# Clinical Development LC350189

# Clinical Study 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

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# 1.0 ADMINISTRATIVE INFORMATION

## 1.1 Contacts

A separate contact information list will be provided.

## 1.2 Approval

Representatives of Sponsor and Principal Investigator will sign the agreement on the protocol.

## 1.3 Document History

| Version | Revision Date | Revision Type | Revision Description |
|---|---|---|---|
| **1.0** | **18 MAR 2019** | Not applicable | Original Document |
| **2.0** | **26 JUN 2019** | Substantial | Removal of a LC350189 400mg treatment group.<br>Sample size change due to removal of the treatment group<br>Inclusion criterion change per Uloric prescribing information (2019)<br>Change of starting dose of febuxostat from 80 mg to 40 mg<br>Addition of dose titration criterion for febuxostat group<br>Change of Visit 5 schedule from Day 7 to Day 14.<br>Addition of a visit on Day 18 to dispense investigational products<br>Change in PK/PD sampling points in consideration of visit schedule change |
| **3.0** | **18 JUL 2019** | Substantial | Change of visit day titrating febuxostat dose from Day 18 to Day 28 based on sUA level on Day 14<br>Rephrasing a selection criterion to exclude patients not on stable dose of drugs known to affect sUA levels<br>Change in inclusion and exclusion criteria related to medications<br>Addition of list of prohibited medications and food as specified in the respective colchicine and febuxostat US prescribing information labels |
| **3.1** | **12 AUG 2019** | Non-substantial | Change in visit window (Visit 1, 2 and 3) to reflect turnaround time for central laboratory result availability |

| Version | Revision Date | Revision Type | Revision Description |
|---|---|---|---|
| **4.0** | **09 APR 2020** | Substantial | Change in inclusion and exclusion criteria<br>Allow of single repeat measurement at screening<br>Addition of contingency measures in response to the COVID-19 Pandemic |
| **5.0** | **11 JUN 2020** | Substantial | Elimination of the active control group (Febuxostat)<br>Sample size reduction related to elimination of the active control group |

**Investigator Approval Page**

Protocol Number: LG-GDCL002

Protocol Title: 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.

The Principal Investigator agrees to conduct this study as outlined in this protocol in reference to national/local regulations and in accordance with current Good Clinical Practice (GCP) guidelines described in the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) Guidance document E6, the FDA regulations for clinical trials, 21 CFR 312, the Health Insurance Portability and Accountability Act (HIPAA), and the most current version of the Declaration of Helsinki. Any modification to the protocol must be agreed upon by both the Investigator and Sponsor and documented in writing. By written agreement to this protocol, the Investigator agrees to allow direct access to all documentation, including source data, to authorized individuals representing the Sponsor (including monitoring staff and auditors), to Institutional Review Boards/Independent Ethics Committees (IRB/IEC) and/or to regulatory authorities.

**Principal Investigator:**

Name:

Title:

Name of Facility:

Address:

| **Name (printed)** | **Signature** | **Date** |
|---|---|---|

**Sponsor Protocol Approval Page**

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Protocol Number: LG-GDCL002

Protocol Version: 5.0

Date: 11JUN2020

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**Approved for the Sponsor by:**

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## 2.0 STUDY SUMMARY

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|---|---|
| **Name of Investigational Product** | LC350189 |
| **Protocol Number** | LG-GDCL002 |
| **Protocol Title** | 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 |
| **Primary Objective and Endpoints** | To assess the efficacy of LC350189 in terms of serum uric acid (sUA) level <5 mg/dL at Week 12 (Day 84) to find therapeutic dose of LC350189.<br>• Proportion of subjects who achieve sUA level <5.0 mg/dL at Day 84 (Visit 8) |
| **Secondary Objectives and Endpoints** | To assess the efficacy of LC350189 in terms of sUA levels.<br>• Proportion of subjects with sUA <6.0 mg/dL at Day 84 (Visit 8)<br>• Proportion of subjects who achieve sUA <5.0 mg/dL at each visit<br>• Proportion of subjects with baseline (Visit 4) sUA >10 mg/dL who achieve <5.0 mg/dL at Day 84 (Visit 8)<br>• Proportion of subjects with baseline (Visit 4) sUA >10 mg/dL who achieve <6.0 mg/dL at Day 84 (Visit 8)<br>• Proportion of subjects per renal function at baseline (Visit 3) who achieve sUA <5.0 mg/dL at Day 84 (Visit 8)<br>• Proportion of subjects per renal function at baseline (Visit 3) who achieve sUA <6.0 mg/dL at Day 84 (Visit 8)<br>To investigate the pharmacokinetic (PK) and pharmacodynamic (PD) characteristics of LC350189 in subjects with hyperuricemia and a diagnosis of gout.<br>• $C_{trough,ss}$ at baseline (Visit 4), Day 14 (Visit 5), Day 28 (Visit 6), Day 56 (Visit 7) and Day 84 (Visit 8)<br>• Change and percent change in sUA levels from baseline (Visit 4) at each visit<br>• Maximum percent reduction in sUA level during treatment<br>To assess antiflare activity in subjects with hyperuricemia and a diagnosis of gout.<br>• Gout flare rate in subjects<br>• Gout flare rate in subjects with sUA <6.0 mg/dL at Day 84 (Visit 8)<br>• Proportion of subjects with episodes of gout flare requiring rescue treatment |
| **Exploratory Objectives and Endpoints** | To explore the metabolic and anti-inflammatory effects of LC350189.<br>• Change in HbA1c from baseline (Visit 4) to Day 84 (Visit 8)<br>• Proportion of subjects with HbA1c <7% at Day 84 (Visit 8)<br>• Proportion of subjects with HbA1c ≤6.5% at Day 84 (Visit 8)<br>• Change in fasting plasma glucose (FPG) from baseline (Visit 4) at Day 84 (Visit 8)<br>• Change in high-sensitivity C-reactive protein (hs-CRP) from baseline (Visit 4) at Day 84 (Visit 8)<br>• Serum concentrations of hypoxanthine and xanthine at baseline (Visit 4) and Day 84 (Visit 8) |

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| **Safety Objectives and Endpoints** | To assess the safety and tolerability of LC350189.<br>• Adverse events (AEs)<br>• Laboratory values<br>• Vital signs<br>• Electrocardiogram (ECG) |
| **Phase of Development** | II |
| **Number of Study Sites** | Multiple sites in the United States |
| **Study Population** | Subjects with hyperuricemia and a diagnosis of gout |
| **Number of Subjects** | The study will be conducted in up to 152 subjects. The total number of subjects does not include subjects who have assigned to an active control group before the implementation of the Protocol version 5.0. Four groups of 38 subjects will be included in the study, including three groups treated with a range of doses of LC350189 and one group treated with placebo. |
| **Summary of Study Design** | This study is a randomized, multicenter, double-blind, parallel-group, placebo-controlled, dose finding, and Phase II study to assess the efficacy and safety of three different doses of LC350189 in subjects with hyperuricemia and a diagnosis of gout.<br><br>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 the placebo group. Each subject will undergo a screening visit 33 to 26 days prior to the first day of the treatment period (Visit 1); a visit 30 to 23 days prior to the first day of the treatment period to enter a washout period and/or initiate prophylaxis (Visit 2); a visit 9 to 4 day(s) prior to the first day of the treatment period to obtain a blood sample to assess eligibility for randomization based on the inclusion criterion of sUA ≥8.0 mg/dL to ≤12.0 mg/dL (Visit 3); a treatment period that will include five visits on Day 1, 14, 28, 56, and 84 (Visits 4 to 8); and a follow-up on-site visit approximately 2 weeks (Day 98) after completion of the dosing period (Visit 9). |
| **Treatments** | Subjects will receive LC350189 50 mg, LC350189 100 mg, LC350189 200 mg or placebo for 12 weeks starting on Day 1 (Visit 4). Gout flare prophylaxis will consist of colchicine 0.6 mg once daily (QD) starting at Visit 2 (between Day -30 to -23) through the end of the treatment period. |
| **Route of Administration** | Subjects will orally self-administer investigational product (two capsules of LC350189 /placebo) and one tablet of gout flare prophylaxis once daily in the morning, at approximately the same time each day, with water and without regard to food. Subjects will withhold the investigational product until after pre-dose laboratory samples on the days of scheduled visits will be collected (Day 14, 28, 56, and 84). |
| **Duration of Participation** | The duration of the study will be up to 19 weeks for each subject. |

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| **Inclusion Criteria** | 1. Subjects or the subject's legally acceptable representatives who sign a written informed consent form prior to the initiation of any study procedures.<br>2. Male or female subjects between the ages of 18-75 years, inclusive.<br>3. Subjects with hyperuricemia and a history or presence of gout per American College of Rheumatology (ACR) criteria (Appendix A) (Neogi et al 2015).<br>4. Subjects with a self-reported history of ≥ 2 gout flares in the prior 12 months to screening (Visit 1).<br>5. Subjects who are currently on urate lowering therapy (ULT; Allopurinol, Febuxostat, Probenecid, Lesinurad) with a sUA level ≥6.0 mg/dL at Visit 1; Or Subjects who are ULT naïve or currently not on ULT with a sUA level ≥8.0 mg/dL to ≤12.0 mg/dL at Visit 1.<br>6. Subjects with a sUA level ≥8.0 mg/dL to ≤12.0 mg/dL at Day -9 to -4 (Visit 3)<br>7. Subjects with a body mass index (BMI) ≤42 kg/$m^2$ at screening (Visit 1).<br>8. Subjects with estimated glomerular filtration rate (eGFR) ≥ 60 mL/min/1.73$m^2$ at screening (Visit 1).<br>9. For childbearing subjects, a negative pregnancy test result at screening (Visit 1). Subjects (female subjects of childbearing potential and male subjects with partners of childbearing potential) must agree to use proper contraceptive methods to avoid pregnancy during the study.<br>10. Subjects who are capable of understanding the study procedures, the risks involved, and are willing to adhere to the visit/protocol schedules. |
| **Exclusion Criteria** | 1. Subjects with secondary hyperuricemia (*e.g.*, due to myeloproliferative disorder, or organ transplant).<br>2. Subjects experiencing an active acute gout attack within 3 weeks prior to screening (Visit 1).<br>3. Subjects with aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 2 times upper limit of normal (ULN) at screening (Visit 1).<br>4. Subjects with creatine kinase > 2.5 times ULN at screening (Visit 1).<br>5. Subjects with previous intolerance to colchicine.<br>6. Subjects who received pegloticase within 3 months prior to screening (Visit 1).<br>7. Subjects who have not been receiving stable doses of drugs known to affect sUA levels (losartan, fibrates, thiazide diuretics, loop diuretics, acetylsalicylic acid [ASA]) for the last six weeks prior to screening (Visit 1). ASA use more than 325 mg/day is not allowed.)<br>8. Subjects who have received systemic corticosteroids more than 10 continuous days within 1 month prior to screening (Visit 1).<br>9. Subjects who require or may require systemic immunosuppressive or immunomodulatory treatment (eg, azathioprine, 6-mercaptopurine, cyclosporine).<br>10. Subjects receiving medications that are strong or moderate CYP3A4 inhibitors or P-glycoprotein (P-gp) inhibitors within 14 days prior to screening (Visit 1).<br>11. Subjects with a history of xanthinuria.<br>12. Subjects with a history of rheumatoid arthritis. |

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| | 13. Subjects with active peptic ulcer disease requiring treatment.<br>14. Subjects with unstable angina, New York Heart Association (NYHA) class III or IV heart failure, myocardial infarction, stroke, deep venous thrombosis (DVT), percutaneous coronary intervention (with or without stent), or coronary artery bypass graft (CABG) in the last 12 months prior to screening (Visit 1); Subjects currently receiving anticoagulants; Or subjects with clinically significant ECG abnormality in the opinion of the Investigator at screening (Visit 1).<br>15. Subjects with uncontrolled hypertension (systolic pressure above 160 mmHg or diastolic pressure above 95 mmHg) at screening (Visit 1).<br>16. Subjects with a history of myositis/myopathy, rhabdomyolysis, Stevens-Johnson syndrome, or toxic epidermal necrolysis.<br>17. Subjects with a history of malignancy within the previous 5 years with the exception of non-melanoma skin cancer that has been treated with no evidence of recurrence, treated cervical dysplasia, or treated in situ Grade 1 cervical cancer.<br>18. Subjects with known hypersensitivity or allergy to any ingredients of LC350189.<br>19. Subjects that consume more than 14 drinks of alcohol per week (*e.g.*, 1 drink = 5 oz [150 ml] of wine, 12 oz [360 ml] of beer, or 1.5 oz [45 ml] of hard liquor).<br>20. Subjects with a history or suspicion of drug abuse (defined as any illicit drug use) within the past 5 years.<br>21. Subjects who are pregnant or lactating.<br>22. Subjects who test positive for human immunodeficiency virus (HIV) or active hepatitis B or hepatitis C virus (HCV) infection. Active HCV infection is defined as a subject with a positive hepatitis C antibody and detectable hepatitis C viral load RNA.<br>23. Subjects who have previously participated in interventional clinical studies within 3 months or 5 half-lives of investigational therapy (whichever is longer) prior to the screening visit (Visit 1).<br>24. Subjects with any other medical or psychological condition, which in the opinion of the Investigator and/or Medical Monitor, might create undue risk to the subject or interfere with the subject's ability to comply with the protocol requirements, or to complete the study. |
| **Sample Size** | Before eliminating active control group, sample size was calculated as 30 subjects (38 including drop-out rate 20%) per group. The size of the control population is based on the FACT trial in which a post hoc analysis of serum urate at final visit showed sUA <5 mg/dL in 118/249 (47%) patients treated with febuxostat 80 mg.<br><br>To have sufficient number of subjects for dose finding, an evaluable population of 30 subjects per group (38 including drop-out rate 20%) remains although elimination of the active control group is made 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 is not sufficient for dose selection. In this study, a total of 152 subjects, not including subjects who have already assigned to an active control group, will be randomized to four groups. The power when compared to placebo group with the current sample size is calculated more than 99%. |
| **Statistical Methods** | Subjects who are randomized into the test (LC350189 50 mg, LC350189 100 mg, or LC350189 200 mg) or placebo groups before the Protocol version 5.0 will be combined and analyzed with |

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| | subjects who will be enrolled after the implementation of the Protocol version 5.0. For subjects randomized into the active control group before the implementation of the Protocol version 5.0, the active control group will be listed and can be summarized for exploratory purpose.<br><br>**Demographic and baseline characteristics**<br>Demographic and baseline characteristics will be summarized for the Safety Analysis Set. Summary statistics (eg, number of subjects, mean, median, standard deviation, and range) will be generated for continuous variables and the number and percentage of subjects within each category will be presented for categorical variables.<br><br>**Analysis of Efficacy Endpoints**<br>All endpoints will be summarized descriptively and will be compared to placebo using descriptive statistics. Efficacy endpoints such as the proportion of subjects meeting target will be analyzed using the Cochran-Mantel Haenszel (CMH) test adjusted by randomization stratification factors. 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. If the Wald asymptotic 95% confidence interval for each pairwise comparison includes zero, superiority of dose group over placebo is demonstrated. However, if a comparison is not statistically significant, that is, confidence interval includes zero, then all subsequent comparisons will be considered exploratory. Change and percent change from baseline (Visit 4) will be analyzed with an analysis of covariance (ANCOVA) model, including treatment, sUA and tophi strata as fixed factors, and baseline values of the dependent variable as a covariate.<br><br>**Safety Analysis and Endpoints**<br>Safety and tolerability of the investigational products will be assessed by collection and review of AEs, laboratory parameters, vital signs, and ECG parameters throughout the duration of the study. Safety analysis will involve examination of the descriptive statistics and individual subject listings for the Safety Analysis Set for any effects of study treatment on clinical tolerability and safety. All AEs will be coded using MedDRA. Data will be summarized using preferred term and primary system organ class. AE summaries will include the overall incidence (by system organ class and preferred term), events by maximum intensity, event by relationship to study treatment, events leading to discontinuation of investigational product, and serious AEs. Laboratory parameters (hematology, chemistry, and urinalysis), vital signs, and ECG will be summarized descriptively by treatment |

## Table 2-1 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 will be instructed to 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 9-3 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.

