CLINICAL STUDY PROTOCOL: RDEA594-401

Protocol Title:	A Phase 4, Randomized, Double-Blind, Multicenter, Placebo-Controlled Study to Evaluate the Safety and Efficacy of Lesinurad 200 mg in Combination With a Xanthine Oxidase Inhibitor (XOI), Compared With an XOI Alone, in Subjects With Gout and Estimated Creatinine Clearance 30 to <60 mL/min Who Have Not Achieved Target Serum Uric Acid Levels on an XOI Alone
Brief Title:	Lesinurad in Subjects With Gout and Moderate Renal Impairment
Study Number:	RDEA594-401
Phase:	4
Investigational Product:	Lesinurad
Population/Indication:	Gout with estimated creatinine clearance 30 to <60 mL/min
Sponsor:	Ironwood Pharmaceuticals, Inc.
Sponsor Medical Monitor:	[redacted]
Protocol Version:	3
Protocol Date:	21 June 2017

PROTOCOL SYNOPSIS

Sponsor:

Ironwood Pharmaceuticals, Inc.

Name of Finished Product:

Lesinurad 200 mg tablets

Name of Active Ingredient:

Lesinurad

Protocol Title: A Phase 4, Randomized, Double-Blind, Multicenter, Placebo-Controlled Study to Evaluate the Safety and Efficacy of Lesinurad 200 mg in Combination With a Xanthine Oxidase Inhibitor (XOI), Compared With an XOI Alone, in Subjects With Gout and Estimated Creatinine Clearance 30 to <60 mL/min Who Have Not Achieved Target Serum Uric Acid Levels on an XOI Alone

Study Number: RDEA594-401

Study Phase: 4

Study Type: Postapproval Controlled Safety and Efficacy Study

Investigators and Study Sites:

Up to approximately 300 study sites in North America and Europe.

Primary Objective:

- To evaluate the safety over 24 months of lesinurad 200 mg once daily (qd) when used in combination with a xanthine oxidase inhibitor (XOI), compared with XOI alone, in subjects with gout and moderate renal impairment (estimated creatinine clearance 30 to <60 mL/min) who have not reached target serum uric acid (sUA) levels on an XOI alone.

Efficacy Objective:

- To evaluate the efficacy over 24 months of lesinurad 200 mg qd in combination with an XOI, compared with XOI alone, in subjects with gout and moderate renal impairment who have not reached target sUA levels on an XOI alone.

Methodology:

Subjects with gout, moderate renal impairment (30 to <60 mL/min), and who are not at target sUA of <6.0 mg/dL on XOI alone will be enrolled in this study. The study will include an approximate 1-month Screening Period, a 24-month Double-Blind Treatment Period, and a 1-month post-treatment Follow-Up Period.

All subjects must be on a stable, medically appropriate dose of XOI as their sole urate-lowering therapy (ULT) indicated for the treatment of gout for at least 4 weeks prior to Screening and throughout the Screening Period. This stable dose of XOI will be maintained throughout the study period. Subjects who qualify for the study will be randomized in a double-blind fashion to 1 of 2 treatment groups in a 1:1 ratio:

- LESU + XOI: lesinurad 200 mg qd and XOI
- PBO + XOI: placebo qd and XOI

Randomization will be stratified by estimated creatinine clearance (eCrCl) subgroup (30.0 to <45.0 mL/min or 45.0 to <60.0 mL/min using the average of the 2 Screening Visits and calculated by the Cockcroft-Gault formula using ideal body weight), Baseline measurable target tophi status (present/absent), and type of XOI (allopurinol or febuxostat). This study will enroll approximately 50% of subjects with eCrCl 30.0 to <45.0 mL/min and approximately 50% with eCrCl 45.0 to <60.0 mL/min.

Subjects will take investigational product (IP; lesinurad or placebo) qd in combination with their prescribed stable dose of XOI in the morning with adequate fluid intake for up to 24 months. Gout flare prophylaxis with colchicine is required from the Baseline Visit through the Month 6 Study Visit, consistent with treatment guideline recommendations for gout flare prophylaxis to reduce the potential for acute gout flares associated with initiation of ULTs. Subjects who have a documented intolerance or allergy to colchicine or who are taking a concomitant medication contraindicated for use with colchicine are permitted to take low-dose oral corticosteroids (defined as ≤10 mg/day of prednisone, or prednisolone, or their equivalent) for a short course, such as through the Month 3 study visit. The use of nonsteroidal anti-inflammatory drugs (NSAIDs) for gout flare prophylaxis is not permitted.

After initiating IP, subjects will return to the study site at Month 1, at Month 3, and every 3 months thereafter until the end of the Treatment Period (Month 24). At each visit, safety and efficacy assessments will be performed.

Subjects who complete the Treatment Period or who plan to withdraw from the study early should complete an End of Study Visit approximately 1 month after study completion/treatment discontinuation.

Subjects who permanently discontinue IP early for any reason, including inability to continue dosing with XOI, should complete an End of Treatment Visit as soon as possible followed by a Post-End of Treatment Visit 1 month after the End of Treatment Visit. Subjects should then continue on study and follow the protocol-defined schedule of events, including the End of Study Visit.

An independent Data Monitoring Committee (IDMC) will evaluate the safety data periodically to protect subject welfare and to identify potential safety signals. An independent Cardiovascular Endpoints Adjudication Committee (CEAC) will routinely assess all serious adverse events (SAEs) and other prospectively-defined adverse events (AEs) for cardiovascular (CV) related events. An independent Renal Events Adjudication Committee (REAC) will routinely evaluate and categorize all serious prospectively-defined renal-related and kidney stone AEs, and any additional SAEs deemed by the REAC Chair to be relevant for adjudication, and will assess the likelihood that potential contributing factors, including IP, contributed to the event. CEAC and

REAC assessments will be performed in a blinded fashion.

AEs of special interest that will be evaluated in this study include renal events (eg, renal-related AEs and kidney stone AEs) that are serious or lead to permanent discontinuation of IP, and all potential CV events. Additional information will be required for these events and recorded on the case report forms (CRFs).

Number of Planned Subjects:

Approximately 600 subjects will be enrolled (300 per treatment group).

Eligibility Criteria (not a complete list):

Key Inclusion Criteria

- Subject is male or female, ≥18 years and ≤85 years of age.
- Subject has a diagnosis of gout.
- Subject has moderate renal impairment with estimated creatinine clearance (eCrCl calculated by the Cockcroft-Gault formula using ideal body weight) 25.0 to ≤65.0 mL/min at Screening Visits 1 and 2 and an average eCrCl for both screening visits of 30.0 to <60.0 mL/min.
- Subject has been taking an XOI as ULT indicated for the treatment of gout for at least 4 weeks prior to Screening and throughout the Screening Period at a stable, medically appropriate dose, as determined by the Investigator. The minimum dose of allopurinol is 200 mg daily, and the minimum dose of febuxostat is the lowest approved dose per the local product label.
- Subject has a serum uric acid level ≥6.0 mg/dL (357 μmol/L) at Screening Visits 1 and 2.

Key Exclusion Criteria

- Subject had unstable angina, New York Heart Association class III or IV heart failure, myocardial infarction, or stroke within the last 6 months prior to randomization; or had a deep venous thrombosis within the previous 3 months prior to randomization.
- Subject has uncontrolled hypertension (defined as systolic pressure above 160 or diastolic pressure above 95 mm Hg at either Screening Visits 1 or 2).
- Subject has severe hepatic impairment (defined as Child-Pugh Class C) or is known human immunodeficiency virus (HIV) positive.
- Subject is a solid organ transplant recipient.
- Subject has a urine protein of 3+ or higher by dipstick by the central laboratory at Screening Visit 2.
- Subject has a history of glomerulonephritis.
- Subject is unable to initiate gout flare prophylaxis with colchicine or low-dose oral corticosteroids at Baseline.
- Subject has a gout flare during the Screening Period.

- Subject is pregnant or breastfeeding.

Investigational Product, Dose, and Mode of Administration:

Lesinurad tablets or matching placebo will be supplied by the Sponsor.
Dose: 200 mg qd.

All doses of IP should be taken in the morning with food and 1 cup (8 oz; 240 mL) of water and must be taken at the same time as the XOI. Missed doses should not be taken later in the day (eg, in the afternoon or evening) or made up on the following day. Subjects should be instructed to drink 2 liters (68 oz) of liquid a day.

Other Study Treatments, Dose, and Mode of Administration:

Commercially available XOI (allopurinol or febuxostat) tablets will be provided at the stable dose that subjects were taking at Screening.
Dose: the dose and dosing regimen of XOI should not be changed during the study, unless decreased for toxicity.

Commercially available gout flare prophylaxis, colchicine, will be provided through the Month 6 study visit. The dose will be 0.5 or 0.6 mg qd based on the local label. The frequency may be adjusted based on the local label, medical history of the subject, and clinical judgement (ie, taken every other day or 3 times a week if needed as appropriate, particularly for subjects with lower eCrCl). Subjects unable to take colchicine are permitted to take low-dose oral corticosteroids (ie, ≤10 mg/day of prednisone, or prednisolone, or their equivalent) for a short course, such as through the Month 3 study visit based on the Investigator's discretion.

Duration of Study and Treatment:

The overall duration of the study is anticipated to be approximately 5 years. The total duration of study participation for each subject (from Screening Visit 1 through the last study visit) is anticipated to be up to approximately 26 months.

Criteria for Evaluation:

Study Assessments:

Safety assessments will include an evaluation of AEs with particular focus on renal and CV events, clinical laboratory parameters (hematology, serum chemistry, urinalysis), and vital signs.

Efficacy assessments will be based on an evaluation of sUA levels. Additional efficacy assessments will explore gout flares, tophi resolution, and patient-reported outcomes (eg, EuroQol Five Dimensions Questionnaire 3 level, Sheehan Disability Score, and Work Productivity and Activity Impairment Questionnaire: Specific Health Problem).

Other assessments will include physical examinations and electrocardiograms (ECGs), as well as collecting medical history, Baseline gout characteristics, previous and concomitant therapies, and treatment compliance.

Safety Endpoints

- Absolute and percent change from Baseline in eCrCl to Month 24.

- Absolute and percent change from Baseline in eCrCl over the study period, including the last value on and off treatment.
- Incidence of serum creatinine (sCr) elevations (≥1.5 × Baseline) over the study period.
- Incidence of subjects meeting criteria (eg, based on sCr or eCrCl criteria) for treatment discontinuations over the study period.
- Incidence of renal-related and kidney stone treatment-emergent AEs (TEAEs) and serious AEs (SAEs).
- Prevalence of contributing factors to renal SAEs as adjudicated by the REAC.
- Incidence of CEAC-adjudicated Major Adverse Cardiovascular Event (MACE; CV death, nonfatal myocardial infarction, and nonfatal stroke).
- Incidence of CEAC-adjudicated MACE or hospitalization for unstable angina (MACE+).

Efficacy Endpoints

- Key efficacy endpoint: Proportion of subjects who achieve sUA <6.0 mg/dL at Month 6.
- Absolute and percent change from Baseline in sUA at each visit.
- Proportions of subjects who achieve sUA <6.0 mg/dL at each visit.

Exploratory Endpoints

- Percent change from Baseline in the sum of the areas of all target tophi at scheduled visits, among subjects with ≥1 target tophus at Baseline.
- Proportion of subjects who experienced complete resolution of at least 1 target tophus at any time during study, among subjects with ≥1 target tophus at Baseline.
- Functional impairment as assessed employing the Sheehan Disability Scale (individual domains as well as total functional impairment) at last on-study visit.
- Work productivity as assessed employing the Work Productivity and Activity Impairment Questionnaire: Specific Health Problem (absenteeism, presenteeism, work productivity loss, and activity impairment) at last on-study visit.
- Health status as assessed employing the EuroQol Five Dimensions Questionnaire 3 level (both descriptive system and visual analogue scale) at last on-study visit.
- Proportion of subjects with gout flares at each 3-month interval during the study period.

Statistical Methods:

The **Intent-to-Treat (ITT) Population** will be defined as all randomized subjects who received at least 1 dose of IP (lesinurad or placebo). This will be the primary population for efficacy analyses and subjects will be analyzed based on the randomized treatment assigned.

The **Safety Population** will be defined as all randomized subjects who received at least 1 dose of IP (lesinurad or placebo). Subjects will be analyzed based on the randomized treatment assigned. Any major deviations from the randomized treatment assignment will be listed and considered

when interpreting the safety data.

The main estimands to address the safety objective are the absolute and percent changes from Baseline to Month 24 in eCrCl, assessed in the Safety Population, with treatment difference estimated using a mixed model repeated measures (MMRM) and missing data imputed separately for each treatment group assuming missing at random (MAR).

Absolute and percent changes from Baseline to Month 24 in eCrCl will be assessed using MMRM analysis that includes terms for treatment (lesinurad [LESU] + XOI and placebo [PBO] + XOI), visit, treatment by visit interaction, stratification factors (type of XOI [allopurinol or febuxostat], Baseline measurable target tophi status [present/absent], and Screening eCrCl [30.0 to <45.0 mL/min or 45.0 to <60.0 mL/min], as appropriate), and Baseline eCrCl as covariates. The model will assume an unstructured covariance matrix. Least-square (LS) mean by treatment and LS mean difference between LESU + XOI and PBO + XOI alone will be estimated from the MMRM analysis, along with the 95% confidence interval (CI) of LS mean difference.

All subjects should be followed for safety events even if they discontinue IP (lesinurad or placebo), as permitted. Prior to performing MMRM analysis, renal function data that are collected after subjects discontinue IP will be set to missing. All missing data will be imputed using multiple imputation methodology assuming MAR and separate imputation models for the LESU + XOI and PBO + XOI groups. Sensitivity analysis will include all available data (including data after subjects discontinue IP) and impute only for missing data assuming MAR. Additional sensitivity analysis will be performed using multiple imputation assuming missing not at random, depending on the nature of missing data and early treatment discontinuations (eg, subjects discontinuing early due to worsening renal function).

Proportion and exposure-adjusted incidence rate analyses will be performed for both renal (including renal-related and kidney stone AEs) and CV outcomes. For exposure-adjusted incidence rate analyses, both on-treatment and on-study exposure will be calculated. In addition, time-to-event for MACE will be analyzed using Cox proportional hazard model.

All safety data will be listed and summarized by treatment group. All TEAEs will be coded and tabulated by Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class and preferred term. Similar methods for estimating proportions and exposure-adjusted incidence rates of TEAE, SAEs, and TEAEs leading to permanent discontinuation of IP will be applied. Changes from Baseline in laboratory and other safety parameters will be summarized and marked abnormalities will be noted.

Efficacy data will be summarized and analyzed in the ITT population. The key sUA efficacy endpoint (proportion of subjects with sUA <6.0 mg/dL at Month 6) will be summarized descriptively by treatment group and a comparison of the response rates will be presented using the Cochran Mantel Haenszel (CMH) test statistic, stratified by type of XOI, Baseline measurable target tophus status (present/absent), and Screening eCrCl (30.0 to <45.0 mL/min or 45.0 to <60.0 mL/min), as appropriate. Results will be expressed as proportions, corresponding adjusted 95% CI of the difference between response rates, and p-values. Subjects who are missing their Month 6 sUA results will be analyzed as non-responders. The key efficacy endpoint will be tested hierarchically, first in the overall study population at two-sided alpha level of 0.05; if successful, then it will be tested in the subset of subjects whose Screening eCrCl

is 30.0 to <45.0 mL/min at two-sided alpha level of 0.05.

Determination of Sample Size

Approximately 600 subjects will be randomized in a 1:1 ratio to either the LESU + XOI or PBO + XOI group in this study.

For safety endpoint analyses, this sample size provides sufficient precision around the estimated between-treatment difference for the absolute and percent changes in eCrCl from Baseline to Month 24 based on the normal distribution CI with 95% two-sided confidence level. For the difference in absolute change from Baseline to Month 24, the estimated precision is ±1.6 mL/min assuming a common standard deviation (SD) for the change from Baseline in each treatment group of 10 mL/min estimated from the lesinurad Phase 3 development program. For the difference in percent change from Baseline to Month 24, the estimated precision is ±3.2% assuming a common SD for the percent change from Baseline in each treatment group of 20% estimated from the lesinurad Phase 3 development program. For the key efficacy endpoint analyses, this sample size will provide >90% power for the overall population and >80% power within each Screening eCrCl stratum to detect a treatment difference for the proportion of subjects achieving sUA <6.0 mg/dL at Month 6 of 15% (20% in the PBO + XOI group versus 35% in the LESU + XOI group, as estimated from the lesinurad Phase 3 development program), using a binomial distribution at an alpha of 0.05 (two-sided).

Date of Protocol Version 3: 21 June 2017

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ACR	American College of Rheumatology
ADR	adverse drug reaction
AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
bid	twice daily
BMI	body mass index
CEAC	Cardiovascular Endpoints Adjudication Committee
CI	confidence interval
CMH	Cochran-Mantel Haenszel
CRF	Case Report Form
CTM	Clinical Trials Material
CV	Cardiovascular
CYP	cytochrome P450
EC	Ethics Committee
eCrCl	estimated creatinine clearance
ECG	Electrocardiogram
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
EQ-5D	EuroQol Five Dimensions Questionnaire
EQ-5D-3L	EQ-5D 3 level
EU	European Union
EULAR	European League Against Rheumatism
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice

HCG	human chorionic gonadotropin
HDPE	high-density polyethylene
HIV	human immunodeficiency virus
HMG-CoA	3-hydroxy-3-methyl-glutaryl-coenzyme A
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IDMC	independent Data Monitoring Committee
IEC	Independent Ethics Committee
IP	investigational product
IRB	Institutional Review Board
ITT	Intent-to-Treat
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
JNC8	Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure
LESU	lesinurad
LS	least-square
MACE	Major Adverse Cardiovascular Event
MACE+	MACE or hospitalization for unstable angina
MAR	missing at random
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed model repeated measures
NSAID	nonsteroidal anti-inflammatory drug
OAT	organic anion transporter
PBO	Placebo
P-gp	P-glycoprotein
qd	once daily

REAC	Renal Events Adjudication Committee
RCTC	Rheumatology Common Toxicity Criteria
SAE	serious adverse event
SAP	Statistical Analysis Plan
sCr	serum creatinine
SD	standard deviation
SDS	Sheehan Disability Scale
SmPC	Summary of Product Characteristics
sUA	serum urate (also referred to as serum uric acid)
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
ULT	urate-lowering therapy
URAT1	uric acid transporter 1
US	United States
USPI	United States Product Insert
VAS	visual analogue scale
WPAI:SHP	Work Productivity and Activity Impairment Questionnaire: Specific Health Problem
XOI	xanthine oxidase inhibitor

1. INTRODUCTION

1.1. Background

Lesinurad 200 mg tablets were approved by the United States (US) Food and Drug Administration (FDA) in December 2015 and by the European Medicines Agency (EMA) in February 2016 for use in combination with a xanthine oxidase inhibitor (XOI; allopurinol or febuxostat) for the chronic treatment of hyperuricemia associated with gout in patients who have not achieved target serum uric acid (sUA) levels with an XOI alone.

Lesinurad is a selective uric acid reabsorption inhibitor that inhibits uric acid transporter 1 (URAT1), which is responsible for the majority of the reabsorption of filtered uric acid from the renal tubular lumen (Reginato 2012, So 2010). By inhibiting URAT1, lesinurad increases uric acid excretion and thereby lowers sUA. Lesinurad also inhibits organic anion transporter 4 (OAT4), a uric acid transporter involved in diuretic-induced hyperuricemia (Handler 2010). Xanthine oxidase inhibitors act by reducing the production of uric acid, primarily in the liver and intestine. Combination therapy with lesinurad and an XOI targets both excretion (lesinurad) and production (XOI) of uric acid, providing a dual-mechanism approach to effectively lower sUA.

This post-marketing study is a randomized, double-blind, placebo-controlled study to evaluate safety (with particular focus on renal and cardiovascular [CV] events) and efficacy of lesinurad 200 mg once daily (qd) in combination with an XOI for up to 24 months compared with XOI monotherapy, in subjects with gout and moderate renal impairment who have not reached target sUA levels (<6.0 mg/dL) on an XOI alone.

