# STATISTICAL ANALYSIS PLAN

# A Randomized, Multicenter, Double-Blind, Parallel-group, Placebo-controlled, Dose Finding, and Phase II Study to Assess Efficacy and Safety of LC350189 in Gout Patients with Hyperuricemia

**STUDY DRUG:** LC350189

**PROTOCOL NUMBER:** LG-GDCL002

**DATE FINAL:**

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# HISTORY OF CHANGES

| Date | Content |
|---|---|
| 2019/12/18 | Initialization per Protocol Version 3.1 |
| 2020/06/29 | Modifications per Protocol Version 5.0:<br>1. Updated the Title of the Protocol;<br>2. Removed contents related to active control group from Study Design and Plan;<br>3. Changed text of sample size (190 to 152 subjects);<br>4. Updated definition of analysis sets<br>5. Inserted a section describing combination of subjects enrolled before and after the implementation of Protocol Version 5.0;<br>6. Changed in IP administration (3 to 2 capsules), and corrected the derivation of Compliance;<br>7. Inserted Section 9.5 for COVID-19 data;<br>8. Incorporated updates to PK/PD sections; |
| 2020/07/13 | Incorporated Client's comments and clarified the identification of rescue medication and occurrence of gout flare. |
| 2021/03/18 | Update to SAP Version 3.0:<br>1. Corrected derivation of 'C (days)' for Overall period in section 7.2.2;<br>2. Revised the definition of Gout Flare Rate in Section 8.1.2, per Sponsor's comment;<br>3. Described the grouping rules for subjects with wrong doses, in newly inserted Section 7.2.4;<br>4. Described the analysis of site-level deviations in Section 5.2.<br>5. Added a PK analysis set exclusion rule based on study treatment compliance, in Section 4.4.5. |
| 2021/03/29 | Modified Section 4.4.4 by updated the statement for determine PPS. |
| 2021/04/06 | Updated wordings per Sponsor's comments.<br>Updated overall compliance calculation for discontinued subjects. |
| 2021/05/17 | Updated to SAP Version 3.1:<br>1. updated All Randomized Set definition;<br>2. updated Per-Protocol Analysis Set definition. |
| 2021/05/19 | Per Sponsor's comment:<br>1. updated Per-Protocol Analysis Set definition;<br>2. added 4) in Section 7.2.4;<br>3. updated sUA and anti-flare activities in Section 8;<br>4. corrected Section 10.3.1. |

# LIST OF ABBREVIATIONS

| | |
|---|---|
| AE | Adverse event |
| ALT | Alanine aminotransferase (SGPT) |
| ANCOVA | Analysis of covariance |
| AR | Adverse reaction |
| AST | Aspartate aminotransferase (SGOT) |
| ATC | Anatomical Therapeutic Chemical |
| BLQ | Below the limit of quantification |
| BMI | Body Mass Index |
| BUN | Blood urea nitrogen |
| CI | Confidence Interval |
| CMH | Cochran-Mantel Haenszel |
| CRP | C-reactive Protein |
| CSR | Clinical Study Report |
| CTCAE | Common Terminology Criteria for Adverse Events |
| CV | Coefficient of variation |
| DBL | Database Lock |
| DBP | Diastolic blood pressure |
| DRM | Data Review Meeting |
| ECG | Electrocardiograms |
| eCRF | Electronic Case Report Form |
| FAS | Full Analysis Set |
| FPG | Fasting plasma glucose |
| hs-CRP | High sensitivity-C-reactive protein |
| IWRS | Interactive Web Response System |
| LDH | Lactic dehydrogenase |
| MCH | Mean corpuscular hemoglobin |
| MCHC | Mean corpuscular hemoglobin concentration |
| MCV | Mean corpuscular volume |
| MedDRA | Medical Dictionary for Regulatory Activities |
| NRI | Non-responder imputation |
| PD | Pharmacodynamic |
| PK | Pharmacokinetic |
| PPS | Per-Protocol Analysis Set |
| PT | Preferred term |
| QD | Once daily |
| RBC | Red blood cell |
| SAP | Statistical Analysis Plan |
| SBP | Systolic blood pressure |
| SD | Standard deviation |
| SE | Standard error |
| SI | System of Units |
| SOC | System organ class |
| sUA | Serum uric acid |
| TEAE | Treatment-emergent adverse event |
| WBC | White blood cell |
| WHODD | World Health Organization Drug Dictionary |

# 1. INTRODUCTION

This statistical analysis plan (SAP) describes the analyses and data presentations for LG Chem's protocol LG-GDCL002 "A Randomized, Multicenter, Double-blind, Parallel-group, Placebo-controlled, Dose Finding, and Phase II Study to Assess Efficacy and Safety of LC350189 in Gout Patients with Hyperuricemia" Version 5.0, which was issued on 11JUN2020. It contains definitions of analysis populations, derived endpoints and statistical methods for efficacy and safety analysis.

The purpose of the SAP is to ensure the credibility of the study findings by pre-specifying the statistical approaches to [redacted] ll statistical analyses detailed in this SAP will be conducted using [redacted]

The SAP will be finalized and signed prior to the clinical database lock (DBL) for the final analysis.

# 2. OBJECTIVES

## 2.1. Primary Objective

The primary objective of this study is:

- To assess the efficacy of LC350189 in terms of sUA level <5mg/dL at Week 12 (Day 84) to find therapeutic dose of LC350189

## 2.2. Secondary Objectives

The secondary objectives of this study are:

- To assess the efficacy of LC350189 in terms of sUA level
- To investigate the pharmacokinetic (PK) and pharmacodynamic (PD) characteristics of LC350189 in subjects with hyperuricemia and a diagnosis of gout
- To assess antiflare activity in subjects with hyperuricemia and a diagnosis of gout

## 2.3. Other objectives

The safety objective of this study is:

- To assess the safety and tolerability of LC350189

The exploratory objective of this study is:

- To explore the metabolic and anti-inflammatory effects of LC350189

Data from exploratory objectives may not be included in the Clinical Study Report (CSR).

# 3. INVESTIGATIONAL PLAN

## 3.1. Overall Study Design and Plan

This study is a double-blind parallel group placebo-controlled dose finding study in gout subjects with hyperuricemia.

The study will be conducted at multiple sites in the United States in up to 152 subjects. The withdrawn subjects will not be replaced. Subjects will be randomized 1:1:1:1 (n=38 per group) to the test groups: LC350189 50 mg, LC350189 100 mg, or LC350189 200 mg, or placebo group. The planned dosing cohorts are listed in Table 1.

**Table 1: Treatment Groups**

| Group | Treatment |
|---|---|
| 1 | Placebo |
| 2 | LC350189 50 mg QD |
| 3 | LC350189 100 mg QD |
| 4 | LC350189 200 mg QD |

Each subject will undergo a screening visit 33 to 26 days prior to the first day of the treatment period, which include five visits on Day 1, 14, 28, 56, and 84 (Visits 4 to 8). During the treatment period, subjects will orally self-administer LC350189 or placebo for 83 days starting on Day 1, and have a follow-up on-site visit approximately 2 weeks after the completion of the dosing period. The duration of the study will be up to 19 weeks for each subject.

