

STRIDES

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

STATISTICAL ANALYSIS PLAN

SM04690-OA-21

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

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SIGNATURE PAGE AND APPROVALS

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Date: 01 April 2024

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TABLE OF CONTENTS

SIGNATURE PAGE AND APPROVALS	2
TABLE OF CONTENTS	3
ABBREVIATIONS	6
1. BACKGROUND.....	8
2. OVERVIEW.....	8
3. STUDY OBJECTIVES AND ENDPOINTS	8
3.1 Study Objective	8
3.2 Study Endpoints	8
3.2.1 Primary Efficacy Endpoint	8
3.2.2 Secondary Efficacy Endpoints	8
3.2.3 Safety Endpoints	9
3.2.4 Other Endpoints	9
4. OVERALL STUDY DESIGN AND PLAN	9
4.1 Selection of Study Population	9
4.2 Method of Treatment Assignment and Randomization	10
4.3 Treatment Blinding	10
4.4 Minimization of Missing Data	10
4.4.1 Collection of Clinical Outcomes.....	10
4.4.2 Rescue Medication.....	10
4.4.3 Prohibited Medications, Treatments, and Procedures.....	10
4.4.4 Intermittent Missing Data	11
5. SAMPLE SIZE DETERMINATION	11
6. ANALYSIS POPULATIONS	11
6.1 Full Analysis Set	11
6.2 Per-Protocol Analysis Set	12
6.3 Safety Analysis Set.....	12
6.4 Duplicate Subjects.....	12
7. GENERAL ISSUES FOR STATISTICAL ANALYSIS	13
7.1 General Statistical Methodology	13
7.1.1 Baseline.....	13

7.1.2	Mixed-Effects Model for Repeated Measures	13
7.1.3	Analysis of Covariance	14
7.1.4	Adjustment for Multiplicity	14
7.1.5	Data Handling for Patients Who Withdrew from the Study	14
7.1.6	Imputation of Missing Data	15
7.1.6.1	Tipping Point Analysis.....	16
7.2	Interim Analysis	16
7.3	Efficacy Assessments.....	16
7.3.1	Pain NRS.....	16
7.3.2	WOMAC.....	16
7.3.3	Patient Global Assessment of Disease Activity.....	17
7.3.4	Knee Injury and Osteoarthritis Outcome Score (KOOS)	17
7.3.5	Patient-Acceptable Symptom State Questionnaire (PASS).....	18
7.3.6	Rescue Medication Usage.....	18
7.4	Safety Assessments	18
7.4.1	Adverse Events	18
7.4.2	Vital Signs and Weight	19
7.4.3	Clinical Laboratory Evaluations	19
8.	STUDY SUBJECTS AND DEMOGRAPHICS	19
8.1	Disposition of Subjects and Withdrawals	19
8.2	Protocol Deviations	20
8.3	Demographics and Other Baseline Characteristics	21
8.4	Medical History.....	21
9.	EFFICACY ANALYSIS	21
9.1	Estimands	22
9.2	Primary Efficacy Analysis	22
9.2.1	Main Analysis	22
9.2.2	Sensitivity Analysis	23
9.3	Secondary Efficacy Analysis	23
9.3.1	Main Analysis	23
9.3.2	Sensitivity Analysis	23
9.4	Other Efficacy Analysis	24

10.	SAFETY AND TOLERABILITY ANALYSIS	24
10.1	Adverse Events	24
10.2	Clinical Laboratory Evaluations	25
10.3	Vital Signs and Weight.....	25
10.4	Physical Examination	25
11.	OTHER/EXPLORATORY ANALYSIS.....	25
11.1	Sites	25
11.2	Subgroups	26
12.	MEDICATIONS	26
12.1	Concomitant Medication	26
12.2	Exposure	27
13.	CHANGES TO PLANNED ANALYSIS	27
14.	REFERENCES.....	28
15.	APPENDICIES	29
15.1	Appendix 1 – Visit Windows	29
15.2	Appendix 2 – Protocol Deviations Leading to Exclusion from Per-Protocol Analysis 30	
15.3	Appendix 3 – Estimands.....	33

ABBREVIATIONS

Abbreviation	Term
AE	Adverse event
ANCOVA	Analysis of covariance
APAP	Acetaminophen
AR1	Autogressive-1
ATC	Anatomical therapeutic chemical
BOCF	Baseline observation carried forward
BMI	Body mass index
CDISC	Clinical Data Interchange Standards Consortium
eCRF	Electronic case report form
EOS	End of study
ET	Early termination
FAS	Full Analysis Set
IP	Investigational Product
KL	Kellgren-Lawrence
LOCF	Last observation carried forward
LOR	Lorecivivint (SM04690)
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	Weekly average of daily pain numeric rating scale

Abbreviation	Term
PBO	Placebo
PPAS	Per-Protocol Analysis Set
SAE	Serious adverse event
SAS	Safety Analysis Set
SD	Standard deviation
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
WOMAC Total	WOMAC Total score
WOCF	Worst observation carried forward
WPI	Widespread Pain Index

1. BACKGROUND

Osteoarthritis (OA) is the most common form of arthritis and the major cause of activity limitation and physical disability in older people.¹ There is an unmet need for pharmacological agents that improve pain and function, and potentially have disease-modifying properties, while still being safe to use by patients with comorbid conditions or concomitant medications.²

To address the need for effective pharmaceutical agents to treat OA, Biosplice has developed lorecivint (LOR; previously SM04690) as a potential OA therapeutic to be administered as a local injection in the affected joint. LOR is a novel, small-molecule IA inhibitor of CLK/DYRK thought to modulate Wnt and inflammatory pathways and being developed as a potential treatment for OA. In clinical trials, LOR improved pain, function and structure compared to treatment with placebo (PBO).^{3,4} In these clinical studies, LOR has been well tolerated with a safety profile similar to that of PBO.

2. OVERVIEW

This study was a multicenter, randomized, double-blind, PBO-controlled, parallel-group study of a single dose of LOR injected into the target knee joint of moderately to severely symptomatic OA subjects.

3. STUDY OBJECTIVES AND ENDPOINTS

3.1 Study Objective

The objective of this study was to determine the efficacy, safety, and tolerability of the LOR Injectable Suspension 0.07 mg dose in the treatment of knee OA.