For the purpose of this document, “investigational product (IP)” is defined as lesinurad or matching placebo. “Study medication” is defined as study-supplied medications, which may include lesinurad or matching placebo, allopurinol or febuxostat, and colchicine.

1.2. Known and Potential Benefits and Risks of Study Medication

1.2.1. Known and Potential Benefits and Risks With Lesinurad in Combination With Xanthine Oxidase Inhibitors

As of 31 December 2016, more than 2600 subjects had been exposed to lesinurad in clinical trials. The maximum duration of exposure was approximately 700 days for lesinurad monotherapy, 1,500 days for lesinurad in combination with febuxostat, and 3,100 days for lesinurad in combination with allopurinol.

In 3 pivotal Phase 3, randomized, placebo-controlled studies of 12-month duration, lesinurad 200 mg qd in combination with an XOI (allopurinol or febuxostat) demonstrated clinically meaningful and statistically significant added benefit compared with an XOI alone. When added to allopurinol in subjects with gout who were inadequate responders to an XOI alone (Studies RDEA594-301 and RDEA594-302), lesinurad provided rapid, stable, and sustained sUA lowering resulting in approximately twice as many subjects achieving the target goal of sUA <6.0 mg/dL. When added to febuxostat in subjects with tophaceous gout (Study RDEA594-304), lesinurad provided rapid, stable, and sustained sUA lowering with significantly more subjects achieving sUA <5.0 mg/dL, <4.0 mg/dL, and <3.0 mg/dL. In addition to superior sUA lowering,

nearly twice the reduction in the total area of target tophi was seen with lesinurad in combination with febuxostat, compared with febuxostat alone in Study RDEA594-304.

Overall, lesinurad 200 mg qd in combination with an XOI was generally well tolerated with a similar adverse event (AE) profile to that observed with an XOI alone. Most treatment-emergent adverse events (TEAEs) were Grade 1 or 2 in severity and resolved while continuing lesinurad therapy. The most common TEAEs reported with lesinurad 200 mg in combination with an XOI were generally comparable to XOI alone. The following adverse drug reactions (ADRs) have been identified: influenza, headache, gastroesophageal reflux disease, renal failure, renal impairment, nephrolithiasis, and blood creatinine increased.

A detailed analysis of renal safety in the pivotal Phase 3 combination therapy studies showed that lesinurad was associated with transient increases in serum creatinine (sCr). These sCr elevations generally resolved, most without treatment interruption. The incidence of renal-related serious TEAEs was low (≤1%), and the exposure-adjusted rates were not increased following long-term exposure during the extension studies.

In the pivotal Phase 3 combination therapy studies, overall rates of adjudicated Major Adverse CV Events (MACE) and of Investigator-reported CV-related AEs, AEs leading to discontinuation of IP, and serious AEs (SAEs) were low. The incidence of MACE was comparable for lesinurad 200 mg in combination with an XOI (4 subjects) and XOI alone (3 subjects). The small number of MACE observed in the pooled analysis of data from the pivotal Phase 3 combination therapy studies places limitations on assessment of treatment-associated differences in MACE risk.

Refer to the lesinurad Investigator's Brochure (IB) for more information on lesinurad.

1.2.2. Known and Potential Benefits and Risks With Xanthine Oxidase Inhibitors

Subjects must be on a stable, medically appropriate dose of XOI, which are recommended as the first line treatment for hyperuricemia associated with gout (Khanna 2012, Zhang 2006).

Allopurinol, approved in 1966 in the United States, is the most commonly used XOI. With allopurinol as a monotherapy, the most common AE is skin rash. Skin reactions may be severe and can be fatal. Other common AEs include diarrhea, nausea, and elevation in liver function tests (alkaline phosphatase, alanine aminotransferase [ALT], and aspartate aminotransferase [AST]). Furthermore, some allopurinol toxicities appear to be dose related, such as nausea, diarrhea, Stevens-Johnson syndrome, and toxic epidermal necrolysis (Chao 2009, Halevy 2008).

Febuxostat, approved in 2009, is another XOI approved for the chronic management of hyperuricemia in patients with gout. The approved dosing in the US is 40 to 80 mg qd, and the approved dosing in the European Union (EU) is 80 to 120 mg qd. With febuxostat as monotherapy, a higher rate of CV thromboembolic events was seen in clinical studies, although a causal relationship has not been established. There have been reports of liver failure (some resulting in death) and rhabdomyolysis in patients taking febuxostat. Other AEs occurring in > 1% of febuxostat-treated patients included liver function abnormalities, nausea, arthralgia, and rash (Uloric [US package insert] Rev March 2013, Febuxostat 80 mg Tablets [SmPC] Rev December 2012).

The local product label for allopurinol (Allopurinol [US package insert] Rev July 2015, Allopurinol 100 mg Tablets [SmPC] Rev February 2013) and febuxostat (Uloric [US package

insert] Rev March 2013, Febuxostat 80 mg Tablets [SmPC] Rev December 2012) should be consulted for detailed information regarding contraindications, warnings and precautions, drug interactions, dosage adjustment and patient monitoring recommendations, and use in special patient populations.

1.2.3. Known and Potential Benefits and Risks With Colchicine

As many as 80% of patients experience an acute gout flare with initiation or increase in dose of urate lowering therapy (ULT) (Borstad 2004). Per the American College of Rheumatology (ACR), European League Against Rheumatism (EULAR), and British Society of Rheumatology treatment guidelines, gout flare prophylaxis is recommended to reduce the potential for acute gout flares that can occur with the initiation of ULT (Khanna 2012, Zhang 2006). The EULAR guidelines note that evidence to support the use of low-dose colchicine for prophylaxis of acute attacks when beginning ULT is reasonable. As such, subjects in this study should take colchicine for gout flare prophylaxis during approximately the first 6 months on study.

Although generally well tolerated, low-dose colchicine has been associated with AEs such as diarrhea, abdominal pain, nausea, and vomiting. Rarely, more severe AEs such as myopathy, neuropathy, and myelosuppression have been reported with colchicine use. The local product label for colchicine should be consulted for detailed information regarding contraindications, warnings and precautions, drug interactions (eg, P-gp or strong/moderate CYP3A4 inhibitors, or 3-hydroxy-3-methyl-glutaryl-coenzyme A [HMG-CoA] reductase inhibitors, or digitalis glycosides, see Section 7.1.3), dosage adjustment and patient monitoring recommendations, and use in special patient populations. Subjects unable to tolerate or that have known contraindications to colchicine will have the option of taking low-dose oral corticosteroids for gout flare prophylaxis. This alternative is also recommended by the ACR treatment guidelines (Khanna 2012).

1.3. Rationale for Study Design and Dose Selection

The efficacy and safety of lesinurad 200 mg qd in combination with an XOI (allopurinol or febuxostat) were demonstrated in 3 pivotal Phase 3 studies. The Phase 3 studies included subjects with normal renal function and those with mild to moderate renal impairment (estimated creatinine clearance [eCrCl] ≥30 mL/min). Subjects with eCrCl <30 mL/min were excluded. Among the limited number of subjects with moderate renal impairment (eCrCl 30 to <60 mL/min; N=294), including those with eCrCl 30 to <45 mL/min (N=84), lesinurad 200 mg in combination with an XOI demonstrated a consistent safety and efficacy profile irrespective of Baseline renal function of eCrCl ≥30 mL/min. Lesinurad 200 mg in combination with an XOI has been approved in the US and EU for the treatment of hyperuricemia associated with gout in patients who have not achieved target serum uric acid levels with an XOI alone.

This Phase 4 randomized, double-blind, placebo-controlled study is designed to provide additional safety and efficacy data with lesinurad 200 mg plus XOI in the important subgroup of subjects with gout and moderate renal impairment who have not achieved the target sUA level <6.0 mg/dL on a medically appropriate dose of an XOI alone. Long-term safety, particularly renal safety, over a 24 month Treatment Period will be assessed. Eligible subjects are required to have an eCrCl 30.0 to <60.0 mL/min and be on a stable, medically appropriate dose of XOI for at least 4 weeks prior to Screening and throughout the Screening Period with sUA levels above

target. The minimum Baseline dose of allopurinol permitted is 200 mg daily; the minimum Baseline dose of febuxostat is the lowest approved dose per the local product label. The maximum dose of each XOI permitted is the highest approved dose per the local product label. Eligible subjects will be randomized to receive lesinurad 200 mg (the dose approved by FDA and EMA) or placebo in combination with their prescribed XOI for up to 24 months. Per the ACR, EULAR, and British Society of Rheumatology treatment guidelines, gout flare prophylaxis is also recommended to reduce the potential for acute gout flares that can occur with the initiation of ULTs (Khanna 2012, Zhang 2006). In this study, subjects are required to take colchicine for gout flare prophylaxis from the Baseline Visit (1 day before starting IP) through their Month 6 study visit as long as they are on IP during this period (Khanna 2012). Subjects who have a documented intolerance or allergy to colchicine or who are taking a concomitant medication contraindicated for use with colchicine are permitted to take low-dose oral corticosteroids (ie, defined as ≤10 mg/day of prednisone, or prednisolone, or their equivalent) for a short course, such as through the Month 3 study visit. Nonsteroidal anti-inflammatory drugs (NSAIDs) for gout flare prophylaxis will not be permitted due to the potential for nephrotoxicity.

The primary objective of this study is to better understand the safety profile of lesinurad 200 mg in combination with an XOI in subjects with moderate renal impairment, focusing on renal safety. Safety endpoints include analyses of absolute and percent change from Baseline in renal function with treatment over a 24 month period and the incidence of renal-related, kidney stone, and CV AEs. The key efficacy endpoint is the proportion of subjects achieving sUA levels of <6.0 mg/dL at Month 6. This sUA target is below the saturation point for monosodium urate and is recommended by the current ACR and EULAR treatment guidelines for ULTs to treat hyperuricemia in order to promote crystal dissolution and prevent crystal formation (Richette 2014, Khanna 2012, Jordan 2007).

2. STUDY OBJECTIVES

The objectives of this study are as follows:

Primary Objective:

- To evaluate the safety over 24 months of lesinurad 200 mg once daily (qd) when used in combination with a xanthine oxidase inhibitor (XOI), compared with XOI alone, in subjects with gout and moderate renal impairment (estimated creatinine clearance 30 to <60 mL/min) who have not reached target serum uric acid (sUA) levels on an XOI alone.

Efficacy Objective:

- To evaluate the efficacy over 24 months of lesinurad 200 mg qd in combination with an XOI, compared with XOI alone, in subjects with gout and moderate renal impairment who have not reached target sUA levels on an XOI alone.

3. INVESTIGATIONAL PLAN

3.1. Overall Study Design and Plan

This study will be conducted in up to approximately 300 sites in North America and Europe. Subjects with gout, moderate renal impairment, and who are not at target sUA of <6.0 mg/dL on XOI alone will be enrolled. The study will include an approximate 1-month Screening Period, a 24-month Double-Blind Treatment Period, and a 1-month post-treatment Follow-Up Period.

To be eligible for the study, subjects must be on a stable, medically appropriate dose of XOI as their sole ULT indicated for the treatment of gout for at least 4 weeks prior to Screening and throughout the Screening Period. Investigators should have followed the treatment guidelines to determine the medically appropriate dose of XOI. During the Screening Period, subjects will complete 2 Screening Visits: Screening Visit 1 (approximately 1 month before the Baseline Visit) and Screening Visit 2 (3 weeks after Screening Visit 1 [±3 days]). To be eligible for the study, estimated creatinine clearance (eCrCl; calculated by the Cockcroft-Gault formula using ideal body weight) must be 25.0 to ≤65.0 mL/min at each Screening Visit and the average eCrCl of both Screening Visits must be 30.0 to <60.0 mL/min, which is the Screening eCrCl. Additionally, subjects must have an sUA level ≥6.0 mg/dL (387 µmol/L) at both Screening Visits.

Subjects who qualify for the study will be randomized at the Baseline Visit (4 to 7 days after Screening Visit 2) in a double-blind fashion to 1 of 2 treatment groups in a 1:1 ratio:

- LESU + XOI: lesinurad 200 mg qd and XOI.
- PBO + XOI: placebo qd and XOI.

Randomization will be stratified by the Screening eCrCl subgroup (30.0 to <45.0 mL/min or 45.0 to <60.0 mL/min), Baseline measurable target tophus status (present/absent), and type of XOI (allopurinol or febuxostat). This study will enroll approximately 50% of subjects with eCrCl 30.0 to <45.0 mL/min and approximately 50% with eCrCl 45.0 to <60.0 mL/min. When the maximum number of subjects in one of the eCrCl subgroups has been reached, subsequent enrollment will be limited to subjects in the other eCrCl subgroup. There are no limitations on the number of subjects enrolled by type of XOI or Baseline tophus status.

After randomization at Baseline, subjects will be dispensed IP (lesinurad or placebo) and study-supplied XOI at the same dose as the subject's prescribed stable dose, which they will start the next day (Day 1). Subjects will take IP qd in combination with their stable dose of XOI for up to 24 months. Gout flare prophylaxis with colchicine is required from the Baseline Visit through the Month 6 study visit, while still on IP. Subjects who have a documented intolerance or allergy to colchicine or who are taking a concomitant medication contraindicated for use with colchicine (eg, P-glycoprotein [P-gp] or strong cytochrome P450 [CYP]3A4 inhibitors) are permitted to take low-dose oral corticosteroids (≤10 mg/day of prednisone, or prednisolone, or their equivalent) for a short course, such as through the Month 3 study visit. The use of NSAIDs for gout flare prophylaxis is not permitted. More information on gout flare prophylaxis dosing is provided in Section 5.3. In order to maintain the blind, post-Baseline sUA levels will remain

blinded to the sites, subjects, and study team; additional blinding information is provided in Section 5.5.

After initiating IP, subjects will return to the study site at Month 1 (±7 days), at Month 3 (±7 days), and every 3 months (±7 days) thereafter until the end of the Treatment Period (Month 24 ±7 days). Safety assessments will include an evaluation of AEs with particular focus on renal and CV events, clinical laboratory parameters (hematology, serum chemistry, urinalysis), and vital signs. Efficacy assessments will be based on an evaluation of sUA levels with assessments on tophus measurements, patient-reported outcomes, and gout flares.

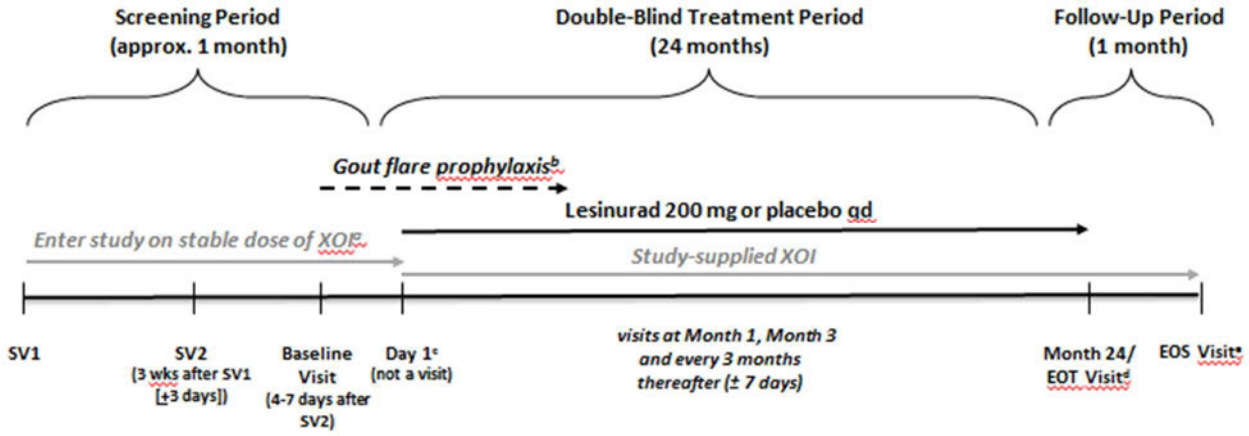
Subjects who permanently discontinue IP early should complete an End of Treatment Visit as soon as possible, followed by a Post-End of Treatment Visit 1 month after the End of Treatment Visit where all AEs must be recorded. Subjects should then continue on study (and may remain on their study-supplied XOI) and follow the protocol-defined schedule of events, including the End of Study Visit.

All subjects who complete the Treatment Period or who plan to withdraw early from the study should complete the End of Study Visit approximately 1 month after IP is completed or discontinued.

An independent Data Monitoring Committee (IDMC) will be appointed by the Sponsor and will evaluate the safety data periodically to protect subject welfare and to identify potential safety signals. An independent Cardiovascular Endpoints Adjudication Committee (CEAC) will routinely assess all SAEs and other prospectively-defined AEs for CV related events. An independent Renal Events Adjudication Committee (REAC) will routinely evaluate and categorize all serious prospectively-defined renal-related and kidney stone AEs, and any additional SAEs deemed by the REAC Chair to be relevant for adjudication, and will assess the likelihood that potential contributing factors, including IP, contributed to the event.

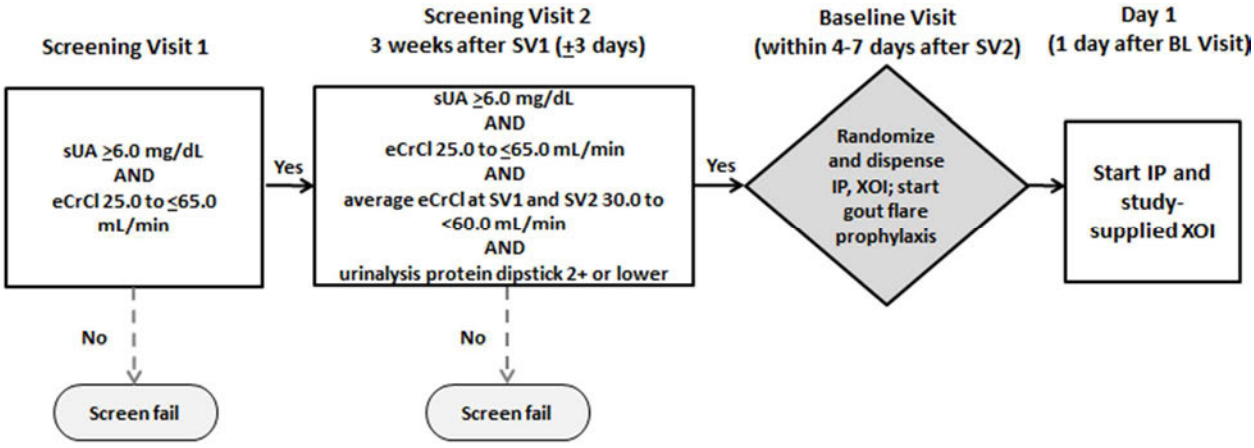
Figure 1 presents the overall study design scheme. Figure 2 presents the laboratory eligibility criteria during the Screening Period.

Figure 1: Overview of Study Design Scheme



Abbreviations: EOS, End of Study; EOT, End of Treatment; qd, once daily; SV, Screening Visit; wk, week; XOI, xanthine oxidase inhibitor.
Note: A clinical month is considered to be 28 days.
[a] Subjects will enter the study on a stable, medically appropriate dose of XOI (allopurinol or febuxostat) for at least 4 weeks prior to Screening and throughout the Screening Period and will continue this dose (study-supplied after Baseline) throughout the study.
[b] Gout flare prophylaxis, colchicine, will be taken through the Month 6 study visit as tolerated. If low-dose corticosteroids are used as gout flare prophylaxis, the course may be through the Month 3 study visit.
[c] Subjects will start investigational product (lesinurad/placebo) and study-supplied XOI on Day 1 (1 day after the Baseline Visit). Day 1 is not a study visit. Gout flare prophylaxis may be started at the Baseline Visit.
[d] Subjects who permanently discontinue lesinurad/placebo early should complete an EOT Visit as soon as possible followed by a Post-End of Treatment Visit 1 month later. Subjects should then continue to follow the protocol-defined schedule of events.
[e] Subjects who complete the study or plan to withdraw from the study early should complete an EOS Visit approximately 28 days after study treatment completion or discontinuation.

Figure 2: Laboratory Eligibility Requirements



Abbreviations: BL, Baseline; eCrCl estimated creatinine clearance; IP, investigational product; sUA, serum uric acid; SV, Screening Visit; XOI, xanthine oxidase inhibitor.

