

STRIDES

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

A Phase 3, 16-Week, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of a Single Injection of Lorecivivint 0.07 mg Dose in the Target Knee Joint of Subjects with Moderate to Severe Osteoarthritis Pain of the Knee

Study Number: SM04690-OA-21

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Protocol SM04690-OA-21
Biosplice Therapeutics, Inc.

AM01V01
November 9, 2022

SPONSOR SIGNATURE PAGE

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LIST OF ABBREVIATIONS

Abbreviation	Term
ACR	American College of Rheumatology
AE	Adverse event
AESEV	Severity/Intensity Scale for Adverse Events
ANCOVA	Analysis of covariance
APAP	Acetaminophen/paracetamol
BMI	Body mass index
BOCF	Baseline observation carried forward
CDISC	Clinical Data Interchange Standards Consortium
CFR	Code of Federal Regulations
CRF	Case report form
EC	Ethics Committee
eCOA	Electronic clinical outcomes assessment
eCRF	Electronic case report form
EDC	Electronic data capture
EOS	End of study
ET	Early termination
FAS	Full analysis set
HbA1c	Hemoglobin A1c
IA	Intra-articular
IB	Investigator's Brochure
ICF	Informed consent form
IP	Investigational product
IRB	Institutional Review Board
KL	Kellgren-Lawrence
KOOS	Knee Injury and Osteoarthritis Outcome Score
LOCF	Last observation carried forward
LOR	Lorecivivint

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Abbreviation	Term
MI	Multiple imputation
MMRM	Mixed-effects model for repeated measures
NRS	Numeric rating scale
NSAID	Nonsteroidal anti-inflammatory drug
OA	Osteoarthritis
PASS	Patient-Acceptable Symptom State
PCP	Phencyclidine
PPAS	Per-protocol analysis set
PRP	Platelet-rich plasma
SAE	Serious adverse event
SD	Standard deviation
SOP	Standard operating procedure
WOCBP	Women of childbearing potential
WOMAC	Western Ontario and McMaster Universities Arthritis Index
WPI&SS	Widespread Pain Index and Symptom Severity Form

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STATEMENT OF COMPLIANCE

Study Title	A Phase 3, 16-Week, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of a Single Injection of Lorecivivint 0.07 mg Dose in the Target Knee Joint of Subjects with Moderate to Severe Osteoarthritis Pain of the Knee		
Protocol Number	SM04690-OA-21		
Protocol Date	November 9, 2022	Protocol Version	AM01V01

I have read and understand the protocol and agree to implement the study in accordance with the procedures set forth in the protocol and in accordance with the Sponsor's guidelines, all applicable government regulations, and the International Council for Harmonisation Guideline for Good Clinical Practice (ICH-GCP) E6 (R2).

I will obtain Institutional Review Board/Ethics Committee (IRB/EC) approval of the protocol and Informed Consent Form (ICF) before 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 before implementation except when such modification is made to remove an immediate hazard to the subject.

I will ensure that a fully executed IRB/EC-approved ICF is obtained from each subject before initiation of any study procedures.

I will allow the Sponsor, Biosplice Therapeutics, Inc. 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 Biosplice Therapeutics, Inc. The information contained herein is provided for the purpose of conducting a clinical trial for Biosplice Therapeutics, Inc.

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 Biosplice Therapeutics, Inc.

Investigator's Signature

Date

Investigator's Printed Name

1. PROTOCOL SUMMARY**1.1 SYNOPSIS**

Title: A Phase 3, 16-Week, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of a Single Injection of Lorecivivint 0.07 mg Dose in the Target Knee Joint of Subjects with Moderate to Severe Osteoarthritis Pain of the Knee

Objective: The objective of this study is to determine the efficacy and safety of the lorecivivint (LOR) 0.07 mg dose compared to placebo in the treatment of moderate to severe osteoarthritis (OA) pain of the knee.

Endpoints: **Primary**

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

Secondary

1. Change from baseline OA function in the target knee as assessed by Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) physical function subscore (WOMAC Function) at Week 12
2. Change from baseline OA disease activity as assessed by Patient Global Assessment at Week 12

Safety

Safety of LOR as assessed by:

1. Safety of SM04690 Injectable Suspension as measured by adverse events (AEs), serious adverse events (SAEs), vital signs, and clinical laboratory tests

Other Endpoints

2. Change from baseline OA pain in the target knee as assessed by the weekly average of daily pain NRS over the course of the study
3. Change from baseline OA function in the target knee as assessed by WOMAC Function over the course of the study
4. Change from baseline OA pain in the target knee as assessed by WOMAC Pain over the course of the study
5. Change from baseline OA disease activity as assessed by Patient Global Assessment over the course of the study
6. Usage of rescue medication over the course of the study
7. Change from baseline symptoms of OA in the target knee as

assessed by WOMAC Total score over the course of the study

8. Change from baseline OA function in the target knee as assessed by Knee Injury and Osteoarthritis Outcome Score (KOOS) subscale of Function (Sports) over the course of the study
9. Change from baseline OA function in the target knee as assessed by KOOS subscale of Quality of Life over the course of the study
10. Patient-Acceptable Symptom State (PASS) over the course of the study

Methodology: This study will be a multicenter, randomized, double-blind, placebo-controlled, parallel-group study of LOR or placebo (vehicle without LOR) injected in the target knee joint in subjects with moderate to severe OA pain of the knee.

Approximately 550 subjects will be enrolled and randomized into 1 of 2 treatment arms at a ratio of 1:1 (0.07 mg LOR per 2 mL injection: 2 mL placebo injection).

Subjects will participate in a screening period of a minimum of 18 days and up to 28 days (including a 2-week oral analgesic washout period) followed by a 16-week evaluation period. Each subject will receive an injection on Day 1. Clinic visits will be scheduled at Screening Visit 1, Screening Visit 2, Day 1, and Weeks 4, 8, 12, and 16 (End of Study [EOS])/Early Termination (ET). Refer to [Figure 1](#) for an overview of the study design.

At Screening Visit 1, participants will be asked to sign the informed consent form (ICF). Subjects will then undergo preliminary eligibility assessments. Subjects who meet preliminary criteria will have bilateral radiographs taken of their knees to further determine eligibility and selection of target knee. Subjects who meet radiological criteria will return to the clinic for Screening Visit 2.

After Screening Visit 2, all subjects who continue to meet eligibility criteria will enter a 2-week washout period during which nonsteroidal anti-inflammatory drug (NSAID) and acetaminophen/paracetamol (APAP) use will be prohibited and subjects will complete baseline pain and function assessments on their study-provided electronic devices. Subjects who fulfill the target and non-target knee pain eligibility criteria, as described under a separate blinded criteria document, will be randomized at the end of this period. The blinded criteria will be available for review by the FDA and Institutional Review Boards (IRBs), but will remain unavailable to participating sites for the duration of the clinical trial.

Following the study injection on Day 1 until Week 16 (EOS)/ET, subjects will be directed to avoid use of prohibited medications, as described in [Section 7.6](#), other than the study-provided rescue medication for any type

of pain. Subjects will be permitted to take study-provided rescue medication to treat worsening knee OA pain or other types of pain that cannot be tolerated by a subject. The study-provided rescue medication is APAP 500 mg, 1-2 tablets every 6-8 hours, up to a maximum of 6 tablets (3000 mg) per 24-hour period.

Starting at Day 1 and at Weeks 4, 8, and 12, subjects will be provided with a sufficient quantity of rescue medication for the interval to the next scheduled visit. Rescue medication use will be reviewed by study personnel during subject clinic visits (i.e., pill count).

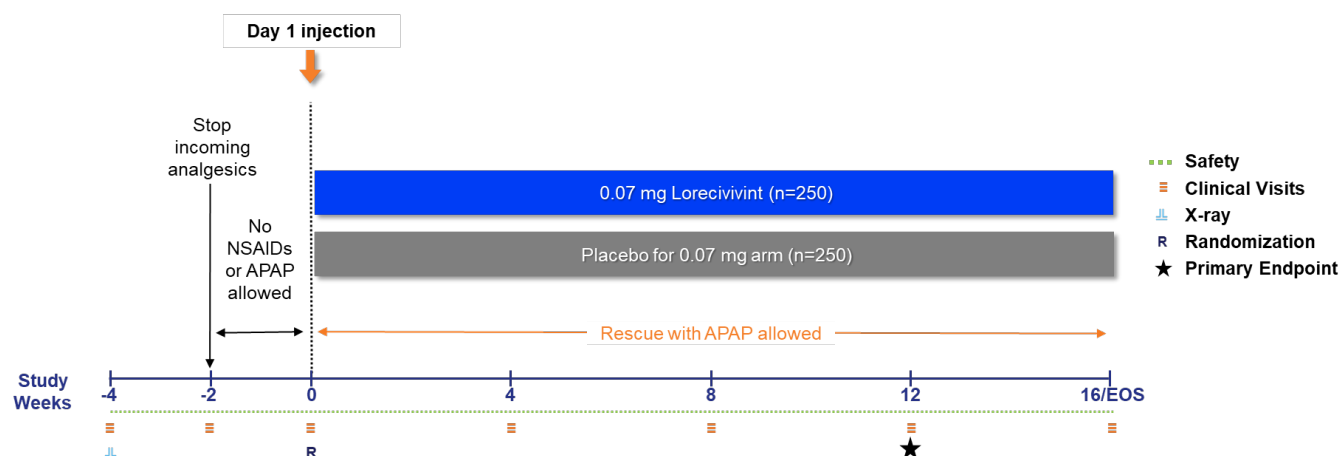
Subjects will be encouraged to use rescue medication only for acute non-tolerable pain. APAP usage will be reviewed at each visit and subjects taking it chronically (e.g., greater than 10 days of aggregate use of APAP) will be counseled on appropriate use of rescue medication as defined by the protocol.

Study Assessments

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

- Daily pain NRS (for target knee OA pain) through Week 16 (EOS)
- Monthly WOMAC through Week 16 (EOS)
- Monthly Patient Global Assessment through Week 16 (EOS)
- Monthly KOOS (Function [Sports] and Quality of Life) through Week 16 (EOS)
- Monthly PASS through Week 16 (EOS)
- Daily documentation of any rescue medication use

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

Figure 1. Overview of Study Design and Endpoints

APAP=acetaminophen/paracetamol

NSAIDs= nonsteroidal anti-inflammatory drug

n=250 per arm are completed evaluable subjects

**Inclusion/
Exclusion
Criteria:****Criteria for Inclusion**

1. Males and females between 40 and 80 years of age, inclusive, in general good health apart from their knee OA
2. Ambulatory (single assistive devices such as canes allowed if needed less than 50% of the time, subjects requiring a walker are excluded)
3. Diagnosis of femorotibial OA in the target knee by standard American College of Rheumatology (ACR) criteria (refer to [Appendix 1](#)) at Screening Visit 1 (clinical AND radiographic criteria); OA of the knee is not to be secondary to any rheumatologic conditions (e.g., rheumatoid arthritis) and the knee(s) should be the primary joint affected by OA.
4. Radiographic disease Grade 2 or Grade 3 in target knee at Screening Visit 1 according to the Kellgren-Lawrence (KL) grading of knee OA as assessed by independent central readers
5. Meeting blinded radiographic criteria for target knee
6. Pain compatible with OA of the knee(s) for at least 26 weeks before Screening Visit 1
7. Primary source of pain throughout the body is due to OA in the target knee
8. Body mass index (BMI) $\leq 35 \text{ kg/m}^2$
9. Meeting blinded criteria for comorbid diffuse pain and related symptoms
10. Meeting blinded criteria for pain reporting for target knee
11. Meeting blinded criteria for pain reporting for non-target knee
12. Willingness to use an electronic diary daily in the evening for the

screening period and 16-week study duration

13. Willingness to not use prohibited medications as listed in [Section 7.6](#) between Screening Visit 2 and Week 16 (EOS)
14. Negative drug test for amphetamine, buprenorphine, cocaine, methadone, methadone metabolite, methamphetamine, ecstasy, morphine, opiates, oxycodone, phencyclidine (PCP), barbiturates, benzodiazepines, tricyclic antidepressants and marijuana unless approved by medical monitor as per inclusion criteria 15
15. Subjects with depression or anxiety must be clinically stable for 12 weeks before Screening Visit 1 and, if on treatment for depression or anxiety, be on 12 weeks of stable therapy
16. Full understanding of the requirements of the study and willingness to comply with all study visits and assessments
17. Subjects must have read and understood the ICF, and must have signed and dated it before any study-related procedure being performed
18. Subject's Screening Visit 2 visit must occur while enrollment into the randomization cohort for which they are eligible is open

