A Long-Term Extension Study Evaluating the Safety and Efficacy of Lorecivivint in Subjects with Osteoarthritis of the Knee

Study Number: SM04690-OA-07

IND Sponsor: Biosplice Therapeutics, Inc. (a subsidiary of Samumed, LLC)

Version Number: Amendment 02 Version 00

Date: 04 May 2021

Original Protocol Date:	12 March 2020
Amendment 00 Version 01:	15 April 2020
Amendment 00 Version 02:	16 April 2020
Amendment 01 Version 00:	22 July 2020

SPONSOR SIGNATURE PAGE

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Protocol Number: SM04690-OA-07 AM02V00

Date: 04 May 2021

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

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

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

Abbreviation	Term
AE	Adverse event
AESEV	Severity/Intensity Scale for Adverse Events
ANCOVA	Analysis of covariance
β-CTX	β-C-terminal telopeptide
CDISC	Clinical Data Interchange Standards Consortium
CFR	Code of Federal Regulations
CLK2	CDC-like kinase 2
COMP	Cartilage oligomeric matrix protein
CRF	Case report form
DYRK1A	Dual-specificity tyrosine phosphorylation-regulated kinase 1A
EC	Ethics Committee
eCRF	Electronic case report form
EDC	Electronic data capture
EOS	End of study
FAS	Full analysis set
FDA	(US) Food and Drug Administration
GCP	Good Clinical Practice
HRQOL	Health-related quality of life
IA	Intra-articular(ly)
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
IP	Investigational product
IRB	Institutional Review Board

Abbreviation	**Term**
IUD	Intrauterine device
mJSW	Medial joint space width
NRS	Numeric rating scale
NSAID	Nonsteroidal anti-inflammatory drug
OA	Osteoarthritis
PA	Posterior-anterior
PASS	Patient Acceptable Symptom State
P1NP	N-terminal propeptides of procollagen type I
PPAS	Per-protocol analysis set
SAE	Serious adverse event
SAS	Safety analysis set
SF-36	36-Item Short Form Health Survey
SOP	Standard operating procedure
UP	Unanticipated problem
US	United States
WOCBP	Women of childbearing potential
WOMAC	Western Ontario and McMaster Universities Arthritis Index

STATEMENT OF COMPLIANCE

Study Title	A Long-Term Extension Study Evaluating the Safety and Efficacy of Lorecivivint in Subjects with Osteoarthritis of the Knee		
Protocol Number	SM04690-OA-07		
Protocol Date	04 May 2021	Protocol Version	AM02V00

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

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

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

I will allow the Sponsor, 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 Long-Term Extension Study Evaluating the Safety and Efficacy of Lorecivivint in Subjects with Osteoarthritis of the Knee

Objectives:

Primary:

The primary objective of this study is to evaluate the safety and efficacy of a second year of use of lorecivivint (LOR) in subjects with knee osteoarthritis (OA).

Secondary:

The secondary objective of this study is to evaluate the safety and efficacy of long-term use of LOR in subjects with knee OA.

Endpoints:

Safety:

- Adverse events (AEs) and serious adverse events (SAEs) (incidence, severity, and relationship to study drug) over the course of the study
- Clinically significant changes from parent-study-baseline clinical laboratory measures and vital signs, as assessed by the Investigator, over the course of the study
- Change in serum bone biomarkers (N-terminal propeptides of procollagen type I [P1NP] and β-C-terminal telopeptide [β-CTX]) from parent-study baseline, and change in a serum cartilage biomarker (cartilage oligomeric matrix protein [COMP]) from parent-study baseline at Visit 3E

Efficacy:

- Change from parent-study-baseline medial joint space width (mJSW) in the target knee as evaluated by radiograph over the course of the study
- Change from parent-study-baseline OA pain in the target knee as assessed by pain NRS over the course of the study
- Change from parent-study-baseline OA pain in the target knee as assessed by WOMAC Pain over the course of the study
- Change from parent-study-baseline OA function in the target knee as assessed by WOMAC Function over the course of the study
- Change from parent-study-baseline OA pain, function, and stiffness as a composite outcome measure as assessed by WOMAC total score (WOMAC Total) over the course of the study
- Change from parent-study-baseline health-related quality of life (HRQOL) as assessed by the 36-Item Short Form Health Survey (SF-36) over the course of the study
- Percentage of subjects who consider themselves to be in a Patient Acceptable Symptom State (PASS) over the course of the study

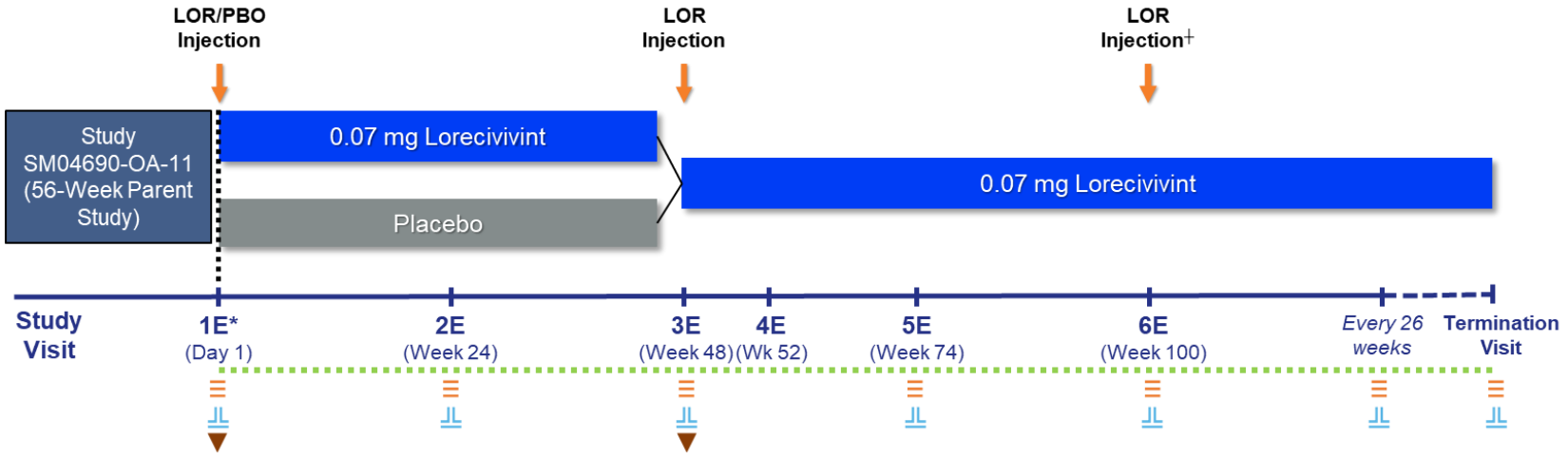
Methodology: This study will be a multicenter study in subjects previously enrolled in study SM04690-OA-11. The first 48 weeks will be single-blind and placebo-controlled while the remainder of the study will be open-label and uncontrolled. The study is planned to continue at least until commercial availability of LOR. Based on previous studies, up to approximately 500 subjects will be enrolled, but there is no set cap on enrollment. Subjects must enroll no later than 6 weeks following completion of study SM04690-OA-11. Clinic visits will be scheduled at Visit 1E (Day 1), Visit 2E (Week 24), Visit 3E (Week 48), Visit 4E (Week 52 phone visit), Visit 5E (Week 74), and every 26 weeks thereafter until the Termination Visit. Refer to Figure 1 for an overview of study design and endpoints.