3.2. Study Endpoints

3.2.1. Safety Endpoints

- Absolute and percent change from Baseline in eCrCl to Month 24.
- Absolute and percent change from Baseline in eCrCl over the study period, including the last value on and off treatment.
- Incidence of sCr elevations (≥1.5 × Baseline) over the study period.
- Incidence of subjects meeting criteria (eg, based on sCr or eCrCl criteria) for treatment discontinuations over the study period.
- Incidence of renal-related and kidney stone TEAEs and SAEs.
- Prevalence of contributing factors to renal SAEs as adjudicated by the REAC.
- Incidence of CEAC-adjudicated MACE (CV death, nonfatal myocardial infarction, and nonfatal stroke).
- Incidence of CEAC-adjudicated MACE or hospitalization for unstable angina (MACE+).

3.2.2. Efficacy Endpoints

- Key efficacy endpoint: Proportion of subjects who achieve sUA <6.0 mg/dL at Month 6.
- Absolute and percent change from Baseline in sUA at each visit.
- Proportions of subjects who achieve sUA <6.0 mg/dL at each visit.

The efficacy endpoints will be repeated by Baseline eCrCl subgroups.

3.2.3. Exploratory Endpoints

- Percent change from Baseline in the sum of the areas of all target tophi at scheduled visits, among subjects with ≥1 target tophus at Baseline.
- Proportion of subjects who experienced complete resolution of at least 1 target tophus at any time during study, among subjects with ≥1 target tophus at Baseline.
- Functional impairment assessed employing the Sheehan Disability Scale (SDS; individual domains as well as total functional impairment) at last on-study visit.
- Work productivity as assessed employing the Work Productivity and Activity Questionnaire: Specific Health Problem (WPAI:SHP; absenteeism, presenteeism, work productivity loss, and activity impairment) at last on-study visit.
- Health status as assessed employing the EuroQol Five Dimensions Questionnaire 3 level (EQ-5D-3L; both descriptive system and visual analogue scale) at last on-study visit.
- Proportion of subjects with gout flares at each 3-month interval during the study period.

3.3. Study Duration

The overall duration of the study is anticipated to be approximately 5 years. The total duration of study participation for each subject (from Screening Visit 1 through the last study visit) is anticipated to be up to approximately 26 months.

For regulatory reporting purposes, the end of the study is defined as the date of the last subject's last assessment (scheduled or unscheduled).

4. STUDY POPULATION SELECTION

4.1. Study Population

Approximately 600 subjects will be enrolled (300 per treatment group).

4.2. Inclusion Criteria

Each subject must meet the following criteria to be enrolled in this study.

1. Subject is able to understand the study procedures, the risks involved, and willing to provide written informed consent before the first study related activity.
2. Subject is willing to adhere to the protocol schedule.
3. Subject is ≥18 years and ≤85 years of age.
4. Subject has a diagnosis of gout.
5. Subject has moderate renal impairment with estimated creatinine clearance (eCrCl calculated by the Cockcroft-Gault formula using ideal body weight) 25.0 to ≤65.0 mL/min at Screening Visits 1 and 2 and an average eCrCl for both screening visits of 30.0 to <60.0 mL/min.
6. Subject has been taking an XOI as urate-lowering therapy (ULT) indicated for the treatment of gout for at least 4 weeks prior to Screening at a stable, medically appropriate dose, as determined by the Investigator. The minimum dose of allopurinol is 200 mg daily, and the minimum dose of febuxostat is the lowest approved dose per the local product label.
7. Subject has a serum uric acid level ≥6.0 mg/dL (357 μmol/L) at Screening Visits 1 and 2.
8. Subject is male or female; females must not be pregnant or breastfeeding and females of childbearing potential must agree to use non-hormonal contraception during the Screening Period and while taking IP.
9. Subject has a body mass index <45 kg/m^2.

4.3. Exclusion Criteria

Subjects who meet the following criterion will be excluded from the study:

1. Subject had unstable angina, New York Heart Association class III or IV heart failure, myocardial infarction, or stroke within the last 6 months prior to randomization; or had a deep venous thrombosis within the previous 3 months prior to randomization.
2. Subject has uncontrolled hypertension (defined as systolic pressure above 160 or diastolic pressure above 95 mm Hg at either Screening Visits 1 or 2).
3. Subject has severe hepatic impairment (defined as Child-Pugh Class C) or is known human immunodeficiency virus (HIV) positive.
4. Subject is a solid organ transplant recipient.

5. Subject has a urine protein of 3+ or higher by dipstick by the central laboratory at Screening Visit 2.
6. Subject has a history of glomerulonephritis.
7. Subject is taking valpromide, progabide, valproic acid, or other known inhibitors of epoxide hydrolase, or subject is taking ranolazone, cyclosporine, azathioprine or mercaptopurine.
8. Subject is receiving chronic treatment with more than 325 mg of salicylates per day.
9. Subject is unable to initiate gout flare prophylaxis with colchicine or low-dose oral corticosteroids at Baseline.
10. Subject is taking any other drug approved for use as a urate-lowering medication other than allopurinol or febuxostat (eg, pegloticase, probenecid, benzbromarone) within 4 weeks prior to Screening or during Screening.
11. For subjects who will be taking colchicine for gout flare prophylaxis: Subject is taking, or anticipated to take during the first 6 months on study, moderate or strong CYP3A inhibitors (ie, verapamil or diltiazem, clarithromycin, and fluconazole; see Section 7.1.3 for more details) or grapefruit or grapefruit juice.
12. Subject previously participated in a clinical study involving lesinurad (RDEA594) or verinurad (RDEA3170) and received active treatment or placebo, or has taken commercially-available lesinurad.
13. Subject has a gout flare during the Screening Period.
14. Subject is pregnant or breastfeeding.
15. Subject consumes more than 14 drinks of alcohol per week (eg, 1 drink = 5 oz [150 mL] of wine, 12 oz [360 mL] of beer, or 1.5 oz [45 mL] of hard liquor).
16. Subject has a history of malignancy and has been on active treatment within the previous 5 years prior to randomization with the exception of non-melanoma skin cancer, treated in situ Grade 1 cervical cancer, or treated ductal carcinoma in situ of the breast.
17. Subject has been hospitalized (other than for elective surgery) or received intravenous contrast (eg, for CT scan or any angiography) within 1 month prior to Screening or during Screening.
18. Subject has participated in a clinical trial within 8 weeks prior to Screening.
19. Subject has any other medical or psychological condition, which in the opinion of the Investigator 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.
20. The maximum number of subjects in the eCrCl stratification subgroup has been reached.

5. STUDY TREATMENT

All subjects will receive IP (lesinurad or matching placebo) and study-supplied XOI (allopurinol or febuxostat), which must be taken in combination. All subjects will also receive colchicine as gout flare prophylaxis through their Month 6 study visit as tolerated. Subjects unable to take colchicine (described in Section 5.2.2.) are permitted to take a short course of low-dose oral corticosteroids.

5.1. Description of Investigational Product

5.1.1. Lesinurad

Lesinurad will be supplied as 200 mg tablets in 100-count high-density polyethylene (HDPE) bottles with induction seals and screw-on polypropylene closures. Lesinurad 200 mg tablets are blue, oval shaped tablets.

5.1.2. Placebo Comparator

Placebo tablets matching the lesinurad 200 mg tablets will be provided by the Sponsor in 100-count HDPE bottles with induction seals and screw-on polypropylene closures.

5.2. Other Study Treatments

Commercially available allopurinol, febuxostat, and colchicine drug product will be used. The relevant product labeling will be provided to Investigators.

5.2.1. Xanthine Oxidase Inhibitors

XOI (allopurinol or febuxostat) tablets will be provided at Baseline based on the individual subject's stable dose during screening. The minimum Baseline dose of allopurinol permitted is 200 mg daily; the minimum Baseline dose of febuxostat is the lowest approved dose per the local product label. The maximum dose of each XOI permitted is the highest approved dose per the local product label. The dose and dosing regimen of XOI should not be changed during the study, unless decreased for toxicity.

5.2.2. Gout Flare Prophylaxis

Gout flare prophylaxis, colchicine, will be provided through the Month 6 study visit. The dose of colchicine will be 0.5 or 0.6 mg qd based on the local label. The frequency may be adjusted based on the local label, medical history of the subject, and clinical judgement (ie, dosed every other day or 3 times a week if needed as appropriate, particularly for subjects with lower eCrCl).

Subjects unable to take colchicine (ie, those who have a documented intolerance or allergy to colchicine or who are taking a concomitant medication contraindicated for use with colchicine [eg, P-gp or strong/moderate CYP3A4 inhibitors, see Section 7.1.3]) are permitted to take low-dose oral corticosteroids (ie, ≤10 mg/day of prednisone, or prednisolone, or their equivalent) for a short course, such as through the Month 3 study visit, at the discretion of the Investigator. The steroid regimen should be individualized for each subject based on the need for gout flare

prophylaxis and potential side effects of persistent corticosteroid use, such as in relation to comorbid conditions.

If IP is permanently discontinued prior to the end of the gout flare prophylaxis period, the gout flare prophylaxis should be discontinued. If IP is interrupted and re-initiated, subjects can re-initiate gout flare prophylaxis at the discretion of the Investigator. Investigators should consider reinitiating gout flare prophylaxis based on the clinical circumstances.

The use of NSAIDs for gout flare prophylaxis is not permitted.

5.3. Selection and Timing of Dose for Each Subject

5.3.1. General Instructions for Dosing

Lesinurad 200 mg once daily is the currently approved dose by the FDA and EMA and is under evaluation in this study. Only doses of XOI that are approved by the local product labels are permitted in this study.

All doses of IP should be taken daily, in the morning with food and 1 cup (8 oz; 240 mL) of water. Subjects should be instructed to drink 2 liters (68 oz) of liquid a day. For example, another 3 cups (24 oz; 720 mL) of liquid during the 3 to 4 hours after taking the IP should be encouraged, and then the subject should remain well hydrated (an additional 4 cups [32 oz; 960 mL] of liquid) throughout the day.

IP must be taken at the same time as the morning dose of XOI. Missed doses of IP should not be taken later in the day (eg, in the afternoon or evening) or made up on the following day.

Subject should take gout flare prophylaxis, colchicine, from the Baseline Visit until their Month 6 study visit as long as they are still on IP. Colchicine will be provided. In the US, colchicine 0.6 mg qd or twice daily (bid) is recommended for subjects with eCrCl >45 mL/min and qd to once every other day for subjects with eCrCl <45 mL/min (Colcrys [US package insert] Rev December 2016). Based on medical history and the clinical judgement of the Investigator, decreasing the frequency to once every other day (or 3 times per week) is permitted. In the EU, colchicine 0.5 mg qd or bid is recommended. For patients with mild/moderate renal impairment (creatinine clearance 10 to 50 mL/min), the prescribing information recommends to reduce the dose or increase the interval between doses (Colchicine 500 micrograms Tablets [SmPC] Rev October 2015), such as decreasing to once every other day or every other day (3 times a week). Subjects who have a documented intolerance or allergy to colchicine or who are taking a concomitant medication contraindicated for use with colchicine (eg, P-gp or strong or moderate CYP3A4 inhibitors; see Section 7.1.3) are permitted to take low-dose oral corticosteroids (≤10 mg/day of prednisone, or prednisolone, or their equivalent) for a short course, such as through the Month 3 study visit, at the discretion of the Investigator. NSAIDs for gout flare prophylaxis will not be permitted due to the potential for nephrotoxicity.

Study site staff should refer to the local product labels for a description and complete prescribing information on XOI and gout flare prophylaxis.

5.3.2. Dose Adjustments, Interruptions, and Discontinuations

IP, XOI, and gout flare prophylaxis should not be interrupted or discontinued if a subject experiences an acute gout flare.

5.3.2.1. Investigational Product and Xanthine Oxidase Inhibitors

IP (lesinurad or placebo) is only permitted at 200 mg qd. No dose reductions or dose escalations of IP are permitted. The prescribed dose and dosing regimen of XOI should also be continued unchanged throughout the study, unless adjusted for toxicity. Study treatment (IP or XOI) may be interrupted due to AEs or for suspected toxicity.

If XOI is interrupted for any reason**, IP must be interrupted concurrently**. When medically appropriate, the XOI should be resumed, at which time IP may also be resumed. The XOI may be resumed at the same dose; lower doses (if available) are only permitted if the XOI had been interrupted due to a TEAE considered related to that XOI. If resumed at a lower dose, the XOI should be increased up to the original dose, as tolerated. Subjects should not be maintained on a dose of allopurinol <200 mg daily.

If IP is interrupted for any reason, the subject is permitted to continue XOI, as tolerated. When medically appropriate, IP should be resumed, but must only be resumed if the subject is taking XOI.

5.3.2.1.1. Interruption or Discontinuation of Investigational Product Due to Changes in Kidney Function

Kidney function will be monitored throughout the study by measuring sCr and calculating eCrCl by Cockcroft-Gault formula using ideal body weight. All clinically meaningful changes in kidney function should be evaluated and managed as medically appropriate, including interrupting IP and study medications if needed.

IP must be **temporarily interrupted** if a subject experiences an absolute sCr ≥4.0 mg/dL or an eCrCl <20 mL/min (based on central laboratory results), and the subject will be required to return to the site for retesting (see Section 6.12). IP may be resumed at the Investigator's discretion if eCrCl is within 15% of Baseline if this occurs through the Month 12 study visit, or if eCrCl is within 20% of Baseline if this occurs from the Month 12 study visit through the Month 24 study visit.

IP should be **permanently discontinued** if there are more than 3 episodes of interruption of IP due to any of the following:

- If the Investigator or Healthcare Provider temporarily interrupts IP due to changes in kidney function,
- If the Investigator or Healthcare Provider temporarily interrupts IP due to any safety concerns due to IP, or
- Protocol-specified criteria for interruption are met (ie, sCR ≥4.0 mg/dL or eCrCl <20 mL/min).

An episode is defined as the interruption and then re-initiation of IP, regardless of the duration of the interruption. The fourth interruption should be considered permanent when based on the above criteria.

5.3.2.1.2. Other Reasons, and Procedures, for Permanent Discontinuation of Investigational Product

As much as possible and permitted by the protocol, subjects should be encouraged to continue on IP for the full 24-month Treatment Period.

Subjects have the right to permanently discontinue IP at any time for any reason. Investigators may also discontinue IP if they determine that it is not in the best interest of the subject to continue. All subjects should be encouraged to remain in the study even if IP has been discontinued for any reason.

IP must be permanently discontinued if the subject meets any of the following criteria:

- Subject permanently discontinues XOI.
- Subject becomes pregnant.
- Subject initiates chronic therapy with any of the following medications:
  - valpromide, progabide, valproic acid, or other known inhibitors of epoxide hydrolase.
  - any approved ULT indicated for the treatment of gout (eg, benzbromarone, probenecid, pegloticase, commercially-available lesinurad), except those required per protocol (allopurinol and febuxostat).
  - azathioprine or mercaptopurine.
- Subject requires dialysis or kidney transplantation.
- Subject has temporarily interrupted IP for more than 3 separate episodes at any time on study due to changes in kidney function, based on any safety concern due to IP by the Investigator or Healthcare Provider, or where protocol-specified criteria for interruption have been met (ie, sCr ≥4.0 mg/dL or an eCrCl <20 mL/min).

The date and the reason must be recorded on the appropriate Case Report Form (CRF) for all subjects who discontinue IP. If the reason is an AE, the specific AE must be identified on the CRF.

Subjects who permanently discontinue IP early should complete an End of Treatment Visit (Section 8.3.3) as soon as possible followed by a Post-End of Treatment Visit (Section 8.4.1) 1 month after the End of Treatment Visit. Subjects should then continue on study and follow the protocol-defined schedule of events, through Month 24. The subject has the option to continue on study-supplied XOI during this time. Although all assessments are encouraged, at a minimum, it is requested that collection of AEs and collection of a blood sample for Analytes 1 (see Table 1) occur. Alternatively, if the subject does not agree to this option, a modified follow-up including, eg, regular telephone contacts or a contact at Month 24, should be arranged, if agreed to by the subject and in compliance with local data privacy laws/practices. Subjects who do not wish to continue on study after discontinuing IP should complete an End of Study Visit (Section 8.4.2) 1 month after treatment discontinuation.

If IP is permanently discontinued prior to the Month 6 study visit, then gout flare prophylaxis should also be discontinued.

5.3.2.2. Gout Flare Prophylaxis

Gout flare prophylaxis should generally only be continued through the Month 6 study visit as tolerated (ie, colchicine alone, or if colchicine is replaced with oral corticosteroids). It is recognized that if oral corticosteroids alone are used for gout flare prophylaxis, the course will generally be shorter. If XOI and IP are interrupted, gout flare prophylaxis may be re-initiated when the study medications are resumed per the discretion of the Investigator based on the clinical circumstances. If IP is permanently discontinued prior to the end of the gout flare prophylaxis period, the gout flare prophylaxis should be discontinued.

5.3.2.2.1. Colchicine

Subjects are required to continue gout flare prophylaxis with colchicine through their Month 6 study visit unless they become intolerant or develop toxicity to the colchicine. Gout flare prophylaxis with colchicine may be interrupted or discontinued prior to the expected Month 6 study visit due to an AE or tolerability. If colchicine is interrupted for any reason in the gout flare prophylaxis period, it should be restarted when medically appropriate. Subjects should be encouraged to continue on colchicine as tolerated through the Month 6 study visit, but may decrease the dose or increase the interval between doses (ie, from once daily to once every other day).

If a subject requires treatment with cyclosporine, ranolazine, or strong/moderate CYP3A inhibitors (eg, clarithromycin, fluconazole, diltiazem; see Section 7.1.3) prior to their Month 6 study visit, then colchicine must be interrupted or discontinued.

Subjects who are unable to take colchicine during the gout flare prophylaxis period should, when medically appropriate, switch to a short course of low-dose oral corticosteroids. If switching is not medically appropriate, randomized subjects may continue in the study without gout flare prophylaxis.

5.3.2.2.2. Low-Dose Corticosteroids

Subjects unable to take colchicine (ie, those who have a documented intolerance or allergy to colchicine or who initiate a concomitant medication contraindicated for use with colchicine [eg, P-gp or strong CYP3A4 inhibitors]) are permitted to take low-dose oral corticosteroids (ie, ≤10 mg/day of prednisone, or prednisolone, or their equivalent) for a short course, such as through the Month 3 study visit, at the discretion of the Investigator, individualizing for each subject the need for gout flare prophylaxis and potential side effects of persistent steroid use, such as in relation to comorbid conditions.

Gout flare prophylaxis with corticosteroids may be interrupted or discontinued due to an AE or tolerability. Subjects should be encouraged to continue on low-dose corticosteroids through the Month 3 study visit but may decrease the dose as needed.

5.4. Method of Assigning Subjects to Treatment Groups

Approximately 600 subjects will be randomized in a 1:1 ratio to lesinurad 200 mg or placebo in combination with an XOI. Subjects will be randomized at their Baseline Visit after the Investigator has verified that they meet all of the study eligibly criteria (Section 4.2 and Section 4.3) and after all screening assessments have been completed (Appendix A).

Randomization will take place across all study sites using a centralized Interactive Voice Response System/Interactive Web Response System (IVRS/IWRS) and will be stratified by Screening eCrCl (30.0 to <45.0 mL/min or 45.0 to <60.0 mL/min), Baseline measurable target tophus status (present/absent), and type of XOI (allopurinol or febuxostat).

Subject randomization numbers will be generated by the IVRS/IWRS company. Subject eligibility information will be provided by the Investigator or the Investigator's research staff to the IVRS/IWRS at randomization. Two site staff members must verify the information entered into the IVRS/IWRS prior to randomization to ensure accuracy and reduce stratification errors. Each subject meeting eligibility criteria and completing all Screening assessments will be randomized, assigned a unique randomization number, and a randomization confirmation will be sent by the IVRS/IWRS to the site.

No subject may begin IP prior to randomization and assignment of a randomization number. Subjects who have been randomized but withdraw from the study may not be replaced.