3.2 Study Endpoints

3.2.1 Primary Efficacy Endpoint

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

3.2.2 Secondary Efficacy Endpoints

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

3.2.3 Safety Endpoints

1. Adverse events (AEs), serious AEs (SAEs), vital signs, and clinical laboratory measures for the duration of the study

3.2.4 Other Endpoints

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

4. OVERALL STUDY DESIGN AND PLAN

This study was a multicenter, randomized, double-blind, PBO-controlled, parallel-group study of a single dose of LOR injected into the target knee joint of moderately to severely symptomatic OA subjects on Day 1.

4.1 Selection of Study Population

The study population included ambulatory males and females between 40 and 80 years of age, inclusive, with moderately to severely symptomatic knee OA. Complete inclusion/exclusion criteria are available in the study protocol.

4.2 Method of Treatment Assignment and Randomization

Subjects were randomized 1:1 (0.07 mg active per 2 mL injection:2 mL PBO) to each treatment group using Zelta's (formerly IBM Clinical Development) randomization module with a permuted block design stratified by study site. 250 blocks of size 6 were generated for a total of 1500 possible subject slots.

4.3 Treatment Blinding

This was a double-blind study. As there are visual differences between the LOR and PBO solution, extra blinding procedures were established at each site as follows:

Study medication was provided to the investigational center, which identified unblinded personnel who were able to prepare and perform the injection of study medication. Study personnel administering or preparing study medication minimized any contact with the subject following the injection and could not perform any study assessments throughout the duration of the study. Each site was required to follow a blinding plan that identified the blinded and unblinded personnel at the investigational center and described how the study blind will be maintained.

4.4 Minimization of Missing Data

4.4.1 Collection of Clinical Outcomes

Clinical outcomes data were collected using electronic diary (see Protocol [Section 7.3.7](#) for schedule of diary data collection). Eligibility criteria for the trial included successful completion of the electronic diary in the collection of both Pain NRS and WOMAC Function (see Inclusion Criteria 10-11). Use of electronic diary as well as enriching for subjects compliant with electronic diary use were specific protocol strategies designed to minimize the loss of key endpoint data.

4.4.2 Rescue Medication

Subjects were instructed to avoid using prohibited medication during this study (see Protocol [Section 7.8](#)). Subjects were permitted to take study-provided rescue medication (acetaminophen [APAP] 500 mg, maximum 3000 mg per 24-hour period) to treat worsening knee OA pain or other types of pain that could not be tolerated. Additionally, sites were instructed to capture the amount and frequency of rescue medication use. This rescue medication policy, in addition to quantifying rescue medication use, was designed to minimize the loss of key endpoint data and provide assessment of the rescue medication's impact on key endpoint data.

4.4.3 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 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. Primary and secondary outcome measures impacted by the use of prohibited medication will be censored and imputed based on the methods described in [Sections 9.2 and 9.3](#).

4.4.4 Intermittent Missing Data

Ongoing programmatic surveillance of electronic diary and visit compliance using intranet dashboards during trial conduct led to the identification of subjects that were not compliant with their electronic diary entries. 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 electronic diary compliance was a specific strategy designed to minimize the loss of key endpoint data.

5. SAMPLE SIZE DETERMINATION

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

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

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

6. ANALYSIS POPULATIONS

6.1 Full Analysis Set

The Full Analysis Set (FAS) includes all subjects who were randomized and received a study injection. The FAS is used to describe the analysis set which is as complete as possible and as close as possible to the intent-to-treat ideal of including all randomized subjects. Subjects will be analyzed as randomized for the FAS.

6.2 Per-Protocol Analysis Set

The Per-Protocol Analysis Set (PPAS) includes FAS subjects who received the correct treatment, completed the study, and did not have any protocol deviations 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. Subjects will be analyzed as treated for the SAS.

6.4 Duplicate Subjects

As part of routine monitoring, a search was conducted for subjects who inappropriately participated in more than one LOR study or at more than one site in OA-21. The following subjects were considered duplicate subjects and were excluded from all analysis sets:

Unique Subject Identifier	Study ID	Subject Identifier for the Study	Comment	Start/End Date of Study Participation
SM04690-OA-21-13021046	SM04690-OA-21	13021046	Randomized and injected left knee on 2023-07-14	2023-06-08 2023-11-08
	SM04690-OA-21	12821038	Randomized and injected right knee on 2023-08-14	2023-07-17 2023-11-29
SM04690-OA-11-0297018	SM04690-OA-11	0297018	Randomized and injected right knee on 2020-06-05	2020-05-29 2021-07-12
	SM04690-OA-21	11521008	Randomized and injected right knee on 2023-03-02	2023-02-06 2023-06-20
SM04690-OA-10-0065128	SM04690-OA-10	0065128	Randomized and injected right knee on 2020-09-01	2020-08-25 2021-03-17
	SM04690-OA-21	11921072	Randomized and injected right knee on 2023-06-13	2023-05-17 2023-09-27
SM04690-OA-10-0025108	SM04690-OA-10	0025108	Randomized and injected right knee on 2020-07-27	2020-07-20 2021-02-09

	SM04690-OA-21	13421018	Randomized and injected left knee on 2023-04-26	2023-03-30 2023-08-22
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Adverse events for the above subjects will be listed separately.

7. GENERAL ISSUES FOR STATISTICAL ANALYSIS

7.1 General Statistical Methodology

Unless otherwise specified, efficacy analyses will be performed on the FAS and PPAS; general safety 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 the summary tables but will be included in subject-level listings as appropriate.

7.1.1 Baseline

Baseline is defined as the last value recorded for any given parameter prior to study medication injection.

7.1.2 Mixed-Effects Model for Repeated Measures

A mixed-effects model for repeated measures (MMRM) will be used to evaluate Pain NRS, WOMAC, and Patient Global Assessment outcome measures. The null hypothesis is that the mean difference in the endpoints between the two treatment groups is zero, versus the alternative hypothesis that this difference is not zero (two-sided hypothesis testing). The hypotheses can be expressed as follows:

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

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

where β_0 refers to the least squares mean change from baseline in the PBO group and β_1 refers to the least squares mean change from baseline in the active treatment group, evaluated at timepoint t .

For Pain NRS, the model will be estimated assuming a Toeplitz variance-covariance matrix. The Toeplitz structure is a more generalized form of autoregressive-1 (AR1) structure, allowing the

data to inform how the correlation between within-subject observations decreases over time instead of implicitly defining a uniform decay structure.⁵ In the event that convergence criteria is not met under the Toeplitz structure, AR1 will be used.