At the first visit in this study (Visit 1E), all subjects will complete PASS and pain NRS assessments and then receive a blinded study injection into their target knee (the same target knee injected in the parent study), with subjects receiving the same treatment (either 0.07 mg LOR or placebo) as they received in the parent study. Subjects will have clinic visits for pain and function assessments, collection of AEs, and knee radiographs. At Visit 3E, subjects will have plasma samples collected for assessment of biomarkers of bone and cartilage turnover, and all subjects, regardless of previous treatment, will receive an injection of 0.07 mg LOR into their target knee. Subjects will receive injections of 0.07 mg LOR into their target knee every 52 weeks thereafter.

Subjects are allowed to use non-steroidal anti-inflammatory drugs (NSAIDs) and/or acetaminophen for pain relief as needed. If a subject has a partial or total knee replacement of the target knee, the subject will be discontinued from the study.

Mode of Administration: At Visit 1E, injection of LOR or placebo into the target knee joint will be performed by an unblinded injector who does not participate in other subject evaluations. At Visit 3E and for any subsequent injections, injection of LOR into the target knee joint does not need to be performed by an unblinded injector due to the open-label nature of the remaining portion of the study.

Figure 1. Overview of SM04690-OA-07 Study Design and Endpoints



Primary objective:

- To evaluate the safety and efficacy of a second year of use of lorecivivint in subjects with knee OA

Secondary objective:

- To evaluate the safety and efficacy of long-term use of lorecivivint in subjects with knee OA

* X-ray is performed at Week 52 of the parent study; some clinical assessments and biomarker collection are performed at Week 56 (EOS) of the parent study.

+ Study injections are to occur every ~52 weeks until termination.

Abbreviations: EOS = End of Study; LOR = lorecivivint; OA = osteoarthritis; PBO = placebo.

Inclusion/ Exclusion Criteria:

Criteria for Inclusion:

1. Completion of study SM04690-OA-11
2. Compliance with procedures in study SM04690-OA-11, in the opinion of the Investigator
3. Fully understanding study requirements and willingness to comply with study visits and assessments
4. Understanding and signing of the informed consent form (ICF) prior to any study-related procedures

Criteria for Exclusion:

1. 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
2. Any contraindications for an intra-articular (IA) injection in the target knee in the opinion of the Investigator
3. Any known reason identified by the Investigator or Sponsor that the subject may not be compliant with study visits or may no longer be an appropriate candidate for the study (e.g., planned surgery of the pelvis/hip, knee, ankle, or foot, knee replacement during the parent study, planning to move away from the research site, or initiation of a prohibited concomitant medication including, but not limited to, IA injection of glucocorticoids, hyaluronic acid derivatives, platelet-rich plasma, stem cell therapies, or other agents with therapeutic intent into the target knee)
4. Participation in a clinical research trial (other than the prior SM04690-OA-11 study) that included the receipt of an investigational product (IP) or any experimental therapeutic procedure within 12 weeks before any study injection, or planned participation in any such trial
5. Current or pending disability claim, workers' compensation, or litigation(s) that may compromise response to treatment
6. 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 Visit 1E
7. Women who are not post-menopausal or permanently surgically sterile who are sexually active, and who are not willing to use birth control as outlined in Section 5.3.1 during the study period

Population: Up to approximately 500 subjects with no cap on enrollment

Phase: 3

Number of Sites Enrolling Participants:	Approximately 50
Description of Study Agent:	LOR is a small molecule Wnt pathway modulator that inhibits CLK2 and DYRK1A intranuclear kinases and thereby potentially (a) reduces signs and symptoms of knee OA via an anti-inflammatory mechanism and (b) inhibits degradation and enhances formation of cartilage through effects on progenitor cells and chondrocytes resident in the joint.
Study Duration:	Approximately 4 years (based on potential commercial availability of LOR) Estimated date first subject consented: August 2020 Estimated date last subject completed: September 2024
Participant Duration:	Subjects are anticipated to stay in the study until conduct completion unless they are withdrawn or choose to withdraw from the study (refer to Section 5.6.1).
Statistical Methods:	**Sample Size:** The sample size of up to approximately 500 subjects was estimated based on practical considerations, such as the number of subjects anticipated to complete study SM04690-OA-11 but there is no set cap on enrollment. **General approach:** For continuous variables, number of subjects in the analysis, mean, standard deviation, median, minimum, and maximum will be reported. All categorical endpoints will be summarized using frequencies and percentages. Baseline values are defined as assessments occurring before the first blinded study injection in the parent study. **Safety Analysis:** 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, by changes in clinical laboratory parameters and vital signs, relative to parent-study baseline. For subjects who cross over from placebo to LOR, subsequent changes in laboratory parameters and vital signs will be relative to Visit 3E. **Efficacy Analysis:** Change over time in mJSW, pain NRS, WOMAC Pain, WOMAC Function, and WOMAC Total will be characterized using mixed-effects

models for repeated measures (MMRM). The models will estimate change from parent-study baseline with treatment, visit, treatment × visit interaction, and parent-study-baseline value as covariates.

Percentage of subjects in a PASS state will be analyzed by logistic regression. Analysis of covariance (ANCOVA) will be used to analyze the change in SF-36 domain scores and summary component scores.

2. INTRODUCTION

2.1 STUDY RATIONALE

Osteoarthritis (OA) is the most common form of arthritis and chronic joint disorder in humans (Dougados et al. 2011). The exact cause of OA is unknown, but it is associated with aging and normal wear on a joint. OA is characterized by the destruction of the articular cartilage, subchondral bone alterations, and synovitis. Patients present with pain and stiffness in the joints, with the joints becoming more stiff and immobile over time (Dougados et al. 2011). OA is a leading cause of physical disability in the United States (US) (Lawrence et al. 2008).

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

To address the need for effective pharmaceutical agents to treat OA, Biosplice Therapeutics, Inc. (Biosplice) has used structure-based drug design to synthesize a small molecule modulator of the Wnt pathway, lorecivivint (LOR), as a potential OA therapeutic to be administered as a local injection into the affected joint. This study is being conducted to assess the long-term safety of repeated LOR injections, as well as the effects of repeated LOR injections on knee OA pain, function, and structural progression over a total of 2 years.

2.2 BACKGROUND INFORMATION

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

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

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

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 POTENTIAL RISKS AND BENEFITS

2.3.1 KNOWN POTENTIAL RISKS

Study Medication LOR

The study drug LOR, which modulates the Wnt pathway, 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.

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 multiple radiographs of the knee joints, with possibly up to 3 retakes for each radiograph. As part of everyday living, everyone is exposed to a small amount of background radiation that comes from soil, rocks, outer space, and within the body itself. The radiation dose for each radiograph that the subject will receive in this study is expected to be about 0.005 millisievert (mSv) or equivalent to approximately <0.5 day of background radiation in the US. The risk from this dose is small. This radiation exposure may not be necessary for the subjects' medical care, but it is necessary to obtain the research information desired.