Criteria for Exclusion

1. Pregnant women, breastfeeding women, and women who are not post-menopausal (defined as 12 months with no menses without an alternative medical cause) or permanently surgically sterile (includes hysterectomy, bilateral salpingectomy, and bilateral oophorectomy) who have a positive or indeterminate pregnancy test result at the Screening Visit 2 or Day 1
2. Women who are not post-menopausal or permanently surgically sterile who are sexually active with males, and who are not willing or able to use birth control (as outlined in [Section 5.3.1](#)) during the study period
3. Subjects exceeding limits of blinded criteria for anatomical axis alignment
4. Aspiration of effusion of the target knee within 12 weeks before Day 1
5. Any suspicion of intra-articular (IA) infection in target knee
6. Partial or complete joint replacement in either knee
7. Presence of hardware in the target knee
8. Currently requires frequent, habitual or daily use of a lower extremity prosthesis and/or use of a structural knee brace on either knee within 26 weeks before Day 1
9. Any surgery (e.g., arthroscopy) in either knee within 26 weeks before Day 1
10. IA injection into the target knee with a therapeutic aim including,

but not limited to, hyaluronic acid, platelet-rich plasma (PRP), stem cell therapies, and extended-release corticosteroids within 26 weeks before Day 1 or IA immediate-release glucocorticoids within 12 weeks before Day 1

11. Use of electrotherapy (refer to [Appendix 2](#)), acupuncture, formalized physical therapy (i.e., prescribed by a medical professional), therapeutic ultrasound, and/or chiropractic treatments for knee OA within 4 weeks before Day 1
12. Previous enrollment in a study of SM04690 (lorecivint)
13. Subjects who have previously failed screening on this protocol and fail to meet rescreening criteria (see [Section 5.4.2](#))
14. Participation in a clinical research trial that included the receipt of an investigational product (IP) or any experimental therapeutic procedure within 4 weeks or 5 half-lives, whichever is greater, before Screening Visit 1, or planned participation in any such trial
15. Use of APAP or NSAIDs during washout period (between Screening Visit 2 and Day 1). Use of aspirin (up to 325 mg/day) for thrombosis prophylaxis is permitted.
16. History of intolerance or hypersensitivity to APAP or any of its excipients or existence of a medical condition (e.g., known Glucose-6-phosphate dehydrogenase [G6PD] deficiency) or use of concomitant medication for which the use of APAP is contraindicated
17. Subjects who have impaired liver function (e.g., aspartate aminotransferase, alanine aminotransferase, or bilirubin $\geq 3\times$ upper limit of normal [ULN]), active hepatic disease, evidence of clinically significant liver disease, or other condition (e.g., alcoholism, cirrhosis, or hepatitis) that suggests the potential for an increased susceptibility to hepatic toxicity with APAP
18. History of consuming more than an average of 3 alcohol-containing drinks daily over the preceding 4 weeks before Day 1
19. Subjects with a current or chronic history of renal impairment defined as serum creatinine $>3\times$ ULN
20. Treatment with systemic (oral, intramuscular, or intravenous) glucocorticoids ≥ 10 mg prednisone or the equivalent per day within 4 weeks before Day 1; or subjects on <10 mg prednisone or the equivalent per day who have not maintained a stable regimen for at least 2 weeks before Day 1 in the opinion of the Investigator
21. Use of centrally acting analgesics (refer to [Appendix 2](#)) within 5 half-lives before Screening Visit 2
22. Use of anticonvulsants (refer to [Appendix 2](#)) within 5 half-lives before Screening Visit 2

23. Use of opioids within 4 weeks before Screening Visit 1
24. Planned surgery scheduled during the study period, not including nonsurgical invasive procedures conducted for a diagnostic or therapeutic purpose scheduled during the study (refer to [Section 7.6](#))
25. History of malignancy within the last 5 years, not including subjects with prior history of adequately treated in situ cervical cancer or basal or squamous cell skin cancer
26. Clinically significant abnormal screening hematology values, blood chemistry values, or urinalysis values as determined by the Investigator
27. Any condition that, in the opinion of the Investigator, constitutes a risk or contraindication for participation in the study or that could interfere with the study objectives, conduct, or evaluation
28. 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 OA, symptomatic degenerative disc disease, and patellofemoral syndrome
29. 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
30. History of uncontrolled mania, bipolar disorder, psychotic disorder, schizophrenia, or schizoaffective disorder
31. Any known active infections, including urinary tract infection, upper respiratory tract infection, sinusitis, hepatitis B or hepatitis C infection, and/or infections that may compromise the immune system such as human immunodeficiency virus (HIV) at Day 1
32. 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
33. Hemoglobin A1c (HbA1c) >9% at Screening Visit 2
34. Any contraindications for an IA injection in the target knee in the opinion of the Investigator
35. Subjects who have a current or pending disability claim, workers' compensation, or litigation(s) that may compromise response to treatment
36. Subjects who are immediate family members (spouse, parent, child, or sibling; biological or legally adoptive) of personnel directly affiliated with the study at any investigative site, or are directly affiliated with the study at any investigative site

37. Subjects employed by Biosplice Therapeutics, Inc., 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 adoptive) of said employees responsible for the conduct of the study

Population: Approximately 550 subjects with moderate to severe OA pain of the knee

Phase: 3

Number of Sites Enrolling Participants: This study will be conducted at approximately 60 investigational centers in the United States.

Description of Study Agent: LOR is a novel intra-articular (IA) CDC-like kinase (CLK)/dual-specificity tyrosine kinase (DYRK) inhibitor.

Study Duration: Approximately 18 months
Estimated date first subject consented: November 2022
Estimated date last subject completed: November 2023

Participant Duration: Up to approximately 20 weeks

Criteria for Evaluation:

Efficacy
Efficacy will be assessed by:

- Weekly averages of daily pain NRS (for target knee OA pain)
- WOMAC questionnaire for WOMAC Pain, Function, and Total score for the target knee
- Patient Global Assessment
- KOOS subscales of Function (Sports) and Quality of Life
- PASS
- Rescue medication usage

Safety

The overall safety of LOR will be assessed by AEs, SAEs, vital signs, and clinical laboratory tests.

2. INTRODUCTION

2.1 STUDY RATIONALE

In order to address the need for safe and effective pharmaceutical agents to treat osteoarthritis (OA), Biosplice is developing lorecivivint (LOR), a small-molecule inhibitor of CDC-like kinases (CLKs) and dual-specificity tyrosine kinases (DYRKs), as an intra-articular (IA) injection for the treatment of pain due to OA of the knee. In previous clinical trials, a single IA injection of LOR has been shown to result in durable improvements in pain and function through 6 months and has no detectable systemic exposure. This study is being conducted to evaluate the safety and efficacy of 1 dose of LOR (0.07 mg) in subjects with moderate to severe OA pain of the knee. The patient population to be studied is made up of subjects with moderate to severe OA pain of the knee, based on previous studies which suggested that these individuals have a greater improvement in pain and function with LOR compared to placebo.

2.2 BACKGROUND INFORMATION

OA is the most common form of arthritis and chronic joint disorder in man,¹ recognized as a disruption of homeostasis affecting the whole joint.² OA is characterized by the destruction of the articular cartilage, subchondral bone alterations, and synovitis. Patients initially present with intermittent, activity-related joint pain, progressing to more constant pain over time.³

An estimated 10% to 15% of all adults aged over 60 have some degree of OA, with prevalence higher among women than men.⁴ The prevalence of OA is increasing due to population aging and an increase in related factors such as obesity. The disease burden is significant, with 528.8 million globally and 51.9 million US adults affected in 2019. Of this, nearly half of the US burden is knee OA, with prevalence of 24.7 million in 2019.^{5,6} Movement limitations are present in about 80% of persons with OA, and 25% are unable to perform major activities of daily living.⁷ The FDA have recognized that OA can be a serious disease with unmet need for medical therapies as described in a 2018 draft guidance for industry regarding the development of structural endpoints for OA clinical trials.⁸

Non-pharmacological management of OA (e.g., education, exercise, weight reduction) is considered core to OA management, but improvements may not provide sufficient relief and can be difficult to sustain.⁹ Pharmacological management, specifically oral nonsteroidal anti-inflammatory drugs (NSAIDs) are conditionally recommended as they show only modest clinical benefits and safety concerns exist with prolonged use in specific populations.¹⁰ Finally, IA injections of corticosteroids may offer short-term pain relief, but may have detrimental long-term effects¹¹ and IA hyaluronic acids have questionable efficacy in treatment of knee OA.¹²

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

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

Lorecivivint

The study drug LOR has risks and discomforts. Refer to the IB for the known potential risks associated with LOR.

Study Placebo

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

Rescue Medication (APAP)

The rescue medication supplied in this study is acetaminophen/paracetamol (APAP). APAP has been associated with cases of acute liver failure, at times resulting in liver transplant or death. Most of the cases of liver injury are associated with the use of APAP at doses that exceed the recommended maximum daily limits, and often involve more than one APAP-containing product. Refer to the package insert for further information.

Risks of Injection

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

Risks of Topical Anesthetics

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

Blood Sampling

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

Radiograph (X-ray)

This study involves radiation exposure from 1 radiograph of the knees at screening; up to 3 retakes (4 total radiographs) may be performed for each radiograph to obtain an acceptable image. 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. Each radiograph in this study exposes subjects to approximately 0.005 millisievert (mSv), equivalent to about one half day of background radiation in the US.¹³ This radiation exposure may not be necessary for the subjects' medical care, but it is necessary to obtain the research information desired.

2.3.2 KNOWN POTENTIAL BENEFITS

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

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

LOR is being evaluated as a new option for the treatment of OA pain of the knee. The safety assessments of LOR rely on data from nonclinical studies and previous clinical trials. Based on nonclinical and clinical data, the conduct of the trial is regarded as justifiable at the planned dose and duration. Previous clinical trials (SM04690-01, SM04690-OA-02, SM04690-OA-04, SM04690-OA-10, SM04690-OA-11) involving over 1000 subjects identified no serious adverse events (SAEs) that were considered related to study medication. In previous trials, LOR was safe and well tolerated at a dose of 0.07 mg dose per injection. Additional information about safety data from nonclinical and clinical studies of LOR is in the IB.

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

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

3. OBJECTIVES AND ENDPOINTS

3.1 OBJECTIVE

The objective of this study is to determine the efficacy and safety of the LOR 0.07 mg dose compared to placebo in the treatment of moderate to severe OA pain of the knee.