5.5. Blinding

Treatment group assignments will be blinded to minimize bias in study assessments and monitoring. In order to maintain the blind, the randomization list generated by the IVRS/IWRS, as well as sUA results post-Baseline, will not be available to subjects, study site staff, or the Sponsor's project team (including the team at the Clinical Research Organization, as applicable) until after database lock with the following exceptions:

- The Clinical Trials Material [CTM] staff is authorized to receive the randomization list to facilitate drug packaging and monitor site inventory for IP.
- The Good Manufacturing Practice Quality Assurance staff is authorized to receive the randomization list to facilitate packaging and release of all CTM.

The IDMC will receive unblinded data to periodically review safety data during the study. For more information on this committee, see Section 11.8.

The pharmacovigilance staff will break the blind only for individual subjects who have SAEs that are both unexpected and suspected to be causally related to IP in order to allow appropriate safety reporting to regulatory authorities. Blinding will not be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual subject have been made and documented.

In the cases of emergency unblinding for safety concerns such as medical emergencies when the appropriate management of the subject requires knowledge of the treatment randomization, the Investigator or designee should contact the Sponsor or designee prior to unblinding a subject's treatment assignment. The IVRS/IWRS will provide the site with the subject's treatment assignment.

5.6. Dispensing Investigational Product

IP will be dispensed at the Baseline Visit and every 3 months thereafter through Month 21 of the Treatment Period. Each bottle will be identified with a unique medication number to protect the blind.

5.7. Packaging and Labeling

IP will be packaged and labeled under the responsibility of the Sponsor in a manner consistent with the study design and according to local regulatory requirements. No repackaging and/or relabeling activities at the study site are allowed. Investigational product will be identified as an investigational compound.

Study site staff should refer to the local product labels for packaging and labeling information for XOIs and gout flare prophylaxis, provided by the Sponsor.

5.8. Study-Supplied Medications Receipt, Storage, Accountability, and Returns

The Investigator must maintain accurate records of all IP, XOI, and colchicine administered as per protocol, including date received, number of units received, and lot number. The Investigator must also ensure that all study-supplied medications are kept secured and accounted for with access limited to only those individuals authorized by the Investigator. The Investigator, his/her designee, or the pharmacist must also maintain adequate records of distribution and dispensing of all study-supplied medications, as well as return of IP to the Drug Depot and destruction of all other study-supplied medications, to be able to reconcile their records (ie, accountability or dispensing logs) periodically throughout the study.

All records must be readily available for inspection by the site monitor and/or auditor. No medications may be returned to the Sponsor or designee (IP) or disposed of at the study site (XOI and colchicine) until the site monitor has verified the accuracy of the records at the study site. All returns, disposals, or destruction must be approved by the Sponsor.

For more complete information regarding study-supplied medication receipt, storage, accountability, return (IP), and destruction (XOI and colchicine), refer to the Study Reference Manual.

5.8.1. Site Receipt of Investigational Product

Within approximately 48 hours upon receipt of study-supplied IP at the study site, the appropriate trained site staff should review the contents and record receipt of the shipment in IVRS/IWRS.

5.8.2. Site Storage

Bottles containing IP must be stored at 15 to 30°C/59 to 86°F. XOI and colchicine should be stored according to the product label. Appropriate storage conditions in the pharmacy or drug storage area must be ensured and temperature must be recorded.

Access to study-supplied medications should be restricted to designated study personnel.

The site monitor should review the supplies of study-supplied medications held by the Investigator or pharmacist at each monitoring visit to ensure accountability and appropriate storage conditions.

5.8.3. Home Storage

The study staff is responsible for providing subjects with instructions on storing all study-supplied medications.

Subjects should be instructed to keep all study-supplied medications in a secure location.

5.8.4. Compliance and Accountability

Accountability will be assessed by maintaining adequate medication dispensing records. Study-supplied medications must be dispensed by a qualified member of the study site staff. Study site staff is responsible for providing subjects with instructions on correct medication administration.

At each study visit, subjects will return all bottles of IP, XOI, and colchicine (used and unused), and study staff will ask about their treatment compliance. The number of tablets returned should be counted and documented in the source documentation. Study site staff is also responsible for accurately completing the subject's medications CRF and appropriate systems (ie, clinical database and IVRS/IWRS).

Study-supplied XOI and colchicine that are returned may be redispensed to the same subject provided accurate accountability records are maintained.

Subjects will be asked to bring study-supplied IP dispensed at Baseline to their Month 1 study visit for compliance check. This IP will be redispensed to the same subject at the Month 1 visit.

Study-supplied medications that are returned should not be redispensed to a different subject.

5.8.5. Return of Investigational Product to the Drug Depot

After accountability has been verified by the site monitor, IP bottles will be returned to the drug depot. The return will be documented within the source documentation and processed by site monitor in IVRS/IWRS prior to shipment to the depot.

5.8.6. Destruction of XOI/Colchicine

After accountability has been verified by the site monitor, returned supplies of XOI and colchicine will be destroyed per the study site's process. The destruction will be documented within the source documentation and processed by the site monitor.

6. STUDY PROCEDURES AND ASSESSMENTS

The following describes the study procedures and assessments that will be performed during the study. See Section 8 and Appendix A for the schedule of events for the study.

6.1. Informed Consent

Prior to undergoing any study-specific procedures and after completing the consent process, the subject must sign a written Informed Consent Form (ICF) that has been approved by an Ethics Committee (EC; eg, an Institutional Review Board [IRB] or an Independent EC [IEC]). The date and time of consent must be documented. Withdrawal of consent must be obtained and documented by the Investigator, or designee, in the CRF and source documentation. Withdrawal of consent is defined to mean that a subject proactively withdraws consent to contribute any additional outcome information.

6.2. Medical History

Medical history data relevant to study inclusion and exclusion criteria will be collected during Screening. A complete medical history will be collected at the Baseline Visit for subjects who meet the eligibility criteria and proceed to randomization. Data collected will include medical and surgical history, select comorbidities, gout diagnosis and disease characteristics, and history of alcohol and tobacco use.

6.3. Prior and Concomitant Medications

Prior ULT, including screening XOI and dose, indicated for the treatment of gout will be recorded on the appropriate CRFs.

Gout flare prophylaxis and treatment for gout flares during the study will be recorded on the appropriate CRFs.

Other concomitant therapies (ongoing at study entry or initiated during the study) must be recorded on the Concomitant Medication CRF. For subjects entering the study on stable doses of medication for chronic medical conditions, any medication dose changes should be documented on the appropriate CRF. When concomitant medication dose changes are the result of the worsening of an ongoing condition, this worsening condition should also be documented on the AE CRF.

6.4. Demographics

Subject demographics include age, sex, race, and ethnicity.

6.5. Physical Examination

Physical examinations include the following: head, eyes, ears, nose, and throat; cardiovascular; respiratory; abdominal; musculoskeletal; neurological; lymph nodes; dermatological; extremities/joints; and the presence or absence of measurable target tophi. Urogenital and rectal examinations are not necessary, unless clinically indicated.

6.6. Vital Signs

Vital signs include systolic and diastolic blood pressure and pulse. Subjects should be advised to avoid smoking, caffeine, or exercise 30 minutes prior to the assessment. Subjects should also be seated quietly for 5 minutes before taking vital signs. Blood pressure should be taken with the subject seated with a straight supported back and with feet flat on the floor. The arm should be supported on a flat surface with the upper arm at heart level, and the appropriate-sized blood pressure cuff should be used. Blood pressure should be managed as appropriate by the subject's health care providers in accordance with guidelines, such as the Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure (JNC8) with a target blood pressure goal of less than 140/90 for patients with renal diseases (James 2014).

6.7. Height and Weight

Height and weight will be measured, and body mass index (BMI) will be calculated (BMI = weight [kg]/height $[m]^2$).

6.8. Electrocardiography

Subjects must be in a supine (includes sitting in a recliner chair) position for at least 5 minutes before performing the 12-lead electrocardiogram (ECG) test. The results will be reviewed by the Investigator.

6.9. Clinical Laboratory Tests

See the Laboratory Manual for sample collection, processing, storage, and shipping procedures.

6.9.1. Clinical Safety Laboratory Assessments

Blood and urine samples will be collected for clinical safety laboratory tests (hematology, serum chemistry, and urinalysis) and will be tested by a central laboratory. Any clinical safety laboratories results post-Baseline that are considered possibly significant may be repeated (see Section 6.12).

See Table 1 for a list of clinical safety laboratory tests.

Table 1: Clinical Safety Laboratory Tests

Hematology: • Hematocrit • Hemoglobin • Mean corpuscular hemoglobin • Mean corpuscular hemoglobin concentration • Mean corpuscular volume • Platelet count • Red blood cell count • Red blood cell morphology • White blood cell count with differential **Urinalysis:** • Appearance • Bilirubin • Color • Glucose • Ketones • Nitrite • Occult blood • pH • Protein • Specific gravity • Urobilinogen • Microscopic examination of sediment including uric acid crystals **Additional urine analyses:** • Creatinine • Total protein	**Serum Chemistry:** Analytes 1 • Blood urea nitrogen • Creatinine (enzymatic method) • Glucose • Uric acid[a] Analytes 2 • Albumin • Calcium • Carbon dioxide • Chloride • Phosphorus • Potassium • Sodium • Total cholesterol • Triglycerides Analytes 3 • Alkaline phosphatase • Alanine aminotransferase • Aspartate aminotransferase • Total bilirubin • Creatine kinase Pregnancy and fertility testing • Human chorionic gonadotropin[b] • Follicle-stimulating hormone[c]

[a] Serum uric acid (sUA) will be used for efficacy analyses. All study personnel, except for those defined in Section 5.5, will be blinded to sUA results collected after Baseline through database lock.
[b] At Screening Visit 2 for all females and again at Month 12 for all females except those who are surgically sterile or not of childbearing potential as confirmed by the Screening Visit 2 follicle-stimulating hormone test.
[c] At Screening Visit 2. Only for females with 12 months of spontaneous amenorrhea who are not surgically sterile.

Estimated CrCl at each visit will be calculated by the Cockcroft-Gault formula using ideal body weight (based on height measured at Screening) as follows:

- eCrCl (male) = [(140 – age) × ideal body weight (kg)] / [72 × serum creatinine (mg/dL)].
- eCrCl (female) = 0.85 × [(140 – age) × ideal body weight (kg)] / [72 × serum creatinine (mg/dL)].

Ideal body weight is calculated as follows:

- Ideal body weight (male) = 50 kg + [2.3 × (height (in) – 60)].
- Ideal body weight (female) = 45.5 kg + [2.3 × (height (in) – 60)].
  - If height <60 in, then ideal body weight = 50 kg for males and 45.5 kg for females.

For any post-randomization laboratory abnormality considered potentially clinically significant, a retest should be considered prior to the subject's next visit.

Cases where a subject shows elevations in liver biochemistry may require further evaluation, and occurrences of AST or ALT ≥3 × upper limit of normal (ULN) together with total bilirubin ≥2 × ULN may need to be reported as SAEs. Please refer to Appendix B for further instruction on cases of increases in liver biochemistry and evaluation of Hy's Law.

6.9.2. Additional Samples for Biomarkers

Plasma and urine samples will be collected for the measurement of metabolic, vascular, and pro-inflammatory biomarkers. These samples may not be used for genetic testing and will be stored for a maximum of 10 years or as allowed by local laws or institutional guidelines.

6.10. Efficacy Assessments

6.10.1. Serum Uric Acid Levels

Efficacy will be assessed based on sUA levels. Serum uric acid levels will be measured using the clinical safety serum chemistry samples and will be tested by a central laboratory. All study personnel, except for those defined in Section 5.5, will be blinded to sUA results collected after screening through database lock.

6.10.2. Tophus Measurements

In subjects with tophi at Baseline, 5 target tophi on the hands/wrists and feet/ankles ≥5 millimeters and ≤20 millimeters in the longest diameter will be selected for evaluation of measurable tophi. If the subject has <5 tophi in these specified locations, then the maximum number of tophi should be selected. Draining, acutely inflamed, or tophi that have ever been infected must not be selected. Tophi will be measured using digital calipers to capture both the longest diameter and longest perpendicular measurement. Calipers will be provided by the Sponsor. Refer to the Study Reference Manual for instructions on selection, measurement, and documentation of tophi.

6.10.3. Patient-Reported Outcomes

Health status as patient-reported outcomes will be assessed employing the EuroQol Five Dimensions Questionnaire 3 level (EQ-5D-3L), work productivity as assessed employing the Work Productivity and Activity Impairment Questionnaire: Specific Health Problem (WPAI:SHP) V2.0, and functional impairment as assessed employing the Sheehan Disability Scale (SDS) (Sheehan 1996). These patient-reported outcomes will be collected from the subjects at the scheduled study visits.

6.10.3.1. Sheehan Disability Scale

The SDS is a patient-rated instrument measuring functional impairment in 3 domains: work impairment, social impairment, and impairment of family life/home responsibilities (Sheehan 1996). Disability scores are reported for each of the questions and a total disability score is calculated as the sum of scores for each question. Higher scores reflect greater impairment.

6.10.3.2. Work Productivity and Activity Impairment Questionnaire: Specific Health Problem

The WPAI:SHP questionnaire quantitatively measures health-related work productivity loss for the employed population. Six questions are used to elicit work productivity over the prior 7 days. Four scores can be determined for absenteeism, presenteeism, work productivity loss, and activity impairment.

6.10.3.3. EuroQol Five Dimensions Questionnaire 3 Level

The EQ-5D-3L is a standardized instrument for use as a measure of health outcome developed by the EuroQol Group. The descriptive system of the questionnaire comprises 5 dimensions (EQ-5D; mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) and each dimension has 5 levels (no problems, slight problems, moderate problems, severe problems, and extreme problems). An EQ visual analogue scale (EQ VAS) will also be included, which records self-rated health on a 20 cm vertical visual analog scale with bottom rate (0) corresponding to "the worst health you can imagine", and the highest rate (100) corresponding to "the best health you can imagine".

6.10.4. Gout Flares

Acute gout flares occur when monosodium urate crystals in the joint(s) cause acute inflammation. A flare is characterized by pain, redness, swelling, and warmth lasting days to weeks. Pain may be mild or excruciating. Most initial attacks occur in lower extremities. The typical presentation in the metatarsophalangeal joint of the great toe (podagra) is the presenting joint for 50% of people with gout (http://www.cdc.gov/arthritis/basics/gout.html, accessed 6 October 2016).

Gout flares will be recorded on the CRF, including information regarding the start and stop date; patient-reported severity (mild/moderate/severe); and the treatment that was required, if any. Medications used for gout flare treatment will be documented on the concomitant medications CRF.

6.11. Adverse Events

6.11.1. Adverse Event Definition

An AE is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (eg, nausea, chest pain), signs (eg, tachycardia, enlarged liver), or the abnormal results of an investigation (eg, laboratory findings, electrocardiogram). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including the screening period, even if no study treatment has been administered.

Gout flares will not be captured on the AE form. New tophi or enlarging tophi that are not clinically adverse will not be captured on the AE form. However, gout flares or changes in tophi that meet the definition of an SAE must be reported as an SAE (Section 6.11.6).

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible, the reporting Investigator uses the clinical rather than the laboratory term (eg, anemia versus low hemoglobin value). In the absence of clinical signs or symptoms, clinically-relevant deteriorations should be reported as AE(s).

Protocol-mandated permanent discontinuation of IP per the sCr/eCrCl criteria described in Section 5.3.2.1.1 should be reported as an AE. Additional CRFs will be completed for any mandated sCr retests (Section 6.12) and for certain diagnostic tests.

6.11.1.1. Adverse Events of Special Interest

AEs of special interest that will be evaluated in this study include renal events (eg, renal-related AEs and kidney stone AEs) that are serious or lead to permanent discontinuation of IP, and all potential CV events. Additional information will be required for these events and recorded on the CRFs.

All renal SAEs and all potential CV events will be adjudicated by the REAC or the CEAC, respectively. For information on the adjudication committees, see Section 11.8.

6.11.2. Timing

AEs will be assessed from the time the subject provides informed consent through at least 28 days after the last dose of IP. For subjects who permanently discontinue IP and do not continue on study, SAEs should be collected for at least 28 days after the last dose of IP unless the subject has withdrawn consent.

AEs that start on or after the first dose of IP in this study, or those AEs with onset prior to the first dose of IP but worsen after the first dose of IP, will be considered TEAEs. AEs that start on or after the date of informed consent but before the date of first dose of IP (ie, non-TEAEs) will be considered pretreatment AEs.

If the subject permanently discontinues IP due to an AE and does not continue with protocol-specific procedures, every effort should be made to follow the AE through resolution or stabilization. Subjects with ongoing AEs/SAEs, including clinically-relevant laboratory

abnormalities, should be followed up by the Investigator for as long as medically indicated. The Sponsor retains the right to request additional information for any subject with ongoing AEs/SAEs at the end of the study, if judged necessary.

6.11.3. Severity

Severity of AEs should be assessed by the Investigator according to the following definitions that are based on the Rheumatology Common Toxicity Criteria (RCTC) version 2.0 (Woodworth 2007):

- **Grade 1 (Mild)**: asymptomatic or transient, short in duration (<1 week), no change in lifestyle, and/or no medications required.
- **Grade 2 (Moderate)**: symptomatic, duration (1 to 2 weeks), alters lifestyle occasionally, medication relieves symptoms (may be prescription), and/or IP is continued.
- **Grade 3 (Severe)**: prolonged symptoms, reversible, major functional impairment; prescription medications provide partial relief; may be hospitalized <24 hours; temporary or permanent IP discontinuation.
- **Grade 4 (includes Life Threatening)**: at risk of death; substantial disability, especially if permanent; hospitalized >24 hours; permanent IP discontinuation.

6.11.4. Relationship

The Investigator should assess the causal relationship between each AE and either IP, XOI, or gout flare prophylaxis (if applicable) individually and answer “yes” or “no” to the question, “Do you consider that there is a reasonable possibility that the event may have been caused by the IP, XOI, or gout flare prophylaxis?” For SAEs, causal relationship will also be assessed for each study medication and study procedures. Note that for SAEs that could be associated with any study procedure, the causal relationship is implied as “yes.”

- Not related (No): there is no evidence for a ‘reasonable possibility’ of a causal relationship for the individual event. An AE for which an alternative explanation is more likely, eg, concomitant medication(s) or concomitant disease(s), and/or the relationship in time suggests that a causal relationship is unlikely.
- Related (Yes): there is evidence for a ‘reasonable possibility’ of a causal relationship for the individual event. The expression ‘reasonable possibility’ of a causal relationship is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship.

The causality assessment is performed based on the available data including enough information to make an informed judgment. With limited or insufficient information in the case, it is likely that the event(s) will be assessed as ‘not related’. Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

6.11.5. Reporting Adverse Events

The Investigator must record all AEs in the source documents (eg, medical record), and report the data on the appropriate CRF pages. The Investigator will notify the local EC per the EC requirements.

AEs must be collected from the Screening Visit 1 through at least 28 days post treatment.

The information recorded will be based on the signs or symptoms reported by the subject. A clinical diagnosis should be provided to the extent feasible instead of listing individual signs or symptoms. Signs and symptoms are to be recorded clearly in a concise manner using standard, acceptable medical terminology to eliminate vague, ambiguous, or colloquial expressions. The Sponsor is responsible for the ongoing collection of safety data and their evaluation in accordance with local and federal guidelines and regulatory requirements. The Sponsor will inform all central EC(s), Investigators (if applicable), and regulatory authorities of findings that could adversely affect the safety of subjects or affect the conduct of the study and will report to regulatory authorities in conformity with expedited and periodic reporting requirements.

6.11.6. Serious Adverse Events

6.11.6.1. Definition

An SAE is defined as any AE occurring during any study phase that fulfills one or more of the following criteria:

- Results in death.
- Is immediately life-threatening.
- Requires in-patient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions.
- Is a congenital abnormality or birth defect.
- Is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above.

Note that an AE or suspected adverse reaction is considered "life-threatening" for reporting as an SAE if, in the view of either the Investigator or Sponsor, its occurrence places the subject at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

The following events do not meet the definition of an SAE: planned hospitalization for a condition present prior to the subject's enrollment in the study; hospitalization of the subject for compliance/convenience reasons; planned hospitalization for an elective medical/surgical procedure, scheduled treatments, or routine check-ups; or a hospitalization or an emergency room visit lasting less than 24 hours.

