STRIDES—EXTRA

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

A 3-Year, Multicenter, Open-Label Study Evaluating the Safety, Tolerability, and Efficacy of Intra-articular Lorecivivint in Subjects with Osteoarthritis of the Knee in a Real-World Setting

Study Number: SM04690-OA-17

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

Version Number: Amendment 00 Version 00

Date: 16 April 2021

SPONSOR SIGNATURE PAGE

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Protocol Number: SM04690-OA-17 AM00V00

Date: 16 April 2021

Name & Title	Signature Date
Mark Fineman, PhD Senior Vice President, Clinical Development	*Document has been electronically signed. Please see the final page of the viewable rendition for electronic signature(s).*
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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 United States (US) Code of Federal Regulations (CFR) 21 Title CFR Parts 50, 54, 56, 312, and 314, and GCP Guidelines, as applicable.

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LIST OF ABBREVIATIONS

Abbreviation	Term
ACR	American College of Rheumatology
AE	Adverse event
AESEV	Severity/Intensity Scale for Adverse Events
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
CDISC	Clinical Data Interchange Standards Consortium
CFR	Code of Federal Regulations
CRF	Case report form
EC	Ethics Committee
eCRF	Electronic case report form
EDC	Electronic data capture
EOS	End of study
ER	Emergency room
ET	Early termination
FAS	Full analysis set
FDA	(US) Food and Drug Administration
GCP	Good Clinical Practice
HA	Hyaluronic acid
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
HRQoL	Health-related quality of life
IA	Intra-articular

Abbreviation	Term
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
IP	Investigational product
IQRMP	Integrated Quality and Risk Management Plan
IRB	Institutional Review Board
IUD	Intrauterine device
KL	Kellgren-Lawrence
KOOS	Knee Injury and Osteoarthritis Outcome Score
LDH	Lactate dehydrogenase
LOR	Lorecivivint
MedDRA	Medical Dictionary for Regulatory Activities
NCS	Not clinically significant
NRS	Numeric rating scale
NSAID	Nonsteroidal anti-inflammatory drug
OA	Osteoarthritis
PASS	Patient Acceptable Symptom State
PCP	Phencyclidine
PRO(s)	Patient reported outcome(s)
PRP	Platelet rich plasma
RBC	Red blood cell
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Safety analysis set
SD	Standard deviation

Abbreviation	Term
SF-12	12-Item Short Form Health Survey
SOP	Standard operating procedure
TUG	Timed Up and Go
UP	Unanticipated problem
US	United States
USPI	US prescribing information
WBC	White blood cell
WOCBP	Women of childbearing potential
WOMAC	Western Ontario and McMaster Universities Arthritis Index
WPAI	Work Productivity and Activity Impairment
WPI&SS	Widespread Pain Index and Symptom Severity Form

STATEMENT OF COMPLIANCE

Study Title	A 3-Year, Multicenter, Open-Label Study Evaluating the Safety, Tolerability, and Efficacy of Intra-articular Lorecivivint in Subjects with Osteoarthritis of the Knee in a Real-World Setting		
Protocol Number	SM04690-OA-17		
Protocol Date	16 April 2021	Protocol Version	AM00V00

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 course of the study must first be approved by the IRB/EC prior to implementation except when such modification is made to remove an immediate hazard to the subject.

I will ensure that a fully executed IRB/EC-approved 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 3-Year, Multicenter, Open-Label Study Evaluating the Safety, Tolerability, and Efficacy of Intra-articular Lorecivivint in Subjects with Osteoarthritis of the Knee in a Real-World Setting

Objectives:

Primary:
The primary objective of this study is to assess the safety and tolerability of lorecivivint (LOR) alone and in addition to other standard of care intra-articular (IA) treatments in subjects with knee osteoarthritis (OA).

Secondary:
The secondary objectives of the study are to evaluate:

1. The efficacy of LOR assessed using patient reported outcomes (PROs) and functional measures
2. The effects of LOR injections on health-related quality of life (HRQoL) and work productivity
3. Treatment patterns of LOR, glucocorticoid, and hyaluronic acid (HA) injections in both knees of subjects with knee OA

Endpoints:

Safety Endpoints:

1. Adverse events (AEs) and serious adverse events (SAEs) (incidence, severity, and relationship to LOR)
2. Clinically significant changes in clinical laboratory measures and vital signs, as assessed by the Investigator

Efficacy Endpoints:

1. Change from baseline in pain numeric rating scale (NRS) score for the knee at Month 3 and annual visits, at each Unscheduled Injection Visit, and 3 months after each injection
2. Change from baseline in Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) physical function subscore (WOMAC Function) at Month 3 and annual visits, at each Unscheduled Injection Visit, and 3 months after each injection
3. Change from baseline in WOMAC total score and pain and stiffness subscores at Month 3 and annual visits, at each Unscheduled Injection Visit, and 3 months after each injection
4. Change from baseline in the Knee Injury and Osteoarthritis Outcome Score (KOOS) subscales of Symptoms, Function (Sports), and Quality of Life at Month 3 and annual visits, at each Unscheduled Injection Visit, and 3 months after each injection
5. Change from baseline in HRQoL (as measured using the 12-Item Short Form Health Survey [SF-12]) and Work Productivity and Activity Impairment (WPAI) at Month 3 and annual visits

6. Patient-Acceptable Symptom State (PASS) at Month 3 and annual visits
7. Change from baseline in 40-meter walk test time at Month 3 and annual visits, at each Unscheduled Injection Visit, and 3 months after each injection (at a subset of sites)
8. Change from baseline in the Timed Up and Go (TUG) test time at Month 3 and annual visits, at each Unscheduled Injection Visit, and 3 months after each injection (at a subset of sites)
9. Frequency of and interval between knee IA injections

Methodology: This study will be a multicenter, open-label study. Up to 300 subjects will be enrolled. After a screening period of up to 14 days, subjects will receive an IA injection of 0.07 mg LOR into one or both knees, followed by a 36-month evaluation period. Clinic visits will be scheduled at Day 1, and Months 3, 12, 24, and 36 (End of study [EOS]) or Early Termination (ET) for completion of all PRO measurements (WOMAC, KOOS, pain NRS, SF-12, PASS, WPAI), functional tests (40-meter walk test and TUG test at a subset of sites), and safety evaluations. On Day 1, the Charlson Comorbidity Index and Widespread Pain Index and Symptom Severity [WPI&SS] assessments will also be completed. A phone visit for safety follow-up will occur 4 weeks after the injection on Day 1. Refer to Figure 1 for an overview of the study design. Subjects may also have Unscheduled Injection Visits for additional injections of LOR, glucocorticoid, or HA, as described in the OA Treatment Algorithm section below. Following each injection, subjects will return to the clinic for 3-Month Post-Injection Follow-Up Visits, unless another visit has occurred between the injection and the 3-month post injection date. At these injection visits and 3-Month Post-Injection Follow-Up Visits, subjects will complete PRO measurements and functional tests (at a subset of sites).

Mode of Administration: Direct IA injection into one or both knee joints. LOR injections into the same knee must be separated by at least 6 months; glucocorticoid and HA injections must be performed in accordance with US prescribing information (USPI).

OA Treatment Algorithm:

LOR Injections:

- On Day 1, after subject eligibility has been confirmed and subjects complete all PRO measurements and functional tests (at applicable sites), subjects will receive an IA injection of 0.07 mg LOR into one or both knees. Bilateral injections of 0.07 mg LOR are allowed.
- Subjects may receive additional injections of LOR into one or both knees, as clinically indicated, at any time between Day 1 and Month 33 with the restriction that LOR injections into the same knee must be separated by at least 6 months; these injections can

occur at Unscheduled Injection Visits, 3-Month Post-Injection Follow-Up Visits, or at the Months 3, 12, or 24 visits after the completion of visit assessments.

- *For LOR injections after Day 1:* Within 6 months of any knee surgery, LOR may not be injected in the affected knee without consultation with and documented approval from the Medical Monitor.