Gout flare prophylaxis will consist of colchicine 0.6 mg once daily (QD) starting at Visit 2 (between Day -30 to Day -23) through the end of the treatment period.

Upon implementation of the Protocol version 5.0, enrollment to the active control group (febuxostat) will be stopped.

## 3.2. Study Endpoints

### 3.2.1. Primary Endpoint(s)

The primary endpoint of this study is:

- Proportion of subjects who achieve sUA level <5.0 mg/dL at Day 84 (Visit 8)

### 3.2.2. Secondary Endpoint(s)

The secondary endpoints of this study are:

- Proportion of subjects who achieve sUA level of <6.0mg/dL at Day 84 (Visit 8)
- Proportion of subjects who achieve sUA level of <5.0 mg/dL at each visit
- Proportion of subjects with baseline (Visit 4) sUA >10 mg/dL who achieve <5.0 mg/dL at Day 84 (Visit 8)
- Proportion of subjects with baseline (Visit 4) sUA >10 mg/dL who achieve <6.0 mg/dL at Day 84 (Visit 8)
- Proportion of subjects per renal function at baseline (Visit 3) who achieve sUA <5.0 mg/dL at Day 84 (Visit 8)
- Proportion of subjects per renal function at baseline (Visit 3) who achieve sUA <6.0 mg/dL at Day 84 (Visit 8)
- Change and percent change in sUA levels from baseline (Visit 4) at each visit
- Maximum percent reduction in sUA level during treatment
- $C_{trough,\ ss}$ at baseline (Visit 4), Day 14 (Visit 5), Day 28 (Visit 6), Day 56 (Visit 7), and Day 84 (Visit 8)
- Gout flare rate in subjects

- Gout flare rate in subjects with sUA <6.0 mg/dL at Day 84 (Visit 8)
- Proportion of subjects with episodes of gout flare requiring rescue treatment

### 3.2.3. Safety Endpoint(s)

The safety endpoints of this study are:

- Adverse events
- Laboratory values
- Vital signs
- ECG

### 3.2.4. Exploratory Endpoint(s)

The exploratory endpoints of this study are:

- Change in HbA1c from baseline (Visit 4) to Day 84 (Visit 8)
- Proportion of subjects with HbA1C <7% at Day 84 (Visit 8)
- Proportion of subjects with HbA1C ≤6.5% at Day 84 (Visit 8)
- Change in fasting plasma glucose (FPG) from baseline (Visit 4) at Day 84 (Visit 8)
- Change in high sensitivity-C-reactive protein (hs-CRP) from baseline (Visit 4) at Day 84 (Visit 8)
- Serum concentrations of hypoxanthine and xanthine at baseline and Day 84 (Visit 8)

# 4. GENERAL STATISTICAL CONSIDERATIONS

## 4.1. Sample Size Determination

Sample size estimation is based on the proportion of subjects meeting target. Calculation of the sample size based on these assumptions is as follows:

$$H_0: p_t - p_c \leq 0 \text{ vs. } H_1: p_t - p_c > 0$$

$$n = \frac{(Z_\alpha + Z_\beta)^2 (p_t(1-p_t) + p_c(1-p_c))}{(p_t - p_c)^2}$$

Evaluable subjects per treatment group (n=30) is determined using estimates of proportion of subjects who achieve sUA <5.0 mg/dL at Day 84 (Visit 8), with $p_t$=0.80 (test group) and $p_c$=0.47 (control group), and directly computed values of $Z_\alpha$=1.96 and $Z_\beta$=0.84, which correspond to a type I error rate of α=0.025 and a type II error rate of β=0.2.

Assuming a dropout rate of 20%, 38 subjects per treatment group are needed to assess the efficacy of LC350189 in an evaluable population of 30 subjects per treatment group.

Originally, sample size was calculated compared to the active control group in previous protocol versions. Although a major modification is made to eliminate the active control group, the sample size of each test and placebo group is not changed because the proportion of meeting target is very low in the placebo group when referring other studies and sample size calculation comparing to placebo which is less than 10 subjects per group gives insufficient number for dose selection. Therefore, the sample size is not changed upon elimination of the active control group and maintained 30 subjects per group (38 including drop-out rate 20%) to be sufficient for dose selection and exploratory purpose.

In this study, with an overall dropout rate of 20%, a total of 152 subjects, not including those already assigned to the active control group (with febuxostat), will be randomized to 4 treatment groups, 114 subjects to three different test doses of LC350189 (38 subjects to each dose), and 38 subjects to placebo.

## 4.2. Randomization, Stratification, and Blinding

Subjects who meet all of the inclusion criteria and none of the exclusion criteria will be assigned a subject randomization number via an Interactive Web Response System (IWRS) on Day 1 after a wash-out/prophylaxis period (from Visit 2 to Visit 3) that will follow screening (Visit 1).

The randomization will be stratified by post-washout/pre-dose sUA (<9.8 mg/dL or ≥9.8 mg/dL) at Visit 3 and by the presence or absence of tophi at screening (Visit 1).

If a subject has experienced a gout flare during the wash-out/prophylaxis period, the subject will not be randomized and can be rescreened once 3 weeks after resolution of gout flare.

If a subject cannot be randomized, the reason will be recorded in the screening disposition page. The IWRS must be notified immediately that the subject was not randomized.

Before unblinding, all individuals involved in this study remain blinded unless the nature of their activities in the study specifically requires them to be unblinded, and surrogate or dummy groups will be applied to statistical analysis.

Client authorization documented via Biostatistics Unblinding Request/Authorization Form should be obtained prior to receipt/transfer of data and/or access is granted to unblinded information.

## 4.3. Reporting Conventions

- Data from all study centers will be combined for analysis;
- Confidence intervals (CIs) will be presented as 2-sided 95% CIs unless specified differently in specific analysis;
- Summary statistics will consist of the number and percentage of subjects in each category for discrete variables, and the number of subjects (or events, if appropriate), mean,

median, standard deviation (SD), minimum, Q1, Q3, and maximum for continuous variables;

- All mean and median values will be formatted to one more decimal place than the measured value. Standard deviation values will be formatted to two more decimal places than the measured value. Minimum and maximum values will be presented to the same number of decimal places as the measured value.
- P-values will be rounded to 4 decimal places. P-values that round to 0.0000 will be presented as '<0.0001' and p-values that round to 1.000 will be presented as '>0.9999'.
- All percentages will be rounded to one decimal. The number and percentage of responses will be presented in the form XX (XX.X%), where the percentage is in the parentheses;
- All laboratory data will be reported using international system of units (SI);
- All listings will be sorted for presentation in order of dose cohort, study center, subject ID, and date of procedure or event;
- All analysis and summary tables will have the analysis population sample size for each dose cohort in the column headers in form of N=XXX;
- The day of the first dose of study treatment will be defined as Day 1;
- Baseline value will be defined as the last non-missing value from the evaluation on or before the first dose of study drug is administered. In case of re-evaluation, value from the last test will be used as the baseline.

## 4.4. Analysis Sets

### 4.4.1. All Randomized Set

The All Randomized Set includes all randomized subjects who are assigned subject randomization numbers.

