A Phase 2, 52 Week, Single Center, Open-Label Study Utilizing Imaging Techniques and Evaluating the Safety and Efficacy of SM04690 Injectable Suspension for the Treatment of Moderately to Severely Symptomatic Knee Osteoarthritis

Study Number: SM04690-OA-08 (NCT03706521)

IND Sponsor: Samumed, LLC

Investigational Product: SM04690 Injectable Suspension

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SPONSOR SIGNATURE PAGE

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Protocol Number: SM04690-OA-08 AM02V00

Date: 26 September 2018

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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
3D-SPGR	Three-dimensional spoiled gradient recalled
ACR	American College of Rheumatology
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
BMI	Body mass index
CFR	Code of Federal Regulations
CRF	Case report form
DLT	Dose-limiting toxicity
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EOS	End of study
ETF	Early termination
FAS	Full Analysis Set
FDA	(US) Food and Drug Administration
GAG	Glycosaminoglycan
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
IA	Intra-articular
IB	Investigator Brochure

Abbreviation	Term
ICF	Informed consent form
ICH	International Conference on Harmonization
IND	Investigational new drug
IP	Investigational product
IQRMP	Integrated Quality and Risk Management Plan
IRB	Institutional Review Board
IUD	Intrauterine device
JSW	Joint space width
KL	Kellgren-Lawrence
LDH	Lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
mJSW	Medial joint space width
mL	Milliliter
mm	Millimeter
MOCBP	Men of childbearing potential
MRI	Magnetic resonance imaging
mSv	Millisievert
NCS	Not clinically significant
NRS	Numeric rating scale
NSAID	Nonsteroidal anti-inflammatory drug
OA	Osteoarthritis
PA	Posterior-anterior
PPAS	Per-protocol Analysis Set
PRO	Patient reported outcome
PRP	Platelet-rich plasma
RBC	Red blood cell
SAE	Serious adverse event

Abbreviation	Term
SAP	Statistical analysis plan
SAS	Safety Analysis Set
SOP	Standard operating procedure
SS	Symptom Severity
SSQ	Symptom Severity Question
ULN	Upper limit of the normal range
UP	Unanticipated problem
US	United States
WBC	White blood cell
WOCBP	Women of childbearing potential
WOMAC	Western Ontario and McMaster Universities Arthritis Index
WORMS	Whole Organ MRI Scoring
WPI	Widespread Pain Index
WPI&SS	Widespread Pain Index and Symptom Severity Form

STATEMENT OF COMPLIANCE

Study Title	A Phase 2, 52 Week, Single Center, Open-Label Study Utilizing Imaging Techniques and Evaluating the Safety and Efficacy of SM04690 Injectable Suspension for the Treatment of Moderately to Severely Symptomatic Knee Osteoarthritis		
Protocol Number	SM04690-OA-08		
Protocol Date	26 September 2018	Protocol Version	AM02V00

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, Single Center, Open-Label Study Utilizing Imaging Techniques and Evaluating the Safety and Efficacy of SM04690 Injectable Suspension for the Treatment of Moderately to Severely Symptomatic Knee Osteoarthritis

Objectives:

Primary:

Evaluate the efficacy of SM04690 Injectable Suspension for the treatment of knee osteoarthritis (OA) via magnetic resonance imaging (MRI)

Secondary:

1. Evaluate the efficacy of SM04690 Injectable Suspension for the treatment of knee OA as assessed by patient reported outcomes (PROs)
2. Evaluate the efficacy of SM04690 Injectable Suspension for the treatment of knee OA via radiographs
3. Evaluate the safety and tolerability of SM04690 Injectable Suspension

Endpoints:

Primary:

1. Change from baseline in cartilage thickness in the target knee as measured by three-dimensional spoiled gradient recalled (3D-SPGR) pulse sequence MRI at Week 26
2. Change from baseline in cartilage volume in the target knee as measured by 3D-SPGR pulse sequence MRI at Week 26
3. Change from baseline in cartilage quality in the target knee determined by the increase or decrease in proteoglycan and glycosaminoglycan (GAG) content and hydration as measured by T1rho and T2 mapping pulse sequence MRI at Week 26

Secondary:

1. Change from baseline in cartilage thickness in the target knee as measured by 3D-SPGR pulse sequence MRI at Weeks 13 and 52
2. Change from baseline in cartilage volume in the target knee as measured by 3D-SPGR pulse sequence MRI at Weeks 13 and 52
3. Change from baseline in cartilage quality in the target knee by the increase or decrease in proteoglycan and GAG content and hydration as measured by T1rho and T2 mapping pulse sequence MRI at Weeks 13 and 52
4. Change from baseline in total Whole Organ MRI Scoring (WORMS) in the target knee at Weeks 13, 26, and 52
5. Change from baseline OA pain in the target knee as assessed by Western Ontario and McMaster Universities Arthritis Index (WOMAC) pain subscore at Weeks 13, 26, and 52

6. Change from baseline OA function in the target knee as assessed by WOMAC physical function subscore at Weeks 13, 26, and 52
7. Change from baseline symptoms of OA in the target knee as assessed by WOMAC total score at Weeks 13, 26, and 52
8. Change from baseline OA disease activity as assessed by Patient Global Assessment at Weeks 13, 26, and 52
9. Change from baseline in medial joint space width (mJSW) as documented by radiograph of the target knee at Weeks 26 and 52
10. Change from baseline in cartilage thickness in the non-target knee as measured by 3D-SPGR pulse sequence MRI at Weeks 13, 26, and 52
11. Change from baseline in cartilage volume in the non-target knee as measured by 3D-SPGR pulse sequence MRI at Weeks 13, 26, and 52
12. Change from baseline in cartilage quality in the non-target knee determined by the increase or decrease in proteoglycan and GAG content and hydration as measured by T1rho and T2 mapping pulse sequence MRI at Weeks 13, 26, and 52
13. Change from baseline in total WORMS in the non-target knee at Weeks 13, 26, and 52
14. Change from baseline in mJSW as documented by radiograph of the non-target knee at Weeks 26 and 52
15. Incidence and severity of adverse events (AEs) throughout the trial

Methodology: This study will be a single center, open-label study of SM04690 injected into the target knee joint of moderately to severely symptomatic osteoarthritis subjects.

Fifteen subjects will be enrolled and receive a dose of 0.07 milligram (mg) SM04690 per 2 milliliter (mL) injection. Subjects will participate in a screening period of a minimum of 7 days and up to 14 days, and a 52-week follow-up period. Clinic visits will be scheduled at the Screening Visit, Day 1, and Weeks 4, 13, 26, 39, and 52 [End of Study (EOS) / Early Termination (ET)].

Inclusion/ Exclusion Criteria:

Criteria for Inclusion:

1. Males and females between 40 and 80 years of age, inclusive, in general good health
2. Ambulatory (single assistive devices such as canes allowed if needed less than 50% of the time, subjects requiring a walker are excluded)
3. Diagnosis of femorotibial OA in the target knee by standard American College of Rheumatology (ACR) criteria at the Screening Visit (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 the Screening Visit
5. Primary source of pain throughout the body is due to OA in the target knee
6. Daily OA knee pain diary average Numeric Rating Scale (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. Baseline mJSW by radiograph between 2 and 4 mm, inclusive, in the target knee at the Screening Visit as assessed by independent central readers
11. Total WOMAC score of 96-192 (out of 240) for the target knee at Day 1 regardless of if the subject is on symptomatic oral treatment
12. Negative drug test for amphetamine, methamphetamine, 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 the Screening Visit
13. Subjects with depression or anxiety must be clinically stable for 12 weeks prior to the Screening Visit and, if on treatment for depression or anxiety, be on 12 weeks of stable therapy
14. Full understanding of the requirements of the study and willingness to comply with all study visits and assessments
15. Subjects must have read and understood the informed consent form, and must have signed it prior to any study-related procedure being performed
16. Subject's Screening Visit must occur while enrollment into the study is open

Criteria for Exclusion:

1. Women who are pregnant, lactating, or have a positive pregnancy test result at the Screening Visit
2. Women of childbearing potential who are sexually active, and who are not willing to use an acceptable method of birth control (as per Section 5.3.1 of the protocol) during the study period

3. Men of childbearing potential who are sexually active and have a partner who is capable of becoming pregnant, neither of whom are agreeable to using an acceptable method of birth control (as per Section 5.3.1 of the protocol) during the study period
4. Body mass index (BMI) > 40
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 the Screening Visit according to the Kellgren-Lawrence (KL) grading of knee OA as assessed by independent central readers
8. Previous treatment with SM04690
9. Subjects who have previously failed screening on this protocol and fail to meet re-screening criteria
10. Any surgery (e.g., arthroscopy) in either knee within 26 weeks prior to the Screening Visit
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 the Screening Visit
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 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. Any diagnosed psychiatric condition that includes, but is not limited to, a history of mania, bipolar disorder, psychotic disorder, schizophrenia, schizoaffective disorder, major depressive disorder, or generalized anxiety disorder
19. Participation in a clinical research trial that included the receipt of an investigational product or any experimental therapeutic procedure, or an observational research trial related to osteoarthritis within 8 weeks prior to to the Screening Visit, or planned participation in any such trial; the last date of participation in the trial, not the last date of receipt of investigational product, must be at least 8 weeks prior to the Screening Visit
20. 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 the Screening Visit; treatment of the target knee with intra-articular glucocorticoids greater than 12 weeks prior to the Screening Visit is allowed
21. Treatment with systemic glucocorticoids greater than 10 mg prednisone or the equivalent per day within 4 weeks prior to the Screening Visit
22. Effusion of the target knee clinically requiring aspiration within 12 weeks prior to the Screening Visit
23. Use of electrotherapy, acupuncture, and/or chiropractic treatments for knee OA within 4 weeks prior to the Screening Visit (refer to Appendix 2)
24. Any known active infections, including urinary tract infection, upper respiratory tract infection, sinusitis, suspicion of intra-articular infection, hepatitis B or hepatitis C infection, and/or infections that may compromise the immune system such as human immunodeficiency virus (HIV) at Day 1
25. Current use, or use within 12 weeks prior to the Screening Visit, of centrally acting analgesics (refer to Appendix 2) ~~w~~
26. Current use, or use within 12 weeks prior to the Screening Visit, of anticonvulsants (refer to Appendix 2)
27. Subjects requiring the usage of opioids >1x per week within 12 weeks prior to the Screening Visit
28. Topical local anesthetic agents (gels, creams, or patches such as the