## 3.0 LIST OF ABBREVIATIONS

| Abbreviation | Definition |
|---|---|
| ACR | American College of Rheumatology |
| AE | Adverse event |
| ALT | Alanine aminotransferase |
| ANCOVA | Analysis of covariance |
| AST | Aspartate aminotransferase |
| ATP | Adenosine triphosphate |
| AUC | Area under the plasma concentration-time curve |
| ASA | Acetylsalicylic acid |
| BMI | Body mass index |
| CABG | Coronary artery bypass graft |
| CDM | Clinical data management |
| CFR | Code of Federal Regulations |
| $C_{max}$ | Maximum plasma drug concentration |
| $C_{mean,24}$ | 24-hour mean serum concentration |
| CMH | Cochran-Mantel Haenszel |
| $C_{trough,ss}$ | Steady-state trough serum concentrations |
| CRA | Clinical research associates |
| CYP | Cytochrome P450 |
| DECT | Dual-energy computed tomography |
| DMP | Data management plan |
| DVT | Deep venous thrombosis |
| ECG | Electrocardiogram |
| $EC_{50}$ | Concentration causing 50% of maximum effect |
| eCRF | Electronic case report form |
| $ED_{50}$ | Dose causing 50% of maximum effect |
| EDC | Electronic Data Capture |
| eDiary | Electronic patient diary |
| EULAR | European League Against Rheumatism |
| eGFR | Estimated glomerular filtration rate |
| FAS | Full Analysis Set |
| FDA | Food and Drug Administration |
| FPG | Fasting plasma glucose |
| FSFV | First subject first visit |
| GCP | Good Clinical Practice |
| HbA1c | Hemoglobin A1c / Glycosylated hemoglobin |
| HCV | Hepatitis C virus |
| HIPAA | Health Insurance Portability and Accountability Act |
| HIV | Human immunodeficiency virus |
| hs-CRP | High sensitivity-C-reactive protein |
| $IC_{50}$ | Half maximal inhibitory concentration |

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| ICF | Informed consent form |
| ICH | International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use |
| IEC | Independent Ethics Committee |
| IND | Investigational new drug |
| INR | International normalised ratio of prothrombin time |
| IRB | Institutional Review Board |
| ISF | Investigator's Site File |
| IWRS | Interactive Web Response System |
| LSLV | Last subject last visit |
| MAD | Multiple ascending dose |
| MDRD | Modification of Diet in Renal Disease |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MRSD | Maximum recommended starting dose |
| MSU | Monosodium urate monohydrate |
| MTP | Metatarsophalangeal |
| NOAEL | No observed adverse effect levels |
| NRI | Non-responder imputation |
| NSAIDs | Non-steroidal anti-inflammatory drugs |
| NYHA | New York Heart Association |
| PD | Pharmacodynamic |
| P-gp | P-glycoprotein |
| PK | Pharmacokinetic |
| PP | Per-Protocol |
| QC | Quality control |
| SAD | Single ascending dose |
| SAE | Serious adverse event |
| SAP | Statistical analysis plan |
| SDV | Source data verify |
| SOA | Schedule of assessments |
| sUA | Serum uric acid |
| SUSAR | Suspected unexpected serious adverse reaction |
| TEAE | Treatment emergent adverse event |
| $t_{max}$ | Time to maximum plasma concentration following drug administration |
| UA | Uric acid |
| ULN | Upper limit of normal |
| ULT | Urate-lowering therapy |
| U.S. | United States |
| WHO | World Health Organization |
| XO | Xanthine oxidase |

# 4.0 INTRODUCTION

## 4.1 Background

Gout affects an estimated 8.3 million adults in the United States (U.S.), 6.4 million adults in the European Union and 2.9 million adults in Japan, and the number of subjects with gout in major markets is forecast to grow to more than 16 million by 2019 (Zhu et al 2011).

Gout is an inflammatory arthritis caused by deposition of monosodium urate crystals in joints. With persistent urate crystal deposition, gout may progress from acute episodic attacks to a disabling chronic deforming arthropathy, with destructive deposits of urate crystals (tophi) in several types of tissues in joints, and in subcutaneous tissue. Renal damage may occur due to interstitial urate crystal deposition and urinary tract stones composed entirely or partly of monosodium urate and uric acid (UA) crystals, and in some cases due to renal medullary tophi (Ragab et al 2017).

Hyperuricemia (elevated levels of urate in the circulation) is a prerequisite for the development of gout. Gout occurs in subjects with serum urate >6.8 mg/dL, which is the solubility limit of monosodium urate (Martillo et al 2014). The prevalence of gout increases with higher serum urate (Choi et al 2005).

Urate is produced in the human body by metabolism of readily absorbable dietary purines (such as guanosine) or catabolism of endogenous purines, including adenosine triphosphate (ATP), which are contained in DNA and other nucleic acids, the essential building blocks of any living organism (Horiuchi et al 1999; Hydman et al 2016). UA is the protonated form of urate (Martillo et al 2014). Lowering serum uric acid (sUA) concentration with xanthine oxidase (XO) inhibitor drugs or accelerating the clearance of UA from the body through the urine with uricosuric agents, or in severe gout, degrading UA using recombinant uricase, is the general pharmacologic approach for management of hyperuricemia in gout (Sattui and Gaffo 2016).

The XO inhibitors allopurinol and febuxostat are the most widely prescribed category of antihyperuricemic drugs in the U.S.; however, the use of allopurinol is limited by rare occurrences of a severe potentially lethal hypersensitivity syndrome and a variety of drug interactions, and the use of febuxostat has been associated with adverse hepatic effects and possibly increased cardiovascular risk (White et al 2018; Sattui and Gaffo 2016; ULORIC 2019). Furthermore, these urate-lowering therapies (ULTs) dramatically increase the chance of experiencing a gout flare, probably because they disrupt intraarticular urate crystals (Neogi et al 2015; Poiley et al 2016). Current anti-inflammatory therapies used for prophylaxis for gout flares include colchicine, non-steroidal anti-inflammatory drugs (NSAIDs) and steroids, some of which is limited by frequent contraindications to at least one of these agents in gout patients. Consequently, there remains a need for safer and more potent ULTs.

In response to these unmet medical needs, LG Chem, Ltd. launched a drug discovery and development program for a best-in-class XO inhibitor. The discovery and optimization process was carried out by applying state-of-the-art computer-aided drug design with known X-ray crystal structures of XO protein-ligand complexes. As a result, LC350189 was discovered as a novel non-purine selective inhibitor of XO for indication of gout with hyperuricemia.

## 4.2 Rationale for the Proposed Study

The aim of this 12-week randomized multicenter double-blind parallel group placebo-controlled dose finding study is to assess the efficacy and safety of three different doses of LC350189 in subjects with hyperuricemia and a diagnosis of gout. Four groups of 38 subjects will be included in the study, including three groups treated with a range of doses of LC350189 and one group treated with placebo.

LC350189 has the potential to address unmet clinical needs for safety and efficacy in subjects with hyperuricemia and a diagnosis of gout. In the first-in-human clinical trial, LC350189 showed good efficacy for lowering sUA and was well tolerated up to 800 mg/day after multiple dosing in healthy subjects. LC350189 has a favorable safety profile in nonclinical studies to support long-term clinical use. Therefore, it is appropriate to investigate several doses of the investigational product in the intended potential target population.

## 4.3 Summary of Pre-Clinical /Clinical Studies

LC350189 is a novel, non-purine selective inhibitor of XO, with potent *in vitro* and *in vivo* pharmacological activity. In preliminary evaluations of the pharmacological effects of this compound, an *in vitro* enzyme activity assay showed the half maximal inhibitory concentration ($IC_{50}$) of LC350189 was 0.003μM in bovine milk, which is similar to that of febuxostat, and 0.073 μM in rat plasma. *In vivo* efficacy studies showed the dose and concentration of LC350189 causing 50% of maximum effect ($ED_{50}$ and $EC_{50}$) were 10 mg/kg and 0.39 μg/ml, respectively. Monitoring of plasma orotic acid and orotidine levels demonstrated that LC350189 has good *in vivo* selectivity for pyrimidine synthesis.

*In vitro* metabolic stability of LC350189 was evaluated in rat, dog, and human liver microsomes for phase I and phase II metabolism. The results showed that LC350189 was metabolically stable in the microsomes of all species. The majority of metabolites were N-deisopropylated LC350189 (M1) and glucuronide conjugates of LC350189 and M1. Prediction of the *in vivo* interaction potential of LC350189 with other drugs showed the inhibitory effect of LC350189 on various cytochrome P450 (CYP) isozyme activities was negligible up to a concentration of 100 μM.

In studies to evaluate systemic toxicity in rats, the no observed adverse effect levels (NOAELs) were determined to be 12.5 mg/kg in males (2-week repeated dose toxicity study) and 50 mg/kg in females (4-week repeated dose toxicity study) based on nephropathy; kidney lesions are a known rodent-specific effect (Horiuchi et al 1999). NOAEL (12.5 mg/kg) in rats was used to calculate the maximum recommended starting dose (MRSD) for the first-in-human study.

In repeated toxicity studies in dogs, there were no significant toxic effects, except soft stool, diarrhea, and mucous stool observed in the high dose group. These clinical signs were not accompanied by changes to hematology parameters or histological findings in the digestive system, and were not evident during the recovery period. LC350189 showed no specific safety concerns in genotoxicity studies.

In the first-in-human clinical trial (LG-GDCL001), 129 healthy volunteers were enrolled and exposed to placebo, active comparator (febuxostat 80 mg), or a range of doses of LC350189. In the single ascending dose (SAD) study, subjects were administered placebo or LC350189 10 to 600

mg. In the multiple ascending dose (MAD, once daily doses for 7-days) study, subjects were administered placebo, febuxostat 80 mg, or LC350189 100 to 800 mg. There were no deaths, serious adverse events (SAEs), severe adverse events (AEs), or discontinuations due to AEs, and no clinically significant AEs. Specifically, in the SAD study, among subjects administered LC350189 10 mg (n=6), one subject experienced back pain; among subjects administered LC350189 25 mg (n=6), one subject each experienced nasal congestion or sneezing; among subjects administered LC350189 100 mg (n=8), one subject each experienced flushing or headache; and among subjects administered LC350189 200 mg (n=8), one subject each experienced diarrhea, feeling hot, headache, nasal congestion, rhinorrhea, or throat irritation. In the MAD study, among subjects administered LC350189 100 mg (n=8), one subject experienced hematochezia; and among subjects administered LC350189 600 mg (n=8), one subject each experienced diarrhea, flatulence, lip ulceration, or nausea.

Systemic exposure to LC350189 increased with increasing dose in both the SAD and MAD studies, with no significant differences in pharmacokinetic (PK) properties between studies. The range of time to reach maximum plasma concentration ($t_{max}$) of LC350189 was 1.0 to 6.0 hours after dosing in the SAD study and 1.0 to 5.0 hours in the MAD study, and elimination half-lives were 5.1 to 15.0 hours and 8.6 to 13.8 hours in the SAD and MAD studies, respectively. In the MAD study, steady state was reached after approximately 2 to 3 days. To evaluate the effect of a high-fat diet on the PK profile of LC350189, the PK with a high-fat diet was compared in the 200 mg dose level group. A high fat diet decreased maximum plasma drug concentration ($C_{max}$) to 62% of the fasting $C_{max}$, but no significant change in area under the curve (AUC) was observed after food intake. The sUA 24-hour mean serum concentration ($C_{mean,24}$) on Day 1 decreased by 8.7 to 31.7% from baseline in the SAD study. In the MAD study, the decrease in sUA reached steady state on Day 5 in the 100 mg, 200 mg and febuxostat groups, and on Day 6 in other dosage groups, and the percentage decreases in the sUA $C_{mean,24}$ ranged from 53.5 to 91.2%, while that of febuxostat 80 mg was 58.8% on Day 7. The percentage changes in sUA increased with higher doses, and the changes in all dose groups except for 100 mg were statistically different from that of the febuxostat group.

Additional preclinical/clinical information can be found in the Investigator's Brochure.

### 4.4 Rationale for Treatment and Dose

For this study, the proposed doses of LC350189 are 50, 100, and 200 mg. These doses were chosen based on the first-in-human clinical trial, which showed that LC350189 10 to 600 mg administered in the SAD study and LC350189 100 to 800 mg administered in the MAD study provided robust sUA lowering in healthy volunteers with no significant safety concerns even at 800mg in the MAD study.

The expected therapeutic dose of LC350189 is between 100 and 200 mg to achieve the treatment target based on modeling and simulation of dose using phase I study data. Therefore, LC350189 50 mg was chosen as the minimal dose and LC350189 200 mg as the maximal dose to explore the appropriate dose range based on safety margins from the NOAEL in rat 13-week repeated dose toxicity and phase I study.

Investigational product will be orally self-administered daily by subjects with water and without regard to food. Regardless of subjects' status on ULT at screening, all subjects will be on gout flare prophylaxis for 3 to 5 weeks (between Days -30 and -23 to -1) prior to receiving study treatment and throughout the study.

A treatment period of 12 weeks and a washout/prophylaxis period of 14-26 days were chosen as these represent the timeframe used in Phase II studies investigating the effect of ULTs on sUA and flare incidence in patients with gout (Gunawardhana et al 2018; Neogi et al 2015; Poiley et al 2016).

# 5.0 STUDY OBJECTIVES

## 5.1 Primary Objective

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

## 5.2 Secondary Objectives

- To assess the efficacy of LC350189 in terms of sUA levels.
- To investigate the 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.