The All Randomized Set will be applied to summaries of subject disposition, based on treatment that subjects were randomized.

### 4.4.2. Safety Set

The Safety Set includes all subjects who received any study medication (LC350189, febuxostat, or placebo). The Safety Set will be applied to demographics and baseline characteristics, and safety analysis, based on treatment that subjects received.

### 4.4.3. Full Analysis Set

The Full Analysis Set (FAS) is defined as all randomized subjects that received at least one dose of investigational products (LC350189, febuxostat, or placebo).

The FAS will be applied as the primary population for efficacy analysis, based on treatment that subjects were randomized.

### 4.4.4. Per-Protocol Analysis Set

The Per-Protocol Analysis Set (PPS) is defined as all subjects in the FAS that are compliant with treatment and have appropriate exposure to study medication for the 12-week treatment period and without any major protocol deviations that may impact primary efficacy analysis.

Major protocol deviations that may impact the primary efficacy analysis, rules for handling subjects who ever took unassigned dose or type of study treatment, algorithm for calculating overall study treatment compliance, and cutoff treatment compliance values for PPS exclusion will be determined during a blinded data review meeting (DRM) prior to DBL. If a subject withdrew from the study prematurely without Week 12 data to assess the primary and/or key secondary endpoints, he or she may be excluded from the PPS. If a subject completed the treatment period and had sUA result within 84 days +/-5 days, he or she will be included in the PPS.

For subjects who ever received unassigned dose of study treatment but stayed in the same dose for the entire study treatment, the subject can be included in the PPS if subject received one of the pre-defined dose in the study (LC350189 50 mg, 100 mg, 200 mg, or placebo).

The PPS will be used for supportive analyses of the efficacy endpoints, based on treatment that subjects received.

#### 4.4.5. Pharmacokinetic Analysis Set

The Pharmacokinetic (PK) Analysis Set will include all subjects who received investigational products with all evaluable PK data appropriate for the evaluation of interest (without major protocol deviations or violations that would have an impact on the absorption, distribution, metabolism, or excretion of investigational products). In other words, PK Analysis Set will include subjects who receive at least 1 dose of LC350189 and have sufficient concentration data to support accurate estimation of at least 1 PK parameter.

The PK analysis set will be used for analysis of PK endpoints, based on treatment that subjects received.

## 4.5. Combination of Subjects in Analysis

Data of subjects who have been randomized into the test (LC350189 50 mg, LC350189 100 mg, or LC350189 200 mg) or placebo groups before the implementation Protocol version 5.0 will be combined and analyzed with subjects who will be enrolled after the implementation of the Protocol version 5.0, as defined in protocol.

# 5. SUBJECT DISPOSITION

## 5.1. Disposition

The number of subjects screened, the number of subjects randomized, and the number of screen failures with the associated reasons for screen failure will be summarized.

Subject disposition (analysis set allocation, entered, discontinued, along with primary reason for discontinuation) will be summarized using frequency and percent for both treatment and follow-up phases based on the All Randomized Set.

Reasons for **End of Treatment or Early Termination**, as well as reasons for **Study Discontinuation** will be collected on the eCRF and will be summarized for all randomized subjects with the following categories:

- Adverse event
- Death
- Lack of efficacy
- Lost to follow-up
- Non-Compliance with Study Drug
- Physician Decision
- Pregnancy
- Progressive Disease
- Protocol Deviation/Violation
- Study Terminated by Sponsor
- Withdrawal by Subject
- Other

In addition, separate listings will be provided for:

- Screen failures
- Subjects excluded from analysis
- Discontinued subjects with reasons for treatment discontinuation

## 5.2. Protocol Deviations/Violations

The protocol deviations/violations will be identified and assessed by the clinical research physician or designee following company standard operational procedure and will be finalized prior to DBL.

The number and percentage of subject-level protocol deviations/violations will be summarized by dose cohort for the All Randomized Set, and a by dose cohort and by-subject listing in the All Randomized Set will be provided.

Site-level deviations will be listed.

# 6. DEMOGRAPHICS AND BASELINE CHARACTERISTICS

The demographics, baseline characteristics will be summarized for the Safety Analysis Set, the Full Analysis Set, and Per-Protocol Set.

Individual by-subject listings will be provided to support the summary tables.

## 6.1. Demographics

Subjects' age (years), height (cm), weight (kg), and Body Mass Index (BMI, $kg/m^2$) at baseline will be summarized using descriptive statistics; while sex, race, ethnicity, BMI categories ( $< 20\ kg/m^2$, $20$ to $< 25\ kg/m^2$, $25$ to $< 30\ kg/m^2$, $\geq 30\ kg/m^2$), and other categorical variables will be provided using frequency tabulations.

## 6.2. Baseline Characteristics

The descriptive statistics for following variables will be presented:

- Smoking status at screening (Visit 1)
- Presence or absence of tophi at screening (Visit 1)
- Post-washout/pre-dose sUA (<9.8 mg/dL or ≥9.8 mg/dL) at baseline (Visit 3)
- Renal function at baseline (Visit 3)

## 6.3. Medical History and Concomitant Illness

Medical histories will be coded according to Medical Dictionary for Regulatory Activities (MedDRA, Version 21.0 or higher) and summarized based on the Safety Set by system organ class (SOC) and preferred term (PT).

Concomitant illness is any significant medical condition or disease that is present at study start (signing of informed consent). This includes clinically significant laboratory, ECG, or physical examination abnormalities noted at screening.

## 6.4. Physical Examination

The baseline physical examination will consist of the following body systems: (1) eyes; (2) ears, nose, throat, neck, thyroid; (3) cardiovascular system; (4) respiratory system; (5) gastrointestinal system, mouth; (6) dermatologic system; (7) extremities; (8) musculoskeletal system; (9) central and peripheral nervous system and (10) lymph nodes.

A summary of physical examination at baseline will be produced by body systems.

# 7. STUDY DRUG AND MEDICATIONS

## 7.1. Prior and Concomitant Medications

### 7.1.1. Prior Medications

A prior medication is any medication that started before the first randomized study dose date, as Medication Start Date < Date of Study Day 1. In case of incomplete date, refer the methods specified in Section 14.3.2.

A summary showing the number and percentage of subjects who have prior medications will be presented by ATC level 2/level 4 and standardized medication name, using WHODD, for the Safety Set.

### 7.1.2. Concomitant Medications

Concomitant medication is any medication given in addition to the investigational product(s), including over-the-counter medications, herbal medications, and vitamin supplements, that administered between screening and follow-up, as Medication End Date is on or after Study Day 1. In case of incomplete date, refer the methods specified in Section 14.3.2.

A medication will be categorized as “Prior/Concomitant” if it started before Study Day 1 and ended after Study Day 1. If a medication is taken on the Study Day 1, it will be counted as a concomitant medication.

Prior/Concomitant medications will be included in both summary for prior medications and summary for concomitant medications.

A summary showing the number and percentage of subjects who took concomitant medications will be presented by ATC level 2/level 4 and standardized medication name, using WHODD, for the Safety Set.