Lidoderm patch) used for the treatment of knee OA within 7 days of the Screening Visit

29. Any chronic condition that has not been well controlled or subjects with a chronic condition who have not maintained a stable therapeutic regimen of a prescription therapy in the opinion of the investigator. In addition, subjects with an HbA1c >9 at the Screening Visit will be excluded.
30. If on nonsteroidal anti-inflammatory drugs (NSAIDs) for the treatment of OA pain, subjects who have not maintained a stable regimen in the opinion of the Investigator at the Screening Visit
31. Any contraindications for performing MRI
32. Subjects who have a current or pending disability claim, workers' compensation, or litigation(s) that may compromise response to treatment
33. 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
34. Subjects employed by Samumed, LLC, or any of its affiliates or development partners (that is, an employee, temporary contract worker, or designee) responsible for the conduct of the study

Population:	Approximately 15 subjects with moderately to severely symptomatic knee OA
Phase:	2
Number of Sites enrolling participants:	This study will be conducted at 1 investigational center 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 18 months Estimated date first subject consented: 01 October 2018 Estimated date last subject completed: 01 April 2020
Participant Duration:	Approximately 52 weeks following a screening period of 7 to 14 days

Criteria for evaluation:

Efficacy:

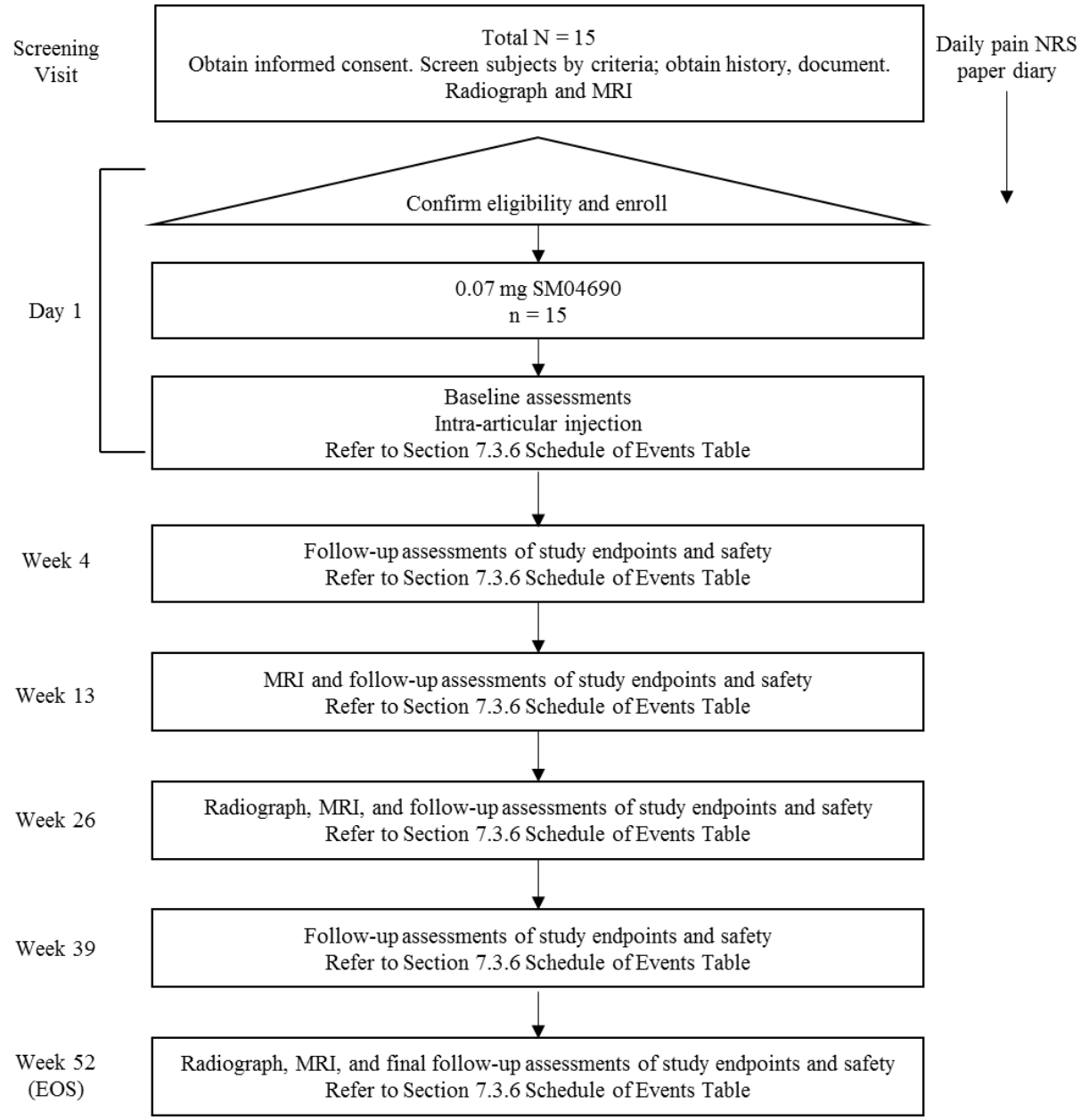
Efficacy will be assessed by:

- Cartilage volume and thickness as measured by MRI (3D-SPGR pulse sequences)
- Cartilage quality as measured by MRI (T1rho and T2 mapping pulse sequences)
- Total WORMS
- WOMAC total score as well as WOMAC pain and physical function subscores for the target knee
- Patient Global Assessment
- Medial JSW as evaluated by radiograph

Safety:

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

SCHEMATIC OF STUDY DESIGN



1. KEY ROLES

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2. INTRODUCTION: BACKGROUND INFORMATION & SCIENTIFIC RATIONALE

2.1 BACKGROUND INFORMATION

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

Therapies available to treat OA are limited. Most current treatments are designed only to relieve pain and reduce or prevent the disability caused by bone and cartilage degeneration. Drug therapies target the symptoms but not the cause of this disease; no treatment inhibits or reverses

the degenerative structural changes that are responsible for its progression (Nevitt, Felson et al. 2006).

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

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

2.2 RATIONALE

Osteoarthritis is the most common form of arthritis and chronic joint disorder in humans (Dougados & 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 & Hochberg 2011). OA is a leading cause of physical disability in the US (Lawrence, Felson et al. 2008).

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

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

This phase 2 study, SM04690-OA-08, is a single center, open-label study of SM04690 Injectable Suspension injected into the target knee joint of moderately to severely symptomatic OA subjects at a single dose of 0.07 mg SM04690 per 2 mL injection. A consistent change in joint space width as measured by radiograph was observed in this dose group in both a phase 1 study (SM04690-OA-01) and a phase 2 study (SM04690-OA-02). Therefore, the 0.07 mg SM04690 dose was selected for further investigation in this study.

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.

Risks of Injection

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

Risks of Topical Anesthetics

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

Blood Sampling

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

Knee Radiograph

This study involves radiation exposure from a total of 3 radiographs of the subjects' knees on 3 different days, each approximately 6 months apart. As part of everyday living, everyone is exposed to a small amount of background radiation that comes from soil, rocks, outer space, and within the body itself. The radiation dose for all knee X-rays that the subject will receive in this study is expected to be approximately 0.015 millisievert (mSv) and is approximately equivalent to 1 day's dose from background radiation. The risk from this dose is small. This radiation exposure may not be necessary for the subjects' medical care, but it is necessary to obtain the research information desired.

Magnetic Resonance Imaging (MRI) Scans

MRI contains no radiation. There have been no reported side effects from the magnetic fields and radio waves. The strong magnetic fields created during an MRI can cause heart pacemakers and other implants to not work as well. It can also cause a piece of metal inside the body to move or shift. For safety reasons, subjects are not to bring anything that contains metal into the scanner room. Receiving an MRI scan requires being positioned in a tunnel-shaped chamber. There is a risk of experiencing symptoms of claustrophobia (for example, a panic attack), due to the narrowness of the chamber. This procedure may not be necessary for the subjects' medical care, but it is necessary to obtain the research information desired.

2.3.2 KNOWN POTENTIAL BENEFITS

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

3. OBJECTIVES AND PURPOSE

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

Primary objective:

Evaluate the efficacy of SM04690 Injectable Suspension for the treatment of knee osteoarthritis (OA) via magnetic resonance imaging (MRI)

Secondary objectives:

1. Evaluate the efficacy of SM04690 Injectable Suspension for the treatment of knee OA as assessed by patient reported outcomes (PROs)
2. Evaluate the efficacy of SM04690 Injectable Suspension for the treatment of knee OA via radiographs
3. Evaluate the safety and tolerability of SM04690 Injectable Suspension

4. STUDY DESIGN AND ENDPOINTS

4.1 DESCRIPTION OF THE STUDY DESIGN

This study is a single center, open-label study of SM04690 injected into the target knee joint of moderately to severely symptomatic OA subjects.

