STRIDES—EXTRA

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

# STATISTICAL ANALYSIS PLAN

# SM04690-OA-17

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| **Study Title:** | A 3-Year, Multicenter, Open-Label Study Evaluating the Safety, Tolerability, and Efficacy of Intra-articular Lorecivivint in Subjects with Osteoarthritis of the Knee in a Real-World Setting |
| **Protocol Number:** | SM04690-OA-17 |
| **Protocol Version:** | Amendment 00 Version 00, 16 April 2021 |
| **SAP Version:** | 00, 18 JAN 2022 |
| **Investigational Product:** | SM04690 Injectable Suspension |
| **Clinical Phase:** | Phase 3b |

# SIGNATURE PAGE AND APPROVALS

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

**Protocol Version:** Amendment 00 Version 00, 16 April 2021

**SAP Version:** Version 00

**Date:** 18 January 2022

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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 |
| ATC | Anatomical therapeutic chemical |
| 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 |
| KOOS | Knee Injury and Osteoarthritis Outcome Score |
| LOR | Lorecivivint |
| MedDRA | Medical Dictionary for Regulatory Activities |
| NRS | Numeric rating scale |
| NSAID | Nonsteroidal anti-inflammatory drug |
| OA | Osteoarthritis |
| PASS | Patient Acceptable Symptom State |
| SAE | Serious adverse event |
| SAS | Safety Analysis Set |
| SD | Standard deviation |
| SF-12 | 12-Item Short Form Health Survey |
| SI | International System of Units |
| SSQ2 | Symptom Severity Question 2 |
| TUG | Timed Up and Go |
| WHODD | World Health Organization Drug Dictionary |
| WOMAC | Western Ontario and McMaster Universities Osteoarthritis Index |

| Abbreviation | Term |
|---|---|
| WOMAC Function | WOMAC physical function subscore |
| WOMAC Pain | WOMAC pain subscore |
| WPAI | Work Productivity and Activity Impairment Questionnaire |
| 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. 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 its (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 effective pharmaceutical agents to treat OA, Biosplice has used structure-based drug design to synthesize a small molecule inhibitor of the Wnt pathway, lorecivivint (LOR; previously SM04690), as a potential OA therapeutic to be administered as a local injection in the affected joint. The Wnt pathway plays a central role in the initiation and progression of OA pathology and is crucial in normal joint metabolism (Hochberg, et al., 2012). The Wnt pathway is a major regulator of joint development and is involved in the formation of bone, cartilage, and synovium. In osteoarthritic joints, increased Wnt signaling stimulates cartilage-destroying protease production and drives local progenitor cells to become bone-forming osteoblasts instead of cartilage-forming chondrocytes, thereby contributing to

osteophyte formation and cartilage loss (Gelse, et al., 2012). Gene polymorphisms involved in Wnt signaling are associated with an increased susceptibility to OA development (Wu, et al., 2012). Established research suggests that modulation of Wnt signaling is an attractive target for the treatment of OA.

Lorecivivint inhibits the Wnt pathway through the dual inhibition of 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 and open-label study evaluating the real-world use of 0.07 mg lorecivivint (LOR) injected into one or both knee joints of subjects with OA.

# 3. STUDY OBJECTIVES AND ENDPOINTS

## 3.1 Study Objective

The objective of this study was to determine the efficacy, safety, and tolerability of the SM04690 Injectable Suspension 0.07 mg alone and in addition to other standard of care intra-articular (IA) treatments in subjects with knee OA.

