STATISTICAL ANALYSIS PLAN

SM04690-OA-07

Study Title:	A Long-Term Extension Study Evaluating the Safety and Efficacy of Lorecivivint in Subjects with Osteoarthritis of the Knee
Protocol Number:	SM04690-OA-07
Protocol Version:	Amendment 02 Version 00, 04 May 2021
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SIGNATURE PAGE AND APPROVALS

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

Protocol Version: Amendment 02 Version 00, 04 May 2021

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

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ABBREVIATIONS

Abbreviation	Term
AE	Adverse event
ANCOVA	Analysis of covariance
ATC	Anatomical therapeutic chemical
β-CTX	β-C-terminal telopeptide
BMI	Body mass index
CDISC	Clinical Data Interchange Standards Consortium
COMP	Cartilage oligomeric matrix protein
eCRF	Electronic case report form
EOS	End of study
ET	Early termination
FAS	Full Analysis Set
mFAS	Modified Full Analysis Set
HRQOL	Health-related quality of life
IP	Investigational Product
KL	Kellgren-Lawrence
MAR	Missing-at-random
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple imputation
mJSW	Medial joint space width
MMRM	Mixed-effects model for repeated measures
NRS	Numeric rating scale
NSAID	Nonsteroidal anti-inflammatory drug
OA	Osteoarthritis
PASS	Patient Acceptable Symptom State
Pain NRS	Pain numeric rating scale
P1NP	N-terminal propeptides of procollagen type I
PPAS	Per-Protocol Analysis Set
SAE	Serious adverse event

Abbreviation	Term
SAS	Safety Analysis Set
SD	Standard deviation
SF-36	36-Item Short Form Health Survey
SI	International System of Units
SSQ2	Symptom Severity Question 2
WHODD	World Health Organization Drug Dictionary
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index
WOMAC Function	WOMAC physical function subscore
WOMAC Pain	WOMAC pain subscore
WPI	Widespread Pain Index
CM	Concomitant Medication

1. BACKGROUND

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

The exact cause of OA is unknown, but it is associated with aging and normal wear on a joint. OA is characterized by the destruction of the articular cartilage, subchondral bone alterations, and synovitis. Patients present with pain and stiffness in their joints, with joints becoming stiffer and more immobile over time (Dougados & Hochberg, 2011). OA is a leading cause of physical disability in the US (Lawrence, et al., 2008).

Non-pharmacological management of OA (e.g., education, exercise, weight reduction) can only slightly reduce symptoms in affected joints (Bannuru, Kent, & McAlindon, 2015) (McAlindon, et al., 2014). Pharmacological management, specifically nonsteroidal anti-inflammatory drug (NSAID) use, has limited impact on clinical outcomes (Bellamy, et al., 2015) (Lapane, et al., 2015). Moreover, any clinical effects are short-lived and the potential side effects (particularly of oral NSAIDs), including but not limited to, cardiac, renal, and gastrointestinal (GI) effects, limit long-term use. Opioids are also frequently used in the management of OA pain, but have numerous potential side effects, ranging from addiction, a major public health concern in the US, to increased risk of falls, especially in the elderly.

There is a significant unmet need for pharmacological agents with disease-modifying properties for the treatment of OA. Most current treatments are designed only to relieve pain and reduce or prevent the disability caused by bone and cartilage degeneration. Available drug therapies target the symptoms, but not the cause, of this disease and no treatment inhibits or reverses the degenerative structural changes that are responsible for it (Nevitt, Felson, & Lester, 2006). There is a need for pharmacological agents to treat OA that have disease-modifying properties but can also provide symptom relief (decreased pain and improved function), while still being safe to use by patients with comorbid conditions or concomitant medications (Pham, et al., 2003). Such agents could also potentially delay or reduce the need for joint replacement surgery, an end-stage option which may not be suitable for OA patients in which surgical risk is deemed too high.

In order to address the need for safe and effective pharmaceutical agents to treat osteoarthritis (OA), Biosplice is developing lorecivivint (LOR; previously SM04690), a small-molecule inhibitor of CDC-like kinases (CLKs) and dual-specificity tyrosine kinases (DYRKs), as an intra-articular (IA) injection for the treatment of pain due to OA of the knee. Lorecivivint inhibits the intranuclear kinases CLK2 and DYRK1A, and thereby potentially (a) reduces signs and symptoms of knee OA via an anti-inflammatory mechanism, (b) inhibits cartilage breakdown through effects on degradative enzymes, and (c) enhances formation of cartilage through effects on progenitor cells and chondrocytes residing in the joint. Thus, LOR has the potential to affect both structural and symptomatic mechanisms underlying OA. In a previous randomized controlled, 52-week Phase 2a trial, LOR demonstrated significant improvements compared with

placebo in pain, function, and medial joint space width (mJSW) in subjects with moderately to severely symptomatic knee OA (Yazici, et al., 2020). In clinical studies to date, LOR has been well tolerated with a safety profile similar to that of placebo.

2. OVERVIEW

This study was a multicenter study in subjects previously enrolled in study SM04690-OA-11. The first 48 weeks were single-blind and placebo-controlled while the remainder of the study was open-label and uncontrolled.

3. STUDY OBJECTIVES AND ENDPOINTS

3.1 Study Objective

The objective of this study was to evaluate the safety and efficacy of a second year as well as long-term use of LOR in subjects with knee OA.

3.2 Study Endpoints

3.2.1 Primary Efficacy Endpoint

Change from parent-study baseline medial joint space width (mJSW) in the target knee as evaluated by radiograph at Visit 3E (Week 48)

3.2.2 Secondary Efficacy Endpoints

1. Change from OA-07-study baseline medial joint space width (mJSW) in the target knee as evaluated by radiograph at Visit 3E (Week 48)
2. Change from parent-study and OA-07-study baseline OA pain in the target knee as assessed by pain NRS at Visit 3E (Week 48)
3. Change from parent-study and OA-07-study baseline OA pain in the target knee as assessed by WOMAC Pain at Visit 3E (Week 48)
4. Change from parent-study and OA-07-study baseline OA function in the target knee as assessed by WOMAC Function at Visit 3E (Week 48)
5. Change from parent-study and OA-07-study baseline OA pain in the target knee as assessed by pain NRS at Visit 2E (Week 24)
6. Change from parent-study and OA-07-study baseline OA pain in the target knee as assessed by WOMAC Pain at Visit 2E (Week 24)
7. Change from parent-study and OA-07-study baseline OA function in the target knee as assessed by WOMAC Function at Visit 2E (Week 24)

3.2.3 Safety Endpoints

1. Adverse events (AEs) and serious adverse events (SAEs) (incidence, severity, and relationship to study drug) over the course of the study up to the end of the single-blind and placebo-controlled portion of the trial (i.e., prior to Second OA-07 injection [Lorecivivint only])
2. Clinically significant changes from parent-study-baseline clinical laboratory measures and vital signs, as assessed by the Investigator, over the course of the study up to Visit 3E (Week 48)

3. Change in serum bone biomarkers (N-terminal propeptides of procollagen type I [P1NP] and β-C-terminal telopeptide [β-CTX]) from parent-study baseline, and change in a serum cartilage biomarker (cartilage oligomeric matrix protein [COMP]) from parent-study baseline at Visit 3E (Week 48)

3.2.4 Other Endpoints

1. Change from parent-study and OA-07-study baseline in medial joint space width (mJSW) as documented by radiograph of the target knee at Visit 2E (Week 24)
2. Change from parent-study and OA-07-study baseline OA pain, function, and stiffness as a composite outcome measure as assessed by WOMAC Total score and Stiffness at Visit 2E (Week 24) and Visit 3E (Week 48)
3. Change from parent-study and OA-07-study baseline in mJSW, pain NRS, WOMAC Pain, and WOMAC Function at Visit 6E (Week 100) compared to test values (carry forward and progression assumptions) derived from the change from baseline estimates from the Placebo group at Visit 3E (Week 48)
4. Change from parent-study baseline health-related quality of life (HRQOL) as assessed by the 36-Item Short Form Health Survey (SF-36) at Visit 3E (Week 48)
5. Percentage of subjects who consider themselves to be in Patient Acceptable Symptom State (PASS) at Visit 3E (Week 48)

4. OVERALL STUDY DESIGN AND PLAN

This study was a multicenter study in subjects previously enrolled in study SM04690-OA-11. The first 48 weeks were single-blind and placebo-controlled while the remainder of the study was open-label and uncontrolled. At Visit 1E (Day 1) subjects received a single dose of LOR or placebo injected into the target knee joint as treated in the SM04690-OA-11 study. On and after Visit 3E (Week 48) subjects only received LOR injections.

4.1 Changes to Overall Study Design and Plan

The sponsor elected to administratively terminate this study. All active subjects were requested to continue the study until they completed Visit 6E (Week 100); subjects injected at this visit were followed-up via phone call 10 days (+/-3 days) for safety data collection. Subjects that had already completed their Visit 6E (Week 100) were asked to schedule a termination visit as soon as possible. All procedures for the termination visit should be performed; however, as provided in the protocol, an additional X-ray was not required if a subject had an X-ray taken within the 12 weeks prior to their termination visit.

4.2 Selection of Study Population

The study population included subjects who completed the SM04690-OA-11 study. Complete inclusion/exclusion criteria are available in the study protocol.