Approximately 15 subjects will be enrolled and receive a dose of 0.07 mg SM04690 per 2 mL injection. Subjects will participate in a screening period of a minimum of 7 days and up to 14 days and a 52-week follow-up period. Clinic visits will be scheduled at the Screening Visit, Day 1, and Weeks 4, 13, 26, 39, and 52 (EOS)/ET. Specific timing of protocol procedures is described in the Schedule of Events Table (Section 7.3.6).

This study will be conducted at 1 investigational center in the US.

In this study, subjects will be required to complete a paper diary during the screening period to capture daily pain NRS (for target knee and non-target knee OA pain).

A Widespread Pain Index and Symptom Severity (WPI&SS) assessment will be administered at Day 1. WOMAC and Patient Global Assessments will be performed at Day 1, and Weeks 4, 13, 26, 39, and 52 (EOS)/ET.

In addition, general medical evaluations including physical examination, knee examination, and recording of vital signs will be performed at the Screening Visit, Day 1, and Weeks 4 (excluding physical examination), 13, 26, 39, and 52 (EOS)/ET. Height will be measured at the Screening Visit and weight will be measured at the Screening Visit and Week 52 (EOS)/ET. Clinical laboratory evaluations will be performed at the Screening Visit and Weeks 4, 13, 26, 39, and 52 (EOS)/ET. Radiographic imaging of the knees will be performed at the Screening Visit and Weeks 26, and 52 (EOS)/ET. MRI scans of the knees will be performed at the Screening Visit and Weeks 13, 26, and 52 (EOS)/ET.

Recording of signs and symptoms of study medication intolerability and AE reporting will start following the injection of the study medication and continue until the subject completes Week 52 (EOS)/ET. 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 for this protocol. 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 and MRI (if taken at previous screen), must be performed at re-screen; no results or data, except for the knee radiograph and MRI, may be used from the previous screen. Target knee selection may not be changed at re-screen.

4.2 STUDY ENDPOINTS

4.2.1 PRIMARY ENDPOINTS

1. Change from baseline in cartilage thickness in the target knee as measured by three-dimensional spoiled gradient recalled (3D-SPGR) pulse sequence MRI at Week 26
2. Change from baseline in cartilage volume in the target knee as measured by 3D-SPGR pulse sequence MRI at Week 26
3. Change from baseline in cartilage quality in the target knee determined by the increase or decrease in proteoglycan and glycosaminoglycan (GAG) content and hydration as measured by T1rho and T2 mapping pulse sequence MRI at Week 26

4.2.2 SECONDARY ENDPOINTS

1. Change from baseline in cartilage thickness in the target knee as measured by 3D-SPGR pulse sequence MRI at Weeks 13 and 52
2. Change from baseline in cartilage volume in the target knee as measured by 3D-SPGR pulse sequence MRI at Weeks 13 and 52
3. Change from baseline in cartilage quality in the target knee by the increase or decrease in proteoglycan and GAG content and hydration as measured by T1rho and T2 mapping pulse sequence MRI at Weeks 13 and 52
4. Change from baseline in total Whole Organ MRI Scoring (WORMS) in the target knee at Weeks 13, 26, and 52
5. Change from baseline OA pain in the target knee as assessed by Western Ontario and McMaster Universities Arthritis Index (WOMAC) pain subscore at Weeks 13, 26, and 52
6. Change from baseline OA function in the target knee as assessed by WOMAC physical function subscore at Weeks 13, 26, and 52
7. Change from baseline symptoms of OA in the target knee as assessed by WOMAC total score at Weeks 13, 26, and 52

8. Change from baseline OA disease activity as assessed by Patient Global Assessment at Weeks 13, 26, and 52
9. Change from baseline in medial joint space width (mJSW) as documented by radiograph of the target knee at Weeks 26 and 52
10. Change from baseline in cartilage thickness in the non-target knee as measured by 3D-SPGR pulse sequence MRI at Weeks 13, 26, and 52
11. Change from baseline in cartilage volume in the non-target knee as measured by 3D-SPGR pulse sequence MRI at Weeks 13, 26, and 52
12. Change from baseline in cartilage quality in the non-target knee determined by the increase or decrease in proteoglycan and GAG content and hydration as measured by T1rho and T2 mapping pulse sequence MRI at Weeks 13, 26, and 52
13. Change from baseline in total WORMS in the non-target knee at Weeks 13, 26, and 52
14. Change from baseline in mJSW as documented by radiograph of the non-target knee at Weeks 26 and 52
15. Incidence and severity of AEs throughout the trial

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 (single assistive devices such as canes allowed if needed less than 50% of the time, subjects requiring a walker are excluded)
3. Diagnosis of femorotibial OA in the target knee by standard American College of Rheumatology (ACR) criteria at the Screening Visit (clinical AND radiographic criteria); 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 the Screening Visit
5. Primary source of pain throughout the body is due to OA in the target knee
6. Daily OA knee pain diary average Numeric Rating Scale (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. Baseline mJSW by radiograph between 2 and 4 mm, inclusive, in the target knee at the Screening Visit as assessed by independent central readers
11. Total WOMAC score of 96-192 (out of 240) for the target knee at Day 1 regardless of if

the subject is on symptomatic oral treatment

12. Negative drug test for amphetamine, methamphetamine, 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 the Screening Visit
13. Subjects with depression or anxiety must be clinically stable for 12 weeks prior to the Screening Visit and, if on treatment for depression or anxiety, be on 12 weeks of stable therapy
14. Full understanding of the requirements of the study and willingness to comply with all study visits and assessments
15. Subjects must have read and understood the informed consent form, and must have signed it prior to any study-related procedure being performed
16. Subject's Screening Visit must occur while enrollment into the study is open

5.2 PARTICIPANT EXCLUSION CRITERIA

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

Criteria for Exclusion:

1. Women who are pregnant, lactating, or have a positive pregnancy test result at the Screening Visit
2. Women of childbearing potential who are sexually active, and who are not willing to use an acceptable method of birth control (as per Section 5.3.1 of the protocol) during the study period
3. Men of childbearing potential who are sexually active and have a partner who is capable of becoming pregnant, neither of whom are agreeable to using an acceptable method of birth control (as per Section 5.3.1 of the protocol) during the study period
4. Body mass index (BMI) > 40
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 the Screening Visit according to the Kellgren-Lawrence (KL) grading of knee OA as assessed by independent central readers
8. Previous treatment with SM04690
9. Subjects who have previously failed screening on this protocol and fail to meet re-screening criteria
10. Any surgery (e.g., arthroscopy) in either knee within 26 weeks prior to the Screening Visit

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 the Screening Visit
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 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. Any diagnosed psychiatric condition that includes, but is not limited to, a history of mania, bipolar disorder, psychotic disorder, schizophrenia, schizoaffective disorder, major depressive disorder, or generalized anxiety disorder
19. Participation in a clinical research trial that included the receipt of an investigational product or any experimental therapeutic procedure, or an observational research trial related to osteoarthritis within 8 weeks prior to the Screening Visit, or planned participation in any such trial; the last date of participation in the trial, not the last date of receipt of investigational product, must be at least 8 weeks prior to the Screening Visit
20. 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 the Screening Visit; treatment of the target knee with intra-articular glucocorticoids greater than 12 weeks prior to the Screening Visit is allowed
21. Treatment with systemic glucocorticoids greater than 10 mg prednisone or the equivalent per day within 4 weeks prior to the Screening Visit
22. Effusion of the target knee clinically requiring aspiration within 12 weeks prior to the Screening Visit
23. Use of electrotherapy, acupuncture, and/or chiropractic treatments for knee OA within 4 weeks prior to the Screening Visit (refer to Appendix 2)
24. Any known active infections, including urinary tract infection, upper respiratory tract infection, sinusitis, suspicion of intra-articular infection, hepatitis B or hepatitis C infection, and/or infections that may compromise the immune system such as human

immunodeficiency virus (HIV) at Day 1

25. Current use, or use within 12 weeks prior to the Screening Visit, of centrally acting analgesics (refer to Appendix 2) ~~w~~
26. Current use, or use within 12 weeks prior to the Screening Visit, of anticonvulsants (refer to Appendix 2)
27. Subjects requiring the usage of opioids >1x per week within 12 weeks prior to the Screening Visit
28. Topical local anesthetic agents (gels, creams, or patches such as the Lidoderm patch) used for the treatment of knee OA within 7 days of the Screening Visit
29. Any chronic condition that has not been well controlled or subjects with a chronic condition who have not maintained a stable therapeutic regimen of a prescription therapy in the opinion of the investigator. In addition, subjects with an HbA1c >9 at the Screening Visit will be excluded.
30. If on nonsteroidal anti-inflammatory drugs (NSAIDs) for the treatment of OA pain, subjects who have not maintained a stable regimen in the opinion of the Investigator at the Screening Visit
31. Any contraindications for performing MRI
32. Subjects who have a current or pending disability claim, workers' compensation, or litigation(s) that may compromise response to treatment
33. 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
34. 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

5.3 LIFESTYLE GUIDELINES

5.3.1 CONTRACEPTION

WOMEN OF CHILD BEARING POTENTIAL (WOCBP)

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

From the Screening Visit until Week 52 (EOS)/ET, sexually active WOCBP must agree to use an acceptable form of contraception as defined by this protocol:

1. Intrauterine device
2. Implantable rod
3. Established hormonal contraceptive methods in combination with a barrier method. This includes injectable, oral, patch, and vaginal ring hormonal contraception. Females who are using hormonal contraceptives must have had consistent use of the same hormonal

contraceptive product for at least 4 weeks prior to dosing and must continue to use the same contraceptive during the study. Barrier methods include male or female condom, diaphragm with spermicide, sponge with spermicide, or cervical cap with spermicide.