## 5.3 Exploratory Objectives

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

## 5.4 Safety Objectives

- To assess the safety and tolerability of LC350189.

For a list of the study endpoints please refer to Table 12-1.

# 6.0 STUDY DESIGN AND DESCRIPTION

## 6.1 Study Design

This randomized, double-blind, parallel group, placebo-controlled dose finding study will assess the efficacy in terms of sUA lowering (primary endpoint, <5 mg/dL; secondary endpoint, <6 mg/dL) and the safety and tolerability of LC350189. The study will be conducted at multiple sites in the U.S. in up to 152 subjects. If a subject withdraws from the study, the subject 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 the placebo. Each subject will undergo a screening visit 33 to 26 days prior to the first day of the treatment period (Visit 1); a visit 30 to 23 days prior to the first day of the treatment period to enter a washout period and/or initiate prophylaxis (Visit 2); a visit 9 to 4 day(s) prior to the first day of the treatment period to obtain a blood sample to assess eligibility for randomization based on the inclusion criterion of sUA ≥8.0 mg/dL to ≤12.0 mg/dL (Visit 3); a treatment period that will include five visits on Day 1, 14, 28, 56, and 84 (Visits 4 to 8); and a follow-up on-site visit approximately 2 weeks (Day 98) after completion of the dosing period (Visit 9). The duration of the study will be up to 19 weeks for each subject.

Eligible subjects receiving ULT will discontinue their ULT and enter a wash-out period starting at Visit 2 prior to receiving study treatment. All subjects will receive gout flare prophylaxis with colchicine 0.6 mg (QD) starting at Visit 2 (between Day -30 to -23) through the end of the treatment period.

During the treatment period, subjects will orally self-administer LC350189 or its placebo for 12 weeks starting on Day 1. To maintain consistency, patients will be instructed to take the investigational product at the same time daily, and to withhold the investigational product until after pre-dose laboratory sampling on the days of scheduled visits (Days 14, 28, 56, and 84). At each visit during the treatment period, blood will be sampled for primary, secondary and exploratory endpoint evaluations, and safety assessments will be performed (Table 12-1). On Day 1 (Visit 4) PK/PD analysis will be conducted pre-dose and 4 hours post-dose for sparse data. For dense data, additional 2, 8 hours and 12 hours post-dose in subjects, who sign written informed consent for dense PK/PD sampling, will be collected on Day 1. On Day 14 and 28 (Visit 5 and 6), PK/PD analysis will be conducted pre-dose for both sparse and dense data. On Days 56 (Visit 7), blood will be sample at pre-dose and 4 hours post-dose for sparse data; and additional 8 hours post-dose for dense data. On Day 84 (Visit 8), pre-dose blood will be sampled at a single time point for PK trough and PD analyses for both sparse and dense data.

Subjects will record the incidence of gout flares using electronic patient diaries (eDiary) from start of prophylaxis (Visit 2) through to end of treatment (Visit 8).

Subjects enrolled to the study before the implementation of the Protocol version 5.0

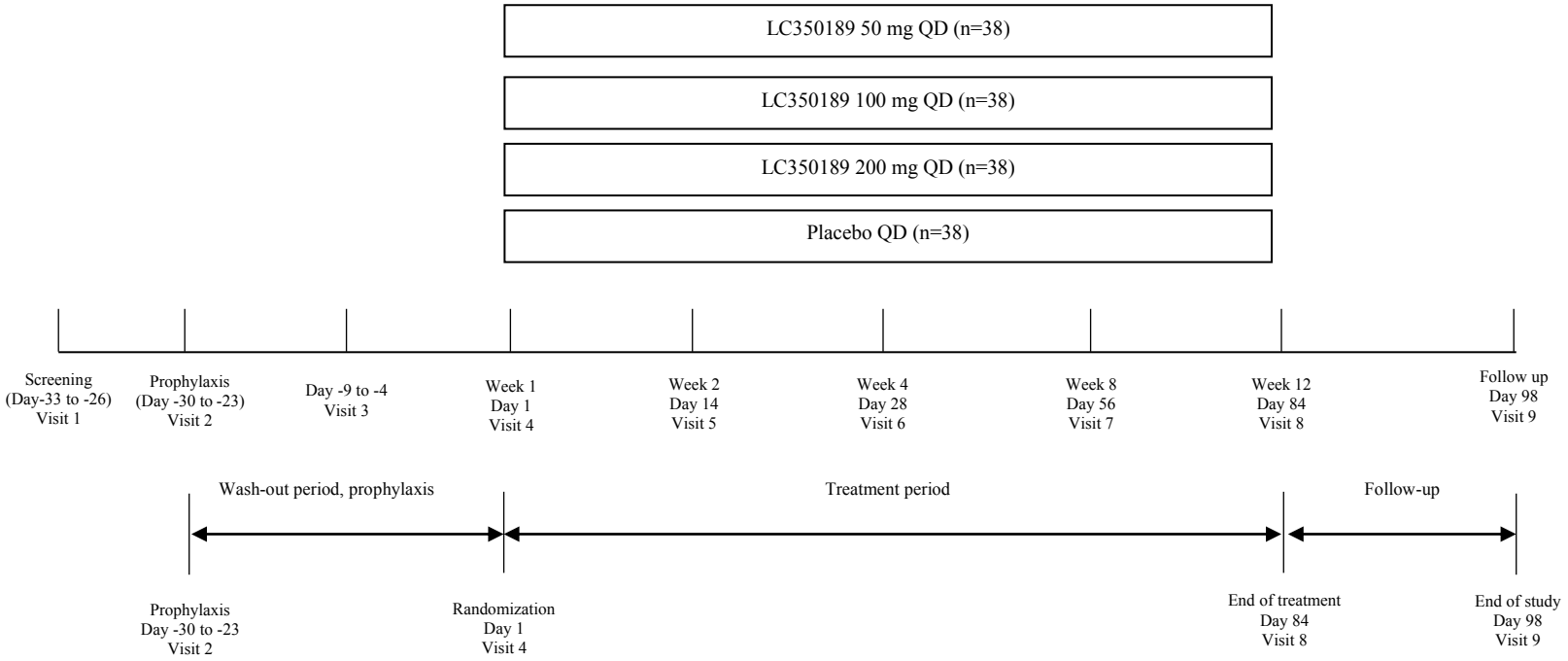
Upon implementation of the Protocol version 5.0, enrollment to the active control group (febuxostat) will be stopped and subjects will be randomized to one of four groups (LC350189 50 mg, LC350189 100 mg, LC350189 200 mg, or placebo).

Subjects who have already randomized to the active control group (febuxostat) on Day 1 (Visit 4) before stopping enrollment of the active control group will stay in the study and continue receiving the treatment regimen (one capsule from each of 2 bottles of LC350189 placebo and 1 bottle of febuxostat 40 mg or 80 mg) that they are initially assigned to. The subjects will receive febuxostat 40 mg on Day 1 (Visit 4) and continue to be on febuxostat 40 mg for the rest of the treatment period if their sUA is < 6.0 mg/dL on Day 14 (Visit 5). If their sUA is ≥6.0 mg/dL on Day 14 (Visit 5), they will receive febuxostat 80 mg QD on Day 28 (Visit 6) and will continue to be on this dose for the rest of the treatment period.

Subjects randomized to the test (LC350189 50 mg, LC350189 100 mg, or LC350189 200 mg) or placebo groups before implementation of the Protocol version 5.0 will stay in the study and continue receiving 3 bottles of investigator products (2 bottles of LC350189 25mg/100mg/placebo and 1 bottle of febuxostat placebo) as they are initially assigned to.

The rest of study procedures will apply as described in Section 6.2 and the SoA (Table 2-1).

**Figure 6-1 Study Design Schematic**



## 6.2 Study Description

Visit 1: Screening visit

Before screening takes place, potential study subjects will be provided with written and oral information about the study and the procedures involved. Subjects must sign the informed consent form (ICF) prior to entering the study (further details are provided in Section 9.1.1). The screening visit to identify eligible subjects for the study will be performed 33 to 26 days prior to first dosing. All assessments performed at the screening visit are stated in the schedule of assessments (SOA) (Table 2-1) and will be recorded in the electronic case report from (eCRF) (further details are provided in Section 9.1.2). Subjects will be assigned screening numbers in an ascending order upon signing the ICF.

Visit 2: Wash-out/prophylaxis period

Following screening, enrolled subjects receiving ULT will discontinue their ULT and enter a wash-out period between Visit 2 and the start of the treatment period. All enrolled subjects will start gout flare prophylaxis with colchicine 0.6 mg (QD) 30 to 23 days prior to the first day of the treatment period to be continued throughout the treatment period. ULT wash-out and prophylaxis treatment should occur approximately 3 days after screening, once screening laboratory results are received and the subject is determined to be eligible. Subjects will record the incidence of gout flares using eDiary throughout the wash-out and prophylactic period, starting at Visit 2.

Visit 3: Assess eligibility for randomization

Subjects will attend the clinic at Day -9 to -4 to assess their eligibility for randomization. sUA will be determined based on a blood sample obtained at Visit 3 to ensure that the inclusion criterion of sUA ≥8.0 mg/dL to ≤12.0 mg/dL is met. Subjects with sUA <8 or >12 mg/dL at Day -9 to -4 will be excluded from further participation in the study.

Visits 4 to 8: Treatment period

All scheduled visit should occur in the morning, if possible.

On the study Day 1, eligible subjects will visit to the clinic after a fast for at least 8 hours (preferably, overnight fast) for pre-dose laboratory sample collection (Visit 4). Subjects will be randomly assigned in a 1:1:1:1 ratio to one of the following treatment groups: LC350189 50 mg, LC350189 100 mg, LC350189 200 mg, or placebo. Subjects will be randomized within the following population strata: sUA, defined as the Day -9 to -4 (Visit 3) value, <9.8 mg/dL or ≥9.8 mg/dL, and presence or absence of tophi, as assessed by palpation, at screening (Visit 1). Note that for all subsequent evaluations of sUA, the baseline value will be the Day 1 (Visit 4) pre-dose value. Subjects will be treated with their first dose of investigational product by oral self-administration with water. Investigational product will be taken from the bottle handed out at the visit. Blood sampling for PK/PD analysis will be performed at the time points stated in the PK/PD sampling schedule (Section 9.1.14, Table 9-3). All attempts should be made to collect the blood samples at, or within 30 minutes prior to administration of investigational products for pre-dose samples and ±10 minutes for post-dose samples of, the scheduled time. The actual time of each sampling will be

recorded on the eCRFs, as well as time that subjects take the medication (t=0). Additional assessments will be made per the SOA (Table 2-1).

Subjects will be instructed to fast for at least 8 hours (preferably, overnight fast) prior to returning to the clinic on Day 14 (Visit 5), 28 (Visit 6), 56 (Visit 7), and 84 (Visit 8). On Day 14, 28, 56, and 84, subjects will withhold the investigational product until pre-dose laboratory samples have been obtained. Subjects will then take investigational product on site on Day 14 (Visit 5), 28 (Visit 6), and 56 (Visit 7), and blood samples will be obtained at the time points stated in the PK/PD sampling schedule (Section 9.1.14, Table 9-3). The last dose of investigational product that a subject will take is on Day 83. AEs will be recorded and measurements of laboratory parameters, vital signs, and 12-lead electrocardiogram (ECG) will be performed for safety evaluation according to the SOA (Table 2-1). Subjects will record the incidence of gout flares and rescue treatment using eDiary. Subjects will be assessed for the presence of tophi by palpation at the end of treatment visit (Visit 8). All tophi will be counted and recorded on the Tophi eCRF page.

Visit 9: Follow-up

A Follow-up on site-visit will be performed on Day 98 for safety assessments (Table 2-1).

### 6.3 Rationale for Study Design and Endpoints

In order to maximize the scientific value of the study and minimize the risk for systemic biases, a parallel group, double-blind, randomized design will be utilized.

The study will recruit subjects with hyperuricemia and a diagnosis of gout per American College of Rheumatology (ACR) criteria (Neogi et al 2015) (Appendix A). To participate in the study, subjects will be required to meet the inclusion criterion of sUA ≥8.0 mg/dL to ≤12.0 mg/dL during the 9 to 4 days prior to the treatment period. To reduce potential safety issues, subjects will be required to have adequate renal function based on an estimated glomerular filtration rate (eGFR) ≥60 mL/min/1.73m$^2$ at screening (Visit 1) and no evidence of medically significant comorbidities.

Patients with gout may experience an acute gout flare event with initiation or an increase in their dose of ULT (Becker et al 2005a; Becker et al 2010; Borstad et al 2004). Consequently, all enrolled subjects will receive gout flare prophylaxis with colchicine from Visit 2 (between Days -30 to -23) through to the end of treatment in accordance with recommendations from the European League Against Rheumatism (EULAR), ACR, and British Society of Rheumatology treatment guidelines (White et al 2018; Zhang et al 2006; Jordan et al 2007; Khanna et al 2012a; Khanna et al 2012b).

The primary endpoint in the study will be the proportion of subjects achieving a sUA level <5.0 mg/dL at Day 84 for LC350189, while a key secondary endpoint is the proportion of subjects achieving a sUA level of <6.0 mg/dL at Day 84 for LC350189. These endpoints were chosen to align with the ACR goals for ULT, which include achieving a sUA <6 mg/dL in all gout patients and a sUA <5 mg/dL in patients with palpable tophi detected by physical examination (Khanna et al 2012a). These are also standard endpoints frequently used in Phase II intervention trials in hyperuricemia and gout (Gunawardhana et al 2018).

As another secondary endpoint, gout flare rate will be captured by eDiary on a background of prophylaxis; gout flares will be defined according to a previous Phase II study (Neogi et al 2015; Poiley et al 2016). Safety endpoints used in this study, including AEs, clinical laboratory values, vital signs, and ECG, conform to accepted clinical and laboratory assessments of subjects participating in clinical trials and are typical of a Phase II study. Additional exploratory assessments (HbA1c, fasting plasma glues [FPG], high-sensitivity C-reactive protein [hs-CRP], serum concentrations of hypoxanthine and xanthine) will be included to inform subsequent studies in the LC350189 clinical development program.

## 6.4 Study Discontinuation and Stopping Criteria

### 6.4.1 Criteria for Premature Termination or Suspension of Study

The study will be completed as planned unless one or more of the following criteria are satisfied that require temporary suspension or early termination of the study.

- New information or other evaluation regarding the safety or efficacy of the investigational product that indicates a change in the known risk/benefit profile for the compound, such that the risk/benefit is no longer acceptable for subjects participating in the study.
- Significant violation of Good Clinical Practice (GCP) that compromises the ability to achieve the primary study objectives, or compromises subject safety or data integrity.