Glucocorticoid and HA Injections:

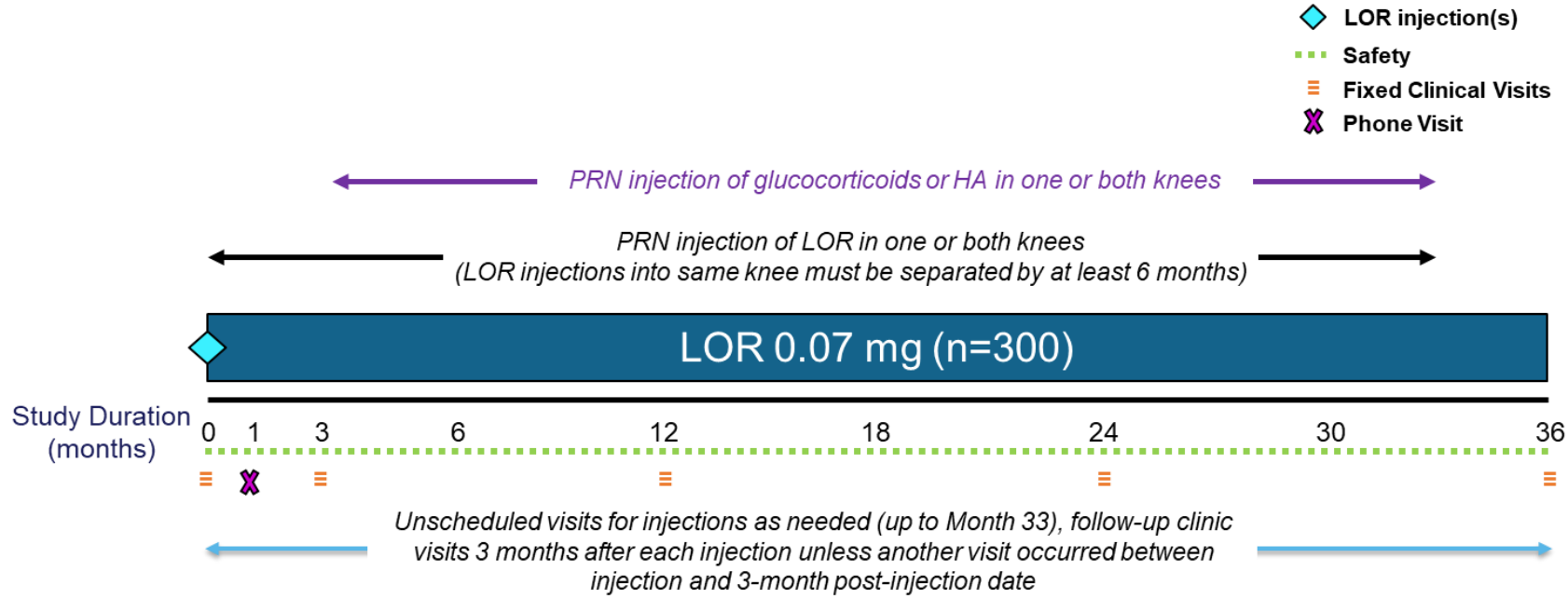
- Between Day 1 and Month 3, subjects are prohibited from receiving any injections other than LOR into either knee.
- Subjects may receive injections of glucocorticoid or HA into one or both knees, as clinically indicated, at any time between Month 3 and Month 33 with the restriction that glucocorticoid and HA injections must be performed in accordance with USPI; these injections can occur at Unscheduled Injection Visits, 3-Month Post-Injection Follow-Up Visits, or at the Months 3, 12, or 24 visits after the completion of visit assessments.
    - For subjects who receive HA as a series of injections, the first injection can occur at an Unscheduled Injection Visit, 3-Month Post-Injection Follow-Up Visit, or at the Months 3, 12, or 24 visits after the completion of visit assessments. The subsequent injections in the series should be entered into the database as Unscheduled Visits (PRO measurements and functional tests do not need to be performed at these visits).

General Injection Guidelines:

- If receiving an injection for the indication of OA, subjects may only be injected in the knee(s) for which OA diagnosis has been confirmed based on ACR criteria (Appendix 1). If one of the subject's knees did not fulfill ACR criteria at Screening, knee OA based on these criteria must be confirmed in that knee prior to the first injection at any time in the study.
- Following each injection that occurs at or after the Month 3 visit, subjects will return to the clinic for a 3-Month Post-Injection Follow-Up Visit unless another visit has occurred between the injection and the 3-month post-injection date.
    - If a subject receives a glucocorticoid or HA injection for the indication of OA at a location different than the study site, a 3-Month Post-Injection Follow-Up Visit should be scheduled unless another visit has occurred between the injection and the 3-month post-injection date.

    - For subjects who receive HA as a series of injections, the first visit will be used to determine when the 3-Month Post-Injection Follow-Up Visit should occur.
- Bilateral injections are allowed and may occur at the same visit, but only one injection per knee can occur at any visit.
- Prior to the injection(s), the Investigator should evaluate the subject for suitability to receive the injection(s). The subject should not have any condition that, in the opinion of the Investigator, constitutes a risk or contraindication for the injection(s).
- Any knee that has undergone a partial or total knee replacement should not be injected.

Figure 1. Overview of study design



Abbreviations: HA = hyaluronic acid; LOR = lorecivivint; PRN = pro re nata (when necessary)

Inclusion/ Exclusion Criteria:

Criteria for Inclusion:

1. Males and females between 40 and 80 years of age, inclusive, in general good health apart from their knee OA
2. Femorotibial OA by standard American College of Rheumatology (ACR) criteria (Appendix 1); knee OA is not to be secondary to any rheumatologic conditions (e.g., rheumatoid arthritis).
3. Pain compatible with knee OA for at least 26 weeks prior to the Screening Visit
4. Negative drug test for amphetamine, buprenorphine, cocaine, methadone, opiates, phencyclidine (PCP), propoxyphene, barbiturates, and benzodiazepine, unless any of these drugs are prescribed by a physician to treat a specific condition
5. Subjects with depression or anxiety must be clinically stable for at least 12 weeks prior to the Screening Visit and, if on treatment for depression or anxiety, be on at least 12 weeks of stable therapy
6. Full understanding of the requirements of the study and willingness to comply with all study visits and assessments
7. Subjects must have read and understood the informed consent form (ICF), and must have signed and dated it prior to any study-related procedure being performed

Criteria for Exclusion:

1. Pregnant women, breastfeeding women, and women who are not post-menopausal (defined as 12 months with no menses without an alternative medical cause) or permanently surgically sterile (includes hysterectomy, bilateral salpingectomy, and bilateral oophorectomy) who have a positive or indeterminate pregnancy test result at Screening and Day 1
2. Women who are not post-menopausal or permanently surgically sterile who are sexually active, and who are not willing to use birth control as outlined in Section 5.3.1 during the study period
3. Any surgery (e.g., arthroscopy) in either knee within 26 weeks prior to Day 1
4. Intra-articular (IA) injection into either knee with a therapeutic aim including, but not limited to, hyaluronic acid (HA), platelet-rich plasma (PRP), and stem cell therapies within 26 weeks prior to Day 1 or IA glucocorticoids within 12 weeks prior to Day 1
5. Previous treatment with lorecivivint
6. Participation in a clinical research trial that included the receipt of an investigational product (IP) or any experimental therapeutic procedure within 4 weeks or 5 half-lives, whichever is greater, prior to the Screening Visit, or planned participation in any such trial

7. Planned surgery scheduled during the study period that, in the Investigator's opinion, would interfere with study conduct or evaluation, not including non-surgical invasive procedures conducted for a diagnostic or therapeutic purpose scheduled during the study period (refer to Section 7.6)
8. 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
9. Any comorbid condition that could affect study endpoint assessments of the knee, including, but not limited to, rheumatoid arthritis, psoriatic arthritis, systemic lupus erythematosus, gout or pseudogout, and fibromyalgia
10. Any contraindications for an IA injection in the knee(s) to be injected at Day 1 in the opinion of the Investigator
11. History of mania, bipolar disorder, psychotic disorder, schizophrenia, or schizoaffective disorder
12. Any known active infections, including urinary tract infection, upper respiratory tract infection, sinusitis, suspicion of IA infection, hepatitis B or hepatitis C infection, and/or infections that may compromise the immune system such as human immunodeficiency virus (HIV) at Day 1
13. Subjects who have a current or pending disability claim, workers' compensation, or litigation(s) that may compromise response to treatment
14. Subjects who are immediate family members (spouse, parent, child, or sibling; biological or legally adopted) of personnel directly affiliated with the study at any investigative site, or are directly affiliated with the study at any investigative site
15. Subjects employed by Biosplice Therapeutics, Inc., or any of its affiliates or development partners (that is, an employee, temporary contract worker, or designee) responsible for the conduct of the study, or who are immediate family members (spouse, parent, child, or sibling; biological or legally adopted) of said employees responsible for the conduct of the study

Population: Approximately 300 subjects with knee OA

Phase: 3b

Number of Sites enrolling participants: Approximately 30 investigational centers

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 breakdown and enhances formation of cartilage through effects on progenitor cells and chondrocytes resident in the joint.
Study Duration:	Approximately 5 years Estimated date first subject consented: June 2021 Estimated date last subject completed: June 2026
Participant Duration:	Approximately 3 years
Statistical Methods:	**Sample Size:** The sample size is not based on statistical considerations. A sample size of 300 subjects is a reasonable sample size to observe patterns of use of LOR and other IA injections. **General approach:** For continuous variables, number of subjects in the analysis, mean, standard deviation (SD), median, minimum, and maximum will be reported. All categorical endpoints will be summarized using frequencies and percentages. **Safety Analysis:** Safety assessments include physical examinations, vital signs, clinical laboratory tests, collection of AEs and concomitant medications, and general medical evaluations. No formal statistical analyses are planned. Safety will be evaluated based on the incidence, seriousness, and severity of AEs, and by changes in clinical laboratory parameters and vital signs, relative to pre-injection. **Efficacy Analysis:** Treatment response over time will be characterized. Response will be defined as both actual change as well as meeting response criteria. Additionally, outcomes will be characterized across time for those subjects seeking additional injections. Frequency of injections will also be summarized.