For WOMAC Function, WOMAC Pain, WOMAC Total and Patient Global Assessment, the model will be estimated assuming an unstructured variance-covariance matrix, allowing the data to fully inform the correlation between within-subject observations.⁵

MMRM presumes that missing data are not caused by something observable within the conduct of the trial (i.e., missing-at-random [MAR]). It is plausible to presume a MAR mechanism as there have been no observed tolerability issues to the administration of study injection during the prior development trials. Additionally, the study injection cannot be removed after it has been administered, eliminating study drug discontinuation as a source of treatment estimate confounding. Special consideration will be given to subjects who discontinue the study for a reason that may suggest lack of efficacy, where the MAR assumption may no longer be appropriate. Details of this special handling are described in [Section 7.1.5](#).

7.1.3 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 PBO and β_1 is the estimate for the active treatment group. The models will be adjusted for baseline value of the outcome.

7.1.4 Adjustment for Multiplicity

Familywise error rate will be controlled in the strong sense using the closed, fixed sequence testing method.⁶ All hypothesis tests will be evaluated in the sequential order described in [Section 9](#).

7.1.5 Data Handling for Patients Who Withdrew from the Study

If a subject discontinues the study, early termination assessments will be performed according to the protocol. If these assessments occur during a scheduled visit, they will be associated with that visit for the purposes of FAS analysis. Subjects who discontinued the study due to a reason that may suggest lack of efficacy (including Lack of Efficacy, Adverse Event and Lost to Follow-Up) will have missing primary and secondary outcome data imputed using the worst observation carried forward (WOCF) method through Week 12.

7.1.6 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 (with the exception described in [Section 7.1.5](#)) following the paradigm first developed by Rubin.⁷ 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.⁷ 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

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

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 original missing records were imputed. Imputations will be performed with a seed of 469021.

7.1.6.1 Tipping Point Analysis

The MI paradigm, as proposed by Rubin⁷, does not require nor assume any specific assumption about the nature of the missing data. Further, imputations can be (theoretically) created under any assumption of missing mechanism. A two-way tipping point analyses will be conducted to evaluate the robustness of the analyses with MI under the MAR assumption. With the tipping point approach, several additional MI datasets are created, each departing slightly from the assumptions used in the original analysis. The intended result is to establish a certain point in which the new shifted imputations have “tipped”, or overturned, the original conclusions from the original analysis (i.e., a statistically significant result is now not statistically significant). The magnitude of the shift required to tip the analysis is then evaluated for plausibility; an implausible shift will lead to the conclusion that the MI analysis is robust to departures from MAR assumption.

The tipping point exercise will be conducted only for MI analysis(es) that is/are statistically significant under the MAR assumption. Applicable MI analyses will be reassessed by shifting the imputed values for the treatment group by intervals of ± 0.5 for Pain NRS and ± 5 for WOMAC and Patient Global. An implausible shift parameter would be higher in magnitude than the observed difference in mean change in the associated outcome between the treatment and PBO groups.

7.2 Interim Analysis

There is no planned interim analysis for this study.

7.3 Efficacy Assessments

7.3.1 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. Subjects were prompted to report average pain in both knees daily on their electronic device (between 5:00 pm and 11:59 pm) during the screening period (Screening Visit 2 until Day 1) and on the target knee only starting from Day 1 through the end of the study. An average weekly score (referred to as Pain NRS) was calculated for each subject if they had provided a response for at least 4 out of 7 days in a given week. Weeks are defined as Day -7 through Day -1 (day before treatment) for baseline, Day 1 (day of treatment) through Day 7 for Week 1, Day 8 through Day 14 for Week 2, and so on as detailed in [Appendix 1 – Visit Windows](#). The day on which subjects completed their scheduled study visits (e.g., Week 4 Visit, Week 12 Visit, etc.) does not impact the above definition of weeks.

7.3.2 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.^{8,9} The WOMAC Version NRS 3.1 was to be

completed once a week by the subject for their target knee in the evening (between 5:00 pm and 11:59 pm) remotely on their electronic device after their Screening Visit 2 and up until the day before the Day 1 visit. After Day 1, WOMAC assessments were to be completed by the subject for their target knee in the evening (between 5:00 pm and 11:59 pm) remotely on their electronic device at Weeks 4, 8, 12, and 16 (with windows of ± 7 days). The devices required subjects to enter a response for each item before proceeding to the next. If an assessment was completed more than once within a window, only the first assessment will be used for analysis. All visit windows are detailed in [Appendix 1 – Visit Windows](#).

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.

7.3.3 Patient Global Assessment of Disease Activity

The Patient Global Assessment is an 11-point [0-10] NRS on which the subjects rated how they felt their target knee OA was doing, considering all the ways in which their target knee OA may have affected them. The NRS was anchored by descriptors at each end (“Very Good” on the left and “Very Bad” on the right). The Patient Global Assessment was to be completed by the subject in the evening (between 5:00 pm and 11:59 pm) remotely on their electronic device once a week after their Screening Visit 2 and up until the day before the Day 1 visit. After Day 1, Patient Global Assessment was to be completed by the subject in the evening (between 5:00 pm and 11:59 pm) remotely on their electronic device at Weeks 4, 8, 12, and 16 (with windows of ± 7 days). If an assessment was completed more than once within a window, only the first assessment will be used for analysis. All visit windows are detailed in [Appendix 1 – Visit Windows](#). For analysis, Patient Global Assessment scores will be scaled to 0-100, where 0 represents “Very Good” and 100 represents “Very Bad”.

7.3.4 Knee Injury and Osteoarthritis Outcome Score (KOOS)

KOOS is a widely used, non-proprietary tool used by health professionals to assess a subject’s opinion about their knee and associated problems. As the KOOS is an extension of the WOMAC and includes pain, function and stiffness subscores, subjects only completed the KOOS subscales for Function (Sports) and knee-related Quality of Life.¹⁰ The KOOS questionnaire subscales were to be completed once a week by the subject for their target knee in the evening (between 5:00 pm and 11:59 pm) remotely on their electronic devices after Screening Visit 2 up until the day before the Day 1 visit. After Day 1, KOOS questionnaires were to be completed by the subject in the evening (between 5:00 pm and 11:59 pm) remotely on their electronic device at Weeks 4, 8, 12, and 16 (with windows of ± 7 days). All visit windows are detailed in [Appendix 1 – Visit Windows](#)

KOOS Function (sports) consists of 5 questions and KOOS Quality of Life consists of 4 questions. All KOOS questions used a five-point Likert scale. For analysis, KOOS subscores will

be totaled and scaled to 0-100, where 0 represents “Severe Knee Problems” and 100 represents “No Knee Problems”.