4.3 Method of Treatment Assignment and Randomization

Subjects were randomized in the SM04690-OA-11 study. Each subject maintained the same treatment assignment of LOR or placebo as in the parent study at Visit 1E (Day 1). At Visit 3E

(Week 48) and for any subsequent injections until the Termination Visit, all subjects received LOR injection(s).

4.4 Treatment Blinding

Subjects consented in this study were previously treated with an IA injection of either LOR or placebo in their target knee in the SM04690-OA-11 parent study that was double-blinded. The blind for the subject's previous treatment with either LOR or placebo will be maintained in this study for Investigators, site personnel, and subjects only. Sponsor was unblinded to treatment assignment once the database from the parent study was locked. At Visit 1E (Day 1), preparation of LOR or placebo for injection and the administration of the injections were to be performed by an Unblinded Investigator who had minimal contact with the subject for other aspects of the study. At Visit 3E (Week 48) and for any subsequent injections, the LOR injections did not need to be performed by a designated Unblinded Investigator due to the open-label nature of the remaining portion of the study.

4.5 Minimization of Missing Data

4.5.1 Collection of Clinical Outcomes

Clinical outcomes data were collected on paper at each applicable study visit. Upon completion of each assessment and questionnaire, the subjects were to sign or initial, then date the source documents to indicate that they were reported accurately.

4.5.2 Rescue Medication

Subjects were allowed to use NSAIDs and/or acetaminophen for pain relief as needed (see Protocol Section 7.8). If a subject's clinical condition significantly deteriorated (defined as experiencing significant pain that cannot be satisfactorily controlled using NSAIDs and/or acetaminophen), the Investigator would consult with the Medical Monitor(s). Sites were instructed to capture the amount and frequency of rescue medication use. This policy, in addition to quantifying NSAIDs and/or acetaminophen medication use, was designed to minimize the loss of key endpoint data and provide assessment of the medication's impact on key endpoint data.

4.5.3 Prohibited Medications, Treatments, and Procedures

During the conduct of the study, certain medications, treatments, and procedures were prohibited (see Protocol Section 7.6). The overall intent of these prohibitions was to minimize any possible bias in the assessment of the clinical trial endpoints. However, the protocol did allow for the use of these prohibited therapies if, and only if, they were required to ensure subject safety. Investigators were instructed to notify the sponsor's Medical Monitor, who would note the prohibited therapy as a protocol deviation. These deviations were categorized as major or minor depending on the nature and timing of the interventions. Subjects were not automatically discontinued based upon prohibited therapy use, allowing for continued data collection and assessment of the impact of prohibited therapy on key endpoint data.

4.5.4 Intermittent Missing Data

Ongoing programmatic surveillance of eCRFs and visit compliance using intranet dashboards during trial conduct led to the identification of subjects that were not compliant with the protocol. Sites were notified of possible non-compliant subjects and were instructed to address

any possible technical or conduct issues with these subjects prior to key endpoint data collection times. The ongoing monitoring of eCRFs was a specific strategy designed to minimize the loss of key endpoint data.

5. SAMPLE SIZE DETERMINATION

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

6. ANALYSIS POPULATIONS

6.1 Full Analysis Set

The Full Analysis Set (FAS) includes all subjects who received a study injection in the current study, analyzed as randomized in the parent study.

6.2 Per-Protocol Analysis Set

The Per-Protocol Analysis Set (PPAS) includes FAS subjects who received the correct treatment, completed Visit 6E (Week 100) and did not have any major protocol deviations in the current or parent study that might impact the evaluation of efficacy outcomes (see Section 8.2). Subjects will be analyzed as randomized for the PPAS.

6.3 Safety Analysis Set

The Safety Analysis Set (SAS) includes all subjects who received a study injection in the current study, analyzed as treated in the current study.

6.4 Modified Full Analysis Set

The Modified Full Analysis Set (mFAS) includes all FAS subjects who completed Visit 3E (Week 48).

6.5 Completers Analysis Set

The Completers Analysis Set (CAS) includes all FAS subjects who have an mJSW result at Visit 6E (Week 100) (including a parent-study baseline value).

7. GENERAL ISSUES FOR STATISTICAL ANALYSIS

7.1 General Statistical Methodology

Unless otherwise specified, efficacy analyses will be performed on the FAS, PPAS, and mFAS; general safety, bone imaging, and biomarker analyses will be performed on the SAS. The number of evaluable subjects in any analysis set may vary by endpoint/timepoint based on missing data.

For continuous variables, the outcome measure at each visit, as well as the absolute change (outcome at visit – outcome at baseline), will be summarized within each treatment group using descriptive statistics (number of subjects, mean, SD, median, minimum, and maximum). Categorical variables will be summarized with counts and percentages.

Data collected from unscheduled visits will not be included in summary tables but will be included in subject-level listings as appropriate.

7.1.1 Baseline

Parent-study baseline is defined as the last value recorded for any given parameter prior to first study medication injection in the OA-11 (parent) study.

OA-07-study baseline is defined as the last value recorded for any given parameter prior to first study medication injection in the OA-07 study and on or after Week 52 of the parent-study.

OA-07-study visit 3E baseline is defined as the value recorded for any given parameter in the OA-07 study Visit 3E.

7.1.2 Analysis of Covariance

Analysis of Covariance (ANCOVA) will be used for continuous efficacy outcome measures to test the following hypotheses:

$$H_0: (\beta_1 - \beta_0) = 0$$

$$H_A: (\beta_1 - \beta_0) \neq 0$$

In the statement above, β is the least squares estimate in the change in the continuous efficacy outcome from baseline, where β_0 is the estimate for placebo and β_1 is the estimate for the active treatment group. The models will be adjusted for baseline value of the outcome.

7.1.3 Data Handling for Patients Who Withdrew from the Study

If a subject discontinued the study, early termination assessments were performed according to the protocol. If these assessments occurred during a scheduled visit, they will be associated with that visit for the purposes of FAS analysis.

7.1.4 Imputation of Missing Data

Sensitivity analysis will be performed using multiple imputation (MI) for the primary and secondary endpoints. Missing data will be imputed based upon the observed data for each outcome under the MAR assumption following the paradigm first developed by Rubin (Shafer, 1999). The imputation will adjust for the outcome's baseline data in a regression model with data imputed independently for each timepoint. A total of 10 imputation datasets will be created and analyzed based upon accepted convention (Shafer, 1999). Error estimates of the multiple imputation itself, as well as an overall summary of the efficacy analysis, will be averaged across the 10 imputed datasets based upon Rubin's paradigm.

Specifically, let Q denote the imputed mean of an efficacy outcome Y subject to missing data at a given timepoint, where the estimate of that mean for any i^{th} imputation would be defined as function of both observed and missing such that

$$\widehat{Q^{(i)}} = E\left(Q^{(i)} | Y_{observed}, Y_{missing}^{(i)}, Y_{Baseline}, I(Group)\right), i = 1, \ldots, 10.$$

After all 10 datasets have been imputed, the overall estimate of Q is a simple average defined as

$$\bar{Q} = \frac{\sum_{i=1}^{10} \widehat{Q^{(i)}}}{10}.$$

For this analysis using 10 imputed datasets, the variance of $\bar{Q}$ is defined as

$$Var(\bar{Q}) = 1.1B + \bar{U}$$

where B is the between imputation variance and U is the within imputation variance:

$$B = \frac{1}{9}\sum_{i=1}^{10}\left(\widehat{Q^{(i)}} - \bar{Q}\right)^2;$$

$$\bar{U} = \frac{\sum_{i=1}^{10} U^{(i)}}{10}.$$

PROC MI in SAS® will be used to impute missing data assuming missingness is monotone in pattern. If a subject is missing a baseline record causing non-monotone missingness, all non-missing post-baseline records will temporarily be set to missing as well. After the 10 imputation datasets are created, the non-missing post-baseline will be merged back in, thus creating complete datasets where only the originally missing records were imputed. Imputations will be performed with a seed of 469007.

7.2 Interim Analysis

There was no planned interim analysis for this study.

7.3 Efficacy Assessments

7.3.1 mJSW

Radiographs of the knee joints were to be taken at all clinic visits after Visit 1E (Day 1). Radiographs were to be taken using a posterior-anterior view.

Upon receipt of images, the central imaging vendor was to assess the image quality as acceptable or unacceptable. It was recommended that the Investigator attempt up to 3 additional image captures in order to obtain an acceptable image. mJSW measurements will be reported to two decimal places.

7.3.2 Pain NRS

The Pain NRS is an 11-point scale [0-10] for subject self-reporting of average knee pain in the previous 24 hours, where 0 represents no pain and 10 represents extreme pain. A pain NRS assessment was to be completed by the subjects at all clinic visits. Upon completion of the pain NRS, subjects were to sign or initial, then date the source document to indicate that the assessment is reported accurately.

7.3.3 WOMAC

The WOMAC is a widely used, proprietary outcome measurement tool used by health professionals to evaluate the condition of patients with OA of the knee and hip, including pain, stiffness, and physical functioning of a target joint. The WOMAC Version NRS 3.1 was to be

completed by the subject for their target knee at all clinic visits after Visit 1E (Day 1). Upon completion of the WOMAC, subjects were to sign or initial, then date the source document to indicate that the assessment is reported accurately.