2.3.2 KNOWN POTENTIAL BENEFITS

Taking part in this study may or may not provide any benefit to the subject. Information from

this study may help doctors learn more about treatments for OA and this information may help future patients, even if it may not help the subjects in this study.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

LOR is being considered as a new option for the treatment of knee OA. The safety assessments of LOR rely on data from product development and previous clinical trials. Based on nonclinical and clinical data, the conduct of the trial is regarded as justifiable at the planned dose and duration. Previous clinical trials (SM04690-01, SM04690-OA-02, SM04690-OA-04) involving over 1000 subjects identified no serious adverse events (SAEs) considered related to study medication. In previous trials, LOR was safe and well tolerated at single doses of up to 0.23 mg per injection, exceeding the 0.07 mg dose used in the current study. At the time of protocol development, no completed studies have examined the safety or efficacy of repeated injections of LOR, although a double-blind study is ongoing in which subjects will receive up to 4 injections of LOR with 6 months between each 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 OBJECTIVES

Primary:

The primary objective of this study is to evaluate the safety and efficacy of a second year of use of lorecivivint (LOR) in subjects with knee osteoarthritis (OA).

Secondary:

The secondary objective of this study is to evaluate the safety and efficacy of long-term use of LOR in subjects with knee OA.

3.2 STUDY ENDPOINTS

3.2.1 SAFETY ENDPOINTS

- Adverse events (AEs) and serious adverse events (SAEs) (incidence, severity, and relationship to study drug) over the course of the study
- Clinically significant changes from parent-study-baseline clinical laboratory measures and vital signs, as assessed by the Investigator, over the course of the study
- Change in serum bone biomarkers (N-terminal propeptides of procollagen type I [P1NP] and β-C-terminal telopeptide [β-CTX]) from parent-study baseline, and change in a serum cartilage biomarker (cartilage oligomeric matrix protein [COMP]) from parent-study baseline at Visit 3E

3.2.2 EFFICACY ENDPOINTS

- Change from parent-study-baseline medial joint space width (mJSW) in the target knee as evaluated by radiograph over the course of the study
- Change from parent-study-baseline OA pain in the target knee as assessed by pain NRS over the course of the study
- Change from parent-study-baseline OA pain in the target knee as assessed by WOMAC Pain over the course of the study
- Change from parent-study-baseline OA function in the target knee as assessed by WOMAC Function over the course of the study
- Change from parent-study-baseline OA pain, function, and stiffness as a composite outcome measure as assessed by WOMAC total score (WOMAC Total) over the course of the study
- Change from parent-study-baseline health-related quality of life (HRQOL) as assessed by the 36-Item Short Form Health Survey (SF-36) over the course of the study
- Percentage of subjects who consider themselves to be in a 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 study in subjects previously enrolled in study SM04690-OA-11. The first 48 weeks will be single-blind and placebo-controlled while the remainder of the study will be open-label and uncontrolled. The study is planned to continue at least until commercial availability of LOR. Based on previous studies, up to approximately 500 subjects will be enrolled, but there is no set cap on enrollment. Subjects must enroll no later than 6 weeks following completion of study SM04690-OA-11. Clinic visits will be scheduled at Visit 1E (Day 1), Visit 2E (Week 24), Visit 3E (Week 48), Visit 4E (Week 52 phone visit), Visit 5E (Week 74), and every 26 weeks thereafter until the Termination Visit. Refer to Figure 1 for an overview of study design and endpoints.

At the first visit in this study (Visit 1E), all subjects will complete PASS and pain NRS assessments and then receive a blinded study injection into their target knee (the same target knee injected in the parent study), with subjects receiving the same treatment (either 0.07 mg LOR or placebo) as they received in the parent study. Subjects will have clinic visits for pain and function assessments, collection of AEs, and knee radiographs. At Visit 3E, subjects will have plasma samples collected for assessment of biomarkers of bone and cartilage turnover, and all subjects, regardless of previous treatment, will receive an injection of 0.07 mg LOR into their target knee. Subjects will receive injections of 0.07 mg LOR into their target knee every 52 weeks thereafter. Specific timing of protocol procedures is described in the Schedule of Events Table (Section 7.3.4).

Subjects are allowed to use non-steroidal anti-inflammatory drugs (NSAIDs) and/or acetaminophen for pain relief as needed. If a subject has a partial or total knee replacement of the target knee, the subject will be discontinued from the study.

Recording of signs and symptoms of study medication intolerability and AE reporting will start immediately following the parent-study EOS (End of Study) visit and continue at all subsequent

visits until the subject completes the Termination Visit. All AEs, whether volunteered, elicited, or noted during examination, will be recorded throughout the study.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

SM04690-OA-07 is a long-term study designed to evaluate the safety and efficacy of a second year and long-term use of LOR in subjects with OA of the knee. The placebo used in this study is the same vehicle used to formulate LOR but without the active ingredient. A vehicle-controlled single-blind design is considered appropriate for year one of this study as it allows for evaluation of the safety and efficacy of the LOR molecule alone through an unbiased comparison of the active and vehicle injections over a total of 2 years. Beyond 2 years (including parent-study SM04690-OA-11 participation), crossing subjects on placebo over to LOR will provide additional long-term safety information in a group of subjects not previously treated with LOR.

4.3 JUSTIFICATION FOR DOSE

The dose of 0.07 mg LOR was selected for this study to remain consistent with the dose used in the parent study. Administration of the 0.07 mg LOR dose resulted in the most consistently positive responses compared to control when the outcome measures of pain NRS, WOMAC Function, and mJSW were assessed in 3 completed clinical studies (SM04690-01, SM04690-OA-02, and SM04690-OA-04).

4.4 END OF STUDY DEFINITION

A participant is considered to have completed the study if he or she has completed all phases of the study including the Termination Visit (Section 7.3.4).

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 the following criteria:

1. Completion of study SM04690-OA-11
2. Compliance with procedures in study SM04690-OA-11, in the opinion of the Investigator
3. Fully understanding study requirements and willingness to comply with study visits and assessments
4. Understanding and signing of the informed consent form (ICF) prior to any study-related procedures

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. 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

2. Any contraindications for an intra-articular (IA) injection in the target knee in the opinion of the Investigator
3. Any known reason identified by the Investigator or Sponsor that the subject may not be compliant with study visits or may no longer be an appropriate candidate for the study (e.g., planned surgery of the pelvis/hip, knee, ankle, or foot, knee replacement during the parent study, planning to move away from the research site, or initiation of a prohibited concomitant medication including, but not limited to, IA injection of glucocorticoids, hyaluronic acid derivatives, platelet-rich plasma, stem cell therapies, or other agents with therapeutic intent into the target knee)
4. Participation in a clinical research trial (other than the prior SM04690-OA-11 study) that included the receipt of an investigational product (IP) or any experimental therapeutic procedure within 12 weeks before any study injection, or planned participation in any such trial
5. Current or pending disability claim, workers' compensation, or litigation(s) that may compromise response to treatment
6. 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 Visit 1E
7. Women who are not post-menopausal or permanently surgically sterile who are sexually active, and who are not willing to use birth control as outlined in Section 5.3.1 during the study period

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 Visit 1E until the Termination Visit, 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); 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 within 30 days after receiving a study injection should remain on an acceptable form of contraception for 30 days after the last study injection.

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 dosed or entered into the study.

5.4.2 SUBJECT RESCREENING

Screen failures are not allowed to rescreen for this study.

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

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

5.6 PARTICIPANT WITHDRAWAL OR TERMINATION

5.6.1 REASONS FOR WITHDRAWAL OR TERMINATION

Best efforts will be made to encourage subjects to attend all study visits. Subjects will be informed that they are free to withdraw from the study at any time and for any reason. A discontinuation from the study will occur when a subject who signed informed consent and was dosed ceases participation in this study, regardless of circumstances.