4. Bilateral tubal occlusion
5. Male partner who had a vasectomy provided that the partner is the sole sexual partner of the WOCBP, and that the vasectomized partner has received medical assessment of the success of the surgical procedure or had the vasectomy greater than 6 months prior to the screening visit
6. Abstinence

MEN OF CHILD BEARING POTENTIAL (MOCBP)

Men are considered of childbearing potential unless permanently sterile by bilateral orchiectomy.

From the screening visit until the end of Week 52 (EOS)/ET, MOCBP who are sexually active with a female partner who is of childbearing potential must agree to use one of the following acceptable forms of contraception as defined by this protocol:

1. Use of a condom for males who have had a vasectomy > 6 months ago or demonstrated success of the surgical procedure
2. Use of a condom for MOCBP without a vasectomy or vasectomy within 6 months prior to the screening visit and no demonstrated success of the surgical procedure. In addition, their female partner(s), if any, must be of non-childbearing potential (surgically sterile or postmenopausal) or instructed to use an acceptable form of birth control. Acceptable methods of birth control include
   - intrauterine device (IUD)
   - implantable rod
   - bilateral tubal occlusion
   - hormonal contraceptive (injectable, oral, patch, vaginal ring) used consistently for at least 4 weeks prior to study inclusion of the MOCBP
3. Abstinence

5.4 STRATEGIES FOR RECRUITMENT AND RETENTION

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

5.5 PARTICIPANT WITHDRAWAL OR TERMINATION

5.5.1 REASONS FOR WITHDRAWAL OR TERMINATION

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

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

5.5.2 HANDLING OF PARTICIPANT WITHDRAWALS OR TERMINATION

In case of premature discontinuation of study participation, Week 52 (EOS)/ET procedures should be conducted within 14 days of discontinuation for any subject who discontinues after the Day 1 visit, if possible. The date the subject is withdrawn from the study and the reason for the discontinuation should be recorded on the electronic case report form (eCRF). The Investigator or designee must complete all applicable eCRF pages for subjects who discontinue from the study prematurely.

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

5.6 PREMATURE TERMINATION OR SUSPENSION OF STUDY

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

6. STUDY AGENT

6.1 STUDY AGENT(S) AND CONTROL DESCRIPTION

6.1.1 ACQUISITION

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

6.1.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

SM04690 drug substance is an off-white powder. SM04690 drug product is a sterile suspension in diluent containing 0.5% carboxymethylcellulose sodium and 0.05% polysorbate 80 in pH 7.4

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

SM04690 and vehicle are manufactured by PrimaPharma, Inc. (San Diego, CA) and will be supplied as single-use injections. SM04690 and vehicle will be supplied to the study pharmacist and labeled according to the applicable local and country regulations. For dispensing, dose preparation, and labeling instructions, refer to the Pharmacy Manual.

6.1.3 PRODUCT STORAGE AND STABILITY

The study medication and vehicle must be stored at the appropriate temperature (15-30°C or 59-86°F) and in a restricted area with limited access. Temperature excursions are allowed between 2-60°C (36-140°F) for a time period not to exceed a cumulative of 72 hours.

6.1.4 PREPARATION

Each dose will be prepared by taking a known volume of SM04690 drug product and adding to a vehicle (diluent) vial, mixing well to re-suspend the product, then injecting 2 mL intra-articularly into the target knee. Refer to the Pharmacy Manual for detailed instructions on study medication preparation.

6.1.5 DOSING AND ADMINISTRATION

SM04690 will be administered in the following dosage strength:

- SM04690 0.07 mg in 2 mL Injectable Suspension

The injectable investigational product is to be administered by the Investigator as a 1-time single injection into the target knee joint. Only 1 knee will be treated for each subject in this study. Although not required, the injection may be guided by ultrasound if it is the standard practice of the Investigator. The injection can be done either through lateral or medial approach, based on the standard practice of the Investigator or the knee examination of the subject.

Only topical anesthetic (absolutely no invasive anesthetic) is allowed for the study injections. Topical anesthetic, if used, may not be combined with the study medication prior to injection.

The 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 is a suspension, prior aspiration of synovial fluid into the syringe containing the injectate should be avoided in order 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) in order to confirm correct needle placement, this will have to be done with a separate empty sterile syringe and the injectate volume subsequently injected via syringe exchange.

6.1.6 ROUTE OF ADMINISTRATION

The injectable investigational product is to be administered as a single intra-articular injection into the target knee joint once at Day 1.

6.1.7 STARTING DOSE AND DOSE ESCALATION SCHEDULE

Not applicable to this study.

6.1.8 DOSE ADJUSTMENTS/MODIFICATIONS/DELAYS

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

6.1.9 DURATION OF THERAPY

The injectable investigational product is to be administered as a single intra-articular injection into the target knee joint once at Day 1.

6.1.10 TRACKING OF DOSE

Not applicable to this study.

6.1.11 DEVICE SPECIFIC CONSIDERATIONS

Not applicable to this study.

6.2 STUDY AGENT ACCOUNTABILITY PROCEDURES

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

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

All study medication and vehicle prepared and dispensed by the Investigator and/or designee will be inventoried and accounted for throughout the study. The Investigator and/or designee must maintain an accurate, up-to-date dispensing log for all study medications supplied by the Sponsor. Study medication and vehicle dispensed for all subjects must be recorded on the drug accountability forms. The study medication dispensing log and remaining drug inventory will be reviewed by the Sponsor-designated clinical monitor.

The study medications supplied for this study are for use only in subjects properly consented into this protocol. Used and unused study medications must be kept in a secure location physically separated from standard clinic or office drug supplies, and with access limited to the Investigator and/or designee. Procedures for Investigator return or destruction of used and unused vials of the study medication will be provided in the Pharmacy Manual.

7. STUDY PROCEDURES AND SCHEDULE

7.1 STUDY PROCEDURES/EVALUATIONS

7.1.1 STUDY SPECIFIC PROCEDURES

Collection of Adverse Events Data

Data regarding AEs will be collected in this study. AEs are events that occur during the 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 Week 52 (EOS) or ET.

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 "Guidance for Industry: Toxicity Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Trials" (Appendix 1), causal relationship to study medication, outcome, and any treatment given.

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.

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. Serious adverse events that are not resolved or stabilized during this time period will be followed until resolution or stabilization.

Medical History

A medical history will be obtained at the Screening Visit and Day 1 with a follow-up at Week 52 (EOS)/ET. Medical history at the Screening Visit 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 nonsymptomatic medical history that could become symptomatic while on the study. Review of medical history at the Week 52 (EOS)/ET visit will only be to capture End Dates of any ongoing medical history collected at screening.

Physical Examination

A general physical examination will be conducted at the Screening Visit, Day 1, and Weeks 13, 26, 39, and 52 (EOS)/ET. Results of the physical examination will be noted in the source documents. Any clinically significant finding noted prior to study medication injection should be recorded as medical history. If it is found after study medication injection, it should be reported as an AE.

Knee Examination

A knee examination of both knees will be conducted at the Screening Visit, Day 1, and Weeks 4, 13, 26, 39, and 52 (EOS)/ET. Results of the knee examination will be noted in the source documents. Any clinically significant finding noted prior to study medication injection should be recorded as medical history. If it is found after study medication injection, it should be reported as an AE.

Presence of bilateral knee OA will be recorded in the eCRF at the Screening Visit. If the subject has OA in both knees, the site is to establish the target knee as the knee with greater pain at the Screening Visit based on the subject's evaluation and the Investigator's clinical judgment.

Misalignment of both knees will be assessed by the Investigator during the knee examination at the Screening Visit. 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 the Screening Visit, Day 1, and Weeks 4, 13, 26, 39, and 52 (EOS)/ET.

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

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

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

Height and Weight

Height measurements will be taken at the Screening Visit only. Weight measurements will be taken at the Screening Visit and Week 52 (EOS)/ET.

Radiograph of the Knee Joints

Radiograph of the knee joints will be taken at the Screening Visit, and at Weeks 26 and 52 (EOS)/ET.

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

All radiographs will be submitted to an independent radiologist 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 inclusion/exclusion criteria and 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.

Magnetic Resonance Imaging (MRI) of the Knee Joints

Magnetic resonance imaging scans of the knee joints will be taken at the Screening Visit and Weeks 13, 26, and 52 (EOS)/ET.

Detailed instructions for obtaining and managing the MRI images will be provided to the site prior to the initiation of subject enrollment. MRI assessments on the knee joints will include, but are not limited to, measurement of cartilage quality by T1rho and T2 mapping pulse sequence MRI, measurement of cartilage volume and thickness by 3D-SPGR pulse sequence MRI, and WORMS.

The MRI scans will be submitted to the site’s radiologist(s) for qualitative and quantitative interpretation.

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 (SSQs) (Clauw 2014). A WPI&SS assessment will be completed by the subject at Day 1 on paper.