## 7.2. Study Drug

Summary and listing of study drug will be produced based on the Safety Set. Descriptive statistics for study drug compliance will be provided by treatment group.

### 7.2.1. Study Drug Dispense

On Day 1 (Visit 4), the appropriate study drug will be dispensed per the randomization code. Additional bottles will be dispensed on Day 28 (Visit 6) and Day 56 (Visit 7). At each of these three dispensing visits, subjects will receive a total of 2 bottles for LC350189/ placebo, and each bottle contains 35 capsules. On Day 28 (Visit 6), Day 56 (Visit 7), and Day 84 (Visit 8), all previously dispensed bottles should be returned for investigational product accountability.

### 7.2.2. Study Drug Compliance

Based on treatment group, study drug compliance will be measured at specific visits using the following formula:

| Treatment Group | Study Drug | | Compliance (D) |
|---|---|---|---|
| | Bottle 1 | Bottle 2 | |
| LC350189 50 mg | LC350189 25 mg | LC350189 25 mg | (B/2)/C*100% |
| LC350189 100 mg | LC350189 100 mg | LC350189 Placebo | B/C*100% |
| LC350189 200 mg | LC350189 100 mg | LC350189 100 mg | (B/2)/C*100% |
| Placebo | LC350189 Placebo | LC350189 Placebo | (B/2)/C*100% |

Where B is the total number of dispensed non-placebo capsules minus the total number of returned non-placebo capsules including lost or damaged ones (for Placebo group, placebo capsules of LC350189 will be considered), and C is the number of days since Day 1 for Day 28 (Visit 6); the number of days since Day 28 for Day 56 (Visit 7), and the number of days since Day 56 for Day 84 (Visit 8).

| Period | Day when Accountability is Measured | Day when Bottles were Dispensed | B | C (days) |
|---|---|---|---|---|
| Visit 4 to Visit 6 | Day 28 | Day 1 | Sum of (35 minus the number of capsules left in each of bottle including lost or damaged ones) | (Date of Visit 6 – Date of First Dose of Study Treatment) |
| Visit 6 to Visit 7 | Day 56 | Day 28 | | (Date of Visit 7 – Date of Visit 6) |
| Visit 7 to Visit 8 | Day 84 | Day 56 | | (Date of Visit 8 – Date of Visit 7) * |
| Overall | Day of Last Dose | Day 1 | Sum of (all dispensed non-placebo capsules) minus Sum of (all returned non-placebo capsules including lost or damaged ones) | (Date of Visit 8 – Date of First Dose of Study Treatment) For early terminated subjects: (End of Treatment Date – Date of First Dose of Study Treatment + 1) |

* Subjects will be guided not to administrate the study drug on Day 84. Even if the drug is administrated, it will be administrated after assessments. Therefore, Day 84 is exclusive to derivation of study drug compliance.

In case of early termination, the number of days of the last treatment period is derived as (Date of Last Dose of Study Treatment – Start Date of the Last Period +1).

**Study Drug Before the Implementation of Protocol Version 5.0**

Subjects who are randomized before the implementation of Protocol Version 5.0 will continue receiving a total of 3 bottles for LC350189/febuxostat/placebo at each dispensing visit.

Based on treatment group, study drug compliance will be measured at specific visits using the following formula:

| Treatment Group | Study Drug | | | Compliance (D) |
|---|---|---|---|---|
| | Bottle 1 | Bottle 2 | Bottle 3 | |
| LC350189 50 mg | LC350189 25 mg | LC350189 25 mg | Febuxostat Placebo | (B/2)/C*100% |
| LC350189 100 mg | LC350189 100 mg | LC350189 Placebo | Febuxostat Placebo | B/C*100% |
| LC350189 200 mg | LC350189 100 mg | LC350189 100 mg | Febuxostat Placebo | (B/2)/C*100% |
| Febuxostat | LC350189 Placebo | LC350189 Placebo | Febuxostat | B/C*100% |
| Placebo | LC350189 Placebo | LC350189 Placebo | Febuxostat Placebo | (B/2)/C*100% |

Where B is the total number of dispensed non-placebo capsules minus the total number of returned non-placebo capsules including lost or damaged ones (for Placebo group, only placebo capsules of LC350189 will be considered), and C is the number of days since Day 1 for Day 28 (Visit 6); the number of days since Day 28 for Day 56 (Visit 7), and the number of days since Day 56 for Day 84 (Visit 8).

For each subject, the Overall study drug compliance is defined as the (sum of B)/(sum of C)*100% throughout the treatment period.

### 7.2.3. Actual Dosage of LC350189

Actual dosage of LC350189 of a subject is calculated as:

Actual dosage = Sum of (dosage of capsules with active ingredient)/Sum of (dosing days)

Example: Subject C was randomized to LC350189 200 mg but took 2 bottles of LC350189 25 mg daily for 28 days, then the actual dosage is LC350189 50 mg.

In Safety Analysis, subjects will be summarized by treatment received.

### 7.2.4. Subjects Who Ever Took Unassigned Dose

In practice, a subject may receive and take LC350189 capsules with unassigned doses therefore actual dosage may be different from pre-defined study doses (LC350189 50 mg, 100 mg, or 200 mg). In that case, subjects will be summarized in the most frequently applied dose level and the "LC350189 All" column in Safety tables. If the most frequently applied dose level is not in the pre-defined doses, the subject will be summarized only in the "LC350189 All" column.

Examples: Assuming a subject was assigned to 50 mg group. 1) If this subject took proper doses during the majority of the treatment period and a few 200 mg doses by chance, this subject will be categorized in 50 mg group; 2) If this subject took 200 mg doses during the majority of the treatment period and a few 50 mg doses, this subject will be categorized in 200 mg group; 3) If

for some reasons this subject took 150 mg doses for the entire treatment period, this subject will be not categorized into any pre-defined doses, and summarized only in the "LC350189 All" column.

In Safety Analysis, 1) subjects in Febuxostat group took both active Febuxostat and its placebo will be summarized in "Febuxostat" column, 2) subjects in Placebo group took both active Febuxostat and its placebo will be summarized in "Febuxostat" column, 3) subjects in Febuxostat group took only Febuxostat placebo will be summarized in "Placebo" column, and 4) subjects who took both active Febuxostat and active LC(50mg, 100mg, or 200mg) dose will be summarized in the most frequently applied dose group..

Subjects who ever took unassigned dose will be excluded from PPS, unless the unassigned doses taken were administered for the entire treatment duration.

## 7.3. Gout Flare Prophylaxis

Gout flare prophylaxis will consist of colchicine 0.6 mg (QD) starting at Visit 2 (between Day -30 to Day -23) through the end of the treatment period.

Summary and listing of gout flare prophylaxis will be produced, by treatment group.

# 8. EFFICACY ANALYSIS

Efficacy analysis will be conducted using FAS and PPS.

For subjects randomized into the active control group (febuxostat) before the implementation of the Protocol version 5.0, efficacy data (sUA and anti-flare activities) and exploratory data (HbA1c, FPG, and hs-CRP) will be only listed.

## 8.1. Analysis of Efficacy Endpoints

The efficacy endpoints of this study are specified in Sections 3.2.1, 3.2.2, and 3.2.4 of this SAP.