7.3.5 Patient-Acceptable Symptom State Questionnaire (PASS)

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 are able to choose the answers of “Yes” or “No.”. The PASS Questionnaire was to be completed by the subject in the evening (between 5:00 pm and 11:59 pm) remotely on their electronic device once a week after their Screening Visit 2 and up until the day before the Day 1 visit. After Day 1, PASS was to be completed by the subject in the evening (between 5:00 pm and 11:59 pm) remotely on their electronic device at Weeks 4, 8, 12, and 16 (with windows of ± 7 days). If an assessment was completed more than once within a window, only the first assessment will be used for analysis. All visit windows are detailed in [Appendix 1 – Visit Windows](#).

7.3.6 Rescue Medication Usage

On Day 1 and Weeks 4, 8, and 12, subjects were dispensed APAP for use as rescue medication (refer to the Pharmacy Manual for further details). Rescue medication usage was documented daily on the study-provided electronic device. Starting on Day 1 after the site visit, daily electronic diary of rescue medication usage was completed by subjects in the evening (between 5:00 pm and 11:59 pm) remotely on their electronic devices. Subjects received notifications reminding them to complete the electronic diary of rescue medication usage. The electronic diary for rescue medication usage was reviewed at all visits after Day 1 except for Week 16 (EOS) or ET for compliance and subject safety. All visit windows are detailed in [Appendix 1 – Visit Windows](#).

Use of rescue medication will be summarized as number and percentage of subjects that reported at least one day of rescue medication use across weeks and by treatment groups. Rescue medication will also be incorporated in sensitivity analyses to account for its use. The rescue medication estimands defined for this study are available in [Appendix 3 – Estimands](#).

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 Screening Visit 2, and Week 16 (EOS) or ET. At each time point, the following vitals were measured:

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

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

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

7.4.3 Clinical Laboratory Evaluations

Fasting specimens for clinical laboratory analysis were to be collected at Screening Visit 2 and Week 16 (EOS) or ET. At a minimum, the following tests were conducted:

- **Chemistry panel:** Albumin, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, blood urea nitrogen, bicarbonate, calcium (corrected total), chloride, creatinine, glucose, lactate dehydrogenase, potassium, sodium, bilirubin (total)
- **Hematology:** Hemoglobin, hematocrit, red blood cell count, white blood cell 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, occult blood, or nitrite values were out of range, or if the Investigator deemed that the microscopy was clinically warranted

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, randomized, treated, completed the study, or discontinued (e.g., adverse event, subject decision, etc.) overall and by treatment group. Additionally, subject

disposition for randomized 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:

- Inclusion/Exclusion Criteria
- Procedure Not Performed
- Procedure Performed Incorrectly
- Procedure Out of Window
- Visit Not Performed
- Visit Out of Window
- Study Treatment Related
- Prohibited medication

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

- 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. Prior to database lock, all protocol deviations were reviewed by blinded 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. 28 subjects with the following types of deviations were excluded from PPAS:

- Inclusion/Exclusion Criteria: n = 9
- Procedure Not Performed: n = 17
- Prohibited medication: n = 2

A final list of protocol deviations resulting in subject or data exclusion from the PPAS can be found in [Appendix 2 – 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.

8.3 Demographics and Other Baseline Characteristics

Demographic and baseline characteristics, including sex, race, ethnicity, age at baseline, weight, height, body mass index (BMI), Kellgren-Lawrence (KL) grade, Widespread Pain Index (WPI), Symptom Severity Question 2 (SSQ2), Osteoarthritis Research Society International joint space narrowing (OARSI JSN) 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

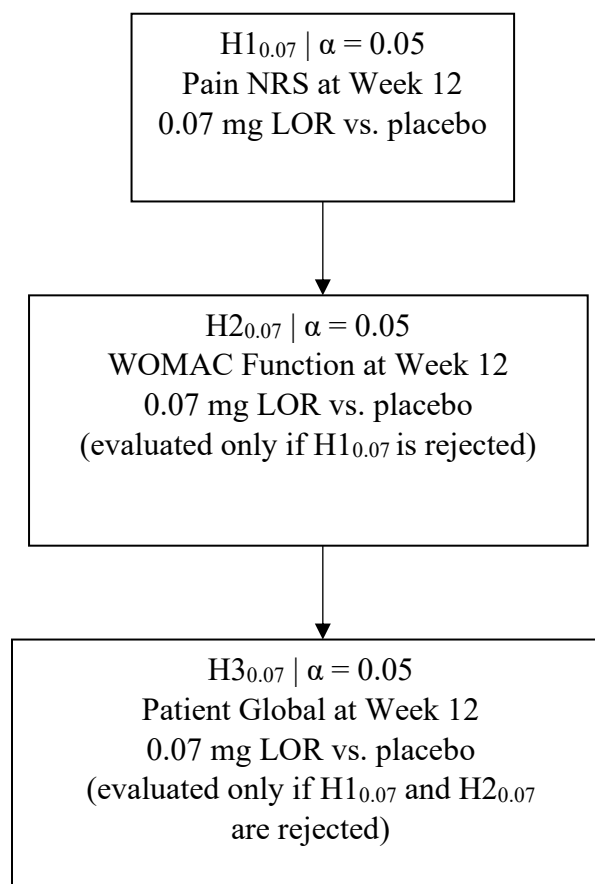
A summary of reported medical history will be provided by MedDRA system organ class on the Safety Analysis Set for each treatment group. A subject-level listing will provide further information on each event.

9. EFFICACY ANALYSIS

The statistical hypotheses being tested in this study are:

1. The least squares estimate of improvement from baseline in Pain NRS at Week 12 is greater for subjects who received LOR compared to PBO.
2. The least squares estimate of improvement from baseline in WOMAC Function at Week 12 is greater for subjects who received LOR compared to PBO.
3. The least squares estimate of improvement from baseline in Patient Global Assessment at Week 12 is greater for subjects who received LOR compared to PBO.

The familywise error rate will be controlled in the strong sense using the closed, fixed sequence testing method.⁶ All hypothesis tests will be evaluated in the sequential order as listed above. Although formal hypothesis testing will stop once the first non-significant result is achieved (i.e., $p > 0.05$), all subsequent results and p-values will still be reported for reference.



9.1 Estimands

A summary of all estimands defined for this study is available in [Appendix 3 – Estimands](#).

9.2 Primary Efficacy Analysis

9.2.1 Main Analysis

The primary estimand for this trial is the difference between a single injection of 0.07 mg LOR versus PBO in mean baseline-adjusted change in weekly average of daily pain NRS at Week 12, whether or not rescue medication is used (i.e. presuming a treatment policy of rescue medication usage as needed), and analyzed with a mixed effects model for repeated measures (MMRM), including all collected Pain NRS data (i.e., Weeks 1 to 16 (EOS)) in subjects in the FAS.