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

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

Pain Numeric Rating Scale (NRS)

The pain NRS is an 11-point scale (0-10) for subject self-reporting of average knee pain in the last 24 hours. A pain NRS for each knee will be completed daily by the subject during the screening period from the Screening Visit until Day 1 to assess the subject’s daily OA knee pain diary average for the 7 days immediately preceding Day 1 and to determine subject eligibility. During the screening period, daily pain NRS assessments will be completed remotely by subjects

on the paper diary. It is recommended that subjects complete the diary in the evening. Subjects need to bring in their paper diary on Day 1. Subject eligibility and paper diary compliance for daily pain NRS and daily OA knee pain diary average for each knee from Day -7 to Day -1 will be reviewed at Day 1 prior to enrollment to determine subject eligibility.

The paper diary will be provided by the Sponsor and may not be reproduced.

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. WOMAC questionnaires will be completed at Day 1 prior to study medication injection. WOMAC questionnaire completion will be reviewed at Day 1 prior to enrollment to determine subject eligibility. After Day 1, WOMAC assessments will be completed at Weeks 4, 13, 26, 39, and 52 (EOS)/ET.

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

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

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 at Day 1 prior to study medication injection and at Weeks 4, 13, 26, 39, and 52 (EOS)/ET.

Upon completion of the Patient Global Assessment, both the subject and the study staff member will sign/initial and date the source document to indicate that the activity assessments are reported accurately. The study staff member will record the Patient Global Assessment score in the eCRF.

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

7.1.2 STANDARD OF CARE STUDY PROCEDURES

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

7.2 LABORATORY PROCEDURES/EVALUATIONS

7.2.1 CLINICAL LABORATORY EVALUATIONS

Non-fasting samples for clinical laboratory analysis by ACM Global Central Laboratory will be collected by a qualified staff member at the Screening Visit and Weeks 4, 13, 26, 39, and 52 (EOS)/ET. At a minimum, the following tests will be conducted:

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

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

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

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

The results of the clinical laboratory tests will be reported on the laboratory's standard reports. The Investigator must review all laboratory reports in a timely manner, noting "not clinically significant" (NCS) or comment on the clinical significance of any result that is outside the normal range for the laboratory or has a toxicity grade of 1 or greater, then date and initial the report. The Investigator must report all laboratory results that are BOTH outside the normal range for the laboratory or have a toxicity grade of 1 or greater AND, in the opinion of the Investigator, are clinically significant. If any abnormal, clinically significant laboratory measure is found prior to study medication injection, the subject is to be excluded. If it is found after study medication injection, it should be reported as an AE.

7.2.2 OTHER ASSAYS OR PROCEDURES

Pregnancy Test

A serum-based pregnancy test will be performed on female subjects at the Screening Visit. Results from the pregnancy test will be utilized to determine subject eligibility. A urine-based pregnancy test will be performed at the Screening Visit, Weeks 13, 26, and 52 (EOS) / ET. A negative urine pregnancy test must be confirmed prior to performing radiographs and MRI scans.

Drug Test

A urine sample for drug testing will be collected at the Screening Visit. The urine drug test will include: amphetamine, methamphetamine, 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.

7.2.3 SPECIMEN PREPARATION, HANDLING, AND STORAGE

Refer to the Laboratory Manual for ACM Global Laboratory.

7.2.4 SPECIMEN SHIPMENT

Refer to the Laboratory Manual for ACM Global Laboratory.

7.3 STUDY SCHEDULE

7.3.1 SCREENING

Screening Visit

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

The following procedures and assessments will be performed 7-14 days prior to Day 1. A negative urine pregnancy test must be confirmed prior to performing radiographs and MRI scans.

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

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.

Starting on the day of the Screening Visit, after the site visit, subjects will begin completion of daily pain NRS assessments remotely on a paper diary. It is recommended that subjects complete the diary in the evening. Subjects need to bring in their paper diary on Day 1.

7.3.2 ENROLLMENT

Day 1

This visit must occur within 7 to 14 days of the Screening Visit.

The following procedures and assessments will be performed at Day 1 prior to study medication injection:

- Review and/or documentation of current and past medical history, documentation of current medications, and review of prior medication excluded by the protocol
- Physical examination, including knee examination of both knees
- Vital signs measurements (pulse, blood pressure, respiration rate, and temperature)
- Review of pain NRS paper diary compliance and daily OA knee pain diary average for each knee from Day -7 to Day -1
- WOMAC

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

Patient Global Assessment and WPI&SS assessment will also be performed prior to enrollment; however, results from these assessments do not determine eligibility.

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

- Intra-articular study medication injection
- Collection of AE and concomitant procedures/medication data

7.3.3 FOLLOW-UP

Week 4

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

The following procedures and assessments will be performed at Week 4:

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

Week 13

The Week 13 visit should occur on Day 92 with a window of ± 7 days.

The following procedures and assessments will be performed at Week 13. A negative pregnancy test must be confirmed prior to performing radiographs and MRI scans.

- Collection of AE and concomitant procedures/medication data
- Physical examination, including knee examination of both knees
- Vital signs measurements (pulse, blood pressure, respiration rate, and temperature)
- Venipuncture and collection of samples for clinical laboratory tests
- Patient Global Assessment
- WOMAC
- Pregnancy test (urine-based)
- MRI scans

Week 26

The Week 26 visit should occur on Day 183 with a window of ± 7 days.

The following procedures and assessments will be performed at Week 26. A negative pregnancy test must be confirmed prior to performing radiographs and MRI scans

- Collection of AE and concomitant procedures/medication data
- Physical examination, including knee examination of both knees
- Vital signs measurements (pulse, blood pressure, respiration rate, and temperature)
- Venipuncture and collection of samples for clinical laboratory tests
- Patient Global Assessment
- WOMAC
- Pregnancy test (urine-based)
- Radiograph – bilateral in weight-bearing fixed flexion position, posterior-anterior (PA) view X-ray
- MRI scans

Week 39

The Week 39 visit should occur on Day 274 with a window of ± 7 days.

The following procedures and assessments will be performed at Week 39:

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

7.3.4 FINAL STUDY VISIT

Week 52 End of Study (EOS)

This final study visit should occur on Day 365 with a window of ± 7 days.

The following procedures and assessments will be performed at Week 52 (EOS). A negative pregnancy test must be confirmed prior to performing radiographs and MRI scans

- Collection of AE and concomitant procedures/therapies/medication data
- Review of medical history
- Vital signs measurements (pulse, blood pressure, respiration rate, and temperature)
- Physical examination, including knee examination of both knees
- Weight measurement
- Venipuncture and collection of samples for clinical laboratory tests
- Pregnancy test (urine-based)
- Radiograph – bilateral in weight-bearing fixed flexion position, posterior-anterior (PA) view X-ray
- Patient Global Assessment
- WOMAC
- MRI scans

7.3.5 EARLY TERMINATION VISIT

If possible, the following procedures and assessments should be performed within 14 days of subject premature withdrawal or termination. A negative pregnancy test must be confirmed prior to performing radiographs and MRI scans

- Collection of AE and concomitant procedures/therapies/medication data
- Review of medical history
- Vital signs measurements (pulse, blood pressure, respiration rate, and temperature)
- Physical examination, including knee examination of both knees
- Weight measurement
- Venipuncture and collection of samples for clinical laboratory tests
- Pregnancy test (urine-based)
- Radiograph – bilateral in weight-bearing fixed flexion position, posterior-anterior (PA) view X-ray
- Patient Global Assessment
- WOMAC
- MRI scans

7.3.6 SCHEDULE OF EVENTS TABLE

Procedure	**Screening Visit**[a] (Days -14 to -7)	**Day 1**[b]	**Week 4** (Day 29 ± 3 days)	**Week 13** (Day 92 ± 7 days)	**Week 26** (Day 183 ± 7 days)	**Week 39** (Day 274 ± 7 days)	**Week 52 (EOS)** (Day 365 ± 7 days) / **ET**
Informed consent	X						
Inclusion & exclusion criteria	X	X					
Demographics	X						
Medical history	X	X					X[c]
Current and prior procedures/medications	X	X					
Pregnancy test[d]	X			X	X		X
Radiograph	X				X		X
MRI	X			X	X		X
Physical examination	X	X		X	X	X	X
Knee examination	X	X	X	X	X	X	X
Selection of target knee	X						
Height	X						
Weight	X						X
Vital signs	X	X	X	X	X	X	X
Clinical laboratory sampling	X		X	X	X	X	X
Urine drug test	X						
WPI&SS		X					
Pain NRS[e, f]		X (Review)					
WOMAC		X	X	X	X	X	X
Patient Global Assessment		X	X	X	X	X	X
Intra-articular injection		X					
AEs and concomitant procedures/medications		X	X	X	X	X	X

[a] The screening period is a minimum of 7 days and a maximum of 14 days.
[b] At Day 1, all procedures should be performed prior to study medication injection except for collection of AEs and any medication data that occurs post injection.
[c] Review medical history to capture End Date(s), if applicable, of any ongoing medical history(ies) collected at screening.
[d] Both a serum- and urine-based pregnancy test will be performed on female subjects at the Screening Visit; a urine-based pregnancy test only will be performed at Weeks 13, 26 , and 52 (EOS) / ET. A negative urine pregnancy test must be confirmed prior to performing radiographs and MRI scans.

[e] Paper diary compliance for daily pain NRS and daily OA knee pain diary average for each knee from Day -7 to Day -1 will be reviewed at Day 1 prior to enrollment to determine subject eligibility.