Subjects can be 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
- Other

5.6.2 HANDLING OF PARTICIPANT WITHDRAWALS OR TERMINATION

All Termination Visit procedures and assessments should be performed on subjects who are withdrawn or who voluntarily withdraw, including subjects who withdraw due to partial or total knee replacement. 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 eCRFs for subjects who discontinue from the study.

Replacement of subjects who withdraw or discontinue is not allowed.

Total or Partial Knee Replacement Follow-Up

A subject who has had total or partial knee replacement of the target knee should be discontinued from the study. In addition to Termination Visit procedures, sites should make every attempt to follow up with these subjects approximately 6 months after the total or partial knee replacement surgery is completed to assess outcomes of the surgery.

5.7 TERMINATION OR SUSPENSION OF STUDY

The Sponsor reserves the right to terminate the study at any time for administrative or safety reasons. Written notification, documenting the reason for study suspension or termination, will be provided to the Investigator and regulatory authorities as appropriate. If the study is terminated or suspended, the Investigator will promptly inform the Institutional Review Board (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, and 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 vials of 2.4 mL of formulated suspension. Placebo product contains 0.5% carboxymethylcellulose sodium and 0.05% polysorbate 80 in pH 7.4 phosphate buffered saline.

LOR drug and placebo products will be supplied as single-use vials to the study pharmacist 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

LOR drug and placebo products 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.

6.1.4 PREPARATION

At Visit 1E, study medication should be well mixed by the Unblinded Investigator (the drug product is a suspension) before injecting 2 mL intra-articularly into the target knee.

At Visit 3E and for any subsequent injections, study drug preparation and injection do not need to be performed by a designated unblinded individual due to the open-label nature of the remaining portion of the study.

Refer to the Pharmacy Manual for detailed instructions on study injection preparation.

6.1.5 DOSING AND ADMINISTRATION

LOR will be administered in the following dosage strengths:

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

Each subject will maintain the same treatment assignment of LOR or placebo as in the parent study at Visit 1E. At Visit 3E and for any subsequent injections until the Termination Visit, all subjects will receive a LOR injection. Subjects should not have any condition that, in the opinion of the Investigator, constitutes a risk or contraindication for the injections.

At Visit 1E, the injectable drug product or placebo product is to be administered by the Unblinded Investigator as a single injection into the target knee joint. 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. The Unblinded Investigator must minimize any contact with the subject aside from the injections and may not perform any study assessments throughout the duration of the study. All other subject contact is limited to the Blinded Investigator and other appropriate blinded study personnel. The Unblinded Investigator does not need to be the same person for the duration of the study. At Visit 3E and for any subsequent injections, the LOR injections do not need to be performed by a designated Unblinded Investigator due to the open-label nature of the remaining portion of the study.

Only 1 knee will be treated for each subject in this study. The injection can be done either through lateral or medial (including superior/suprapatellar, midpatellar, and inferior/anterior) approaches, based on the standard practice of the Unblinded Investigator/injector or the knee examination of the subject. Although not required, the injection may be guided by ultrasound or

fluoroscopy without contrast if it is the standard practice of the Unblinded Investigator/injector.

Only topical anesthetics are allowed before the study injection. Local anesthetic injections 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. Aspiration of joint fluid into a separate empty syringe is allowed if it is the standard practice of the injector to confirm correct needle placement. For subjects with moderate to large effusion in the target knee, aspiration of the effusion prior to injection of study medication is recommended. The study medication should then subsequently be injected via syringe exchange. The approximate volume of fluid aspirated should be recorded in the eCRF.

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

6.1.6 ROUTE OF ADMINISTRATION

Injectable LOR drug product or placebo product is to be administered as an IA injection into the target knee joint.

6.1.7 STARTING DOSE AND DOSE ESCALATION SCHEDULE

Not applicable to this study.

6.1.8 DOSE ADJUSTMENTS/MODIFICATIONS/DELAYS

No modification in the specified dose concentration or volume (2 mL) of the study injection will be allowed.

6.1.9 DURATION OF THERAPY

Injectable LOR drug product or placebo product is to be administered as a single IA injection into the target knee joint at Visit 1E. LOR is to be administered as an IA injection in the target knee joint every 52 weeks starting at Visit 3E until the Termination Visit.

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

The study medications supplied for this study are for use only in subjects properly consented and

enrolled into this protocol.

All used and unused vials of LOR drug and placebo products received must be returned and accounted for. All injections prepared and dispensed must also be logged. The log includes, but is not limited to, the following:

- Subject number and initials
- Date that study medication was injected
- Quantity dispensed (drug product vials and placebo vials)
- Quantity returned/used (drug product vials and placebo vials)

All study medication dispensed by the Unblinded Investigator and/or unblinded designee will be inventoried and accounted for throughout the study until all subjects at each site complete Visit 3E. The Unblinded Investigator and/or unblinded designee must maintain an accurate, up-to-date dispensing log for all study medications supplied by the Sponsor. Study medication dispensed for all subjects must be recorded on the drug accountability forms. The study medication dispensing log and remaining drug inventory will be reviewed by the Sponsor-designated unblinded clinical monitor.

Starting at Visit 3E and for subsequent injections, subjects will receive open-labeled IP. Accountability will be documented on a new, separate accountability log with the same information as noted above. The open-labeled IP and the separate IP accountability log will be reviewed, and dosing will be verified by a Sponsor-designated clinical monitor (not the unblinded clinical monitor).

For the Visit 1E injections, 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. Once all subjects at a site have had their Visit 1E injection, IP will be accounted for by the unblinded clinical monitor, and the IP can be returned to the depot. Procedures for return or destruction of used and unused vials of the study medication will be provided in the Pharmacy Manual. Open-labeled IP to be used for Visit 3E and subsequent injections will need to be kept in a secure, temperature-controlled location separate from the blinded IP. Accountability for the initial blinded IP will be separate from the open-label IP and sites will need to maintain separate accountability records and pharmacy binders until all subjects at the site are receiving the open-labeled IP, the blind has been lifted, and the parent-study (SM04690-OA-11) database has been locked.

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. As this is an extension trial, AE collection will continue from the parent study, ongoing AEs at the end of the parent study will continue to be monitored, and new AEs that occur during this study will be recorded. Changes to ongoing

AEs that occur after the parent-study EOS visit will not be recorded in the parent study. AEs will be assessed through the Termination Visit.

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

Medical History

A follow-up on Medical History (collected in the parent study) will be performed at the Termination Visit to capture End Dates of any ongoing medical history.

Physical Examination

A general physical examination will be conducted at Visit 3E and the Termination Visit. Results of the physical examination will be noted in the source documents. Any clinically significant finding should be reported as an AE.

Knee Examination

A knee examination of both knees will be conducted at all clinic visits after Visit 1E. Results of the knee examination will be noted in the source documents. Any clinically significant finding should be reported as an AE.

Weight

Weight measurements will be taken at Visit 2E, Visit 3E, every 52 weeks thereafter (e.g., Visits 6E, 8E, etc.), and at the Termination Visit.

Vital Signs

Vital signs will be measured by a qualified staff member at Visit 2E, Visit 3E, every 52 weeks thereafter (e.g., Visits 6E, 8E, etc.), and at the Termination Visit.

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

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

At visits when the subject will receive an IA injection (e.g., Visits 3E, 6E, 8E, etc.), temperature will also be measured.

Any measurement that is, in the opinion of the Investigator, abnormal AND clinically significant must be recorded as an AE.

