic condition that has not been well controlled or subjects with a chronic condition who have not maintained a stable therapeutic regimen of a prescription therapy in the opinion of the Investigator. In addition, subjects with an HbA1c >9 at Screening Visit 2 will be excluded.
31. 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
32. Any contraindications for performing DXA scans of the hips or spine including but not limited to:
    a. other radiological investigations using contrast media or radionuclides within 7 days of Screening Visit 2
    b. weight that precludes scanning at these sites
33. Subjects who have had a single or bilateral hip replacement
34. Subjects who have a current or pending disability claim, workers' compensation, or litigation(s) that may compromise response to treatment
35. 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
36. 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
37. Subject has non-evaluable DXA scans of the hips or spine (i.e., pins, screws, any surgical implant, fracture, or severe degenerative changes in the region of interest), as assessed by the central imaging vendor at the time of screening

5.3 LIFESTYLE GUIDELINES

5.3.1 CONTRACEPTION

From Screening Visit 1 until their last study visit, 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.

Acceptable forms of contraception are:

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

post-menopausal or permanently surgically sterile, or must use another form of birth control which includes the following:

a. Barrier methods of contraception such as a diaphragms or cervical/vault caps
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. Tubal ligation/occlusion/division

3. Women who are not post-menopausal or permanently surgically sterile must agree to use birth control (as described in #2 above) and be instructed that their male partner(s) must use a condom

Subjects who withdraw from the study after receiving study medication should remain on an acceptable form of contraception for 24 weeks after their last study injection.

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 two injections in Phase A and two injections in Phase B, best efforts will be made to encourage subjects to attend all follow-up visits even if they are withdrawn from treatment. 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 study medication and/or 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
- AE
- Subject non-compliance
- Request by regulatory authority
- Study terminated by Sponsor

The Investigator may withdraw a subject from study medication or the study if, in the Investigator's opinion, it is not in the best interest of the subject to continue with treatment or the study.

5.5.2 HANDLING OF PARTICIPANT WITHDRAWALS OR TERMINATION

In case of premature discontinuation of study participation, ET procedures should be conducted within 14 days of discontinuation for any subject who 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.

Subjects who are withdrawn from study medication for safety reasons will continue with all planned study visits per protocol, without any further dosing.

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 placebo 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 2.5 mL of formulated suspension in a ready-to-use 3 mL polypropylene vial. SM04690 placebo product is supplied as 2.5 mL of formulated vehicle in a ready-to-use 3 mL polypropylene vial. SM04690 placebo product contains 0.5% carboxymethylcellulose sodium and 0.05% polysorbate 80 in pH 7.4 phosphate buffered saline.

SM04690 drug product and placebo product are manufactured by Catalent Pharma Solutions, (Woodstock, IL) and will be supplied as a ready-to-use single-use injection. SM04690 drug product and placebo product 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 placebo 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. Refer to the Pharmacy Manual for detailed instructions on how to manage temperature excursions.

6.1.4 PREPARATION

Each dose of ready-to-use SM04690 drug product or placebo product should be well mixed (the drug product is a suspension) prior to injecting 2 mL intra-articularly into the target knee. Refer to the Pharmacy Manual for detailed instructions on study medication preparation.

6.1.5 DOSING AND ADMINISTRATION

SM04690 will be administered in the following dosage strengths:

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

The injectable investigational product or placebo is to be administered by the Unblinded Investigator as a single injection into the target knee joint once each at Day 1 and Week 24 (Phase A), and once each at Week 52 (EOSa) and Week 76 (Phase B). The Week 24, 52 (EOSa), and 76 injections may occur up to two weeks later than the Week 24, 52 (EOSa), and 76 visits, respectively, to allow for resolution of any intercurrent illness (e.g., infection) prior to the injection. The Unblinded Investigator must minimize any contact with the subject following the injections and may not perform any study assessments throughout the duration of the study. All subject contact for the remainder of the study is limited to the Blinded Investigator and other appropriate blinded study personnel.

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

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

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

sterile syringe and, via syringe exchange, subsequently inject study medication using a new syringe.

6.1.6 ROUTE OF ADMINISTRATION

The injectable investigational product or placebo is to be administered as a single intra-articular injection into the target knee joint once each at Day 1 and Week 24 (Phase A), and once each at Week 52 (EOSa) and Week 76 (Phase B).

6.1.7 STARTING DOSE AND DOSE ESCALATION SCHEDULE

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

6.1.8 DOSE ADJUSTMENTS/MODIFICATIONS/DELAYS

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

6.1.9 DURATION OF THERAPY

The injectable investigational product or placebo is to be administered as a single intra-articular injection into the target knee joint once each at Day 1 and Week 24 (Phase A), and once each at Week 52 (EOSa) and Week 76 (Phase B).

At the Week 24, 52 (EOSa), and 76 visits, the Investigator should evaluate the subject for suitability to receive the study medication injection. The subject should not have any condition, including laboratory findings and findings in pre-injection assessments, that, in the opinion of the Investigator, constitutes a risk or contraindication for the injection, or that could interfere with the study objectives, conduct, or evaluation. The injections may occur up to two weeks later than the Week 24, 52 (EOSa), and 76 visits, respectively, to allow for resolution of any intercurrent illness (e.g., infection) prior to the injection. If, in the opinion of the Investigator, the subject should not receive any of the injections, the subject will discontinue treatment but will continue with all planned study visits per protocol.

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 placebo 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 injected
- Quantity dispensed (active vial, placebo vial)
- Quantity returned/used (active vial, placebo vial)

All study medication and vehicle 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 placebo 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 Unblinded Investigator return or destruction of used and unused vials of the study medication and placebo will be provided in the Pharmacy Manual.

7. STUDY PROCEDURES AND SCHEDULE

7.1 STUDY PROCEDURES/EVALUATIONS

7.1.1 STUDY SPECIFIC PROCEDURES

Collection of Adverse Events Data

Data regarding AEs will be collected in this study. AEs are events that occur during the 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. AEs will be assessed at each study visit from the time of study medication injection on study visit Day 1 through the subject's last study visit.

Each subject will be observed and queried by the Investigator or the Investigator's designee at each study visit for any continuing AEs or new AEs since the previous visit. The subject may be asked to return to the site for an unscheduled visit if an AE occurs between study visits, and if, in the opinion of the Investigator, the AE requires a study visit for full evaluation. Any AE reported by the subject or noted by the Investigator or the Investigator's designee will be recorded within the eCRF. The following information will be recorded for each AE: description of the event, date of onset and resolution, etiology, and severity as assessed by the Investigator according to the Clinical Data Interchange Standards Consortium (CDISC) Severity/Intensity Scale for Adverse Events (AESEV) (Table 1), causal relationship to study medication, outcome, and any treatment given.

In this protocol, signs and symptoms of exacerbation or worsening of target knee OA will be captured in the context of efficacy assessments and recorded on specific pages of the eCRF.

Anticipated fluctuations or anticipated deterioration (in the opinion of the Investigator) of the underlying disease (target knee OA) will not be considered as AEs nor captured on the AE page of the eCRF.

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

AEs that are ongoing at a subject's last visit will be followed for 30 days after administration of the last dose of study medication or until resolution, whichever comes first. Resolution is defined as the return to baseline status or stabilization of the condition. SAEs that are ongoing at a subject's last visit will be followed until resolution.

Medical History

A medical history will be obtained at Screening Visit 1 and Day 1 with a follow-up at Weeks 52 (EOSa) and 104 (EOSb) or ET to capture End Dates of any ongoing medical history collected at screening. 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. Examples of medical conditions and disease states that should be considered relevant to the subject's study participation include history of current disease, medical history that confirms the eligibility criteria of the subject, and asymptomatic medical history that could become symptomatic while on the study.

Physical Examination

A general physical examination will be conducted at all visits except Screening Visit 2. Results of the physical examination will be noted in the source documents. Any clinically significant finding noted prior to study medication injection should be recorded as medical history. If it is found after study medication injection, it should be reported as an AE.

Knee Examination

A knee examination of both knees will be conducted at all visits except Screening Visit 2. Results of the knee examination will be noted in the source documents. Any clinically significant finding noted prior to study medication injection should be recorded as medical history. If it is found after study medication injection, it should be reported as an AE.

Presence of unilateral or bilateral knee OA 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 all visits except Screening Visit 2.

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

- Body temperature
- Pulse rate
- Respiratory rate
- Blood pressure (systolic and diastolic) after the subject rests (sitting or supine) for at least 5 minutes; 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 an AE 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 at Weeks 24, 52 (EOSa), 76, and 104 (EOSb) or ET.