[f] Pain NRS should be completed daily starting the day of the Screening Visit until Day -1. Subjects will complete the paper diary remotely. It is recommended that subjects complete the diary in the evening.

7.4 JUSTIFICATION FOR SENSITIVE PROCEDURES

Not applicable for this study.

7.5 CONCOMITANT MEDICATIONS, TREATMENTS, AND PROCEDURES

Details regarding the name, indication, route of administration, dose, and frequency of all medications taken within 30 days prior to the Screening Visit through Week 52 (EOS)/ET will be recorded in the 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 2)
  - Other anticonvulsants not listed in Appendix 2
  - 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, methamphetamine, buprenorphine, cocaine, methadone, opiates, PCP, propoxyphene, barbiturates, benzodiazepine, methaqualone, and tricyclic antidepressants
- Electrotherapy (refer to Appendix 2), acupuncture, and/or chiropractic treatments for knee OA are prohibited while the subject is on study.
- Any new formalized (i.e., prescribed by a medical professional) physical therapy exercise programs for knee OA are prohibited while the subject is on study; continuation of formalized physical therapy exercise programs that are already in progress at the time of screening are allowed.

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

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

7.7 PROPHYLACTIC MEDICATIONS, TREATMENTS, AND PROCEDURES

Not applicable to this study.

7.8 RESCUE MEDICATIONS, TREATMENTS, AND PROCEDURES

Not applicable to this study.

7.9 PARTICIPANT ACCESS TO STUDY AGENT AT STUDY CLOSURE

Not applicable to this study.

8. ASSESSMENT OF SAFETY

8.1 SPECIFICATION OF SAFETY PARAMETERS

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

8.1.1 DEFINITION OF ADVERSE EVENTS (AEs)

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

An 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).

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

8.1.3 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

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

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

8.2 CLASSIFICATION OF AN ADVERSE EVENT

8.2.1 SEVERITY OF EVENT

The Investigator will assess AEs for severity utilizing the "Guidance for Industry: Toxicity Scale

for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Trials". This toxicity scale is presented in Appendix 1. Laboratory values not listed on the toxicity scale will be assessed for severity by the clinical Investigator.

8.2.2 RELATIONSHIP TO STUDY AGENT

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

1. Not Related

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

2. Unlikely Related

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

3. Possibly Related

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

4. Probably Related

Exposure to the investigational product or administration of the study injection and AE are probably related if (1) the investigational product or study injection and AE are considered reasonably related in time **and** (2) the investigational product 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 must be followed until resolution by the Investigator. Resolution is defined as the return to baseline status or stabilization of the condition with the expectation that it will remain chronic. 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. SAEs that are not resolved or stabilized during this time period will be followed until resolution or stabilization.

8.4 REPORTING PROCEDURES

8.4.1 ADVERSE EVENT REPORTING

The Investigator is responsible for reporting AEs to the Sponsor and IRB according to the protocol as well as 21 CFR Parts 50, 56, and 312. The Investigator is responsible for ensuring accurate AE information is reviewed and recorded in the subject source and the AE eCRF in a timely manner. The Sponsor is responsible for submitting reports of AEs associated with the use of study medication that are both serious and unexpected to the FDA according to 21 CFR 312.32. All Investigators participating in ongoing studies with the study medication will receive copies of these reports from the Sponsor for prompt submission to their IRB/EC according to their institution's requirements.

8.4.2 SERIOUS ADVERSE EVENT REPORTING

The Investigator is responsible for reporting SAEs to the Sponsor and IRB according to 21 CFR Parts 50, 56, and 312. The Investigator and Samumed will manage SAEs according to the study document "Guidelines for the Management of Serious Adverse Events (SAEs) and Pregnancies".

All SAEs must be reported as described in the study manual by the Investigator, Study Coordinator, other designated study personnel, or Clinical Research Associate within 24 hours of notification of the SAE. The Investigator or designee should submit the SAE report to the Samumed Study SAE email address: sae@samumed.com or FAX: +1 858 408 4470. Follow-up information must be detailed in a follow-up SAE report and reported to the Samumed Study SAE email address or fax number as it becomes available. The Investigator also must report all SAEs promptly to the appropriate IRB/EC as required by the institution. Sponsor contact information for questions regarding SAE reporting is provided in Table 1.

Table 1: Sponsor Contact Information for Questions on SAE Reporting

Primary Contact		**Alternative Contact**	
Medical Monitor: Naina Rastalsky, MD		Clinical Project Manager, Clinical Development: Ashley Gantt	
Office Tel:	(858) 371-3874	Office Tel:	(858) 371-3880
Cellular:	(858) 926-8490	Cellular:	(858) 232-3426
Email:	naina@samumed.com	Email:	ashleyg@samumed.com

8.4.3 UNANTICIPATED PROBLEM REPORTING

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

- Protocol identifying information: protocol title and number, Investigator's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP; and
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

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

- UPs that are SAEs will be reported to the IRB and to the Sponsor within 24 hours of the Investigator becoming aware of the event.
- Any other UP will be reported to the IRB and to the Sponsor within the IRB-required reporting timeframe.
- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures) and IRB within the timeframe specified by the institution procedures and IRB.

8.4.4 EVENTS OF SPECIAL INTEREST

Not applicable to this study.

8.4.5 REPORTING OF PREGNANCY

Although pregnancy is not a formal SAE, if a study participant or the partner of a study participant becomes pregnant while the study participant is on study, the pregnancy is to be reported via SAE reporting procedures. The Investigator and Samumed will manage reporting of pregnancies according to the study document "Guidelines for the Management of Serious Adverse Events (SAEs) and Pregnancies".

8.5 STUDY HALTING RULES

Not applicable to this study.

8.6 SAFETY OVERSIGHT

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

9. CLINICAL MONITORING

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

Clinical monitoring will be performed per the Clinical Monitoring Plan. Clinical monitors will

periodically evaluate the progress of the study, including the verification of appropriate consent form procedures and the verification of the accuracy and completeness of eCRFs. Clinical monitors will also ensure that all protocol requirements, applicable US FDA regulations, other regulatory requirements, and the Investigator's obligations are being fulfilled.

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

10. STATISTICAL CONSIDERATIONS

10.1 STATISTICAL AND ANALYTICAL PLANS

This section describes the planned statistical analyses in general terms. A complete description of the statistical analyses will be specified in a statistical analysis plan (SAP), finalized prior to database lock.

10.2 STATISTICAL HYPOTHESES

No formal hypotheses are being tested in this study.

10.3 ANALYSIS DATASETS

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

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

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

10.4 DESCRIPTION OF STATISTICAL METHODS

10.4.1 GENERAL APPROACH

For continuous variables, the number of subjects in the analysis, mean, standard deviation, median, minimum, and maximum will be reported. All categorical endpoints will be summarized using frequencies and percentages.

10.4.2 ANALYSIS OF THE PRIMARY ENDPOINT(S)

Analysis of covariance (ANCOVA) will be used to estimate change from baseline in cartilage volume and thickness as measured by 3D-SPGR pulse sequence MRI as well as change from baseline in cartilage quality as determined by proteoglycan levels and GAG content hydration as measured by T1rho and T2 mapping pulse sequence MRI. The models will be evaluated at Week 26 and adjusted for baseline value. Unadjusted 95% confidence intervals and P values will be reported.

Change from baseline in all primary endpoints will be summarized with descriptive statistics.

10.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

Imaging assessments of the target knee will be used to evaluate cartilage volume, thickness, and quality (as determined by proteoglycan levels and GAG content hydration) at Weeks 13 and 52 as well as mJSW at Weeks 26 and 52. Imaging assessments of the non-target knee will be used to evaluate cartilage volume, thickness, and quality (as determined by proteoglycan levels and GAG content hydration) at Weeks 13, 26, and 52 as well as mJSW at Weeks 26 and 52.

Total WORMS of the target knee and non-target knee will be summarized with means and standard deviations, as well as percentages of maximum possible score at Weeks 13, 26 and 52.

WOMAC total score, WOMAC pain subscore, WOMAC function subscore, and Patient Global Assessment of the target knee will be assessed at Weeks 13, 26, and 52. Change from baseline will be summarized with descriptive statistics.

ANCOVA will be used to estimate change from baseline in all secondary endpoints. The models will be adjusted for baseline value and unadjusted 95% confidence intervals and P values will be reported.

The number and percent of subjects experiencing AEs will be summarized by seriousness, severity, and relationship for all subjects who receive the study injection.

10.4.4 SAFETY ANALYSES

Safety analyses will be performed on subjects who receive a study injection. Safety assessments include physical examinations, vital signs, clinical laboratory tests, solicitation of AEs and concomitant medications, and general medical evaluations. No formal statistical analyses are planned. Safety will be evaluated based on the incidence, seriousness, severity, and relationship of AEs and by changes in clinical laboratory parameters and vital signs, relative to baseline.

10.4.5 BASELINE DESCRIPTIVE STATISTICS

Baseline is defined as the last value recorded for any given parameter prior to study medication injection. In the case of questionnaires, all items collected from the last timepoint prior to study medication injection will be collectively flagged as baseline.

Descriptive statistics will be provided for age, weight, height, BMI, and WPI&SS assessments at baseline, while frequencies and percentages will be provided for sex, race, ethnicity, KL grade, and the presence of bilateral OA.

10.4.6 PLANNED INTERIM ANALYSES

Not applicable to this study.

10.4.6.1 SAFETY REVIEW

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

10.4.6.2 EFFICACY REVIEW

Not applicable to this study.