Radiograph of Knee Joints

Radiograph of the knee joints will be taken at all clinic visits after Visit 1E.

Detailed instructions for obtaining and managing the radiographs will be provided to the investigational center before 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. It is recommended that the Investigator attempt up to 3 additional image captures in order to obtain an acceptable image.

All radiographs will be submitted to an independent radiologist at the central imaging vendor who will document mJSW. The central imaging vendor does not provide medical advice, clinical diagnosis, or treatment recommendations. These imaging assessments and quantitative measurements provided to the Sponsor do not and shall not constitute a medical diagnosis, treatment recommendation, or medical advice, and are not intended to be used as a substitute for the study Investigator's or other qualified health care professional's medical diagnosis, treatment, or advice. If any unusual pathology is noted in the study images, the Sponsor will be notified of the finding and will promptly notify the Investigator. The Investigator will then assess the clinical significance as well as any follow-up procedures that need to be completed.

Pain Numeric Rating Scale

The pain NRS is an 11-point scale [0-10] for subject self-reporting of average knee pain in the last 24 hours. The NRS will be anchored by descriptors at each end ("No Pain" on the left and "Pain as bad as you can imagine" on the right). A pain NRS assessment will be completed by the subjects at all clinic visits.

Pain NRS questionnaires will be provided by the Sponsor. Upon completion of the pain NRS, subjects will sign or initial, then date the source document to indicate that the assessment is reported accurately.

Western Ontario and McMaster Universities Arthritis Index

The WOMAC is a widely used, proprietary outcome measurement tool used by health professionals to evaluate the condition of patients with OA of the knee and hip, including pain, stiffness, and physical functioning of a target joint. The WOMAC Version NRS 3.1 questionnaire will be completed by the subject for their target knee at all clinic visits after Visit 1E.

WOMAC questionnaires will be provided by the Sponsor and may not be reproduced. Upon completion of the WOMAC, subjects will sign or initial, then date the source document to indicate that the assessment is reported accurately.

Patient Acceptable Symptom State Questionnaire

At Visit 1E, Visit 3E, every 52 weeks thereafter (e.g., Visits 6E, 8E, etc.), and at the Termination Visit, subjects will be asked the following, using a paper 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.”

PASS questionnaires will be provided by the Sponsor. Upon completion of the questionnaire, subjects will sign or initial, then date the source document to indicate that the assessment is reported accurately.

36-Item Short Form Health Survey

The SF-36 is a widely used questionnaire that relies upon subject self-reporting to measure the subject’s health-related quality of life. The SF-36 will be completed by the subject at Visit 3E, every 52 weeks thereafter (e.g., Visits 6E, 8E, etc.), and at the Termination Visit.

The SF-36 is a paper questionnaire that will be provided by the Sponsor and may not be reproduced. Upon completion of the SF-36, the subject will sign or initial, then date the source document to indicate that the quality of life assessment is reported accurately.

Assessment of NSAID/Acetaminophen Usage

Information about NSAID and acetaminophen usage will be collected at all clinic visits after Visit 1E. Subjects will be asked to recall the name, indication, route of administration, usual total daily dose, and usual number of days taken per week of any NSAID or acetaminophen medications during the previous 4 weeks. Assessment of NSAID/acetaminophen usage will be documented on the “NSAID/Acetaminophen Usage” eCRF.

7.1.2 STANDARD-OF-CARE STUDY PROCEDURES

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

7.2 LABORATORY PROCEDURES/EVALUATIONS

7.2.1 CLINICAL LABORATORY EVALUATIONS

Specimens for clinical laboratory analysis by the central laboratory will be collected by a qualified staff member at Visit 2E, Visit 3E, every 52 weeks thereafter (e.g., Visits 6E, 8E, etc.), and at the Termination Visit. Subjects should fast prior to the Visit 3E clinical laboratory collection. 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

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 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, clinically significant. If any abnormal, clinically significant laboratory measure is found, it should be reported as an AE.

7.2.2 OTHER ASSAYS OR PROCEDURES

Pregnancy Test

A urine-based pregnancy test will be performed on WOCBP at Visit 1E, Visit 3E, and every 52 weeks thereafter (e.g., Visits 6E, 8E, etc.).

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).

Biomarkers

Fasting blood samples for biomarker analysis will be collected by a qualified staff member at Visit 3E. Biomarkers that will be assessed include bone biomarkers, P1NP and β-CTX, and a cartilage biomarker, COMP.

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/ENROLLMENT

Visit 1E

Visit 1E should occur at the subject's parent-study EOS visit, with a window of + 6 weeks.

Collection of NSAID/acetaminophen usage, physical and knee examination, weight measurement, vital sign measurements, and venipuncture and collection of samples for clinical laboratory tests and biomarker analysis will be performed at the parent-study Week 56 (EOS) visit and therefore do not need to be repeated at Visit 1E.

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

Subjects who sign the ICF at Visit 1E will be considered consented. For WOCBP, a urine-based pregnancy test will then be performed.

After the subject is deemed eligible for the study based on inclusion/exclusion criteria, the following procedures and assessments will be performed at Visit 1E:

- PASS assessment
- Pain NRS assessment
- Collection of AE and concomitant procedures/therapies/medication data
- IA injection of study medication by the Unblinded Investigator (injector) into the target knee; **the target knee must be the same as the knee injected in the parent study**.

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.

7.3.2 STUDY VISITS

Visit 2E

Visit 2E should occur 24 weeks after the Visit 1E injection with a window of ± 4 weeks.

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

- Pain NRS assessment
- WOMAC questionnaire
- Collection of AE and concomitant procedures/therapies/medication data
- Assessment of NSAID/acetaminophen usage
- Knee examination
- Weight measurement
- Vital sign measurements (pulse rate and blood pressure)
- Venipuncture and collection of samples for clinical laboratory tests
- Radiograph – bilateral in weight-bearing fixed flexion position, PA view X-ray

Visit 3E

Visit 3E should occur 48 weeks after the Visit 1E injection with a window of ± 4 weeks. Subjects should fast for 8 hours prior to this visit.

The following procedures and assessments will be performed at Visit 3E:

- Pain NRS assessment
- WOMAC questionnaire
- PASS assessment
- SF-36
- Collection of AE and concomitant procedures/therapies/medication data
- Assessment of NSAID/acetaminophen usage
- Pregnancy test (urine-based) in WOCBP
- Physical examination
- Knee examination
- Weight measurement
- Vital sign measurements (temperature, pulse rate, and blood pressure)
- Venipuncture and collection of samples for clinical laboratory tests and biomarkers
- Radiograph – bilateral in weight-bearing fixed flexion position, PA view X-ray
- IA injection of LOR into the target knee; **the target knee must be the same as the knee injected in the parent study**.

Visit 4E (Phone Visit)

The Visit 4E phone visit should occur on Week 52 (with a window of ± 7 days). Sites will contact subjects to collect AE and concomitant procedures/therapies/medication data.

Visit 5E, 7E, 9E, etc.

These visits should occur on Weeks 74, 126, 178, etc. with a window of ± 4 weeks.

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

- Pain NRS assessment
- WOMAC questionnaire
- Collection of AE and concomitant procedures/therapies/medication data
- Assessment of NSAID/acetaminophen usage
- Knee examination
- Radiograph – bilateral in weight-bearing fixed flexion position, PA view X-ray

Visit 6E, 8E, 10E, etc.

These visits should occur on Weeks 100, 152, 204, etc. with a window of ± 4 weeks.