All endpoints will be summarized descriptively and will be compared to placebo using descriptive statistics.

Proportions will be analyzed using the Cochran-Mantel Haenszel (CMH) test adjusted by following stratification factors: 1) tophi status at Visit 1, and 2) sUA (level <9.8 mg/dL or >=9.8 mg/dL) at Visit 4. The Wald asymptotic 95% confidence limit will be calculated for the risk difference point estimate for pairwise comparisons between each dose group and placebo in pre-specified order of 200 mg versus placebo, 100 mg versus placebo and 50 mg versus placebo; however, if the data suggest and warrant it, the continuity correction adjusting for the difference between the normal approximation and the binomial distribution will be applied. Subgroup analyses of proportions of subjects with sUA level < 5.0 mg/dL (and 6.0 mg/dL as well) will be performed by above stratification factors.

Change and percent change from baseline will be analyzed with an analysis of covariance (ANCOVA) model, including treatment, sUA and tophi strata at screening, and baseline values of the dependent variable as a covariate.

As this is not a rigorous confirmatory trial, no multiplicity adjustment is planned for multiple treatment comparisons or multiple endpoints.

Dropouts will be treated according to non-responder imputation (NRI).

### 8.1.1. sUA Levels

Serum uric acid (sUA) is one of the key parameters to efficacy endpoints.

Proportion of subjects meeting pre-specified criteria at Day 84 (Visit 8) is derived as: 100% * number of subjects meeting criteria / number of all subjects at Day 1 (Visit 4), where dropout subjects will be considered as not meeting the criteria.

Change and percent change in sUA from Baseline (Visit 4) at each visit are derived as:

- Change = (Value - Baseline)
- Percent change = 100% * (Value - Baseline)/Baseline

Missing sUA values will be imputed with Last Observation Carried Forward (LOCF) method.

### 8.1.2. Antiflare Activities

For this study, a gout flare is defined as an episode of subject-reported acute articular or bursal pain that occurs at rest and is typical of past gout attacks. In addition, both of the following criteria must be met: the intensity of pain at rest must be>=4 on an 11-point numerical rating scale, and the pain must be determined by the patient and/or the Investigator to require anti-inflammatory/analgesic treatment (i.e. rescue medication). Finally, at least 2 of 3 possible joint symptoms (swelling, warmth, or tenderness) must be present, and at least 1 of the following must be present: rapid onset of pain, decreased range of joint motion, or joint redness.

To assess occurrence of gout flare, parameters related to joint pain will be evaluated by the data collected through eDiary, but in the case of rescue medication, data collected by eCRF will also be evaluated:

- When evaluating administration of rescue medication collected through eDiary, the date of rescue medication administration, eDiary entry date, should match with the date of the reported joint pain.
- When using concomitant medication data collected by eCRF, the date of reported joint pain should be within start and stop dates of rescue medication administration.

If subjects report to have join pain continuously in several days or time, it will be counted as one event.

Gout flare rate will be calculated as: number of episodes of gout flare in a specific period (or during the study) / number of subjects, for each treatment group. Summaries of gout flare rate will be produced for 1) all subjects and 2) subjects with sUA < 6.0 mg/dL at Day 84 (Visit 8).

Proportion of subjects with episodes of gout flare, i.e. the percentage of subjects experienced gout flare out of all subjects, will be summarized.

### 8.1.3. Other Efficacy Endpoints

Change from baseline to Day 84 (Visit 8) in HbA1c, in fasting plasma glucose (FPG), and in high-sensitivity C-reactive protein (hs-CRP) will be summarized. Missing values will be imputed with Last Observation Carried Forward (LOCF) method.

Proportions of subjects with HbA1c < 7% at Day 84 (Visit 8) and proportions of subjects with HbA1c <= 6.5% at Day 84 (Visit 8) will be summarized, where dropout subjects will be considered as not meeting the criteria.

Serum concentrations of hypoxanthine and xanthine will be summarized by visit.

## 8.2. Sensitivity Analysis of Efficacy Endpoints

In sensitivity analysis of the primary efficacy endpoint, using Last Observation Carried Forward (LOCF) method, sUA values at Day 84 (Visit 8) of dropout subjects will be imputed and applied to determine if meeting pre-specified criteria.

# 9. SAFETY ANALYSIS

The purpose of this section is to define the safety endpoints for the study, which consist of adverse events (AEs), clinical laboratory tests, vital sign measurements, and electrocardiograms (ECG), and to describe associated analysis.

All summaries and listings of safety data will be conducted using the Safety Set.

## 9.1. Adverse Events

### 9.1.1. Definitions

An adverse event (AE) is any undesirable and unintended medical event occurring to a subject in a clinical study, whether or not related to the study products. This includes events from the first study related activity after the subject has signed the informed consent and until post treatment follow-up period as defined in the protocol.

A treatment-emergent AE (TEAE) is defined as any undesirable and unintended medical event after exposure to investigational product or any event already present that worsens in either intensity or frequency after exposure to investigational product. An AE occurs on and after Study Day 1 is categorized as treatment-emergent.

Assessed by the Investigator or Sub-Investigator on the basis of his/her clinical judgment, the relationship of each AE to the investigational products are categorized as **Related** and **Not Related**.

Determined by Investigator or Sponsor, an AE will be categorized as Related to study treatment, if an AE follows a reasonable temporal sequence from investigational product administration and cannot be reasonably explained by the subject's clinical state or other factors.

### 9.1.2. Analysis of Adverse Events

Tables summarizing the incidence of AEs will be categorized by SOC and PT, for each of the following:

- All AEs;
- Treatment-emergent AEs;
- Treatment-emergent AEs related to study treatment;
- Treatment-emergent AEs by severity;
- Treatment-emergent AEs related to study treatment by severity;
- All serious treatment-emergent AEs;
- Serious treatment-emergent AEs related to study treatment;
- AEs leading to study treatment discontinuation;
- Deaths

If subject experiences the same AE more than once with different severity (mild, moderate, and severe), then the event with the highest severity will be tabulated in "by severity" tables. If a subject experienced multiple TEAEs under the same PT (or SOC), then the subject will be counted only once for that PT (or SOC).

In summary tables, TEAEs are sorted by alphabetical order of system organ class, and then descending frequencies of preferred term within all subjects exposed to LC350189.

## 9.2. Clinical Laboratory Evaluations

Clinical laboratory results include:

- Hematology: red blood cell (RBC) count, white blood cell (WBC) count with differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils), hemoglobin, hematocrit, platelet count, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC)
- Serum chemistry: alanine aminotransferase (ALT) or serum glutamate pyruvic transaminase (SGPT), albumin, alkaline phosphatase, aspartate aminotransferase (AST) or serum glutamic oxaloacetic transaminase (SGOT), total bilirubin, total protein, creatinine, blood urea nitrogen (BUN), creatine kinase, Gamma-glutamyl transferase,

potassium, sodium, carbon dioxide, calcium, magnesium, chloride, glucose, lactate dehydrogenase (LDH), phosphorus, and serum uric acid (sUA)
- Urinalysis: qualitative, appearance, color, pH, specific gravity, ketones, protein, glucose, nitrate, urobilinogen, and blood
- Serology (only at screening): HBsAg, anti-HCV, anti-HIV-1/2

Clinical laboratory values from laboratories will be graded according to CTCAE Version 4.03 for following analytes programmatically. For laboratory values that do not fall in the grade criteria of CTCAE Version 4.03, a state of 'Normal' will be assigned. In addition, normal ranges will be used to determine the categories of High, Low, and Normal for laboratory tests that have no severity grade.