2. INTRODUCTION

2.1 STUDY RATIONALE

Clinical studies of LOR to date have only administered LOR into one knee (the "target knee") and on a fixed schedule (given once, given once every 6 months, or given every 12 months). In addition, in previous safety and efficacy studies, other injectable agents, specifically glucocorticoids and hyaluronic acid (HA), were prohibited. This study is being conducted to gain an understanding of how LOR is used when the previous clinical trial restrictions (i.e., unilateral use only, fixed injection schedule, and use with other agents) are removed, which should be more representative of real-life clinical practice if LOR were to be approved. This study will also provide information about safety and efficacy with longer-term use, as LOR has not previously been used in studies of more than 2 years in duration.

2.2 BACKGROUND INFORMATION

OA is the most common form of arthritis and chronic joint disorder in man (Katz, Arant, and Loeser 2021). The exact causes of OA are unknown, but it is recognized as a disruption of homeostasis affecting the whole joint (Loeser et al. 2012). 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 stiffer and more immobile over time (Lawrence, Felson et al. 2008).

An estimated 10% to 15% of all adults aged over 60 have some degree of OA, with prevalence higher among women than men (WHO Department of Chronic Diseases and Health Promotion). The prevalence of OA is increasing due to population aging and an increase in related factors such as obesity. According to the United Nations, by 2050 people aged over 60 will account for more than 20% of the world's population (World population to 2300). Of that 20%, a conservative estimate of 15% will have symptomatic OA, and one-third of these people will be severely disabled. This means that by 2050, 130 million people will suffer from OA worldwide (Maiese 2016). The prevalence of knee OA in US adults was an estimated 10.2%, totaling 24.7 million individuals in 2019 (IHME 2021). Movement limitations are present in about 80% of persons with OA, and 25% are unable to perform major activities of daily living (Neogi 2013).

Non-pharmacological management of OA (e.g., education, exercise, weight reduction) is considered core to OA management, but improvements may not provide sufficient relief and can be difficult to sustain (Gelse, Ekici et al. 2012). Pharmacological management, specifically nonsteroidal anti-inflammatory drug (NSAID) use, has shown only modest benefits on clinical outcomes and are not recommended for those who are frail or with cardiac or gastrointestinal comorbidities (Bannuru et al. 2019). Oral and transdermal opioid use are not recommended for the treatment of OA, due both to the limited therapeutic benefit and the potential for dependency (Hochberg et al. 2012). Finally, IA injections of corticosteroids may offer short-term pain relief, but may have detrimental long-term effects. IA hyaluronic acids have questionable efficacy in treatment of knee OA.

One area of significant unmet need in the treatment of OA is the lack of pharmacological agents with disease-modifying properties. The development of agents with measurable, reliable disease-modifying effects that also provide safe symptom relief has been identified as a significant need

in the treatment of OA (Gelse et al. 2012). Such agents could also potentially delay or reduce the need for joint replacement surgery, an end-stage option that may not be suitable for OA patients in whom surgical risk is deemed too high.

The Wnt pathway is crucial in joint homeostasis and plays a central role in the initiation and progression of OA pathology (Monteagudo and Lories 2017). Mechanical stress/trauma on the joint has been shown to increase Wnt pathway signaling (Thomas et al. 2011) which, in turn, promotes cartilage degradation, tissue remodeling, and inflammation (Conaghan et al. 2019; Zhu et al. 2008; Zhu et al. 2009). These effects are associated with initiation and progression of disease in animal models of OA (Zhou et al. 2017). Moreover, Wnt signaling is upregulated in the joint tissue of patients with OA (Luyten, Tylzanowski, and Lories 2009). Thus, modulation of the Wnt pathway offers a potential disease modifying approach for OA treatment.

LOR is a small-molecule inhibitor of cdc-like kinases (CLKs) and dual-specificity tyrosine kinases (DYRKs), delivered as an injection into the affected joint, where it locally reduces Wnt signaling and inflammation to ameliorate OA progression and symptoms, and protect joint health. Preclinical studies indicate that therapeutic modulation of Wnt signaling by LOR is a consequence of direct inhibition of CLK2-dependent alternative splicing of Wnt pathway genes. This leads to cartilage protection and chondrocyte differentiation in multiple laboratory models of OA. Concomitant inhibition of DYRK1A both enhances Wnt pathway modulation and reduces inflammatory cytokine production. Together, these observations indicate a mechanism of action whereby direct inhibition of CLK2 and DYRK1A activity by LOR leads to combined modulation of both inflammation and the Wnt pathway to provide symptom improvement and cartilage protection, and potentially promote chondrogenesis.

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

Lorecivivint

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

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.

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 SAEs that were considered related to study medication. In previous trials, LOR was safe and well tolerated at single doses of 0.23 mg per injection, exceeding the 0.07 mg single dose used in the current study. 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 Monitors per the Medical Monitoring Plan. In addition, appropriate review of data 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 assess the safety and tolerability of lorecivivint (LOR) alone and in addition to other standard of care intra-articular (IA) treatments in subjects with knee osteoarthritis (OA).

Secondary:
The secondary objectives of the study are to evaluate:

1. The efficacy of LOR assessed using patient reported outcomes (PROs) and functional measures
2. The effects of LOR injections on health-related quality of life (HRQoL) and work productivity
3. Treatment patterns of LOR, glucocorticoid, and hyaluronic acid (HA) injections in both knees of subjects with knee OA

3.2 STUDY ENDPOINTS

3.2.1 SAFETY ENDPOINTS

1. Adverse events (AEs) and serious adverse events (SAEs) (incidence, severity, and relationship to LOR)
2. Clinically significant changes in clinical laboratory measures and vital signs, as assessed by the Investigator

3.2.2 EFFICACY ENDPOINTS

1. Change from baseline in pain numeric rating scale (NRS) score for the knee at Month 3 and annual visits, at each Unscheduled Injection Visit, and 3 months after each injection
2. Change from baseline in Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) physical function subscore (WOMAC Function) at Month 3 and annual visits, at each Unscheduled Injection Visit, and 3 months after each injection
3. Change from baseline in WOMAC total score and pain and stiffness subscores at Month 3 and annual visits, at each Unscheduled Injection Visit, and 3 months after each injection
4. Change from baseline in the Knee Injury and Osteoarthritis Outcome Score (KOOS) subscales of Symptoms, Function (Sports), and Quality of Life at Month 3 and annual visits, at each Unscheduled Injection Visit, and 3 months after each injection
5. Change from baseline in HRQoL (as measured using the 12-Item Short Form Health Survey [SF-12]) and Work Productivity and Activity Impairment (WPAI) at Month 3 and annual visits
6. Patient-Acceptable Symptom State (PASS) at Month 3 and annual visits
7. Change from baseline in 40-meter walk test time at Month 3 and annual visits, at each Unscheduled Injection Visit, and 3 months after each injection (at a subset of sites)
8. Change from baseline in the Timed Up and Go (TUG) test time at Month 3 and annual visits, at each Unscheduled Injection Visit, and 3 months after each injection (at a subset of sites)
9. Frequency of and interval between knee IA injections

4. STUDY DESIGN

4.1 DESCRIPTION OF THE STUDY DESIGN

This study will be a multicenter, open-label study. Up to 300 subjects will be enrolled. After a screening period of up to 14 days, subjects will receive an IA injection of 0.07 mg LOR into one or both knees, followed by a 36-month evaluation period. Clinic visits will be scheduled at Day 1, and Months 3, 12, 24, and 36 (End of study [EOS]) or Early Termination (ET) for completion of all PRO measurements (WOMAC, KOOS, pain NRS, SF-12, PASS, WPAI), functional tests (40-meter walk test and TUG test at a subset of sites), and safety evaluations. On Day 1, the Charlson Comorbidity Index and Widespread Pain Index and Symptom Severity [WPI&SS] assessments will also be completed. A phone visit for safety follow-up will occur 4 weeks after the injection on Day 1. Refer to Figure 1 for an overview of the study design. Subjects may also have Unscheduled Injection Visits for additional injections of LOR, glucocorticoid, or HA, as described in the OA Treatment Algorithm section below. Following each injection, subjects will return to the clinic for 3-Month Post-Injection Follow-Up Visits, unless another visit has

occurred between the injection and the 3-month post injection date. At these injection visits and 3-Month Post-Injection Follow-Up Visits, subjects will complete PRO measurements and functional tests (at a subset of sites). Specific timing of protocol procedures is described in the Schedule of Events Table (Section 7.3.7).