3.2 STUDY ENDPOINTS

3.2.1 PRIMARY ENDPOINT

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

3.2.2 SECONDARY ENDPOINTS

1. Change from baseline OA function in the target knee as assessed by Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) physical function subscore (WOMAC Function) at Week 12
2. Change from baseline OA disease activity as assessed by Patient Global Assessment at Week 12

3.2.3 SAFETY ENDPOINTS

Safety of LOR as assessed by:

1. Safety of SM04690 Injectable Suspension as measured by adverse events (AEs), SAEs, vital signs, and clinical laboratory tests

Other Endpoints:

2. Change from baseline OA pain in the target knee as assessed by the weekly average of daily pain NRS over the course of the study
3. Change from baseline OA function in the target knee as assessed by WOMAC Function over the course of the study
4. Change from baseline OA pain in the target knee as assessed by WOMAC Pain over the course of the study
5. Change from baseline OA disease activity as assessed by Patient Global Assessment over the course of the study
6. Usage of rescue medication over the course of the study
7. Change from baseline symptoms of OA in the target knee as assessed by WOMAC Total score over the course of the study
8. Change from baseline OA function in the target knee as assessed by Knee Injury and Osteoarthritis Outcome Score (KOOS) subscale of Function (Sports) over the course of the study
9. Change from baseline OA function in the target knee as assessed by KOOS subscale of Quality of Life over the course of the study
10. Patient-Acceptable Symptom State (PASS) over the course of the study

4. STUDY DESIGN**4.1 DESCRIPTION OF THE STUDY DESIGN**

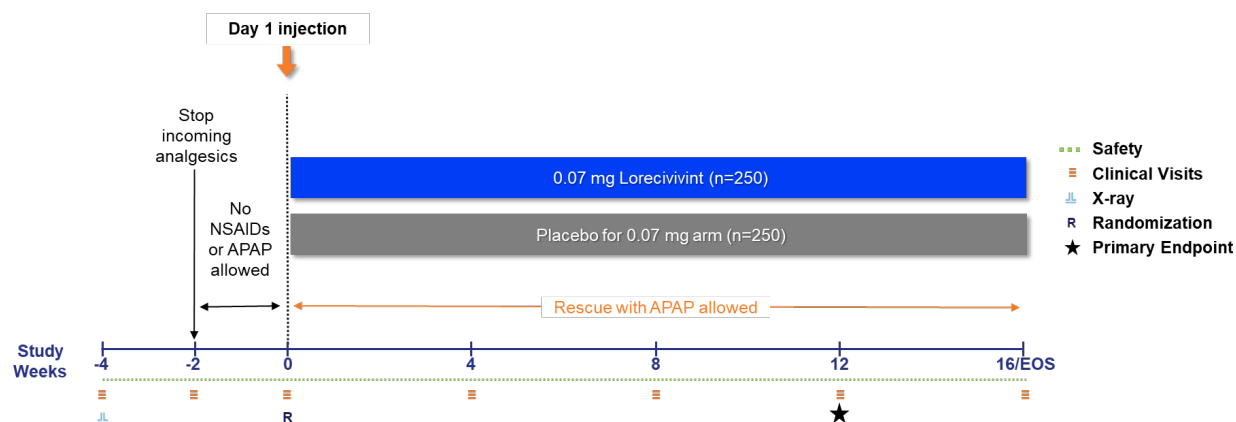
This study will be a multicenter, randomized, double-blind, placebo-controlled, parallel-group study of LOR or placebo (vehicle without LOR) injected in the target knee joint in subjects with moderate to severe OA pain of the knee.

Approximately 550 subjects will be enrolled and randomized into 1 of 2 treatment arms at a ratio of 1:1 (0.07 mg LOR per 2 mL injection: 2 mL placebo injection).

Subjects will participate in a screening period of a minimum of 18 days and up to 28 days (including a 2-week oral analgesic washout period) followed by a 16-week evaluation period. Each subject will receive an injection on Day 1. Clinic visits will be scheduled at Screening Visit 1, Screening Visit 2, Day 1, and Weeks 4, 8, 12, and 16 (End of Study [EOS])/Early Termination (ET). Refer to [Figure 2](#) for an overview of the study design. Specific timing of protocol procedures is described in the Schedule of Events Table ([Section 7.3.6](#)). Specific timing

of electronic diary and questionnaire completion is described in the Schedule of Electronic Diary and Questionnaire Completion Table (Section 7.3.7).

Figure 2. Overview of Study Design and Endpoints



APAP=acetaminophen/paracetamol
NSAIDs= nonsteroidal anti-inflammatory drug
n=250 per arm are completed evaluable subjects

At Screening Visit 1, participants will be asked to sign the informed consent form (ICF) before initiation of any screening evaluations or other study-related procedures. Subjects will then undergo preliminary eligibility assessments. Subjects who meet these preliminary criteria will have bilateral radiographs taken of their knees to further determine eligibility and selection of target knee. Subjects who meet radiological criteria will return to the clinic for Screening Visit 2.

After Screening Visit 2, all subjects who continue to meet eligibility criteria will enter a 2-week washout period during which NSAID and APAP use will be prohibited, and baseline pain and function assessments will be completed by subjects on their electronic devices. Subjects who fulfill the target and non-target knee pain eligibility criteria, as described under a separate blinded criteria document, will be randomized at the end of this period. The blinded criteria will be available for review by the FDA and Institutional Review Boards (IRBs) but will remain unavailable to participating sites for the duration of the clinical trial.

Following the study injection on Day 1 until Week 16 (EOS)/ET, subjects will be directed to avoid use of prohibited medications other than the study-provided rescue medication for any type of pain. Subjects will be permitted to take study-provided rescue medication to treat worsening knee OA pain or other types of pain that cannot be tolerated by a subject. The study-provided rescue medication is APAP 500 mg, 1-2 tablets every 6-8 hours, up to a maximum of 6 tablets (3000 mg) per 24-hour period.

Starting at Day 1 and at Weeks 4, 8, and 12, subjects will be provided with a sufficient quantity of rescue medication for the interval to the next scheduled visit. Subjects will return their bottles containing unused APAP to the clinic for rescue medication accountability.

Best efforts will be made to encourage subjects to use rescue medication only for acute non-tolerable pain. APAP usage will be reviewed at each visit and subjects taking it chronically

(e.g., greater than 10 days of aggregate use of APAP) will be counseled on appropriate use of rescue medication.

This study will be conducted at approximately 60 investigational centers in the United States. Subjects will be required to complete an electronic diary for the following (see [Section 7.3.7](#)):

- Daily pain NRS (for target knee OA pain) through Week 16 (EOS)
- Monthly WOMAC through Week 16 (EOS)
- Monthly Patient Global Assessment through Week 16 (EOS)
- Monthly KOOS (Function [Sports] and Quality of Life) through Week 16 (EOS)
- Monthly PASS through Week 16 (EOS)
- Daily documentation of any rescue medication use

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

In addition, general medical evaluations including physical examination and recording of vital signs will be performed at Screening Visit 2 and Week 16 (EOS) or ET and a knee examination will be performed at Screening Visit 1 and Week 16 (EOS) or ET. Height will be measured at Screening Visit 1 only and weight will be measured at Screening Visit 1 and Week 16 (EOS) or ET. Clinical laboratory evaluations will be performed at Screening Visit 2 and Week 16 (EOS) or ET.

Recording of signs and symptoms of study medication intolerability and AE reporting will start following the injection of the study medication and continue at all subsequent in-person and phone visits until the subject completes Week 16 (EOS) or ET. All AEs, whether volunteered, elicited, or noted during examination, will be recorded throughout the study.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

This Phase 3 study, SM04690-OA-21, is a multicenter, randomized, double-blind, placebo-controlled, parallel-group study of a single dose of 0.07 mg LOR injected in the target knee joint of subjects with moderate to severe OA pain of the knee at Day 1. The placebo to be used in this study is a vehicle-only control. The placebo injection contains all components of the LOR injectable suspension with the exception of LOR. Vehicle is considered the appropriate control in this study as it allows for evaluation of the efficacy and safety of the LOR molecule alone through comparison of the LOR and placebo arms. The patient population to be studied is made up of subjects with moderate to severe OA pain of the knee, based on previous studies which suggested that these individuals have a greater improvement in pain and function with LOR compared to placebo.

4.3 JUSTIFICATION FOR DOSE

The dose of 0.07 mg LOR was selected for this study based on evidence from 3 completed clinical studies (SM04690-01, SM04690-OA-02, and SM04690-OA-04). In these trials,

administration of LOR 0.07 mg appeared safe and well tolerated and resulted in clinically relevant improvements in pain and function.

4.4 END OF STUDY DEFINITION

A subject is considered to have completed the study if he or she has completed all phases of the study including the last visit shown in the Schedule of Events Table ([Section 7.3.6](#)).

5. STUDY POPULATION

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

5.1 PARTICIPANT INCLUSION CRITERIA

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

1. Males and females between 40 and 80 years of age, inclusive, in general good health apart from their knee OA
2. Ambulatory (single assistive devices such as canes allowed if needed less than 50% of the time, subjects requiring a walker are excluded)
3. Diagnosis of femorotibial OA in the target knee by standard American College of Rheumatology (ACR) criteria (refer to [Appendix 1](#)) at Screening Visit 1 (clinical AND radiographic criteria); OA of the knee is not to be secondary to any rheumatologic conditions (e.g., rheumatoid arthritis) and the knee(s) should be the primary joint affected by OA.
4. Radiographic disease Grade 2 or Grade 3 in target knee at Screening Visit 1 according to the Kellgren-Lawrence (KL) grading of knee OA as assessed by independent central readers
5. Meeting blinded radiographic criteria for target knee
6. Pain compatible with OA of the knee(s) for at least 26 weeks before Screening Visit 1
7. Primary source of pain throughout the body is due to OA in the target knee
8. Body mass index (BMI) ≤ 35 kg/m²
9. Meeting blinded criteria for comorbid diffuse pain and related symptoms
10. Meeting blinded criteria for pain reporting for target knee
11. Meeting blinded criteria for pain reporting for non-target knee
12. Willingness to use an electronic diary daily in the evening for the screening period and 16-week study duration
13. Willingness to not use prohibited medications as listed in [Section 7.6](#) between Screening Visit 2 and Week 16 (EOS)
14. Negative drug test for amphetamine, buprenorphine, cocaine, methadone, methadone metabolite, methamphetamine, ecstasy, morphine, opiates, oxycodone, phencyclidine (PCP), barbiturates, benzodiazepines, tricyclic antidepressants, and marijuana unless approved by medical monitor as per inclusion criteria 15
15. Subjects with depression or anxiety must be clinically stable for 12 weeks before Screening Visit 1 and, if on treatment for depression or anxiety, be on 12 weeks of stable

therapy

16. Full understanding of the requirements of the study and willingness to comply with all study visits and assessments
17. Subjects must have read and understood the ICF, and must have signed and dated it before any study-related procedure being performed
18. Subject's Screening Visit 2 visit must occur while enrollment into the randomization cohort for which they are eligible is open

5.2 PARTICIPANT EXCLUSION CRITERIA

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

1. Pregnant women, breastfeeding women, and women who are not post-menopausal (defined as 12 months with no menses without an alternative medical cause) or permanently surgically sterile (includes hysterectomy, bilateral salpingectomy, and bilateral oophorectomy) who have a positive or indeterminate pregnancy test result at the Screening Visit 2 or Day 1
2. Women who are not post-menopausal or permanently surgically sterile who are sexually active with males, and who are not willing or able to use birth control (as outlined in [Section 5.3.1](#)) during the study period
3. Subjects exceeding limits of blinded criteria for anatomical axis alignment
4. Aspiration of effusion of the target knee within 12 weeks before Day 1
5. Any suspicion of IA infection in target knee
6. Partial or complete joint replacement in either knee
7. Presence of hardware in the target knee
8. Currently requires frequent, habitual or daily use of a lower extremity prosthesis and/or use of a structural knee brace on either knee within 26 weeks before Day 1
9. Any surgery (e.g., arthroscopy) in either knee within 26 weeks before Day 1
10. IA injection into the target knee with a therapeutic aim including, but not limited to, hyaluronic acid, platelet-rich plasma (PRP), stem cell therapies, and extended-release corticosteroids within 26 weeks before Day 1 or IA immediate release glucocorticoids within 12 weeks before Day 1
11. Use of electrotherapy (refer to [Appendix 2](#)), acupuncture, formalized physical therapy (i.e., prescribed by a medical professional), therapeutic ultrasound, and/or chiropractic treatments for knee OA within 4 weeks before Day 1
12. Previous enrollment in a study of SM04690 (lorezivint)
13. Subjects who have previously failed screening on this protocol and fail to meet rescreening criteria (see [Section 5.4.2](#))
14. Participation in a clinical research trial that included the receipt of an investigational product (IP) or any experimental therapeutic procedure within 4 weeks or 5 half-lives, whichever is greater, before Screening Visit 1, or planned participation in any such trial
15. Use of APAP or NSAIDs during washout period (between Screening Visit 2 and Day 1). Use of aspirin (up to 325 mg/day) for thrombosis prophylaxis is permitted.
16. History of intolerance or hypersensitivity to APAP or any of its excipients or existence of

a medical condition (e.g., known Glucose-6-phosphate dehydrogenase [G6PD] deficiency) or use of concomitant medication for which the use of APAP is contraindicated