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

- Pain NRS assessment
- WOMAC questionnaire
- PASS assessment
- SF-36
- Collection of AE and concomitant procedures/therapies/medication data
- Assessment of NSAID/acetaminophen usage
- Pregnancy test (urine-based) in WOCBP
- Knee examination
- Weight measurement
- Vital sign measurements (temperature, pulse rate, and blood pressure)
- Venipuncture and collection of samples for clinical laboratory tests
- Radiograph – bilateral in weight-bearing fixed flexion position, PA view X-ray
- IA injection of LOR into the target knee; **the target knee must be the same as the knee injected in the parent study**.

7.3.3 TERMINATION VISIT

The following procedures and assessments should be performed on subjects who withdraw or are discontinued from the study.

- Pain NRS assessment
- WOMAC questionnaire
- PASS assessment
- SF-36
- Collection of AE and concomitant procedures/therapies/medication data
- Assessment of NSAID/acetaminophen usage

- Review of medical history
- Physical examination
- Knee examination
- Weight measurement
- Vital sign measurements (pulse rate and blood pressure)
- Venipuncture and collection of samples for clinical laboratory tests
- Radiograph – bilateral in weight-bearing fixed flexion position, PA view X-ray (if not completed within 12 weeks before the Termination Visit)

Note: Subjects who withdraw from the study after having a partial or total knee replacement are not required to complete the pain NRS assessment, WOMAC questionnaire, PASS assessment, SF-36, or radiograph.

7.3.4 SCHEDULE OF EVENTS TABLE

	Visit 1E (Day 1) + 6 weeks	**Visit 2E (Week 24)** ± 4 weeks	**Visit 3E (Week 48)** ± 4 weeks	**Visit 4E Phone visit (Week 52)** ± 7 days	**Visit 5E, 7E, 9E, etc. (Week 74, 126, 178, etc.)** ± 4 weeks	**Visit 6E, 8E, 10E, etc. (Week 100, 152, 204, etc.)** ± 4 weeks	**Termin-ation Visit[d]**
Informed consent	X						
Inclusion & exclusion criteria	X						
Medical history							X
Urine pregnancy test[a]	X		X			X	
Injection into target knee[b]	X		X			X	
Physical examination[c]			X				X
Knee examination[c]		X	X		X	X	X
Weight[c]		X	X			X	X
Vital signs[c]		X	X			X	X
Clinical laboratory sampling[c]		X	X			X	X
Pain NRS	X	X	X		X	X	X
WOMAC		X	X		X	X	X
PASS	X		X			X	X
SF-36			X			X	X
Knee Radiograph		X	X		X	X	X[e]
Collection of biomarker samples[c]			X				
AEs and concomitant procedures/therapies/ medications	X	X	X	X	X	X	X
Assessment of NSAID/ acetaminophen usage[c]		X	X		X	X	X

Abbreviations: AEs, adverse events; NRS, numeric rating scale; PASS, Patient Acceptable Symptom State; SF-36, 36-Item Short Form Health Survey; WOMAC, Western Ontario and McMaster Universities Arthritis Index.

[a] Urine pregnancy tests are to be performed on WOCBP only.

[b] Study injection should be the last procedure performed at injection visits (e.g., Visit 1E, 3E, 6E, etc.).

[c] Collection of NSAID/acetaminophen usage, physical and knee examination, weight measurement, vital sign measurements, and venipuncture and collection of samples for clinical laboratory tests and biomarker analysis will be performed at the parent-study Week 56 (EOS) visit and therefore do not need to be repeated at Visit 1E.

[d] Subjects who discontinue from the study *after* having a partial or total knee replacement are not required to complete the pain NRS assessment, WOMAC questionnaire, PASS assessment, SF-36, or radiograph at the Termination Visit.

[e] Radiograph is only to be performed at the Termination Visit, when applicable, if not performed within 12 weeks before the Termination Visit.

7.4 JUSTIFICATION FOR SENSITIVE PROCEDURES

Not applicable for this study.

7.5 CONCOMITANT MEDICATIONS, TREATMENTS, AND PROCEDURES

Details regarding the name, indication, route of administration, dose, and frequency of all parent-study medications will be recorded in this study. Changes to medications ongoing at Visit 1E will be recorded in this study. Changes to ongoing medications that occur after the parent-study EOS visit will not be recorded in the parent study. All new medications, therapies, or procedures taken or received from Visit 1E through the Termination Visit will be recorded in the eCRF at each visit. Documented medications should include prescription, over the counter, supplements, as well as herbal or alternative medications.

All new or modified concomitant medications must be recorded on the "Concomitant Medications" eCRF.

Procedures or non-drug therapies that are ongoing, new, or modified at or after Visit 1E 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 in the study:
  - Opioids; short-term use of opioids as part of anesthesia or procedural sedation during the study period is permitted
  - Centrally acting analgesics (e.g., duloxetine) (refer to Appendix 1)
  - Topical local anesthetic agents; short-term use as part of anesthesia, including for study injections during the study period is permitted
  - Other anticonvulsants not listed in Appendix 1
  - Systemic glucocorticoids ≥10 mg of prednisone per day or the equivalent; epidural, inhaled, intranasal, and topical glucocorticoids are permitted

  - Drugs screened to assess eligibility in the parent study, unless clinically indicated and allowed by the protocol: amphetamine, buprenorphine, cocaine, methadone, opiates, phencyclidine, propoxyphene, barbiturates, benzodiazepine, methaqualone, and tricyclic antidepressants

- Electrotherapy (refer to Appendix 1), 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.
- Elective surgery of the pelvis/hip, knee, ankle, or foot is prohibited while the subject is on the study.
- 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 in the study.

The Investigator should notify the 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

Subjects are allowed to use NSAIDs and/or acetaminophen for pain relief as needed. If a subject's clinical condition significantly deteriorates (defined as experiencing significant pain that cannot be satisfactorily controlled using NSAIDs and/or acetaminophen), the Investigator should consult with the Medical Monitor(s).

7.9 PARTICIPANT ACCESS TO STUDY AGENT AT STUDY CLOSURE

Not applicable to this study.

8. ASSESSMENT OF SAFETY

8.1 SPECIFICATION OF SAFETY PARAMETERS

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

8.1.1 DEFINITION OF ADVERSE EVENTS

AEs in the eCRF will be classified according to the most recent US Food and Drug Administration (FDA) definitions and in a manner consistent with International Council for Harmonisation Guideline for Good Clinical Practice (ICH-GCP) guidelines. As such the following definitions will be used:

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

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

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

8.1.2 DEFINITION OF SERIOUS ADVERSE EVENTS

According to the ICH-GCP Guidelines E6 (R2), an SAE is any untoward medical occurrence during a clinical investigation that is characterized by one or more of the following:

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

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

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

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

8.1.3 DEFINITION OF UNANTICIPATED PROBLEMS

An AE observed during the conduct of a study should be considered an Unanticipated Problem

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

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

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

8.2 CLASSIFICATION OF AN ADVERSE EVENT

8.2.1 SEVERITY OF EVENT

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

Table 1: CDISC Definitions of Adverse Event Severity

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

8.2.2 RELATIONSHIP TO STUDY AGENT

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

Not Related

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

Unlikely Related

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

Possibly Related

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

Probably Related

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

8.4 REPORTING PROCEDURES

8.4.1 ADVERSE EVENT REPORTING

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

8.4.2 SERIOUS ADVERSE EVENT REPORTING

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

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

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 study SAE email address or fax number as it becomes available. The Investigator also must report all SAEs promptly to the appropriate IRB/EC as required by the institution. Sponsor contact information for questions regarding SAE reporting is provided in Table 2.