WOMAC consists of 24 questions in three domains: physical function (17 questions), pain (5 questions) and stiffness (2 questions). The response for each question in the NRS format ranges from 0 to 10. Each domain subscore as well as a total score are calculated by adding together the numerical responses for a range of 0 to 240 total points. For analysis, WOMAC scores will be linearly transformed to a 0-100 scale, where 0 represents no difficulty and 100 represents extreme difficulty.

7.3.4 Patient Acceptable Symptom State Questionnaire

The Patient Acceptable Symptom State (PASS) Questionnaire consists of a single question "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 were asked to choose the answers of "Yes" or "No". The PASS Questionnaire was to be completed by the subject at Visit 1E (Day 1), Visit 3E (Week 48), every 52 weeks thereafter (e.g., Visits 6E, 8E, etc.), and at the Termination Visit. Upon completion of the PASS Questionnaire, subjects were to sign or initial, then date the source document to indicate that the assessment is reported accurately.

7.3.5 SF-36

The SF-36 is a widely used questionnaire that relies upon subject self-reporting to measure the subject's HRQOL. The SF-36 was to be completed by the subject at Visit 3E (Week 48), every 52 weeks thereafter (e.g., Visits 6E, 8E, etc.), and at the Termination Visit. The subject's responses will be used to calculate norm-based scores for eight scales (physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, mental health) and two component summary measures (physical health, mental health). Scoring software provided by the SF-36 vendor, Optum, will be utilized to calculate the standardized scores.

7.3.6 NSAID/Acetaminophen Usage

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

7.4 Safety Assessments

7.4.1 Adverse Events

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. Signs and symptoms of exacerbation or worsening of target knee OA were captured in the context of efficacy assessments. Anticipated fluctuations or anticipated deterioration (in the opinion of the Investigator) of the underlying disease (target knee OA) were not considered as AEs.

Severity was assessed utilizing the CDISC AESEV, which classifies AEs as mild, moderate, or severe. For analysis, relationship will be dichotomized into Unrelated (combining Not Related and Unlikely Related) and Related (combining Possibly Related and Probably Related).

7.4.2 Vital Signs and Weight

Vital signs were measured by a qualified staff member at Visit 2E, Visit 3E, every 52 weeks thereafter (e.g., Visits 6E, 8E, etc.), and at the Termination Visit. At each time point, the following vital signs were measured:

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

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

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

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

7.4.3 Clinical Laboratory Evaluations

Specimens for clinical laboratory analysis were to be collected at Visit 2E, Visit 3E, every 52 weeks thereafter (e.g., Visits 6E, 8E, etc.), and at the Termination Visit. Subjects were asked to fast prior to the Visit 3E clinical laboratory collection. At a minimum, the following tests were conducted:

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

Urine microscopy was to be performed if urinalysis urine protein, leukocyte esterase (WBC esterase), occult blood, or nitrite values were out of range, or if the Investigator deemed that the microscopy was clinically warranted.

7.4.4 Biomarkers

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

8. STUDY SUBJECTS AND DEMOGRAPHICS

8.1 Disposition of Subjects and Withdrawals

Subject disposition will be presented in a summary table detailing the number and percentage of subjects who were consented, treated, or discontinued (e.g. study terminated by sponsor, adverse event, subject decision, etc.) overall and by treatment group. Additionally, subject disposition for treated subjects will be presented by treatment group and study site. Additional tables will be prepared to summarize the number of subjects enrolled under each protocol version and included in each analysis set. The disposition for individual subjects will be listed along with additional information on discontinued and screen failed subjects.

8.2 Protocol Deviations

A protocol deviation is defined as any noncompliance with the clinical trial protocol requirements. The noncompliance may be either on the part of the subject, the Investigator, or the study site staff.

Deviations are summarized into one of the following categories:

- Informed Consent Form
- Enrollment
- Procedures
- Labs/Specimens
- Study Visits
- Investigational Product
- Subject Non-Compliance
- Serious Adverse Events

Deviations are categorized as major or minor by a cross-functional team according to pre-defined criteria established in the Protocol Deviation Classification Guideline.

- A major deviation is defined as a divergence from the protocol that materially (a) reduces the quality or completeness of efficacy data, (b) makes the informed consent inaccurate, or (c) impacts a subject's safety, rights or welfare.
- A minor deviation is defined as a divergence from the protocol that deviates from the procedures and guidelines outlined in the protocol, but is not classified as a major deviation (i.e. the deviation does not materially (a) reduce the quality or completeness of the data, (b) make the informed consent inaccurate, or (c) impact a subject's safety, rights or welfare).

Protocol deviations may result in subject exclusion from the PPAS. All protocol deviations were reviewed by study team members to determine if the deviation could reasonably affect/confound interpretation of key efficacy endpoints and should result in the subject being excluded from the PPAS. 27 subjects (29 protocol deviations) with the following types of deviations were excluded from PPAS:

- Major parent study protocol deviation impacting efficacy outcome(s):

  - Major EN01 deviations (subject randomized or enrolled without meeting eligibility criteria): n = 3
  - Major NC03 deviations (prohibited procedure done): n = 2
- Major OA-07 study protocol deviation impacting efficacy outcome(s):
  - Major NC03 deviations (prohibited procedure done): n = 1
  - Major NC04 deviations (prohibited concomitant medication taken) that would affect efficacy analysis at Visit 3E (Week 48) or Visit 6E (Week 100): n = 5
  - Major P01 deviations (procedure performed incorrectly): n = 5
  - Major P02 deviations (Procedure not attempted or not performed): n = 13

A final list of protocol deviations resulting in subject or data exclusion from the PPAS can be found in Appendix 1 – Protocol Deviations Leading to Exclusion from Per-Protocol Analysis.

Major protocol deviations will be summarized by site and category, and all protocol deviations will be listed for each subject. Additionally, the COVID-19 pandemic related protocol deviations will be summarized separately.

8.3 Demographics and Other Baseline Characteristics

Demographic and parent-study baseline characteristics, including sex, race, ethnicity, age at consent, weight, height, body mass index (BMI), Kellgren-Lawrence (KL) grade, Widespread Pain Index (WPI), Symptom Severity Question 2 (SSQ2), mJSW, and investigator-assessed OA laterality will be presented overall and by treatment group. Continuous variables will be summarized with descriptive statistics and categorical variables will be summarized with frequencies and percentages. Summaries will be provided for each analysis set. Subject level listings will also be provided.

8.4 Medical History

A summary of reported medical history will be provided by MedDRA system organ class on the Safety Analysis Set for each treatment group. A subject-level listing will provide further information on each event.

9. EFFICACY ANALYSIS

9.1 Hypothesis Testing using Parent-Study (OA-11 Study) Baseline

The primary and secondary statistical hypotheses being tested, using parent-study baseline, in this study are:

1. The least squares estimate of improvement from parent-study baseline in medial joint space width in the target knee at Visit 3E (Week 48) is greater for subjects who received LOR compared to placebo.
2. The least squares estimate of improvement from parent-study baseline in Pain NRS at Visit 3E (Week 48) is greater for subjects who received LOR compared to placebo.
3. The least squares estimate of improvement from parent-study baseline in WOMAC Pain at Visit 3E (Week 48) is greater for subjects who received LOR compared to placebo.

4. The least squares estimate of improvement from parent-study baseline in WOMAC Function at Visit 3E (Week 48) is greater for subjects who received LOR compared to placebo.
5. The least squares estimate of improvement from parent-study baseline in Pain NRS at Visit 2E (Week 24) is greater for subjects who received LOR compared to placebo.
6. The least squares estimate of improvement from parent-study baseline in WOMAC Pain at Visit 2E (Week 24) is greater for subjects who received LOR compared to placebo.
7. The least squares estimate of improvement from parent-study baseline in WOMAC Function at Visit 2E (Week 24) is greater for subjects who received LOR compared to placebo.

Other statistical hypotheses being tested, using parent-study baseline, in this study are:

1. The least squares estimate of improvement from parent-study baseline in medial joint space width in the target knee at Visit 2E (Week 24) is greater for subjects who received LOR compared to placebo.
2. The least squares estimate of improvement from parent-study baseline in WOMAC Total score at Visit 3E (Week 48) is greater for subjects who received LOR compared to placebo.
3. The least squares estimate of improvement from parent-study baseline in WOMAC Stiffness at Visit 3E (Week 48) is greater for subjects who received LOR compared to placebo.
4. The least squares estimate of improvement from parent-study baseline in WOMAC Total score at Visit 2E (Week 24) is greater for subjects who received LOR compared to placebo.
5. The least squares estimate of improvement from parent-study baseline in WOMAC Stiffness at Visit 2E (Week 24) is greater for subjects who received LOR compared to placebo.
6. The least squares estimate of improvement from parent-study baseline in medial joint space width in the target knee at Visit 6E (Week 100) is greater for subjects who received “Placebo-LOR”, “LOR-LOR” and All (pooled “Placebo-LOR” and “LOR-LOR”) subjects compared to test values (carry forward and progression assumptions) derived from the change from baseline estimates from the Placebo group at Visit 3E (Week 48)

9.2 Hypothesis Testing using OA-07-Study Baseline

The secondary statistical hypotheses being tested, using OA-07-study baseline, in this study are:

1. The least squares estimate of improvement from OA-07-study baseline in medial joint space width in the target knee at Visit 3E (Week 48) is greater for subjects who received LOR compared to placebo.
2. The least squares estimate of improvement from OA-07-study baseline in Pain NRS at Visit 3E (Week 48) is greater for subjects who received LOR compared to placebo.
3. The least squares estimate of improvement from OA-07-study baseline in WOMAC Pain at Visit 3E (Week 48) is greater for subjects who received LOR compared to placebo.