Radiograph of Knee Joints

Radiograph of the knee joints will be taken at Screening Visit 1 and at Weeks 24, 52 (EOSa), 76, and 104 (EOSb) or 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 at the central imaging vendor 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. The central imaging vendor does not provide medical advice, clinical diagnosis, or treatment recommendations. These imaging assessments and quantitative measurements provided to the Sponsor do not and shall not constitute a medical diagnosis, treatment recommendation, or medical advice, and are not intended to be used as a substitute for the study Investigator's or other qualified health care professional's medical diagnosis, treatment, or advice. If any AEs or other unusual pathology is noted in the study images, the Sponsor will be notified of the finding and will promptly notify the Investigator. The Investigator will then assess the clinical significance as well as any follow-up procedures that need to be completed. Clinically significant findings that are not part of an existing diagnosis will be recorded as medical history or an AE as appropriate.

Dual-energy X-ray Absorptiometry (DXA)

Bone density DXA scans of the spine and hips will be taken at Screening Visit 2 and at Weeks 24, 52 (EOSa), 76, and 104 (EOSb) or ET. The DXA scans should be obtained in the posterior-

anterior (PA) view.

Detailed instructions for obtaining and managing the DXA scans will be provided to the investigational center prior to the initiation of subject enrollment.

The DXA scanning will assess changes in BMD of the hips and spine. The DXA scans will be submitted to an independent reviewer at the central imaging vendor for interpretation. An eligibility report identifying whether subject anatomy can be longitudinally evaluated for the Screening Visit 2 DXA and the DXA scan T score and Z scores for each DXA scan will be reported to the Investigator. The central imaging vendor does not provide medical advice, clinical diagnosis, or treatment recommendations. These imaging assessments and quantitative measurements provided to the Sponsor do not and shall not constitute a medical diagnosis, treatment recommendation, or medical advice, and are not intended to be used as a substitute for the study Investigator's or other qualified health care professional's medical diagnosis, treatment, or advice. If any AEs or other unusual pathology is noted in the study images, the Sponsor will be notified of the finding and will promptly notify the Investigator. The Investigator will then assess the clinical significance as well as any follow-up procedures that need to be completed. Clinically significant findings that are not part of an existing diagnosis will be recorded as medical history or an AE as appropriate.

Quantitative Computed Tomography (qCT)

Quantitative computed tomography of both knee joints will be taken at Screening Visit 2 and at Weeks 12, 24, 36, 52 (EOSa), 64, 76, 88, and 104 (EOSb) or ET.

Detailed instructions for obtaining and managing the qCT scans will be provided to the investigational center prior to the initiation of subject enrollment.

The CT scanning will document changes in bone health. The CT scans will be submitted to an independent reviewer at the central imaging vendor for interpretation. A quality assessment report will be provided to the Investigator by the central imaging vendor to confirm subject eligibility. The central imaging vendor does not provide medical advice, clinical diagnosis, or treatment recommendations. These imaging assessments and quantitative measurements provided to the Sponsor do not and shall not constitute a medical diagnosis, treatment recommendation, or medical advice, and are not intended to be used as a substitute for the study Investigator's or other qualified health care professional's medical diagnosis, treatment, or advice. If any AEs or other unusual pathology is noted in the study images, the Sponsor will be notified of the finding and will promptly notify the Investigator. The Investigator will then assess the clinical significance as well as any follow-up procedures that need to be completed. Clinically significant findings that are not part of an existing diagnosis will be recorded as medical history or an AE as appropriate.

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. The WPI&SS assessment used in this study is modified from that described in (Clauw 2014). A WPI&SS assessment will be completed by the subject at Screening Visit 1.

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. 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 the subject's last study visit.

Pain Numeric Rating Scale (NRS)

The pain NRS is an 11-point scale [0-10] for subject self-reporting of their knee pain for that day. The NRS will be anchored by descriptors at each end ("No Pain" on the left and "Worst Possible Pain" on the right). 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 daily knee pain. 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 7.3.8 for a schedule of electronic diary and questionnaire completion.

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

Western Ontario and McMaster Universities Arthritis Index (WOMAC)

The WOMAC is a widely used, proprietary outcome measurement tool used by health professionals to evaluate the condition of patients with OA of the knee and hip, including pain, stiffness, and physical functioning of a target joint. The WOMAC Version NRS 3.1 questionnaire will be completed by the subject for their target knee in the evening (between 5:00 pm and 11:59 pm) remotely on their electronic devices 5 days after their Screening Visit 2 (i.e., 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, with a window of ± 3 days) 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 7.3.8 for a schedule of electronic diary and questionnaire completion. At Weeks 24, 52 (EOSa), and 76, the WOMAC questionnaire must be completed prior to the Weeks 24, 52 (EOSa), and 76 study medication injections, respectively.

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

Patient Global Assessment of Disease Activity

The Patient Global Assessment is an 11-point (0-10) NRS on which the subjects will rate how they feel their target knee OA is, considering all the ways in which their target knee OA may

affect them. The NRS will be anchored by descriptors at each end ("Very Good" on the left and "Very Bad" on the right). The Patient Global Assessment will be completed by the subject in the evening (between 5:00 pm and 11:59 pm) remotely on their electronic devices 5 days after their Screening Visit 2 (i.e., Screening Visit 2 + 5 days) or up until the day before the Day 1 visit. After Day 1, monthly (every 4 weeks, with a window of ± 3 days) 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 7.3.8 for a schedule of electronic diary and questionnaire completion. At Weeks 24, 52 (EOSa), and 76, the Patient Global Assessment must be completed prior to the Weeks 24, 52 (EOSa), and 76 study medication injections, respectively.

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.

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

Fasting samples for clinical laboratory analysis by Medpace Central Laboratories will be collected by a qualified staff member at Screening Visit 2 and Weeks 4, 12, 24, 36, 52 (EOSa), 64, 76, 88, and 104 (EOSb) or 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 2.

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 2 clinical laboratory test results prior to the Day 1 visit. The subject must not be randomized on Day 1 if any of the Screening Visit 2 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, then date and initial the report. The Investigator must report all laboratory results that are BOTH outside the normal range for the laboratory AND, in the opinion of the Investigator, are clinically significant. If any abnormal, clinically significant laboratory measure is found prior to study medication injection, the subject is to be excluded. If it is found after study medication injection, it should be reported as an AE.

7.2.2 OTHER ASSAYS OR PROCEDURES

Pregnancy Test

A serum-based pregnancy test will be performed on female subjects at Screening Visit 2 and a urine-based pregnancy test will be performed on female subjects of childbearing potential at Day 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: amphetamine, buprenorphine, cocaine, methadone, opiates, phencyclidine (PCP), propoxyphene, barbiturates, benzodiazepine, methaqualone, and tricyclic antidepressants. Results from the drug test will be utilized to determine subject eligibility.

Biomarkers

Blood samples for biomarker analysis will be collected by a qualified staff member at Screening Visit 2 and Weeks 4, 12, 24, 36, 52 (EOSa), 64, 76, 88, and 104 (EOSb) or ET.

Biomarkers that will be assessed in serum include, but are not limited to, bone biomarkers (PINP and β-CTX), and a cartilage biomarker (COMP).

7.2.3 SPECIMEN PREPARATION, HANDLING, AND STORAGE

Refer to the Laboratory Manual for Medpace Central Laboratories.

7.2.4 SPECIMEN SHIPMENT

Refer to the Laboratory Manual for Medpace Central Laboratories.

7.3 STUDY SCHEDULE

7.3.1 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 10-19 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 rate, blood pressure, respiratory rate, and temperature)
- Height and weight measurements
- 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.

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 7-16 days (inclusive) prior to Day 1. Subjects should fast for 8 hours prior to this visit.

This visit should occur after confirmation of eligible radiograph and urine drug test report results.

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

- qCT of both knees
- DXA of the spine and hips
- Venipuncture and collection of samples for clinical laboratory tests and biomarker analysis
- Pregnancy test (serum-based)
- 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 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 and Patient Global Assessment, in addition to the pain NRS assessment, in the evening (between 5:00 pm and 11:59 pm) remotely on their electronic devices. Refer to Section 7.3.8 for a schedule of electronic diary and questionnaire completion.

7.3.2 RANDOMIZATION

Day 1

This visit must occur within 10-19 days of Screening Visit 1.

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
- Pregnancy test (urine-based) (for female subjects of childbearing potential)
- Physical examination, including knee examination of both knees
- Vital signs measurements (pulse rate, blood pressure, respiratory rate, and temperature)
- Review of pain NRS electronic diary compliance from Screening Visit 2 to Day 1
- Electronic questionnaire review (WOMAC)

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

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

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

Note: After the Day 1 site visit, subjects will complete monthly (every 4 weeks, with a window of ± 3 days) WOMAC and Patient Global Assessment, and daily pain NRS assessments in the evening (between 5:00 pm and 11:59 pm) remotely on their electronic devices. Refer to Section 7.3.8 for a schedule of electronic diary and questionnaire completion.