- A hypothetical treatment strategy will be presumed for the use prohibited medication, which will censor Pain NRS data that were reported while on the prohibited therapy and impute the subject's last recorded weekly Pain NRS prior to the start of the prohibited

therapy (LOCF).

- A not missing-at-random (NMAR) assumption will be applied to missing Pain NRS data as a result of subject's discontinuation from the study due to a reason that may suggest lack of efficacy. The subject's highest recorded weekly Pain NRS will be used for this imputation (WOCF) through Week 12 in order to assume the subject's perceived lack of treatment effectiveness.

9.2.2 Sensitivity Analysis

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

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

9.3 Secondary Efficacy Analysis

9.3.1 Main Analysis

Change over time in WOMAC Function and Patient Global Assessment will be characterized using MMRM to estimate change from baseline with treatment group, week, treatment×week interaction and baseline value as covariates. The models will include all timepoints where WOMAC and Patient Global were assessed (i.e., Week 4, Week 8, Week 12, and Week 16 (EOS)) for subjects in the FAS and will be evaluated for LOR versus PBO at Week 12. A treatment policy strategy will be presumed for the use of rescue medication and hypothetical treatment strategy will be presumed for the use prohibited medication. Subjects who discontinue the trial due to a reason that may suggest lack of efficacy will have their highest recorded WOMAC Function and Patient Global Assessment value imputed for missing data through Week 12.

9.3.2 Sensitivity Analysis

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

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

9.4 Other Efficacy Analysis

Change over time in WOMAC Pain and WOMAC Total scores as well as KOOS Function (Sports) and KOOS Quality of Life subscores will be characterized using a MMRM to estimate change from baseline with treatment group, week, treatment $\times$ week interaction and baseline value as covariates. The model will include all timepoints where WOMAC was assessed. Unadjusted 95% confidence intervals and P values will be reported for all timepoints.

The number and percent of subjects reporting “Yes” to Patient Acceptable Symptom State (PASS), reporting rescue medication usage, as well as 30% improvement, 50% improvement, and 70% improvement in Pain NRS, WOMAC Function, and Patient Global Assessment will be summarized. Logistic regression analysis will be implemented for improvement in these assessments as well, with 95% confidence intervals and P values reported.

The analyses described above will be performed on subjects in the FAS.

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

All AEs collected in this study are treatment emergent events that occur during the course of the study that are not present prior to Day 1 study medication injection, or, if present at the time of study medication injection, have worsened in severity during the course of the study. AEs will be presented in summary tables depicting the number and percent of unique subjects experiencing each AE and the number of AEs overall and within each treatment group. 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
- 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
- SAEs in subjects diagnosed with COVID-19

Separate subject-level listings will be provided for all AEs and all SAEs.

10.2 Clinical Laboratory Evaluations

All chemistry, hematology and quantitative urinalysis results from the central laboratory will be summarized into shift tables as normal (within), low (below), and high (above). Qualitative urinalysis results from the central laboratory will be summarized into shift tables as normal vs abnormal. Shift tables will compare the number and percent of assessments from each visit to baseline values for each treatment group. If any abnormal, clinically significant laboratory measure is found before study medication injection, the subject is to be excluded. If it is found after study medication injection, it should be reported as an AE.

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 the subsequent visit (i.e., Week 16 (EOS)). If more than one result is available at Week 16 (EOS), only the first result will be used for analysis. If a result is below or above the limit of quantification, it will be set to the limit of quantification (e.g., “<3” will be analyzed as 3; “>60 will be analyzed as 60”). The International System of Units (SI) will be used for all summaries.

Abnormal/Low/High chemistry, hematology, urinalysis, and urine microscopy results for each subject will be provided in listings that will include laboratory test name, result, and normal range. HbA1c values will be listed in conventional units (%).

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 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 were recorded as medical history. If it was found after study medication injection, it was reported as an AE.

11. OTHER/EXPLORATORY ANALYSIS

11.1 Sites

Randomization was stratified by site. Although this should minimize site differences and potential interactions, exploratory analyses taking site into account may be conducted if anomalies in the data are observed.

11.2 Subgroups

Efficacy analyses described in [Sections 9.2](#) and [9.3](#) will be further explored with the following subgroups:

- Baseline pain NRS [4-7)
- Baseline pain NRS [7-9]
- Unilateral symptomatic OA
- Bilateral symptomatic OA
- Study site
- BMI <30 kg/m²
- BMI ≥30 kg/m²
- Age < 65
- Age [65 – 74]
- Age 75+

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 prior and concomitant medications by Anatomical Main Group (Anatomical Therapeutic Chemical, ATC, Level 1), Therapeutic Subgroup (ATC Level 2), and preferred term. Prior and concomitant medication usage will be summarized by the number and percentage of subjects receiving each medication by treatment group.

The subgroup of medications initiated after first exposure to study product will be summarized in the same manner. If a medication start or end date is incomplete, it will be imputed in a way that assumes maximum exposure time (see Table below).

Partial Date Availability	Impute Start Date		Impute End Date	
Year (YYYY)	Prior to Injection year	YYYY-12-31	Prior to end of study year	YYYY-12-31
	Same as Injection year	Injection Date	Same as end of study year	End of Study Date
	After Injection year	YYYY-01-01	After end of study year	YYYY-01-01
Year and Month (YYYY-MM)	Prior to 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 Injection year and month	Injection Date	Same as end of study year and month	End of Study Date
	After 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.	

Subject-level listings containing prior and 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

All treated subjects received a single injection. A list of lot numbers used in this study will be provided in the clinical study report.

13. CHANGES TO PLANNED ANALYSIS

Change	Protocol Section	Rationale
Analysis by KL grade was removed from the subgroup section.	10.4.9	The enrolled study population was almost entirely KL Grade 2.
Analysis of Baseline pain NRS is defined as [4-7).	10.4.9	The protocol defined a closed set for both baseline pain NRS groups that included 7.
Analysis by age group was added to the subgroup section.	10.4.9	Exploration of efficacy across age groups may be informative.
Analysis by study site was added to the subgroup section.	10.4.9	Due to regulatory agency feedback.
Trial enrolled 499 subjects.	10.5	Administrative decision to close enrollment was made given the enrolled study population being almost entirely KL Grade 2.