4. The least squares estimate of improvement from OA-07-study baseline in WOMAC Function at Visit 3E (Week 48) is greater for subjects who received LOR compared to placebo.
5. The least squares estimate of improvement from OA-07-study baseline in Pain NRS at Visit 2E (Week 24) is greater for subjects who received LOR compared to placebo.
6. The least squares estimate of improvement from OA-07-study baseline in WOMAC Pain at Visit 2E (Week 24) is greater for subjects who received LOR compared to placebo.
7. The least squares estimate of improvement from OA-07-study baseline in WOMAC Function at Visit 2E (Week 24) is greater for subjects who received LOR compared to placebo.

Other statistical hypotheses being tested, using OA-07-study baseline, in this study are:

1. The least squares estimate of improvement from OA-07-study baseline in medial joint space width in the target knee at Visit 2E (Week 24) is greater for subjects who received LOR compared to placebo.
2. The least squares estimate of improvement from OA-07-study baseline in WOMAC Total score at Visit 3E (Week 48) is greater for subjects who received LOR compared to placebo.
3. The least squares estimate of improvement from OA-07-study baseline in WOMAC Stiffness at Visit 3E (Week 48) is greater for subjects who received LOR compared to placebo.
4. The least squares estimate of improvement from OA-07-study baseline in WOMAC Total score at Visit 2E (Week 24) is greater for subjects who received LOR compared to placebo.
5. The least squares estimate of improvement from OA-07-study baseline in WOMAC Stiffness at Visit 2E (Week 24) is greater for subjects who received LOR compared to placebo.
6. The least squares estimate of improvement from OA-07-study baseline in medial joint space width in the target knee at Visit 6E (Week 100) is greater for subjects who received “Placebo-LOR”, “LOR-LOR” and All (pooled “Placebo-LOR” and “LOR-LOR”) subjects compared to test values (carry forward and progression assumptions) derived from the change from baseline estimates from the Placebo group at Visit 3E (Week 48)

9.3 Estimands

The primary estimand for this trial is the difference between an additional injection of LOR versus placebo in mean parent-study baseline-adjusted change in medial joint space width in the target knee at Visit 3E (Week 48) analyzed with parent-study baseline-adjusted ANCOVA in the FAS.

A summary of all estimands defined for this study is available in Appendix 2 – Estimands.

9.4 Primary Efficacy Analysis

9.4.1 Main Analysis

Parent-study baseline-adjusted ANCOVA will be used to assess the change in mJSW at Visit 3E (Week 48) in the FAS.

9.4.2 Sensitivity Analysis

Missing data will be imputed using the MI method as described in Section 7.1.4. The main primary analysis will also be repeated for subjects in the mFAS, CAS, and PPAS.

9.5 Secondary Efficacy Analysis

9.5.1 Main Analysis

Parent-study baseline-adjusted and OA-07-study baseline-adjusted ANCOVA will be used to assess the change in Pain NRS, WOMAC Pain, and WOMAC Function at Visit 2E (Week 24) and Visit 3E (Week 48) in the FAS. Additionally, the OA-07-study baseline-adjusted ANCOVA will be used to assess the change mJSW at Visit 3E (Week 48) in the FAS.

9.5.2 Sensitivity Analysis

Missing data will be imputed using the MI method as described in Section 7.1.4. The main secondary analyses will also be repeated for subjects in the mFAS, CAS, and PPAS.

9.6 Other Efficacy Analysis

The analyses described below will be performed on subjects in the FAS, mFAS, CAS, and PPAS.

9.6.1 Using Parent-Study Baseline

Parent-study Baseline-adjusted ANCOVA will be used to assess change in mJSW (at Visit 2E), WOMAC Total (at Visit 2E and Visit 3E), WOMAC Stiffness (at Visit 2E and Visit 3E), and in SF-36 (at Visit 3E). Unadjusted 95% confidence intervals and P values will be reported.

9.6.2 Using OA-07-Study Baseline

OA-07-study baseline-adjusted ANCOVA will be used to assess the change in mJSW (at Visit 2E), WOMAC Total (at Visit 2E and Visit 3E), WOMAC Stiffness (at Visit 2E and Visit 3E), and in SF-36 (at Visit 3E).

9.6.3 PASS and Response Analysis

The number and percent of subjects reporting “Yes” to Patient Acceptable Symptom State (PASS) at Visit 3E (Week 48) and Visit 6E (Week 100) will be summarized. Logistic regression analysis will be implemented for “Yes” responses in PASS adjusted for their response at Visit 1E (Day 1), with 95% confidence intervals and P values reported.

The number and percent of subjects reporting Outcome Measures in Rheumatology Clinical Trials (OMERACT)-Osteoarthritis Research Society International (OARSI) ’strict’ responders will be summarized. An OMERACT-OARSI ‘strict’ responder must have a 50% improvement with corresponding 20 point (out of 100) actual scale improvement in pain or function outcomes. Two ‘strict’ responder outcomes will be estimated, one using WOMAC Pain and WOMAC Function and the other using Pain NRS (2-point improvement out of 10) and WOMAC Function.

Additionally, the number and percent of subjects reporting 20% improvement, 30% improvement, 50% improvement, and 70% improvement in Pain NRS, WOMAC Pain, and WOMAC Function will be summarized. Logistic regression analysis will be implemented for improvement in these assessments as well, with 95% confidence intervals and P values reported.

9.6.4 Concordance Analysis

Logistic regression will be conducted within each treatment group to determine whether parent-study baseline-adjusted change in mJSW is concordant with response criteria for Pain NRS, WOMAC Pain, and WOMAC Function. Response criteria will model 20%, 30%, 50%, and 70% improvement in each outcome. Each outcome will be modeled individually. Receiver operator characteristic (ROC) areas under the curve (AUC) will be provided, along with odds ratios and 95% confidence intervals. The analysis will be repeated using OA-07-study baseline-adjusted change as well as OA-07 Visit 3E (Week 48) baseline-adjusted change as follows:

Group of interest	Baseline	Visit
LOR-LOR[1]	Parent-Study	Visit 3E (Week 48)
		Visit 6E (Week 100)
	OA-07-Study	Visit 3E (Week 48)
		Visit 6E (Week 100)
	OA-07-Study Visit 3E (Week 48)	Visit 6E (Week 100)
Placebo-Placebo[2]	Parent-Study	Visit 3E (Week 48)
		Visit 6E (Week 100)
	OA-07-Study	Visit 3E (Week 48)
Placebo-LOR[3]	OA-07-Study Visit 3E (Week 48)	Visit 6E (Week 100)

[1] Includes subjects treated with, at least, LOR during the OA-11 study and LOR at the OA-07 Visit 1E (Day 1)
[2] Includes subjects treated with, at least, PBO during the OA-11 study and PBO at the OA-07 Visit 1E (Day 1)
[3] Includes subjects treated with, at least, PBO during the OA-11 study, PBO at the OA-07 Visit 1E (Day 1) and LOR at the OA-07 Visit 3E (Week 48)

9.6.5 Open Label Portion of Study (Placebo Subjects Cross Over to LOR)

On and after Visit 3E (Week 48) all subjects only received LOR injections.

9.6.5.1 Groups of interest

The following groups will be analyzed:

- "Placebo-LOR" group includes subjects treated with Placebo during the OA-11 study, Placebo at the OA-07 Visit 1E (Day 1) and LOR at the OA-07 Visit 3E (Week 48).
- "LOR-LOR" group includes subjects treated with LOR during the OA-11 study, LOR at the OA-07 Visit 1E (Day 1) and LOR at the OA-07 Visit 3E (Week 48).
- Pooled "Placebo-LOR" and "LOR-LOR" groups.

9.6.5.2 Analysis

For each group of interest described in Section 9.6.5.1, we will estimate an mJSW baseline-adjusted ANCOVA at Visit 6E (Week 100) and test the difference against two test values:

- Carry-forward (i.e., no change) assumption test value will use the mJSW baseline-adjusted ANCOVA estimate at Visit 3E (Week 48) from the Placebo group.
- Progression (i.e., worsening) assumption test value will use the mJSW baseline-adjusted ANCOVA estimate at Visit 3E (Week 48) from the Placebo group extrapolated to a presumption of continued Placebo use.

Analysis will be performed using the parent and OA-07 study baselines.

9.6.6 Subgroup Analysis

The efficacy analyses described in Sections 9.4, 9.5, and 9.6 will be further analyzed by KL Grade.

10. SAFETY AND TOLERABILITY ANALYSIS

The analysis of safety outcome measures will be performed on the Safety Analysis Set. No formal statistical tests are planned for safety.