This study will be conducted at approximately 30 investigational centers.

Recording of AEs will start following study injection on Day 1 and continue at all subsequent in-person and phone visits until the subject completes Month 36 (EOS)/ET. All AEs, whether volunteered, elicited, or noted during examination, will be recorded throughout the study.

4.1.1 OA TREATMENT ALGORITHM

LOR Injections:

- On Day 1, after subject eligibility has been confirmed and subjects complete all PRO measurements and functional tests (at applicable sites), subjects will receive an IA injection of 0.07 mg LOR into one or both knees. Bilateral injections of 0.07 mg LOR are allowed.
- Subjects may receive additional injections of LOR into one or both knees, as clinically indicated, at any time between Day 1 and Month 33 with the restriction that LOR injections into the same knee must be separated by at least 6 months; these injections can occur at Unscheduled Injection Visits, 3-Month Post-Injection Follow-Up Visits, or at the Months 3, 12, or 24 visits after the completion of visit assessments.
- *For LOR injections after Day 1:* Within 6 months of any knee surgery, LOR may not be injected in the affected knee without consultation with and documented approval from the Medical Monitor.

Glucocorticoid and HA Injections:

- Between Day 1 and Month 3, subjects are prohibited from receiving any injections other than LOR into either knee.
- Subjects may receive injections of glucocorticoid or HA into one or both knees, as clinically indicated, at any time between Month 3 and Month 33 with the restriction that glucocorticoid and HA injections must be performed in accordance with US prescribing information (USPI); these injections can occur at Unscheduled Injection Visits, 3-Month Post-Injection Follow-Up Visits, or at the Months 3, 12, or 24 visits after the completion of visit assessments.
    - For subjects who receive HA as a series of injections, the first injection can occur at an Unscheduled Injection Visit, 3-Month Post-Injection Follow-Up Visit, or at the Months 3, 12, or 24 visits after the completion of visit assessments. The subsequent injections in the series should be entered into the database as Unscheduled Visits (PRO measurements and functional tests do not need to be performed at these visits).

General Injection Guidelines:

- If receiving an injection for the indication of OA, subjects may only be injected in the knee(s) for which OA diagnosis has been confirmed based on ACR criteria (Appendix 1). If one of the subject's knees did not fulfill ACR criteria at Screening, knee OA based on

these criteria must be confirmed in that knee prior to the first injection at any time in the study.

- Following each injection that occurs at or after the Month 3 visit, subjects will return to the clinic for a 3-Month Post-Injection Follow-Up Visit unless another visit has occurred between the injection and the 3-month post-injection date.
    - If a subject receives a glucocorticoid or HA injection for the indication of OA at a location different than the study site, a 3-Month Post-Injection Follow-Up Visit should be scheduled unless another visit has occurred between the injection and the 3-month post-injection date.
    - For subjects who receive HA as a series of injections, the first visit will be used to determine when the 3-Month Post-Injection Follow-Up Visit should occur.
- Bilateral injections are allowed and may occur at the same visit, but only one injection per knee can occur at any visit.
- Prior to the injection(s), the Investigator should evaluate the subject for suitability to receive the injection(s). The subject should not have any condition that, in the opinion of the Investigator, constitutes a risk or contraindication for the injection(s).
- Any knee that has undergone a partial or total knee replacement should not be injected.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

This Phase 3b study, SM04690-OA-17, is a multicenter, open-label study of a single concentration of 0.07 mg LOR per 2 mL injection injected into the knee joint(s) of OA subjects at Day 1. Subjects and Investigators will be able to choose to give additional injections of LOR (between Day 1 and Month 33) or glucocorticoids or HA (between Month 3 and Month 33) into either knee, as clinically warranted, with both safety and efficacy follow-up visits performed. This is being conducted as an open-label study with limited restrictions on how LOR is to be used to more closely represent how LOR would be used in clinical practice post-approval.

4.3 JUSTIFICATION FOR DOSE

The dose of 0.07 mg LOR was selected for this study based on evidence available from nonclinical studies and 3 completed clinical studies (SM04690-01, SM04690-OA-02, and SM04690-OA-04). Administration of the 0.07 mg dose resulted in the most consistently positive responses compared to control when the outcome measures of pain NRS, WOMAC Function, and medial joint space width were assessed.

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 last visit shown in the Schedule of Events Table (Section 7.3.7).

5. STUDY POPULATION

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

5.1 PARTICIPANT INCLUSION CRITERIA

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

1. Males and females between 40 and 80 years of age, inclusive, in general good health apart from their knee OA
2. Femorotibial OA by standard American College of Rheumatology (ACR) criteria (Appendix 1); knee OA is not to be secondary to any rheumatologic conditions (e.g., rheumatoid arthritis).
3. Pain compatible with knee OA for at least 26 weeks prior to the Screening Visit
4. Negative drug test for amphetamine, buprenorphine, cocaine, methadone, opiates, phencyclidine (PCP), propoxyphene, barbiturates, and benzodiazepine, unless any of these drugs are prescribed by a physician to treat a specific condition
5. Subjects with depression or anxiety must be clinically stable for at least 12 weeks prior to the Screening Visit and, if on treatment for depression or anxiety, be on at least 12 weeks of stable therapy
6. Full understanding of the requirements of the study and willingness to comply with all study visits and assessments
7. Subjects must have read and understood the informed consent form (ICF), and must have signed and dated it prior to any study-related procedure being performed

5.2 PARTICIPANT EXCLUSION CRITERIA

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

1. Pregnant women, breastfeeding women, and women who are not post-menopausal (defined as 12 months with no menses without an alternative medical cause) or permanently surgically sterile (includes hysterectomy, bilateral salpingectomy, and bilateral oophorectomy) who have a positive or indeterminate pregnancy test result at Screening and Day 1
2. Women who are not post-menopausal or permanently surgically sterile who are sexually active, and who are not willing to use birth control as outlined in Section 5.3.1 during the study period
3. Any surgery (e.g., arthroscopy) in either knee within 26 weeks prior to Day 1
4. Intra-articular (IA) injection into either knee with a therapeutic aim including, but not limited to, hyaluronic acid (HA), platelet-rich plasma (PRP), and stem cell therapies within 26 weeks prior to Day 1 or IA glucocorticoids within 12 weeks prior to Day 1
5. Previous treatment with lorecivivint
6. Participation in a clinical research trial that included the receipt of an investigational product (IP) or any experimental therapeutic procedure within 4 weeks or 5 half-lives, whichever is greater, prior to the Screening Visit, or planned participation in any such trial
7. Planned surgery scheduled during the study period that, in the Investigator's opinion, would interfere with study conduct or evaluation, not including non-surgical invasive procedures conducted for a diagnostic or therapeutic purpose scheduled during the study period (refer to Section 7.6)
8. 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

9. Any comorbid condition that could affect study endpoint assessments of the knee, including, but not limited to, rheumatoid arthritis, psoriatic arthritis, systemic lupus erythematosus, gout or pseudogout, and fibromyalgia
10. Any contraindications for an IA injection in the knee(s) to be injected at Day 1 in the opinion of the Investigator
11. History of mania, bipolar disorder, psychotic disorder, schizophrenia, or schizoaffective disorder
12. Any known active infections, including urinary tract infection, upper respiratory tract infection, sinusitis, suspicion of IA infection, hepatitis B or hepatitis C infection, and/or infections that may compromise the immune system such as human immunodeficiency virus (HIV) at Day 1
13. Subjects who have a current or pending disability claim, workers' compensation, or litigation(s) that may compromise response to treatment
14. Subjects who are immediate family members (spouse, parent, child, or sibling; biological or legally adopted) of personnel directly affiliated with the study at any investigative site, or are directly affiliated with the study at any investigative site
15. Subjects employed by Biosplice Therapeutics, Inc., or any of its affiliates or development partners (that is, an employee, temporary contract worker, or designee) responsible for the conduct of the study, or who are immediate family members (spouse, parent, child, or sibling; biological or legally adopted) of said employees responsible for the conduct of the study

5.3 LIFESTYLE GUIDELINES

5.3.1 CONTRACEPTION

WOMEN OF CHILDBEARING POTENTIAL

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

From the Screening Visit until Month 36 (EOS)/ET, 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 after receiving study medication should remain on an acceptable form of contraception for 1 month after their last LOR 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 enrolled in the study.

5.4.2 SUBJECT RESCREENING

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

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

Any rescreened subject must be reconsented and will be issued a new subject number. All screening procedures and assessments must be performed at rescreen; no results or data may be used from the previous screen.