14. REFERENCES

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15. APPENDICIES

15.1 Appendix 1 – Visit Windows

Visit	WOMAC, KOOS, PASS, and Patient Global Assessment	Pain NRS
Baseline	Last value before first injection	Day -7 to -1
Week 1		Day 1 to 7
Week 2		Day 8 to 14
Week 3		Day 15 to 21
Week 4	Day 21 to 35	Day 22 to 28
Week 5		Day 29 to 35
Week 6		Day 36 to 42
Week 7		Day 43 to 49
Week 8	Day 49 to 63	Day 50 to 56
Week 9		Day 57 to 63
Week 10		Day 64 to 70
Week 11		Day 71 to 77
Week 12	Day 77 to 91	Day 78 to 84
Week 13		Day 85 to 91
Week 14		Day 92 to 98
Week 15		Day 99 to 105
Week 16 (EOS)	Day 105 to 119	Day 106 to 112

For the purpose of analysis, Day 1 is the date the subject was treated/injected.

15.2 Appendix 2 – Protocol Deviations Leading to Exclusion from Per-Protocol Analysis

Subject	Category	Deviation Description	Related Visit
10121071	INCLUSION/EXCLUSION CRITERIA	SITE WAS NOTIFIED BY STUDY MANAGEMENT AFTER SCREENING AND BASELINE WAS COMPLETED, THAT THIS SUBJECT WAS ALREADY SCREENED AT ANOTHER SITE (SUBJECT NUMBER 15521015)).	SCREENING VISIT 1
10921040	PROCEDURE NOT PERFORMED	SUBJECT DID NOT COMPLETE WOMAC, KOOS, PASS, AND PGA QUESTIONNAIRES IN THE SCREENING PERIOD RESULTING IN NO BASELINE FOR THESE. BASELINE NEEDED FOR SECONDARY ENDPOINTS ON THE STUDY.	NA
11021024	PROCEDURE NOT PERFORMED	WOMAC, PGA, KOOS AND PASS NOT COMPLETED IN THE SCREENING PERIOD.	NA
11121016	PROCEDURE NOT PERFORMED	SUBJECT DID NOT COMPLETE WOMAC, KOOS, PASS, AND PGA QUESTIONNAIRES IN THE SCREENING PERIOD RESULTING IN NO BASELINE FOR THESE. BASELINE NEEDED FOR SECONDARY ENDPOINTS ON THE STUDY.	NA
11121075	PROCEDURE NOT PERFORMED	WOMAC, PGA, KOOS AND PASS NOT COMPLETED IN THE SCREENING PERIOD.	NA
11121198	INCLUSION/EXCLUSION CRITERIA	SUBJECT HAD PREVIOUSLY SCREEN FAILED AS SUBJECT 13021009 DUE TO INCL CRITERIA #10 UNBEKNOWN TO SITE, AND THEREFORE SHOULD NOT HAVE BEEN ENROLLED INTO THE STUDY.	DAY 1
11321012	PROCEDURE NOT PERFORMED	SUBJECT DID NOT COMPLETE WOMAC, KOOS, PASS, AND PGA QUESTIONNAIRES IN THE SCREENING PERIOD RESULTING IN NO BASELINE FOR THESE. BASELINE NEEDED FOR SECONDARY ENDPOINTS ON THE STUDY.	NA
11521021	INCLUSION/EXCLUSION CRITERIA	SUBJECT WAS RANDOMIZED WITHOUT BEING ELIGIBLE FOR THE STUDY DUE TO INCORRECT CALCULATION OF BLINDED PAIN REPORTING CRITERIA IN THE REPORT PULLED FROM ASSISTEK WEB PORTAL. THIS ISSUE HAS BEEN RESOLVED, BUT A CAPA IS ALSO IN PREPERATION BY ASSISTEK REGARDING THIS ISSUE.	DAY 1
11921023	INCLUSION/EXCLUSION CRITERIA	SUBJECT HAD PREVIOUSLY SCREEN FAILED AS SUBJECT 10221019 DUE TO INCL CRITERIA #5 UNBEKNOWN TO SITE 119, AND THEREFORE SHOULD NOT HAVE BEEN ENROLLED INTO THE STUDY. PER SITE SOURCE, MMI REVIEWER STATES ELIGIBLE ON MMI REPORT COLLECTED ON 28 MAR 2023.	SCREENING VISIT 1
11921031	INCLUSION/EXCLUSION CRITERIA	SUBJECT HAD PREVIOUSLY SCREEN FAILED AS SUBJECT 10221024 DUE TO INCL CRITERIA #10 UNBEKNOWN TO SITE 119, AND THEREFORE SHOULD NOT HAVE BEEN ENROLLED INTO THE STUDY.	SCREENING VISIT 1