17. Subjects who have impaired liver function (e.g., aspartate aminotransferase, alanine aminotransferase, or bilirubin $\geq 3\times$ upper limit of normal [ULN]), active hepatic disease, or other condition (e.g., alcoholism, cirrhosis, or hepatitis) that suggests the potential for an increased susceptibility to hepatic toxicity with APAP
18. History of consuming more than an average of 3 alcohol-containing drinks daily over the preceding 4 weeks before Day 1
19. Subjects with a current or chronic history of renal impairment defined as serum creatinine $>3\times$ ULN
20. Treatment with systemic (oral, intramuscular, or intravenous) glucocorticoids ≥ 10 mg prednisone or the equivalent per day within 4 weeks before Day 1; or subjects on <10 mg prednisone or the equivalent per day who have not maintained a stable regimen for at least 2 weeks before Day 1 in the opinion of the Investigator
21. Use of centrally acting analgesics (refer to [Appendix 2](#)) within 5 half-lives before Screening Visit 2
22. Use of anticonvulsants (refer to [Appendix 2](#)) within 5 half-lives before Screening Visit 2
23. Use of opioids within 4 weeks before Screening Visit 1
24. Planned surgery scheduled during the study period, not including nonsurgical invasive procedures conducted for a diagnostic or therapeutic purpose scheduled during the study (refer to [Section 7.6](#))
25. History of malignancy within the last 5 years, not including subjects with prior history of adequately treated in situ cervical cancer or basal or squamous cell skin cancer
26. Clinically significant abnormal screening hematology values, blood chemistry values, or urinalysis values as determined by the Investigator
27. Any condition that, in the opinion of the Investigator, constitutes a risk or contraindication for participation in the study or that could interfere with the study objectives, conduct, or evaluation
28. 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 OA, symptomatic degenerative disc disease, and patellofemoral syndrome
29. 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
30. History of uncontrolled mania, bipolar disorder, psychotic disorder, schizophrenia, or schizoaffective disorder
31. Any known active infections, including urinary tract infection, upper respiratory tract infection, sinusitis, hepatitis B or hepatitis C infection, and/or infections that may compromise the immune system such as human immunodeficiency virus (HIV) at Day 1
32. 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

33. Hemoglobin A1c (HbA1c) >9% at Screening Visit 2
34. Any contraindications for an IA injection in the target knee in the opinion of the Investigator
35. Subjects who have a current or pending disability claim, workers' compensation, or litigation(s) that may compromise response to treatment
36. Subjects who are immediate family members (spouse, parent, child, or sibling; biological or legally adoptive) of personnel directly affiliated with the study at any investigative site, or are directly affiliated with the study at any investigative site
37. Subjects employed by Biosplice Therapeutics, Inc., 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 adoptive) of said employees responsible for the conduct of the study

5.3 LIFESTYLE GUIDELINES

5.3.1 CONTRACEPTION

Women of Childbearing Potential

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

From the Screening Visit 1 until Week 16 (EOS), sexually active WOCBP must agree to use an acceptable form of contraception. Acceptable forms of contraception are:

1. Intrauterine device (IUD)
2. Implantable rod
3. Established hormonal contraceptive methods. This includes combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, or transdermal) and progestogen only hormonal contraception associated with inhibition of ovulation (oral, injectable, or implantable). Females who are using hormonal contraceptives must have had consistent use of the same hormonal contraceptive product for at least 4 weeks.
4. Bilateral tubal ligation/occlusion/division
5. Male partner who had a vasectomy provided that the partner is the sole sexual partner of the WOCBP, and that the vasectomized partner has received medical assessment of the success of the surgical procedure or had the vasectomy for at least 6 months

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

Men

For men, no contraception measures are required.

5.4 SCREEN FAILURES**5.4.1 SCREEN FAILURES**

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

5.4.2 SUBJECT RESCREENING

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

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

Any rescreened subject must be re-consented and should be assigned a new subject number. All screening procedures and assessments must be performed at rescreen; no results or data may be used from the previous screen, except for the knee radiograph (if acceptable images were acquired within the previous 12 weeks). Target knee selection may not be changed at rescreen.

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

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

5.6 PARTICIPANT WITHDRAWAL OR TERMINATION**5.6.1 REASONS FOR WITHDRAWAL OR TERMINATION**

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

- AE

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

5.6.2 HANDLING OF PARTICIPANT WITHDRAWALS OR TERMINATION

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

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

5.7 PREMATURE TERMINATION OR SUSPENSION OF STUDY

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

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

6.1.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

LOR drug substance is an off-white powder. LOR 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. LOR drug and placebo products are supplied as 2.4 mL of formulated suspension in vials. Placebo product contains 0.5% carboxymethylcellulose sodium and 0.05% polysorbate 80 in pH 7.4 phosphate buffered saline.

Study medication will be supplied as single-use vials and labeled according to the applicable local and national regulations. For dispensing, dose preparation, and labeling instructions, refer to the Pharmacy Manual.

6.1.3 PRODUCT STORAGE AND STABILITY

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

6.1.4 PREPARATION

Each dose of study medication should be well mixed (the drug product is a suspension) before 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

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

LOR will be administered in the following dosage strengths:

- LOR 0.07 mg in 2 mL injectable suspension
- LOR 0 mg; 2 mL vehicle-only injection (placebo)

The injectable drug product or placebo product is drawn into the syringe by the Unblinded Pharmacist, or unblinded designee and is to be administered by the Unblinded Investigator (injector) as a single injection into the target knee joint once at Day 1. The Unblinded Investigator must minimize any contact with the subject following the injection and may not perform any study assessments throughout the duration of the study. All subject contact for the

remainder of the study is limited to the Blinded Investigator and other appropriate blinded study personnel.

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

Only topical anesthetics are allowed before study injection. Local anesthetic injections, administered either subcutaneously or intra-articularly, are prohibited.

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

Sterile needles and syringes that should be used for the injection of study medication will be provided by the Sponsor or Sponsor's designee.

6.1.6 ROUTE OF ADMINISTRATION

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

6.1.7 STARTING DOSE AND DOSE ESCALATION SCHEDULE

Not applicable to this study. Each subject will be randomly assigned to either 0.07 mg LOR or placebo on Day 1.

6.1.8 DOSE ADJUSTMENTS/MODIFICATIONS/DELAYS

No modification to the specified dose (0.07 mg) or volume (2 mL) of the study medication injected into the target knee joint will be allowed.

6.1.9 DURATION OF THERAPY

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

6.1.10 STUDY INTERVENTION COMPLIANCE

Not applicable to this study.

6.1.11 DEVICE SPECIFIC CONSIDERATIONS

Not applicable to this study.

6.2 STUDY AGENT ACCOUNTABILITY PROCEDURES

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

- Subject number and initials
- Date on which the study medication was injected
- Quantity dispensed (drug product vial and placebo vial)
- Quantity returned/used (drug product vial and placebo vial)

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

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

7. STUDY PROCEDURES AND SCHEDULE

7.1 STUDY PROCEDURES/EVALUATIONS

7.1.1 STUDY SPECIFIC PROCEDURES

Collection of Adverse Events Data

Data regarding AEs will be collected in this study. AEs are events that occur during the study that are not present before Day 1 study medication injection, or, if present at the time of study medication injection, have worsened in severity during the study. AEs will be assessed at each visit from the time of study medication injection on Day 1 through Week 16 (EOS) or ET.

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

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

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

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

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

Medical History

A limited medical history (inclusion/exclusion focused) will be obtained at Screening Visit 1, a full medical history will be obtained at Screening Visit 2 and Day 1 with a follow-up at Week 16 (EOS) or ET to capture End Dates of any ongoing medical history collected at the Screening Visits and Day 1. Medical history at Screening Visit 1 will include demographic data (e.g., sex, age, race, ethnicity) and use of assistive devices. In addition, medical information will also be recorded, including all (1) medical conditions and disease states that require current or ongoing therapy, and (2) other medical conditions and disease states that, in the opinion of the Investigator, are relevant to the subject's study participation. Examples of medical conditions and disease states that should be considered relevant to the subject's study participation include history of current disease, medical history that confirms the eligibility criteria of the subject, and asymptomatic medical history that could become symptomatic while on the study.

Past Treatments for Knee OA Pain

Subjects will be asked at Screening Visit 2 about their previous use, at any time in the past, of the following treatments for their knee OA pain: NSAIDs, APAP, opioids, IA steroids, and IA hyaluronic acid. Responses will be recorded on the eCRF as Yes/No/Unknown.

Physical Examination

A general physical examination will be conducted by a trained medical professional at Screening Visit 2 and at Week 16 (EOS) or ET. Results of the physical examination will be noted in the source documents. Any clinically significant finding noted before 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 by a trained medical professional at Screening Visit 1 and at Week 16 (EOS) or ET. Results of the knee examination will be noted in the source documents. Any clinically significant finding noted before study medication injection

should be recorded as medical history. If it is found after study medication injection, it should be reported as an AE.

Presence of unilateral or bilateral symptomatic knee OA will be recorded in the eCRF at Screening Visit 1. If the subject has OA in both knees, the site is to establish the target knee as the knee with greater pain at Screening Visit 1 based on the subject's evaluation and the Investigator's clinical judgment. If the Investigator's clinical judgment of the target knee differs from the subject-reported target knee, sites should contact the Medical Monitor for further guidance.

Vital Signs

Vital signs will be measured by a qualified staff member at Screening Visit 2 and at Week 16 (EOS) or ET.

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

- Body temperature
- Pulse rate
- Respiratory rate
- Blood pressure (systolic and diastolic) after the subject rests (sitting or supine) for at least 5 minutes

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

Height and Weight

Height measurements will be taken at Screening Visit 1 only. Weight measurements will be taken at Screening Visit 1 and at Week 16 (EOS) or ET.

Radiograph of Knee Joints

Radiograph of the knee joints will be taken at Screening Visit 1 to confirm eligibility for the study. At Screening Visit 1, after confirmation of the target knee by the Investigator, the subject's radiograph must be reviewed for the target knee to confirm compliance with inclusion/exclusion criteria.

Detailed instructions for obtaining and managing radiographs will be provided to the investigational center before the initiation of subject enrollment. As described in the Image Review Charter–Image Acquisition Guidelines, radiographs should be obtained in the posterior-anterior (PA) view.

Upon receipt of images, the central imaging vendor will assess the image quality as acceptable or unacceptable. If necessary, it is recommended that the Investigator attempt up to 4 image captures in order to obtain acceptable images. At all times, the Investigator should use his/her

clinical judgment to assess how many retakes a subject may require in order to obtain an acceptable image.

All radiographs will be submitted to an independent radiologist at the central imaging vendor. The central imaging vendor does not provide medical advice, clinical diagnosis, or treatment recommendations. These imaging assessments and quantitative measurements provided by the central imaging vendor 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 AE or other unusual pathology is noted in the study images, the Sponsor or their representative will be notified of the finding and will promptly notify the Investigator. The Investigator will then assess the clinical significance as well as any follow-up procedures that need to be completed. Clinically significant findings that are not part of an existing diagnosis will be recorded as medical history or an AE as appropriate.

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

The WPI&SS assessment consists of a body map that determines a subject's areas of pain or tenderness (WPI) and symptom severity (SS) questions. The WPI&SS assessment used in this study includes questions 1, 2 and 3 as questions 4 and 5 are not formally scored¹⁴. A WPI&SS assessment will be completed by the subject at Screening Visit 1.

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

The WPI&SS assessment sheets will be provided to the site and may not be modified or reproduced.

Electronic Diary Device Provision and Training

Detailed instructions and site training regarding subject electronic questionnaire completion will be provided to the investigational center. Electronic diary device provisioning to the subject will occur at Screening Visit 2 and electronic diary devices are to be returned to the site at Week 16 (EOS) or ET.

Subject training for electronic diary and questionnaire completion is required at the Screening Visit 2 before subject completion of the pain NRS, WOMAC, KOOS, PASS, and Patient Global Assessment questionnaires. Training will remain available throughout the study in case subject retraining is needed.

Additionally, at Screening Visit 2, Day 1, and Weeks 4, 8, and 12, subjects will have training on participant responsibility, accurate pain reporting and placebo response reduction before subject completion of the pain NRS, WOMAC, KOOS, PASS, and Patient Global Assessment questionnaires.

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. The NRS will be anchored by descriptors at each end ("No Pain" on the left and "Pain as bad as you can imagine" on the right). A pain NRS for each knee will be completed daily by the subject during the screening period from Screening Visit 2 until Day 1 to assess subject

ability to be compliant with a daily pain assessment and to determine subject eligibility. During the screening period, daily pain NRS assessments will be completed by subjects in the evening (between 5:00 pm and 11:59 pm) remotely on their electronic devices for each knee to collect average knee pain in the last 24 hours. Subject eligibility and electronic diary compliance for daily pain NRS over the screening period will be reviewed at Day 1 before randomization. After randomization, starting on Day 1, daily pain NRS assessments are to be completed by subjects in the evening (between 5:00 pm and 11:59 pm) remotely on their electronic devices for the target knee only. Refer to [Section 7.3.7](#) for a schedule of electronic diary and questionnaire completion.