## 3.2 Study Endpoints

### 3.2.1 Safety Endpoints

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

### 3.2.2 Efficacy Endpoints

1. Change from baseline in pain numeric rating scale (NRS) score for the knee at Month 3 and annual visits, at each Unscheduled Injection Visit, and 3 months after each injection
2. Change from baseline in Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) physical function subscore (WOMAC Function) at Month 3 and annual visits, at each Unscheduled Injection Visit, and 3 months after each injection
3. Change from baseline in WOMAC total score and pain and stiffness subscores at Month 3 and annual visits, at each Unscheduled Injection Visit, and 3 months after each injection

4. Change from baseline in the Knee Injury and Osteoarthritis Outcome Score (KOOS) subscales of Symptoms, Function (Sports), and Quality of Life at Month 3 and annual visits, at each Unscheduled Injection Visit, and 3 months after each injection
5. Change from baseline in HRQoL (as measured using the 12-Item Short Form Health Survey [SF-12]) and Work Productivity and Activity Impairment (WPAI) at Month 3 and annual visits
6. Patient-Acceptable Symptom State (PASS) at Month 3 and annual visits
7. Change from baseline in 40-meter walk test time at Month 3 and annual visits, at each Unscheduled Injection Visit, and 3 months after each injection (at a subset of sites)
8. Change from baseline in the Timed Up and Go (TUG) test time at Month 3 and annual visits, at each Unscheduled Injection Visit, and 3 months after each injection (at a subset of sites)
9. Frequency of and interval between knee IA injections

# 4. OVERALL STUDY DESIGN AND PLAN

This study was a multicenter and open-label study evaluating the real-world use of 0.07 mg lorecivivint (LOR) injected into one or both knee joints of subjects with OA at Day 1. Additional injections were to be performed per the OA treatment algorithm available in the study protocol.

*The sponsor elected to terminate this study early for business reasons. All active subjects were requested to complete an early termination (ET) visit. Subjects who were recently injected were requested to participate in an ET visit 30 days (+14 days) after their last injection. Subjects on study more than 30 days since their last injection, were requested to participate in an ET visit as soon as possible. During the ET visit, only safety data were to be collected.*

## 2.1 Selection of Study Population

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

## 2.2 Method of Treatment Assignment and Randomization

This was an open-label study.

## 2.3 Treatment Blinding

This was an open-label study.

## 2.4 Minimization of Missing Data

### 2.4.1 Collection of Clinical Outcomes

As part of the real-world setting design, the clinical outcomes data were collected on paper at each applicable study visits. 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.

### 2.4.2 Rescue Medication

Not applicable to this study (see protocol section 7.8).

### 2.4.3 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 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.

### 2.4.4 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 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.

# 3. SAMPLE SIZE DETERMINATION

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

# 4. ANALYSIS POPULATIONS

## 4.1 Full Analysis Set

The Full Analysis Set (FAS) includes all subjects who receive a study injection.

## 4.2 Safety Analysis Set

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

## 4.3 Duplicate Subjects

As part of routine monitoring, a search was conducted for subjects who inappropriately participated in more than one SM04690 study or at more than one site in OA-17. The following subject was considered a duplicate subject and was excluded from the analysis sets:

| Unique Subject Identifier | Study ID | Subject Identifier for the Study | Comment | Start/End Date of Study Participation |
|---|---|---|---|---|
| SM04690-OA-10-0025117 | SM04690-OA-10 | 0025117 | Randomized and left knee injected with LOR on 2020-08-19 | 2020-08-11<br>2021-02-04 |
| | SM04690-OA-17 | 0021007 | Enrolled and injected with LOR in both right and left knees on | 2021-07-21<br>2021-11-11 |

| | | | | |
|---|---|---|---|---|
| | | | 2021-07-29. Left knee was also injected with DUROLANE, as part of the OA-17 study, on 2021-11-01 | |

Adverse events for the above subjects will be listed separately.

# 5. GENERAL ISSUES FOR STATISTICAL ANALYSIS

## 5.1 General Statistical Methodology

Efficacy analyses will not be performed as the sponsor elected to terminate this study early; subject-level listings will be provided for all efficacy assessments. General safety analyses will be performed on the SAS. The number of evaluable subjects 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 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.