### 6.4.2 Criteria for Premature Termination or Suspension of Investigational Sites

Premature termination or suspension of investigational sites will occur if any of the following criteria are satisfied:

- Failure to meet expected enrollment goals.
- Administrative reasons.

In the event that the Sponsor, an institutional review board (IRB)/ independent ethics committee (IEC), or regulatory authority elects to terminate or suspend the study or the participation of an investigational site, a study-specific procedure for early termination or suspension will be provided by the Sponsor. The procedure will be followed by applicable investigational sites during the course of termination or study suspension.

### 6.4.3 Criteria for Early Termination of Individual Subjects

Subjects (or their guardians, or legally acceptable representatives) may withdraw their consent to participate in the clinical study. If a subject (or their guardians, or legally acceptable representatives) withdraws consent, the date and reason for consent withdrawal should be documented. Subjects will be encouraged to continue all study assessments. Subject data will be included in the analysis up to the date of the consent withdrawal, unless otherwise indicated by the Sponsor. If the subject refuses to continue all study procedures, they should undergo a 2-week safety follow-up period per study design.

Early termination will also occur if any of the following conditions apply:

- AE or SAE that requires discontinuation at the discretion of the Investigator.
- Subject becomes pregnant or begins breastfeeding (mandatory).
  - Administration of investigational product should be discontinued immediately after pregnancy is confirmed, and the Sponsor should be notified within 24 hours. Information on the subject, the pregnancy and its outcomes, and information on the infant's status at 12 weeks after delivery, if applicable, should be obtained.
- Unexplainable elevations in liver enzymes. Subjects should be monitored until all abnormal values return to normal or baseline values, and the outcomes should be recorded in the eCRF.
  - Subjects should discontinue the investigational product immediately if alanine aminotransferase (ALT) or aspartate aminotransferase (AST) elevations are ≥8 times the upper limit of normal (ULN) at any time during the clinical study.
  - If ALT or AST elevations are ≥5 times ULN at any time during the clinical study, laboratory tests should be repeated within 3 days. If elevations ≥5 times ULN are confirmed, subjects should discontinue the investigational product.
  - Subjects should discontinue the investigational product if ALT or AST are elevated ≥3 times ULN in combination with laboratory finding of either total bilirubin is ≥2 times ULN or international normalised ratio of prothrombin time (INR) is ≥1.5 times ULN at any time during the clinical study.
  - Subjects should discontinue the investigational product immediately if ALT or AST are elevated ≥3 times ULN and clinical symptoms (fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia [>5%]) are present at any time during the clinical study.
- Subjects with serum creatinine elevations at any visit >1.5 times baseline level will be closely monitored. If serum creatinine elevations are >2.0 times compared to baseline, and if this observation cannot be explained by concomitant disease or another alternative etiology, subjects should discontinue the investigational product.
- Treatment will be interrupted in subjects presenting with signs or symptoms that may indicate acute UA nephropathy including flank pain, urine color change, nausea, or vomiting; in these cases, serum creatinine will be promptly measured. Subjects should discontinue the investigational product.
- Lost to follow up. The subject did not return to the clinic and attempts to contact the subject were unsuccessful. Attempts to contact the subject must be documented.
  - Subjects are not required to provide reasons for not attending study visits; however, Investigators should make an effort to identify the pertinent reasons while respecting the subject's rights. Available information should be recorded in the eCRF.
- Protocol violation: If protocol violation occurs, which, in the clinical judgment of the Investigator or after discussion with the Sponsor, may invalidate the study by interfering

pharmacokinetically or pharmacodynamically with the investigational product(s), or affect the safety of the subject, the subject will be withdrawn by the Investigator.

- Subject conduct or any other events, which, in the clinical judgment of the Investigator or after discussion with the Sponsor, may invalidate the study.
- Study discontinuation by the Sponsor.

Wherever possible, the tests and evaluations, including those listed for the follow-up Visit (Visit 9), should be performed for all subjects who discontinue prior to completion of the study.

In the event the Investigator determines to terminate a subject's participation in the clinical study, the Investigator must notify the Sponsor of such decision and rationale immediately in writing.

# 7.0 STUDY POPULATION

## 7.1 Inclusion Criteria

1. Subjects or the subject's legally acceptable representatives who sign a written ICF prior to the initiation of any study procedures.
2. Male or female subjects between the ages of 18-75 years, inclusive.
3. Subjects with hyperuricemia and a history or presence of gout per ACR criteria (Appendix A) (Neogi et al 2015).
4. Subjects with a self-reported history of ≥2 gout flares in the prior 12 months to screening (Visit 1).
5. Subjects who are currently on urate lowering therapy (ULT; Allopurinol, Febuxostat, Probenecid, Lesinurad) with a sUA level ≥6.0 mg/dL at Visit 1; Or subjects who are ULT naïve or currently not on ULT with a sUA level ≥8.0 mg/dL to ≤12.0 mg/dL at Visit 1.
6. Subjects with a sUA level ≥8.0 mg/dL to ≤12.0 mg/dL at Day -9 to -4 (Visit 3).
7. Subjects with a body mass index (BMI) ≤42 kg/$m^2$ at screening (Visit 1).
8. Subjects with eGFR ≥60 mL/min/1.73$m^2$ at screening (Visit 1).
9. For childbearing subjects, a negative pregnancy test result at screening (Visit 1). Subjects (female subjects of childbearing potential and male subjects with partners of childbearing potential) must agree to use proper contraceptive methods to avoid pregnancy during the study.
10. Subjects who are capable of understanding the study procedures, the risks involved, and are willing to adhere to the visit/protocol schedule.

## 7.2 Exclusion Criteria

1. Subjects with secondary hyperuricemia (*e.g.*, due to myeloproliferative disorder, or organ transplant).
2. Subjects experiencing an active acute gout attack within 3 weeks prior to screening (Visit 1).
3. Subjects with AST or ALT >2 times ULN at screening (Visit 1).
4. Subjects with creatine kinase >2.5 times ULN at screening (Visit 1).
5. Subjects with previous intolerance to colchicine.
6. Subjects who received pegloticase within 3 months prior to screening (Visit 1).
7. Subjects who have not been receiving stable doses of drugs known to affect sUA levels (losartan, fibrates, thiazide diuretics, loop diuretics, acetylsalicylic acid [ASA]) for the last six weeks prior to screening (Visit 1). ASA use more than 325 mg/day is not allowed.

8. Subjects who have received systemic corticosteroids more than 10 continuous days within 1 month prior to screening (Visit 1).
9. Subjects who require or may require systemic immunosuppressive or immunomodulatory treatment (eg, azathioprine, 6-mercaptopurine, cyclosporine).
10. Subjects receiving medications that are strong or moderate CYP3A4 inhibitors or P-glycoprotein (P-gp) inhibitors within 14 days prior to screening (Visit 1).
11. Subjects with a history of xanthinuria.
12. Subjects with a history of rheumatoid arthritis.
13. Subjects with active peptic ulcer disease requiring treatment.
14. Subjects with unstable angina, New York Heart Association (NYHA) class III or IV heart failure, myocardial infarction, stroke, deep venous thrombosis (DVT), percutaneous coronary intervention (with or without stent), or coronary artery bypass graft (CABG) in the last 12 months prior to screening (Visit 1); Subjects currently receiving anticoagulants; Or subjects with clinically significant ECG abnormality in the opinion of the Investigator at screening (Visit 1).
15. Subjects with uncontrolled hypertension (systolic pressure above 160 mmHg or diastolic pressure above 95 mmHg) at screening (Visit 1).
16. Subjects with a history of myositis/myopathy, rhabdomyolysis, Stevens-Johnson syndrome, or toxic epidermal necrolysis.
17. Subjects with a history of malignancy within the previous 5 years with the exception of non-melanoma skin cancer that has been treated with no evidence of recurrence, treated cervical dysplasia, or treated in situ Grade 1 cervical cancer.
18. Subjects with known hypersensitivity or allergy to any ingredients of LC350189.
19. Subjects that consume more than 14 drinks of alcohol per week (*e.g.*, 1 drink = 5 oz [150 ml] of wine, 12 oz [360 ml] of beer, or 1.5 oz [45 ml] of hard liquor).
20. Subjects with a history or suspicion of drug abuse (defined as any illicit drug use) within the past 5 years.
21. Subjects who are pregnant or lactating.
22. Subjects who test positive for human immunodeficiency virus (HIV) or active hepatitis B or hepatitis C virus (HCV) infection. Active HCV infection is defined as a subject with a positive hepatitis C antibody and detectable hepatitis C viral load RNA.
23. Subjects who have previously participated in interventional clinical studies within 3 months or 5 half-lives of investigational therapy (whichever is longer) prior to the screening visit (Visit 1).
24. Subjects with any other medical or psychological condition, which in the opinion of the Investigator and/or Medical Monitor, might create undue risk to the subject or interfere

with the subject's ability to comply with the protocol requirements, or to complete the study.

## 7.3 Prohibited or Precaution Medications / Food

Use of the agents listed in Table 7-1 (prescription or nonprescription) is prohibited or with precaution from the time points specified until completion of all study activities.

**Table 7-1 Prohibited or Precaution Medications / Food**

| Medication or Class / Food | Noted or anticipated outcome | From time point specified |
|---|---|---|
| **Prohibited Medications/Food** | | |
| Allopurinol, Febuxostat* | Urate-lowering drug; Potential interference with study related outcome measures – sUA levels. | Wash-out/prophylaxis period (Visit 2) |
| Lesinurad | | |
| Uricosuric agent (Probenecid, Sulfinpyrazone) | | |
| Atazanavir, Clarithromycin, Indinavir, Itraconazole, Ketoconazole, Nefazodone, Nelfinavir, Ritonavir, Saquinavir, Telithromycin, Darunavir/Ritonavir, Lopinavir/Ritonavir, Tipranavir/Ritonavir | Strong CYP3A4 inhibitors; Potential PK interaction with prophylactic medication. | Screening (Visit 1) |
| Amprenavir, Aprepitant, Diltiazem, Erythromycin, Fluconazole, Fosamprenavir, Grapefruit, grapefruit related citrus fruits and their juices, Verapamil | Moderate CYP3A4 Inhibitors; Potential PK interaction with prophylactic medication. | Screening (Visit 1) |
| Cyclosporine, Ranolazine | P-gp inhibitors; Potential PK interaction with prophylactic medication. | Screening (Visit 1) |
| Theophylline, Azathioprine, 6-Mercaptopurine | XO substrate; Potential PK interaction with investigational products. | Screening (Visit 1) |
| Systemic corticosteroid (Prednisone >10 mg/day or its equivalent; Or prednisone ≤10 mg/day or its equivalent for more than 7 days) | - | Screening (Visit 1) |
| **Precautions** | | |
| HMG-Co A Reductase Inhibitors: Atorvastatin, Fluvastatin, Lovastatin, Pravastatin, Simvastatin | Potential PK interaction with prophylactic medication, Increase risk for muscle-related toxicity when administer with prophylactic medication. | Screening (Visit 1) |
| Other Lipid Lowering Drugs: Fibrates, Gemfibrozil | | |
| Digitalis glycosides: Digoxin | Potential PK interaction with prophylactic medication; Increase risk for muscle-related toxicity when administer with prophylactic medication. | Screening (Visit 1) |

* Not applicable to the subjects randomized to the active control group before the implementation of the Protocol version 5.0.

Subjects will continue taking any other medications prescribed for chronic conditions at stable dose from screening (Visit 1) to Day 84 (Visit 8), with the exception of those listed above. Females will be permitted to use hormone replacement therapy.

Subjects will refrain from receipt of any other investigational drug within 5 half-lives or 90 days, whichever is longer, prior to study entry and during the entire study. Females of childbearing potential will refrain from using hormonal contraception.

During participation in the study, subjects will be instructed not to take any prescription medications without first consulting the Investigator.

Any medication taken by a subject during the course of the study and the reason for its use will be documented in the source documents and the eCRF.

# 8.0 STUDY MATERIALS

## 8.1 Investigational Products

### 8.1.1 LC350189

LC350189 50, 100, or 200 mg will be supplied by LG Chem, Ltd. as hard gelatin capsules with StarCap 1500 and magnesium stearate.

### 8.1.2 Placebo

Placebo will be supplied as capsules identical in appearance to the LC350189 capsule.

## 8.2 Packaging, and Labeling of Investigational Products

The Sponsor or a Sponsor-designated third party will provide the Investigator with the labeled investigational products in accordance with specific country regulatory requirements.

## 8.3 Storage and Drug Accountability of Investigational Products

All clinical material must be kept in an appropriate, limited-access, secure location.

The investigational products and their storage and preparation instructions will be provided by the Sponsor. All investigational products will be stored at room temperature. Investigational products should not be exposed to excessive heat or direct sunlight.

The study staff is required to document the receipt, dispensing, and return/destruction of investigational products and supplies provided by or on behalf of the Sponsor.

The Investigator or Investigator's authorized staff must ensure the availability of proper storage conditions. The temperature of all investigational products will be monitored 24 hours a day, 7 days a week (24/7). In case of incorrect storage, the Sponsor and monitor must be contacted without delay.

No investigational products may be dispensed to any person not enrolled in the study.

## 8.4 Dose Regimen

Subjects will receive LC350189 50 mg, LC350189 100 mg, LC350189 200 mg, or placebo. LC350189 or placebo capsules will be packaged in 60 mL bottles, each containing 35 capsules. On Day 1 (Visit 4), the appropriate investigational product per the randomization code will be dispensed. Additional bottles will be dispensed on Day 28 (Visit 6) and Day 56 (Visit 7). At visits where investigational product is being returned and new investigational product is being dispensed, all bottles should be returned for investigational product accountability. In order to facilitate investigational product accountability, the subjects ID as well as the visit number must be filled in on the label before dispensing.

Subjects will self-administer investigational product (two capsules of LC350189/placebo) and one tablet of gout flare prophylaxis orally once daily in the morning, if possible, at approximately the same time each day, with water and without regard to food.

Subjects will self-administer investigational product from the following bottles:

- Subjects randomized to LC350189 50 mg will self-administer one capsule from each of 2 bottles of LC350189 25 mg.
- Subjects randomized to LC350189 100 mg will self-administer one capsule from each of 1 bottle of LC350189 100 mg and 1 bottle of LC350189 placebo.
- Subjects randomized to LC350189 200 mg will self-administer one capsule from each of2 bottles of LC350189 100mg.
- Subjects randomized to placebo will self-administer one capsule from each of 2 bottles of LC350189 placebo.

Subjects will be instructed to stay adequately hydrated. On Day 1 (Visit 4), investigational product will be taken at site from the bottle handed out at the visit. On Day 14 (Visit 5), investigator product will be taken at site from the bottle dispensed on Day 1 (Visit 4). On Day 28 (Visit 6) and 56 (Visit 7), investigational product will be taken from the bottle newly dispensed and handed out at the visit.