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

Western Ontario and McMaster Universities Arthritis Index (WOMAC)

The WOMAC is a widely used, proprietary outcome measurement tool used by health professionals to evaluate the condition of patients with OA of the knee and hip, including pain, stiffness, and physical functioning of a target joint. The WOMAC Version NRS 3.1 questionnaire will be completed once a week by the subject for their target knee in the evening (between 5:00 pm and 11:59 pm) remotely on their electronic device after their Screening Visit 2 up until the day before the Day 1 visit. WOMAC questionnaire completion will be reviewed before randomization to determine subject eligibility. The baseline WOMAC questionnaire should be completed within 8 days before Day 1. After Day 1, WOMAC assessments will be completed by the subject for their target knee in the evening (between 5:00 pm and 11:59 pm) remotely on their electronic device at Weeks 4, 8, 12, and 16 (with a window of ± 7 days). Refer to [Section 7.3.7](#) for a schedule of electronic diary and questionnaire completion.

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

Patient Global Assessment of Disease Activity

The Patient Global Assessment is an 11-point [0–10] NRS on which the subjects will rate how they feel their target knee OA is doing ("Considering all the ways your [target] knee OA has affected you, how do you feel your knee OA is today? "). 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 once a week by the subject in the evening (between 5:00 pm and 11:59 pm) remotely on their electronic device after Screening Visit 2 up until the day before the Day 1 visit. The baseline Patient Global Assessment questionnaire should be completed within 8 days before Day 1. After Day 1, Patient Global Assessments will be completed by the subject in the evening (between 5:00 pm and 11:59 pm) remotely on their electronic device at Weeks 4, 8, 12, and 16 (with windows of ± 7 days). Refer to [Section 7.3.7](#) for a schedule of electronic diary and questionnaire completion.

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

Knee Injury and Osteoarthritis Outcome Score (KOOS)

KOOS is a widely used, non-proprietary tool used by health professionals to assess a subject's

opinion about their knee and associated problems. Subjects will complete the KOOS subscales for Function (Sports) and knee-related Quality of Life. The KOOS questionnaire subscales will be completed once a week by the subject for their target knee in the evening (between 5:00 pm and 11:59 pm) remotely on their electronic devices after Screening Visit 2 up until the day before the Day 1 visit. After Day 1, KOOS questionnaires will be completed by the subject in the evening (between 5:00 pm and 11:59 pm) remotely on their electronic device at Weeks 4, 8, 12, and 16 (with windows of ± 7 days). Refer to [Section 7.3.7](#) for a schedule of electronic diary and questionnaire completion.

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

Patient-Acceptable Symptom State Questionnaire (PASS)

Subjects will be asked the following, using an electronic questionnaire: “Taking into account all the activities you have during your daily life, your level of pain, and also your functional impairment, do you consider that your current state is satisfactory?” Subjects are able to choose the answers of “Yes” or “No.” Refer to [Section 7.3.7](#) for a schedule of electronic diary and questionnaire completion.

Rescue Medication Dispensation and Accountability

At Day 1 and Weeks 4, 8, and 12, subjects will be dispensed APAP for use as rescue medication (refer to the Pharmacy Manual for further details). Rescue medication usage will be documented daily on the study-provided electronic device. Starting on Day 1 after the site visit, daily electronic diary of rescue medication usage is to be completed by subjects in the evening (between 5:00 pm and 11:59 pm) remotely on their electronic devices. Subjects will receive notifications reminding them to complete the electronic diary of rescue medication usage. The electronic diary for rescue medication usage will be reviewed at all visits after Day 1 except for Week 16 (EOS) or ET for compliance and subject safety. It is recommended that the site re-train the subject if the site determines it is necessary after review. Refer to [Section 7.3.6](#) for a schedule of rescue medication dispensation and accountability.

Subjects will also return the APAP containers to the site where rescue medication usage and pill counts will be documented.

Subjects may take 1-2 tablets (500 mg each) every 6-8 hours, up to a maximum of 6 tablets (3000 mg) per 24-hour period. Refer to [Section 7.8](#) for further details regarding rescue medication.

7.1.2 STANDARD OF CARE STUDY PROCEDURES

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

7.2 LABORATORY PROCEDURES/EVALUATIONS

7.2.1 CLINICAL LABORATORY EVALUATIONS

Samples for clinical laboratory analysis by the central laboratory will be collected by a qualified

staff member at Screening Visit 2 and Week 16 (EOS) or ET. Refer to the Laboratory Manual for details about collection of specimens.

At a minimum, the following tests will be conducted:

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

An HbA1c test will be performed on all subjects at Screening Visit 2.

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

The Investigator or designee must review the results of each subject's Screening Visit 2 clinical laboratory test results before the Day 1 visit. The subject must not be randomized on Day 1 if any of the Screening Visit 2 results are outside the normal range for the laboratory AND, in the opinion of the Investigator, are clinically significant.

The results of the clinical laboratory tests will be reported on the laboratory's standard reports. The Investigator must review all laboratory reports in a timely manner, noting "not clinically significant" (NCS) or comment on the clinical significance of any result that is outside the normal range for the laboratory, then date and initial the report. The Investigator must report all laboratory results that are BOTH outside the normal range for the laboratory AND, in the opinion of the Investigator, are clinically significant. If any abnormal, clinically significant laboratory measure is found before 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 pregnancy test will be performed on WOCBP at Screening Visit 2 and a urine pregnancy test will be performed on WOCBP by local laboratory at Day 1 and Week 16 (EOS) or ET. Results from the pregnancy tests will be used to determine subject eligibility.

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

Drug Test

A urine sample for drug testing will be collected at Screening Visit 2. The urine drug test (performed by a local laboratory) will include amphetamine, barbiturates, buprenorphine,

benzodiazepines, cocaine, methadone metabolite, methamphetamine, ecstasy, methadone, morphine, opiates, oxycodone, PCP, tricyclic antidepressants, and marijuana. Results from the drug test will be used to determine subject eligibility.

7.2.3 SPECIMEN PREPARATION, HANDLING, AND STORAGE

Refer to the Laboratory Manual for the central laboratory.

7.2.4 SPECIMEN SHIPMENT

Refer to the Laboratory Manual for the central laboratory.

7.3 STUDY SCHEDULE

7.3.1 SCREENING

Screening Visit 1

Screening Visit 1 must occur within 18 to 28 days before Day 1.

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

Investigators will maintain a confidential log of all subjects who have been screened for participation in the study whether or not the subject was eligible for study participation.

The following procedures and assessments will be performed initially during Screening Visit 1:

- Documentation of demographic information, including date of birth, sex, race, and ethnicity
- Limited medical history
- Radiographs
- Knee examination and selection of target knee
- WPI&SS assessment
- Height and weight measurements

Screening Visit 2

Screening Visit 2 must occur at least 3 days after Screening Visit 1 and within 15 to 21 days before Day 1.

It is recommended that the results from Screening Visit 1 be compared with inclusion/exclusion criteria to determine subject eligibility and to determine eligibility for one of the randomization

cohorts. The following randomization cohorts will be available:

- KL Grade 2
- KL Grade 3

If the subject is confirmed eligible and the randomization cohort for which they are eligible is open, the following procedures and assessments will be performed:

- Review of current and past medical history, documentation of current medications, and review of prior medications excluded by the protocol
- Physical examination
- Documentation of past treatments for knee OA
- Vital sign measurements (pulse rate, blood pressure, respiratory rate, and temperature)
- Serum pregnancy test in WOCBP
- Urine drug test (performed by a local laboratory)
- Venipuncture and collection of samples for clinical laboratory tests
- Electronic diary device provision and subject training for electronic diary and questionnaire completion on the electronic device
- Training and documentation of training on participant responsibility, accurate pain reporting and placebo response reduction
- Washout of NSAID and APAP

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

Note: Once a week after Screening Visit 2 up until the day before the Day 1 visit, subjects will complete the WOMAC, KOOS, PASS, and Patient Global Assessment, in addition to the pain NRS assessment, in the evening (between 5:00 pm and 11:59 pm) remotely on their electronic devices. Refer to [Section 7.3.7](#) for a schedule of electronic diary and questionnaire.

7.3.2 RANDOMIZATION

Day 1

This visit must occur within 15 to 21 days of Screening Visit 2.

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

- Review of current and past medical history
- Review of pain NRS electronic diary compliance from the Screening Visit 2 to Day 1
- Training and documentation of training on participant responsibility, accurate pain reporting and placebo response reduction
- Electronic questionnaire review (WOMAC, KOOS, PASS, and Patient Global

Assessment)

- Pregnancy test (urine) for WOCBP (performed by a local laboratory)
- Rescue medication dispensation

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

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

- IA injection of randomized study medication by the Unblinded Investigator (injector)
- Collection of AEs and concomitant medications, therapies and procedures data

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

- Daily pain NRS assessments
- WOMAC, KOOS, PASS, and Patient Global Assessment questionnaires at Weeks 4, 8, 12, and 16 (with windows of ± 7 days)
- Daily documentation of rescue medication use

Refer to [Section 7.3.7](#) for a schedule of electronic diary and questionnaire completion.

7.3.3 FOLLOW-UP

Weeks 4, 8, and 12

The Week 4 visit should occur on Day 28 (with a window of ± 7 days), the Week 8 visit should occur on Day 56 (with a window of ± 7 days), and the Week 12 visit should occur on Day 84 (with a window of ± 7 days).

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

- Collection of AE and concomitant medications, therapies and procedures
- Review of pain NRS electronic diary compliance from the previous 4 weeks
- Electronic questionnaire review (WOMAC, KOOS, PASS, and Patient Global Assessment)
- Rescue medication dispensation and accountability
- Training and documentation of training on participant responsibility, accurate pain reporting and placebo response reduction

7.3.4 FINAL STUDY VISIT

Week 16 End of Study

This final study visit should occur on Day 112 with a window of ± 7 days.

The following procedures and assessments will be performed at Week 16 (EOS):

- Collection of AE and concomitant medications, therapies, and procedures data
- Review of medical history
- Urine pregnancy test for WOCBP (performed by a local laboratory)
- Rescue medication accountability
- Physical examination, including knee examination of both knees
- Weight measurement
- Vital sign measurements (pulse rate, blood pressure, respiratory rate, and temperature)
- Venipuncture and collection of samples for clinical laboratory tests

7.3.5 EARLY TERMINATION VISIT

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

- Collection of AE and concomitant medications, therapies and procedures
- Review of medical history
- Urine pregnancy test for WOCBP (performed by a local laboratory)
- Rescue medication accountability
- Physical examination, including knee examination of both knees
- Weight measurement
- Vital sign measurements (pulse rate, blood pressure, respiratory rate, and temperature)
- Venipuncture and collection of samples for clinical laboratory tests

7.3.6 SCHEDULE OF EVENTS TABLE

Procedure	Screening Period ^a (Days -28 to -1)		Day 1 ^b	Week 4 Day 28 ± 7 days	Week 8 Day 56 ± 7 days	Week 12 Day 84 ± 7 days	Week 16 (EOS) Day 112 ± 7 days/ET
	Screening Visit 1 (Days -28 to -18)	Screening Visit 2 (Days -21 to -15)					
Informed consent	X						
Inclusion and exclusion criteria	X (limited)	X	X				
Demographics	X						
Medical history	X (limited)	X (full)	X (full)				X ^c
Current and prior procedures/therapies/medications		X					
Past treatments for knee OA pain		X					
Washout NSAIDs and APAP		X					
Serum pregnancy test ^d		X					
Radiographs	X						
WPI&SS	X						
Physical examination		X					X
Knee examination	X						X
Selection of target knee	X						
Height	X						
Weight	X						X
Vital signs		X					X
Central laboratory sampling		X					X
Urine drug test (locally performed)		X					
Urine pregnancy test (locally performed) ^d			X				X
Electronic diary provision and training ^e		X					
Participant responsibility and pain reporting training ^e		X	X	X	X	X	
Review Pain NRS compliance			X ^f	X	X	X	
Review WOMAC compliance			X ^g	X	X	X	
Review KOOS compliance			X	X	X	X	
Review Patient Global Assessment compliance			X	X	X	X	
Review PASS compliance			X	X	X	X	

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Procedure	Screening Period ^a (Days -28 to -1)		Day 1 ^b	Week 4 Day 28 ± 7 days	Week 8 Day 56 ± 7 days	Week 12 Day 84 ± 7 days	Week 16 (EOS) Day 112 ± 7 days/ET
	Screening Visit 1 (Days -28 to -18)	Screening Visit 2 (Days -21 to -15)					
Rescue medication dispensation			X	X	X	X	
Rescue medication accountability				X	X	X	X
Randomization			X				
Intra-articular injection			X				
Adverse event assessment			X	X	X	X	X
Concomitant medications/ procedures/ therapies			X	X	X	X	X

AEs=adverse events; APAP=acetaminophen/paracetamol; EOS=end of study; ET=early termination; KOOS= Knee Injury and Osteoarthritis Outcome Score; NRS=numeric rating scale; NSAID=nonsteroidal anti-inflammatory drug; OA=osteoarthritis; PASS=Patient-Acceptable Symptom State; WOCBP=woman of childbearing potential; WOMAC= Western Ontario and McMaster Universities Arthritis Index; WPI&SS= Widespread Pain Index and Symptom Severity Form

^a The screening period is a minimum of 18 days and a maximum of 28 days and includes Screening Visit 1 and Screening Visit 2; Screening Visit 2 should occur at least 3 days after Screening Visit 1, at least 15 days before Day 1, and after confirmation of eligibility by radiograph.