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

Subjects will be informed they are free to withdraw from the study at any time and for any reason. A premature discontinuation from the study will occur when a subject who was enrolled ceases participation in this study, regardless of circumstances, prior to completion of the defined study period.

Reasons for premature discontinuation from the study might include:

- AE
- Total or partial knee replacement of the knee diagnosed with OA in unilateral OA subjects or of both knees in bilateral OA subjects
- 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 non-compliance
- 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

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

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

Total or Partial Knee Replacement Follow-Up

A subject who has had total or partial knee replacement of the knee diagnosed with OA in unilateral OA or of **both** knees in bilateral OA should be discontinued from the study. In addition to ET procedures as described above, sites should follow up with these subjects approximately 6 months after the total or partial knee replacement surgery as described in Section 7.1.1.

5.7 PREMATURE TERMINATION OR SUSPENSION OF STUDY

The Sponsor reserves the right to prematurely terminate the study at any time for administrative or safety reasons. Written notification, documenting the reason for study suspension or termination, will be provided to the Investigator, Sponsor, and regulatory authorities as appropriate. If the study is prematurely terminated or suspended, the Investigator will promptly inform the IRB and will provide the reason(s) for the termination or suspension.

6. STUDY AGENT

For glucocorticoid and/or HA injections, specific products to be used are at the discretion of the

Investigator. Refer to USPIs for product descriptions, storage conditions, and method of administration. Sites are to inform subjects of risks associated with use of the selected product(s).

6.1 STUDY AGENT DESCRIPTION

6.1.1 ACQUISITION

The Sponsor will be responsible for the manufacturing, labeling, packaging, distribution, and reconciliation of LOR, and the ultimate destruction of unused LOR.

6.1.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

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 product is supplied as vials of 2.4 mL of formulated suspension.

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

6.1.3 PRODUCT STORAGE AND STABILITY

LOR 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

Each dose of LOR should be well mixed (the drug product is a suspension) before injection. Refer to the Pharmacy Manual for detailed instructions on LOR preparation.

6.1.5 DOSING AND ADMINISTRATION

LOR will be administered as a 2 mL injection containing 0.07 mg LOR. The Investigator will administer the injection into one or both knee joints once at Day 1. Between Day 1 and Month 33, subjects may have unscheduled visits at any time for additional injections of LOR into either knee as clinically indicated, with the restriction that LOR injections into the same knee must be separated by at least 6 months.

The IA LOR injections can be done through lateral or medial (including superior/suprapatellar, midpatellar, and inferior/anterior) approaches, based on the standard practice of the Investigator and the knee examination of the subject. Although not required, the injections may be guided by ultrasound or fluoroscopy without contrast if it is the standard practice of the Investigator.

Only topical anesthetics are allowed before any IA LOR injection. Local anesthetic injections are prohibited before or concurrent with any IA LOR injection.

The 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 a small amount (0.3-0.5 mL) of joint fluid 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. Aspirations should be done with an empty sterile syringe. Using the same needle, the study medication should then be injected with a separate syringe. 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 IA LOR injections. Refer to the Pharmacy Manual for further information.

6.1.6 ROUTE OF ADMINISTRATION

LOR is to be administered as an IA injection into the knee joint.

6.1.7 STARTING DOSE AND DOSE ESCALATION SCHEDULE

Not applicable to this study.

6.1.8 DOSE ADJUSTMENTS/MODIFICATIONS/DELAYS

No dose modifications of LOR are allowed.

6.1.9 DURATION OF THERAPY

LOR is to be administered as an IA injection into one or both knee joints once at Day 1. Subjects may have unscheduled visits at any time for additional injections of LOR (between Day 1 and Month 33) or glucocorticoid or HA (between Month 3 and Month 33) into either knee as clinically indicated, with the restrictions that 1) LOR injections into the same knee must be separated by at least 6 months, and 2) glucocorticoid and HA injections must be performed in accordance with their USPIs. The subject should not have any condition that, in the opinion of the Investigator, constitutes a risk or contraindication for the injection.

6.1.10 STUDY INTERVENTION COMPLIANCE

Not applicable to this study.

6.1.11 DEVICE SPECIFIC CONSIDERATIONS

Not applicable to this study.

6.2 STUDY AGENT ACCOUNTABILITY PROCEDURES

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

- Subject number and initials
- Date that LOR was injected

- Quantity dispensed (LOR vial)
- Quantity returned/used (LOR vial)

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

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

Details regarding accountability procedures for glucocorticoid and HA supplied by the Sponsor will be provided in the Pharmacy Manual.

7. STUDY PROCEDURES AND SCHEDULE

7.1 STUDY PROCEDURES/EVALUATIONS

7.1.1 STUDY SPECIFIC PROCEDURES

Collection of Adverse Events Data

Data regarding AEs will be collected in this study. AEs are events that occur during the study that are not present before the Day 1 study injection(s), or, if present at the time of the Day 1 study injection(s), have worsened in severity during the study. AEs will be assessed at each in-person and phone visit from the time of study injection(s) on Day 1 through Month 36 (EOS)/ET.

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

In this protocol, signs and symptoms of exacerbation or worsening of 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 (knee OA) will not be considered as AEs nor captured on the AE page of the eCRF.

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

AEs will be followed until the subject's last visit or resolution, whichever comes first. Non-

serious AEs that are ongoing at the subject's last visit will be followed for 30 days after their last study injection or until resolution, whichever comes first. Resolution is defined as the return to baseline status or stabilization of the condition. At the discretion of the Medical Monitor and in consultation with the Investigator, certain non-serious AEs may be followed beyond 30 days. All SAEs will be followed until resolution.

Medical History

A medical history will be obtained at the Screening Visit with a follow-up at Month 36 (EOS)/ET to capture End Dates of any ongoing medical history collected at the Screening Visit. Medical history at the Screening Visit will include demographic data (e.g., age, race, ethnicity, payer/insurance type). In addition, medical information will also be recorded, including all (1) medical conditions and disease states that require current or ongoing therapy and (2) other medical conditions and disease states that, in the opinion of the Investigator, are relevant to the subject's study participation. Examples of medical conditions and disease states that should be considered relevant to the subject's study participation include history of current disease, medical history that confirms the eligibility criteria of the subject, and asymptomatic medical history that could become symptomatic while on the study.

Past Treatments for Knee OA Pain

Subjects will be asked at the Screening Visit about their previous or current use of the following treatments for their knee OA pain: NSAIDs, acetaminophen, opioids, IA steroids, and IA HA. For medications that have been used in the past but are no longer being used, the reason for discontinuation will also be collected on the eCRF.

Physical Examination

A general physical examination will be conducted at the Screening Visit, Day 1, and Months 12, 24, and 36 (EOS)/ET. Results of the physical examination will be noted in the source documents. Any clinically significant finding noted after the Day 1 study injection(s) should be reported as an AE.

Knee Examination

A knee examination of both knees will be conducted at the Screening Visit, Day 1, Months 3, 12, 24, and 36 (EOS)/ET, and at each Unscheduled Injection Visit and 3-Month Post-Injection Follow-Up Visit. Results of the knee examination will be noted in the source documents. Any clinically significant finding noted after the Day 1 study injection(s) should be reported as an AE.

Presence of unilateral or bilateral symptomatic knee OA will be recorded in the eCRF at the Screening Visit. Following confirmation of knee OA based on ACR criteria (Appendix 1) at the Screening Visit and any Unscheduled Injection Visit, as necessary, the date of the radiograph and the Investigator-assessed Kellgren-Lawrence (KL) grade will be recorded in the eCRF. Refer to Appendix 2 for KL Grading Scale.

Vital Signs

Vital signs will be measured by a qualified staff member at all in-person visits.

At each visit, the following vital signs will be measured:

- Body temperature
- Pulse rate
- Blood pressure (systolic and diastolic)

Any measurement that is, in the opinion of the Investigator, abnormal AND clinically significant must be recorded as an AE if found after the Day 1 study injection(s).

Height and Weight

A height measurement will be taken at the Screening Visit. Weight measurements will be taken at the Screening Visit and Months 12, 24, and 36 (EOS)/ET.

Charlson Comorbidity Index

The Charlson Comorbidity Index will be completed by the Investigator at Day 1. The Charlson Comorbidity Index is a method of assessing and categorizing a subject's comorbid conditions. The index provides a weighted score that can be used to predict short- and long-term outcomes (e.g., resource use, mortality rates).

Instructions for completion of the Charlson Comorbidity Index will be provided to sites prior to initiation of subject enrollment. Upon completion of the Charlson Comorbidity Index, the Investigator will sign or initial, then date the source document.