### 8.4.1 Compliance

The administration of investigational products will be recorded in the appropriate sections of the eCRF. During the study, subjects will receive a total of 2 bottles for LC350189/ placebo. Subjects who are randomized to the study groups before the implementation of the Protocol version 5.0 will continue receiving a total of 3 bottles for LC350189/febuxostat/placebo. Subjects will be required to bring investigational product containers to each clinic visit, regardless of whether the investigational product container is empty. If a patient is persistently noncompliant with an investigational product, (taking <80% or >120% of the allocated investigational product for the period since the last visit) it may be appropriate to withdraw the subject from the study. All subjects should be reinstructed about the dosing requirement during study visits. Compliance will be measured using the following formula:

(B) ÷ (C) = (D)
(D) X100 = % Compliance

Where (B) = the total number of capsules minus the number of capsules in the bottle and (C) = the number of days during treatment period.

## 8.5 Gout Flare Prophylaxis

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

## 8.6 Overdose

If a study medication error of greater than 3 pills occurs, it must be documented as a Protocol Deviation. A brief description should be provided in the deviation, including whether the subject was symptomatic (list symptoms) or asymptomatic, and if the event was accidental or intentional.

Dosing details should be captured on the eCRF. If the subject takes a dose of investigational product that exceeds protocol specifications and the subject is symptomatic, then the symptom(s) should be documented as an AE and be reported.

Should an overdose occur, the Investigator or designee should contact the Sponsor or designee within 24 hours.

## 8.7 Randomization and Blinding

Subjects who meet all of the inclusion criteria and none of the exclusion will be assigned a subject randomization number via an Interactive Web Response System (IWRS) on Day 1 after the wash-out/prophylaxis period that will follow screening (Visit 1), and the study drug blind will be maintained using the IWRS. Blind of the subjects randomized to study groups before the implementation of the Protocol version 5.0 will be maintained by giving treatment regimen (3 bottles of LC350189/febuxostat/placebo) as they are initially assigned to.

Randomization will continue until a total of 152 subjects have been randomized, this total number of randomized subjects will exclude the number of subjects who are assigned to the active control group (febuxostat) before implementation of the active control group elimination. The randomization will be stratified by post-washout/pre-dose sUA (<9.8 mg/dL or ≥9.8 mg/dL) at Visit 3 and the presence or absence of tophi at screening (Visit 1).

If a subject has experienced a gout flare during the screening and 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 entered into the screening disposition page.

## 8.8 Breaking of Blinded Code

The code for a subject may be broken in a medical emergency, if knowing the identity of the treatment allocation would influence the treatment decision of the subject or if demanded by the subject. Whenever a code is broken, the person breaking the code must record the time, date, and reason as well as his/her initials in the source documents. During un-blinding procedure in case of medical emergency, it should be ensured that no study personnel is unblinded to other subjects. Study site personnel and Sponsor personnel directly associated with the conduct of the study will not be unblinded.

If the study site needs to unblind a subject, the Sponsor and Study Medical Monitor must be notified within 24 hours after emergency unblinding.

All codes (whether broken or not) must be kept throughout the study period. Accountability of all broken or unbroken codes (hard copy or electronic) will be performed at or after study closure and codes will be maintained in the Investigator's Site File (ISF) at the site or with the retention product.

## 8.9 Auxiliary Supply

The Sponsor or delegate will supply laboratory materials necessary for PK/PD sampling, all the safety testing (hematology, biochemistry, and urinalyses [incl. pregnancy test]) in collaboration with the laboratory.

# 9.0 STUDY PLAN

## 9.1 Study Procedures

### 9.1.1 Informed Consent and HIPAA Release

Written informed consent will be obtained from each subject prior to performing any study-specific evaluations. The Health Insurance Portability and Accountability Act (HIPAA) release is included in the informed consent process. The informed consent document is subject to review and approval by the Sponsor and will be approved by a legally authorized representative and a qualified IRB. The IRB-approved document must contain, at minimum, the eight basic elements of informed consent set forth in applicable law. Only the most recently IRB-approved informed consent document must be used to consent prospective study subjects. The Investigator (according to applicable regulatory requirements), or a person designated by the Investigator and under the Investigator's responsibility, will fully inform the potential study subject of all pertinent aspects of the clinical study, including written information given approval/favorable opinion by the IRB/IEC.

Prior to the potential subject's participation in the clinical study, the written ICF must be signed, name filled in, and personally dated by the subject and by the person who conducted the informed consent discussion, and by the Investigator. One copy of the signed and dated informed consent document will be given to the subject and the original retained by the Investigator/site.

### 9.1.2 Screening

Investigators must account for all subjects who sign ICFs. The Investigator will keep a Subject Screening and Enrollment Log at the investigational site.

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, a single repeat of test is permitted during the screening period, and all efforts should be made to maintain protocol-defined visit windows.

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

Rescreening of subject who fails screening is allowed one time if the investigator believes there is an appropriate rationale to rescreen the subject and rescreening does not present a safety issue for the subject.

Subjects who meet all of the inclusion criteria and none of the exclusion criteria are eligible for this study and will be invited to participate in the study. Subjects will be instructed on factors influencing study outcomes, such as avoidance of alcohol, prescription or non-prescription medication, and illness/infection. Please refer to Section 7.3.

If subjects are fasting (only water for ≥8 hours), all screening assessments may be done on the same day. If subjects are not fasting, they will be invited to return for a second screening visit to complete any missing screening procedures (eg. laboratory assessments).

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.

### 9.1.3 Demographics and Medical History

Demographic information and medical history, including smoking status and medication history will be obtained at screening.

### 9.1.4 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.

### 9.1.5 Height, Weight, and BMI

Height (without shoes) will be measured once, during screening (Table 2-1). Weight (without shoes) will be measured with light clothing. BMI ($kg/m^2$) will be calculated from height and weight.

### 9.1.6 Vital Signs

Vital signs will include body temperature (aural), blood pressure (after 5 minutes resting), respiration rate and pulse rate (after 5 minutes resting). Vital sign measurements will be performed at days and times indicated in the SOA (Table 2-1). A single repeat measurement is permitted at screening (Visit 1) for eligibility determination if the investigator believes there is an appropriate rationale to perform a repeat such as due to an intercurrent condition which has quickly resolved.

### 9.1.7 Concomitant Illness and Prior and Concomitant Therapy

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.

A prior therapy is any medication that started before the first randomized study dose date.

Concomitant therapy is any medication given in addition to the investigational product(s) (including over-the-counter medications, herbal medications, and vitamin supplements) administered between screening and follow-up. Details of all concomitant illnesses and prior and concomitant therapies must be recorded at study entry and must be recorded on the subject's eCRF. Any changes in concomitant therapy must be recorded at each visit. If the change influences the subject's eligibility to continue in the study, the Sponsor must be informed. The information collected for each prior/concomitant medication includes, at a minimum, start date, stop date or continuing, and indication.

AEs related to administration of these therapies or procedures must also be documented in the appropriate eCRF.

### 9.1.8 Procedures for Clinical Laboratory Samples

All samples will be collected in accordance with acceptable laboratory procedures. Laboratory samples will be taken as described in the SOA (Table 2-1) and sent to a central lab per the laboratory manual. The laboratory variables listed in Table 9-1 will be measured.

The results of laboratory tests will be sent to the Investigator or designee, who is responsible for reviewing these results. All laboratory safety data will be faxed or transferred electronically.

Laboratory reports must be signed and dated by the Investigator or designee indicating that the report has been reviewed and any abnormalities have been assessed for clinical significance.

Clinically significant laboratory abnormalities will be recorded as an AE.

**Table 9-1 Clinical Laboratory Samples**

| **Serum chemistry** | **Hematology** |
|---|---|
| ALT | Red blood cell count |
| Albumin | White blood cell count with auto differential |
| Alkaline phosphatase | Hemoglobin |
| AST | Hematocrit |
| Total bilirubin | Platelet count |
| Total protein | Mean corpuscular volume |
| Creatinine (e) | Mean corpuscular hemoglobin |
| Blood urea nitrogen | Mean corpuscular hemoglobin concentration |
| Creatine kinase | **Urinalysis** |
| Gamma-glutamyl transferase | Qualitative |
| Potassium | Appearance |
| Sodium | Color |
| Carbon dioxide | pH |
| Calcium | Specific gravity |
| Magnesium | Ketones |
| Chloride | Protein |
| Glucose | Glucose |
| Lactate dehydrogenase | Nitrate |
| Phosphorus | Urobilinogen |
| Serum uric acid* | Blood |
| **Serology (at screening only)** | |
| HBsAg | |

Anti-HCV

Hepatitis C, Viral Load RNA (if applicable)

Anti-HIV-1

Anti-HIV-2

*Uricase method

### 9.1.9 Renal Function

Renal function will be determined based on eGFR calculated by the Modification of Diet in Renal Disease (MDRD) equation. Subjects with eGFR ≥60 mL/min/1.73m$^2$ (normal renal function or mild renal impairment) at screening (Visit 1) are allowed to participate in the study. Subjects' baseline renal function will be based on eGFR on Day -9 to -4 (Visit 3).

**Table 9-2 Classification of Renal Function Based on eGFR (MDRD equation)**

| Stage | Description | eGFR (mL/min/1.73 m$^2$) |
|---|---|---|
| 1 | Normal | ≥ 90 |
| 2 | Mild | 60-89 |
| 3 | Moderate | 30-59 |
| 4 | Severe | 15-29 |
| 5 | End Stage Renal Disease | <15 not on dialysis, or Requiring dialysis |

MDRD equation:

eGFR (mL/min/1.73 m$^2$) = 175 x ($S_{cr, std}$ [mg/dL]) $^{-1.154}$ x (Age [years])$^{-0.203}$ x (0.742 if female) x (1.212 if African American)

$S_{cr, std}$: serum creatinine measured with a standardized assay

### 9.1.10 Contraception

Males must be surgically sterile (at least 1 year post vasectomy), abstinent, or if engaged in sexual relations of child-bearing potential, the subject and his partner must be using an acceptable contraceptive method from screening through the follow up visit. Acceptable methods of contraception are the use of condoms together with spermicidal foam/gel/film/cream/suppository. In addition, they must be advised not to donate sperm during this period. Male subjects must also encourage their female partner to use effective contraception. Effective contraception for the female partner includes surgical sterilization (eg, bilateral tubal ligation, bilateral salpingectomy, bilateral oophorectomy), hormonal contraception, intrauterine contraception/device, or barrier methods (female condom, diaphragm, sponge, cervical cap) together with spermicidal foam/gel/film/cream/suppository. The adequacy of other methods of contraception will be assessed on a case-by-case basis by the Investigator.

Females must be non-pregnant and non-lactating; serum pregnancy testing will be conducted at screening (Visit 1) and urine pregnancy testing during the treatment period (Visit 4, 5, 6, 7 and 8) if subjects are women of childbearing potential.

Female subjects of childbearing potential must use nonhormonal contraception beginning from screening, throughout the study (including the washout period), and until 2 weeks after the last dose of investigational product. Effective contraception includes surgical sterilization (eg, bilateral tubal ligation, bilateral salpingectomy, bilateral oophorectomy), intrauterine contraception/device, or barrier methods (female condom, diaphragm, sponge, cervical cap) together with spermicidal foam/gel/film/cream/suppository. The adequacy of other methods of contraception will be assessed on a case-by-case basis by the Investigator.

### 9.1.11 Pregnancy

Women known to be of childbearing potential are allowed to participate in the study. In the event a subject becomes pregnant during the study, she should be withdrawn and the investigational product should be immediately discontinued. However, the subject will be encouraged to complete the post-treatment follow-up portion of the study to the extent that study procedures do not interfere with the pregnancy.

In addition, any pregnancies in the partner of a male subject during the treatment period or the follow-up period should be recorded.

If the pregnancy occurs at any time during the treatment period or the follow-up period, the pregnancy should be reported immediately to the Sponsor, using a pregnancy notification form.

Study subjects will give consent that the Investigator will report any pregnancy during the study to the Sponsor and that they will be asked to provide information about the pregnancy and delivery. Payment for all aspects of obstetrical care, child, or related care will be the subject's responsibility.

All reported pregnancies will be followed up to final outcome, using the pregnancy and pregnancy follow-up forms. The outcome, including any premature termination, will be reported to the Sponsor.

Pregnancy complications must be recorded as AE(s). If the infant has a congenital anomaly/birth defect this must be reported and followed up as a SAE.

### 9.1.12 ECG Procedure

A standard 12-lead ECG will be recorded after 5 minutes in a supine position. The Investigator (or designee) will interpret the ECGs using the following categories: within normal limits, abnormal but not clinically significant, or abnormal with clinical significance. ECGs will be performed according to the SOA (Table 2-1). The following parameters will be recorded from the subject's ECG trace as calculated by the machine algorithm: heart rate, QT interval, PR interval, QRS interval, RR interval, and QTc (corrected) using the Fridericia correction (QTcF = QT ÷ cube root of the R-R interval [where R-R is the duration of the entire cardiac cycle]).

When ECGs are to be collected at the same time point as a blood collection, ECGs should be collected first to avoid any artificially increased heart rates due to the blood collection.

The baseline ECG measurement collected pre-dose on Day 1 (Visit 4) will serve as each subject's baseline for all post-dose comparisons.

In some cases, it may be appropriate to repeat abnormal ECGs. If a machine-read QTc value is prolonged, repeat measurements may not be necessary if the Investigator's interpretation determines that the QTc value is in the acceptable range.

### 9.1.13 Diet

There are no specific dietary restrictions in the study.

### 9.1.14 Blood Sampling and Schedule

All blood samples will be collected in accordance with acceptable laboratory procedures. Details of these procedures and required safety monitoring will be given in the laboratory manual.

If the subject consents to the dense PK/PD sampling, the subject will have the sparse PK/PD samples drawn in addition to an extra draw at the following timepoints - 2, 8 and 12 hours post -dose at Visit 4 and 8 hours post-dose at Visit 7. Blood for the PK/PD analysis will be collected at the time points indicated in the SOA (Table 2-1) and follow the PK/PD sampling schedule (Table 9-3).

**Table 9-3 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) |

### 9.1.15 Urine sampling

Urine will be collected at the time points indicated in the SOA (Table 2-1) into provided containers. Samples will be collected, labeled, stored, and shipped as detailed in the Laboratory Manual.

### 9.1.16 Accountability

Study drug accountability check will occur at the time points indicated in the SOA (Table 2-1). Subjects will be required to bring study drug containers to each site visit, regardless of whether the study drug container is empty. The study site staff will account for all study drugs dispensed to and returned from the subject.

### 9.1.17 Gout Flares

For this study, a gout flare occurring after study participation 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 is ≥4 on an 11-point numerical rating scale, and the pain is determined by the subject 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 (Neogi et al 2015; Poiley et al 2016).