6.11.6.2. Managing Serious Adverse Events

Subjects experiencing an SAE or an emergency situation will be examined by a physician as soon as possible and be treated as medically appropriate. Appropriate laboratory tests will be conducted until all parameters return to normal or are otherwise explained or stable. The subject will be followed until the SAE resolves or until the subject is medically stabilized.

6.11.6.3. Reporting Serious Adverse Events

The Investigator or designee will notify the Sponsor immediately and not later than 24 hours after knowledge of the SAE and at the outcome of the SAE. SAE reporting instructions (including forms, e-mail addresses, and facsimile and telephone numbers) will be provided in the Study Reference Manual. An SAE report must follow within 24 hours of knowledge, including a full description (to the extent possible) of the event and any sequelae.

6.12. Retest Requirements for Subjects With Changes in Kidney Function

Retesting of laboratory values, including sCr and eCrCl, as well as the interruption of IP due to safety concerns, can occur any time on study at the Investigator's discretion.

If a subject experiences any of the following changes in kidney function (using central laboratory results), the subject must return to the site for retesting and be evaluated for potential contributing factors:

- eCrCl declines >30% from Baseline in the period starting at Baseline through Month 12 study visit, or eCrCl declines >40% from Baseline in the period from the Month 12 study visit through the Month 24 study visit.
- Absolute sCr ≥4.0 mg/dL or eCrCl <20 mL/min at any time on study (Note: this is also the criteria for when IP must be interrupted; see Section 6.12.1.)

The underlying cause of the change in kidney function should be evaluated, treated, and managed as medically appropriate by the Investigator. Additional information will be collected on these events in the CRFs.

During any Retest periods throughout the study period, IP does not need to be interrupted unless warranted as determined by the Investigator and treating Healthcare Providers or if specific criteria are met (sCr ≥ 4.0 mg/dL or an eCrCl < 20 mL/min; see Section 6.12.2).

For IP discontinuation criteria see Section 5.3.2.1.2. Retesting schema for subjects with changes in kidney function is presented in Appendix C.

6.12.1. Estimated Creatinine Clearance Decline From Baseline

Baseline Through the Month 12 Study Visit

From Baseline through the Month 12 study visit, if a subject experiences an eCrCl decline >30% from Baseline, the subject will return to the site within 1 to 2 weeks (Retest 1) for a retest.

- If any retest eCrCl declines ≤15% from Baseline, no further retests are required and the subject may continue the protocol-scheduled visits.

- If the Week 1 to 2 retest (Retest 1) eCrCl declines >15% from Baseline, the subject will return to the site for a retest approximately 3 to 4 weeks (Retest 2) after the initial eCrCl decline was noted.
- If the Week 3 to 4 retest (Retest 2) eCrCl declines >15% from Baseline, the subject will return to the site for a retest approximately 7 to 8 weeks (Retest 3) after the initial eCrCl decline was noted.
- Thereafter, additional retests may be done at the Investigators discretion or the subject may continue the protocol-scheduled visits. If subject's eCrCl does not return to ≤15% of Baseline, IP can be continued and additional retesting is not required; medical treatment and evaluation should be sought as appropriate.

If a subject has persistent decline in their renal function (ie, stable at an eCrCl level 15% to 30% below Baseline) or has permanently discontinued IP, retesting may be at the Investigator's discretion based on medical appropriateness.

Month 12 Study Visit to Month 24 Study Visit

From the Month 12 study visit to the Month 24 study visit, if a subject experiences an eCrCl decline >40% from Baseline, the subject will return to the site within 1 to 2 weeks for a retest (Retest 1).

- Retests 2 (Weeks 3 to 4) and 3 (Weeks 7 to 8) should be performed unless eCrCl declines ≤20% from Baseline.
- If any retest eCrCl declines ≤20% from Baseline, no further retests are required and the subject may continue the protocol-scheduled visits.
- If a subject has persistent decline in their renal function (ie, stable at an eCrCl level 20% to 40% below Baseline) or has permanently discontinued IP, retesting may be at the Investigator's discretion based on medical appropriateness.

Investigators are encouraged to keep subjects on IP during the Retest periods as clinically appropriate and providing sCr is <4.0 mg/dL and eCrCl ≥20.0 mL/min.

6.12.2. Absolute Serum Creatinine ≥4.0 mg/dL or Estimated Creatinine Clearance <20 mL/min

If a subject experiences an absolute sCr ≥4.0 mg/dL or an eCrCl <20 mL/min at any time during the study, IP must be **temporarily interrupted**, and the subject will return to the site within 1 to 2 weeks (Retest 1) for a retest.

Baseline Through the Month 12 Study Visit

- From Baseline through the Month 12 study visit, if any retest eCrCl declines ≤15% from Baseline and sCr <4.0 mg/dL and an eCrCl ≥20 mL/min, no further retests are required and the subject may restart IP, at the Investigator's discretion, and continue the protocol-scheduled visits. The re-initiation of IP may occur regardless of the duration of the interruption.

- If Retest 1 eCrCl declines >15% from Baseline or sCr ≥4.0 mg/dL or an eCrCl <20 mL/min, the subject will return to the site for a retest approximately 3 to 4 weeks (Retest 2) after the initial decline was noted.
- If Retest 2 eCrCl declines >15% from Baseline or sCr ≥ 4.0 mg/dL or an eCrCl <20 mL/min, the subject will return to the site for a retest approximately 7 to 8 weeks (Retest 3) after the initial decline was noted.
- After Retest 3, subjects should continue the protocol-scheduled visits. If eCrCl is ≤15% of the Baseline and sCr <4.0 mg/dL and eCrCl ≥20 mL/min, the subject may restart IP, at the Investigator's discretion.

Month 12 Study Visit to Month 24 Study Visit

- From the Month 12 study visit to the Month 24 study visit, Retests 2 (Weeks 3 to 4) and 3 (Weeks 7 to 8) should be performed if eCrCl declines >20% from Baseline or sCr ≥4.0 mg/dL or eCrCl <20 mL/min.
- If any retest eCrCl declines ≤20% from Baseline and sCr <4.0 mg/dL and an eCrCl ≥20 mL/min, no further retests are required and the subject may restart IP, at the Investigator's discretion, and continue the protocol-scheduled visits. The re-initiation of IP may occur regardless of the duration of the interruption.

6.13. Management of Acute Gout Flares

If a subject experiences an acute gout flare, study medications, including gout flare prophylaxis, should continue uninterrupted. Gout flares should be treated aggressively as appropriate by the treating Healthcare Providers individualized to the subject and the clinical circumstances.

There are no current specific guidelines for the treatment of acute gout flares in patients with chronic kidney disease (CKD). Corticosteroids are often the preferred treatment option (alone or in combination, as applicable, with ongoing colchicine prophylaxis) for patients with CKD though dosages and administration (ie, oral or intra-articular) vary for individual patients (Curiel 2012, Gaffo 2008, El-Zawawy 2010). EULAR guidelines state that acute gout flares can be managed using intra-articular aspiration and injection of a long acting steroid, especially when safety or tolerability concerns limit the use of NSAIDs and colchicine (Zhang 2006).

Treatment with NSAIDs should generally be avoided (or used judiciously) for acute gout flares (Curiel 2012, Gaffo 2008, El-Zawawy 2010) and is not permitted for gout flare prophylaxis (Section 5.2.2).

6.14. Suspected Pregnancy (Exposure in Utero)

If a subject becomes pregnant, IP, XOI, and gout flare prophylaxis (if applicable) should be discontinued immediately. The Investigator or other site personnel must notify the Sponsor or designee of a pregnancy associated with IP exposure within 1 day; ie, immediately, but **no later than 24 hours**, after the Investigator becomes aware of it and record the event and the course of the pregnancy, including perinatal and neonatal outcome (when is known) on the Pregnancy Report Form that will be provided to each site. The same timelines apply when outcome information is available.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the IP under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) should be followed up and documented even if the subject was withdrawn from the study. Partner pregnancy data may not be collected.

6.15. Overdose

An overdose is defined as a daily dose of IP more than 200 mg (>1 tablet).

AEs associated with an overdose should be recorded on the appropriate AE CRF; however, all overdoses, including those not associated with an AE, should be recorded on the appropriate CRF.

6.16. Premature Withdrawal From the Study

Subjects are free to withdraw from the study at any time without prejudice to further treatment. A subject who withdraws consent will always be asked about the reason(s) and the presence of any AE. The Investigator will follow up AEs outside of the clinical study. At the time of study withdrawal, subjects should complete the End of Study Visit. If a subject withdraws from participation in the study, then his/her enrollment/randomization code cannot be reused. Subjects who withdraw early from the study will not be replaced.

Possible reasons for early withdrawal of subjects from the study include the following:

- Subject withdraws consent
- Death
- Lost to follow up.

To ensure validity of study data, it is important to collect as much data as possible throughout the study. It is essential that Investigators maintain contact with the subjects. This contact will assist with subject retention and prevent missing data. Several approaches may be implemented to increase communication and retention (eg, telephone calls to the subject's emergency contact, emails, texts, offers of transportation arrangements, etc). Certain approaches must be approved by appropriate IRBs/ECs in compliance with local privacy laws/practices.

For subjects who withdraw early or do not have an End of Study Visit, the site or delegate should attempt to collect vital status information (dead or alive). Vital status, based on publicly available sources, may also be investigated at Month 24 for subjects who did not complete the study.

The date and the reason must be recorded on the CRF for all subjects who withdraw early from the study. See Section 8.4.1 for End of Study Visit procedures.

7. STUDY RESTRICTIONS

7.1. Potential Drug Interactions

7.1.1. Interactions With Lesinurad

CYP2C9 Inhibitors, CYP2C9 Poor Metabolizers, and CYP2C9 Inducers

Lesinurad exposure is increased when it is co-administered with inhibitors of CYP2C9, and in CYP2C9 poor metabolizers. Lesinurad should be used with caution in patients taking moderate inhibitors of CYP2C9 (eg, fluconazole, amiodarone) and in CYP2C9 poor metabolizers.

Lesinurad exposure is decreased when lesinurad is coadministered with moderate inducers of CYP2C9 (eg, rifampin, carbamazepine), which may decrease the therapeutic effect of lesinurad.

CYP3A Substrates

In interaction studies with lesinurad and CYP3A substrates conducted in healthy subjects, lesinurad reduced the plasma concentrations of sildenafil and amlodipine. Although there was not a clinically significant interaction with atorvastatin, HMG-CoA reductase inhibitors that are sensitive CYP3A substrates may be affected. The possibility of reduced efficacy of concomitant drugs that are CYP3A substrates should be considered and their efficacy (eg, blood pressure and cholesterol levels) should be monitored.

Salicylates

Salicylates at doses higher than 325 mg per day may decrease the sUA lowering activity of lesinurad in combination with allopurinol. There are no restrictions for doses of salicylates of 325 mg or less per day (ie, for CV protection).

7.1.2. Interactions With Xanthine Oxidase Inhibitors

Investigators should be aware of potentially serious interactions when allopurinol and febuxostat are given in combination with other drugs. The following sections list the drugs that should not be administered or should be administered with caution (eg, may require dose adjustments or additional patient monitoring) with allopurinol and febuxostat according to the United States Product Insert (USPI) and/or the Summary of Product Characteristics (SmPC) (Febuxostat 80 mg Tablets [SmPC] Rev December 2012, Allopurinol [US package insert] Rev July 2015, Allopurinol 100 mg Tablets [SmPC] Rev February 2013, Uloric [US package insert] Rev March 2013). Refer to the local product labels for complete information on drug interactions.

7.1.2.1. Allopurinol

Drugs that should not be administered or should be administered with caution while taking allopurinol include, but are not limited to, the following:

- 6-mercaptopurine
- azathioprine
- coumarin anticoagulants
- theophylline
- captopril
- ampicillin/amoxicillin
- cyclosporine
- didanosine
- vidarabine (adenine arabinoside)
- oxipurinol
- thiazide diuretics
- cyclophosphamide
- tolbutamide
- chlorpropamide

7.1.2.2. Interactions With Febuxostat

Febuxostat should not be administered with 6-mercaptopurine or azathioprine.

7.1.3. Interactions With Colchicine

Moderate or strong CYP3A inhibitors that should not be administered while taking colchicine prophylaxis include, but are not limited to, the following:

- atazanavir
- clarithromycin
- darunavir
- indinavir
- itraconazole
- ketoconazole
- lopinavir
- nefazodone
- nelfinavir
- ritonavir
- tipranavir
- saquinavir
- telithromycin
- amprenavir
- aprepitant
- diltiazem
- erythromycin
- fluconazole
- fosamprenavir
- verapamil

Inhibitors of P-gp that are prohibited while taking colchicine prophylaxis include, but are not limited to, the following:

- cyclosporine
- ranolazine

Potentially significant drug interactions have been reported between colchicine and HMG-CoA reductase inhibitors, other lipid-lowering drugs, and digitalis glycosides. Subjects receiving these medications are to be carefully monitored for any signs or symptoms of muscle pain, tenderness, or weakness, particularly during initial therapy with colchicine.

Refer to the local product label for complete information on drug interactions with colchicine or other gout flare prophylaxis medications (eg, prednisone, prednisolone, or their equivalent).

Subjects must discontinue colchicine for gout flare prophylaxis (expected through the Month 6 study visit) if inhibitors of P-gp or moderate or strong CYP3A inhibitors are administered while on colchicine. This includes intake of grapefruit or grapefruit juice.

Subjects who are randomized and who subsequently develop intolerance or toxicity to colchicine or need to take inhibitors of P-gp or moderate to strong CYP3A inhibitors prior to the Month 6 study visit should, when medically appropriate, switch to the alternate gout flare prophylaxis, low-dose oral corticosteroids for a short course, such as through the Month 3 study visit. If switching is not medically appropriate, randomized subjects may continue in the study without gout flare prophylaxis.

7.2. Food and Fluid Intake

All doses of study treatment should be taken with water. Subjects should be encouraged to stay well hydrated. Grapefruit juice, a moderate CYP3A inhibitor, should not be consumed if the subject is taking colchicine.

7.3. Subject Activity Restrictions

There are no special requirements or restrictions on activity level.

7.4. Contraception

Current data from nonclinical studies suggest that lesinurad is not a reproductive hazard and showed no evidence of a genotoxic risk to humans at the planned lesinurad dosing in this study (see lesinurad IB for more information). There are no available human data on use of lesinurad in pregnant women. As a precaution, female subjects of childbearing potential (including peri-menopausal women who had menstrual bleeding within 1 year) must use an effective non-hormonal method of birth control (see Study Reference Manual) while taking IP. Because of a potential for lesinurad to affect the efficacy of hormonal contraceptives, subjects using a hormonal contraceptive must also use an effective non-hormonal method of birth control.

Male study subjects and their partners are not required to use contraception during this study.

8. STUDY ACTIVITIES

This section lists study activities by study day or month. In this study, a month is defined as 28 days. Unless there is a safety concern, every effort should be made to avoid protocol deviations. Additional visits will be required if subjects experience changes in renal function as outlined in Section 6.12.

During the Double-Blind Treatment Period, all visits will occur at the end of the study month (ie, the Month 3 Visit will occur on Day 84 [±7 days]). All scheduled visits should be referenced back to the Baseline Visit.

See Section 6 and the Study Reference Manual for detailed information on study procedures. See Appendix A for the schedule of events.

NOTE: subjects will be required to return to the site for additional visits if they have changes in renal function as outlined in Section 6.12. At timepoints when there are multiple assessments, patient-reported outcomes (including SDS, WPAI:SHP, EQ-5D-3L),vital sign measurements, and ECG (if applicable) should be performed prior to other assessments, particularly prior to laboratory sample collections.

8.1. Screening Period (Day -28 to the Baseline Visit)

At the start of the Screening Period, prospective study subjects will be fully informed about the nature of the study and possible AEs. Subjects must read the ICF and sign the document after the Investigator has answered all questions to the subject's satisfaction. Further procedures can begin only after the consent form has been signed. Prospective subjects will be evaluated for entry into the study according to the eligibility criteria. The Investigator must evaluate the results of all examinations, clinical laboratory tests, and medical history to determine each subject's suitability for the study prior to randomization and starting IP.

8.1.1. Screening Visit 1 (Approximately 28 Days Before the Baseline Visit)

The following procedures and assessments will be performed:

- Obtain written informed consent.
- Review eligibility criteria.
- Record demographics.
- Record prior ULTs (including current XOI with dose) indicated for the treatment of gout.
- Take vital signs.
- Measure height and weight measurements and calculate BMI.
- Assess AEs (pretreatment events).
- Collect blood sample for the following serum chemistry analyses:
  - Analytes 1.

8.1.2. Screening Visit 2 (Within 3 Weeks After Screening Visit 1 [±3 Days])

The following procedures and assessments will be performed:

- Review eligibility criteria (including a review of targeted medical history and concomitant medications).
- Take vital signs.
- Assess AEs (pretreatment events).
- Assess compliance with prescription XOI.
- Collect blood sample for the following serum chemistry analyses:
  - Analytes 1.
  - Human chorionic gonadotropin (HCG) pregnancy test for all females and follicle-stimulating hormone (FSH) test for females who report 12 months of spontaneous amenorrhea and are not surgically sterile.
- Collect urine sample for the following analysis:
  - Urinalysis.

8.1.3. Baseline Visit (4 to 7 Days After Screening Visit 2)

The following procedures and assessments will be performed:

- Review gout flare history prior to Screening and during the Screening period.
- Confirm continued eligibility.
- Record complete medical history.
- Record concomitant medications.
- Administer patient report outcome assessments.
- Take vital signs.
- Record 12-lead ECG.
- Assess AEs (pretreatment).
- Perform physical examination.
- Identify and measure target tophi.
- Collect blood sample for hematology.
- Collect blood sample for the following serum chemistry analyses:
  - Analytes 1.
  - Analytes 2.
  - Analytes 3.

- Collect blood sample for plasma biomarkers.
- Collect urine sample for the following analyses:
  - Urinalysis.
  - Protein-creatinine ratio.
  - Urine biomarkers.
- Assess compliance with prescription XOI and discontinue.
- Randomize subject.
- Dispense IP (lesinurad or placebo), XOI, and colchicine (if applicable).

8.2. Rescreening of Subjects

Subjects who fail to meet the eligibility requirements for the study may be rescreened up to 3 times, as appropriate, using a new screening number each time. The minimum time required before each rescreening is 1 month (28 days).

8.3. Treatment Period (Day 1 Through Month 24)

Subjects must meet all of the eligibility criteria listed in Section 4.2 and Section 4.3 before being randomized and starting IP, study-supplied XOI, and colchicine (as applicable). Subjects will receive IP in combination with an XOI for up to 24 months. Subjects who permanently discontinue IP early should complete an End of Treatment Visit (Section 8.3.3) as soon as possible after discontinuing IP, and a Post-End of Treatment Visit (Section 8.4.1) 1 month after the End of Treatment Visit, but should remain on the study and follow the protocol-scheduled visits.

8.3.1. Day 1 (1 Day After Baseline Visit)

This is not a study visit. Subjects will receive study-supplied medications (IP, XOI, and colchicine, as applicable) at their Baseline Visit and will start taking these medications at home on Day 1 (1 day after Baseline Visit). Colchicine may be taken at Baseline. All study-supplied medications should be taken in the morning. Refer to Section 5.3 for details on administration of study-supplied medications.

8.3.2. Month 1 (Day 28 ±7 Days) and Months 3 Through 21 (Visits Every 3 Months ±7 Days)

The following procedures and assessments will be performed at each visit, except where otherwise noted:

- Administer patient-reported outcome assessments (except at Month 1).
- Review gout flares that occurred since the last study visit.
- Take vital signs.
- Assess AEs.
- Record concomitant medications.

- Assess compliance with IP (lesinurad/placebo).
- Assess compliance with XOI.
- Assess compliance with gout flare prophylaxis (Months 1, 3, and 6).
- Measure target tophi (Months 6, 12, 18).
- Collect blood sample for hematology (Months 6, 12, and 18).
- Collect blood sample for the following serum chemistry analyses:
  - Analytes 1.
  - Analytes 2.
  - Analytes 3 (Months 6, 12, and 18).
  - Pregnancy test for women of childbearing potential (Month 12).
- Collect blood sample for plasma biomarkers (Months 6, 12, and 18).
- Collect urine sample for the following analyses:
  - Urinalysis.
  - Protein-creatinine ratio (Months 6, 12, and 18).
  - Urine biomarkers (Months 6, 12, and 18).
- Except at Month 1, dispense IP (lesinurad or placebo), XOI, and colchicine (as needed at Month 3).