Patient Reported Outcome Measures

All PRO measures will be completed on paper, will be provided by the Sponsor, and may not be reproduced. Upon completion of each assessment and questionnaire, the subject will sign or initial, then date the source documents to indicate that they were reported accurately.

The following PRO measure will be completed by the subject at the Day 1 visit only:

- **Widespread Pain Index and Symptom Severity Form** - The WPI&SS assessment consists of a body map that determines a subject's areas of pain or tenderness (WPI) and symptom severity (SS) questions. The WPI&SS assessment used in this study is modified from that described in (Clauw 2014).

The following PRO measures will be completed by the subject at Day 1 and Months 3, 12, 24, and 36 (EOS)/ET:

- **12-Item Short Form Health Survey** - The SF-12 is a widely used questionnaire that relies upon subject self-reporting to measure the subject's health-related quality of life.
- **Patient Acceptable Symptom State Questionnaire** - 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."
- **Work Productivity and Activity Impairment Questionnaire** - The WPAI questionnaire is a validated instrument to assess the impact of disease on paid work and activities.

The following PRO measures will be completed by the subject at Day 1, Months 3, 12, 24, and 36 (EOS)/ET, and at each Unscheduled Injection Visit and 3-Month Post-Injection Follow-Up Visit:

- **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 both knees.
- **Knee Injury and Osteoarthritis Outcome Score** - KOOS is used to assess a subject's opinion about their knee and associated problems. Subjects will complete the KOOS subscales for Symptoms, Function (Sports), and knee-related Quality of Life. The KOOS subscales will be completed by the subject for both knees.
- **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). The pain NRS will be completed by the subject for both knees.

Functional Tests

At a subset of sites, the following functional tests will be administered to subjects by a qualified staff member at Day 1, Months 3, 12, 24, and 36 (EOS)/ET, and at each Unscheduled Injection Visit and each 3-Month Post-Injection Follow-Up Visit:

- **40-meter Walk Test** - The 40-meter walk test is a performance-based measure used to assess walking speed over the distance of 40 meters.
- **Timed Up and Go Test** - The TUG test is a performance-based measure of mobility, balance, walking ability, and fall risk.

The results of each test will be recorded in the eCRF. Refer to the functional test guide for details regarding test performance and scoring (provided to select sites).

Total or Partial Knee Replacement Follow-Up

For any subjects who have a total or partial knee replacement of the knee diagnosed with OA in unilateral OA or of either knee in bilateral OA, sites should follow up with these subjects approximately 6 months after the total or partial knee replacement surgery is completed to assess outcomes of the surgery.

Note: A subject who has had total or partial knee replacement of the knee diagnosed with OA in unilateral OA or of **both** knees in bilateral OA should be discontinued from the study. See Section 5.6 for additional information.

7.1.2 STANDARD OF CARE STUDY PROCEDURES

All Investigators are to provide appropriate care to their subjects as they deem necessary, including prescribing the use of NSAIDs/acetaminophen and/or glucocorticoid and HA injections as needed; however, additional standard of care study procedures are not required by this protocol.

7.2 LABORATORY PROCEDURES/EVALUATIONS

7.2.1 CLINICAL LABORATORY EVALUATIONS

Samples for clinical laboratory analysis by the central laboratory will be collected by a qualified staff member at the Screening Visit and Months 12, 24, and 36 (EOS)/ET. Refer to the Laboratory Manual for details about collection of specimens. At a minimum, the following tests will be conducted:

- ***Chemistry panel:*** Albumin, alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen, bicarbonate, calcium, calcium (corrected total), chloride, creatinine, glucose, lactate dehydrogenase (LDH), potassium, sodium, bilirubin (total), and uric acid
- ***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 Investigator or designee must review the results of each subject's Screening Visit clinical laboratory test results prior to the Day 1 visit. The subject must not be enrolled on Day 1 if any of the Screening Visit results are outside the normal range for the laboratory AND, in the opinion of the Investigator, are indicative of a condition that should prevent the subject from participating.

The results of the clinical laboratory tests will be reported on the laboratory's standard reports. The Investigator must review all laboratory reports in a timely manner, noting "not clinically significant" (NCS) or comment on the clinical significance of any result that is outside the normal range for the laboratory, then date and initial the report. The Investigator must report all laboratory results that are BOTH outside the normal range for the laboratory AND, in the opinion of the Investigator, are clinically significant. If any abnormal, clinically significant laboratory measure is found before study injection on Day 1 that, in the opinion of the Investigator, is not indicative of a condition that should prevent the subject from participating in the study, it should be reported as medical history. Any abnormal, clinically significant AE that is found after Day 1 study injection should be reported as an AE.

7.2.2 OTHER ASSAYS OR PROCEDURES

Pregnancy Test

A serum-based pregnancy test will be performed on WOCBP at the Screening Visit and a urine-based pregnancy test will be performed on WOCBP at Day 1 and Month 36 (EOS)/ET. Results from the Screening Visit and Day 1 pregnancy tests will be utilized to determine subject eligibility.

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

Drug Test

A urine sample for drug testing will be collected at the Screening Visit. The urine drug test will identify amphetamine, buprenorphine, cocaine, methadone, opiates, PCP, propoxyphene, barbiturates, and benzodiazepine. Results from the drug test will be utilized to determine subject eligibility.

7.2.3 SPECIMEN PREPARATION, HANDLING, AND STORAGE

Refer to the Laboratory Manual for the central laboratory.

7.2.4 SPECIMEN SHIPMENT

Refer to the Laboratory Manual for the central laboratory.

7.3 STUDY SCHEDULE

7.3.1 SCREENING

Screening Visit

The Screening Visit must occur within 14 days prior to Day 1. The screening visit window begins with participant signature of the study informed consent.

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. After written informed consent is obtained, the subject will be assigned a subject number.

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

- Documentation of demographic information, including date of birth, sex, race, ethnicity, and payer/insurance type
- Documentation of current and past medical history including prior procedures and non-drug therapies, documentation of current medications, and review of prior medications excluded by the protocol
- Documentation of past treatments for knee OA pain
- Assessment/confirmation of diagnosis of knee OA based on ACR criteria (Appendix 1) for both knees
- Physical examination, including knee examination of both knees
- Height and weight measurements

- Pregnancy test (serum-based) for WOCBP
- Vital sign measurements (temperature, pulse rate, and blood pressure)
- Urine drug test
- Collection of samples for clinical laboratory tests

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 ENROLLMENT

Day 1

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

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

- Documentation of current medications, and review of prior medication excluded by the protocol
- Pregnancy test (urine-based) for WOCBP

Results from the Screening Visit and Day 1 evaluations will be compared with inclusion/exclusion criteria to determine subject eligibility. Eligible subjects will then be enrolled in the study. The following procedures and assessments will be performed at Day 1 following enrollment:

- Physical examination, including knee examination of both knees
- Vital sign measurements (temperature, pulse rate, and blood pressure)
- WPI&SS assessment
- Charlson Comorbidity Index assessment
- WOMAC questionnaire
- KOOS questionnaire
- Pain NRS
- SF-12 questionnaire
- PASS questionnaire
- WPAI questionnaire
- 40-meter walk test (at a subset of sites)
- TUG test (at a subset of sites)
- IA injection of LOR into one or both knees
- Collection of AE and concomitant procedures/medication data

7.3.3 FOLLOW-UP

Month 1 (Phone Visit)

The Month 1 phone visit should occur on Day 30 (with a window of ± 7 days). Sites will contact subjects to collect AE and concomitant procedures/therapies/medication data.

Month 3

The Month 3 visit should occur on Day 90 (with a window of ± 14 days).

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

- Knee examination of both knees
- Vital sign measurements (temperature, pulse rate, and blood pressure)
- WOMAC questionnaire
- KOOS questionnaire
- Pain NRS
- SF-12 questionnaire
- PASS questionnaire
- WPAI questionnaire
- 40-meter walk test (at a subset of sites)
- TUG test (at a subset of sites)
- Collection of AE and concomitant procedures/therapies/medication data

Once all study assessments are completed, and if clinically indicated, subjects may receive an injection of glucocorticoid, or HA into one or both knees, or an injection of LOR into the knee not injected on Day 1. Refer to Section 4.1.1 for restrictions and guidelines.

Months 12 and 24

The Month 12 visit should occur on Day 360 (with a window of ± 28 days) and the Month 24 visit should occur on Day 720 (with a window of ± 28 days).

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

- Collection of AE and concomitant procedures/therapies/medication data
- Physical examination, including knee examination of both knees
- Weight measurement
- Vital sign measurements (temperature, pulse rate, and blood pressure)
- WOMAC questionnaire
- KOOS questionnaire
- Pain NRS
- SF-12 questionnaire
- PASS questionnaire

- WPAI questionnaire
- 40-meter walk test (at a subset of sites)
- TUG test (at a subset of sites)
- Collection of samples for clinical laboratory tests

Once all study assessments are completed, and if clinically indicated, subjects may receive an injection of LOR, glucocorticoid, or HA into one or both knees. Refer to Section 4.1.1 for restrictions and guidelines.