Table 2: Sponsor Contact Information for Questions on SAE Reporting

Primary Contact	**Alternative Contact**
Sherry Beckman, Associate Director, Drug Safety and Pharmacovigilance (DSPV)	Famina Hemani, Executive Director, DSPV
Email: sherry.beckman@biosplice.com	Email: famina.hemani@biosplice.com
DSPV Phone: (858) 371-4144	

8.4.3 UNANTICIPATED PROBLEM REPORTING

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

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

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

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

8.4.4 EVENTS OF SPECIAL INTEREST

Not applicable to this study.

8.4.5 REPORTING OF PREGNANCY

If the subject or partner of the subject becomes pregnant, the pregnancy is to be followed until the outcome is known. An IRB-approved Pregnant Subject 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 Sponsor 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 designees with respect to current GCP and Standard Operating Procedures (SOPs) for compliance with applicable government

regulations. It is the responsibility of the Investigator to provide all study records, including eCRFs and source documents among other records, for review and inspection by the clinical monitor.

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

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

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

10. STATISTICAL CONSIDERATIONS

10.1 STATISTICAL AND ANALYTICAL PLANS

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

10.2 STATISTICAL HYPOTHESES

The statistical hypotheses being tested in this study are: the least squares estimate of improvement from parent-study baseline in clinical and radiographic outcomes at Visit 3E (i.e., after 24 months of treatment) is greater for subjects who received LOR compared to those who received placebo. Details of the statistical hypothesis tests will be outlined in the SAP.

10.3 ANALYSIS DATASETS

Full Analysis Set (FAS): All subjects who receive a study injection in the current study, analyzed as randomized in the parent study.

Per-Protocol Analysis Set (PPAS): FAS subjects who complete the study and do not have any major protocol deviations in the current or parent study that might impact efficacy.

Safety Analysis Set (SAS): All subjects who receive a study injection in the current study, analyzed as treated in the current study.

10.4 DESCRIPTION OF STATISTICAL METHODS

10.4.1 GENERAL APPROACH

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

10.4.2 ANALYSIS OF SAFETY ENDPOINT(S)

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 parent-study baseline. For subjects who cross over from placebo to LOR, subsequent changes in laboratory parameters and vital signs will be relative to Visit 3E.

10.4.3 ANALYSIS OF EFFICACY ENDPOINT(S)

Change over time through Visit 3E in mJSW, pain NRS, WOMAC Pain, WOMAC Function, and WOMAC Total will be characterized using mixed-effects models for repeated measures (MMRM). The models will estimate change from parent-study baseline with treatment, visit, treatment × visit interaction, and parent-study baseline value as covariates. Unadjusted 95% confidence intervals and *P* values will be reported. The potential confounding effect of change in NSAID/acetaminophen usage on the treatment effect will be considered for sensitivity analysis.

ANCOVA will be used to analyze the change in SF-36 domain scores and summary component scores through Visit 3E. Change will be assessed from parent-study baseline between the active and placebo treatment groups. The models will be adjusted for parent-study baseline. Unadjusted 95% confidence intervals and *P* values will be reported.

PASS will be analyzed using logistic regression. Logistic regression will also be used to compare the proportion of Outcome Measures in Rheumatology Clinical Trials (OMERACT)-Osteoarthritis Research Society International (OARSI) responders and “strict” responders (Pham et al. 2003) between treatment groups through Visit 3E, as well as proportion of subjects achieving a 20%, 50%, and 70% improvement.

Maintenance of LOR’s effects on pain and function of the target knee will be characterized by summarizing likelihood of response in pain NRS, WOMAC Pain, and WOMAC Function in the current study for those subjects that had a response in the parent study. Response will be characterized as a 20%, 50%, and 70% improvement.

After all subjects have received LOR at Visit 3E, all further efficacy analyses will be descriptive in nature.

10.4.4 BASELINE DESCRIPTIVE STATISTICS

Baseline is defined as the last value recorded before a study injection of the parent study (i.e., parent-study baseline). Baseline descriptive statistics from parent study will include age, sex, race, height, weight, body mass index (BMI), mJSW, Kellgren-Lawrence (KL) grade, and the presence of symptomatic and radiographic OA.

For subjects who cross over from placebo to LOR, Visit 3E (i.e., first exposure to LOR) will serve as an additional reference point for analysis.

10.4.5 PLANNED INTERIM ANALYSES

Not applicable to this study.

10.4.5.1 SAFETY REVIEW

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

10.4.5.2 EFFICACY REVIEW

Not applicable to this study.

10.4.6 EXPLORATORY ANALYSES

Not applicable to this study.

10.4.7 SUB-GROUP ANALYSES

Not applicable to this study.

10.5 SAMPLE SIZE

The sample size of up to approximately 500 subjects was estimated based on practical considerations, such as the number of subjects anticipated to complete study SM04690-OA-11, but there is no set cap on enrollment.

10.6 MEASURES TO MINIMIZE BIAS

10.6.1 BLINDING PROCEDURES

Subjects consented in this study will have been previously treated with an IA injection of either LOR or placebo in their target knee in a parent study that was double-blinded. The blind for the subject's previous treatment with either LOR or placebo will be maintained in this study for Investigators, site personnel, and subjects only, although the Sponsor will remain blinded to treatment assignment until the database from the parent study has been locked. At Visit 1E, preparation of LOR or placebo for injection and the injections are to be performed by an Unblinded Investigator who has minimal contact with the subject for other aspects of the study, as described in Section 6.1.5. At Visit 3E and for any subsequent injections, the LOR injections do not need to be performed by a designated Unblinded Investigator due to the open-label nature of the remaining portion of the study.

10.6.2 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. Details regarding the emergency unblinding will be documented in Medidata Rave Randomization and Trial Supply Management (RTSM) and medical records. Instructions on how to unblind treatment assignment will be provided to each Investigator and kept within a guidance document at each site. No other blinded site users will have access roles to Medidata Rave RTSM that will allow treatment assignment unblinding.

Any subject whose blind has been broken (to parent-study treatment assignment) will continue their follow-up visits per protocol.

In circumstances when the blind is unintentionally broken at the investigational center, the breaking of the blind should be reported to the designated Sponsor 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. 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), 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)

12. QUALITY ASSURANCE AND QUALITY CONTROL

This study will be organized, performed, and reported in compliance with the protocol, SOPs, site/Investigator training, and applicable regulations and guidelines. Clinical Investigator sites

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

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

13. ETHICS/PROTECTION OF HUMAN SUBJECTS

13.1 ETHICAL STANDARD

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

13.2 INSTITUTIONAL REVIEW BOARD

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

13.3 INFORMED CONSENT PROCESS

13.3.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

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

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

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

Not applicable to this study.

13.5 FUTURE USE OF STORED SPECIMENS

Not applicable to this study.

14. DATA HANDLING AND RECORD KEEPING

14.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

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

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

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

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

14.2 STUDY RECORDS RETENTION

During this study, the Investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated with the IP or entered as a control in the investigation. CRFs will be provided for each subject by the Sponsor. Data reported on the eCRFs and derived from source documents must be consistent with the source documents or the discrepancies must be explained. The completed eCRFs must be promptly reviewed, and electronically signed and dated in EDC by a qualified physician who is an Investigator on the study once all data is considered final. During this study, the Investigator must retain copies of eCRFs (or electronic files), and source documents for the maximum period required by (1) applicable regulations and guidelines or institution procedures or (2) for the period specified by the Sponsor, whichever is longer. The Investigator must contact the Sponsor before destroying any records associated with the study.