10.1 Adverse Events

Data regarding AEs will be collected in this study. As this is an extension trial, AE collection will continue from the parent study, ongoing AEs at the end of the parent study will continue to be monitored, and new AEs that occur during this study will be recorded. Changes to ongoing AEs that occur after the parent-study EOS visit will not be recorded in the parent study. AEs will be assessed through the Termination Visit. AEs will be presented in summary tables depicting the number and percent of unique subjects experiencing each AE and the number of AEs by the following analysis periods: (1) AEs that started prior to a Second OA-07 Injection (end of the single-blind, placebo-controlled period of the study; including all AEs for subjects who only received the First OA-07 Injection to End of Study, EOS), (2) on or after Second OA-07 Injection to prior to Third OA-07 Injection (including all AEs for subjects who received the Second OA-07 Injection to EOS), and (3) on or after Third OA-07 Injection to EOS. The following summaries will be provided:

- All AEs and all SAEs by severity and relationship to study product
- AEs by highest degree of seriousness, severity, and relationship to study drug
- AEs by MedDRA system organ class and preferred term
- SAEs sorted by preferred term incidence
- AEs with incidence of greater than 2% in the active treatment group sorted by preferred term incidence
- Target-knee-related AEs and SAEs sorted by preferred term incidence
- AEs leading to study withdrawal, discontinuation of study drug, or death
- SAEs in subjects diagnosed with COVID-19

If an AE start or end date is incomplete, it will be imputed in a way that assumes maximum exposure time (see table in Appendix 3 – Partial Date Imputation). Separate subject-level listings will be provided for all AEs and all SAEs.

10.2 Clinical Laboratory Evaluations

All chemistry, hematology and urinalysis results from the central laboratory will be summarized into shift tables as normal, non-clinically significant abnormal, and clinically significant abnormal. Assessments of clinical significance for abnormal values were made by the investigator on results that were outside of the normal range. Shift tables will compare the number and percent of assessments from each visit to baseline values for each treatment group.

All chemistry and hematology results from the central laboratory will be summarized for each treatment group. Descriptive statistics of each laboratory test at all timepoints will be provided along with the change from baseline at each subsequent visit. If a result is below the limit of quantification, it will be set to half the value for analysis (e.g., "< 3" will be analyzed as 1.5). The International System of Units (SI) will be used for all summaries.

Abnormal chemistry, hematology, urinalysis, and urine microscopy results for each subject will be provided in listings that will include laboratory test name, result, normal range, and an explanation for clinically significant values.

10.3 Vital Signs and Weight

Weight and vital signs (including systolic blood pressure, diastolic blood pressure, pulse rate, respiratory rate, and body temperature) will be summarized for each treatment group. Descriptive statistics of each parameter at baseline will be provided along with the change from parent-study baseline at each subsequent visit. A subject-level listing will also be provided.

10.4 Physical Examination

Results of the general physical and knee examinations were noted in the source documents. Any clinically significant finding noted prior to study medication injection was recorded as medical history. If it was found after study medication injection, it was reported as an AE.

11. OTHER/EXPLORATORY ANALYSIS

11.1 Biomarkers

Parent-study baseline-adjusted ANCOVA will be used to assess change in biomarkers COMP, P1NP and β-CT and evaluated at Visit 3E (Week 48). Unadjusted 95% confidence intervals and P values will be reported.

A statistical description of each biomarker at baseline will be provided along with the change from parent-study baseline at Visit 3E (Week 48). A subject-level listing will also be provided. COMP values will be summarized and listed in ng/mL (i.e. original results in pg/mL will be divided by 1000).

12. MEDICATIONS

The summary of medications will be performed on the SAS.

12.1 Concomitant Medication

The World Health Organization Drug Dictionary (WHODD) will be used to classify concomitant medications by Anatomical Main Group (Anatomical Therapeutic Chemical, ATC, Level 1), Therapeutic Subgroup (ATC Level 2), and preferred term. Concomitant medication (CM) usage will be summarized by the number and percentage of subjects receiving each medication by treatment group. A similar table will be used to summarize the subset of CMs identified as NSAID/Acetaminophen medications.

Additional tables will summarize CMs that started prior to a Second OA-07 Injection (single-blind, placebo-controlled period of the study; including all CMs for subjects who only received

the First OA-07 Injection). If a medication start or end date is incomplete, it will be imputed in a way that assumes maximum exposure time (see table in Appendix 3 – Partial Date Imputation). Subject-level listings containing concomitant medications (WHODD coding), and procedures/non-drug therapies (MedDRA coding) will be provided and will display the dates as they were entered (not the imputed version described above).

12.2 Exposure and Compliance

A subject-level exposure listing will be provided.

13. CHANGES TO PLANNED ANALYSIS

Change	Protocol Section	Rationale
Per protocol, efficacy endpoints were simply listed. In the SAP, we clearly define efficacy endpoints into categories of primary, secondary, and other. Additionally, an mFAS for completers of Visit 3E (Week 48) was defined as well as a CAS for subjects with an available mJSW at Visit 6E (Week 100).	3.2 and 6.4	Based on study team decision and clinicaltrials.gov reporting.
Per protocol, mixed-effects models for repeated measures (MMRM) would be used. In SAP we describe the use of ANCOVA. Additionally, the protocol mentioned 'potential confounding effect of change in NSAID/acetaminophen usage on the treatment effect' will not be considered as a sensitivity analysis.	9	More appropriate model and elimination of a sensitivity analysis given the spacing of the visits/assessment collection in the OA-07 study as compared to the OA-11 study.
Per protocol, "After all subjects have received LOR at Visit 3E, all further efficacy analyses will be descriptive in nature." See section 9.4.4 regarding the efficacy analysis pertaining to the "Open-label" portion of the study.	9	Based on study team decision.
Per protocol, "Outcome Measures in Rheumatology Clinical Trials (OMERACT)-Osteoarthritis Research Society International (OARSI) responders and 'strict' responders" would be estimated. Only "strict" responders will be estimated.	10.4.3	One of the components comprising OMERACT-OARSI response, Patient Global Assessment of Disease Activity, was not collected.

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15. APPENDICES

15.1 Appendix 1 – Protocol Deviations Leading to Exclusion from Per-Protocol Analysis

15.1.1 Parent Study Protocol Deviations

Subject	Deviation	Category	Class	Details
0307026	NC03 - Prohibited procedure (not allowed per protocol) done	Subject Non-Compliance	Major	PROHIBITED PROCEDURE, RIGHT KNEE ARTHROPLASTY, CONDUCTED ON NON-TARGET KNEE ON 23MAR2020.
4177102	EN01 - Subject randomized or enrolled without meeting eligibility criteria	Enrollment	Major	SUBJECT DID NOT MEET IC #15 WITH AN INELIGIBLE WOMAC FUNCTION SCORE OF 137 BUT WAS RANDOMIZED.
7057030	EN01 - Subject randomized or enrolled without meeting eligibility criteria	Enrollment	Major	PATIENT DID NOT MEET INC 12 - YPRIME CRITERIA PER THE NRS SCORE OF THE TARGET KNEE WHICH WAS 8.43. EXCL 17 - SUBJECT ALSO TAKING TOPIRAMATE FOR HEADACHES 100 MG QD STARTING 2017.
7077005	NC03 - Prohibited procedure (not allowed per protocol) done	Subject Non-Compliance	Major	SUBJECT HAD RIGHT TOTAL HIP ARTHROPLASTY PERFORMED ON 20JUL2020 WHILE ON STUDY.
7077008	EN01 - Subject randomized or enrolled without meeting eligibility criteria	Enrollment	Major	SUBJECT KNEES WERE INCORRECTLY MARKED DURING SCREENING X-RAY. UPON ANALYSIS OF CORRECT TARGET KNEE, SUBJECT DID NOT MEET IC #4

15.1.2 OA-07 Study Protocol Deviations

Subject	Deviation	Category	Class	Details
0027092	NC04 - Prohibited concomitant medication taken	Subject Non-Compliance	Major	SUBJECT IS TAKING HYDROCODONE 5MG PRN SINCE JUN2022 FOR BILATERAL KNEE PAIN.
0167082	P02 - Procedure not attempted or not performed except in cases where not done due to subject safety or subject refusal	Procedures	Major	X-RAY FOR VISIT 3E NOT PERFORMED. VISIT IS NOW OUT OF WINDOW AND CANNOT BE TAKEN.
0197079	P02 - Procedure not attempted or not performed except in cases where not done due to subject safety or subject refusal	Procedures	Major	6E X-RAY NOT ACQUIRED
0357016	P01 - Procedure performed incorrectly	Procedures	Major	THE X-RAY PERFORMED AT THE 3E VISIT HAD UNACCEPTABLE IMAGE QUALITY WITH NO RESULTS AVAILABLE FROM THESE IMAGES. THE X-RAYS ARE NOW OUT OF WINDOW AND CANNOT BE RE-TAKEN.
4367002	P02 - Procedure not attempted or not performed except in cases where not done due to subject safety or subject refusal	Procedures	Major	VISIT 6E X-RAY NOT COMPLETED.
4367026	P02 - Procedure not attempted or not performed except in cases where not done due to subject safety or subject refusal	Procedures	Major	VISIT 6E X-RAY NOT PERFORMED.
4367050	P02 - Procedure not attempted or not performed except in cases where not done due to subject safety or subject refusal	Procedures	Major	VISIT 6E X-RAY NOT PERFORMED.
4367053	P02 - Procedure not attempted or not performed except in cases where not done due to subject safety or subject refusal	Procedures	Major	VISIT 6E X-RAY NOT DONE.
4367067	P02 - Procedure not attempted or not performed except in cases where not done due to subject safety or subject refusal	Procedures	Major	VISIT 6E X-RAY NOT PERFORMED.