Alanine Aminotransferase (Serum)
Albumin (Serum)
Alkaline Phosphatase (Serum)
Aspartate Aminotransferase (Serum)
Bilirubin (Serum)
Calcium (Serum)
Creatine Kinase (Serum)
Creatinine (Serum)
Glucose (Serum Fasting)
Magnesium (Serum)
Potassium (Serum)
Sodium (Serum)
Hemoglobin (Blood)
Leukocytes (Blood)
Lymphocytes (Blood)
Neutrophils, Segmented (Blood)
Platelets (Blood)

Descriptive statistics of baseline value, post-baseline value by visit, and change from baseline will be summarized by visit, for laboratory tests with continuous values.

Shift table representing the shift in status from baseline (e.g. positive and negative) to each visit will be produced for laboratory test with categorical values.

In addition, shift table representing the shift from baseline grade (per CTCAE criteria) to the most severe post-baseline grade for all applicable laboratory tests, and shift table representing the shift from baseline category (High, Normal, and Low) to the worst post-baseline category for laboratory test based on normal ranges of local laboratories.

Listings of clinical laboratory data with CTCAE grades or flags of abnormalities will be provided by test and subject for applicable tests.

Pregnancy test results will be listed.

## 9.3. Vital Sign Measurements

Vital signs include body temperature (aural), blood pressure (after 5 minutes resting), respiration rate, and pulse rate (after 5 minutes resting).

Descriptive statistics will be applied to summarize observed values, change from baseline values.

By-subject listing will be produced for vital signs.

## 9.4. Electrocardiograms

Electrocardiogram (ECG) parameters to be recorded are: heart rate, QT interval, PR interval, QRS interval, RR interval, and QTc (corrected) using the Fridericia correction.

The ECG will be summarized in descriptive manner including the changes from baseline by visit.

The overall ECG interpretation by investigator (or designee) in categories of 'within normal limits', 'abnormal but not clinically significant', and 'abnormal with clinically significance' will be summarized by visit, the shift from baseline to worst status during the treatment in the overall ECG interpretation will be displayed in cross–tabulations by visit.

The source values of the ECG parameter will be listed by subject, and visit.

## 9.5. Events Related to the COVID-19 Public Health Emergency

Missed or altered visits due to the COVID-19 public health emergency will be recorded in specific eCRF, diagnosed COVID-19 cases will be recorded as AE or SAE, and these data will be presented in listings.

# 10. PHARMACOKINETICS AND PHARMACODYNAMICS

## 10.1. Pharmacokinetic Analysis

### 10.1.1. Pharmacokinetic Sample Concentrations

Blood samples from sparse and dense sampling schedules will be collected and analyzed for investigational products (LC350189) in plasma as outlined in Section 14.2.

Individual plasma concentrations and time deviation data for investigational products (LC350189) will be listed by treatment using the safety set. Individual plasma concentration versus actual time profiles will be plotted on both linear and semi logarithmic scales for each subject using the safety set.

Plasma concentration data will be summarized by time point for each treatment using the following descriptive statistics for the PK analysis set: number of subjects in a given treatment group (N), number of non-missing observations (n), arithmetic mean, arithmetic standard deviation (SD), arithmetic coefficient of variation (CV%), geometric mean, geometric CV%, median, minimum, and maximum values. Plasma concentrations will be reported to 3 significant figures in summary statistics except for CV% which will be reported to 1 decimal place.

Plasma LC350189 concentrations that are below the limit of quantification (BLQ) will be set to zero for calculation of summary statistics for concentration data at each timepoint.

Geometric mean and geometric CV% will be set to missing if minimum is zero. Mean plasma concentration versus nominal time profiles will be plotted using the PK analysis set on both linear and semi-logarithmic scales.

In addition, individual trough levels of investigational products (LC350189) collected before dosing on Days 1, 14, 28, 56 and 84 will be plotted for each treatment on both linear and semi-logarithmic scales for each subject using the PK analysis set and mean trough concentration versus nominal time profiles will be plotted for each treatment using the PK analysis set on both linear and semi-logarithmic scales.

For subjects randomized into the active control group (febuxostat) before the implementation of the Protocol version 5.0, febuxostat concentration data will be listed.

### 10.1.2. Pharmacokinetic Parameters

The individual plasma concentration versus actual time data for LC350189 and febuxostat will

-

| PK Parameter | Definition |
|---|---|
| **Sparse and Dense Sampling** | |
| $C_{trough,ss}$ | Plasma concentration observed at the end of a dosing interval [collected before the next administration. |
| **PK Parameter** | **Definition** |
| **Dense Sampling** | |
| $C_{max}$ | Maximum observed concentration in plasma |
| $T_{max}$ | Time to maximum concentration in plasma |
| $t_{1/2}$ | Apparent terminal elimination half-life, calculated as [ln(2) / $\lambda_z$]; if data permits |
| $AUC_{0-t}$ | Area under the concentration versus time curve (AUC) from time 0 to the last quantifiable concentration, calculated using the linear-up/log-down trapezoidal rule |
| $AUC_{0-8h}$ | AUC from time 0 to 8 hours post dose, calculated by the linear-up/log-down trapezoidal rule |
| $AUC_{0-12h}$ | AUC from time 0 to 12 hours post dose, calculated by the linear-up/log-down trapezoidal rule |

For the calculation of PK parameters, all plasma concentrations that are BLQ prior to the first measurable concentration will be set to zero. The BLQ values that are between measurable concentrations will be set to missing. If two or more consecutive BLQ concentrations are followed by quantifiable concentrations, these quantified values will be set to missing. The BLQ values following the last quantifiable time-points will be set to missing except the first BLQ can be set to 1/2 the lower limit of quantification if needed to facilitate the terminal phase slope estimation. No concentration estimates will be imputed for missing sample values. Any sample

with a missing value will be treated as if the sample had not been scheduled for collection and will be ignored when calculating mean concentrations or PK parameters.

AUC values will be calculated by numeric integration using linear trapezoidal linear interpolation rule.

The individual PK parameters of investigational products (LC350189 and febuxostat) will be presented in a data listing. The PK parameters of LC350189 will be summarized using the following descriptive statistics: N, n, arithmetic mean, SD, median, CV%, minimum, and maximum. Note that mean, SD and CV% will not be presented for Tmax. Geometric means and geometric CV% will also be included for AUC and Cmax values.

Plasma PK parameters will be displayed to 3 significant figures in all data listings and summary tables.

## 10.2. Pharmacodynamic Analysis

### 10.2.1. Serum Uric Acid Concentrations

Blood samples will be collected and analyzed for sUA as outlined in Section 14.2.