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

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

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

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

transferred to a different facility, or 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 with the Sponsor in connection with this study. These procedures are in place to ensure coordination of study data publication and adequate review of data for publication against the validated study database for accuracy. Names of all Investigators and Sponsor representatives responsible for designing the study and analyzing the results will be included in the publication(s).

15. STUDY ADMINISTRATION

15.1 STUDY LEADERSHIP

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

15.2 KEY ROLES

Medical monitor	Ismail Simsek, MD - Medical Director Biosplice Therapeutics, Inc. 9360 Towne Centre Drive San Diego, CA 92121 *ismail.simsek@biosplice.com* (858) 926-2999
Central radiology reader	Medical Metrics, Inc. (MMI) 2121 Sage Road, Suite 300 Houston, Texas 77056 (713) 850-7500
Central laboratory	Medpace Central Laboratories 5365 Medpace Way Cincinnati, Ohio 45227 (800) 749-1737

16. LITERATURE REFERENCES

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APPENDIX

Appendix 1. Prohibited Concomitant Medications and Procedures (Supplement)

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

2) Other non-listed anticonvulsants are also prohibited.

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

Appendix 2. Amendments

AMENDMENT 02 VERSION 00 SUMMARY OF CHANGES

Study Title: A Long-Term Extension Study Evaluating the Safety and Efficacy of Lorecivivint in Subjects with Osteoarthritis of the Knee

Purpose: The purpose of this amendment is to refine the study design into a long-term extension study in which subjects will receive study injections annually and placebo subjects will cross over to LOR after the first study injection.

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

Change	Sections Affected	Rationale
Protocol Amendment 02 Version 00 has been added on the title page.	Title Page	Change was made to capture the dates of previous and current protocol versions
Protocol date and version have been updated as applicable	All	Change was made to reflect current protocol amendment
Study title was changed (replaced "48-Week, Placebo-Controlled, Single-Blind" with "Long-Term")	Throughout	Changes were made to align with revised study design.
"Samumed, LLC" was replaced with "Biosplice Therapeutics, Inc." or deleted.	Throughout	Change was made for administrative reasons.
Titles of signatories were updated.	Sponsor Signature Page	Change was made for administrative reasons.
Primary and secondary objectives were edited.	Sections 1.1 and 3.1	Edits were made to align with new long-term study design.
Efficacy endpoints were updated to be "over the course of the study" where applicable.	Sections 1.1 and 3.2	Edits were made to align with new long-term study design.
Study design was revised, including: • Limiting single-blind and placebo-control to the first 48 weeks; remainder of the study is open-label and uncontrolled. • Study visits were added (phone visit at Week 52 and clinic visits approximately every 26 weeks). • Subjects will receive LOR injections approximately every 52 weeks after Visit 3E. • Study and participant duration were updated accordingly. • EOS and ET visits were replaced with a single Termination Visit.	Sections 1.1, 2.3.1, 4.1, 4.2, 4.4, 5.6, 6.1.4, 6.1.5, 6.1.9, 7.5, and 7.8	Study design was refined to allow for long-term evaluation of safety and efficacy.
Exclusion #3 was revised to include, "Any known reason *identified by the Investigator or Sponsor* that the subject may not be compliant…"	Sections 1.1 and 5.2	Change was made to refine exclusion criteria.
Exclusion criterion #8 (regarding men who are sexually active and of reproductive potential) was deleted.	Sections 1.1 and 5.2	Male contraception requirements were removed to align with PK studies demonstrating no detectable systemic exposure following IA injection of LOR.

Change	Sections Affected	Rationale
Estimated subject number and number of sites were edited.	Sections 1.1, 4.1, and 10.5	Change was made for accuracy
Contraception guidelines were revised for WOCBP and removed for men.	Section 5.3.1	Male contraception requirements were removed to align with PK studies demonstrating no detectable systemic exposure following IA injection of LOR.
Instructions for a Total or Partial Knee Replacement Follow-Up were added to the protocol.	Section 5.6.2	Follow-up was added to allow for assessment of TKR/PKR surgery outcomes.
Guidance on study drug injection was updated, including adding a recommendation for aspiration of moderate to large effusions in the target knee prior to injection.	Section 6.1.5	Changes were made to provide further guidance on IA injections.
Accountability procedures were revised.	Section 6.2	Accountability procedures for blinded versus open-label IP were clarified.
Timing of study specific procedures was revised where applicable.	Sections 7.1 and 7.2	Changes were made to align with revised study design.
Fasting requirements for labs was removed (except for Visit 3E).	Section 7.2.1	Change was made as fasting was more relevant to biomarker sample collection.
Study visits and Schedule of Events were revised.	Section 7.3	Changes were made to align with revised study design.
Prohibited procedures were modified.	Section 7.6	Changes were made to refine prohibited procedures.
SAE reporting information and sponsor contact information was updated.	Section 8.4.2	Changes were made to clarify initial SAE reporting and for administrative reasons.
Reporting of pregnancy was limited to pregnant subjects (not pregnant partners of a male subject).	Section 8.4.5	Changes were made to align with removal of male contraception requirements.
Descriptions of statistical methods were updated.	Sections 1.1 and 10.4	Changes were made to align with revised study design.
Medical monitor roles were updated.	Section 15.2	Change was made for administrative reasons.
General editorial/grammatical edits.	Throughout	Changes were made for clarity and accuracy.

AMENDMENT 01 VERSION 00 SUMMARY OF CHANGES

Study Title: A 48-Week, Placebo-Controlled, Single Blind Extension Study Evaluating the Safety and Efficacy of Lorecivivint in Subjects with Osteoarthritis of the Knee

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

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

Change	Sections Affected	Rationale
Protocol Amendment 01 Version 00 has been added on the title page.	Title Page	Change was made to capture the dates of previous and current protocol versions
Protocol date and version have been updated as applicable	All	Change was made to reflect current protocol amendment
"Estimated date first subject consented" was changed from July to August 2020. "Estimated date last subject completed" was changed from December to September 2022.	Section 1.1	Change was made for accuracy
The window between the parent-study EOS visit and Visit 1E was extended from 2 to 6 weeks.	Sections 1.1, 4.1, 7.3.1, and 7.3.4	Change was made to allow Visit 1E to occur up to 6 weeks after the parent-study EOS visit.
Made the following correction: "…recorded on specific pages of the eCRF~~ or electronic diary.~~"	Sections 7.1.1 and 8.1.1	An electronic diary is not being used in this study
The following addition was made: "**Per-Protocol Analysis Set (PPAS):** FAS subjects who complete the study and do not have any major protocol deviations in the current or parent study *that might impact efficacy.*"	Section 10.3	Change was made to provide further clarification to the analysis datasets.

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Reason for signing: Approved	Name: Ismail Simsek Role: Medical Director Date of signature: 05-May-2021 03:09:28 GMT+0000

Reason for signing: Approved	Name: Christopher Swearingen Role: Vice President, Clinical Outcomes and Analytics Date of signature: 05-May-2021 03:29:30 GMT+0000

Reason for signing: Approved	Name: Mark Fineman Role: Vice President, Clinical Development Date of signature: 05-May-2021 03:40:05 GMT+0000

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