5147020	P02 - Procedure not attempted or not performed except in cases where not done due to subject safety or subject refusal	Procedures	Major	X-RAY NOT PERFORMED. Visit reported: VISIT 6E (WEEK 100)
5147033	P02 - Procedure not attempted or not performed except in cases where not done due to subject safety or subject refusal	Procedures	Major	X-RAY NOT PERFORMED Visit reported: VISIT 6E (WEEK 100)
5147044	P02 - Procedure not attempted or not performed except in cases where not done due to subject safety or subject refusal	Procedures	Major	X-RAY NOT PERFORMED Visit reported: VISIT 6E (WEEK 100)
7057004	NC04 - Prohibited concomitant medication taken	Subject Non-Compliance	Major	SUBJECT TAKING GABAPENTIN, EXCLUDED CONCOMITANT MEDICATION, FOR LOW BACK PAIN, STARTING UNJUN2021
7057032	NC04 - Prohibited concomitant medication taken	Subject Non-Compliance	Major	SUBJECT IS TAKING BUTALBITAL/ACETAMINOPHEN/CAFFEINE FOR MIGRAINE HEADACHES, 50/325/40 MG. BUTALBITAL IS A BARBITUATE AND IS AN EXCLUDED CONCOMITANT MEDICATION, STARTING IN 2004.
7077017	NC03 - Prohibited procedure (not allowed per protocol) done	Subject Non-Compliance	Major	DUE TO AN AE OF LEFT KNEE PAIN, SUBJECT HAD PROCEDURE OF LEFT KNEE TOTAL ARTHROPLASTY PERFORMED ON 20JUL2021.
7077017	NC04 - Prohibited concomitant medication taken	Subject Non-Compliance	Major	PROHIBITED MEDICATION WAS TAKEN - DEPOMEDROL 40MG, IA INJECTION, ONCE 16APR2021
7097019	P01 - Procedure performed incorrectly	Procedures	Major	ACCEPTABLE 3E X-RAY NOT OBTAINED.
7097044	P02 - Procedure not attempted or not performed except in cases where not done due to subject safety or subject refusal	Procedures	Major	ACCEPTABLE VISIT 3E X-RAY NOT OBTAINED.
7137013	P01 - Procedure performed incorrectly	Procedures	Major	VISIT 3E X-RAY WAS DEEMED UNACCEPTABLE BY MMI AND A RE-TAKE WAS NOT COMPLETED DUE TO THE SUBJECT BEING OUT OF TOWN.

7137013	P02 - Procedure not attempted or not performed except in cases where not done due to subject safety or subject refusal	Procedures	Major	X-RAY NOT PERFORMED DUE TO SITE'S RADIOLOGY VENDOR NO LONGER SUPPORTING RADIOGRAPHS. Visit reported: VISIT 6E (WEEK 100)
7137022	P02 - Procedure not attempted or not performed except in cases where not done due to subject safety or subject refusal	Procedures	Major	X-RAY NOT PERFORMED DUE TO SITE'S RADIOLOGY VENDOR NO LONGER SUPPORTING RADIOGRAPHS. Visit reported: VISIT 6E (WEEK 100)
7157021	P01 - Procedure performed incorrectly	Procedures	Major	VISIT 3E X-RAYS HAD UNACCEPTABLE IMAGE QUALITY WITH NO RESULTS AVAILABLE FROM THESE IMAGES. THE X-RAYS ARE NOW OUT OF WINDOW AND CANNOT BE TAKEN.
7287270	P01 - Procedure performed incorrectly	Procedures	Major	ACCEPTABLE X-RAY NOT OBTAINED AT VISIT 3E. WINDOW HAS CLOSED AND IMAGES CANNOT BE RETAKEN.
7297042	NC04 - Prohibited concomitant medication taken	Subject Non-Compliance	Major	SUBJECT RECEIVED PROHIBITED IA INJECTION OF METHYLPREDNISONE 40MG, ONCE, INTO THE TARGET KNEE, ON 29JUL2021.

15.2 Appendix 2 – Estimands

	Estimator	Variable	Population	Intercurrent events	Population level summary
Primary	Main	Change from parent-study baseline in mJSW at Visit 3E (Week 48)	FAS	Prohibited medications and NSAID/acetaminophen use: treatment policy strategy; analysis will be conducted regardless of use of prohibited medications or NSAID/acetaminophen use.	Difference in the change from parent-study between LOR and placebo using parent-study baseline-adjusted ANCOVA with available data.
	Sensitivity 1	Change from parent-study baseline in mJSW at Visit 3E (Week 48)	FAS	Prohibited medications and NSAID/acetaminophen use: treatment policy strategy; analysis will be conducted regardless of use of prohibited medications or NSAID/acetaminophen use.	Difference in the change from parent-study between LOR and placebo using parent-study baseline-adjusted ANCOVA with missing data imputed using the MI method.
	Sensitivity 2	Change from parent-study baseline in mJSW at Visit 3E (Week 48)	mFAS	Prohibited medications and NSAID/acetaminophen use: treatment policy strategy; analysis will be conducted regardless of use of prohibited medications or NSAID/acetaminophen use.	Difference in the change from parent-study between LOR and placebo using parent-study baseline-adjusted ANCOVA with available data.
	Sensitivity 3	Change from parent-study baseline in mJSW at Visit 3E (Week 48)	PPAS	1) Prohibited medications: principal stratum strategy; subjects who used prohibited medications will be excluded from this analysis. 2) NSAID/acetaminophen: treatment policy strategy; analysis will be conducted regardless of NSAID/acetaminophen use.	Difference in the change from parent-study baseline between LOR and placebo using parent-study baseline-adjusted ANCOVA.
Estimand is repeated using the OA-07-study baseline as Secondary					

	Estimator	Variable	Population	Other intercurrent events	Population level summary
Secondary	Main	Change from parent-study baseline in Pain NRS at Visit 3E (Week 48)	FAS	Prohibited medications and NSAID/acetaminophen use: treatment policy strategy; analysis will be conducted regardless of use of prohibited medications or NSAID/acetaminophen use.	Difference in the change from parent-study baseline between LOR and placebo using parent-study baseline-adjusted ANCOVA with available data.
	Sensitivity 1	Change from parent-study baseline in Pain NRS at Visit 3E (Week 48)	FAS	Prohibited medications and NSAID/acetaminophen use: treatment policy strategy; analysis will be conducted regardless of use of prohibited medications or NSAID/acetaminophen use.	Difference in the change from parent-study baseline between LOR and placebo using parent-study baseline-adjusted ANCOVA with missing data imputed using the MI method.
	Sensitivity 2	Change from parent-study baseline in Pain NRS at Visit 3E (Week 48)	mFAS	Prohibited medications and NSAID/acetaminophen use: treatment policy strategy; analysis will be conducted regardless of use of prohibited medications or NSAID/acetaminophen use.	Difference in the change from parent-study baseline between LOR and placebo using parent-study baseline-adjusted ANCOVA with available data.
	Sensitivity 3	Change from parent-study baseline in Pain NRS at Visit 3E (Week 48)	PPAS	1) Prohibited medications: principal stratum strategy; subjects who used prohibited medications will be excluded from this analysis. 2) NSAID/acetaminophen: treatment policy strategy; analysis will be conducted regardless of NSAID/acetaminophen use.	Difference in the change from parent-study baseline between LOR and placebo using parent-study baseline-adjusted ANCOVA.
Estimand is repeated using the OA-07-study baseline					

	Estimator	Variable	Population	Other intercurrent events	Population level summary
Secondary	Main	Change from parent-study baseline in WOMAC Pain at Visit 3E (Week 48)	FAS	Prohibited medications and NSAID/acetaminophen use: treatment policy strategy; analysis will be conducted regardless of use of prohibited medications or NSAID/acetaminophen use.	Difference in the change from parent-study baseline between LOR and placebo using parent-study baseline-adjusted ANCOVA with available data.
	Sensitivity 1	Change from parent-study baseline in WOMAC Pain at Visit 3E (Week 48)	FAS	Prohibited medications and NSAID/acetaminophen use: treatment policy strategy; analysis will be conducted regardless of use of prohibited medications or NSAID/acetaminophen use.	Difference in the change from parent-study baseline between LOR and placebo using parent-study baseline-adjusted ANCOVA with missing data imputed using the MI method.
	Sensitivity 2	Change from parent-study baseline in WOMAC Pain at Visit 3E (Week 48)	mFAS	Prohibited medications and NSAID/acetaminophen use: treatment policy strategy; analysis will be conducted regardless of use of prohibited medications or NSAID/acetaminophen use.	Difference in the change from parent-study baseline between LOR and placebo using parent-study baseline-adjusted ANCOVA with available data.
	Sensitivity 3	Change from parent-study baseline in WOMAC Pain at Visit 3E (Week 48)	PPAS	1) Prohibited medications: principal stratum strategy; subjects who used prohibited medications will be excluded from this analysis. 2) NSAID/acetaminophen: treatment policy strategy; analysis will be conducted regardless of NSAID/acetaminophen use.	Difference in the change from parent-study baseline between LOR and placebo using parent-study baseline-adjusted ANCOVA.
Estimand is repeated using the OA-07-study baseline					