7.3.3 FOLLOW-UP

Week 4

The Week 4 visit should occur on Day 29 (with a window of + 3 days). Subjects should fast for 8 hours prior to this visit.

The following procedures and assessments will be performed at this visit:

- Collection of AE and concomitant procedures/medication data
- Physical examination, including knee examination of both knees
- Vital signs measurements (pulse rate, blood pressure, respiratory rate, and temperature)

- Venipuncture and collection of samples for clinical laboratory tests and biomarker analysis

Week 12

The Week 12 visit should occur on Day 85 (with a window of ± 3 days). Subjects should fast for 8 hours prior to this visit.

The following procedures and assessments will be performed at this visit:

- Collection of AE and concomitant procedures/medication data
- Physical examination, including knee examination of both knees
- Vital signs measurements (pulse rate, blood pressure, respiratory rate, and temperature)
- Venipuncture and collection of samples for clinical laboratory tests and biomarker analysis
- qCT of both knees

Week 24

The Week 24 visit should occur on Day 169 (with a window of + 3 days). Subjects should fast for 8 hours prior to this visit. Prior to study medication injection, the Investigator should evaluate the subject for suitability to receive the second injection (refer to Section 6.1.9). The injection may occur up to two weeks later than the Week 24 visit to allow for resolution of any intercurrent illness (e.g., infection) prior to the injection. The subject should complete all other Week 24 assessments and return for an unscheduled visit and injection in the case that they are not able to receive the injection at the Week 24 visit.

The following procedures and assessments will be performed at this visit:

- Collection of AE and concomitant procedures/medication data
- Physical examination, including knee examination of both knees
- Vital signs measurements (pulse rate, blood pressure, respiratory rate, and temperature)
- Weight measurement
- Venipuncture and collection of samples for clinical laboratory tests and biomarker analysis
- Radiograph – bilateral in weight-bearing fixed flexion position, posterior-anterior (PA) view X-ray
- qCT of both knees
- DXA of the spine and hips
- Intra-articular study medication injection (or placebo)

Note: The Week 24 WOMAC and Patient Global Assessment must have already been completed prior to the Week 24 study medication injection.

Week 36

The Week 36 visit should occur on Day 253 (with a window of -3 to + 7 days). Subjects should fast for 8 hours prior to this visit.

The following procedures and assessments will be performed at this visit:

- Collection of AE and concomitant procedures/medication data
- Physical examination, including knee examination of both knees
- Vital signs measurements (pulse rate, blood pressure, respiratory rate, and temperature)
- Venipuncture and collection of samples for clinical laboratory tests and biomarker analysis
- qCT of both knees

7.3.4 FINAL STUDY VISIT

Week 52 Phase A End of Study (EOSa)

This study visit should occur on Day 365 with a window of -3 to + 7 days. Subjects should fast for 8 hours prior to this visit.

The following procedures and assessments will be performed at Week 52 (EOSa):

- Collection of AE and concomitant procedures/therapies/medication data
- Review of medical history
- Vital signs measurements (pulse rate, blood pressure, respiratory rate, and temperature)
- Physical examination, including knee examination of both knees
- Weight measurement
- Venipuncture and collection of samples for clinical laboratory tests and biomarker analysis
- Radiograph – bilateral in weight-bearing fixed flexion position, posterior-anterior (PA) view X-ray
- qCT of both knees
- DXA of the spine and hips

For subjects who consent to participate in Phase B, prior to study medication injection, the Investigator should evaluate the subject for suitability to receive the injection (refer to Section 6.1.9). The injection may occur up to two weeks later than the Week 52 (EOSa) visit to allow for resolution of any intercurrent illness (e.g., infection) prior to the injection. The subject should complete all other Week 52 (EOSa) assessments and return for an unscheduled visit and injection in the case that they are not able to receive the injection at the Week 52 (EOSa) visit. If the subject is determined to be suitable for injection, the subject will receive an intra-articular study medication injection (or placebo).

Note: The Week 52 (EOSa) WOMAC and Patient Global Assessment must be completed prior to the Week 52 (EOSa) study medication injection

7.3.5 EXTENSION PHASE (PHASE B)

Week 64 and Week 88

The Week 64 visit should occur on Day 449 (with a window of +7 days) and the Week 88 visit should occur on Day 617 (with a window of + 7 days). Subjects should fast for 8 hours prior to these visits.

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

- Collection of AE and concomitant procedures/medication data
- Physical examination, including knee examination of both knees
- Vital signs measurements (pulse rate, blood pressure, respiratory rate, and temperature)
- Venipuncture and collection of samples for clinical laboratory tests and biomarker analysis
- qCT of both knees

Week 76

The Week 76 visit should occur on Day 533 (with a window of + 7 days). Subjects should fast for 8 hours prior to this visit. Prior to study medication injection, the Investigator should evaluate the subject for suitability to receive the injection (refer to Section 6.1.9). The injection may occur up to two weeks later than the Week 76 visit to allow for resolution of any intercurrent illness (e.g., infection) prior to the injection. The subject should complete all other Week 76 assessments and return for an unscheduled visit and injection in the case that they are not able to receive the injection at the Week 76 visit.

The following procedures and assessments will be performed at this visit:

- Collection of AE and concomitant procedures/medication data
- Physical examination, including knee examination of both knees
- Vital signs measurements (pulse rate, blood pressure, respiratory rate, and temperature)
- Weight measurement
- Venipuncture and collection of samples for clinical laboratory tests and biomarker analysis
- Radiograph – bilateral in weight-bearing fixed flexion position, posterior-anterior (PA) view X-ray
- qCT of both knees
- DXA of the spine and hips
- Intra-articular study medication injection (or placebo)

Note: The Week 76 WOMAC and Patient Global Assessment must be completed prior to the Week 76 study medication injection.

Week 104 Phase B End of Study (EOSb)

This final study visit should occur on Day 729 with a window of + 7 days. Subjects should fast for 8 hours prior to this visit.

The following procedures and assessments will be performed at Week 104 (EOSb):

- Collection of AE and concomitant procedures/therapies/medication data
- Review of medical history
- Vital signs measurements (pulse rate, blood pressure, respiratory rate, and temperature)
- Physical examination, including knee examination of both knees
- Weight measurement
- Venipuncture and collection of samples for clinical laboratory tests and biomarker analysis
- Radiograph – bilateral in weight-bearing fixed flexion position, posterior-anterior (PA) view X-ray
- qCT of both knees
- DXA of the spine and hips

7.3.6 EARLY TERMINATION VISIT

If possible, the following procedures and assessments should be performed within 14 days of subject premature withdrawal or termination. Subjects should fast for 8 hours prior to this visit.

- Collection of AE and concomitant procedures/therapies/medication data
- Review of medical history
- Vital signs measurements (pulse rate, blood pressure, respiratory rate, and temperature)
- Physical examination, including knee examination of both knees
- Weight measurement
- Venipuncture and collection of samples for clinical laboratory tests and biomarker analysis
- Radiograph – bilateral in weight-bearing fixed flexion position, posterior-anterior (PA) view X-ray
- qCT of both knees
- DXA of the spine and hips

7.3.7 SCHEDULE OF EVENTS TABLE

Procedure	Phase A							Phase B					ET
	Screening Period[a] (Days -19 to -1)		**Day 1**[b]	**Week 4** (Day 29 +3 days)	**Week 12** (Day 85 ±3 days)	**Week 24**[c] (Day 169 +3 days)	**Week 36** (Day 253 -3 to + 7 days)	**Week 52**[c] **(EOSa)** (Day 365 -3 to +7 days)	**Week 64** (Day 449 +7 days)	**Week 76**[c] (Day 533 +7 days)	**Week 88** (Day 617 +7 days)	**Week 104 (EOSb)** (Day 729 +7 days)	
	Screening Visit 1 (Days -19 to -10)	**Screening Visit 2** (Days -16 to -7)											
Informed consent	X												
Inclusion & exclusion criteria	X		X										
Demographics	X												
Medical history	X		X					X[d]				X[d]	X[d]
Current and prior procedures/medications	X		X										
Serum pregnancy test		X											
Urine pregnancy test			X[e]										
Urine drug test	X												
WPI & SS	X												
Radiograph	X					X		X		X		X	X
qCT		X			X	X	X	X	X	X	X	X	X
DXA		X				X		X		X		X	X
Physical examination	X		X	X	X	X	X	X	X	X	X	X	X
Knee examination	X		X	X	X	X	X	X	X	X	X	X	X
Selection of target knee	X												
Height	X												
Weight	X					X		X		X		X	X