^b At Day 1, all procedures should be performed before study medication injection except for collection of AEs.

^c Review medical history to capture End Date(s), if applicable, of any ongoing medical history(ies) collected at Screening Visit 1, Screening Visit 2, and Day 1.

^d Serum and urine pregnancy tests are to be performed on WOCBP only.

^e Electronic diary devices and training will be provided to subjects at Screening Visit 2; questionnaire training and documentation of training including participant responsibility, accurate pain reporting and placebo response reduction will be conducted at Screening Visit 2, Day 1, and Weeks 4, 8, and 12.

^f Electronic diary compliance and assessment of target and non-target knee pain scores for daily pain NRS during the screening period will be reviewed at Day 1 before randomization to determine subject eligibility.

^g WOMAC questionnaire will be reviewed at Day 1 before randomization to determine subject eligibility.

7.3.7 SCHEDULE OF ELECTRONIC DIARY AND QUESTIONNAIRE COMPLETION TABLE

	WOMAC, KOOS, PASS, and Patient Global Assessment	Daily Pain NRS
Study Week/Day	WOMAC, KOOS, PASS, and Patient Global Assessment will be completed once a week by subjects after Screening Visit 2 up until the day before the Day 1 visit, and at Weeks 4, 8, 12, and 16 (with a window of ± 7 days) in the evening (between 5:00 pm and 11:59 pm) local time remotely on their electronic devices, as outlined below; ranges shown are inclusive.	Pain NRS should be completed daily starting after Screening Visit 2. Subjects will complete the diary in the evening (between 5:00 pm and 11:59 pm) local time remotely on their electronic devices. Diary completion should occur every day including on study visit days.
Screening Visit 1		
Screening Visit 2		Complete daily starting on the same day of Screening Visit 2 (after the visit); pain NRS assessments are to be completed for each knee.
After Screening Visit 2	Baseline WOMAC, KOOS, PASS, and Patient Global Assessment questionnaires (once a week after Screening Visit 2 up until the day before the Day 1 visit)	
Day 1	N/A	Starting on the same day of Day 1 (after the visit), pain NRS assessments are to be completed daily for the target knee only. Starting on the same day of Day 1 (after the visit), documentation of rescue medication use will be completed daily.
Week 4 (Day 28)	Complete between Day 21 and 35	
Week 8 (Day 56)	Complete between Day 49 and 63	
Week 12 (Day 84)	Complete between Day 77 and 91	
Week 16 (Day 112)	Complete between Day 105 and 119	

KOOS= Knee Injury and Osteoarthritis Outcome Score

NRS=numeric rating scale

PASS=Patient-Acceptable Symptom State

WOMAC=Western Ontario and McMaster Universities Arthritis Index

7.4 JUSTIFICATION FOR SENSITIVE PROCEDURES

Not applicable for this study.

7.5 CONCOMITANT MEDICATIONS, TREATMENTS, AND PROCEDURES

Details regarding the name, indication, route of administration, dose, and frequency of all medications taken within 30 days prior to Screening Visit 1 through Week 16 (EOS) or ET will be recorded in the “Prior and Concomitant Medications” eCRF. “All medications” should include prescription, over the counter, supplements, as well as herbal or alternative medications.

Procedures or non-drug therapies that are ongoing, new, or modified at or after the Screening Visit 2 must be recorded on the “Procedures and Non-Drug Therapies” eCRF.

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

7.5.1 PRECAUTIONARY MEDICATIONS, TREATMENTS, AND PROCEDURES

Not applicable to this study.

7.6 PROHIBITED MEDICATIONS, TREATMENTS, AND PROCEDURES**Prohibited Concomitant Medications and Procedures**

- Any IA injection, including glucocorticoids, hyaluronic acid derivatives, PRP, stem cell therapies, or other agents with therapeutic intent, into either knee is prohibited while the subject is on study; IA injection of glucocorticoids, hyaluronic acid derivatives, PRP, stem cells, or other therapeutic agents into joints other than the knee is allowed.
- The following medications are prohibited while the subject is on study (starting from Screening Visit 2 up until Week 16 [EOS]/ET):
 - NSAIDs, including cyclooxygenase-2 (COX-2) inhibitors; the use of up to 325 mg aspirin per day for cardiovascular and thrombosis prophylaxis is permitted, and the short-term (i.e., no more than 3 days) use of NSAIDs for acute pain conditions unrelated to knee OA pain (e.g., menstrual pain, tooth extraction) is also permitted
 - Opioids; short-term use of opioids as part of anesthesia or procedural sedation during the study period is permitted
 - Topical NSAIDs (e.g., diclofenac) applied for the treatment of knee OA
 - Centrally acting analgesics (e.g., duloxetine, pregabalin, gabapentin) (refer to [Appendix 2](#))
 - Topical local anesthetic agents (gels, creams, or patches such as the Lidoderm patch) used for the treatment of knee OA; use as part of anesthesia, for study injections during the study period is permitted for the target knee
 - Other anticonvulsants not listed in [Appendix 2](#)

- Systemic glucocorticoids ≥ 10 mg of prednisone per day or the equivalent; epidural, inhaled, intranasal, and topical glucocorticoids are permitted
- Drugs screened to assess eligibility: amphetamine, buprenorphine, cocaine, methadone, methadone metabolite, methamphetamine, ecstasy, morphine, opiates, oxycodone, PCP, barbiturates, benzodiazepines, tricyclic antidepressants, and marijuana
- Electrotherapy (refer to [Appendix 2](#)), acupuncture, therapeutic ultrasound, 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. Nonsurgical 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 the following: endoscopy, colonoscopy, bronchoscopy, cystoscopy, radiologic procedures such as coronary artery catheterization with or without intervention, and nonsurgical cosmetic procedures such as Botox or other cosmetic injections.
- Subjects are prohibited from participating in any other clinical research trial that includes the receipt of an IP or any experimental therapeutic procedure. Subjects are also prohibited from participating in any observational research trial while on study.

The Investigator should notify the Biosplice Medical Monitor(s) 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

Following the study injection on Day 1 until Week 16 (EOS)/ET, subjects will be directed to avoid use of prohibited medications other than the study-provided rescue medication for any type of pain. Subjects will be permitted to take study-provided rescue medication to treat worsening knee OA pain or other types of pain that cannot be tolerated by a subject. The study-provided rescue medication is APAP 500 mg, 1-2 tablets every 6-8 hours, up to a maximum of 6 tablets (3000 mg) per 24-hour period.

Starting at Day 1 and at Weeks 4, 8, and 12, subjects will be provided with a sufficient quantity of rescue medication for the interval to the next scheduled visit. Subjects will return their bottles containing unused APAP to the clinic for rescue medication accountability. Refer to [Section 7.1](#) for further details.

Best efforts will be made to encourage subjects to use rescue medication only for acute non-tolerable pain. APAP usage will be reviewed at each visit and subjects taking it chronically (e.g., greater than 10 days of aggregate use of APAP) will be counseled on appropriate use of rescue medication.

If a change in the subject's condition necessitates treatment beyond the provided rescue medication, the Medical Monitor should be contacted.

7.9 PARTICIPANT ACCESS TO STUDY AGENT AT STUDY CLOSURE

Not applicable to this study.

8. ASSESSMENT OF SAFETY

8.1 SPECIFICATION OF SAFETY PARAMETERS

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

8.1.1 DEFINITION OF ADVERSE EVENTS

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

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

Whenever possible, it is preferable to record a diagnosis as the AE term rather than a series of signs and symptoms relating to a diagnosis. Fluctuations of pre-existing conditions, including the disease under study, that do not represent a clinically significant exacerbation or worsening, need not be considered AEs. In order to classify AEs and diseases, preferred terms will be assigned by the Sponsor to the original terms entered on the eCRF, using the Medical Dictionary for Regulatory Activities (MedDRA).

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

8.1.2 DEFINITION OF SERIOUS ADVERSE EVENTS

An SAE is any untoward medical occurrence during the course of a clinical investigation that is characterized by one or more of the following:

- Results in death
- Is life threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect

- Is an important medical event, defined as an event that does not fit one of the other outcomes, but based on appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention (treatment) to prevent one of the other outcomes. Examples include:
 - Allergic bronchospasm requiring intensive treatment in an emergency room (ER) or at home
 - Blood dyscrasias or convulsions that do not result in inpatient hospitalization
 - Development of drug dependence or drug abuse

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

"Inpatient hospitalization" is clarified as hospitalization lasting ≥ 24 hours. Admission to the hospital or prolongation of hospitalization qualifies as an SAE only if it is the result of an AE. A planned hospitalization for an elective procedure or a pre-existing condition that has not worsened does not meet this criterion. If anything untoward is reported during the procedure, that occurrence must be reported as an AE.

An AE is incapacitating or disabling if the experience results in a substantial disruption of the person's ability to conduct normal life functions.

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.

8.2 CLASSIFICATION OF AN ADVERSE EVENT

8.2.1 SEVERITY OF EVENT

The Investigator will assess AEs for severity utilizing the CDISC AESEV, which classifies AEs as mild, moderate, or severe ([Table 1](#)). It should be noted that the term "severe" used to assess severity is not synonymous with the term "serious."

Table 1: CDISC Definitions of Adverse Event Severity

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

CDISC = Clinical Data Interchange Standards Consortium.

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 definitions listed below. An AE is deemed associated with the use of study treatment “if there is a reasonable possibility that the treatment caused the AE” (suspected adverse reaction). Reasonable possibility means there is evidence to suggest a causal relationship between the study treatment and the AE (Title 21 Code of Federal Regulations [CFR] 312.32 [a]).

Not Related

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

Unlikely Related

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

Possibly Related

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

Probably Related

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

8.2.3 EXPECTEDNESS

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

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

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

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

Any SAEs that occur after the reporting period that the Investigator assesses as related to study medication should also be reported and managed as an SAE.

8.4 REPORTING PROCEDURES

8.4.1 ADVERSE EVENT REPORTING

The Investigator is responsible for reporting AEs to the Sponsor or representative via the eCRF and to the IRB according to the protocol and 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 suspected adverse reactions 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/Ethics Committee (EC) according to their institution's requirements.

8.4.2 SERIOUS ADVERSE EVENT REPORTING

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

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

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

- A description of the SAE (including event term and serious criteria)
 - If the subject died, the report should include the cause of death as the event term (with fatal outcome)
- Causal relationship to the study drug
- Subject number, sex, and age
- Details of study drug administration
- The date of the report

Follow-up information must be detailed in a follow-up SAE report and reported to the Sponsor Study SAE email address within 3 business days of study site personnel's receipt of the follow-up information. The Investigator also must report all SAEs promptly to the appropriate IRB/EC as required by the institution. The sponsor contact information for questions regarding SAE reporting is provided in Table 2.

Table 2: Sponsor Contact Information for Questions on SAE Reporting

Biosplice Drug Safety and Pharmacovigilance	Phone: (858) 371-4144 Email: DSPV@biosplice.com
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8.4.3 EVENTS OF SPECIAL INTEREST

Not applicable to this study.

8.4.4 REPORTING OF PREGNANCY

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

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

8.5 STUDY HALTING RULES

Not applicable to this study.