For subjects that have permanently discontinued IP, maintaining the visit schedule is recommended. Although all assessments are encouraged, at a minimum, it is requested that collection of AEs and collection of a blood sample for Analytes 1 occur.

8.3.3. Month 24 (±7 Days) and/or End of Treatment Visit

The following procedures and assessments will be performed at Month 24 (for subjects who complete the Treatment Period) or as soon as possible after permanently discontinuing IP (for subjects who discontinue IP early):

- Collect reasons for discontinuing IP, if applicable.
- Administer patient-reported outcome assessments.
- Review gout flares that occurred since the last study visit.
- Take vital signs.
- Measure weight.
- Assess AEs.
- Record concomitant medications.
- Assess compliance with IP (lesinurad/placebo).
- Assess compliance with XOI.

- Measure target tophi.
- Collect blood sample for hematology.
- Collect blood sample for the following serum chemistry analyses:
  - Analytes 1.
  - Analytes 2.
  - Analytes 3.
  - Pregnancy test for females of childbearing potential.
- Collect blood sample for plasma biomarkers.
- Collect urine sample for the following analyses:
  - Urinalysis.
  - Protein-creatinine ratio.
  - Urine biomarkers.
- Dispense XOI.

8.4. Follow-Up Period

All subjects who complete the Treatment Period will return to the site for an End of Study Visit 1 month later (Section 8.4.2).

Subjects who permanently discontinue IP early should return to the site for an End of Treatment visit (Section 8.3.3) as soon as possible after discontinuing IP, then a Post-End of Treatment Visit (Section 8.4.1) 1 month after the End of Treatment Visit. They should remain on study and follow the protocol schedule (with the exception of dispensing and taking IP) and have an End of Study Visit (Section 8.4.2) at the conclusion of their study period. Alternatively, if the subject does not agree to this option, a modified follow-up including, eg, regular telephone contacts or a contact at Month 24, should be arranged, if agreed to by the subject and in compliance with local data privacy laws/practices. Subjects who do not wish to continue on study after discontinuing IP should complete an End of Study Visit 1 month after treatment discontinuation (Section 8.4.1), which should be performed in place of the Post-End of Treatment Visit.

8.4.1. Post-End of Treatment Visit for Subjects Who Discontinue Investigational Product But Remain on Study (~30 Days Post-Discontinuation)

Subjects who permanently discontinue IP but remain on study should complete a Post-End of Treatment Visit approximately 28 days after the End of Treatment Visit. The following procedures and assessments will be performed:

- Administer patient-reported outcome assessments.
- Review gout flares that occurred since the last study visit.
- Take vital signs.
- Assess AEs.

- Record concomitant medications.
- Measure target tophi.
- Collect blood sample for hematology.
- Collect blood sample for the following serum chemistry analyses:
  - Analytes 1.
  - Analytes 2.
  - Analytes 3.
- Collect urine sample for the following analyses:
  - Urinalysis.
  - Protein-creatinine ratio.
- Assess compliance with XOI, if applicable.
- Dispense XOI, if applicable.

8.4.2. End of Study Visit

All subjects should complete an End of Study Visit. This visit should occur approximately 28 days after completing the Treatment Period or after permanent treatment discontinuation if the subject is no longer continuing in the study. Subjects should return all study supplies to the site. The following procedures and assessments will be performed:

- Collect reasons for early study withdrawal if applicable.
- Administer patient-reported outcome assessments.
- Review gout flares that occurred since the last study visit.
- Take vital signs.
- Assess AEs.
- Record concomitant medications.
- Measure target tophi.
- Collect blood sample for hematology.
- Collect blood sample for the following serum chemistry analyses:
  - Analytes 1.
  - Analytes 2.
  - Analytes 3.
- Collect blood sample for plasma biomarkers.
- Collect urine sample for the following analyses:
  - Urinalysis.

  - Protein-creatinine ratio.
  - Urine biomarkers.
- Assess compliance with XOI, if applicable.

9. PLANNED STATISTICAL METHODS

This section describes the statistical considerations and data analyses to address the objectives of the study. Further details will be provided in the Statistical Analysis Plan (SAP).

9.1. General Considerations

All subjects will be randomized to either lesinurad 200 mg or matching placebo in combination with an XOI in a 1:1 ratio and stratified by the following stratification factors:

- Screening eCrCl: the average eCrCl of Screening Visit 1 and Screening Visit 2 (30.0 to <45.0 mL/min or 45.0 to <60.0 mL/min).
- Baseline measurable target tophus status: present or absent.
- Type of XOI: allopurinol or febuxostat.

This study will enroll approximately 50% of subjects with eCrCl 30.0 to <45.0 mL/min and approximately 50% with eCrCl 45.0 to <60.0 mL/min. There is no planned sample size requirement on the number of subjects enrolled by type of XOI or Baseline tophus status. However, a stratification variable (eg, Baseline measurable target tophus status [present/absent]) may be dropped from the stratified analysis (eg, mixed model repeated measures [MMRM] or Cochran Mantel Haenszel [CMH]) if the number of subjects in any stratum is very low (eg, <10% of total subjects). The decision to drop a stratification variable will be made prior to database lock and will be documented in the SAP.

All safety and efficacy data will be listed and summarized by treatment group.

Baseline is defined as the last observed measurement prior to the first dose of IP, unless otherwise specified.

Descriptive statistics will consist of the number of subjects (n), mean, standard deviation (SD), median, minimum, and maximum for continuous variables, and counts and percentages for categorical variables.

Unless otherwise specified, all confidence intervals (CIs) will be calculated at the 95% level and all hypothesis tests will be performed at the 0.05 level. All analyses including summaries and listings will be performed using SAS® software version 9.1 or higher.

9.2. Determination of Sample Size

Approximately 600 subjects will be randomized 1:1 to either the lesinurad (LESU) + XOI or placebo (PBO) + XOI group in this study.

For safety endpoint analyses, this sample size provides sufficient precision around the estimated between-treatment difference for the absolute and percent changes in eCrCl from Baseline to Month 24 based on the normal distribution CI with 95% two-sided confidence level. For the difference in absolute change from Baseline to Month 24, the estimated precision is ±1.6 mL/min assuming a common SD for the change from Baseline in each treatment group of 10 mL/min estimated from the lesinurad Phase 3 development program. For the difference in percent change from Baseline to Month 24, the estimated precision is ±3.2% assuming a common SD for the

percent change from Baseline in each treatment group of 20% estimated from the lesinurad Phase 3 development program.

For the key efficacy endpoint analyses, this sample size will provide >90% power for the overall population and >80% power within each Screening eCrCl stratum to detect a treatment difference for the proportion of subjects achieving sUA <6.0 mg/dL at Month 6 of 15% (20% in the PBO + XOI group versus 35% in the LESU + XOI group, as estimated from the lesinurad Phase 3 development program), using a binomial distribution at an alpha of 0.05 (two-sided). Based on the assumptions above, this sample size provides sufficient precision such that the minimum statistically significant difference in response rate is approximately 10% in the overall population, and approximately 11% in the Screening eCrCl 30.0 to <45.0 mL/min stratum, at the two-sided 5% level.

9.3. Analysis Populations

The **Intent-to-Treat (ITT) Population** will be defined as all randomized subjects who received at least 1 dose of IP (lesinurad or placebo). This will be the primary population for efficacy analyses and subjects will be analyzed based on the randomized treatment assigned.

The **Safety Population** will be defined as all randomized subjects who received at least 1 dose of IP (lesinurad or placebo). Subjects will be analyzed based on the randomized treatment assigned. Any major deviations from the randomized treatment assignment will be listed and considered when interpreting the safety data.

The **Per-Protocol Population** will be defined as all subjects in the ITT population without major protocol deviations, defined prior to unblinding of the study. Select analyses (to be specified in the SAP), will be repeated on the PP population.

9.4. Analysis Methods

9.4.1. Disposition, Demographics, and Baseline Characteristics

Subject disposition, demographics, gout diagnosis, and Baseline disease and treatment characteristics will be summarized for the ITT Population.

Compliance with IP (lesinurad or placebo) will be summarized and will include the number of subjects estimated to be <80% compliant, 80% to 120% compliant, and >120% compliant. The total dose and average daily dose will also be summarized.

9.4.2. Safety Analyses

Safety data will be analyzed descriptively using the Safety Population.

The main estimands to address the safety objective are the absolute and percent changes from baseline to Month 24 in eCrCl, assessed in the Safety population, with treatment difference estimated using MMRM and missing data imputed separately for each treatment group assuming missing at random (MAR).

9.4.2.1. Change From Baseline in Estimated Creatinine Clearance

Absolute and percent changes from Baseline to Month 24 in eCrCl will be assessed using a MMRM analysis that includes terms for treatment (LESU + XOI and PBO + XOI), visit, treatment by visit interaction, stratification factors (type of XOI [allopurinol or febuxostat], Baseline measurable target tophi status [present/absent], and Screening eCrCl [30.0 to <45.0 mL/min or 45.0 to <60.0 mL/min], as appropriate as stated in Section 9.1), and Baseline eCrCl as covariate. The model will assume an unstructured covariance matrix. If convergence issues are encountered, alternative covariance structure will be explored (details will be provided in the SAP). Least-square (LS) mean by treatment and LS mean difference between LESU + XOI and PBO + XOI alone will be estimated from the MMRM analysis, along with the 95% CI of LS mean difference.

All subjects should be followed for safety events even if they discontinue IP (lesinurad or placebo), as permitted. Prior to performing MMRM analysis, renal function data that are collected after subjects discontinue IP will be set to missing. All missing data will be imputed using multiple imputation methodology assuming MAR and separate imputation models for the LESU + XOI and PBO + XOI groups. Sensitivity analysis will include all available data (including data after subjects discontinue IP) and impute only for missing data assuming MAR. Additional sensitivity analysis will be performed using multiple imputation assuming missing not at random, depending on the nature of missing data and early treatment discontinuations (eg, subjects discontinuing early due to worsening renal function).

In addition to using the Cockcroft-Gault equation for eCrCl, renal function will also be evaluated using estimated glomerular filtration rate (eGFR) equations (eg, the Modification of Diet in Renal Disease [MDRD]), and may be explored using similar methods as above.

9.4.2.2. Renal-Related Outcomes

The following renal-related outcomes will be reported as both incidence proportions and exposure-adjusted incidence rates:

- Incidence of sCr elevation (≥1.5 × Baseline).
- Incidence of subjects meeting criteria (eg, based on sCr or eCrCl criteria) for treatment discontinuations.
- Incidences of renal-related and kidney stone TEAEs and SAEs.
- Prevalence of contributing factors to renal SAEs as adjudicated by the REAC.

The proportion will be calculated as the number of subjects with an outcome of interest (ie, unique subjects) during the study divided by the total number of subjects in that treatment group. The 95% CIs will be calculated based on the Wilson Score method.

The on-treatment exposure-adjusted incidence rates for an outcome of interest will be calculated as the number of subjects with that outcome of interest during the Treatment Period divided by the total duration of treatment in each treatment group (ie, “on-treatment” analysis). Similarly, the on-study exposure-adjusted incidence rates will be calculated as the number of subjects with outcome of interest during the study divided by the total duration of study in each treatment group (ie, “on-study” analysis). Exposure-adjusted incidence rates and associated exact CIs

based on the Poisson distribution will be calculated for each treatment group and reported per 100 patient-years.

Similar exposure-adjusted analysis will also be performed with the number of events as the numerator dividing by on-treatment or on-study exposure as described above.

Estimates of treatment differences with corresponding 95% CIs will be calculated. The appropriate approaches may depend on the number of events observed during blinded data review and will be detailed in the SAP prior to database lock.

Additional assessments may include the proportion of subjects who require dialysis, those who advance in their chronic kidney disease, those who have persistent decreases in eCrCl, and those who have persistent sCr elevations.

9.4.2.3. Cardiovascular Outcomes

The following cardiovascular outcomes will be reported as both incidence proportions and exposure-adjusted incidence rates:

- Incidence of CEAC-adjudicated MACE (CV death, nonfatal myocardial infarction, and nonfatal stroke).
- Incidence of CEAC-adjudicated MACE or hospitalization for unstable angina (MACE+).

Similar methods for estimating incidence proportions and exposure-adjusted incidence rates will be applied, as described in Section 9.4.2.2. In addition, the incidences of the individual MACE+ components will also be reported.

In addition, the time-to-event of MACE will be analyzed using Cox proportional hazards model with treatment as the only predictor (base model). The estimated hazard ratio and associated 95% CI will be presented. Extended models (eg, including stratification factors, other Baseline covariates, etc.) may be explored depending on the number of events observed.

Two types of analyses will be conducted: on-study analysis and on-treatment analysis. For the on-study analysis, subjects with an event during the study will contribute actual time of first occurrence, while those without an event will be censored at the end of study. For the on-treatment analysis, subjects with an event during the Treatment Period will contribute actual time of first occurrence, while those without an event during Treatment Period will be censored at the end of treatment. Sensitivity analysis may be conducted to explore different ascertainment windows for which to attribute the MACE outcome to treatment (eg, 1 month post-treatment discontinuation).

9.4.2.4. General Safety

All AEs will be coded and tabulated by Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class and preferred term. Similar methods will be applied for estimating proportions and exposure-adjusted incidence rates (ie, on-study and on-treatment exposure-adjustment) of TEAE, SAEs, and TEAEs leading to permanent discontinuation of IP, as described in Section 9.4.2.2.

Associated laboratory parameters such as hepatic profile, renal function, serum chemistry, hematology, and urinalysis values will be grouped and presented together. Individual subject values will be listed and values outside of the standard reference range will be flagged. Marked abnormalities meeting RCTC version 2.0 grading will also be noted. Shift tables and analyses of changes from Baseline will be included.

The change from Baseline for each of the vital signs variables will be summarized.

9.4.3. Efficacy Analyses

Efficacy data will be summarized and analyzed in the ITT population.

The key sUA efficacy endpoint (proportion of subjects with sUA <6.0 mg/dL at Month 6) will be summarized descriptively by treatment group and a comparison of the response rates will be presented using the CMH test statistic, stratified by type of XOI, Baseline measurable target tophus status (present/absent), and Screening eCrCl (30.0 to <45.0 mL/min or 45.0 to <60.0 mL/min), as appropriate as stated in Section 9.1. Results will be expressed as proportions, corresponding adjusted 95% CI of the difference between response rates, and p-values. Subjects who are missing their Month 6 sUA results will be analyzed as non-responders.

The LESU + XOI group will be deemed superior compared with the PBO + XOI group if there is sufficient statistical evidence to reject the following null hypothesis:

> **H_0: $p_1 = p_2$** ie, no evidence that the proportion of subjects achieving an sUA response by Month 6 in the LESU + XOI group is different from the PBO + XOI group.

and in favor of the alternative hypothesis:

> **H_1: $p_1 \neq p_2$** ie, the proportion of subjects achieving an sUA response by Month 6 in the LESU + XOI group is different from the PBO + XOI group.

The key efficacy endpoint will be tested in the overall study population as well as the subset of subjects whose Screening eCrCl is 30.0 to <45.0 mL/min. To account for multiplicity, a hierarchical testing procedure will be performed to preserve an overall alpha at 0.05 level. First, the null hypothesis for the key efficacy endpoint will be tested in the overall population at an alpha level of 0.05. If the null hypothesis is not rejected, the testing will be stopped. Otherwise, the endpoint will then be tested in the subset of subjects whose screening eCrCl is 30.0 to <45.0 mL/min at an alpha level of 0.05.

Sensitivity analyses (eg, observed cases or other imputation approaches) will be explored to assess the impact of missing data (details provided in the SAP).

Absolute and percent change from Baseline in sUA concentration will be summarized by visit and analyzed using MMRM that includes terms for treatment (LESU + XOI and PBO + XOI), visit, treatment by visit interaction, stratification factors (type of XOI [allopurinol or febuxostat], Baseline measurable target tophi status [present/absent], and Screening eCrCl [30.0 to <45.0 mL/min or 45.0 to <60.0 mL/min], as appropriate as stated in Section 9.1), and Baseline sUA as covariates. The model will assume an unstructured covariance matrix. If convergence issues are encountered, alternative covariance structure will be explored (details will be provided in SAP). LS mean by treatment and LS mean difference between LESU + XOI and PBO + XOI alone will be estimated from the MMRM analysis, along with the 95% CI of LS mean difference.

The proportion of subjects reaching sUA <6.0 mg/dL at each visit will also be presented. Additional efficacy analyses to support the key efficacy endpoint will include the proportion of subjects reaching sUA <6.0 mg/dL at multiple consecutive visits (eg, Months 3 and 6). CMH estimates of 95% CI for difference will also be presented.

9.4.4. Exploratory Endpoints

For all exploratory endpoints, descriptive statistics will be provided at each scheduled visit.

For percent change from Baseline in the sum of target tophi area among subjects with target tophus at Baseline, the between-treatment difference will be assessed using similar MMRM analysis as appropriate as in Section 9.4.2.1.

For the proportion of subjects with target tophi at Baseline who experience complete resolution of at least 1 target tophus at any time during study, the between-treatment difference in tophus resolution rates in this subset of subjects will be assessed using the CMH test statistic, stratified by type of XOI, and Screening eCrCl (as appropriate as stated in Section 9.1). Results will be summarized by randomized treatment group and expressed as proportions and corresponding adjusted 95% CI of the difference between response rates.

The proportion of subjects reporting gout flares will also be summarized at each visit.

The patient-reported outcomes (ie, SDS, WPAI:SHP, and EQ-5D-3L) will be summarized by visit (Visits 3, 6, 9, . . . 24). In addition, the mean score at last on-study visit will be analyzed using analysis of covariance (ANCOVA), which include terms for treatment stratification factors (as appropriate as stated in Section 9.1) and Baseline patient reported outcome value as covariate.

9.4.5. Interim Analyses

No formal interim analysis is planned.

10. QUALITY CONTROL AND ASSURANCE

Quality assurance and quality control systems will be implemented and maintained with Standard Operating Procedures by the Sponsor and its designee(s), as appropriate, to ensure that this clinical study is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, International Conference on Harmonisation (ICH) E6 Good Clinical Practice (GCP): Consolidated Guidance, and the applicable regulatory requirements.

This study will be monitored by the Sponsor in accordance with GCP, and may be audited or reviewed by an independent Quality Assurance department, EC, and/or regulatory authorities. This implies that monitors and auditors/inspectors will have the right to inspect the study sites at any time during and/or after completion of the study and will have direct access to data/source documents, including the subject's file. By participating in this study, Investigators agree to this requirement.

Measures will be undertaken to protect the confidentiality of records that could identify subjects, respecting the privacy and confidentiality rules in accordance with applicable regulatory requirements.

11. ADMINISTRATIVE CONSIDERATIONS

11.1. Ethics Committee Approval

At a minimum, the following documents must be reviewed and approved by ECs (including IRBs and IECs), as required by local laws and EC requirements, before subjects are screened for entry into the study:

- Study protocol and amendment(s).
- Written Informed Consent Form(s) and consent form updates.
- Subject recruitment procedures (eg, advertisements).
- Written information to be provided to subjects.
- IB and available safety information. Note: ECs do not approve IBs but are responsible for acknowledging receipt.
- Information about payments and compensation available to subjects.

The EC approval must be in writing, clearly identifying the study (by protocol date and/or version), the documents reviewed, including informed consent form, and date of the review. The Investigator has the responsibility to provide the Sponsor with the written EC approval prior to initiating any study-related procedures. The Investigator also has the responsibility to inform the EC of serious and unexpected AEs and protocol deviations, and to provide the EC with a synopsis of the study report upon study completion according to the EC's policy.

11.2. Ethical Conduct of the Study

This study is to be conducted in accordance with the protocol, ICH E6 GCP, and all other applicable regulatory requirements. Investigators must immediately notify the Sponsor or designee (if applicable) of serious breaches in GCP that have occurred at their study site, which are likely to effect to a significant degree (a) the safety or physical or mental integrity of the subjects of the study or (b) the scientific value of the study.