11921073	INCLUSION/EXCLUSION CRITERIA	SUBJECT HAD PREVIOUSLY SCREEN FAILED AS SUBJECT 10321002 DUE TO INCL CRITERIA #10 UNBEKNOWN TO SITE 119, AND THEREFORE SHOULD NOT HAVE BEEN ENROLLED INTO THE STUDY.	SCREENING VISIT 1
12121012	INCLUSION/EXCLUSION CRITERIA	SUBJECT WAS RANDOMIZED DESPITE NOT BEING ELIGIBLE ACCORDING TO THE PARTICIPANT ELIGIBILITY REPORT.	DAY 1
12621046	PROCEDURE NOT PERFORMED	WOMAC, PGA, KOOS AND PASS NOT COMPLETED IN THE SCREENING PERIOD.	NA
13221004	PROCEDURE NOT PERFORMED	SUBJECT DID NOT COMPLETE WOMAC, KOOS, PASS, AND PGA QUESTIONNAIRES IN THE SCREENING PERIOD RESULTING IN NO BASELINE FOR THESE. BASELINE NEEDED FOR SECONDARY ENDPOINTS ON THE STUDY.	NA
13221037	PROCEDURE NOT PERFORMED	WOMAC, PGA, KOOS AND PASS NOT COMPLETED IN THE SCREENING PERIOD.	NA
13421020	PROHIBITED MEDICATION	SUBJECT IS CONSUMING TRAMADOL 20MG PRN FROM 18JUL2023 TO TREAT PAIN RESULTING FROM SURGERY ON LEFT HAND.	WEEK 12
13521055	PROCEDURE NOT PERFORMED	WEEKLY QUESTIONNAIRES- WOMAC, KOOS, PGA, PASS NOT COMPLETED BETWEEN SCREENING VISIT 2 AND DAY 1.	DAY 1
13521125	INCLUSION/EXCLUSION CRITERIA	SUBJECT DIDN'T MEET BLINDED PAIN CRITERIA (INCLUSION 10 AND 11)	DAY 1
13521126	INCLUSION/EXCLUSION CRITERIA	SUBJECT DIDN'T MEET BLINDED PAIN CRITERIA (INCLUSION 10 AND 11)	DAY 1
13921077	PROCEDURE NOT PERFORMED	WEEKLY QUESTIONNAIRES- WOMAC, KOOS, PGA, PASS NOT COMPLETED BETWEEN SCREENING VISIT 2 AND DAY 1.	DAY 1
13921137	PROCEDURE NOT PERFORMED	WEEKLY QUESTIONNAIRES- WOMAC, KOOS, PGA, PASS NOT COMPLETED BETWEEN SCREENING VISIT 2 AND DAY 1.	DAY 1
14821007	PROCEDURE NOT PERFORMED	SUBJECT DID NOT COMPLETE WOMAC, KOOS, PASS, AND PGA QUESTIONNAIRES IN THE SCREENING PERIOD RESULTING IN NO BASELINE FOR THESE. BASELINE NEEDED FOR SECONDARY ENDPOINTS ON THE STUDY.	DAY 1
15121125	PROHIBITED MEDICATION	SUBJECT CONSUMED 5MG OXYCODONE AS NEEDED DAILY FROM 02JAN2024 (ONGOING) TO TREAT AE#1 RIGHT SHOULDER REPAIR SURGERY..	WEEK 12
15621032	PROCEDURE NOT PERFORMED	SUBJECT DID NOT COMPLETE WOMAC, KOOS, PASS, AND PGA QUESTIONNAIRES IN THE SCREENING PERIOD RESULTING IN NO BASELINE FOR THESE. BASELINE NEEDED FOR SECONDARY ENDPOINTS ON THE STUDY.	DAY 1
15921018	PROCEDURE NOT PERFORMED	SUBJECT DID NOT COMPLETE WOMAC, KOOS, PASS, AND PGA QUESTIONNAIRES IN THE SCREENING PERIOD RESULTING IN NO BASELINE FOR THESE. BASELINE NEEDED FOR SECONDARY ENDPOINTS ON THE STUDY.	DAY 1

16121021	PROCEDURE NOT PERFORMED	SUBJECT DID NOT COMPLETE WOMAC, KOOS, PASS, AND PGA QUESTIONNAIRES IN THE SCREENING PERIOD RESULTING IN NO BASELINE FOR THESE. BASELINE NEEDED FOR SECONDARY ENDPOINTS ON THE STUDY.	DAY 1
16221064	PROCEDURE NOT PERFORMED	WOMAC, PGA, KOOS AND PASS NOT COMPLETED IN THE SCREENING PERIOD.	DAY 1
18021025	PROCEDURE NOT PERFORMED	SUBJECT DID NOT COMPLETE WOMAC, KOOS, PASS, AND PGA QUESTIONNAIRES IN THE SCREENING PERIOD RESULTING IN NO BASELINE FOR THESE. BASELINE NEEDED FOR SECONDARY ENDPOINTS ON THE STUDY.	DAY 1

NA = not applicable

15.3 Appendix 3 – Estimands

	Estimator	Variable	Population	Intercurrent events	Population level summary
Primary	Main	Change from baseline in Pain NRS at Week 12	0.07 mg LOR vs. PBO FAS	1) Prohibited medication: hypothetical strategy; analysis will be conducted as if the prohibited medication(s) had not been taken. 2) Rescue medication: treatment policy strategy; analysis will be conducted regardless of rescue medication usage.	Difference in the change from baseline between 0.07 mg LOR and PBO using MMRM with treatment group, week, treatment×week interaction and baseline value as covariates. If prohibited medication is taken, censor and impute weekly Pain NRS average using LOCF. If a subject discontinued the study for a reason that may suggest lack of efficacy, missing Pain NRS data will be imputed with WOCF through Week 12.
	Sensitivity 1	Change from baseline in Pain NRS at Week 12	0.07 mg LOR vs. PBO FAS	1) Prohibited medication: hypothetical strategy; analysis will be conducted as if the prohibited medication(s) had not been taken. 2) Rescue medication: treatment policy strategy; analysis will be conducted regardless of rescue medication usage.	Difference in the change from baseline between 0.07 mg LOR and PBO using baseline-adjusted ANCOVA with missing data imputed using the MI method; followed by two-way tipping point analysis. If prohibited medication is taken, censor and impute weekly Pain NRS average using LOCF. If a subject discontinued the study for a reason that may suggest lack of efficacy, missing Pain NRS data will be imputed with WOCF through Week 12.
	Sensitivity 2	Change from baseline in Pain NRS at Week 12	0.07 mg LOR vs. PBO FAS	1) Prohibited medication: hypothetical strategy; analysis will be conducted as if the prohibited medication(s) had not been taken. 2) Rescue medication: hypothetical strategy; analysis will be conducted as if the rescue medication had not been taken.	Difference in the change from baseline between 0.07 mg LOR and PBO using MMRM with treatment group, week, treatment×week interaction and baseline value as covariates. If prohibited medication is taken, censor and impute weekly Pain NRS average using LOCF. The following considerations are made for rescue medication usage: 1) if rescue is taken for target knee pain, censor and impute affected daily Pain NRS assessment using BOCF; 2) if rescue is taken for other pain, censor and impute affected daily Pain NRS assessment using LOCF. If a subject discontinued the study for a reason that may suggest lack of efficacy, missing Pain NRS data will be imputed with WOCF through Week 12.
	Sensitivity 3	Change from baseline in Pain NRS at Week 12	0.07 mg LOR vs. PBO PPAS	1) Prohibited medication: hypothetical strategy; analysis will be conducted as if the prohibited medication(s) had not been taken. 2) Rescue medication: treatment policy strategy; analysis will be conducted regardless of rescue medication usage.	Difference in the change from baseline between 0.07 mg LOR and PBO using baseline-adjusted ANCOVA. Analysis includes subjects with Pain NRS data available at Baseline and Week 12. If prohibited medication is taken, censor and impute weekly Pain NRS average using LOCF.