Gout flares will be assessed using eDiary. Subjects will respond to simple questions appearing in the eDiary (e.g., "was the pain similar to prior attacks?"). Subjects will have opportunity to assess their understanding of each question during a training session during Visit 2.

### 9.1.18 Gout flare rescue treatment

Subjects who experience a gout flare and who are taking colchicine for prophylaxis and have taken their daily dose, may take an additional colchicine 0.6 mg tablet at the onset of the flare, with another tablet one hour later, for a maximum of 3 tablets (1.8 mg) in a 24 hour period. After 12 hours, the original prophylaxis dose may be resumed (Colcrys [colchicine] tablet Package Insert). Gout flares may also be treated at the discretion of the Investigator, as long as this treatment is in compliance with the prohibited medications for this study. This may be done at the discretion of the Investigator and in accordance with their practice guidelines. Any gout flare rescue treatment will be recorded in the eDiary.

Subjects should be instructed to contact the Investigator as soon as they begin to have a gout flare. An unscheduled visit can be conducted if deemed appropriate by the Investigator. All subjects that experience flares while on the study will have the option to receive acute gout flare treatment if deemed appropriate by the Investigator. The Investigator may also consult with the Sponsor Medical Monitor for further discussion.

### 9.1.19 Physical treatment of tophi

Tophi will be examined by palpitation at the time points indicated in the SOA (Table 2-1).

### 9.1.20 Study contingency measures during the COVID-19 pandemic

Following contingency measures can be implemented to ensure safety of study participants and to manage study conduct during disruption of the study as a result of COVID-19 control measures. Site staffs should consult with the Sponsor or a Sponsor designated third party to implement

contingency measure and document the reason including but not limited to missing data or out of window visits.

Following approach can be implemented; however, further modification of existing processes may be in place depending on local situation.

Investigator should take all precautions to protect the rights, safety, and well-being of subjects.

Screening visit & Wash-out/prophylaxis period

- If subjects screen fail because subjects are unable or not willing to make visit to the site due to COVID-19, reason for screening fail should be documented as COVID-19. Rescreening will be allowed for subjects who are not able to complete screening process or randomization due to the COVID-19 pandemic related reason.
- For subjects who have passed screening at Visit 1 but are not able to make on-site visit for Visit 2, one bottle of colchicine and an eDiary device can be provided to subject alternatively by secured delivery method.

Treatment period

- Out of window visit is allowed as long as the subjects continue to take investigational products.
- If scheduled visits are significantly impacted, investigational products and colchicine for Visit 6 and 7 can be delivered direct to subjects in secure method.
- Missing visits may be allowed in case of a complete shutdown of a study site or subjects/sites' concerns with COVID-19. If a subject is unable to have labs drawn per protocol schedule, site should consult the medical monitor and/or Sponsor to review the subject's participation in the study to ensure safety of subjects for continuing in the study.
- In case of a complete shutdown of a study site per a government order or a subject being concerned with visiting the site, a home health nurse may visit a subject to assist laboratory tests and to check subject's health status.
- Site using a local laboratory would be allowed in case of shutdown of a central laboratory or vendor for sample shipment. Local laboratory is for safety assessment only.
- If a patient is diagnosed with COVID-19, an AE or SAE should be recorded and site should contact the medical monitor and sponsor to discuss.

Safety follow-up

- Subjects who cannot make on-site visit for safety follow-up (Visit 9) due to the COVID-19 pandemic related reason, visit 9 could be conducted by phone contact or virtual visit.

# 10.0 ADVERSE EVENTS

## 10.1 Definitions

### 10.1.1 Adverse Event

An 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. The following should not be recorded as AEs, if recorded as medical history/concomitant illness on the eCRF at screening:

- Pre-planned procedure, unless the condition for which the procedure was planned has worsened from the first study related activity after the subject has signed the informed consent.
- Pre-existing conditions found as a result of screening procedures.
- Pre-existing events that have not worsened in intensity or frequency from baseline.

### 10.1.2 Treatment Emergent Adverse Event

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.

### 10.1.3 Clinical Laboratory Event

A clinical laboratory AE is any clinically significant laboratory abnormality that causes symptoms or suggests a disease and/or organ toxicity and is of a severity that requires active management (*i.e.* change of dose, discontinuation of investigational product, more frequent follow-up, or other intervention). A laboratory re-test and/or continued monitoring of an abnormal value is not considered an intervention. In addition, repeated or additional noninvasive testing for verification, evaluation, or monitoring of an abnormality is not considered an intervention.

### 10.1.4 Adverse Reaction

An adverse reaction is defined as any AE caused by a drug. Adverse reactions are a subset of all suspected adverse reactions where there is reason to conclude that the drug caused the event.

### 10.1.5 Suspected Adverse Reaction

Suspected adverse reaction is defined as a subset of any AE for which there is a reasonable possibility that the drug caused the AE. For the purposes of investigational new drug (IND) safety reporting, ‘reasonable possibility’ means there is evidence to suggest a causal relationship between the drug and the AE. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by a drug.

Reasonable possibility is given:

- A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure.
- One or more occurrences of an event that is not commonly associated with drug exposure, but otherwise uncommon in the population exposed to the drug.
- An aggregate analysis of specific events observed in a clinical study that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group.

### 10.1.6 Unexpected Adverse Event

An unexpected AE is an AE that is not listed in the Investigator Brochure or Protocol, or is not listed at the specificity or severity that has been observed.

### 10.1.7 Serious Adverse Event

An SAE is defined as any untoward medical occurrence that at any dose:

1. Results in death.
2. Is life threatening.
   - The term "life threatening" refers to an event in which the subject is at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.
3. Requires inpatient hospitalization or prolongation of existing hospitalization. Hospitalization is defined as an admission of greater than 24 hours to a medical facility and does not always qualify as an AE. Hospitalization for the following reasons are exceptions:
   - Hospitalization during the period of PK/PD sampling
   - Hospitalization to have scheduled treatment for the target disorder of the clinical study.
   - Hospitalization to have a scheduled treatment or operation for an existing disorder, which is irrelevant to the indication under clinical study and has not been exacerbated.
   - Hospitalization for convenience and social reasons (e.g. plastic surgery).
4. Results in persistent or significant disability/incapacity.
5. Leads to a congenital anomaly/birth defect.
6. Is an important medical event that satisfies any of the following:
   - May require intervention to prevent items 1 through 5 above.
   - May expose the subject to danger, even though the event is not immediately life threatening or fatal or does not result in hospitalization.

### 10.1.8 Life-Threatening Adverse Event

A life-threatening AE, in the view of either the Investigator or Sponsor, places the patient or suspect at immediate risk of death. It does not include an adverse reaction that, had it occurred in a more severe form, might have caused death.

The determination of whether an AE is life threatening can be based on the opinion of the Investigator or Sponsor. If either the Sponsor or Investigator believes that the event is serious or life threatening, the event must be considered serious and evaluated by the Sponsor for expedited reporting (21 Code of Federal Regulations [CFR] 312.32(a) and 312.32(c)(1)).

### 10.1.9 Severity of AEs

The different categories of intensity (severity) are characterized as follows:

| | |
|---|---|
| Mild: | The event is transient, easily tolerated by the subject and does not affect the subject's daily activities. |
| Moderate: | The event causes the subject discomfort and interrupts the subject's usual daily activities. |
| Severe: | The event is incapacitating and causes considerable interference with the subject's usual activities. |

### 10.1.10 Relationship to Study Treatment

The relationship of each AE to the investigational products will be assessed by the Investigator or Sub-Investigator on the basis of his/her clinical judgment and the following definitions:

1= **Related**:
The AE follows a reasonable temporal sequence from investigational product administration and cannot be reasonably explained by the subject's clinical state or other factors (*e.g.*, disease under study, concurrent diseases, or concomitant medications).

The AE follows a reasonable temporal sequence from investigational product administration and represents a known reaction to the investigational product or other drugs in its class, or is predicted by the known pharmacological properties of the drug.

The AE resolves with discontinuation of the investigational product and/or recurs with re-challenge, if applicable.

2 = **Not Related**:
The AE does not follow a reasonable temporal sequence from investigational product administration or can be reasonably explained by the subject's clinical state or other factors (*e.g.*, disease under study, concurrent diseases and concomitant medications).

## 10.2 Procedures

### 10.2.1 Collection and Recording of AEs

Collection of all AEs (SAEs and non-serious AEs) will commence from the time the subject signs the informed consent to participate in the study until the post-treatment follow-up visit. At each study visit, the Investigator will assess whether any subjective AEs have occurred. In order to avoid bias in eliciting AEs, a non-specific question, such as "How have you been feeling since your last visit?" may be asked. Subjects may report AEs occurring at any other time during the study.

All subjects experiencing AEs, whether considered associated with the use of the study medication or not, must be monitored and given appropriate medical treatment at the discretion and judgement of the Investigator until the symptoms subside and any clinically relevant changes in laboratory values have returned to baseline or until there is a satisfactory explanation for the changes observed. All AEs will be documented in the AE page of the eCRF, whether or not the Investigator concludes that the event is related to the drug treatment. The event term, start and stop dates, severity, action taken with the investigational product and outcome, will be documented, along with the Investigator's opinion of the causal relationship between the event and the investigational product.

### 10.2.2 Collection and Reporting of SAEs

When an SAE occurs, it must be reported according to the following procedure:

An SAE form must be completed within 24 hours of first onset or notification of the event. The information should be completed as fully as possible but contain, at a minimum a short description of the event and the reason why the event is categorized as serious, subject identification number, Investigator's name, name of the study medication, and a causality assessment.

In the interest of subject safety, and in order to fulfill regulatory requirements**,** all SAEs (regardless of their relationship to investigational product) must be reported to the Sponsor or a designated qualified vendor within 24 hours of the Study Center's first knowledge of the event.

The collection of SAEs will begin after the subject signs the informed consent form and stop at the end of the subject's follow-up period. An Initial Serious Adverse Event Form should be completed and submitted via electronic data capture (EDC) system to the Sponsor or designated qualified vendor. If the EDC system is unavailable for more than 24 hours, the site will use a paper SAE form and fax it to the Sponsor or designated qualified vendor.

All serious and unexpected AE reporting will adhere to 21 CFR 312.32 for IND drugs and 21 CFR 314.80 for marketed drugs (15-day alerts). The IRB and all Investigators will be notified of the alert reports per FDA regulations.

## 10.3 Anticipated Adverse Events

An anticipated AE is defined as any AEs described in the Investigator Brochure or this protocol, including gout flares, liver function abnormalities, diarrhea, rash, nausea, and dizziness. Anticipated AEs also include procedure related AEs.

Normal precautions taken for a human study, including the provision of emergency equipment, will be taken during this study. Qualified and well-trained physicians and medical staff will instruct the subjects.

### 10.3.1 Procedure related adverse events

Study procedures may involve the placement of a catheter, which may lead to allergic reaction, redness, swelling, bruising, pain, bleeding or infection at catheter insertion site. The study procedures may also involve the use of adhesive to secure the placement of medical equipment. The adhesive may cause an allergic reaction, inflammation, redness, swelling, or itching when in contact with the skin.

### 10.3.2 Risks related to repeated blood draws

Subjects will participate in several blood draws throughout the course of the study, which have the potential to cause a venous line-vasovagal response, bruising, tenderness, and rarely infection.

## 10.4 Follow-up of AEs and SAEs

All AEs should be followed up and subjects will be rendered appropriate medical care and treatment at the discretion of the Investigator until resolution or until the Investigator and Sponsor concludes that further follow-up is not necessary. If the AE has not resolved by the post-treatment follow-up visit, the stop date will be recorded as "ongoing."

All SAEs should be followed up until resolution or permanent outcome of the event or until the Investigator and Sponsor judge that further follow-up is not necessary.

If information is not available at the time of the first report and becomes available at a later date, the Investigator should complete a follow-up SAE form at the earliest possible time or provide other written documentation and fax/email it immediately within 24 hours of receipt of information to the Sponsor or designee. Copies of any relevant data from the hospital notes (*e.g.*, ECGs, laboratory tests, discharge summary, postmortem results) should be sent accordingly, if required.

All other non-serious AEs must be followed until the outcome of the event is "recovering" (for chronic conditions), or "recovered", or until the end of the post-treatment follow-up stated in the protocol, whichever comes first, and until all queries related to these AE's have been resolved.

### 10.4.1 Safety Reporting to IRBs or IECs, and Regulatory Authorities

The Sponsor or designated qualified vendor will be responsible for reporting all suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to regulatory

authorities, Investigators and IRBs or IECs, as applicable, in accordance with national regulations in the countries where the study is conducted and per the Safety Management Plan.

# 11.0 DATA HANDLING AND MANAGEMENT

Clinical Data Management (CDM) is the responsibility of the Sponsor or delegate.

## 11.1 Data Management

The full details of procedures for data handling will be documented in the Data Management Plan (DMP).

AEs and medical history will be coded using the current version of the Medical Dictionary for Regulatory Activities (MedDRA). Concomitant medications will be coded using the current version of the World Health Organization (WHO) Drug Dictionary. The dictionary versions used will be documented in the DMP and recorded in the Study Master File documentation.

Unique numbers will identify the subject and the biological material obtained from the subject. Appropriate measures such as encryption or deletion will be enforced to protect the identity of human subjects in all presentations and publications as required by local/regional/national requirements.

Data from screening failures will be entered into the database.

Laboratory data will be electronically transferred to the responsible Data Management Unit for database reconciliation purposes. The electronic laboratory data will be considered source data. In cases where sensitive non-PK laboratory data is transferred via non-secure electronic networks, data will be encrypted during transfer.

The laboratory will provide one copy of the laboratory reports to the site staff. The site staff will receive all safety laboratory data electronically or based on fax reports directly from the laboratory. An Investigator must review, evaluate, sign, and date the laboratory print-outs upon receipt. The signed print-out of the laboratory reports are source data.

All other results, including PK data and laboratory tests will be transferred electronically to the responsible Data Management Unit.

## 11.2 Electronic Case Report Forms

### 11.2.1 Clinical Data Management Workflow

eCRFs will be developed by the Sponsor or delegate's CDM or an authorized CDM department, in collaboration with the clinical study team and statistician. CDM will document the process workflow in the DMP. After data entry, monitor(s) will source data verify (SDV) the eCRFs against the source documents. Queries may be issued to clarify the data entered. The Principal Investigator will electronically sign the eCRFs after all data have been entered and all queries have been resolved. If corrections and/or resolution of queries are required after Principal Investigator approvals, those eCRFs affected by changes will be re-signed by the Principal Investigator. The database may be locked after the Principal Investigator approvals are completed.

### 11.2.2 Data Entry of eCRFs

Data required for analyses and subject safety assessments will be entered from source documentation into eCRFs. Instructions for data entry will be provided in the eCRF Completion Guidelines. All site staff involved with entering data into the eCRFs will be trained prior to gaining access to the study database.