11.3. Subject Information and Consent

Note: all references to "subject" in this section refer to the study subject or his/her legally acceptable representative.

Prior to participation in any study-specific procedures, each subject must sign and date an EC-approved written ICF in a language the subject can understand.

The language in the written information about the study should be as non-technical as practical, and should be understandable to the subject. Before informed consent is obtained, the Investigator should provide the subject ample time and opportunity to inquire about the study and to decide whether or not to participate.

All questions about the study should be answered to the satisfaction of the subject. The written ICF should be signed and personally dated by the subject and by the person who conducted the

informed consent discussion, with any additional signatures obtained as required by applicable local regulations and EC requirements. Each subject will be informed that participation is voluntary and that he/she can withdraw from the study at any time. All subjects will receive a copy of their signed and dated ICF.

11.4. Subject Confidentiality

The collection of personal data for this study will be limited to data that are necessary to investigate the utility of the IP used in this study. These data will be processed with adequate precautions to ensure confidentiality according to local laws.

The Sponsor ensures that the personal data are as follows:

- Collected for a specified and legitimate purpose.
- Processed fairly and lawfully.
- Accurate and up to date.

Explicit consent for the processing of personal data will be obtained prospectively from the participating subject.

The Sponsor, whose responsibilities require access to personal data, agrees to keep the identity of study subjects confidential. This confidentiality will be maintained throughout the complete data processing.

Study subjects will be entitled to request confirmation of the existence of personal data held by the Sponsor and will have the right to rectify erroneous or inaccurate data up until database lock.

11.5. Study Monitoring

The Sponsor will monitor this clinical study through central analysis, on-site monitoring visits, and remote data checks to check the adequacy of site staff and facilities, and to ensure adherence to the protocol, study procedures, and applicable regulations. The site monitor will also assess proper CRF completion and source document retention. The Investigator and study site staff are expected to provide adequate space for monitoring visits and to allocate sufficient time to permit adequate review of the study's progress. The Investigator will permit study-related monitoring, audits, EC review and regulatory inspection(s), providing direct access to source data/documents and study-related facilities (eg, pharmacy, diagnostic laboratories).

11.6. Study Records and Case Report Forms

11.6.1. Study Records and Case Report Forms Records

The Investigator and affiliated institution shall maintain the study documents and records as specified in "Essential Documents for the Conduct of a Clinical Trial" (ICH E6 Section 8), and as required by the applicable regulatory requirement(s). These include, but are not limited to, the protocol, CRFs, AE reports, subject source data (original records or certified copies), correspondence with health authorities and EC, consent forms, Investigator's curriculum vitae, monitor visit logs, laboratory reference ranges and laboratory certification or quality control procedures, and laboratory director curriculum vitae. Subject source data must be maintained as

original records or a certified copy (ie, copy of original information that has been verified, as indicated by a dated signature, as an exact copy having all of the same attributes and information as the original). The Investigator and affiliated institution should take measures to prevent accidental or premature destruction of documents.

Study sites may utilize site-owned electronic medical record systems and/or other computer systems to generate, collect, and store subject source data. When such systems will be used for the study, their use and supporting infrastructure (eg, access/security, written procedures, technical support, and training as applicable) will be identified and documented in site assessment or site visit reports by the Sponsor or designee, and will be reviewed and monitored in accordance with applicable procedures and regulatory requirements. If electronic medical records are maintained (eSource data), the method of verification must be agreed upon between the investigational staff and the Sponsor or designee prior to enrollment of the first subject.

11.6.2. Case Report Form

A CRF must be completed for each subject who has given informed consent. In the case of a screening failure, at a minimum the following data will be entered into the CRF: visit date, demography, and reason for screening failure. All entries into the CRF are ultimately the responsibility of the Investigator before adding his/her signature.

The CRF must be completed at the time of, or shortly after, the subject's visit, with the exception of results of tests performed outside the Investigator's office, so that they always reflect the latest observations of the subjects participating in the study. If certain information is Not Done, Not Available, or Not Applicable, the Investigator must record this according to the CRF completion instructions.

The CRF and source documents must be made available to the site monitor. During monitoring visits, the site monitor will review the CRF entries and evaluate them for completeness and consistency. The CRF entries will be compared with the source documents to ensure that there are no discrepancies between critical data. All entries, corrections, and alterations are to be made by the responsible Investigator or his/her designee. The site monitor may query the data, but cannot edit CRF entries recorded by the site designee.

A copy of each subject’s CRF will be maintained by the Investigator.

In addition to the clinical data management systems/databases, other systems may be used to collect and analyze study data:

- A Safety Database will be used by the Sponsor or designee to collect, medically evaluate, document, report, and store SAEs as individual case safety reports, and to generate periodic reports, as required.
- Laboratory Information Systems or proprietary systems will be used by laboratories for storing and/or analyzing safety and bioanalytical laboratory data collected throughout the study.
- Statistical software will be used for the statistical analysis of the study data, as outlined in the SAP.

- Electronic Document Management Systems will be used for storing essential documents (electronic trial master file).

11.6.3. Source Data and Source Documents

The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the CRF are known to the Sponsor or designee and investigational staff. These source documents are to be accessible for verification by the site monitor.

Source documents should at minimum include the following information for each subject:

- Subject identification (name, year of birth, sex).
- Documentation that subject meets eligibility criteria, eg, medical history, gout diagnosis, laboratory results (to support inclusion and exclusion criteria).
- Participation in study (including study number).
- Date and time of informed consent(s).
- Dates of visits including last study visit.
- Documentation that protocol-specific procedures were performed.
- Study-supplied medication dispensing and accountability.
- All AEs and other safety parameters (including AE start and stop dates, Investigator assessment of severity and relationship to and actions taken for study medications).
- All gout flare events (including start date, stop date, and subject-reported severity [mild/moderat/severe]) and corresponding medications (to be recorded on the concomitant medications CRF).
- Concomitant medications (including start and stop dates and indication for use).
- Date and reason for permanently discontinuing IP, if applicable.
- Date of study completion and reason for early withdrawal, if applicable.
- Documentation of withdrawal of consent, if applicable.

The author of an entry in the source documents, as well as the date of the entry, should be identifiable. Direct access to source documentation (medical records) must be allowed for the purpose of verifying that the data recorded in the CRF are consistent with the original source data. The Investigator will provide certified copies of the subject's medical records in the event that site's policy does not permit direct access to the electronic medical records.

11.6.4. Participation Cards

An EC-approved participation card will be provided to the site by the Sponsor for studies involving IPs or investigational use of marketed products. This card should be provided to study subjects, where required.

11.6.5. Subject Identification Information

To permit easy identification of the individual subject during and after the study, the Investigator is responsible for keeping an updated log that contains the subject identification information. This document will be reviewed by the site monitor for completeness. However, in order to ensure the subject's confidentiality, the document will be maintained at the site and no copy will be made.

11.7. Use of Computerized Systems

Information on the computerized systems will be provided to the Investigator, site personnel, and other personnel as appropriate. Measures will be taken to ensure data security and accuracy, including, but not limited to, user training, granting of user accounts and privileges to trained and authorized personnel in a role-based manner, username/password/electronic signature requirements enforcement, programmed and manual edit checks as outline in data validation specifications, computer-generated audit trails, centralized data management, and routine study monitoring. The systems used will be compliant with US 21 Code of Federal Regulations Part 11 and Annex 11 on Computerized Systems (annex to the Guide to Good Manufacturing Practice for Medicinal Products) in the EU and Canada, and the data collected will be archived (at minimum) for the period specified by applicable regulatory requirements.

11.7.1. Electronic Data Capture

An electronic data capture system will be used to capture protocol-required subject data. Sites will enter data from source documents onto electronic CRFs for each study visit using a web-based interface. Study monitors, data management, and safety personnel will use this system to review data and generate queries and reports as needed.

11.7.2. Interactive Voice/Web Response System

An IVRS/IWRS will be used to randomize subjects, manage IP inventory, and facilitate IP reconciliation. Sites will enter data from source documents into IWRS for Screening and each study visit using a web-based interface. Study monitors will use this system to review data and generate queries and reports as needed.

The IVRS/IWRS will also be used to request IP as needed during the treatment Period.

11.7.3. Centralized Data Check System

A centralized analytics monitoring tool will be used to integrate data from different clinical data streams for the purpose of identifying data patterns and flagging unexpected data.

11.8. Independent Monitoring and Adjudication Committees

11.8.1. Independent Data Monitoring Committee

An IDMC will be appointed by the Sponsor to assess the safety of subjects participating in the study, to evaluate data periodically, to protect subject welfare, and to identify potential safety signals.

The IDMC will consist of members with clinical expertise in a variety of specialties, as appropriate, and will operate under a written, detailed IDMC Charter. The IDMC members will have had no involvement in the design or conduct of the study except through their role on the IDMC, and have no financial or other important connections to the Sponsor other than their compensation for serving on the IDMC.

The IDMC will be responsible for evaluating the safety of lesinurad in combination with an XOI based on unblinded safety data, which includes SAE reports, nonserious AEs, and laboratory data. A list of CEAC- and REAC-adjudicated AEs and the committees' findings will be provided to the IDMC, who will assess the frequency and significance of those events for the study.

The IDMC may also advise the Sponsor if the safety data suggest that lesinurad be stopped or the study be modified or prematurely terminated for any reason.

11.8.2. Renal Events Adjudication Committee

An independent REAC will routinely evaluate and categorize all serious prospectively-defined renal-related and kidney stone AEs. In addition, the REAC chair will review all other SAEs in the clinical database and determine whether any additional SAEs should be adjudicated by the REAC. The REAC, in a blinded fashion, will assess the likelihood that potential contributing factors, including IP, contributed to the event. The committee will operate under a written, detailed REAC Charter. See the REAC Charter for details.

11.8.3. Cardiovascular Endpoints Adjudication Committee

An independent CEAC will routinely adjudicate all SAEs and other prospectively-defined AEs for CV-related events in a blinded fashion using MACE and non-MACE CV criteria. The CEAC will operate under a written, detailed CEAC Charter. See the CEAC charter for details.

11.9. Protocol Violations/Deviations

Unless there is a safety concern, there should be no deviations to or violations of the study protocol. In the event of a safety concern, the Investigator or designee must document and explain the reason for any deviation from the approved protocol. The Investigator may implement a deviation from, or a change to, the protocol to eliminate an immediate hazard to study subjects without prior EC approval. Immediately after the implemented deviation or change, the Investigator must submit a report explaining the reasons for the protocol violation or deviation to the EC and the Sponsor. The Sponsor is responsible for notifying the regulatory authorities, if required.

11.10. Retention of Data

The Sponsor will inform the Investigator in writing when it is acceptable to dispose of any study records. To enable evaluation and/or audits from regulatory authorities or the Sponsor, the Investigator agrees to keep records, including the identity of all study subjects (eg, subject identification code list and all source documents), all original signed ICFs, copies of all CRFs, original laboratory reports, detailed records of IP disposition, and all essential documents for the conduct of a clinical study. To comply with international regulations, the records should be retained by the Investigator for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an

ICH region, or until at least 2 years have elapsed since the formal discontinuation of clinical development of the IP. However, the Investigator may need to retain these documents for a longer period if required by the local regulatory requirements or by an agreement with the Sponsor.

11.11. Financial Disclosure

The Investigator's disclosable financial interests must be obtained prior to initiation of the study site, at completion of the study at the investigational site, and 1 year following study completion.

The Investigator should promptly update this information if any relevant changes occur during the above described period.

Disclosable financial interests will be recorded on the Investigator Financial Disclosure Form.

Any Investigator(s) added as investigational staff to the form FDA 1572 must complete the Investigator Financial Disclosure Form at the beginning of his/her participation in the study.

Any Investigator(s) leaving the study site during the study period will be required to provide disclosable financial interest changes prior to leaving the study site.

11.12. Site Closure or Study Termination

The Sponsor reserves the right to close any investigational site(s) or terminate the study at any time for any reason. Reasons for the closure of a study site or termination of a study by the Sponsor may include (but are not limited to) the following:

- Successful completion of the study at the investigational site.
- The required number of subjects for the study has been recruited.
- Failure of the Investigator to comply with the protocol, GCP guidelines, or local requirements.
- Safety concerns.
- Inadequate recruitment of subjects by the Investigator.

11.13. Protocol Modification

This protocol cannot be modified except in a formal protocol amendment by the Sponsor.

11.14. Publication and Disclosure Policy

The data and results of the study will be owned solely by the Sponsor and shall be confidential information of the Sponsor, subject to the Investigator's publication rights outlined in the agreement between the Investigator/institution and the Sponsor regarding the conduct of the clinical study (the "Clinical Study Agreement"). It is understood by the Investigator that the Sponsor may use the information developed in this clinical study in connection with the development of its compounds and therefore, may disclose it as required to other clinical investigators or to regulatory agencies. To allow for the use of the information derived from this clinical study, the Investigator understands that he/she has an obligation to provide and disclose test results and all data developed during this study to the Sponsor.

Any publication or presentation of the results of this clinical study by the Investigator may only be made in strict compliance with the provisions of the Clinical Study Agreement. The Investigator should understand that it is not the Sponsor's intention to prevent publication of the data generated in the clinical study. However, the Sponsor reserves the right to control the form and timing of such publication for commercial reasons.

12. REFERENCE LIST

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APPENDIX A. SCHEDULE OF EVENTS

	Screening Period			Double-Blind Treatment Period[a]			Follow-Up Period	
Assessment/Procedure	**SV1**	**SV2 (3 weeks [±3 days] after SV1)**	**Baseline Visit (4-7 days after SV2)**	**Day 1 (not a visit)**	**M1, 3, 6, 9, 12, 15, 18, 21**	**Month 24/ EOT Visit**	**Post-EOT Visit for Subjects off IP[b]**	**Month 25/ EOS Visit[c]**
Obtain informed consent	X							
Review eligibility criteria	X	X	X					
Record demographics	X							
Record prior ULTs, including XOI and dose	X							
Assess AEs	X	X	X		X[d]	X	X	X
Randomize in IVRS/IWRS			X[e]					
Complete medical history			X					
Record concomitant medications			X		X	X	X	X
Administer patient-reported outcomes			X		X (except at M1)	X	X	X
Vital signs	X	X	X		X	X	X	X
Physical examination			X					
Height and weight (BMI)	X					Weight only		
12-lead ECG			X					
Assess gout flares[f]			X		X	X	X	X
Measure target tophi			X		M6, 12, 18	X	X	X
Laboratory Assessments								

Assessment/Procedure	Screening Period			Double-Blind Treatment Period[a]			Follow-Up Period	
	SV1	SV2 (3 weeks [±3 days] after SV1)	Baseline Visit (4-7 days after SV2)	Day 1 (not a visit)	M1, 3, 6, 9, 12, 15, 18, 21	Month 24/ EOT Visit	Post-EOT Visit for Subjects off IP[b]	Month 25/ EOS Visit[c]
Hematology blood collection			X		M6, 12, 18	X	X	X
Serum collection for the following chemistry analyses:								
Analytes 1	X[g]	X[g]	X		X[d]	X	X	X
Analytes 2			X		X	X	X	X
Analytes 3			X		M6, 12, 18	X	X	X
Pregnancy tests[h]		X			M12	X		
Urine collection for the following analyses:								
Urinalysis		X[i]	X		X	X	X	X
Protein-creatinine ratio			X		M6, 12, 18	X	X	X
Plasma and urine samples for biomarker collection			X		M6, 12, 18	X		X
Study Medication[j]								
Dispense Study Medication (lesinurad/placebo, XOI, colchicine)[k]			X		X (except at M1)	X (XOI only)	X (XOI only)	
Assess compliance with XOI[l]		X	X		X	X	X	X
Assess compliance with gout flare prophylaxis[m]					M3 and 6			
Assess compliance with IP					X	X		
Vital status								X

Abbreviations: AE, adverse event; BMI, body mass index; ECG, electrocardiogram; EOS, End of Study; EOT, End of Treatment; IP, investigational product; IVRS, Interactive Voice Response System; IWRS, Interactive Web Response System; M, study month, SV, Screening Visit; ULT, urate-lowering therapy; XOI, xanthine oxidase inhibitor.

Note: A clinical month is considered to be 28 days. All scheduled visits should be referenced to the Baseline Visit. See Section 6 for more information on study procedures and assessments. Additional visits will be required if subjects experience changes in renal function as outlined in Section 6.12.

[a] The visit window during the Double-Blind Treatment Period is ±7-days beginning with the Month 1 Visit.

[b] Subjects who permanently discontinue IP early but remain on study should complete a Post-End of Treatment Visit approximately 28 days after the End of Treatment Visit.

[c] All subjects should complete an End of Study Visit approximately 28 days after completing the Treatment Period or withdrawing early from the study.

[d] For subjects who have permanently discontinued IP, at a minimum AE should be assessed and blood drawn for Analyte panel 1.

[e] Investigator must confirm eligibility prior to randomization.

[f] Baseline assessment is an assessment of gout flare history and post-Baseline assessment is an assessment of gout flares since the last visit.

[g] The estimated creatinine clearance (eCrCl) for each Screening Visit and the average of both Screening Visits (the "Screening eCrCl") will be calculated by the Cockcroft-Gault formula using ideal body weight.

[h] The follicle-stimulating hormone (FSH) test will be done at SV2 only, and only for females with 12 months of spontaneous amenorrhea who are not surgically sterile. The human chorionic gonadotropin (HCG) test will be done at SV2 for all females and again at Month 12 for all females except those who are surgically sterile or not of childbearing potential as confirmed by the SV2 FSH.

[i] Includes assessment of protein by dipstick by the central laboratory.

[j] After a subject permanently discontinues IP, dispensing and compliance are not required.

[k] Colchicine will be dispensed at Baseline Visit and Month 3 Visit as applicable.

[l] Prescription XOI compliance will be assessed from Screening to Baseline. Study-supplied XOI compliance will be assessed from Day 1 through Month 25/End of Study.

[m] Corticosteroids for gout flare prophylaxis may be taken through Month 3.

APPENDIX B. ACTIONS REQUIRED IN CASES OF INCREASES IN LIVER BIOCHEMISTRY AND EVALUATION OF HY'S LAW

1. Introduction

This Appendix describes the process to be followed in order to identify and appropriately report cases of Hy's Law. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries.

During the course of the study the Investigator will remain vigilant for increases in liver biochemistry. The investigator is responsible for determining whether a subject meets potential Hy's Law (PHL) criteria at any point during the study.

The Investigator participates, together with the Sponsor clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether Hy's Law (HL) criteria are met. HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than Drug Induced Liver Injury (DILI) caused by the Investigational Medicinal Product (IMP).

The Investigator is responsible for recording data pertaining to PHL/HL cases and for reporting adverse events (AE) and serious adverse events (SAE) according to the outcome of the review and assessment in line with standard safety reporting processes.

2. Definitions

Potential Hy's Law (PHL)

Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥3 × upper limit of normal (ULN) **together with** total bilirubin (TBL) ≥2 × ULN at any point during the study following the start of study medication irrespective of an increase in alkaline phosphatase (ALP).

Hy's Law (HL)

AST or ALT ≥3 × ULN **together with** TBL ≥2 × ULN, where no other reason, other than the IMP, can be found to explain the combination of increases, eg, elevated ALP indicating cholestasis, viral hepatitis, another drug.

For PHL and HL, the elevation in transaminases must precede or be coincident with (ie, on the same day) the elevation in TBL, but there is no specified timeframe within which the elevations in transaminases and TBL must occur.

3. Identification of Potential Hy's Law Cases

In order to identify cases of PHL, it is important to perform a comprehensive review of laboratory data for any subject who meets any of the following identification criteria in isolation or in combination:

- ALT ≥3 × ULN.
- AST ≥3 × ULN.
- TBL ≥2 × ULN.

When a subject meets any of the identification criteria, in isolation or in combination, the central laboratory will immediately send an alert to the Investigator (also sent to the Sponsor representative).

The Investigator will also remain vigilant for any local laboratory reports where the identification criteria are met. Where this is the case, the Investigator will:

- Notify the Sponsor representative.
- Request a repeat of the test (new blood draw) by the central laboratory.
- Complete the appropriate unscheduled laboratory CRF module(s) with the original local laboratory test result.