	Estimator	Variable	Population	Other intercurrent events	Population level summary
Secondary	Main	Change from parent-study baseline in WOMAC Function at Visit 3E (Week 48)	FAS	Prohibited medications and NSAID/acetaminophen use: treatment policy strategy; analysis will be conducted regardless of use of prohibited medications or NSAID/acetaminophen use.	Difference in the change from parent-study baseline between LOR and placebo using parent-study baseline-adjusted ANCOVA with available data.
	Sensitivity 1	Change from parent-study baseline in WOMAC Function at Visit 3E (Week 48)	FAS	Prohibited medications and NSAID/acetaminophen use: treatment policy strategy; analysis will be conducted regardless of use of prohibited medications or NSAID/acetaminophen use.	Difference in the change from parent-study baseline between LOR and placebo using parent-study baseline-adjusted ANCOVA with missing data imputed using the MI method.
	Sensitivity 2	Change from parent-study baseline in WOMAC Function at Visit 3E (Week 48)	mFAS	Prohibited medications and NSAID/acetaminophen use: treatment policy strategy; analysis will be conducted regardless of use of prohibited medications or NSAID/acetaminophen use.	Difference in the change from parent-study baseline between LOR and placebo using parent-study baseline-adjusted ANCOVA with available data.
	Sensitivity 3	Change from parent-study baseline in WOMAC Function at Visit 3E (Week 48)	PPAS	1) Prohibited medications: principal stratum strategy; subjects who used prohibited medications will be excluded from this analysis. 2) NSAID/acetaminophen: treatment policy strategy; analysis will be conducted regardless of NSAID/acetaminophen use.	Difference in the change from parent-study baseline between LOR and placebo using parent-study baseline-adjusted ANCOVA.
Estimand is repeated using the OA-07-study baseline					

	Estimator	Variable	Population	Other intercurrent events	Population level summary
Secondary	Main	Change from parent-study baseline in Pain NRS at Visit 2E (Week 24)	FAS	Prohibited medications and NSAID/acetaminophen use: treatment policy strategy; analysis will be conducted regardless of use of prohibited medications or NSAID/acetaminophen use.	Difference in the change from parent-study baseline between LOR and placebo using parent-study baseline-adjusted ANCOVA with available data.
	Sensitivity 1	Change from parent-study baseline in Pain NRS at Visit 2E (Week 24)	FAS	Prohibited medications and NSAID/acetaminophen use: treatment policy strategy; analysis will be conducted regardless of use of prohibited medications or NSAID/acetaminophen use.	Difference in the change from parent-study baseline between LOR and placebo using parent-study baseline-adjusted ANCOVA with missing data imputed using the MI method.
	Sensitivity 2	Change from parent-study baseline in Pain NRS at Visit 2E (Week 24)	mFAS	Prohibited medications and NSAID/acetaminophen use: treatment policy strategy; analysis will be conducted regardless of use of prohibited medications or NSAID/acetaminophen use.	Difference in the change from parent-study baseline between LOR and placebo using parent-study baseline-adjusted ANCOVA with available data.
	Sensitivity 3	Change from parent-study baseline in Pain NRS at Visit 2E (Week 24)	PPAS	1) Prohibited medications: principal stratum strategy; subjects who used prohibited medications will be excluded from this analysis. 2) NSAID/acetaminophen: treatment policy strategy; analysis will be conducted regardless of NSAID/acetaminophen use.	Difference in the change from parent-study baseline between LOR and placebo using parent-study baseline-adjusted ANCOVA.
Estimand is repeated using the OA-07-study baseline					

	Estimator	Variable	Population	Other intercurrent events	Population level summary
Secondary	Main	Change from parent-study baseline in WOMAC Pain at Visit 2E (Week 24)	FAS	Prohibited medications and NSAID/acetaminophen use: treatment policy strategy; analysis will be conducted regardless of use of prohibited medications or NSAID/acetaminophen use.	Difference in the change from parent-study baseline between LOR and placebo using parent-study baseline-adjusted ANCOVA with available data.
	Sensitivity 1	Change from parent-study baseline in WOMAC Pain at Visit 2E (Week 24)	FAS	Prohibited medications and NSAID/acetaminophen use: treatment policy strategy; analysis will be conducted regardless of use of prohibited medications or NSAID/acetaminophen use.	Difference in the change from parent-study baseline between LOR and placebo using parent-study baseline-adjusted ANCOVA with missing data imputed using the MI method.
	Sensitivity 2	Change from parent-study baseline in WOMAC Pain at Visit 2E (Week 24)	mFAS	Prohibited medications and NSAID/acetaminophen use: treatment policy strategy; analysis will be conducted regardless of use of prohibited medications or NSAID/acetaminophen use.	Difference in the change from parent-study baseline between LOR and placebo using parent-study baseline-adjusted ANCOVA with available data.
	Sensitivity 3	Change from parent-study baseline in WOMAC Pain at Visit 2E (Week 24)	PPAS	1) Prohibited medications: principal stratum strategy; subjects who used prohibited medications will be excluded from this analysis. 2) NSAID/acetaminophen: treatment policy strategy; analysis will be conducted regardless of NSAID/acetaminophen use.	Difference in the change from parent-study baseline between LOR and placebo using parent-study baseline-adjusted ANCOVA.
Estimand is repeated using the OA-07-study baseline					

	Estimator	Variable	Population	Other intercurrent events	Population level summary
Secondary	Main	Change from parent-study baseline in WOMAC Function at Visit 2E (Week 24)	FAS	Prohibited medications and NSAID/acetaminophen use: treatment policy strategy; analysis will be conducted regardless of use of prohibited medications or NSAID/acetaminophen use.	Difference in the change from parent-study baseline between LOR and placebo using parent-study baseline-adjusted ANCOVA with available data.
	Sensitivity 1	Change from parent-study baseline in WOMAC Function at Visit 2E (Week 24)	FAS	Prohibited medications and NSAID/acetaminophen use: treatment policy strategy; analysis will be conducted regardless of use of prohibited medications or NSAID/acetaminophen use.	Difference in the change from parent-study baseline between LOR and placebo using parent-study baseline-adjusted ANCOVA with missing data imputed using the MI method.
	Sensitivity 2	Change from parent-study baseline in WOMAC Function at Visit 2E (Week 24)	mFAS	Prohibited medications and NSAID/acetaminophen use: treatment policy strategy; analysis will be conducted regardless of use of prohibited medications or NSAID/acetaminophen use.	Difference in the change from parent-study baseline between LOR and placebo using parent-study baseline-adjusted ANCOVA with available data.
	Sensitivity 3	Change from parent-study baseline in WOMAC Function at Visit 2E (Week 24)	PPAS	1) Prohibited medications: principal stratum strategy; subjects who used prohibited medications will be excluded from this analysis. 2) NSAID/acetaminophen: treatment policy strategy; analysis will be conducted regardless of NSAID/acetaminophen use.	Difference in the change from parent-study baseline between LOR and placebo using parent-study baseline-adjusted ANCOVA.
Estimand is repeated using the OA-07-study baseline					

	Estimator	Variable	Population	Intercurrent events	Population level summary
Other	Main	Change from parent-study baseline in mJSW at Visit 2E (Week 24)	FAS	Prohibited medications and NSAID/acetaminophen use: treatment policy strategy; analysis will be conducted regardless of use of prohibited medications or NSAID/acetaminophen use.	Difference in the change from baseline between LOR and placebo using parent-study baseline-adjusted ANCOVA with available data.
	Sensitivity 1	Change from parent-study baseline in mJSW at Visit 2E (Week 24)	FAS	Prohibited medications and NSAID/acetaminophen use: treatment policy strategy; analysis will be conducted regardless of use of prohibited medications or NSAID/acetaminophen use.	Difference in the change from baseline between LOR and placebo using parent-study baseline-adjusted ANCOVA with missing data imputed using the MI method.
	Sensitivity 2	Change from parent-study baseline in mJSW at Visit 2E (Week 24)	mFAS	Prohibited medications and NSAID/acetaminophen use: treatment policy strategy; analysis will be conducted regardless of use of prohibited medications or NSAID/acetaminophen use.	Difference in the change from baseline between LOR and placebo using parent-study baseline-adjusted ANCOVA with available data.
	Sensitivity 3	Change from parent-study baseline in mJSW at Visit 2E (Week 24)	PPAS	1) Prohibited medications: principal stratum strategy; subjects who used prohibited medications will be excluded from this analysis. 2) NSAID/acetaminophen: treatment policy strategy; analysis will be conducted regardless of NSAID/acetaminophen use.	Difference in the change from parent-study baseline between LOR and placebo using parent-study baseline-adjusted ANCOVA.
Estimand is repeated using the OA-07-study baseline					

	Estimator	Variable	Population	Other intercurrent events	Population level summary
Other	Main	Change from parent-study baseline in WOMAC Total at Visit 3E (Week 48)	FAS	Prohibited medications and NSAID/acetaminophen use: treatment policy strategy; analysis will be conducted regardless of use of prohibited medications or NSAID/acetaminophen use.	Difference in the change from parent-study baseline between LOR and placebo using parent-study baseline-adjusted ANCOVA with available data.
	Sensitivity 1	Change from parent-study baseline in WOMAC Total at Visit 3E (Week 48)	FAS	Prohibited medications and NSAID/acetaminophen use: treatment policy strategy; analysis will be conducted regardless of use of prohibited medications or NSAID/acetaminophen use.	Difference in the change from parent-study baseline between LOR and placebo using parent-study baseline-adjusted ANCOVA with missing data imputed using the MI method.
	Sensitivity 2	Change from parent-study baseline in WOMAC Total at Visit 3E (Week 48)	mFAS	Prohibited medications and NSAID/acetaminophen use: treatment policy strategy; analysis will be conducted regardless of use of prohibited medications or NSAID/acetaminophen use.	Difference in the change from parent-study baseline between LOR and placebo using parent-study baseline-adjusted ANCOVA with available data.
	Sensitivity 3	Change from parent-study baseline in WOMAC Total at Visit 3E (Week 48)	PPAS	1) Prohibited medications: principal stratum strategy; subjects who used prohibited medications will be excluded from this analysis. 2) NSAID/acetaminophen: treatment policy strategy; analysis will be conducted regardless of NSAID/acetaminophen use.	Difference in the change from parent-study baseline between LOR and placebo using parent-study baseline-adjusted ANCOVA.
Estimand is repeated using the OA-07-study baseline					