Procedure	Phase A							Phase B					ET
	Screening Period[a] (Days -19 to -1)		**Day 1**[b]	**Week 4** (Day 29 +3 days)	**Week 12** (Day 85 ±3 days)	**Week 24**[c] (Day 169 +3 days)	**Week 36** (Day 253 -3 to + 7 days)	**Week 52**[c] **(EOSa)** (Day 365 -3 to +7 days)	**Week 64** (Day 449 +7 days)	**Week 76**[c] (Day 533 +7 days)	**Week 88** (Day 617 +7 days)	**Week 104 (EOSb)** (Day 729 +7 days)	
	Screening Visit 1 (Days -19 to -10)	**Screening Visit 2** (Days -16 to -7)											
Vital signs	X		X	X	X	X	X	X	X	X	X	X	X
Clinical laboratory sampling		X		X	X	X	X	X	X	X	X	X	X
Biomarkers[f]		X		X	X	X	X	X	X	X	X	X	X
Electronic diary and questionnaire training		X[g] (eDiary device provision & training)											
Pain NRS (Review)			X[h]										
WOMAC (Review)			X[i]										
Randomization			X										
Intra-articular injection			X			X		X		X			
AEs and concomitant procedures/medications			X	X	X	X	X	X	X	X	X	X	X

[a] The screening period is a minimum of 10 days and a maximum of 19 days and includes Screening Visit 1 and Screening Visit 2; Screening Visit 2 should occur at least 3 days after Screening Visit 1, at least 7 days prior to Day 1, and after confirmation of eligible radiograph and urine drug test report results.
[b] At Day 1, all procedures should be performed prior to study medication injection except for collection of AE and concomitant procedures/medication data.
[c] At Week 24, 52 (EOSa), and 76, all procedures should be performed prior to study medication injection.
[d] Review medical history to capture End Date(s), if applicable, of any ongoing medical history(ies) collected at screening.
[e] Urine pregnancy test on Day 1 will only be performed on female subjects of childbearing potential.
[f] Concentrations of bone and cartilage biomarkers are analyzed in the serum.
[g] 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.
[h] Electronic diary compliance for daily pain NRS over the screening period will be reviewed at Day 1 prior to randomization to determine subject eligibility.
[i] WOMAC questionnaire will be reviewed at Day 1 prior to randomization to determine subject eligibility.

7.3.8 SCHEDULE OF ELECTRONIC DIARY AND QUESTIONNAIRE COMPLETION TABLE

	Monthly WOMAC and Patient Global Assessment	**Daily pain NRS**
Study Week/Day (Study Visits are denoted with grey shading.)	WOMAC and Patient Global Assessment will be completed by subjects 5 days after Screening Visit 2 (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 within a window of ± 3 days as outlined below; ranges shown are inclusive.	Pain NRS 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.
5 days after Screening Visit 2	Baseline WOMAC and Patient Global Assessment questionnaires (or up until the day before the Day 1 visit)	
Day 1		Starting on the same day of Day 1 (after the visit), pain NRS assessments are to be completed for the target knee only. Complete daily.
Week 4 (Day 29)	Complete between Day 26 and 32	
Week 8 (Day 57)	Complete between Day 54 and 60	
Week 12 (Day 85)	Complete between Day 82 and 88	
Week 16 (Day 113)	Complete between Day 110 and 116	
Week 20 (Day 141)	Complete between Day 138 and 144	
Week 24 (Day 169)*	Complete between Day 166 and 172	
Week 28 (Day 197)	Complete between Day 194 and 200	
Week 32 (Day 225)	Complete between Day 222 and 228	
Week 36 (Day 253)	Complete between Day 250 and 256	
Week 40 (Day 281)	Complete between Day 278 and 284	
Week 44 (Day 309)	Complete between Day 306 and 312	
Week 48 (Day 337)	Complete between Day 334 and 340	
Week 52 (Day 365)*	Complete between Day 362 and 368	
Week 56 (Day 393)	Complete between Day 390 and 396	
Week 60 (Day 421)	Complete between Day 418 and 424	
Week 64 (Day 449)	Complete between Day 446 and 452	

	Monthly WOMAC and Patient Global Assessment	Daily pain NRS
Week 68 (Day 477)	Complete between Day 474 and 480	
Week 72 (Day 505)	Complete between Day 502 and 508	
Week 76 (Day 533)*	Complete between Day 530 and 536	
Week 80 (Day 561)	Complete between Day 558 and 564	
Week 84 (Day 589)	Complete between Day 586 and 592	
Week 88 (Day 617)	Complete between Day 614 and 620	
Week 92 (Day 645)	Complete between Day 642 and 648	
Week 96 (Day 673)	Complete between Day 670 and 676	
Week 100 (Day 701)	Complete between Day 698 and 704	
Week 104 (Day 729)	Complete between Day 726 and 732	

***Note:** At Weeks 24, 52 (EOSa), and 76, the WOMAC and Patient Global Assessment must be completed prior to the Week 24, 52 (EOSa), and 76 study medication injections, respectively.

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 the subject's last visit will be recorded in the "Prior and Concomitant Medications" eCRF. "All medications" should include prescription, over the counter, supplements, as well as herbal or alternative medications.

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

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

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 1)
  - Other anticonvulsants not listed in Appendix 1 are also prohibited unless used for seizure or migraine prophylaxis
  - Systemic glucocorticoids greater than 10 mg of prednisone per day or the equivalent
  - Drugs screened to assess eligibility, unless clinically indicated and allowed by the protocol: amphetamine, buprenorphine, cocaine, methadone, opiates, PCP, propoxyphene, barbiturates, benzodiazepine, methaqualone, and tricyclic antidepressants

- Electrotherapy (refer to Appendix 1), 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.
- 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 OA 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, collection of AEs, SAEs, and concomitant medications, and general medical evaluations.

8.1.1 DEFINITION OF ADVERSE EVENTS (AE)

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

An AE is any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an 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 AE term rather than a series of symptoms relating to a diagnosis. Fluctuations of pre-existing conditions, including the disease under study that does not represent a clinically significant exacerbation or worsening, need not be considered AEs. In order to classify AEs and diseases, preferred terms will be assigned by the Sponsor to the original terms entered on the eCRF, using the Medical Dictionary for Regulatory Activities (MedDRA).

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

8.1.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

According to the ICH 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 inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is an important medical event, defined as an event that does not fit one of the other outcomes, but may jeopardize the subject and may require medical or surgical intervention (treatment) to prevent one of the other outcomes. Examples include allergic bronchospasm (a serious problem with breathing) requiring treatment in an emergency room, 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.

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

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

8.1.3 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

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

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

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

8.2 CLASSIFICATION OF AN ADVERSE EVENT

8.2.1 SEVERITY OF EVENT

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

Table 1: CDISC Definitions of Adverse Event Severity

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

8.2.2 RELATIONSHIP TO STUDY AGENT

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

1. Not Related

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

2. Unlikely Related

The AE is unlikely related if (1) the AE is unlikely related in time **or** (2) the AE is considered unlikely to be related to use of the study medication or study injection (i.e., there are no facts [evidence] or arguments to suggest a causal relationship), or the AE is considered possibly related to another event, medical condition, or product not associated with the study medication.

3. Possibly Related

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

4. Probably Related

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

8.2.3 EXPECTEDNESS

The Sponsor will be responsible for determining whether an AE/SAE is expected or unexpected. An AE/SAE will be considered unexpected if the nature, severity, or frequency of the event is

not consistent with the risk information previously described for the study agent in the IB or is not listed in the IB at the specificity or severity that has been observed.

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

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

AEs that are ongoing at a subject's last visit will be followed for 30 days after administration of the last dose of study medication or until resolution, whichever comes first. Resolution is defined as the return to baseline status or stabilization of the condition. SAEs that are ongoing at a subject's last visit will be followed until resolution.

8.4 REPORTING PROCEDURES

8.4.1 ADVERSE EVENT REPORTING

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

8.4.2 SERIOUS ADVERSE EVENT REPORTING

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

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 should review the SAE information and sign the SAE report, and the Investigator or designee should submit the SAE report to the Samumed Study SAE email address: sae@samumed.com or FAX: +1 858 408 4470. Follow-up information must be detailed in a follow-up SAE report and reported to the Samumed Study SAE email address or fax number as it becomes available. The Investigator also must report all SAEs promptly to the appropriate IRB/EC as required by the institution. Sponsor contact information for questions regarding SAE reporting is provided in Table 2.