10.4.7 EXPLORATORY ANALYSES

Not applicable to this study.

10.4.8 ADDITIONAL SUB-GROUP ANALYSES

Not applicable to this study.

10.5 SAMPLE SIZE

A sample size of 15 subjects is selected for this exploratory study in order to have approximately 12 subjects complete the study. This sample size is based upon accepted statistical practice (Julious 2005).

10.6 MEASURES TO MINIMIZE BIAS

10.6.1 BLINDING PROCEDURES

This is an open-label study. Not applicable to this study.

10.6.2 EVALUATION OF SUCCESS OF BLINDING

Not applicable to this study.

10.6.3 BREAKING THE STUDY BLIND/PARTICIPANT CODE

Not applicable to this study.

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. The source documents should include detailed notes on the following:

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

12. QUALITY ASSURANCE AND QUALITY CONTROL

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

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

13. ETHICS/PROTECTION OF HUMAN SUBJECTS

13.1 ETHICAL STANDARD

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

13.2 INSTITUTIONAL REVIEW BOARD

The Investigator agrees to provide the IRB/EC with all appropriate material, including a copy of the informed consent form (ICF). The study will not be initiated until the Investigator obtains written approval of the research plan and the ICF from the appropriate IRB/EC and copies of these documents are received by the Sponsor. Appropriate reports on the progress of this study will be made by the Investigator to the IRB/EC and Sponsor in accordance with applicable government regulations and in agreement with the policies established by the Sponsor and the

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

13.3 INFORMED CONSENT PROCESS

13.3.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

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

13.3.2 CONSENT PROCEDURES AND DOCUMENTATION

The informed consent and consent process should be in accordance with the current Declaration of Helsinki, ICH, GCP, federal, state, and local regulations. The Investigator or designee must explain the nature of the study protocol and associated risks to the potential study participant. The potential participant must be allowed to review the study information and to ask questions before being asked to sign and date the ICF. Written informed consent must be provided (signed and dated) by the potential study participant prior to initiation of any screening evaluations or other study-related procedures. A copy of the ICF will be given to the participants for their records. The signature, date, and the name of the individual at the site who obtained the informed consent will be recorded.

13.4 PARTICIPANT AND DATA CONFIDENTIALITY

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

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

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

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

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

Not applicable to this study.

13.5 FUTURE USE OF STORED SPECIMENS

Not applicable to this study.

14. DATA HANDLING AND RECORD KEEPING

14.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

As defined by ICH guidelines, the CRF is a printed, optical, or electronic document designed to record all 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 (EDC) system fully compliant with regulatory expectations for software developers and service providers within the global regulatory environment, including but not limited to ICH E6 and US 21 CFR Parts 312, 812, and 11. Data to be transferred external to Rave may include imaging results.

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

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

14.2 STUDY RECORDS RETENTION

During this study, an Investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated with the IP or entered as a control in the investigation. CRFs will be provided for each subject by the Sponsor. Data reported on the eCRFs and derived from source documents must be consistent with the source documents or the discrepancies must be explained. The completed eCRFs must be promptly reviewed, and electronically signed and dated in EDC by a qualified physician who is an Investigator on the study once all data is considered final. During this study, the Investigator must retain copies of eCRFs (or electronic files), and source

documents for the maximum period required by (1) applicable regulations and guidelines or institution procedures **or** (2) for the period specified by the Sponsor, whichever is longer. The Investigator must contact the Sponsor prior to destroying any records associated with the study.

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

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

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

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

14.3 PROTOCOL DEVIATIONS

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

Refer to the current version of Samumed SOP-300-13 Protocol Deviations for Sponsor procedures related to protocol deviations.

14.4 PUBLICATION AND DATA SHARING POLICY

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

15. STUDY ADMINISTRATION

15.1 STUDY LEADERSHIP

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

16. LITERATURE REFERENCES

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APPENDIX

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

Table A1: Tables for Clinical Abnormalities

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

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

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

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

* Subject should be at rest for all vital sign measurements. ** Oral temperature; no recent hot or cold beverages or smoking.

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

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

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

Table A2: Tables for Laboratory Abnormalities

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

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

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

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

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

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

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

Appendix 2. Prohibited Concomitant Medications and Procedures (Supplement)

Excluded and prohibited centrally acting analgesics include, but are not limited to, the following:

Gabapentin (Neurontin, Horizant, Gaberone, Gralise, Fusepaq Fanatrex)

Pregabalin (Lyrica)

Carbamazepine (Tegretol, Carbatrol, Epitol, Equetrol)

Duloxetine (Cymbalta, Irenka)

Milnacipran (Savella)

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

Tapentadol (Nucynta)

Orphenadrine Citrate (Norflex, Orfro, Orphenate, Mio-Rel, Antiflex)

Amitriptyline (Elavil, Vanatrip)

Clomipramine (Anafranil)

Nortriptyline (Aventyl, Pamelor)

Desipramine (Norpramin)

Imipramine (Tofranil)

Doxepin (Prudoxin, Sinequan, Zonalon, Silenor)

Ketamine (Ketalar)

Sodium Oxybate (Xyrem, GHB)

Other non-listed anticonvulsants are also prohibited

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

Diathermy

TENS

NMES

Interferential therapy

Shortwave therapy

Iontophoresis

LASER

Ultrasound

Appendix 3. Amendment

AMENDMENT 02 VERSION 00 SUMMARY OF CHANGES

Study Title: A Phase 2, 52 Week, Single Center, Open-Label Study Utilizing Imaging Techniques and Evaluating the Safety and Efficacy of SM04690 Injectable Suspension for the Treatment of Moderately to Severely Symptomatic Knee Osteoarthritis

Purpose: The purpose of this amendment is to add pregnancy tests to visits at Screening and Weeks 13, 26, and 52; update language regarding contraception and AEs; and refine exclusion criteria.

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 all previous and current protocol versions
Added a confidentiality disclaimer to the Title Page.	Title Page	Change was made to correct an oversight
Protocol date and version have been updated as applicable.	All	Change was made to reflect current protocol amendment
Added Ismail Simsek as a signatory	Signature Page	Change was made to comply with sponsor SOP
Updated titles for Ismail Simsek and Christopher Swearingen	Signature Page and Key Roles	Change was made for administrative reasons
Changed to Naina Rastalsky as Medical Monitor	Key Roles, Section 8.4.2	Change was made for administrative reasons
Updated list of abbreviations	List of Abbreviations	Change was made for accuracy
Changed terminology from treatment-emergent adverse events (AEs) to adverse events (AEs)	Throughout	Change was made to align current protocol with sponsor SOP
Changed terminology from “contralateral knee” to “non-target knee” to describe knee that does not receive injection	Throughout	Change was made to more precisely describe procedures
Updated dates of study duration	Protocol Summary	Change was made to reflect estimated time of study
Added information to Inclusion Criteria #2: “Ambulatory (*single assistive devices such as canes allowed if needed less than 50% of the time, subjects requiring a walker are excluded*)”	Protocol Summary, Section 5.2	Change was made to better define ambulatory
Added information to Inclusion Criteria #11: “Negative drug test for ~~opioids and drugs of abuse, except alcohol and marijuana,~~ amphetamine, methamphetamine, buprenorphine, cocaine, methadone, opiates,	Protocol Summary, Section 5.2	Change was made to better define drugs of abuse

Change	Sections Affected	Rationale
phencyclidine (PCP), propoxyphene, barbiturates, benzodiazepine, methaqualone, and tricyclic antidepressants, except if any such drugs are clinically indicated and allowed by the protocol, at the Screening Visit"		
Updated Exclusion Criteria 1-3 regarding pregnancy and birth control	Protocol Summary, Section 5.2	Change was made to provide clarity to our criteria
Changed Exclusion Criteria #4 from >35 BMI to >40 BMI	Protocol Summary, Section 5.2	Change was made to allow more subjects to meet criteria
Modified Exclusion Criteria #8: "Previous ~~randomization~~ *enrollment* into a Samumed clinical trial investigating SM04690"	Protocol Summary, Section 5.2	Change was made to refine criteria
Changed Exclusion Criterion #10: Any ~~planned~~ surgery ~~scheduled~~ during…	Protocol Summary, Section 5.2	Change was made to refine exclusion criteria
Removed Exclusion Criteria #19: Treatment with systemic glucocorticoids greater than 10 mg prednisone or the equivalent per day within 4 weeks prior to the Screening Visit	Protocol Summary, Section 5.2	Change was made because this Exclusion Criteria was redundant with later Exclusion Criteria regarding glucocorticoids
Modified Exclusion Criteria #24 (#25 in previous Amendment): "~~Chronic use (i.e., regular and consistent use ≥ 3 days per week for ≥ 12 weeks)~~ *Current use, or use within 12 weeks prior to the Screening Visit,* of centrally acting analgesics ~~(e.g., duloxetine and tramadol)~~ (*refer to* Appendix 2) ~~within 12 weeks prior to the Screening Visit"~~	Protocol Summary, Section 5.2	Change was made to refine Exclusion Criteria
Modified Exclusion Criteria #25 (#26 in previous Amendment): "~~Chronic use (i.e., regular and consistent use ≥ 3 days per week for ≥ 12 weeks)~~ Current use, or use within 12 weeks prior to the Screening Visit, of anticonvulsants ~~not listed in~~ (*refer to* Appendix 2) ~~within 12 weeks prior to the Screening Visit, unless used for seizure or migraine prophylaxis"~~	Protocol Summary, Section 5.2	Change was made to refine Exclusion Criteria
Modified Exclusion Criterion #32 (#31 in this Amendment): 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~~	Protocol Summary, Section 5.2	Deleted section was repeated verbatim in an earlier Exclusion Criterion
Updated dates and information for clinical trials OA-04 and OA-05	Section 2.3	Change was made to provide most recent information