Serum uric acid concentrations that are below the limit of quantification (BLQ) will be set to zero for calculation of summary statistics for sUA concentration data at each timepoint.

Individual serum concentrations for sUA will be listed by treatment using the FAS and PPS for original, change from baseline, and percent change from baseline. Individual serum sUA concentration versus actual time profiles will be plotted on both linear and semi logarithmic scales for each subject using the FAS and PPS (original, change from baseline, and percent change from baseline).

Serum concentration data for sUA will be summarized by time point for each treatment using the following descriptive statistics for FAS and PPS: N, n, arithmetic mean, arithmetic SD, arithmetic CV%, geometric mean, geometric CV%, median, minimum, and maximum values for original scale, change from baseline, and percent change from baseline. Baseline will be pre-dose concentration for Visit 4 (Day 1). Mean serum uric acid concentration versus nominal time profiles will be plotted using the FAS and PPS on both linear and semi-logarithmic scales (original, change from baseline, and percent change from baseline).

In addition, individual trough levels of sUA collected before dosing on Days 1, 14, 28, 56 and 84 will be plotted for each treatment on both linear and semi-logarithmic scales for each subject and mean trough concentration versus nominal time profiles will be plotted for each treatment using the FAS and PPS on both linear and semi-logarithmic scales.

### 10.2.2. Pharmacodynamic Parameters

The individual serum concentration versus actual time data for sUA and change from baseline sUA will be used to derive the following PD parameters using non-compartmental analysis, using Phoenix® WinNonlin® (Certara USA, Inc., Princeton, NJ, 8.0 or higher) or SAS® software (SAS Institute, Inc., Cary, NC, Version 9.4 or higher).

| **PD Parameter** | **Definition** |
|---|---|
| **Sparse and Dense Sampling** | |
| $C_{trough,ss}$ | Serum concentration observed at the end of a dosing interval (collected before the next administration). |
| **PD Parameter** | **Definition** |
| **Dense Sampling** | |
| $E_{max}$ | Maximum observed effect |
| $TE_{max}$ | Time to maximum observed effect |
| $AUEC_{0-t}$ | Area under effect curve (AUEC) from time 0 to the last quantifiable concentration, calculated using the linear-up/log-down trapezoidal rule |
| $AUEC_{0-8h}$ | AUEC from 0 to 8 hours post-dose calculated using the linear-up/log-down trapezoidal rule |
| $AUEC_{0-12\ h}$ | AUEC from 0 to 12 hours post-dose calculated using the linear-up/log-down trapezoidal rule |

For the calculation of PD parameters, all sUA concentrations that are BLQ prior to the first measurable concentration will be set to zero. The BLQ values that are between measurable concentrations will be set to missing. If two or more consecutive BLQ concentrations are followed by quantifiable concentrations, these quantified values will be set to missing. The BLQ values following the last quantifiable time-points will be set to missing except the first BLQ can be set to 1/2 the lower limit of quantification if needed to facilitate the parameter estimation.

AUEC values will be calculated by numeric integration using linear trapezoidal linear interpolation rule.

Serum PD parameters will be presented in data listings and summarized using descriptive statistics (n, arithmetic mean, SD, CV%, median, minimum, and maximum) by treatment on the original scale and change from baseline/percent change from baseline scale. Note that mean, SD and CV% will not be presented for $TE_{max}$. Geometric means and geometric CV% will also be included for AUEC and $C_{max}$ values.

Serum PD parameters will be displayed to 3 significant figures in all data listings and summary tables.

## 10.3. Exploratory Pharmacodynamic Analysis

### 10.3.1. Serum Hypoxanthine and Xanthine Concentrations

Blood samples will be collected and analyzed for hypoxanthine and xanthine at baseline (Visit 4) and Day 84 (Visit 8).

Serum concentration data for hypoxanthine and xanthine will be summarized by change from baseline for each treatment using the following descriptive statistics for PPS: N, n, arithmetic mean, arithmetic SD, arithmetic CV%, geometric mean, geometric CV%, median, minimum, and maximum values. Serum hypoxanthine and xanthine concentrations that are BLQ will be set to zero for calculation of summary statistics for concentration data at each timepoint.

# 11. INTERIM ANALYSIS

No formal interim analysis is planned.

# 12. CHANGES TO THE PLANNED ANALYSIS

No changes to the statistical analyses section of the protocol are made in this SAP.

# 13. REFERENCES

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# 14. APPENDICES

## 14.1. Schedule of Assessments

| Study Period[1] | SCREENING & WASH-OUT/PROPHYLAXIS[2] | | | TREATMENT PERIOD[3] | | | | | FOLLOW-UP |
|---|---|---|---|---|---|---|---|---|---|
| | | | | _ | | | | End of treatment/ early termination | |
| **Visit number** | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** |
| **Time point (Weeks)** | **-5 to -3[4]** | **-5 to -3[4]** | **-2 to -1** | **1** | **2** | **4** | **8** | **12** | **14** |
| **Time point (Days)** | **-33 to -26** | **-30 to -23** | **-9 to -4** | **1** | **14 (±2D)** | **28 (±2D)** | **56 (±2D)** | **84 (±2 D)** | **98 (±2 D)** |
| Informed consent | X | | | | | | | | |
| Assess eligibility criteria | X[5] | X | | X[6] | | | | | |
| Demographics | X | | | | | | | | |
| Medical history | X | | | | | | | | |
| Physical examination | X | | | | | | | | |
| Height | X | | | | | | | | |
| Weight, BMI | X | | | X | X | X | X | X | X |
| Tophi assessment | X | | | | | | | X | |
| Pregnancy test[7] | X[8] | | | X | X | X | X | X | |
| Hep B, Hep C, HIV test | X | | | | | | | | |
| Record prior[9]/concomitant medications | X | | X | X | X | X | X | X | X |
| 12-lead ECG | X | | | X | | | | X | |
| Vital signs | X[10] | | X | X[11] | X | X | X | X | X |
| Blood sampling for endpoints and laboratory tests | X[4] | | X[5] | X[12] | X | X | X | X | |
| Blood sampling for PK/PD[13] | | | | X | X | X | X | X | |
| Urine sampling - urinalysis | X | | X | X | X | X | X | X | |
| sUA blood sampling for randomization | | | X[5] | | | | | | |
| Randomization | | | | X[14,15] | | | | | |
| Dispense prophylaxis[16] | | X | | X | | X | X | | |
| Dispense study drug | | | | X | | X | X | | |
| Collect unused prophylaxis | | | | X | | X | X | X | |
| Collect unused study drug | | | | | | X | X | X | |
| Drug accountability/compliance | | | | X[17] | | X | X | X | |
| Assess and record adverse events | X | X | X | X | X | X | X | X | X |
| Gout Flare eDiary[18] | | X[19] | X | X | X | X | X | X | |
| eDiary device return | | | | | | | | X | |