Table 2: Sponsor Contact Information for Questions on SAE Reporting

Primary Contact		**Alternative Contact**	
Medical Monitor: Ismail Simsek, MD		Sr. Manager, Drug Safety and Pharmacovigilance: Kathleen Toscano	
Office Tel:	(858) 926-2968	Office Tel:	(858) 371-4057
Cellular:	(858) 334-5374	Cellular:	(858) 287-0274
Email:	ismail@samumed.com	Email:	kathleent@samumed.com

8.4.3 UNANTICIPATED PROBLEM REPORTING

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

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

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

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

8.4.4 EVENTS OF SPECIAL INTEREST

Not applicable to this study.

8.4.5 REPORTING OF PREGNANCY

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

Pregnancy is not considered an AE; however, any pregnancy will be collected on a Samumed Pregnancy Report Form. Information will be collected for any pregnancy in a female subject or the pregnant female partner of a male subject (if consenting), which occurs during the study, including perinatal and neonatal outcome. Infants resulting from such pregnancies should be followed for a minimum of 12 weeks.

8.5 STUDY HALTING RULES

Not applicable to this study.

8.6 SAFETY OVERSIGHT

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

9. CLINICAL MONITORING

All aspects of the study will be monitored by the Sponsor or the Sponsor's designees with respect to current 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 Phase A statistical analyses will be specified in a statistical analysis plan (SAP). A second SAP will be prepared for Phase B analyses.

10.2 STATISTICAL HYPOTHESES

No formal hypothesis test will be performed in this study.

10.3 ANALYSIS DATASETS

Full Analysis Set (FAS): All subjects who are randomized and receive at least one 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 received injections into the target knee both on Day 1 and at Week 24.

Per-Protocol Analysis Set (PPAS): mFAS subjects who complete the study and do not have any protocol deviations that may impact the evaluation of efficacy outcomes.

Safety Analysis Set (SAS): All subjects who receive at least one 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. The principal analysis of the Phase A endpoints will be conducted on data extracted from the study database after the last subject completes the Week 52 (EOSa) visit.

10.4.2 ANALYSIS OF PHASE A GENERAL SAFETY AND BONE IMAGING ENDPOINTS

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

Change over time in BMD in the target knee as assessed by qCT will be characterized using a mixed-effects model for repeated measures (MMRM) in order to estimate change from baseline with treatment group, week, treatment×week, and baseline as covariates. The model will be evaluated at Week 52. Unadjusted 95% confidence intervals and P values will be reported. The model will be estimated assuming an unstructured variance-covariance matrix, allowing the data to fully inform the correlation between within-subject observations (Kincaid 2005).

As a sensitivity analysis, analysis of covariance (ANCOVA) will be used to estimate baseline-adjusted BMD in the target knee at Weeks 12, 24, 36, and 52. The ratio of baseline-adjusted BMD between SM04690 and placebo will be presented with a one-sided 95% confidence interval.

Baseline-adjusted ANCOVA will also be used to analyze the within-subject difference in BMD between the target and non-target knee by qCT for SM04690, within-subject difference in BMD between the target and non-target knee by qCT for placebo, and change from baseline in BMD of the spine and hips by DXA for SM04690 subjects versus placebo. The models will be adjusted for baseline and evaluated at Weeks 12, 24, 36, and 52 for qCT and Weeks 24 and 52 for DXA. Unadjusted 95% confidence intervals and P values will be reported.

10.4.3 ANALYSIS OF PHASE A EFFICACY AND EXPLORATORY BIOMARKER ENDPOINTS

Changes in the target knee from baseline in Pain NRS, WOMAC Function, WOMAC Pain, mJSW, and Patient Global Assessment will be characterized using MMRM; the models will be evaluated through Week 52. All models will use treatment group, week, treatment×week

interaction, and baseline values as covariates. Unadjusted 95% confidence intervals and P values will be reported.

For WOMAC, mJSW, and Patient Global Assessment, the model will be estimated assuming an unstructured variance-covariance matrix. For Pain NRS, the model will be estimated assuming a Toeplitz variance-covariance matrix. The Toeplitz structure is a more generalized form of autogressive-1 structure, allowing the data to inform how the correlation between within-subject observations decreases over time instead of implicitly defining a uniform decay structure (Kincaid 2005).

To assess response durability, changes in the target knee from Week 24 (i.e., after second injection) in Pain NRS, WOMAC Function, WOMAC Pain, mJSW, and Patient Global Assessment will be characterized using MMRM; the models will be evaluated through Week 52. All models will use treatment group, week, treatment×week interaction, and Week 24 values as covariates. Unadjusted 95% confidence intervals and P values will be reported.

Baseline-adjusted ANCOVA will be used to analyze the change from baseline in serum bone biomarkers (e.g. PINP and β-CTX) and a serum cartilage biomarker (e.g., COMP) for SM04690 subjects versus placebo. The models will be adjusted for baseline and evaluated at Weeks 4, 12, 24, 36, and 52. Unadjusted 95% confidence intervals and P values will be reported.

10.4.4 ANALYSIS OF PHASE B ENDPOINTS

Phase B endpoints will be analyzed in a similar fashion as Phase A endpoints. A separate SAP will be prepared for Phase B analyses.

10.4.5 SAFETY ANALYSES

Safety analyses will be performed on subjects who receive a study injection (treatment emergent adverse events). Safety assessments include imaging, physical examinations, vital signs, clinical laboratory tests, collection of AEs, SAEs, and concomitant medications, and general medical evaluations. Safety will be evaluated based on the incidence, seriousness, severity, and relationship of AEs and SAEs, and by changes in clinical laboratory parameters and vital signs, relative to baseline.

10.4.6 BASELINE DESCRIPTIVE STATISTICS

Baseline is defined as the last value recorded for any given parameter prior to study medication injection at Day 1. If a subject never received a study injection, baseline is defined as the last value recorded prior to study termination.

Baseline descriptive statistics will include age, gender, race, height, weight, BMI, and KL Grade

10.4.7 PLANNED INTERIM ANALYSES

This safety study was initially designed as a one-year double-blind study. The protocol was amended to add a built-in, one-year single blind extension (Phase B) after the formal, one-year core study (Phase A) completes. The primary analysis will be after last subject completes Week 52 in Phase A and should not be considered an interim analysis.

10.4.7.1 SAFETY REVIEW

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

10.4.7.2 EFFICACY REVIEW

Not applicable to this study.

10.4.8 EXPLORATORY ANALYSES

Refer to Section 10.4.3.

10.4.9 ADDITIONAL SUB-GROUP ANALYSES

Not Applicable.

10.5 SAMPLE SIZE

The sample size for this trial is based upon accepted investigational studies exploring changes in bone density.

Additionally, sample size was also estimated assuming a non-inferiority statistical design. Based upon the subchondral BMD data obtained using qCT in SM04690-01, a coefficient of variation (CV) of 0.30 was presumed to be shared by both treatment and placebo groups; this presumed CV is larger than the observed CVs in SM04690-01. Assuming a Type 1 error of 0.05, SM04690-OA-06 will have 81.6% power to estimate a BMD ratio of 0.93 with a one-sided confidence interval extending to 0.80 with a sample size of 50 subjects per group.

10.6 MEASURES TO MINIMIZE BIAS

10.6.1 BLINDING PROCEDURES

Phase A is a double-blind study. Study medication will be provided to the investigational center. The investigational center must identify unblinded personnel who are able to prepare and perform the injection of study medication and/or placebo. Study personnel administering or preparing study medication and reference therapy must minimize any contact with the subject following the injection and may not perform any study assessments throughout the duration of the study. 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 Rave database. Upon randomization of a subject, a Dispensation email will be sent from *Medidata-Notification@mdsol.com* to the designated unblinded investigational staff member(s). Subjects will be randomized 1:1 (0.07 mg active per 2 mL injection : 2 mL placebo) to each treatment group using a permuted block design. Specific information regarding the use of Medidata Rave RTSM to store and implement the permuted block design will be detailed within the SAP.

Primary analysis of Phase A data will be completed after the last subject completes Week 52 (EOSa). While the Sponsor will be unblinded to study treatment after the Phase A analysis, the Investigator and the subject will remain blinded.

10.6.2 EVALUATION OF SUCCESS OF BLINDING

Not applicable to this study.

10.6.3 BREAKING THE STUDY BLIND/PARTICIPANT CODE

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

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

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

In circumstances when the blind is unintentionally broken at the investigational center, the breaking of the blind should be reported to the designated Sponsor-unblinded Clinical Research Associate as soon as possible after breaking the blind for a subject.

11. SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

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

- The oral and written communication with the subject regarding the study (including the risks and benefits of the study); the date of informed consent(s) must be recorded in the source documentation

- The subject's medical and disease history before participation in the study
- The subject's basic identifying information, such as subject number, that links the subject's source documents with the eCRFs
- The results of all diagnostic tests performed, diagnoses made, therapy provided, and any other data on the condition of the subject
- All AEs (All AEs 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, eCOA questionnaire results are not transferred to eCRFs.

12. QUALITY ASSURANCE AND QUALITY CONTROL

This study will be organized, performed, and reported in compliance with the protocol, SOPs, site/Investigator training, and applicable regulations and guidelines. Clinical Investigator sites will be trained at 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, representatives of the Sponsor, and regulatory authorities, as needed.

The Integrated Quality and Risk Management Plan (IQRMP) details the trial specific quality management plans to indicate how risks are mitigated and data quality is addressed in the clinical trial.

13. ETHICS/PROTECTION OF HUMAN SUBJECTS

13.1 ETHICAL STANDARD

The study will be conducted in accordance with the Declaration of Helsinki (1964), including all amendments up to and including the Brazil revision (2013). The Investigator will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Subjects of Research set forth in US 21 Code of Federal Regulations Part 50, 21 Code of Federal Regulations Part 56, and/or the ICH-GCP 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 or designee will maintain a personal subject identification list (subject numbers with the corresponding subject names) to make it possible for records to be identified.

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

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

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

Not applicable to this study.

13.5 FUTURE USE OF STORED SPECIMENS

Not applicable to this study.

14. DATA HANDLING AND RECORD KEEPING

14.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

As defined by ICH guidelines, the CRF is a printed, optical, or electronic document designed to record all 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-GCP E6 and US 21 CFR parts 312, 812, and 11. Data to be transferred external to Rave may include eCOA questionnaires, central laboratory data, and imaging results.

Data collection on the eCRF will follow the instructions described in the eCRF Completion Guidelines. The Investigator has ultimate responsibility for the collection and reporting of all clinical data entered on the eCRF. The Investigator or designee as identified on Form FDA 1572 will 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.

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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Lawrence RC, Felson DT, Helmick CG, Arnold LM, Choi H, Deyo RA, Gabriel S, Hirsch R, Hochberg MC, Hunder GG, Jordan JM, Katz JN, Kremers HM, Wolfe F, and National Arthritis Data W. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part II. Arthritis Rheum 2008;58:26-35.

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APPENDIX

Appendix 1. 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)

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 2. Amendments

AMENDMENT 04 VERSION 00 SUMMARY OF CHANGES

Study Title: A Phase 2, 52-Week, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Safety, Tolerability, and Efficacy of Two Injections of SM04690 Injected in the Target Knee Joint of Moderately to Severely Symptomatic Osteoarthritis Subjects

Purpose: The purpose of this amendment is to refine the study design and to further clarify the primary study phase and the built-in extension phase of the protocol.

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

Change	Sections Affected	Rationale
Protocol Amendment 04 Version 00 has been added on the title page.	Title Page	Change was made to capture the dates of previous and current protocol versions
Protocol date and version have been updated as applicable	All	Change was made to reflect current protocol amendment
Signatories were removed	Sponsor Signature Page	Updated to reflect personnel changes
Study objectives were refined	Protocol Summary, Section 3	Change was made to refine the study design
Study endpoints were refined and reorganized	Protocol Summary, Section 4.2	Change was made to refine the study design
Description of the study design was updated	Protocol Summary, Section 4.1	Change was made to further clarify study design
Key roles were updated, as well as Sponsor address	Section 1	Change made to reflect personnel changes and Sponsor address change
Language change removing biomarkers from Safety endpoints/assessments	Protocol Summary, Section 2.2, Section 8.1	Change was made to refine study design
Language describing allowed use of topical anesthetics was updated	Section 6.1.5	Change was made for clarification
Language describing the planned Statistical Analysis Plans (SAPs) was updated	Section 10.1	Change made to clarify plans for the SAPs
Statistical Hypotheses were updated	Section 10.2	Change was made to refine the planned analyses
Definition of the Per-Protocol Analysis Set (PPAS) was updated	Section 10.3	Change was made to refine the definition of the PPAS
Language was updated to reflect changes in the study endpoints and timing of planned analyses	Sections 10.4.1, 10.4.2, 10.4.3, 10.4.5, 10.4.6, 10.4.7, 10.4.8, 10.6.1, and 10.6.3	Change was made to further clarify the study design
Sample size language updated	Section 10.5	Change was made to further refine sample size calculations
The following text was added: “representatives of the Sponsor, and regulatory authorities, as needed.”	Section 12	Change was made for clarification
Removed “tapentadol (Nucynta)” from the list of prohibited concomitant medications	Appendix 1	Change made to refine prohibited concomitant medications

AMENDMENT 03 VERSION 00 SUMMARY OF CHANGES

Study Title: A Phase 2, 52-Week, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Safety, Tolerability, and Efficacy of Two Injections of SM04690 Injected in the Target Knee Joint of Moderately to Severely Symptomatic Osteoarthritis Subjects

Purpose: The purpose of this amendment is to refine the study design and add an Extension Phase (Phase B) to the study.

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

Change	Sections Affected	Rationale
Protocol Amendment 03 Version 00 has been added on the title page.	Title Page	Change was made to capture the dates of previous and current protocol versions
Protocol date and version have been updated as applicable	All	Change was made to reflect current protocol amendment
An Extension Phase (Phase B) was added to the study. Phase B is an additional 52 weeks of treatment. Additional secondary and "other" endpoints were added accordingly.	Protocol Summary, Sections 2.2, 3, 4.1, 6.1.5, 6.1.6, 6.1.9	Change was made to refine study design in order to gather long term safety and efficacy data following multiple injections of SM04690
Study endpoints were revised/re-ordered into Phase A Primary Endpoints and Phase A Secondary Endpoints. Phase B Endpoints were added. Description of Statistical Methods was updated accordingly.	Protocol Summary, Sections 4.2, 10.2, 10.3, 10.4	Change was made to align with addition of Phase B and to identify a single primary endpoint for alpha-controlled hypothesis testing.
Endpoints and study procedures related to serum biomarkers were edited to indicate that testing includes *but is not limited to* PINP, β-CTX, and COMP.	Protocol Summary, Sections 7.2.2 and 10.4.3	Change was made to refine study design and allow for additional biomarker testing
Inclusion criterion #12 was edited from "52-week" to "104-week" study duration.	Protocol Summary, Section 5.1	Change was made to align with addition of Phase B
Exclusion criterion #18 was edited to: "History of mania, bipolar disorder, psychotic disorder, schizophrenia, schizoaffective disorder, major depressive disorder, or generalized anxiety disorder"	Protocol Summary, Section 5.2	Change was made to refine exclusion criteria
Exclusion criterion #19 was edited: "…any experimental therapeutic procedure ~~for knee OA~~ within 26 weeks prior to Screening Visit 1…" is excluded.	Protocol Summary, Section 5.2	Change was made to refine exclusion criteria
Exclusion criterion #22 was edited to clarify systemic as "(oral, intramuscular, or intravenous)".	Protocol Summary, Section 5.2	Change was made to clarify what constitutes systemic glucocorticoids
Study and participant durations were updated.	Protocol Summary	Change was made to reflect addition of Phase B
Schematic of Study Design was updated.	Schematic of Study Design	Change was made to reflect addition of Phase B
Risks associated with radiographs, qCT, and DXA were updated to reflect the additional imaging assessments performed in Phase B.	Section 2.3.1	Change was made to reflect the new number of imaging assessments to be performed
Where applicable, "Week 52 (EOS)/ET" was changed to "last study visit" (e.g., guidelines on	Sections 5.3.1, 7.1.1, 7.5.1	Change was made to clarify that these instances refer to the subject's last

Change	Sections Affected	Rationale
contraception).		study visit, whether that be in Phase A or Phase B
Clarification and further guidelines were added to Section 5.3.1 Contraception.	Section 5.3.1	Changes were made to refine lifestyle guidelines pertaining to contraception
Edits were made to indicate that subjects who are withdrawn from study medication for safety reasons will continue with all planned study visits per protocol.	Sections 5.5.1, 5.5.2, 6.1.9	Change was made to follow subjects for safety despite withdrawing from study medication
Further information regarding injections was added to Section 6.1.5.	Section 6.1.5	Change was made to provide further guidance on IA injections
Study Procedures and Schedule were updated to include Phase B assessments and visits. Schedule of Events and Schedule of Electronic Diary and Questionnaire Completion tables were also revised.	Section 7	Change was made to reflect addition of Phase B
The following was added to Section 10.1: “A second SAP will be prepared for Phase B analyses and finalized prior to the Week 104 data lock.”	Section 10.1	Change was made to reflect addition of Phase B
The following was added to Section 10.4.6: “If a subject never received a study injection, baseline is defined as the last value recorded prior to study termination.”	Section 10.4.6	Addition was made to be consistent with other SM04690 studies
Details in Section 10.4.9 Additional Sub-Group Analyses were deleted.	Section 10.4.9	Deletion was made to be consistent with other SM04690 studies
The following was added to Section 10.6.3: “After the last subject completes Phase A [Screening Visit 1 through Week 52 (EOSa)], Phase A study visit data will be locked for a 52-week Phase A full analysis. While the Sponsor will be unblinded to study treatment after this lock, the Investigator and the subject will remain blinded.”	Section 10.6.3	Addition was made to describe the breaking of the blind between Phase A and Phase B