### 11.2.3 Corrections to eCRFs

Queries may be generated by the eCRF system during data entry, and queries may be generated by CDM staff, monitors, Principal Investigators, the Sponsor, and other data reviewers during the course of the study. Only specific site personnel will be authorized to make corrections to the eCRFs; CDM will ensure personnel are trained prior to granting access in the eCRF system. Corrections will be made directly in the eCRF – by modifying existing data, adding new data, or deleting data, as appropriate. All data corrections will be logged in the electronic audit trail.

### 11.2.4 Principal Investigator Approval of eCRF Data

The Investigator or Investigator's authorized staff must ensure that all information derived from source documentation is consistent with the source information and accurately reflected in the eCRFs. By electronically signing the eCRFs, the Investigator confirms that the information is complete and correct.

## 11.3 Retention of Documents

At the completion of the study, all records created by and under the supervision of the Investigator should be maintained in accordance with the requirements of the regulatory authority guideline and the GCP Guideline. These will be available for inspection at any time by the Sponsor or the FDA.

Clinical study documents are archived upon completion of the study and maintained for at least 15 years from the study closure or longer in accordance with local regulation and applicable regulatory authority guidelines, and the study Sponsor will be notified prior to destruction of study records.

Current FDA guidelines require records to be retained for a period of 2 years following the date a marketing application is approved for the drug, for the indication for which it is being investigated. If no application is filed or if the application for the investigated indication is not approved, documents will be kept for a minimum of 2 years after the investigation is discontinued and the FDA is notified.

# 12.0 STATISTICAL METHODS

## 12.1 Statistical and Analytical Plans

A statistical analysis plan (SAP), including the statistical analysis and tables/listings/figures will be developed. Subjects who are randomized into the test (LC350189 50 mg, LC350189 100 mg, or LC350189 200 mg) or placebo groups before the Protocol version 5.0 will be combined and analyzed with subjects who will be enrolled after the implementation of the Protocol version 5.0. For subjects randomized into the active control group before the implementation of the Protocol version 5.0, the active control group will be listed and can be summarized for exploratory purpose and further details will be described in a SAP.

## 12.2 Study Endpoints

The study endpoints are measured or derived parameters used to assess whether the study objectives have been met. The endpoints for this study are shown in Table 12-1. Additional endpoints may be added to the SAP as needed to address the needs of the study.

**Table 12-1 Study Endpoints**

| **Primary Objective** | **Endpoint** |
|---|---|
| To assess the efficacy of LC350189 in terms of sUA level <5 mg/dL at Week 12 (Day 84) to find therapeutic dose of LC350189. | • Proportion of subjects who achieve sUA level <5.0 mg/dL at Day 84 (Visit 8). |
| **Secondary objectives** | **Endpoints** |
| To assess the efficacy of LC350189 in terms of sUA levels | • Proportion of subjects with sUA <6.0 mg/dL at Day 84 (Visit 8).<br>• Proportion of subjects who achieve sUA <5.0 mg/dL at each visit.<br>• Proportion of subjects with baseline (Visit 4) sUA >10 mg/dL who achieve <5.0 mg/dL at Day 84 (Visit 8).<br>• Proportion of subjects with baseline (Visit 4) sUA >10 mg/dL who achieve <6.0 mg/dL at Day 84 (Visit 8).<br>• Proportion of subjects per renal function at baseline (Visit 3) who achieve sUA <5.0 mg/dL at Day 84 (Visit 8).<br>• Proportion of subjects per renal function at baseline (Visit 3) who achieve sUA <6.0 mg/dL at Day 84 (Visit 8). |
| To investigate the PK and PD characteristics of LC350189 in subjects with hyperuricemia and a diagnosis of gout. | • $C_{trough,ss}$ at baseline (Visit 4), Day 14 (Visit 5), Day 28 (Visit 6), Day 56 (Visit 7) and Day 84 (Day 8).<br>• Change and percent change in sUA levels from baseline (Visit 4) at each visit.<br>• Maximum percent reduction in sUA level during treatment. |
| To assess antiflare activity in subjects in subjects with hyperuricemia and a diagnosis of gout. | • Gout flare rate in subjects.<br>• Gout flare rate in subjects with sUA <6.0 mg/dL at Day 84 (Visit 8).<br>• Proportion of subjects receiving gout flare rescue treatment. |

| **Exploratory objectives** | **Endpoints** |
|---|---|
| To explore the metabolic and anti-inflammatory effects of LC350189. | • Change in HbA1c from baseline (Visit 4) to Day 84 (Visit 8).<br>• Proportion of subjects with HbA1c <7% at Day 84 (Visit 8).<br>• Proportion of subjects with HbA1c ≤6.5% at Day 84 (Visit 8).<br>• Change in FPG from baseline (Visit 4) at Day 84 (Visit 8).<br>• Change in hs-CRP from baseline (Visit 4) at Day 84 (Visit 8).<br>• Serum concentrations of hypoxanthine and xanthine at baseline (Visit 4) and Day 84 (Visit 8). |
| **Safety Objectives** | **Endpoints** |
| To assess the safety and tolerability of LC350189 | • Adverse events<br>• Laboratory values<br>• Vital signs<br>• ECG |

### 12.2.1 Analysis Sets

#### 12.2.1.1 Safety Set

The Safety Analysis Set will include all subjects who received study medication. The Safety Analysis Set will be used for demographic and baseline characteristics, and safety summaries.

#### 12.2.1.2 Full Analysis Set

All efficacy analyses will be performed on the Full Analysis Set (FAS). The FAS will be the main population for efficacy. The FAS will consist of all randomized subjects that have received at least one dose of investigational product.

#### 12.2.1.3 Per-Protocol Analysis Set

The Per-Protocol (PP) Analysis Set is defined as all subjects in the FAS that have appropriate exposure to study medication for the 12-week treatment period and without any major protocol deviations that may impact primary efficacy analysis. The set of major protocol deviations and the range of treatment compliance percentage required will be finalized prior to database lock. 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 PP Analysis Set.

#### 12.2.1.4 Pharmacokinetic Analysis Set

The PK Analysis Set will include all subjects who received investigational product 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 product). The PK analysis set will be used for analysis of PK endpoints.

### 12.2.2 Analysis of Demographics and Other Baseline Characteristics

Demographic and baseline characteristics will be summarized for the Safety Analysis Set and the Full Analysis Set. Summary statistics (*e.g.*, number of subjects, mean, median, standard deviation, and range) will be generated for continuous variables and the number and percentage of subjects within each category will be presented for categorical variables.

### 12.2.3 Analysis of Efficacy Endpoints

All endpoints will be summarized descriptively and will be compared to placebo using descriptive statistics. Efficacy endpoints such as the proportion of subjects meeting target will be analyzed using the Cochran-Mantel Haenszel (CMH) test adjusted by randomization stratification factors. 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. Dropouts will be treated according to non-responder imputation (NRI). If the Wald asymptotic 95% confidence interval for each pairwise comparison includes zero, superiority of dose group over placebo is demonstrated. However, if a comparison is not statistically significant, that is, confidence interval includes zero, then all subsequent comparisons will be considered exploratory.

Change and percent change from baseline (Visit 4) will be analyzed with an analysis of covariance (ANCOVA) model, including treatment, sUA and tophi strata as fixed factors, and baseline values of the dependent variable as a covariate.

The planned analyses will be described in more detail in the SAP.

### 12.2.4 Safety Analysis and Endpoints

Safety and tolerability of the investigational products will be assessed by collection and review of AEs, laboratory parameters, vital signs, and ECG parameters throughout the duration of the study. Safety analysis will involve examination of the descriptive statistics and individual subject listings for the Safety Analysis Set for any effects of study treatment on clinical tolerability and safety.

All AEs will be coded using MedDRA. Data will be summarized using preferred term and primary system organ class.

AE summaries will include the overall incidence (by system organ class and preferred term), events by maximum intensity, event by relationship to study treatment, events leading to discontinuation of investigational product, and SAEs. Laboratory parameters (hematology, chemistry, and urinalysis), vital signs, and ECG will be summarized descriptively by treatment.

## 12.3 Interim Analysis

No formal interim analysis is planned.

### 12.4 Determination of Sample Size

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

[Hypothesis]

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

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

Where $p$ is the estimated proportion for each group expressed as the proportion of subjects who achieve sUA <5.0 mg/dL at Day 84 (Visit 8), $p_t$ is the proportion of a test group, and $p_c$ is the proportion of a control group. The values $Z_\alpha$ and $Z_\beta$ represent values of the standard normal distribution that correspond to a type I error rate of $\alpha$=0.025 and a type II error rate of $\beta$=0.2. Evaluable subjects per study group is determined using estimates of $p_t$=0.80 and $p_c$=0.47, and directly computed values of $Z_\alpha$ =1.96 and $Z_\beta$ =0.84. Assuming a dropout rate of 20%, 38 subjects per study group are needed to assess the efficacy of LC350189 in an evaluable population of 30 subjects per study group.

The size of the control population is based on the FACT trial (Becker et al 2005a), in which a post hoc analysis of sUA at final visit showed sUA <5 mg/dL in 118/249 (47%) patients treated with febuxostat 80 mg.

| Power | Alpha, one-sided | P (test) | P (control) | N (per group) | N (Including drop-out 20%) |
|---|---|---|---|---|---|
| 80% | 0.025 | 0.80 | 0.47 | 30 | 38 |

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.

The power when compared to placebo group with the current sample size is calculated more than 99% as follows.

| Power | Alpha, one-sided | P (test) | P (placebo) | N (per group) | N (Including drop-out 20%) |
|---|---|---|---|---|---|
| >99.9% | 0.025 | 0.80 | 0.1 | 30 | 38 |

P(placebo) is considered 0.1 based on the below two studies. Although cut-off level of sUA level and assessment time is different in this study, proportion in placebo is assumed conservatively up to 10%.

| Study | Endpoint | N | P(plabeco)(%) |
|---|---|---|---|
| TMX-00-004 (Becker et al 2005b) | sUA level <6.0 mg/dl at Day 28 | 35 | 0% |
| APEX study (Schumacher et al 2008) | sUA level <6.0 mg/dl at Week 28 | 99 | 1% |

Since the comparisons will be done sequentially using a closed testing procedure with pre-specified order, no multiplicity adjustment is planned for multiple comparisons.

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

# 13.0 QUALITY CONTROL AND QUALITY ASSURANCE

## 13.1 Monitoring

The study will be monitored by a qualified monitor.

Monitoring visits to the study site(s) will be made periodically during the study to ensure that all aspects of the protocol and GCP are followed, eCRFs are completed correctly and completely, and drug accountability is monitored. The Monitor should visit the study site (physically or remotely) at least once before First Subject First Visit (FSFV) for an Initiation Visit, at least once during the clinical part of the study, and at least once after Last Subject Last Visit (LSLV). Furthermore, the Monitor must be available for discussions by telephone.

The Sponsor or delegate may assign additional Clinical Research Associates (CRAs)/Monitors on an ad hoc basis for training purposes and to meet required timelines. In addition, if study timelines are modified for any reason, *e.g.*, delays in recruitment or accelerated enrollment, the Sponsor or delegate may use additional CRAs at its discretion to ensure study expectations are met.

The Monitor must be given direct access to source documents, such as original documents, data, and records. Direct access includes permission to examine, analyze, and verify any record(s) and report(s) that are important to evaluation of the clinical study. The study will be monitored to verify integrity and validity of the data. Monitors will follow a study-specific Monitoring Plan.

Additional quality control (QC) monitoring of the clinical study for protocol and GCP compliance will be conducted periodically by qualified staff of the Sponsor or delegate.

## 13.2 Protocol Deviations

The Investigator should not deviate from the protocol, except where necessary to eliminate an immediate hazard to study subjects. Should other circumstances arise that will require deviation from protocol-specified procedures, unless there is an emergency or immediate need, the Investigator should contact the Medical Monitor and Sponsor to review and discuss the implications of the deviation and determine the appropriate course of action. Any deviation must be documented, stating the reason and date, the action taken, and the impact for the subject and/or the study. The documentation must be kept in the ISF and the Trial Master File.

## 14.0 ETHICAL ASPECTS OF THE STUDY

This study will be conducted in accordance with the Protocol, the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH), Guideline for Good Clinical Practice: Consolidated Guidance (E6) and applicable regulatory requirements including clinical research guidelines established by the Basic Principles defined in the U.S. 21 CFR Parts 50, 56, and 312 and the principles enunciated in the Declaration of Helsinki (prior to 2000).

### 14.1 Institutional Review Board and/or Independent Ethics Committee

Prior to commencement of the study, the protocol, any amendments, subject information/ ICF, any other written information to be provided to the subject, subject recruitment procedures, information about payments and compensation available to subjects if not mentioned in the subject information, the Investigator's current curriculum vitae and/or other documentation evidencing qualifications, and other documents as required by the local IEC/ IRB should be submitted. Written approval/favorable opinion must be obtained from IEC/IRB prior to commencement of the clinical study start.

The Investigator or designee shall provide to Sponsor or its designee a copy of the written and dated approval/favorable opinion by the applicable IRB/IEC.

During the study, the Investigator must promptly report the following to the IEC/IRB: Updates to the Investigator Brochure, unexpected SAEs where a causal relationship cannot be ruled out, substantial amendments to the protocol, non-substantial amendments, deviations to the protocol implemented to eliminate immediate hazards to the subjects, new information that may affect adversely the safety of the subjects or the conduct of the study (including new risk/benefit analysis in case it will have an impact on the planned follow-up of the subjects), annually written summaries of the study status, and other documents as required by the local IEC/IRB.

Substantial amendments must not be implemented before approval/favorable opinion, unless necessary to eliminate hazards to the subjects.

The Investigator must maintain an accurate and complete record of all submissions made to the IEC/IRB. The records should be filed in the Investigator's Study File and copies must be provided to the Sponsor.

### 14.2 Regulatory Authorities

Regulatory Authorities will receive the clinical study application, protocol, amendments to the protocol, reports on SUSARs and other applicable SAEs and the integrated clinical study report according to national regulations.

### 14.3 Responsibilities of the Investigator

The Investigator will conduct this clinical study in compliance with all applicable national, state, local or regional laws and regulatory requirements of the countries in which the clinical study is

performed. The Investigator will align his or her conduct in accordance with the "Responsibilities of the Investigator".

The Investigator may appoint such other individuals as he/she may deem appropriate as Sub-Investigators to assist in the conduct of the Clinical Study in accordance with the Clinical Study Protocol. All Sub-Investigators shall be timely appointed and listed, and will be supervised by and under the responsibility of the Investigator, and that will be noted in the Delegation of Authority log at the clinical study site. Those Sub-Investigators will have the appropriate documented training in a written training log. The Investigator will provide them with a Clinical Study Protocol and all necessary information. Each Sub-Investigator is fully responsible for fulfilling all of the obligations of an Investigator as identified in 21 CFR 312.60. Thus under 21 CFR 312.3(b), the Investigator and each Sub-Investigator must sign a separate Form FDA 1572 before participating in this study.