### 5.1.1 Baseline

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

### 5.1.2 Data Handling for Patients Who Withdrew from the Study

If a subject discontinues the study, early termination assessments were to be performed according to the protocol. If these assessments occurred during a scheduled visit, they will be associated with that visit for the purposes of SAS analysis. The sponsor elected to terminate this study early. All active subjects were requested to complete an early termination (ET) visit. Subjects who were recently injected were requested to participate in an ET visit 30 days (+14 days) after their last injection. Subjects on study more than 30 days since their last injection, were requested to participate in an ET visit as soon as possible. During the ET visit, only safety data would be collected.

## 5.2 Interim Analysis

Not applicable.

## 5.3 Efficacy Assessments

### 5.3.1 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. The pain NRS was to be completed by the subject for both knees at Day 1, Months 3, 12, 24, and 36 (EOS)/ET, and at each Unscheduled Injection Visit and 3-Month Post-Injection Follow-Up Visit.

### 5.3.2 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. The WOMAC Version NRS 3.1 was to be completed by the subject for both knees at Day 1, Months 3, 12, 24, and 36 (EOS)/ET, and at each Unscheduled Injection Visit and 3-Month Post-Injection Follow-Up Visit.

WOMAC consists of 24 questions in three domains: physical function (17 questions), pain (5 questions) and stiffness (2 questions). If one pain, one stiffness, or 1-3 physical function items are missing, the average value for the subscale will be used as the missing item value(s). 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. If two or more pain, both stiffness, or four or more physical function items are missing, the subject's WOMAC is regarded as invalid, and the subscale(s) or total will not be computed (Bellamy, WOMAC Osteoarthritis Index User Guide XI, 2015). For the listing, WOMAC scores will be linearly transformed to a 0-100 scale, where 0 represents no difficulty and 100 represents extreme difficulty.

### 5.3.3 Knee Injury and Osteoarthritis Outcome Score (KOOS)

The KOOS Assessment is used to assess a subject's opinion about their knee and associated problems. Subjects will complete the KOOS subscales for Symptoms, Function (Sports), and knee-related Quality of Life. The KOOS was to be completed by the subject for both knees at Day 1, Months 3, 12, 24, and 36 (EOS)/ET, and at each Unscheduled Injection Visit and 3-Month Post-Injection Follow-Up Visit.

### 5.3.4 12-Item Short Form Health Survey (SF-12)

The SF-12 is a widely used questionnaire that relies upon subject self-reporting to measure the subject's health-related quality of life. The SF-12 was to be completed by the subject at Day 1, Months 3, 12, 24, and 36 (EOS)/ET.

### 5.3.5 Work Productivity and Activity Impairment (WPAI) Questionnaire

The WPAI questionnaire is a validated instrument to assess the impact of disease on paid work and activities. The WPAI was to be completed by the subject at Day 1, Months 3, 12, 24, and 36 (EOS)/ET.

### 5.3.6 Patient Acceptable Symptom State (PASS) Questionnaire

The PASS questionnaire was used to ask subjects the following using a paper questionnaire: "Taking into account all the activities you have during your daily life, your level of pain, and also your functional impairment, do you consider that your current state is satisfactory?" Subjects were able to choose the answers of "Yes" or "No.". The PASS was to be completed by the subject at Day 1, Months 3, 12, 24, and 36 (EOS)/ET.

### 5.3.7 40-meter Walk Test

At a subset of sites, the 40-meter walk test was to be administered. The 40-meter walk test was a performance-based measure used to assess walking speed over the distance of 40 meters. The 40-

meter walk was to be completed by the subject at Day 1, Months 3, 12, 24, and 36 (EOS)/ET, and at each Unscheduled Injection Visit and 3-Month Post-Injection Follow-Up Visit.

### 5.3.8 Timed Up and Go (TUG) Test

At a subset of sites, TUG test was to be administered. The TUG test is a performance-based measure of mobility, balance, walking ability, and fall risk. The TUG test was to be completed by the subject at Day 1, Months 3, 12, 24, and 36 (EOS)/ET, and at each Unscheduled Injection Visit and 3-Month Post-Injection Follow-Up Visit.