8.6 SAFETY OVERSIGHT

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

9. CLINICAL MONITORING

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

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

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

The accuracy of the data will be verified by reviewing the documents described in [Section 11](#).

10. STATISTICAL CONSIDERATIONS

10.1 STATISTICAL AND ANALYTICAL PLANS

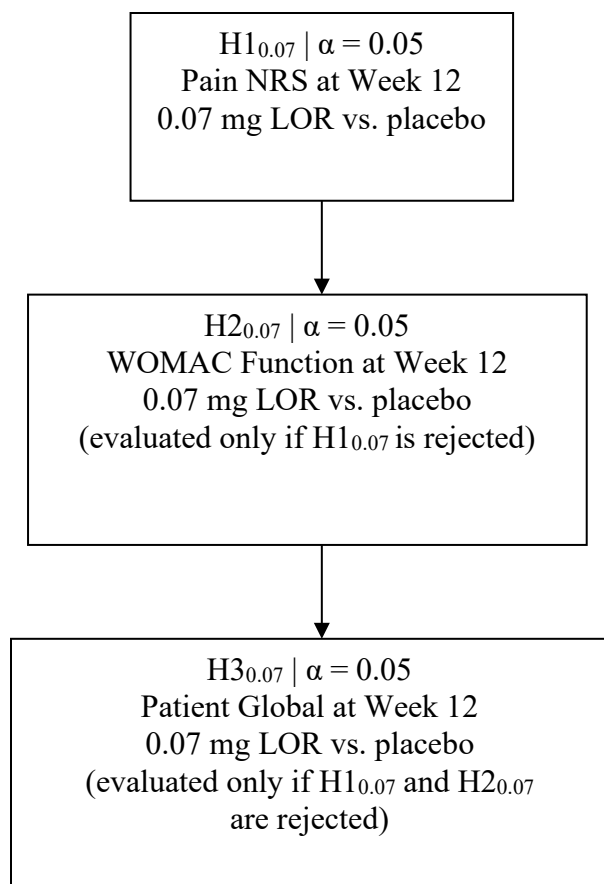
This section describes the planned statistical analyses in general terms. A complete description of the statistical analyses will be specified in a statistical analysis plan (SAP), finalized before database lock.

10.2 STATISTICAL HYPOTHESES

The statistical hypotheses being tested in this study include:

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

The familywise error rate will be controlled in the strong sense using the closed, fixed sequence testing method¹⁵ with an alpha level set to 0.05 for the comparison between LOR and placebo. All hypothesis tests comparing LOR to placebo will be evaluated in the pre-specified sequential orders outlined below.



10.3 ANALYSIS DATASETS

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

Per-Protocol Analysis Set (PPAS): FAS subjects who complete baseline and Week 12 efficacy assessments and do not have any major protocol deviations that might impact the evaluation of efficacy outcomes.

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

10.4 DESCRIPTION OF STATISTICAL METHODS

10.4.1 GENERAL APPROACH

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

10.4.2 ANALYSIS OF THE PRIMARY ENDPOINT

The primary estimands for this trial are the differences between single injections of 0.07 mg

LOR versus placebo in mean baseline-adjusted change in weekly average of daily pain NRS at Week 12, whether or not rescue medication is used (i.e. presuming a treatment policy of rescue medication usage as needed), and analyzed with a mixed-effects model for repeated measures (MMRM), including all collected pain NRS data in subjects in the FAS.

Sensitivity analyses will be performed to assess the change in weekly average of daily pain NRS at Week 12 using baseline-adjusted analysis of covariance (ANCOVA) in the FAS and PPAS. Missing values for subjects in the FAS will be imputed using the multiple imputation (MI) method followed by a two-way tipping point analysis.

The potential confounding effect of rescue medication usage on the treatment effect will be considered for further sensitivity analysis. If rescue medication is taken for target knee pain within 24 hours of a daily pain assessment during Week 12, that assessment will be censored and imputed using the baseline observation carried forward (BOCF) method. If rescue medication is taken for pain that does not involve the target knee, the last observation carried forward (LOCF) approach will be used. The weekly average of daily pain NRS for Week 12 will then be calculated with the imputed values where applicable and used for analysis.

A summary of all estimands defined for the primary endpoint is available in [Appendix 3](#).

10.4.3 ANALYSIS OF THE SECONDARY ENDPOINTS

Change over time in WOMAC Function and Patient Global Assessment will be characterized using MMRM to estimate change from baseline with treatment group, week, treatment×week interaction and baseline value as covariates. The models will include all timepoints for subjects in the FAS and will be evaluated for each LOR dose group versus placebo at Week 12.

Sensitivity analyses will be performed to assess the change in WOMAC Function and Patient Global Assessment at Week 12 using baseline-adjusted ANCOVA in the FAS and PPAS. Missing values for subjects in the FAS will be imputed using the MI method followed by a two-way tipping point analysis.

The potential confounding effect of rescue medication usage on the treatment effect will be considered for further sensitivity analysis. If rescue medication is taken for target knee pain within 24 hours of the WOMAC Function or Patient Global Assessment at Week 12, that assessment will be censored and imputed using the BOCF method. If rescue medication is taken for pain that does not involve the target knee, the LOCF approach will be used.

A summary of all estimands defined for the secondary endpoints is available in [Appendix 3](#).

10.4.4 SAFETY ANALYSES

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

10.4.5 OTHER ENDPOINTS

Change over time in weekly average of daily pain NRS, WOMAC Function, WOMAC Pain, WOMAC Total, Patient Global Assessment, PASS and KOOS will be characterized using MMRM in order to estimate change from baseline with treatment group, week, treatment×week interaction and baseline value as covariates. Unadjusted 95% confidence intervals and *P*-values will be reported.

The use of rescue medication over time will also be summarized.

10.4.6 BASELINE DESCRIPTIVE STATISTICS

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

Baseline descriptive statistics will include age, sex, race, height, weight, BMI, Osteoarthritis Research Society International joint space narrowing (OARSI JSN), and the presence of symptomatic and radiographic OA.

10.4.7 PLANNED INTERIM ANALYSES

Not applicable to this study.

10.4.7.1 SAFETY REVIEW

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

10.4.7.2 EFFICACY REVIEW

Not applicable to this study.

10.4.8 EXPLORATORY ANALYSES

Not applicable to this study.

10.4.9 SUBGROUP ANALYSES

Efficacy analyses described in [Sections 10.4.2](#) and [10.4.3](#) will be further explored with the following subgroups:

- KL Grade 2
- KL Grade 3
- Baseline pain NRS [4-7]
- Baseline pain NRS [7-9]
- Unilateral symptomatic OA
- Bilateral symptomatic OA

- BMI <30 kg/m²
- BMI ≥30 kg/m²

10.5 SAMPLE SIZE

A sample size of approximately 550 subjects was estimated for this study to yield 250 evaluable subjects per treatment group assuming 10% dropout.

One thousand Monte Carlo simulations generated baseline and follow-up data from a bivariate normal distribution for each treatment group and estimated the least squares difference between treatment and placebo in an outcome's change using a baseline-adjusted ANCOVA. The proportion of statistically significant results at $\alpha=0.05$ was estimated as the approximate power for a sample size of 250 subjects per group.

For Pain NRS, assuming a baseline mean (SD) of 6.0 (1.0), follow-up mean (SD) of 3.35 (2.5) for LOR and 4.10 (2.5) for placebo (presumed treatment difference -0.75), and a baseline to follow-up correlation of 0.25, power is estimated to be 88.5%. The assumptions made here are based upon observed data in previous Phase 2 and Phase 3 studies.

10.6 MEASURES TO MINIMIZE BIAS

10.6.1 BLINDING PROCEDURES

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

Subjects will be assigned a subject number at their Screening Visit 1. On Day 1, eligible subjects will be randomized and assigned a kit number. Subjects will be randomized 1:1 (0.07 mg LOR per 2 mL injection: 2 mL placebo injection) to each treatment group using a permuted block design. Specific information regarding the use of the IBM Clinical Development-NBCD randomization module electronic data capture (EDC) and interactive web response systems (IWRS) will be included in relevant work instructions to the site.

10.6.2 EVALUATION OF SUCCESS OF BLINDING

Not applicable to this study.

10.6.3 BREAKING THE STUDY BLIND/PARTICIPANT CODE

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

If deemed necessary to break the blind for a study subject, the Medical Monitor(s) is to be contacted to obtain concurrence. If it is not possible to contact the Medical Monitor(s) beforehand, he or she should be contacted as soon as possible after breaking the blind for a subject. Procedure for performing emergency unblinding will be detailed in the work instruction to the site. Rationale for unblinding must be documented in the subject source.

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

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

11. SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

The Investigator must maintain required records for all study subjects. Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data for this study will be recorded in the subject's source documents and on the eCRFs, unless otherwise noted. All data on these eCRFs should be recorded completely and promptly. A copy of the completed eCRFs for each subject will be retained by the investigational center.

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

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

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

12. QUALITY ASSURANCE AND QUALITY CONTROL

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

13. ETHICS/PROTECTION OF HUMAN SUBJECTS**13.1 ETHICAL STANDARD**

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

13.2 INSTITUTIONAL REVIEW BOARD

The Investigator agrees to provide the IRB/EC with all appropriate material, including a copy of the ICF. The study will not be initiated until the Investigator obtains written approval of the research plan and the ICF from the appropriate IRB/EC and copies of these documents are received by the Sponsor. Appropriate reports on the progress of this study will be made by the Investigator to the IRB/EC and Sponsor in accordance with applicable government regulations and in agreement with the policies established by the Sponsor and the IRB/EC. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB-approved; a determination will be made regarding whether previously consented participants need to be re-consented. The Sponsor ensures that the IRB/EC complies with the requirements set forth in US 21 CFR Part 56.

13.3 INFORMED CONSENT PROCESS**13.3.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS**

Consent forms describing in detail the study procedures and risks will be given to the potential participant and written documentation of informed consent is required before 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 before 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, the study Sponsor or its designee.

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.

13.5 FUTURE USE OF STORED SPECIMENS

Data collected in this study may be useful for other research studies. The Sponsor will only use protected health information in other research studies upon approval from the IRB/EC. If the IRB/EC determines it to be necessary, the Sponsor will obtain informed consent before starting the other research study(ies). Subjects may withdraw permission for use of their data for future research by notifying the site by letter.

14. DATA HANDLING AND RECORD KEEPING

14.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

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

Data required by the protocol will either be collected within eCRFs of the study-specific database or provided directly via data transfers. IBM Clinical Development, the selected EDC is

a validated EDC system fully compliant with regulatory expectations for software developers and service providers within the global regulatory environment, including but not limited to ICH-GCP E6 (R2) and US 21 CFR Parts 312, 812, and 11. Data to be transferred externally to IBM Clinical Development-NBCD may include eCOA questionnaires, central laboratory data, and imaging results.

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

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

14.2 STUDY RECORDS RETENTION

During this study, the Investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated with the IP or entered as a control in the investigation. CRFs will be provided for each subject by the Sponsor or Sponsor's designee. 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 before destroying any records associated with the study.

The Sponsor or Sponsor's designee 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 or Sponsor's designee.

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 or designee 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 or Sponsor's designee will maintain correspondence with the Investigator after study closeout to ensure that study documentation is retained for the appropriate amount of time. Subject files and other source data must be kept for the maximum period of time permitted by the hospital, institution, or private practice and should be retained in accordance with applicable

regulations. The Investigator must inform the Sponsor or Sponsor's designee immediately if any documents are to be destroyed, to be transferred to a different facility, or to be transferred to a different owner.

14.3 PROTOCOL DEVIATIONS

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

14.4 PUBLICATION AND DATA SHARING POLICY

The Sponsor encourages the scientific publication of data from clinical research studies. Investigators, however, may not present or publish partial or complete study results individually without the participation of the Sponsor. The Investigator(s) and the Sponsor may propose appropriate scientific manuscripts or abstracts from the study data. All proposed publications must be reviewed and commented on by the Sponsor before submission for publication. The detailed procedures for the review of publications are set out in the Clinical Trial Agreement entered into with the Sponsor or designee 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. International Committee of Medical Journal Editors (ICMJE) guidelines for authorship will be considered to determine authors for publications.

15. STUDY ADMINISTRATION

15.1 STUDY LEADERSHIP

The study will be led and conducted by Biosplice Therapeutics, Inc.