7.3.4 ADDITIONAL VISITS

Unscheduled Injection Visit

Subjects may have Unscheduled Injection Visits at any time for additional injections of LOR (between Day 1 and Month 33) or glucocorticoid or HA (between Month 3 and Month 33) into one or both knees as clinically indicated. Refer to Section 4.1.1 for restrictions and guidelines.

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

- Collection of AE and concomitant procedures/therapies/medication data
- Knee examination of both knees
- Vital sign measurements (temperature, pulse rate, and blood pressure)
- WOMAC questionnaire
- KOOS questionnaire
- Pain NRS
- 40-meter walk test (at a subset of sites)
- TUG test (at a subset of sites)
- IA injection of LOR, glucocorticoid, or HA into the knee(s)

Note: PRO measurements (WOMAC, KOOS, and pain NRS) and functional tests (40-meter walk test and TUG test) do not need to be completed at this visit if they were completed within 2 weeks prior.

3-Month Post-Injection Follow-Up Visit

This visit should occur 90 days after any Unscheduled Injection Visit or after any IA glucocorticoid or HA injection occurring at a location different than the study site (with a window of ± 14 days) unless another visit has occurred between the injection and the 3-month post injection date.

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

- Collection of AE and concomitant procedures/therapies/medication data
- Knee examination of both knees
- Vital sign measurements (temperature, pulse rate, and blood pressure)
- WOMAC questionnaire

- KOOS questionnaire
- Pain NRS
- 40-meter walk test (at a subset of sites)
- TUG test (at a subset of sites)

Once all study assessments are completed, and if clinically indicated, subjects may receive an injection of LOR, glucocorticoid, or HA into one or both knees. Refer to Section 4.1.1 for restrictions and guidelines.

7.3.5 FINAL STUDY VISIT

Month 36 End of Study

The Month 36 visit should occur on Day 1080 (with a window of ± 28 days).

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

- Collection of AE and concomitant procedures/therapies/medication data
- Physical examination, including knee examination of both knees
- Weight measurement
- Pregnancy test (urine-based) for WOCBP
- Vital sign measurements (temperature, pulse rate, and blood pressure)
- WOMAC questionnaire
- KOOS questionnaire
- Pain NRS
- SF-12 questionnaire
- PASS questionnaire
- WPAI questionnaire
- 40-meter walk test (at a subset of sites)
- TUG test (at a subset of sites)
- Collection of samples for clinical laboratory tests

7.3.6 EARLY TERMINATION VISIT

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

- Collection of AE and concomitant procedures/therapies/medication data
- Physical examination, including knee examination of both knees
- Weight measurement
- Pregnancy test (urine-based) for WOCBP
- Vital sign measurements (temperature, pulse rate, and blood pressure)

- WOMAC questionnaire
- KOOS questionnaire
- Pain NRS
- SF-12 questionnaire
- PASS questionnaire
- WPAI questionnaire
- 40-meter walk test (at a subset of sites)
- TUG test (at a subset of sites)
- Collection of samples for clinical laboratory tests

Note: PRO measurements (WOMAC, KOOS, pain NRS, SF-12, PASS, WPAI) and functional tests (40-meter walk test and TUG test) do not need to be completed at this visit if they were completed within 2 weeks prior.

7.3.7 SCHEDULE OF EVENTS TABLE

Schedule of Study Procedures	**Screening** (Day -14 to Day -1)	**Day 1**[a]	**Month 1 (Phone)** (Day 30 ± 7 days)	**Month 3** (Day 90 ± 14 days)	**Months 12 and 24** (Days 360 and 720 ± 28 days)	**Unscheduled Injection Visit**[b]	**3-Month Post-Injection Follow-Up Visit**[c] (± 14 days)	**Month 36 (EOS)** (Day 1080 ± 28 days)/ **ET**[d]
Informed consent	X							
Inclusion & exclusion criteria	X	X						
Demographics	X							
Medical history	X							X[e]
Current and prior procedures/medications	X	X						
Past treatments for knee OA pain	X							
Pregnancy test[f]	X	X						X
Urine drug test	X							
Injection into knee[g]		X[h]				X		
Physical examination	X	X			X			X
Knee examination	X	X		X	X	X	X	X
Weight	X				X			X
Height	X							
Vital signs	X	X		X	X	X	X	X
Clinical laboratory sampling	X				X			X
WPI&SS		X						
Charlson Comorbidity Index		X						
WOMAC		X		X	X	X	X	X
KOOS		X		X	X	X	X	X
Pain NRS		X		X	X	X	X	X

Schedule of Study Procedures	**Screening** (Day -14 to Day -1)	**Day 1**[a]	**Month 1 (Phone)** (Day 30 ± 7 days)	**Month 3** (Day 90 ± 14 days)	**Months 12 and 24** (Days 360 and 720 ± 28 days)	**Unscheduled Injection Visit**[b]	**3-Month Post-Injection Follow-Up Visit**[c] (± 14 days)	**Month 36 (EOS)** (Day 1080 ± 28 days)/ **ET**[d]
SF-12		X		X	X			X
PASS Question		X		X	X			X
WPAI		X		X	X			X
40-meter walk test[i]		X		X	X	X	X	X
TUG test[i]		X		X	X	X	X	X
AEs & concomitant procedures[j]/ therapies/medications		X	X	X	X	X	X	X

[a] All Day 1 procedures should be performed prior to study medication injection except for collection of AE and concomitant procedures/medication data.
[b] The Unscheduled Injection Visit may only occur between Day 1 and Month 33 if the subject is receiving an IA LOR injection, or between Month 3 and Month 33 if the subject is receiving an IA glucocorticoid or HA injection. PRO measurements (WOMAC, KOOS, and pain NRS) and functional tests (40-meter walk test and TUG test) do not need to be completed at the Unscheduled Injection Visit if they were completed within 2 weeks prior.
[c] This visit should occur 90 days after the Unscheduled Injection Visit or any IA glucocorticoid or HA injection occurring at a location different than the study site (with a window of ± 14 days) unless another visit has occurred between the injection and the 3-month post injection date.
[d] If possible, the ET visit should be performed within 14 days of subject premature withdrawal or termination. PRO measurements (WOMAC, KOOS, pain NRS, SF-12, PASS, WPAI) and functional tests (40-meter walk test and TUG test) do not need to be completed at the ET visit if they were completed within 2 weeks prior.
[e] Review medical history to capture End Date(s), if applicable, of any ongoing medical history(ies) collected at the Screening Visit.
[f] A serum pregnancy test will be performed on WOCBP at the Screening visit and a urine pregnancy test will be performed on WOCBP at Day 1 and Month 36 (EOS)/ET.
[g] At Unscheduled Injection Visits, 3-Month Post-Injection Follow-Up Visits, or at Months 3, 12, or 24 (after completion of all visit assessments), subjects may receive LOR, glucocorticoid, or HA in either knee. Refer to the OA Treatment Algorithm in Section 4.1.1 for further details.
[h] Subjects are to receive an IA injection of LOR into one or both knees on Day 1.
[i] Functional tests will only be performed at a subset of sites.
[j] For any subjects who have a total or partial knee replacement of the knee diagnosed with OA in unilateral OA or of either knee in bilateral OA, sites should follow up with these subjects approximately 6 months after the total or partial knee replacement surgery is completed to assess outcomes of the surgery.

7.4 JUSTIFICATION FOR SENSITIVE PROCEDURES

Not applicable for this study.

7.5 CONCOMITANT MEDICATIONS, TREATMENTS, AND PROCEDURES

Details regarding the name, indication, route of administration, dose, and frequency of all medications taken within 30 days prior to the Screening Visit through Month 36 (EOS)/ET will be recorded in the "Prior and Concomitant Medications" eCRF. "All medications" should include prescription, over-the-counter, supplements, and herbal or alternative medications, as well as glucocorticoid and HA injections for indications other than OA.

Procedures or non-drug therapies that are ongoing, new, or modified at or after the Screening Visits must be recorded on the "Procedures and Non-Drug Therapies" 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 other than LOR, glucocorticoids, and HA including 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, HA derivatives, PRP, stem cells, or other therapeutic agents into joints other than the knee is allowed.
- Drugs screened to assess eligibility (i.e., amphetamine, buprenorphine, cocaine, methadone, opiates, PCP, propoxyphene, barbiturates, and benzodiazepine) are prohibited while the subject is on study unless prescribed by a physician to treat a specific condition.
- Subjects are prohibited from participating in any other clinical research trial that includes the receipt of an IP or any experimental therapeutic procedure.