1. Subjects should attend all Visits following a fast for at least 8 hours except visit at Day 98 (Visit 9).
2. All efforts should be made to maintain protocol-defined visit windows, but if an extenuating circumstance arises preventing this, the Sponsor and/or designee should be consulted. If the Sponsor and/or designee determine that the scientific integrity of data and subject safety would not be compromised, an out of window visit may be permitted.
3. Subjects will be instructed to withhold the investigational products on Visit days.
4. Screening Visit will be between Day -33 to -26; prophylaxis will start between Day -30 to -23, once a subject is confirmed eligible. Subjects will be instructed to discontinue their current ULT the same day they begin prophylaxis if they are on ULT at screening.
5. Single retest is permitted during the screening period if the investigator believes there is an appropriate rationale to perform a retest, which is believed to be due to an intercurrent condition and does not present a safety issue for the subject to participate in the study, and all efforts should be made to maintain protocol-defined visit windows.
6. Gout per ACR criteria will be confirmed.
7. Female with childbearing potential only, urine pregnancy test except Screening Visit (Visit 1).
8. Serum pregnancy test.
9. Any medications that are started before the first randomized study dose date will be prior medications.
10. A single repeat measurement is permitted at screening for eligibility determination.
11. On Day 1, vital signs will be taken pre-dose and at 4 hours post-dose.
12. Pre-dose sUA (Day 1; Visit 4) will be used as baseline throughout the study.
13. Refer to Table 14.2 for PK/PD sampling schedule time points.
14. sUA inclusion criterion of >=8.0mg/dL to <=12.0mg/dL must be met from the blood sample taken at Day -9 to -4 (Visit 3).
15. Subjects who have gout flare during the screening and wash-out/prophylaxis period will not be randomized; the subjects can be rescreened once 3 weeks after resolution of gout flare.
16. Prophylaxis with colchicine (0.6 mg QD) will be started at Day -30 to -23, once a subject is confirmed eligible, and will continue through the end of the treatment period.
17. Accountability for Colchicine only.
18. A gout flare will be defined as an episode of patient-reported acute articular or bursal pain that occurs at rest and is typical of past gout attacks. In addition, both of the following criteria must be met: the intensity of pain at rest must be ≥4 on an 11-point

numerical rating scale, and the pain must be determined by the patient and/or the Investigator to require anti-inflammatory/analgesic treatment. Finally, at least 2 of 3 possible joint symptoms (swelling, warmth, or tenderness) must be present, and at least 1 of the following must be present: rapid onset of pain, decreased range of joint motion, or joint redness. These parameters will be captured and evaluated by the electronic patient diary (eDiary).

[19.] Device distribution and training on eDiary record will be provided to the subjects.

## 14.2. PK/PD Sampling Schedule

| PK/PD data | Subjects | Time point |
|---|---|---|
| Sparse data | All subjects | • Pre-dose, 4 hours post-dose at Day 1 (Visit 4)<br>• Pre-dose at Day 14 (Visit 5)<br>• Pre-dose at Day 28 (Visit 6)<br>• Pre-dose and 4 hours post-dose at Day 56 (Visit 7)<br>• Pre-dose at Day 84 (Visit 8) |
| Dense data | Subjects who sign written informed consent for dense PK/PD sampling | • Pre-dose, 2, 4, 8 and 12 hours post-dose at Day 1 (Visit 4)<br>• Pre-dose at Day 14 (Visit 5)<br>• Pre-dose at Day 28 (Visit 6)<br>• Pre-dose and 4, 8 hours post-dose at Day 56 (Visit 7)<br>• Pre-dose at Day 84 (Visit 8) |

## 14.3. Handling of Dates

Dates will be stored as numeric variables in the SAS analysis files and reported in DDMMMYYYY format (i.e., the Date9. datetime format in SAS).

No imputation will be applied to incomplete or partial date.

### 14.3.1. Calculation Using Dates

Calculations using dates (e.g., subject's age or relative day after the first dose of study drug) will adhere to the following conventions:

Study days after the start day of study drug will be calculated as the difference between the date of interest and the first date of dosing of study treatment plus 1 day. The generalized calculation algorithm for relative day is the following:

- If Target Date >= Start Date, then Study Day = (Target Date - Start Date) + 1;
- Else Study Day = (Target Date - Start Date);

Note that Study Day 1 is the first day of treatment of study drug. Negative study days are reflective of observations obtained during the baseline/screening period.

- Intervals that are presented in weeks will be transformed from days to weeks by using (without truncation) the following conversion formula of Weeks = Days /7
- Intervals that are presented in months will be transformed from days to months by using (without truncation) the following conversion formula of Months = Days /30.4167

### 14.3.2. Handling of Incomplete Dates

When date of an event is incomplete (missing Year, Month, or Day), following rules will be applied in comparison:

- If the event start date is clearly on or after the Study Day 1 (i.e. Month of event > Month of Study Day 1 or Year or event > Year of Study Day 1), the medication is categorized as concomitant;
- If the event end date is clearly before the Study Day 1, (i.e. Month of event < Month of Study Day 1 or Year or event < Year of Study Day 1), the medication is categorized as prior;
- Otherwise, the medication is categorized as prior/concomitant;
- In case of start date is after end date, a query will be raised.

**Determination of prior or concomitant medications:**

| End Date | | Start Date | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Year Missing | Year < YEAR | Year =YEAR | | | | | Year > YEAR |
| | | | | Month Missing | Month < MONTH | Month = MONTH | Day =DAY | Month > MONTH | |
| Year Missing | | Prior/Con | Prior/Con | Prior/Con | Prior/Con | Prior/Con | Con | Con | Con |
| Year < YEAR | | Prior | Prior | N/A | N/A | N/A | N/A | N/A | N/A |
| Year =YEAR | Month Missing | Prior/Con | Prior/Con | Prior/Con | Prior/Con | Prior/Con | Con | Con | N/A |
| | Month < MONTH | Prior | Prior | Prior | Prior | N/A | N/A | N/A | N/A |
| | Month = MONTH | Prior/Con | Prior/Con | Prior/Con | Prior/Con | Prior/Con | Con | N/A | N/A |
| | Day =DAY | Prior/Con | Prior/Con | Prior/Con | Prior/Con | Prior/Con | Con | N/A | N/A |
| | Month > MONTH | Prior/Con | Prior/Con | Prior/Con | Prior/Con | Prior/Con | Con | Con | N/A |
| Year > YEAR | | Prior/Con | Prior/Con | Prior/Con | Prior/Con | Prior/Con | Con | Con | Con |

- Year/Month/Day: Year, Month, and Day of the event date;
- YEAR/MONTH/DAY: Year, Month, and Day of the Study Day 1;
- Except the scenario of Day=DAY, day of event date are missing;

**Determination of TEAEs:**

- Year of AE start date is missing, set it as TEAE unless AE end date is clearly earlier than Study Day 1;
- Year of AE start date < Year of Study Day 1, set it as non TEAE;
- Year of AE start date = Year of Study Day 1:
  - If Month of AE start date < Month of Study Day 1, set it as non TEAE;
  - If Month of AE start date = Month of Study Day 1, set it as TEAE unless AE end date is clearly earlier than Study Day 1;
  - If Month of AE start date > Month of Study Day 1, set it as TEAE;
- Year of AE start date > Year of Study Day 1, set it as TEAE;