Secondary	Estimator	Variable	Population	Intercurrent events	Population level summary
	Main	Change from baseline in WOMAC Function at Week 12	0.07 mg LOR vs. PBO FAS	1) Prohibited medication: hypothetical strategy; analysis will be conducted as if the prohibited medication(s) had not been taken. 2) Rescue medication: treatment policy strategy; analysis will be conducted regardless of rescue medication usage.	Difference in the change from baseline between 0.07 mg LOR and PBO using MMRM with treatment group, week, treatment×week interaction and baseline value as covariates. If prohibited medication is taken, censor and impute WOMAC Function using LOCF. If a subject discontinued the study for a reason that may suggest lack of efficacy, missing WOMAC Function data will be imputed with WOCF through Week 12.
	Sensitivity 1	Change from baseline in WOMAC Function at Week 12	0.07 mg LOR vs. PBO FAS	1) Prohibited medication: hypothetical strategy; analysis will be conducted as if the prohibited medication(s) had not been taken. 2) Rescue medication: treatment policy strategy; analysis will be conducted regardless of rescue medication usage.	Difference in the change from baseline between 0.07 mg LOR and PBO using baseline-adjusted ANCOVA with missing data imputed using the MI method; followed by two-way tipping point analysis. If prohibited medication is taken, censor and impute WOMAC Function using LOCF. If a subject discontinued the study for a reason that may suggest lack of efficacy, missing WOMAC Function data will be imputed with WOCF through Week 12.
	Sensitivity 2	Change from baseline in WOMAC Function at Week 12	0.07 mg LOR vs. PBO FAS	1) Prohibited medication: hypothetical strategy; analysis will be conducted as if the prohibited medication(s) had not been taken. 2) Rescue medication: hypothetical strategy; analysis will be conducted as if the rescue medication had not been taken.	Difference in the change from baseline between 0.07 mg LOR and PBO using MMRM with treatment group, week, treatment×week interaction and baseline value as covariates. If prohibited medication is taken, censor and impute WOMAC Function using LOCF. The following considerations are made for rescue medication usage: 1) if rescue is taken for target knee pain, censor and impute affected WOMAC Function assessment using BOCF; 2) if rescue is taken for other pain, censor and impute affected WOMAC Function assessment using LOCF. If a subject discontinued the study for a reason that may suggest lack of efficacy, missing WOMAC Function data will be imputed with WOCF through Week 12.
	Sensitivity 3	Change from baseline in WOMAC Function at Week 12	0.07 mg LOR vs. PBO PPAS	1) Prohibited medication: hypothetical strategy; analysis will be conducted as if the prohibited medication(s) had not been taken. 2) Rescue medication: treatment policy strategy; analysis will be conducted regardless of rescue medication usage.	Difference in the change from baseline between 0.07 mg LOR and PBO using baseline-adjusted ANCOVA. Analysis includes subjects with WOMAC Function data available at Baseline and Week 12. If prohibited medication is taken, censor and impute weekly WOMAC Function average using LOCF.

	Estimator	Variable	Population	Intercurrent events	Population level summary
Secondary	Main	Change from baseline in Patient Global Assessment at Week 12	0.07 mg LOR vs. PBO FAS	1) Prohibited medication: hypothetical strategy; analysis will be conducted as if the prohibited medication(s) had not been taken. 2) Rescue medication: treatment policy strategy; analysis will be conducted regardless of rescue medication usage.	Difference in the change from baseline between 0.07 mg LOR and PBO using MMRM with treatment group, week, treatment×week interaction and baseline value as covariates. If prohibited medication is taken, censor and impute Patient Global Assessment using LOCF. If a subject discontinued the study for a reason that may suggest lack of efficacy, missing Patient Global Assessment data will be imputed with WOCF through Week 12.
	Sensitivity 1	Change from baseline in Patient Global Assessment at Week 12	0.07 mg LOR vs. PBO FAS	1) Prohibited medication: hypothetical strategy; analysis will be conducted as if the prohibited medication(s) had not been taken. 2) Rescue medication: treatment policy strategy; analysis will be conducted regardless of rescue medication usage.	Difference in the change from baseline between 0.07 mg LOR and PBO using baseline-adjusted ANCOVA with missing data imputed using the MI method; followed by two-way tipping point analysis. If prohibited medication is taken, censor and impute Patient Global Assessment using LOCF. If a subject discontinued the study for a reason that may suggest lack of efficacy, missing Patient Global Assessment data will be imputed with WOCF through Week 12.
	Sensitivity 2	Change from baseline in Patient Global Assessment at Week 12	0.07 mg LOR vs. PBO FAS	1) Prohibited medication: hypothetical strategy; analysis will be conducted as if the prohibited medication(s) had not been taken. 2) Rescue medication: hypothetical strategy; analysis will be conducted as if the rescue medication had not been taken.	Difference in the change from baseline between 0.07 mg LOR and PBO using MMRM with treatment group, week, treatment × week interaction and baseline value as covariates. If prohibited medication is taken, censor and impute Patient Global Assessment using LOCF. The following considerations are made for rescue medication usage: 1) if rescue is taken for target knee pain, censor and impute affected Patient Global Assessment using BOCF; 2) if rescue is taken for other pain, censor and impute affected Patient Global Assessment using LOCF. If a subject discontinued the study for a reason that may suggest lack of efficacy, missing Patient Global Assessment data will be imputed with WOCF through Week 12.
	Sensitivity 3	Change from baseline in Patient Global Assessment at Week 12	0.07 mg LOR vs. PBO PPAS	1) Prohibited medication: hypothetical strategy; analysis will be conducted as if the prohibited medication(s) had not been taken.	Difference in the change from baseline between 0.07 mg LOR and PBO using baseline-adjusted ANCOVA. Analysis includes subjects with Patient Global Assessment data available at Baseline and Week 12. If prohibited medication is taken, censor and impute Patient Global Assessment using LOCF.

				2) Rescue medication: treatment policy strategy; analysis will be conducted regardless of rescue medication usage.	
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ANCOVA=analysis of variance; BOCF=baseline observation carried forward; FAS=full analysis set; LOCF=last observation carried forward; WOCF=worst observation carried forward; LOR= lorecivint; MI=multiple imputation; MMRM=mixed-effects model for repeated measures; NRS=numeric rating scale; PPAS=per-protocol analysis set; WOMAC=Western Ontario and McMaster Universities Arthritis Index

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Reason for signing: Approved	Name: Victor Lopez Role: Associate Director, Biostatistics Date of signature: 01-Apr-2024 20:59:37 GMT+0000
Reason for signing: Approved	Name: Christopher Swearingen Role: Vice President, Biometrics Date of signature: 01-Apr-2024 21:19:47 GMT+0000
Reason for signing: Approved	Name: Heli Ghandehari Role: Director of Biostatistics Date of signature: 01-Apr-2024 21:34:20 GMT+0000
Reason for signing: Approved	Name: Yusuf Yazici Role: Chief Medical Officer Date of signature: 01-Apr-2024 23:10:00 GMT+0000

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