Change	Sections Affected	Rationale
Updated date for allergic reactions to study medication	Section 2.3.1	Change was made to provide most recent information
Defined women and men of childbearing age and modified language for contraception for women and men	Section 5.3.1	Change was made to clarify rules regarding contraception for subjects
Changed language regarding administration of medication by Investigator	Section 6.1.5	Change was made to provide better guidance to Investigators for proper injections
The following was added: "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."	Section 7.1.1	Change was made to provide guidance for study personnel
Added the following to description of knee radiographs: "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."	Section 7.1.1	Section was added to ensure that patient information was handled properly by study personnel.
Changed measure of Patient Global Assessment of Disease Activity from a 100 mm visual analog scale to an 11-point numerical rating scale	Section 7.1.1	Change was made for more accurate assessments
Modified language for clinical laboratory tests: "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)~~"	Section 7.2.1	Change was made to provide clarity to investigators

Change	Sections Affected	Rationale
Added a urine-based pregnancy test at Screening and Weeks 13, 26, and 52 (EOS) / ET. Added language that pregnancy tests must be negative prior to performing radiography and MRI	Sections 7.2.2, 7.3.3, 7.3.4	Change was requested by study site for subject safety
Added information to the informed consent process at the screening visit.	Section 7.3.1	Change was made to ensure compliance with sponsor and government regulations
Modified Day 1 description: "The following procedures and assessments will be performed at Day 1 prior to ~~enrollment~~ *study medication injection*"	Section 7.3.2	Change was made to avoid confusion with the timing of enrollment
Changed window for Week 39 visit from ± 3 days to ± 7 days	Sections 7.3.3 and 7.3.6	Change was made to correct an error
Changed description of prohibited medication: "Other anticonvulsants not listed in Appendix 2 are also prohibited ~~unless used for seizure or migraine prophylaxis~~"	Section 7.6	Change was made to align with Exclusion Criteria
Changed description of prohibited proecures: "~~Planned or~~ elective surgery…"	Section 7.6	Change was made to align with Exclusion Criteria
Added the following to definition of Adverse Events: "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."	Section 8.1.1	Change was made to better define adverse events
Changed one of the definitions of SAEs: Requires ~~nonscheduled (not routine or planned) subject~~ *inpatient* hospitalization or prolongation of existing hospitalization ~~for ≥ 24 hours and admission to the hospital~~ *…"Inpatient hospitalization" is clarified as hospitalization lasting ≥24 hours.*	Section 8.1.2	Change was made to align with the FDA's definitions of SAEs and with Sponsor's AE SOP
Removed the phrase "(or placebo)" from the definition of adverse events (AEs).	Section 8.2.2	Change was made to avoid confusion since this study does not have a placebo.
Modified language for AE reporting: "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 8.3	Change was made to provide better guidance to investigators
Added Ashley Gantt as Clinical Project Manager	Section 8.4.2	Change was made for administrative reasons
Removed paragraph relating to centralized data monitoring	Section 9	Removed because trial is a single-center study

Change	Sections Affected	Rationale
Changed title of Intent-to-Treat (ITT) Analysis Set to Full Analysis Set (FAS).	Section 10.3	Change was made for clarity
Refined description of consent procedures	Section 13.3.2	Change was made to ensure better compliance with sponsor SOPs and government regulations
Minor grammatical and formatting edits	Throughout	Changes were made for consistency.

AMENDMENT 01 VERSION 00 SUMMARY OF CHANGES

Study Title: A Phase 2, 52 Week, Single Center, Open-Label Study Utilizing Imaging Techniques and Evaluating the Safety and Efficacy of SM04690 Injectable Suspension for the Treatment of Moderately to Severely Symptomatic Knee Osteoarthritis

Purpose: The purpose of this amendment is to refine and clarify the study design. Primary changes include removal of MRI at Week 39, removal of electronic diaries, removal of NRS as an endpoint assessment tool in the study, and addition of exploratory endpoints related to the contralateral (non-target) knee.

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

Change	Sections Affected	Rationale
Protocol Amendment 01 Version 00 has been added on the title page.	Title Page	Change was made to capture the dates of all previous and current protocol versions
Protocol date and version have been updated as applicable.	All	Change was made to reflect current protocol amendment
Updated list of abbreviations	List of Abbreviations	Change was made for accuracy
The primary objective was updated: 1. Evaluate the ~~clinical~~ efficacy of SM04690 Injectable Suspension for the treatment of knee osteoarthritis (OA) via magnetic resonance imaging (MRI)	Protocol Summary Section 3	Change was made for accuracy
The following secondary objectives were updated: 2. Evaluate the ~~clinical~~ efficacy of SM04690 Injectable Suspension for the treatment of knee OA as assessed by patient reported outcomes (PROs). 3. Evaluate the ~~clinical~~ efficacy of SM04690 Injectable Suspension for the treatment of knee OA via radiograph	Protocol Summary Section 3	Change was made for accuracy
The following secondary endpoints were updated/added to the study: 1.Change from baseline in cartilage volume and thickness	Protocol Summary Section 4.2.2 Section 10.4.3	Change was made for accuracy

Change	Sections Affected	Rationale
in the target knee as measured by 3D-SPGR pulse sequence MRI at Weeks 13, ~~39,~~ and 52. 2. Change from baseline in cartilage quality in the target knee by the increase or decrease in proteoglycan and GAG content and hydration as measured by T1rho and T2 mapping pulse sequence MRI at Weeks 13, ~~39,~~ and 52. 3. Change from baseline in total Whole Organ MRI Scoring (WORMS) in the target knee at Weeks 13, 26, and 52.		
The following exploratory endpoints were added to the study: 1. Change from baseline in cartilage volume and thickness in the contralateral knee as measured by 3D-SPGR pulse sequence MRI at Weeks 13, 26, and 52. 2. Change from baseline in cartilage quality in the contralateral knee determined by the increase or decrease in proteoglycan and GAG content and hydration as measured by T1rho and T2 mapping pulse sequence MRI at Weeks 13, 26, and 52. 3. Change from baseline in total WORMS in the contralateral knee at Weeks 13, 26, and 52. 4. Change from baseline in medial joint space width (JSW) as documented by radiograph of the contralateral knee at Weeks 26 and 52	Protocol Summary Section 4.2 Section 10.4	Change was made for accuracy
Daily pain NRS (except during the screening period) was removed from the study.	Protocol Summary Schematic of Study Design Section 7.1.1 Section 7.3.2 Section 7.3.6 Section 10.4.2	Change was made to refine study design
The following secondary endpoints were removed from the study: 4. Change from baseline OA pain in the target knee as assessed by the weekly averages of daily pain numeric rating score (NRS) at Weeks 4, 13, 26, 39, and 52. 5. Change from baseline OA pain in the contralateral knee as assessed by the weekly averages of daily pain NRS at Weeks 4, 13, 26, 39, and 52.	Protocol Summary Section 4.2.2	Change was made to align with pain NRS removal from the study
The following exclusion criteria were updated 25. *Chronic* use *(i.e., regular and consistent use ≥ 3 days per week for ≥ 12 weeks)* of centrally acting analgesics (e.g., duloxetine *and tramadol*) (refer to Appendix 2) within 12 weeks prior to the Screening Visit. 26. *Chronic* use *(i.e.,*	Protocol Summary Section 5.2	Change was made to refine study design

Change	Sections Affected	Rationale
regular and consistent use ≥ 3 days per week for ≥ 12 weeks) of anticonvulsants not listed in Appendix 2 within 12 weeks prior to the Screening Visit, unless used for seizure or migraine prophylaxis		
Estimated date first subject consented was updated to January 2018 (previously November 2017). Estimated date last subject completed was updated to May (previously July)	Protocol Summary	Change was made for accuracy
Total WORMS analysis was added to the study	Protocol Summary Section 7.1.1 Section 10.4.3	Change was made to refine study design
MRI was removed from Week 39 Follow-up Visit.	Protocol Summary Schematic of Study Design Section 4.1 Section 4.2.2 Section 7.1.1 Section 7.3.3 Section 7.3.6 Section 10.4.3	Change was made to refine study design
Study information for OA-04 and OA-05 were updated	Section 2.2	Change was made for accuracy
Electronic Diary/Training/Return of devices were removed from the study	Schematic of Study Design Section 1 Section 4.1 Section 7.1.1 Section 7.3.1 Section 7.3.2 Section 7.3.4 Section 7.3.5 Section 7.3.6 Section 11 Section 14.1	Change was made to refine study design
The pain NRS diary and study questionnaires for WOMAC and PGA are to be completed on paper (previously on electronic devices)	Section 4.1 Section 7.1.1 Section 7.3.1 Section 7.3.2 Section 7.3.6	Change was made to refine study design
The following inclusion criteria was removed from the study: 11. Willingness to use an electronic diary on a daily basis in the evening for the screening period and 52 week study duration.	Protocol Summary Section 5.1	Change was made to align with electronic diary removal from the study

Change	Sections Affected	Rationale
Windows for Follow-up Visits where MRIs will be performed were expanded to ±7 days (previously ±3 days).	Section 7.3.3 Section 7.3.6	Change was made to refine study design