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

7.7 PROPHYLACTIC MEDICATIONS, TREATMENTS, AND PROCEDURES

Not applicable to this study.

7.8 RESCUE MEDICATIONS, TREATMENTS, AND PROCEDURES

Not applicable to this study.

7.9 PARTICIPANT ACCESS TO STUDY AGENT AT STUDY CLOSURE

Not applicable to this study.

8. ASSESSMENT OF SAFETY

8.1 SPECIFICATION OF SAFETY PARAMETERS

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

8.1.1 DEFINITION OF ADVERSE EVENTS (AE)

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

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

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

In this protocol, signs and symptoms of exacerbation or worsening of 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 (knee OA) will not be considered as AEs nor captured on the AE page of the eCRF.

8.1.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

An SAE is an AE that meets one or more of the following criteria:

- 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 that hypothetically might have caused death if it were more severe.

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

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

8.1.3 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

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

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

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

8.2 CLASSIFICATION OF AN ADVERSE EVENT

8.2.1 SEVERITY OF EVENT

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

Table 1: CDISC Definitions of Adverse Event Severity

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

8.2.2 RELATIONSHIP TO STUDY AGENT

The relationship of LOR 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 LOR or administration of the LOR 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 LOR or the LOR 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 LOR or the LOR 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 LOR or the LOR study injection.

Possibly Related

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

Probably Related

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

8.2.3 EXPECTEDNESS

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

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

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

The reporting period for AEs starts after the Day 1 study injection(s) and ends after the final study visit.

AEs will be followed until the subject's last visit or resolution, whichever comes first. Non-serious AEs that are ongoing at the subject's last visit will be followed for 30 days after their last IA injection or until resolution, whichever comes first. Resolution is defined as the return to baseline status or stabilization of the condition. At the discretion of the Medical Monitor and in consultation with the Investigator, certain non-serious AEs may be followed beyond 30 days. All SAEs 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 LOR that are both serious and unexpected to the FDA according to 21 CFR 312.32. All Investigators participating in ongoing studies with LOR 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 Sponsor 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 Sponsor 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	Famina Hemani, Executive Director, Drug Safety and Pharmacovigilance
Cellular: (858) 500-6021	
Email: *sherry.beckman@biosplice.com*	Email: *famina.hemani@biosplice.com*

8.4.3 UNANTICIPATED PROBLEM REPORTING

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

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

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

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

8.4.4 EVENTS OF SPECIAL INTEREST

Not applicable to this study.

8.4.5 REPORTING OF PREGNANCY

If a 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 subject pregnancy will be collected on a Pregnancy Report Form. Information will be collected for any pregnancy in a female subject which occurs during the study, including

perinatal and neonatal outcome. Infants resulting from such pregnancies should be followed for a minimum of 12 weeks.

8.5 STUDY HALTING RULES

Not applicable to this study.

8.6 SAFETY OVERSIGHT

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

9. CLINICAL MONITORING

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

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

Centralized data monitoring will be performed 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 which have the most potential to impact subject safety and data quality.

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

10. STATISTICAL CONSIDERATIONS

10.1 STATISTICAL AND ANALYTICAL PLANS

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

10.2 STATISTICAL HYPOTHESES

No formal hypotheses are being tested in this study.

10.3 ANALYSIS DATASETS

Full Analysis Set (FAS): All subjects who receive a study injection.

Safety Analysis Set (SAS): All subjects who receive a study injection. In this study, FAS and SAS will be identical.

Additional analysis sets may be defined and included in the SAP.

10.4 DESCRIPTION OF STATISTICAL METHODS

10.4.1 GENERAL APPROACH

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

10.4.2 ANALYSIS OF THE SAFETY ENDPOINTS

Safety assessments will be performed on an ongoing basis throughout the study on all subjects in the SAS. Safety assessments include physical examinations, vital signs, clinical laboratory tests, collection of AEs and concomitant medications, and general medical evaluations.

Safety will be evaluated based on the incidence, severity, and seriousness of AEs and by changes in clinical laboratory parameters and vital signs relative to pre-injection. AEs may be summarized separately by study medication injected and by the injected knee(s). No formal statistical analyses are planned.

10.4.3 ANALYSIS OF THE EFFICACY ENDPOINTS

Change over time in the efficacy endpoints will be characterized for each knee and each medication using a pre-injection adjusted analysis of covariance (ANCOVA) with time and pre-injection value as covariates. Unadjusted 95% confidence intervals and *P* values will be reported for the estimated change over time from pre-injection. Percentage of subjects achieving 30%, 50%, and 70% improvement will also be summarized over time from pre-injection.

Frequency and interval of time between injections will be summarized by medication and subsequent number of injections. Efficacy will be characterized by study medication and injection number.

10.4.4 SAFETY ANALYSES

Refer to Section 10.4.2.

10.4.5 BASELINE DESCRIPTIVE STATISTICS

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

Baseline descriptive statistics will include age, sex, race, ethnicity, weight, BMI, the presence of symptomatic OA, KL grade, and insurer/payor.

10.4.6 PLANNED INTERIM ANALYSES

Not applicable to this study.

10.4.6.1 SAFETY REVIEW

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

10.4.6.2 EFFICACY REVIEW

Not applicable to this study.

10.4.7 EXPLORATORY ANALYSES

Not applicable to this study.

10.4.8 SUB-GROUP ANALYSES

No subgroup analysis is planned for this study.

10.5 SAMPLE SIZE

The sample size is not based on statistical considerations. A sample size of 300 subjects is a reasonable sample size to observe patterns of use of LOR and other IA injections.

10.6 MEASURES TO MINIMIZE BIAS

10.6.1 BLINDING PROCEDURES

This is an open-label study.

10.6.2 EVALUATION OF SUCCESS OF BLINDING

Not applicable to this study.

10.6.3 BREAKING THE STUDY BLIND/PARTICIPANT CODE

Not applicable to this study.

11. SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

The Investigator must maintain required records for all study subjects. Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data for this study will be recorded in the subject's source documents and on the eCRFs, 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), both at the site and by phone, and the date of informed consent(s) must be recorded in the source documentation
- The subject's medical and disease history before participation in the study
- The subject's basic identifying information, such as subject number, that links the subject's source documents with the eCRFs
- The results of all diagnostic tests performed, diagnoses made, therapy provided, and any other data on the condition of the subject
- All AEs
- The subject's exposure to any concomitant therapy (including start and stop dates, route of administration, and dosage)

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 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, representatives of the Sponsor, and regulatory authorities, as needed.

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

13. ETHICS/PROTECTION OF HUMAN SUBJECTS

13.1 ETHICAL STANDARD

The study will be conducted in accordance with the Declaration of Helsinki (1964), including all amendments up to and including the Brazil revision (2013). The Investigator will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Subjects of Research set forth in US 21 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 prior to starting any screening evaluations or other study-related procedures.

13.3.2 CONSENT PROCEDURES AND DOCUMENTATION

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

13.4 PARTICIPANT AND DATA CONFIDENTIALITY

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

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

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

Any information, inventions, or discoveries (whether patentable or not), innovations, suggestions, ideas, and reports made or developed by the Investigator(s) as a result of conducting this study shall be promptly disclosed to the Sponsor and shall be the sole property of the

Sponsor. The Investigator agrees, upon the Sponsor's request and at the Sponsor's expense, to execute such documents and to take such other actions, as the Sponsor deems necessary or appropriate, to obtain patents in the Sponsor's name covering any of the foregoing.

13.5 FUTURE USE OF STORED SPECIMENS AND DATA

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

14. DATA HANDLING AND RECORD KEEPING

14.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

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

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

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 prior to destroying any records associated with the study.

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

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

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

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

14.3 PROTOCOL DEVIATIONS

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

14.4 PUBLICATION AND DATA SHARING POLICY

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

15. STUDY ADMINISTRATION

15.1 STUDY LEADERSHIP

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

15.2 KEY ROLES

Medical monitor	Ismail Simsek, MD - Medical Director Biosplice Therapeutics, Inc. 9360 Towne Centre Drive San Diego, CA 92121 (858) 926-2968 *ismail.simsek@biosplice.com*

16. LITERATURE REFERENCES

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APPENDIX

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

Per American College of Rheumatology (ACR) clinical and radiographic classification criteria (Altman, Asch et al. 1986), the presence of all 3 of the following items classifies knee OA in patients:

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

Appendix 2. Kellgren-Lawrence Grading Scale

Grade 0: Normal appearance of the knee

Grade 1: Doubtful narrowing of joint space and possible osteophyte lipping

Grade 2: Definite osteophytes and possible narrowing of joint space

Grade 3: Multiple osteophytes, definite narrowing of joint space, some sclerosis, and possible deformity of bone ends

Grade 4: Large osteophytes, marked narrowing of joint space, severe sclerosis, and definite deformity of bone ends