AMENDMENT 02 VERSION 00 SUMMARY OF CHANGES

Study Title: A Phase 2, 52-Week, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Safety, Tolerability, and Efficacy of Two Injections of SM04690 Injected in the Target Knee Joint of Moderately to Severely Symptomatic Osteoarthritis Subjects

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
Protocol Amendment 02 Version 00 has been added on the title page.	Title Page	Change was made to capture the dates of previous and current protocol versions
Protocol date and version have been updated as applicable	All	Change was made to reflect current protocol amendment
Updated titles for Hutch Humphreys and Ismail Simsek; added Cristina Damatarca and Mark Fineman as signatories and removed Anita DiFrancesco	Sponsor Signature Page, Section 1	Changes were made for administrative reasons
Updated List of Abbreviations	List of Abbreviations	Change was made due to new abbreviations
Extended the screening period to 19 days (previously 14 days).	Protocol Summary, Sections 4.1 and 7.3	Change was made to allow sufficient time to complete and receive imaging reports
Added "serious adverse events (SAEs), vital signs, and clinical laboratory measures for the duration of the study" to the safety endpoint.	Protocol Summary, Section 4.2.1 and 10.4.5	Change was made to refine the safety endpoint
Removed methamphetamine as tested drug.	Protocol Summary and Sections 5.2, 7.1.1, and 7.6	Drug is included with "Amphetamines" in the list of drugs
Modified inclusion criterion #16: "Subjects must have read and understood the informed consent form … signed *and dated* it …"	Protocol Summary, Section 5.1	Change was made to be consistent with documentation requirements
Added a new inclusion criterion #18: "Subject is able to have a Screening Visit 2 qCT image acquired that does not require a re-scan as determined by the central imaging vendor."	Protocol Summary, Section 5.1	Change was made to clarify qCT eligibility requirements
Exclusion criterion #1 was modified to: "Pregnant and breastfeeding women, and women who are not post-menopausal (defined as 12 months with no menses without an alternative medical cause) or permanently surgically sterile (includes hysterectomy, bilateral salpingectomy, and bilateral oophorectomy) and have a positive or indeterminate pregnancy result at Screening Visit 2 or Day 1"	Protocol Summary, Section 5.2	Change was made to refine exclusion criteria
Exclusion criterion #2 was modified to remove the definitions of post-menopausal and permanently surgically sterile since they were added to exclusion criterion #1.	Protocol Summary, Section 5.2	Change was made to avoid redundancy
Exclusion criterion #19 was updated to: "Participation in a clinical research trial that included the receipt of an investigational product	Protocol Summary, Section 5.2	Change was made to refine exclusion criteria and align with other SM04690 trials

Change	Sections Affected	Rationale
(IP) or any experimental therapeutic procedure for knee OA within 26 weeks prior to Screening Visit 1, or planned participation in any such trial"		
Exclusion criterion #32 was modified and exclusion criterion #37 was added.	Protocol Summary, Section 5.2	Change was made to refine exclusion criteria related to DXA imaging
Description of Study Agent was revised.	Protocol Summary	Change was made to align with current description being used in other SM04690 trials
Study duration was revised to 24 months and the estimated date last subject completed was updated to August 2020.	Protocol Summary	Change was made for accuracy
Deleted information related to previous and ongoing SM04690 clinical trials from the Rationale section.	Section 2.2	Change was made to simplify the Rationale section; pertinent information regarding previous SM04690 trials is in the IB
Modified description of risks associated with Study Medication SM04690, Study Placebo, and Risks of Injection.	Section 2.3.1	Change was made to refine description and to align protocol with current IB.
An update was made to the allowable windows for re-using screening images.	Section 4.1	Change was made to refine re-screening guidance
"Tubal ligation/occlusion/division" was added as an acceptable form of birth control.	Section 5.3.1	Change was made to correct a previously erroneous omission
The following was added to Section 6.1.3: "Refer to the Pharmacy Manual for detailed instructions on how to manage temperature excursions."	Section 6.1.3	Change was made to provide further guidance on temperature excursions
Added following information on blinding: "The Unblinded Investigator must minimize any contact with the subject following the injections and may not perform any study assessments throughout the duration of the study. All subject contact for the remainder of the study is limited to the Blinded Investigator and other appropriate blinded study personnel."	Section 6.1.5	Drug product and placebo have different appearances; injections therefore must be performed by unblinded personnel. Change was made to remind sites that Unblinded Investigators who administer injections should not participate in any study evaluations.
Additional information/guidance was added regarding the injection by the Unblinded Investigator.	Section 6.1.5	Change was made to clarify the injection process
Changed scale for collecting AEs from "Guidance for Industry: Toxicity Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Trials" to "*Clinical Data Interchange Standards Consortium (CDISC) Severity/Intensity Scale for Adverse Events (AESEV)*."	Sections 7.1.1, 7.2.1, 8.2.1, and Appendix 1	The Toxicity Scale is applicable for vaccine trials with healthy volunteers, whereas this is a Phase 2 trial of a non-vaccine drug.
Further clarification of AEs was provided. ("Anticipated fluctuations or anticipated deterioration (in the opinion of the Investigator) of the underlying disease (target knee OA) will not be considered as AEs…")	Sections 7.1.1 and 8.1.18.3	Changes were made to clarify which events should be considered AEs
Reworded timing of AE reporting to: "AEs that are ongoing at a subject's last visit will be followed for 30 days after administration of the last dose of study medication or until resolution, whichever comes first. Resolution is defined as the return to baseline status or stabilization of the	Sections 7.1.1 and 8.3	Changes were made to refine definitions and timing of collection

Change	Sections Affected	Rationale
condition. SAEs that are ongoing at a subject's last visit will be followed until resolution."		
Minor edits were made in the Medical History subsection including adding examples of medical conditions and disease states that should be considered relevant to the subject's study participation.	Section 7.1.1	Edits were made for clarity
A clarification was made in the Knee Examination subsection; presence of unilateral or bilateral knee OA will be recorded.	Section 7.1.1	Change was made to align with eCRF
Revised vital sign terminology.	Sections 7.1.1 and 7.3	Changes were made to align with CDISC standard terminology
The following was added to the qCT subsection: "A quality assessment report will be provided to the Investigator by the central imaging vendor to confirm subject eligibility."	Section 7.1.1	Change was made for clarification
Clarified description of assessment: "The WPI&SS assessment used in this study is modified from that described in (*Clauw 2014*)"	Section 7.1.1	Change was made to indicate that our assessment is not the same as that in reference
Added anchor descriptors to Pain NRS and corrected the description of the questionnaire.	Section 7.1.1	Changes were made to clarify procedures and for accuracy
The following sentence was deleted from the Pain NRS subsection: "Increases in pain should only be considered AEs if reported by the subject, regardless of pain NRS scores."	Section 7.1.1	Change was made to align with the updates made to the AE subsection (regarding anticipated fluctuations or deterioration of the underlying disease).
The urine pregnancy test on Day 1 will only be performed on women of childbearing potential.	Sections 7.2.2, 7.3.2, and 7.3.7	Change was made to align with edit to exclusion criterion #1
The following was deleted from the Day 1 study visit: "Subjects with a period of more than 11 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 refine study design; subjects need not be screen failed since baseline questionnaires do not contribute to the primary endpoint.
Clarified which eCRF page prior and concomitant medications will be recorded on.	Section 7.5	Addition was made for clarification
The following was added to definitions of SAEs: "Admission to the hospital or prolongation of hospitalization qualifies as an SAE only if it is the result of an AE."	Section 8.1.2	Change was made to align with current ICH definitions of SAEs.
Descriptions for Unanticipated Problems (UPs) changed.	Sections 8.1.3 and 8.4.3	Change was made for clarity and to align with current reporting guidelines.
Section 8.2.2 Relationship to Study Agent was revised.	Section 8.2.2	Changes were made to clarify definitions of relatedness to study drug
Removed phrase: ~~"The Investigator and Samumed will manage SAEs according to the study document "Guidelines for the Management of Serious Adverse Events (SAEs) and Pregnancies".~~	Section 8.4.2	Change was made because document is no longer used.
Added following: "*The Investigator should review the SAE*	Section 8.4.2	Change was made to clarity reporting requirements