In compliance with the Clinical Study Protocol, GCP, and applicable regulatory requirements, the Investigator must permit auditing by or on the behalf of the Sponsor and inspection by applicable regulatory authorities. The Investigator agrees to allow the auditors/inspectors to have direct access to his/her study records for review; being understood that these personnel are bound by professional secrecy and as such will not disclose any personal identity or personal medical information. The Investigator will make every effort to help with the performance of the audits and inspections, giving access to all necessary facilities, data, and documents. As soon as the Investigator is notified of a future inspection by the authorities, he or she will inform the Sponsor or its designee and authorize the Sponsor or its designee to participate in this inspection. Any results and information arising from the inspections by the regulatory authorities will be immediately communicated to the Sponsor. The Investigator shall take appropriate measures required by the Sponsor to take corrective actions for all problems found during the audit or inspections.

Clinical research studies sponsored by the Sponsor are subject to ICH GCP and all the applicable local laws and regulations. The responsibilities imposed on Investigators by the FDA are summarized in the "Statement of Investigators" (Form FDA 1572) or the investigator agreement (device studies), which must be completed and signed before the Investigator may participate in this study.

### 14.4 Informed Consent

Once signed, the original ICF, subject authorization form (if applicable), and subject information sheet (if applicable) will be stored in the Investigator's site file. The Investigator must document the date the subject signs the informed consent in the subject's medical record. Copies of the signed ICF, the signed subject authorization form (if applicable), and subject information sheet (if applicable) shall be given to the subject.

All revised ICFs must be reviewed and signed by relevant subjects or the relevant subject's legally acceptable representative in the same manner as the original informed consent. The date the revised consent was obtained should be recorded in the subject's medical record, and the subject should receive a copy of the revised ICF.

## 14.5 Subject Confidentiality

The Sponsor and designees affirm and uphold the principle of the subject's right to protection against invasion of privacy. Subject records will be kept private except when ordered by law. The following individuals will have access to study subject records: Principal Investigator and designees, study Sponsor, monitors and auditors, the FDA, other government offices, and the IRB.

Throughout this study, a subject's source data will only be linked to the Sponsor's clinical study database or documentation via a unique identification number. As permitted by all applicable laws and regulations, limited subject attributes, such as sex, age, or date of birth, and subject initials may be used to verify the subject and accuracy of the subject's unique identification number.

The Investigator must agree to permit the Sponsor's monitor or designee's monitor, representatives from any regulatory authority, the Sponsor's designated auditors, and the appropriate IRBs and IECs to review the subject's source data or documents, including, but not limited to, laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a subject's study participation, and autopsy reports. Access to a subject's original medical records requires the specific authorization of the subject as part of the informed consent process. The confidentiality of the data verified and the protection of the subjects must be respected during these inspections.

Copies of any subject source documents that are provided to the Sponsor must have certain personally identifiable information removed.

## 14.6 Property Rights

All information disclosed or provided by the Sponsor (or any company/institution acting on their behalf), or produced during the Clinical Study, including but not limited to, the Clinical Study Protocol, the case report forms, the Investigator's Brochure and results obtained during the course of the Clinical Study, is confidential and the property of the Sponsor. No rights, title, or license to such data are granted by this protocol. The Investigator or any person under his/her authority agrees to undertake to keep confidential and not to disclose the information to any third party without the prior written approval of the Sponsor.

All information, documents and investigational product provided by Sponsor or its designee are and remain the sole property of the Sponsor. The Investigator shall not mention any information or the investigational product in any application for a patent or for any other intellectual property rights.

All results, data, documents and inventions, which arise directly or indirectly from the clinical study in any form, shall be the immediate and exclusive property of the Sponsor. The Sponsor may use or exploit all of the results at its own discretion, without limitation to its property right (territory, field, continuance). The Sponsor shall be under no obligation to patent, develop, market or otherwise use the results of the clinical study.

## 14.7 Publication, Disclosure, and Clinical Study Registration Policy

The Investigator will provide the Sponsor with truthful, accurate and complete test results and all data derived from the study. During the study, only the Sponsor may make study information available to other study Investigators or to regulatory agencies, except as required by law or regulation. Except as otherwise allowable in the clinical study site agreement, any public disclosure (including publicly accessible websites) related to the protocol or study results, other than study recruitment materials and/or advertisements, is the sole responsibility of the Sponsor.

The Investigator or qualified designee agrees to use this information only and strictly in connection with this clinical study and must not use it for other purposes without the prior written permission from the Sponsor.

The study may be registered on publicly accessible websites (eg, ClinicalTrials.gov) according to applicable law, regulation and guidance, after discussion with the Sponsor.

## 14.8 Insurance and Compensation for Injury

The Sponsor shall carry applicable insurance in the types and amounts necessary to cover its obligations herein in accordance with local laws and requirements and/or guidelines for conducting clinical studies in any country, unless others have shown negligence. The Sponsor renounces liability in the event of negligence or any other liability by the clinics or doctors conducting experiments or by persons for whom the said clinic or doctors are responsible. The Sponsor accepts liability in accordance with all applicable regulations per the CFR and all other applicable federal or state regulations.

Each subject in the study must be insured in accordance with the regulations applicable to the site where the subject is participating.

## 15.0 REFERENCES

**Becker et al 2005a**
Becker et al. (2005). Febuxostat compared with allopurinol in patients with hyperuricemia and gout. *N Engl J Med* 353:2450–2461.

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Becker MA, Schumacher HR Jr, Wortmann RL, et al. (2005). Febuxostat, a novel nonpurine selective inhibitor of xanthine oxidase: a twenty-eight-day, multicenter, phase II, randomized, double-blind, placebo-controlled, dose-response clinical trial examining safety and efficacy in patients with gout. *Arthritis Rheum*. 52(3):916-923.

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## Appendix A

## ACR/EULAR classification criteria for gout (Neogi et al 2015)

### Definitions and considerations for each domain*

| Domain† | Definitions and special considerations |
|---|---|
| 1. Pattern of joint/bursa involvement during symptomatic episode(s) ever<br>Categories are defined as per the description of the distribution of joints involved | Distribution of joints: involvement (ever) of<br>i) Joint(s) or bursa(e) other than ankle, midfoot or first metatarsophalangeal (MTP) joint (or their involvement only as part of a polyarticular presentation)<br>ii) Ankle or midfoot joint(s) as monoarticular or part of an oligoarticular presentation without first MTP joint involvement<br>iii) MTP joint involvement as monoarticular or part of an oligoarticular presentation |
| 2. Characteristics of symptomatic episode(s) ever<br>Categories are defined as<br>No characteristics present<br>1 characteristic present<br>2 characteristics present<br>3 characteristics present | Characteristics to consider: presence (ever) of<br>i) Great difficulty with walking or inability to use the affected joint(s) during a symptomatic episode ever (patient-reported)<br>ii) Can't bear touch or pressure to the affected joint during a symptomatic episode ever (patient-reported)<br>iii) Erythema overlying affected joint during a symptomatic episode ever (patient-reported or physician-observed) |
| 3. Time course of symptomatic episode(s) ever<br>Categories are defined as<br>No typical episodes<br>1 typical episode<br>Recurrent typical episodes | "Typical symptomatic episode": presence (ever) of >2 of the following, irrespective of antiinflammatory treatment<br>i) Time to maximal pain <24 hours<br>ii) Resolution of symptoms in ≤14 days<br>iii) Complete resolution (to baseline level) between symptomatic episodes |
| 4. Clinical evidence of tophus<br>Categories are defined as<br>Present<br>Absent | Appearance: draining or chalk-like subcutaneous nodule under transparent skin, often with overlying vascularity<br>Location: classic locations—joints, ears, olecranon bursae, finger pads, tendons (*e.g.*, Achilles) |
| 5. sUA, off-treatment<br>Categories are defined as<br><4 mg/dL (0.24 mmoles/liter)<br>4–<6 mg/dL (0.24–<0.36 mmoles/liter)<br>6–<8 mg/dL (0.36–<0.48 mmoles/liter)<br>8–<10 mg/dL (0.48–<0.60 mmoles/liter)<br>≥10 mg/dL (≥0.60 mmoles/liter) | Which sUA measurement to use: highest reading on record, off ULT<br>Special considerations: Ideally, the sUA level should be scored if tested at a time when the patient was not receiving ULT and it was >4 weeks from the start of an episode; *if* practicable, retest under those conditions.<br>If sUA level is ≥10 mg/dL, no need to retest. |
| 6. Synovial fluid analysis<br>Categories are defined as<br>MSU negative<br>Not done | Location: symptomatic (ever) joint or bursa<br>Special considerations: Assessment should be performed by a trained observer. |

| | |
|---|---|
| | Note: MSU positive is a sufficient criterion. |
| 7. Imaging evidence of urate deposition<br>Categories are defined as<br>Absent *or* not done<br>Present (either modality) | Modality: ultrasound or DECT<br>Appearance: double-contour sign on ultrasound‡ or urate deposition on DECT§<br>Location: symptomatic (ever) joint or bursa |
| 8. Imaging evidence of gout-related joint damage<br>Categories are defined as<br>Absent or not done<br>Present | Modality: radiography<br>Appearance of gout-related erosion: cortical break with sclerotic margin and overhanging edge; excludes gull wing appearance<br>Location: radiograph of hands and/or feet; excludes distal interphalangeal joints |

* Symptomatic (ever) refers to pain and/or swelling.
† Categories within each domain are hierarchical; if a subject fulfills more than 1 category, the highest category should be selected.
‡ A false-positive double-contour sign (artifact) may appear at the cartilage surface, but should disappear with a change in the insonation angle of the probe.
§ Images should be acquired using a dual-energy computed tomography (DECT) scanner, with data acquired at 80 kV and 140 kV and analyzed using gout-specific software with a 2-material decomposition algorithm that color-codes urate. A positive scan result is defined as the presence of color-coded urate at articular or periarticular sites. Nailbed, submillimeter, skin, motion, beam hardening, and vascular artifacts should not be interpreted as DECT evidence of urate deposition.

## The ACR/EULAR gout classification criteria*

To classify a subject as having gout, a subject must meet
1) "Step 1: Entry criterion" and meet either
2-1) "Step 2: Sufficient criterion"; *or*
2-2) a score of ≥ 8 in "Step 3: Criteria", if a subject does not meet "Step 2: Sufficient Criterion."

| | Categories | Score |
|---|---|---|
| **Step 1**: Entry criterion (only apply criteria below to those meeting this entry criterion) | At least 1 episode of swelling, pain, or tenderness in a peripheral joint or bursa | |
| **Step 2**: Sufficient criterion (if met, can classify as gout without applying criteria below) | Presence of MSU crystals in a symptomatic joint or bursa (*i.e.*, in synovial fluid) or tophus | |
| **Step 3**: Criteria (to be used if sufficient criterion not met) | | |
| Clinical | | |
| Pattern of joint/bursa involvement during symptomatic episode(s) ever† | Ankle *or* midfoot (as part of monoarticular or oligoarticular episode without involvement of the first metatarsophalangeal joint) | 1 |
| | Involvement of the first metatarsophalangeal joint (as part of monoarticular or oligoarticular episode) | 2 |
| Characteristics of symptomatic episode(s) ever | | |
| • Erythema overlying affected joint (patient-reported or physician-observed)<br>• Can't bear touch or pressure to affected joint<br>• Great difficulty with walking or inability to use affected joint | One characteristic<br>Two characteristics<br>Three characteristics | 1<br>2<br>3 |
| Time course of episode(s) ever | | |
| Presence (ever) of ≥2, irrespective of antiinflammatory treatment:<br>• Time to maximal pain ,24 hours<br>• Resolution of symptoms in ≤14 days<br>• Complete resolution (to baseline level) between symptomatic episodes | One typical episode<br>Recurrent typical episodes | 1<br>2 |
| Clinical evidence of tophus<br>Draining or chalk-like subcutaneous nodule under transparent skin, often with overlying vascularity, located in typical locations: joints, ears, olecranon bursae, finger pads, tendons (*e.g.*, Achilles) | Present | 4 |
| Laboratory | | |
| sUA: Measured by uricase method.<br>Ideally should be scored at a time when the patient was not receiving ULT and it was >4 weeks from the start of an episode (*i.e.*, during intercritical period); if practicable, retest under those | <4 mg/dL (,0.24 mmoles/liter)‡<br>6–8 mg/dL (0.36–<0.48 mmoles/liter)<br>8–<10 mg/dL (0.48–<0.60 mmoles/liter<br>≥10 mg/dL (≥0.60 mmoles/liter) | -4<br>2<br>3<br>4 |

| | | |
|---|---|---|
| conditions. The highest value irrespective of timing should be scored. | | |
| Synovial fluid analysis of a symptomatic (ever) joint or bursa (should be assessed by a trained observer)§ | MSU negative | -2 |
| Imaging¶ | | |
| Imaging evidence of urate deposition in symptomatic (ever) joint or bursa: ultrasound evidence of double-contour sign# *or* DECT demonstrating urate deposition** | Present (either modality) | 4 |
| Imaging evidence of gout-related joint damage: conventional radiography of the hands and/or feet demonstrates at least 1 erosion†† | Present | 4 |

* A web-based calculator can be accessed at: http://goutclassificationcalculator.auckland.ac.nz, and through the ACR and EULAR web sites.

† Symptomatic episodes are periods of symptoms that include any swelling, pain, and/or tenderness in a peripheral joint or bursa.

‡ If sUA level is <4 mg/dL (<0.24 mmoles/liter), *subtract 4 points*; if serum urate level is ≥4-<6 mg/dL (≥0.24-<0.36 mmoles/liter) score this item as 0.

§ If polarizing microscopy of synovial fluid from a symptomatic (ever) joint or bursa by a trained examiner fails to show monosodium urate monohydrate (MSU) crystals, *subtract 2 points*. If synovial fluid was not assessed, score this item as 0.

¶ If imaging is not available, score these items as 0.

# Hyperechoic irregular enhancement over the surface of the hyaline cartilage that is independent of the insonation angle of the ultrasound beam (note: false-positive double-contour sign [artifact] may appear at the cartilage surface but should disappear with a change in the insonation angle of the probe).

** Presence of color-coded urate at articular or periarticular sites. Images should be acquired using a DECT scanner, with data acquired at 80 kV and 140 kV and analyzed using gout-specific software with a 2-material decomposition algorithm that color-codes urate. A positive scan is defined as the presence of color-coded urate at articular or periarticular sites. Nailbed, submillimeter, skin, motion, beam hardening, and vascular artifacts should not be interpreted as DECT evidence of urate deposition.

†† Erosion is defined as a cortical break with sclerotic margin and overhanging edge, excluding distal interphalangeal joints and gull wing appearance.