16. LITERATURE REFERENCES

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APPENDICES

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

Per American College of Rheumatology (ACR) clinical and radiographic classification criteria¹⁶, the presence of all 3 of the following items classifies knee osteoarthritis (OA) in patients:

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

Appendix 2. Prohibited Concomitant Medications and Procedures (Supplement)

- 1) Excluded and prohibited centrally acting analgesics include, but are not limited to, the following:
 - Gabapentin (Neurontin, Horizant, Gaberone, Gralise, Fusepaq Fanatrex)
 - Pregabalin (Lyrica)
 - Carbamazepine (Tegretol, Carbatrol, Epitol, Equetrol)
 - Duloxetine (Cymbalta, Irenka)
 - Milnacipran (Savella)
 - Orphenadrine Citrate (Norflex, Orfro, Orphenate, Mio-Rel, Antiflex)
 - Amitriptyline (Elavil, Vanatrip)
 - Clomipramine (Anafranil)
 - Nortriptyline (Aventyl, Pamelor)
 - Desipramine (Norpramin)
 - Imipramine (Tofranil)
 - Doxepin (Prudoxin, Sinequan, Zonalon, Silenor)
 - Ketamine (Ketalar)
 - Sodium Oxybate (Xyrem, GHB)
- 2) Other non-listed anticonvulsants are also prohibited.
- 3) Excluded and prohibited electrotherapy treatments include, but are not limited to, the following:
 - Diathermy
 - Transcutaneous electrical nerve stimulation (TENS)
 - Neuromuscular Electrical Stimulation (NMES)
 - Interferential therapy
 - Shortwave therapy
 - Iontophoresis
 - LASER

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Appendix 3. Estimands

	Estimator	Variable	Population	Intercurrent events	Population level summary
Primary	Main	Change from baseline in Pain NRS at Week 12	0.07 mg LOR vs. Placebo FAS	1) Prohibited medications: treatment policy strategy; analysis will be conducted regardless of prohibited medications usage. 2) Rescue medication: treatment policy strategy; analysis will be conducted regardless of rescue medication usage.	Difference in the change from baseline between 0.07 mg LOR and placebo using MMRM with treatment group, week, treatment×week interaction and baseline value as covariates.
	Sensitivity 1	Change from baseline in Pain NRS at Week 12	0.07 mg LOR vs. Placebo FAS	1) Prohibited medications: treatment policy strategy; analysis will be conducted regardless of prohibited medications usage. 2) Rescue medication: treatment policy strategy; analysis will be conducted regardless of rescue medication usage.	Difference in the change from baseline between 0.07 mg LOR and placebo using baseline-adjusted ANCOVA with missing data imputed using the MI method; followed by two-way tipping point analysis.
	Sensitivity 2	Change from baseline in Pain NRS at Week 12	0.07 mg LOR vs. Placebo FAS	1) Prohibited medications: treatment policy strategy; analysis will be conducted regardless of prohibited medications usage. 2) Rescue medication: hypothetical strategy; analysis will be conducted as if the rescue medication had not been taken.	Difference in the change from baseline between 0.07 mg LOR and placebo using MMRM with treatment group, week, treatment×week interaction and baseline value as covariates with the following considerations for rescue medication usage: 1) if rescue is taken for target knee pain, censor and impute affected daily pain NRS assessment using BOCF; 2) if rescue is taken for other pain, censor and impute affected daily pain NRS assessment using LOCF.
	Sensitivity 3	Change from baseline in Pain NRS at Week 12	0.07 mg LOR vs. Placebo PPAS	1) Prohibited medications: principal stratum strategy; subjects who used prohibited medications will be excluded from this analysis. 2) Rescue medication: treatment policy strategy; analysis will be conducted regardless of rescue medication usage.	Difference in the change from baseline between 0.07 mg LOR and placebo using baseline-adjusted ANCOVA. By definition, the PPAS will not include subjects with missing data.

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Secondary	Estimator	Variable	Population	Intercurrent events	Population level summary
	Main	Change from baseline in WOMAC Function at Week 12	0.07 mg LOR vs. Placebo FAS	1) Prohibited medications: treatment policy strategy; analysis will be conducted regardless of prohibited medications usage. 2) Rescue medication: treatment policy strategy; analysis will be conducted regardless of rescue medication usage.	Difference in the change from baseline between 0.07 mg LOR and placebo using MMRM with treatment group, week, treatment×week interaction and baseline value as covariates.
	Sensitivity 1	Change from baseline in WOMAC Function at Week 12	0.07 mg LOR vs. Placebo FAS	1) Prohibited medications: treatment policy strategy; analysis will be conducted regardless of prohibited medications usage. 2) Rescue medication: treatment policy strategy; analysis will be conducted regardless of rescue medication usage.	Difference in the change from baseline between 0.07 mg LOR and placebo using baseline-adjusted ANCOVA with missing data imputed using the MI method; followed by two-way tipping point analysis.
	Sensitivity 2	Change from baseline in WOMAC Function at Week 12	0.07 mg LOR vs. Placebo FAS	1) Prohibited medications: treatment policy strategy; analysis will be conducted regardless of prohibited medications usage. 2) Rescue medication: hypothetical strategy; analysis will be conducted as if the rescue medication had not been taken.	Difference in the change from baseline between 0.07 mg LOR and placebo using MMRM with treatment group, week, treatment×week interaction and baseline value as covariates with the following considerations for rescue medication usage: 1) if rescue is taken for target knee pain, censor and impute affected WOMAC Function assessment using BOCF; 2) if rescue is taken for other pain, censor and impute affected WOMAC Function assessment using LOCF.
	Sensitivity 3	Change from baseline in WOMAC Function at Week 12	0.07 mg LOR vs. Placebo PPAS	1) Prohibited medications: principal stratum strategy; subjects who used prohibited medications will be excluded from this analysis. 2) Rescue medication: treatment policy strategy; analysis will be conducted regardless of rescue medication usage.	Difference in the change from baseline between 0.07 mg LOR and placebo using baseline-adjusted ANCOVA. By definition, the PPAS will not include subjects with missing data.

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Secondary	Estimator	Variable	Population	Intercurrent events	Population level summary
	Main	Change from baseline in Patient Global Assessment at Week 12	0.07 mg LOR vs. Placebo FAS	1) Prohibited medications: treatment policy strategy; analysis will be conducted regardless of prohibited medications usage. 2) Rescue medication: treatment policy strategy; analysis will be conducted regardless of rescue medication usage.	Difference in the change from baseline between 0.07 mg LOR and placebo using MMRM with treatment group, week, treatment×week interaction and baseline value as covariates.
	Sensitivity 1	Change from baseline in Patient Global Assessment at Week 12	0.07 mg LOR vs. Placebo FAS	1) Prohibited medications: treatment policy strategy; analysis will be conducted regardless of prohibited medications usage. 2) Rescue medication: treatment policy strategy; analysis will be conducted regardless of rescue medication usage.	Difference in the change from baseline between 0.07 mg LOR and placebo using baseline-adjusted ANCOVA with missing data imputed using the MI method; followed by two-way tipping point analysis.
	Sensitivity 2	Change from baseline in Patient Global Assessment at Week 12	0.07 mg LOR vs. Placebo FAS	1) Prohibited medications: treatment policy strategy; analysis will be conducted regardless of prohibited medications usage. 2) Rescue medication: hypothetical strategy; analysis will be conducted as if the rescue medication had not been taken.	Difference in the change from baseline between 0.07 mg LOR and placebo using MMRM with treatment group, week, treatment × week interaction and baseline value as covariates with the following considerations for rescue medication usage: 1) if rescue is taken for target knee pain, censor and impute affected Patient Global Assessment using BOCF; 2) if rescue is taken for other pain, censor and impute affected Patient Global Assessment using LOCF.
	Sensitivity 3	Change from baseline in Patient Global Assessment at Week 12	0.07 mg LOR vs. Placebo PPAS	1) Prohibited medications: principal stratum strategy; subjects who used prohibited medications will be excluded from this analysis. 2) Rescue medication: treatment policy strategy; analysis will be conducted regardless of rescue medication usage.	Difference in the change from baseline between 0.07 mg LOR and placebo using baseline-adjusted ANCOVA. By definition, the PPAS will not include subjects with missing data.

ANCOVA=analysis of variance; BOCF=baseline observation carried forward; FAS=full analysis set; LOCF=last observation carried forward; LOR=lorecivint; MI=multiple imputation; MMRM=mixed-effects model for repeated measures; NRS=numeric rating scale; PPAS=per-protocol analysis set; WOMAC=Western Ontario and McMaster Universities Arthritis Index

Appendix 4. Amendments**AMENDMENT 01 VERSION 01 SUMMARY OF CHANGES**

Study Title: A Phase 3, 16-Week, Multicenter, Randomized, Double Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of a Single Injection of Lorecivivint 0.07 mg Dose in the Target Knee Joint of Subjects with Moderate to Severe Osteoarthritis Pain of the Knee

Purpose: The main purpose of this amendment is to make minor, administrative updates to the protocol and correct typographical errors regarding the protocol version and date.

Change	Sections Affected	Rationale
Update Version Number to Protocol Amendment 01 Version 01	Title Page	Revised to correctly identify the current protocol version.
Update version date to November 9, 2022	Title Page	Revised to correctly identify the date of the current protocol version.
Protocol date and version have been updated as applicable.	All - Headers	Revisions were made to reflect current protocol amendment version and date.
Update version date to November 9, 2022.	Sponsor Signature Page and Statement of Compliance – Page 7	Revised to correctly identify the date of the current protocol version.
Update estimated date of first subject to November 2022	Section 1.1 Page 15	Revised to accurately reflect planned study start date.

AMENDMENT 01 VERSION 00 SUMMARY OF CHANGES

Study Title: A Phase 3, 16-Week, Multicenter, Randomized, Double Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of a Single Injection of Lorecivivint 0.07 mg Dose in the Target Knee Joint of Subjects with Moderate to Severe Osteoarthritis Pain of the Knee

Purpose: The main purpose of this amendment is to refine the study treatment to one single injection of Lorecivivint at a dose of 0.07 mg.

Change	Sections Affected	Rationale
Protocol Amendment 01 Version 00	Title Page	Revision was made to capture the dates of all previous and current

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Change	Sections Affected	Rationale
		protocol versions.
The word “Injected” was removed	Title Page	Changes were made to improve reader clarity.
Protocol date and version have been updated as applicable.	All	Revisions were made to reflect current protocol amendment.
The higher dose of 0.23 mg was removed from the protocol.	All	A company decision was made to utilize only the 0.07 mg dose.
The number of treatment arms was revised to 2 instead of 3	Section 1.1 and 4.1	Revisions were made to clarify the removal of the higher dose.
The ratio of treatment arms was revised to 1:1 instead of 1:1:1	Section 1.1 , 4.1 , and 10.6.1	Revisions were made to clarify the removal of the higher dose.
The number of subjects enrolled and randomized was revised to 550 instead of 825 subjects.	Sections 1.1 , 4.1 , and 10.5	Revisions were made to decrease the subject sample size to accommodate the removal of the higher dose.
Figures 1 and 2 were revised to remove the higher dose 0.23 mg and include the number of completed evaluable subjects as 250.	Section 1.1 , Figure 1 Section 4.1 , Figure 2	Revisions were made to clarify the removal of the higher dose.
The number of investigational sites was revised to 60 instead of 75.	Section 1.1 and 4.1	Revisions were made to decrease the number of investigational sites to accommodate the removal of the higher dose
The number of doses was revised to 1 instead of 2	Section 2.1	Revisions were made to clarify the removal of the higher dose.

Change	Sections Affected	Rationale
The three statements regarding the least squares estimates of improvement from baseline were removed for subjects who received 0.23 mg of LOR compared to placebo	Section 10.2	Revisions were made to clarify the removal of the higher dose.
The statical hypotheses values were revised as 0.05 instead of 0.02	Section 10.2	Revisions were made to clarify the removal of the higher dose.
Minor editorial corrections were done for consistency.	All	Changes were made to improve reader clarity.

Signature Page for VV-TMF-207282 v1.0

Reason for signing: Approved	Name: Christopher Swearingen Role: Vice President, Biometrics Date of signature: 09-Nov-2022 20:58:23 GMT+0000
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Reason for signing: Approved	Name: Yusuf Yazici Role: Chief Medical Officer Date of signature: 09-Nov-2022 22:14:14 GMT+0000
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Signature Page for VV-TMF-207282 v1.0