Change	Sections Affected	Rationale
information and sign the SAE report, and the…"		
Added Kathleen Toscano as Alternative Contact for SAE Reporting and to Key Role overseeing Drug Safety and Pharmacovigilance	Section 8.4.2	Changes were made for administrative reasons
Removed text from UP Reporting: 1: ~~"A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP."~~ 2: ~~"All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures) and IRB within the timeframe specified by the institution procedures and IRB."~~	Section 8.4.3	Changes were made because 1) Investigators are not responsible for protocol changes, and 2) This information was already indicated in the section
Section 8.4.5 Reporting of Pregnancy was revised to provide guidance on pregnancy reporting during the study.	Section 8.4.5	Change was made to clarify pregnancy reporting process within the protocol
Section 10.2 Statistical Hypotheses was revised.	Section 10.2	Formal hypothesis testing was added for clarity given the sample size justification
Further details regarding BMD analysis were added to Section 10.3.2 Analysis of Primary Endpoint(s).	Section 10.4.2	Analysis was clarified in support of hypothesis testing.
Additional sample size justification was added to Section 10.4 Sample Size.	Section 10.5	Sample size was estimated upon request from the regulatory agency.
Changed e-mail for Medidata notification to sites and "Treatment Arm Notification" was changed to "Dispensation."	Section 10.6.1	Change was made for administrative reasons
Medidata Balance was revised to Medidata Rave RTSM.	Section 10.6.3	Change was made for correctness
Time of informed consent was deleted from Section 11.	Section 11	Change was made because time is not collected on the informed consent form
Deleted the following from Section 14.3 Protocol Deviations: "Refer to the current version of Samumed SOP-300-013 Protocol Deviations for Sponsor procedures related to protocol deviations."	Section 14.3	Change was made because this information is not applicable to the sites
Updated Section 16 Literature References.	Section 16	Change was made to reflect references cited in this amendment.
Removed Appendix 1 (Toxicity Vaccine Scale)	Appendix 1	Scale was replaced by CDISC scale for AE collection
Formatting, spelling, and grammar/terminology were refined	Throughout	Changes were made for clarity and presentation

AMENDMENT 01 VERSION 00 SUMMARY OF CHANGES

Study Title: A Phase 2, 52-Week, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Safety, Tolerability, and Efficacy of Two Injections of SM04690 Injected in the Target Knee Joint of Moderately to Severely Symptomatic Osteoarthritis Subjects

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 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.
List of Abbreviations was updated.	List of Abbreviations	Change was made for correctness to reflect the terms used in the protocol.
The use of "Treatment-emergent adverse events" and "TEAEs" was changed to "Adverse events" and "AEs", respectively.	Summary and throughout	Change was made to align protocol with the EDC and eCRF.
Wording of primary endpoint 1e was modified to "Change in serum bone biomarkers (N-terminal propeptides of procollagen type I [PINP] and β-C-terminal telopeptide [β-CTX]) from baseline, and change in a serum cartilage biomarker (cartilage oligomeric matrix protein [COMP]) from baseline at Weeks 4, 12, 24, 36, and 52".	Summary and Section 4.2.1	Change was made for clarity.
Measurement of bone and cartilage biomarkers was added at Week 36.	Summary, Schematic of Study Design, Section 4.1, Section 4.2.1, Section 7.2.2, Section 7.3.7, and Section 10.4.2	Change was made to refine study design. Biomarkers will be assessed at Screening Visit 2 and at Weeks 4, 12, 24, 36, and 52 (EOS)/ET.
The following sentence was removed from the Methodology section of the Protocol Summary: "Comparisons to baseline for primary endpoints will be of a qualitative nature with no formal statistical analysis performed."	Summary	Change was made for accuracy. Unadjusted 95% confidence intervals and P values will be reported.
Inclusion criterion #10 was updated to: "WOMAC pain subscore of 20-40 (out of 50) *and* WOMAC physical function subscore of 68-136 (out of 170) for the target knee at baseline regardless of if the subject is on symptomatic oral treatment (baseline questionnaire completed during the screening period prior to randomization)"	Summary and Section 5.1	Change was made to refine study design; the inclusion criterion was modified to identify required ranges for WOMAC pain and physical function subscores, instead of WOMAC total score.

Change	Sections Affected	Rationale
Corrections were made to exclusion criteria #1, 15, and 30 to reflect the fact that the pregnancy test and clinical laboratory evaluations will be performed at Screening Visit 2 (not Screening Visit 1).	Summary and Section 5.2	Changes were made for accuracy. These tests will be performed at Screening Visit 2.
Exclusion criterion #32 was modified to add/clarify exclusionary contraindications to DXA scans of the hips or spine.	Summary and Section 5.2	Changes were made to clarify which contraindications should be considered exclusionary.
The address for the Central Laboratory was corrected.	Section 1	Change was made for correctness.
Enrollment information was updated for ongoing SM04690 clinical trials (to "as of 25 May 2018") and additional information and/or edits were made to further support or clarify the study rationale.	Section 2.2	Change was made to provide more current information regarding ongoing studies and to clarify the study rationale.
The following (and related text) was added throughout the protocol: "The second injection may occur up to two weeks later than the Week 24 visit to allow for resolution of any intercurrent illness (e.g., infection) prior to the injection."	Section 6.1.5, Section 6.1.6, Section 6.1.9, Section 7.3.3	Change was made to refine study design. A 2 week window was added to allow for resolution of intercurrent illness prior to the second IA injection.
The following was added in Section 6.2: "Procedures for *unblinded* Investigator return or destruction of used and unused vials…"	Section 6.2	Change was made to clarify that these procedures would be performed by the unblinded Investigator.
The following clarification was added: "AEs that are not serious and are ongoing at the subject's last visit will be followed until the study close-out visit, if requested *by the Sponsor. If not requested, AEs that are not serious and are ongoing at the subject's last visit will be followed for a maximum of 30 days*."	Section 7.1.1 and Section 8.3	Change was made to clarify how AEs that are not serious and are ongoing at the subject's last visit should be followed.
It was clarified that the monthly questionnaires for Week 24 should be completed prior to the Week 24 study medication injection.	Section 7.1.1, Section 7.3.3, and Section 7.3.8	Change was made to clarify the timing of Week 24 monthly questionnaires in relation to the second study medication injection.
The Patient Global Assessment of Disease Activity was changed from a 50 mm visual analog scale to an 11-point NRS, and the description of the questionnaire was updated.	Section 7.1.1	Change was made to reflect an update to the Patient Global Assessment.
Study visit windows were modified: • Week 12 now has a window of ± 3 days	Section 7.3.3, Section 7.3.4, and Section 7.3.7	Change was made to refine study design and aid with study logistics.

Change	Sections Affected	Rationale
• Week 36 and 52 now have a window of -3 to +7 days		
The day of the Week 52 visit was corrected from 366 to 365.	Section 7.3.4 and Section 7.3.7	Change was made to correct an error.
Clarifications were made regarding the baseline WOMAC and Patient Global Assessment questionnaires. "Screening Visit 2 + 5 days" was clarified to "5 days after Screening Visit 2."	Section 7.3.8	Change was made to avoid confusion related to the timing of the baseline questionnaires.
"Biomarker assessments" was added to the Specification of Safety Parameters.	Section 8.1	Change was made for completeness.
An additional analysis set was added to Section 10.3. • **Modified Full Analysis Set (mFAS):** FAS subjects who received injections into the target knee both on Day 1 and at Week 24. • (PPAS was revised to refer to mFAS instead of FAS.)	Section 10.3	Change was made to refine study design.
The following edits were made: "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 *prepare and* perform the injection of study medication and/or placebo."	Section 10.6.1	Change was made for accuracy. There is no study medication dilution in this study.
The following was added in Section 13.4: "The Investigator *or designee* will maintain a personal subject identification list…"	Section 13.4	Change was made for accuracy. This may be performed by the Investigator or his/her designee.
Minor grammatical edits were made.	Throughout	Changes were made for correctness.
Appendix 3 was added to outline amendment revisions.	Appendix 2	Change was made to reflect protocol amendment.

Signature Page for VV-TMF-145687 v1.0

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Reason for signing: Approved	Name: Christopher Swearingen Role: Vice President, Clinical Outcomes and Analytics Date of signature: 24-Aug-2020 15:17:20 GMT+0000

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