	Estimator	Variable	Population	Other intercurrent events	Population level summary
Other	Main	Change from parent-study baseline in WOMAC Stiffness at Visit 3E (Week 48)	FAS	Prohibited medications and NSAID/acetaminophen use: treatment policy strategy; analysis will be conducted regardless of use of prohibited medications or NSAID/acetaminophen use.	Difference in the change from parent-study baseline between LOR and placebo using parent-study baseline-adjusted ANCOVA with available data.
	Sensitivity 1	Change from parent-study baseline in WOMAC Stiffness at Visit 3E (Week 48)	FAS	Prohibited medications and NSAID/acetaminophen use: treatment policy strategy; analysis will be conducted regardless of use of prohibited medications or NSAID/acetaminophen use.	Difference in the change from parent-study baseline between LOR and placebo using parent-study baseline-adjusted ANCOVA with missing data imputed using the MI method.
	Sensitivity 2	Change from parent-study baseline in WOMAC Stiffness at Visit 3E (Week 48)	mFAS	Prohibited medications and NSAID/acetaminophen use: treatment policy strategy; analysis will be conducted regardless of use of prohibited medications or NSAID/acetaminophen use.	Difference in the change from parent-study baseline between LOR and placebo using parent-study baseline-adjusted ANCOVA with available data.
	Sensitivity 3	Change from parent-study baseline in WOMAC Stiffness at Visit 3E (Week 48)	PPAS	1) Prohibited medications: principal stratum strategy; subjects who used prohibited medications will be excluded from this analysis. 2) NSAID/acetaminophen: treatment policy strategy; analysis will be conducted regardless of NSAID/acetaminophen use.	Difference in the change from parent-study baseline between LOR and placebo using parent-study baseline-adjusted ANCOVA.
Estimand is repeated using the OA-07-study baseline					

	Estimator	Variable	Population	Other intercurrent events	Population level summary
Other	Main	Change from parent-study baseline in WOMAC Total at Visit 2E (Week 24)	FAS	Prohibited medications and NSAID/acetaminophen use: treatment policy strategy; analysis will be conducted regardless of use of prohibited medications or NSAID/acetaminophen use.	Difference in the change from parent-study baseline between LOR and placebo using parent-study baseline-adjusted ANCOVA with available data.
	Sensitivity 1	Change from parent-study baseline in WOMAC Total at Visit 2E (Week 24)	FAS	Prohibited medications and NSAID/acetaminophen use: treatment policy strategy; analysis will be conducted regardless of use of prohibited medications or NSAID/acetaminophen use.	Difference in the change from parent-study baseline between LOR and placebo using parent-study baseline-adjusted ANCOVA with missing data imputed using the MI method.
	Sensitivity 2	Change from parent-study baseline in WOMAC Total at Visit 2E (Week 24)	mFAS	Prohibited medications and NSAID/acetaminophen use: treatment policy strategy; analysis will be conducted regardless of use of prohibited medications or NSAID/acetaminophen use.	Difference in the change from parent-study baseline between LOR and placebo using parent-study baseline-adjusted ANCOVA with available data.
	Sensitivity 3	Change from parent-study baseline in WOMAC Total at Visit 2E (Week 24)	PPAS	1) Prohibited medications: principal stratum strategy; subjects who used prohibited medications will be excluded from this analysis. 2) NSAID/acetaminophen: treatment policy strategy; analysis will be conducted regardless of NSAID/acetaminophen use.	Difference in the change from parent-study baseline between LOR and placebo using parent-study baseline-adjusted ANCOVA.
Estimand is repeated using the OA-07-study baseline					

	Estimator	Variable	Population	Other intercurrent events	Population level summary
Other	Main	Change from parent-study baseline in WOMAC Stiffness at Visit 2E (Week 24)	FAS	Prohibited medications and NSAID/acetaminophen use: treatment policy strategy; analysis will be conducted regardless of use of prohibited medications or NSAID/acetaminophen use.	Difference in the change from parent-study baseline between LOR and placebo using parent-study baseline-adjusted ANCOVA with available data.
	Sensitivity 1	Change from parent-study baseline in WOMAC Stiffness at Visit 2E (Week 24)	FAS	Prohibited medications and NSAID/acetaminophen use: treatment policy strategy; analysis will be conducted regardless of use of prohibited medications or NSAID/acetaminophen use.	Difference in the change from parent-study baseline between LOR and placebo using parent-study baseline-adjusted ANCOVA with missing data imputed using the MI method.
	Sensitivity 2	Change from parent-study baseline in WOMAC Stiffness at Visit 2E (Week 24)	mFAS	Prohibited medications and NSAID/acetaminophen use: treatment policy strategy; analysis will be conducted regardless of use of prohibited medications or NSAID/acetaminophen use.	Difference in the change from parent-study baseline between LOR and placebo using parent-study baseline-adjusted ANCOVA with available data.
	Sensitivity 3	Change from parent-study baseline in WOMAC Stiffness at Visit 2E (Week 24)	PPAS	1) Prohibited medications: principal stratum strategy; subjects who used prohibited medications will be excluded from this analysis. 2) NSAID/acetaminophen: treatment policy strategy; analysis will be conducted regardless of NSAID/acetaminophen use.	Difference in the change from parent-study baseline between LOR and placebo using parent-study baseline-adjusted ANCOVA.
Estimand is repeated using the OA-07-study baseline					

	Estimator	Variable	Population	Other intercurrent events	Population level summary
Other	Main	Change from parent-study baseline in mJSW at Visit 6E (Week 100)	FAS: "Placebo-LOR" subjects	Prohibited medications and NSAID/acetaminophen use: treatment policy strategy; analysis will be conducted regardless of use of prohibited medications or NSAID/acetaminophen use.	Difference in the change from parent-study baseline between "Placebo-LOR" subjects compared to test values (carry forward and progression assumptions) derived from the Placebo group change from baseline estimates at Visit 3E (Week 48). Estimates will use parent-study baseline-adjusted ANCOVA with available data.
	Main	Change from parent-study baseline in mJSW at Visit 6E (Week 100)	FAS: "LOR-LOR" subjects	Prohibited medications and NSAID/acetaminophen use: treatment policy strategy; analysis will be conducted regardless of use of prohibited medications or NSAID/acetaminophen use.	Difference in the change from parent-study baseline between "LOR-LOR" subjects compared to test values (carry forward and progression assumptions) derived from the Placebo group change from baseline estimates at Visit 3E (Week 48). Estimates will use parent-study baseline-adjusted ANCOVA with available data.
	Main	Change from parent-study baseline in mJSW at Visit 6E (Week 100)	FAS: Pooled "Placebo-LOR" and "LOR-LOR" subjects	Prohibited medications and NSAID/acetaminophen use: treatment policy strategy; analysis will be conducted regardless of use of prohibited medications or NSAID/acetaminophen use.	Difference in the change from parent-study baseline between pooled "Placebo-LOR" and "LOR-LOR" subjects compared to test values (carry forward and progression assumptions) derived from the Placebo group change from baseline estimates at Visit 3E (Week 48). Estimates will use parent-study baseline-adjusted ANCOVA with available data.
Estimand is repeated using the OA-07-study baseline					

15.3 Appendix 3 – Partial Date Imputation

Partial Date Availability	Impute Start Date		Impute End Date	
Year (YYYY)	**Prior to first OA-07 injection year**	YYYY-12-31	**Prior to end of study year**	YYYY-12-31
	Same as first OA-07 injection year	Injection Date	**Same as end of study year**	End of Study Date
	After first OA-07 injection year	YYYY-01-01	**After end of study year**	YYYY-01-01
Year and Month (YYYY-MM)	**Prior to first OA-07 injection year and month**	YYYY-MM-[DD, last day of month]	**Prior to end of study year and month**	YYYY-MM-[DD, last day of month]
	Same as first OA-07 injection year and month	Injection Date	**Same as end of study year and month**	End of Study Date
	After first OA-07 injection year and month	YYYY-MM-01	**After end of study year and month**	YYYY-MM-01
Ongoing or unknown status at end of study (e.g., no end date and unknown whether ongoing)	Not Applicable		End of Study Date	
Additional Considerations	If the end date is not missing, and the imputed start date is after the end date, the start date will be set equal to the end date.		If the imputed end date is before the start date, then the imputed end date will be set equal to the start date.	

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Reason for signing: Approved	Name: Victor Lopez Role: Associate Director, Biostatistics Date of signature: 03-Nov-2023 19:05:16 GMT+0000

Reason for signing: Approved	Name: Yusuf Yazici Role: Chief Medical Officer Date of signature: 03-Nov-2023 19:06:55 GMT+0000

Reason for signing: Approved	Name: Christopher Swearingen Role: Vice President, Biometrics Date of signature: 03-Nov-2023 19:14:51 GMT+0000

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