## 5.4 Safety Assessments

### 5.4.1 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 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 (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).

### 5.4.2 Vital Signs and Weight

Vital signs were measured by a qualified staff member at all in-person visits. At each time point, the following vitals were measured:

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

Any measurement that was, in the opinion of the Investigator, abnormal AND clinically significant was considered as an AE if found after the Day 1 study medication injection(s).

Weight measurements were to be taken at the Screening Visit and at Months 12, 24 and 36 (EOS) or ET.

### 5.4.3 Clinical Laboratory Evaluations

Fasting specimens for clinical laboratory analysis were to be collected at Screening Visit and Months 12, 24, and 36 (EOS) or ET. 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), and uric acid
- ***Hematology***: Hemoglobin, hematocrit, red blood cell (RBC) count, white blood cell (WBC) count with differential, and platelet count

- ***Urinalysis:*** Clarity, specific gravity, pH, protein, glucose, ketones, nitrite, leukocyte esterase, and occult blood

Urine microscopy 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.

# 6. STUDY SUBJECTS AND DEMOGRAPHICS

## 6.1 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. adverse event, subject decision, etc.) overall. As the sponsor terminated the study, no subjects were considered to have completed. Subject disposition for treated subjects will be presented by study site. An additional table will be prepared to summarize the number of subjects included in the analysis sets. The disposition for individual subjects will be listed along with additional information on discontinued and screen failed subjects.

## 6.2 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).

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.

### 6.3 Demographics and Other Baseline Characteristics

Demographic and baseline characteristics, including sex, race, ethnicity, age at consent, weight, height, body mass index (BMI), Kellgren-Lawrence (KL) grade for each knee, Widespread Pain Index (WPI), Symptom Severity Question 2 (SSQ2), investigator-assessed OA laterality, LOR treatment on Day 1, and primary insurance coverage will be presented overall. Continuous variables will be summarized with descriptive statistics and categorical variables will be summarized with frequencies and percentages. The summaries will be provided for the safety analysis set. Subject level listings of above parameters and a separate listing containing the individual responses for the Charlson Comorbidity Index will also be provided.

### 6.4 Medical History

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

## 7. EFFICACY ANALYSIS

Efficacy analyses will not be performed as the sponsor elected to terminate this study early. Subject-level listings will be provided for all efficacy assessments.

### 7.1 Estimands

Not applicable for this study.

## 8. 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.

### 8.1 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.

Since the study was terminated early, and only 2 adverse events were reported, tables will not be generated. Only subject-level listings will be provided.

### 8.2 Clinical Laboratory Evaluations

Since the study was terminated early, no subjects completed a post baseline clinical laboratory visit per protocol section 7.3.7, tables will not be generated. Only listings for abnormal chemistry, hematology, urinalysis, and urine microscopy results for each subject will be provided.

## 8.3 Vital Signs and Weight

Weight and vital signs (including systolic blood pressure, diastolic blood pressure, pulse rate, and body temperature) will be summarized overall. 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.

## 8.4 Physical Examination

Results of the general physical and knee examinations were noted in the source documents. If any clinically significant finding was noted after study medication injection, it was to be reported as an AE.

# 9. MEDICATIONS

The summary of medications will be performed on the SAS.

## 9.1 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 overall.

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).

### 9.2 Exposure and Compliance

A subject-level exposure listing will be provided.

## 10. CHANGES TO PLANNED ANALYSIS

| Change | Protocol Section | Rationale |
|---|---|---|
| Analysis of the AEs and clinical laboratory evaluations will not be performed. All available safety data will be listed. | 10.4.2 | Limited available data. See section 8.1 and 8.2. |
| Analysis of the efficacy endpoints will not be performed. Available efficacy data will be listed. | 10.4.3 | Study was terminated early. |

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