When the identification criteria are met from central or local laboratory results, the Investigator will without delay:

- Determine whether the subject meets PHL criteria (see Section 2 of this Appendix for definition) by reviewing laboratory reports from all previous visits (including both central and local laboratory results).

4. Follow-Up

4.1 Potential Hy's Law Criteria Not Met

If the subject does not meet PHL criteria the Investigator will:

- Inform the Sponsor representative that the subject has not met PHL criteria.
- Perform follow-up on subsequent laboratory results according to the guidance provided in the Clinical Study Protocol.

4.2 Potential Hy's Law Criteria Met

If the subject does meet PHL criteria the Investigator will:

- Notify the Sponsor representative who will then inform the central Study Team.

The Study Physician contacts the Investigator to provide guidance, to discuss and agree on an approach for the study subjects' follow-up, and for the continuous review of data. Subsequent to this contact the Investigator will:

- Monitor the subject until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or Baseline levels, or as long as medically indicated.
- Investigate the etiology of the event and perform diagnostic investigations as discussed with the Study Physician. This includes deciding which tests available in the Hy's law lab kit should be used.
- Complete the 3 Liver CRF Modules as information becomes available.
- If at any time (in consultation with the Study Physician) the PHL case meets serious criteria, report it as an SAE using standard reporting procedures.

5. Review and Assessment of Potential Hy's Law Cases

The instructions in this Section should be followed for all cases where PHL criteria are met.

No later than 3 weeks after the biochemistry abnormality was initially detected, the Study Physician contacts the Investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the IMP. The Sponsor Study Physician and Global Safety Physician will also be involved in this review, together with other subject matter experts as appropriate.

According to the outcome of the review and assessment, the Investigator will follow the instructions below.

If there is an agreed alternative explanation for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for an SAE:

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate CRF.
- If the alternative explanation is an AE/SAE, record the AE/SAE in the CRF accordingly and follow the Sponsor's standard processes.

If it is agreed that there is **no** explanation that would explain the ALT or AST and TBL elevations other than the IMP:

- Report an SAE (report term 'Hy's Law') according to the Sponsor's standard processes.
  - The 'Medically Important' serious criterion should be used if no other serious criteria apply.
  - As there is no alternative explanation for the HL case, a causality assessment of 'related' should be assigned.

If there is an unavoidable delay of longer than 3 weeks in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

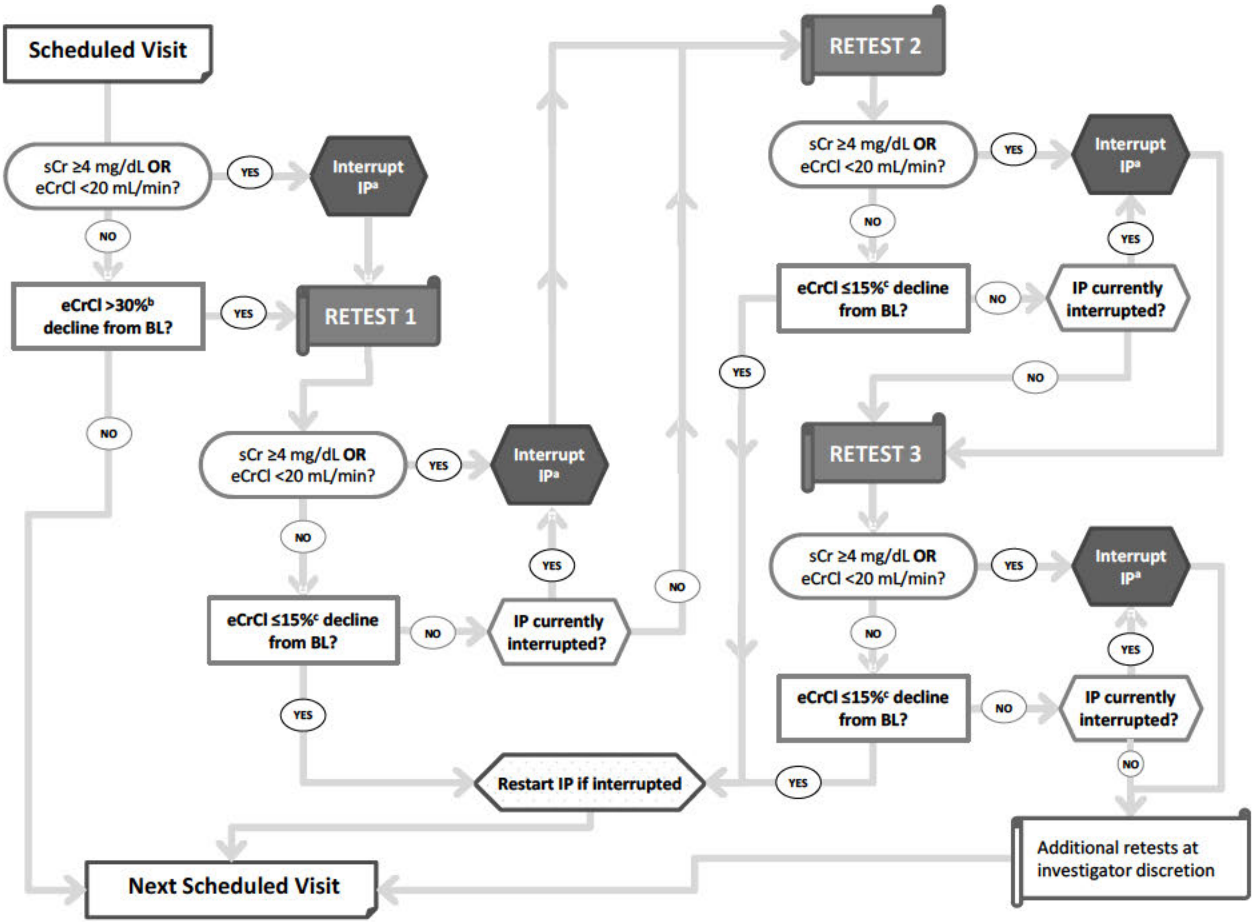
- Report an SAE (report term 'Potential Hy's Law') applying serious criteria and causality assessment as per above.
- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are met. Update the SAE report according to the outcome of the review.

6. References

FDA Guidance for Industry (issued July 2009) 'Drug-induced liver injury: Premarketing clinical evaluation':

http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

APPENDIX C. RETESTING SCHEMA FOR SUBJECTS WITH CHANGES IN KIDNEY FUNCTION



Abbreviations: BL, Baseline; eCrCl, estimated creatinine clearance; IP, investigational product; sCr, serum creatinine.

RETEST 1, RETEST 2, and RETEST 3 are performed approximately 1 to 2 weeks, 2 to 4 weeks, and 7 to 8 weeks relative to the test result that first met the criteria.

[a] If the criteria for IP interruption have been met on 3 separate episodes during the course of the study, IP needs to be permanently discontinued.

[b] For all assessments after the Month 12 study visit, the criterion for retesting changes to "eCrCl >40% decline from BL".

[c] For all assessments after the Month 12 study visit, the criterion for resolution changes to "eCrCl ≤20% decline from BL".

APPENDIX D. SPONSOR SIGNATURES

Protocol Title: A Phase 4, Randomized, Double-Blind, Multicenter, Placebo-Controlled Study to Evaluate the Safety and Efficacy of Lesinurad 200 mg in Combination With a Xanthine Oxidase Inhibitor (XOI), Compared With an XOI Alone, in Subjects With Gout and Estimated Creatinine Clearance 30 to <60 mL/min Who Have Not Achieved Target Serum Uric Acid Levels on an XOI Alone

Study Number: RDEA594-401

Protocol Version: 3

This clinical study protocol was approved by the following:

The electronic signatures are appended.

Name [redacted]
Function Associate Medical Director, Clinical Research
Ironwood Pharmaceuticals, Inc.

Name [redacted]
Function Executive Medical Director, Clinical Development
Ardea Biosciences, Inc.

APPENDIX E. INVESTIGATOR'S SIGNATURE

Protocol Title: A Phase 4, Randomized, Double-Blind, Multicenter, Placebo-Controlled Study to Evaluate the Safety and Efficacy of Lesinurad 200 mg in Combination With a Xanthine Oxidase Inhibitor (XOI), Compared With an XOI Alone, in Subjects With Gout and Estimated Creatinine Clearance 30 to <60 mL/min Who Have Not Achieved Target Serum Uric Acid Levels on an XOI Alone

Study Number: RDEA594-401

Protocol Version: 3

I have read the protocol described above. I agree to comply with all applicable regulations and guidelines and to conduct the study as described in the protocol.

Signed:_____ Date:_____

<enter name and credentials>
<enter title>
<enter affiliation>
<enter address>
<enter phone number>

Lesinurad PMR Study 401 protocol, version 3

rdea594-401-protocol-v3.docx

rdea594-401-protocol

Clinical Study Protocol

21Jun2017 09:36:54 PM GMT-08:00

ELECTRONIC SIGNATURES

Signed By	Signature Meaning	Outcome	Date
[redacted]	Medical	Approve	21Jun2017 11:55:35 AM GMT-08:00
[redacted]	Medical	Approve	21Jun2017 09:36:54 PM GMT-08:00

CLINICAL STUDY PROTOCOL: RDEA594-401

AMENDMENT 1

Protocol Title:	A Phase 4, Randomized, Double-Blind, Multicenter, Placebo-Controlled Study to Evaluate the Safety and Efficacy of Lesinurad 200 mg in Combination With a Xanthine Oxidase Inhibitor (XOI), Compared With an XOI Alone, in Subjects With Gout and Estimated Creatinine Clearance 30 to <60 mL/min Who Have Not Achieved Target Serum Uric Acid Levels on an XOI Alone
Brief Title:	Lesinurad in Subjects With Gout and Moderate Renal Impairment
Study Number:	RDEA594-401
Phase:	4
Investigational Product:	Lesinurad
Population/Indication:	Gout with estimated creatinine clearance 30 to <60 mL/min
Sponsor:	Ironwood Pharmaceuticals, Inc.
Sponsor Medical Monitor:	[redacted]
Amendment Number:	1
Amendment Date:	16 March 2017

Protocol Sign-Off Sheet

Protocol RDEA594-401 Amendment 1

A Phase 4, Randomized, Double-Blind, Multicenter, Placebo Controlled Study to Evaluate the Safety and Efficacy of Lesinurad 200 mg in Combination With a Xanthine Oxidase Inhibitor (XOI), Compared With an XOI Alone, in Subjects With Gout and Estimated Creatinine Clearance 30 to <60 mL/min Who Have Not Achieved Target Serum Uric Acid Levels on an XOI Alone

Reviewed and approved by the Sponsor:

The electronic signature is appended.

Name [redacted]
Function [redacted]
Ironwood Pharmaceuticals, Inc.

Name [redacted]
Function [redacted]
Ardea Biosciences, Inc.

TABLE OF CONTENTS

Clinical Study Protocol

Protocol RDEA594-401 Amendment 1

A PHASE 4, RANDOMIZED, DOUBLE-BLIND, MULTICENTER, PLACEBO CONTROLLED STUDY TO EVALUATE THE SAFETY AND EFFICACY OF LESINURAD 200 MG IN COMBINATION WITH A XANTHINE OXIDASE INHIBITOR (XOI), COMPARED WITH AN XOI ALONE, IN SUBJECTS WITH GOUT AND ESTIMATED CREATININE CLEARANCE 30 TO <60 ML/MIN WHO HAVE NOT ACHIEVED TARGET SERUM URIC ACID LEVELS ON AN XOI ALONE

1. RATIONALE FOR AMENDMENT

The primary purpose of this amendment is to address regulatory feedback and to add a Month 1 study visit. Per the original protocol, the first on-treatment visit was scheduled for Month 3.

In addition, minor revisions to improve clarity or provide additional detail have been made to language describing study entry criteria; pregnancy and fertility testing; sourcing, dispensing, and dosing of study medications; premature discontinuation from the study; analysis populations; definition of adverse events (AEs); AEs of special interest; gout flare assessments; and current cumulative lesinurad exposure data.

Finally, minor editorial changes have been made to improve readability; these changes will not be discussed in this document.

2. SUMMARY OF CHANGES

2.1. Addition of a Site Visit at Month 1 (Day 28 ± 7 Days)

The Month 1 visit will include all of the same assessments and procedures as the Month 3 visit, except for patient-report outcomes (PROs) and dispensing of study medication. In addition to data collection, it will be an earlier opportunity for subject education regarding the importance of study medication compliance, particularly taking investigational product (IP; lesinurad or placebo) in combination with their xanthine oxidase inhibitor (XOI).

This additional visit is reflected in the following sections of the protocol:

- Synopsis (Methodology section)

- Section 3.1. Overall Study Design and Plan
- Section 8.3.2. Month 1 (Day 28 ±7 days) and Months 3 Through 21 (Visits Every 3 Months ±7 days)
- Appendix A Schedule of Events.

2.2. Inclusion and Exclusion Criteria

The language regarding ineligibility of women who are pregnant or breastfeeding has been strengthened (appearing now under both Inclusion Criteria and Exclusion Criteria), an exclusion criterion for subjects with a history of glomerulonephritis has been added, and the exclusion criterion regarding concomitant use of CYP3A inhibitors has been revised to specify that it applies to subjects who will be taking colchicine for gout flare prophylaxis.

These changes are reflected in the following sections of the protocol:

- Synopsis (Eligibility Criteria section)
- Section 4. Study Population Selection

In addition, in order to emphasize the distinction between the key eligibility criteria in the Synopsis and the full list of criteria presented in Section 4, the following changes have been made in the Synopsis:

- "(not a complete list)" has been added to the Eligibility Criteria heading.
- The criteria are bulleted rather than numbered.
- The list of Key Exclusion Criteria has been shortened by removing the following criteria:

  6. Subject is taking valpromide, progabide, valproic acid, or other known inhibitors of epoxide hydrolase, or subject is taking azathioprine or mercaptopurine.
  7. Subject is receiving chronic treatment with more than 325 mg of salicylates per day.
  9. Subject is taking any other drug approved for use as a urate-lowering medication other than allopurinol or febuxostat (eg, pegloticase, probenecid, benzbromarone) within 4 weeks prior to Screening or during Screening.
  10. Subject previously participated in a clinical study involving lesinurad (RDEA594) or verinurad (RDEA3170) and received active treatment or placebo, or has taken commercially-available lesinurad.

Finally, the following have been added under Key Exclusion Criteria in the Synopsis:

- Subject has a history of glomerulonephritis.
- Subject is pregnant or breastfeeding.

2.3. Pregnancy and Fertility Testing

A follicle-stimulating hormone test (FSH) test has been added. The FSH test will be done at Screening Visit 2 (SV2) only, and only for females with 12 months of spontaneous amenorrhea who are not surgically sterile. The human chorionic gonadotropin (HCG) test will be done at SV2 for all females and again at Month 12 for all females except those who are surgically sterile or not of childbearing potential as confirmed by the SV2 FSH.

Text regarding pregnancy and fertility tests is included in the following sections of the protocol:

- 6.9.1. Clinical Safety Laboratory Assessment
- 8.1.2. Screening Visit 2 (3 Weeks After Screening Visit 2 [±3 Days])
- Appendix A. Schedule of Events.

2.4. Medical History

Section 6.2. Medical History was revised to clarify that a complete medical history will not be collected until the Baseline Visit; only medical history data needed to determine subject eligibility for the study will be collected during Screening.

Text in the following sections was revised accordingly:

- 8.1.1. Screening Visit 1 (Approximately 28 Days Before Day 1)
- Appendix A. Schedule of Events.

2.5. Rescreening of Subjects

Section 8.1.4. Option for Rescreening was renumbered and renamed Section 8.2 Rescreening of Subjects. Text specifying that a subject being rescreened should receive a new screening number was added.

2.6. Study Medications

2.6.1. Sourcing and Dispensing of Study Medications

Text has been added to Section 5.2. Other Study Treatments to specify that commercially available allopurinol, febuxostat, and colchicine drug product will be used, and that the relevant product labeling will be provided to Investigators.

Section 5.8.1. Site Receipt was revised to clarify that it is specific to IP.

Section 5.8.4. Compliance and Accountability was revised to specify that except at the Month 1 Visit, IP will not be redispensed.

2.6.2. XOI Use Prior to Randomization

Text in the following sections has been revised to consistently specify that subjects should be on a stable, medically appropriate dose of XOI for at least 4 weeks prior to Screening and throughout the Screening Period:

- Synopsis (Methodology section)

- Synopsis (Eligibility Criteria section)
- 1.3. Rationale for Study Design and Dose Selection
- 3.1. Overall Study Design and Plan.

2.6.3. XOI Use After Permanent Discontinuation of IP

Text in the following sections of the protocol was amended to reflect that subjects who discontinued IP have the option to continue on study-supplied XOI until their End of Study Visit:

- Section 3.1. Overall Study Design and Plan
- Section 5.3.2.1.2. Other Reasons, and Procedures, for Permanent Discontinuation of Investigational Product.
- Section 8.4. Follow-Up Period.
- Appendix A. Schedule of Events.

2.6.4. Interruption and Discontinuation of Study Medications

Section 5.3 Selection and Timing of Dose for Each Subject was reorganized as follows to clarify in which subsection the Investigator can find instructions on each topic:

5.3.1. General Instructions for Dosing

5.3.2. Dose Adjustments, Interruptions, and Discontinuations

5.3.2.1. Investigational Product and Xanthine Oxidase Inhibitors

5.3.2.1.1. Interruption or Discontinuation of Investigational Product due to Changes in Kidney Function

5.3.2.1.2. Other Reasons, and Procedures, for Permanent Discontinuation of Investigational Product

5.3.2.2. Gout Flare Prophylaxis

5.3.2.2.1.Colchicine

5.3.2.2.2.Low-Dose Corticosteroids

In addition, text was added to Section 5.3.2.1.2. to stress the importance of subject retention in the study after discontinuation of IP.

2.6.5. Gout Flare Prophylaxis

The protocol now more clearly states that gout flare prophylaxis is required, and the rationale for this requirement has been added to the Synopsis.

The following sections of the protocol are affected:

- Synopsis (Methodology section)
- 1.3. Rationale for Study Design and Dose Selection
- 3.1. Overall Study Design and Plan

- Colchicine.

2.7. Premature Discontinuation From the Study

Section 6.16. Early Study Withdrawal has been renamed "Premature Discontinuation from the Study" to clarify that the text covers all reasons for subject failure to complete the study, whether subject-initiated or not. "Investigator decision" has been added as a potential reason for premature discontinuation. In addition, language encouraging Investigators to maximize subject retention and minimize missing data has been added.

2.8. Analysis Populations

The following text has been added to Section 9.3. Analysis Populations: "The Per-Protocol Population will be defined as all subjects in the Intent-to-Treat (ITT) population without major protocol deviations, defined prior to unblinding of the study. Select analyses (to be specified in the Statistical Analysis Plan [SAP]), will be repeated on the PP population."

2.9. Definition of Adverse Events

The language in Section 6.11.1. Adverse Event Definition was revised to remove redundant text, clarify that any clinically relevant deterioration in clinical laboratory values or vital signs should be reported as an AE, and to specify that protocol-mandated permanent discontinuation of IP per the sCr/eCrCl criteria described should be reported as an AE.

2.10. Analyses of Adverse Events

To improve clarity, the amended protocol specifies that the incidences of treatment-emergent adverse events (TEAEs), TEAEs leading to permanent discontinuation of IP, and serious TEAEs (SAEs) will be summarized by treatment group.

The revised text is in the following sections of the protocol:

- Synopsis (Statistical Methods section)
- Section 9.4.2.2. Renal-Related Outcomes.

2.11. Adverse Events of Special Interest

Text regarding the proposed assessments of renal and cardiovascular (CV) safety has been amended to more clearly describe the planned assessments and the roles of the adjudication committees.

An independent Renal Events Adjudication Committee (REAC) will routinely evaluate all serious prospectively-defined renal-related and kidney stone AEs, which will be defined in the REAC Charter. In addition, the REAC chair will review all other SAEs in the clinical database and determine whether any additional SAEs should be adjudicated by the REAC. The REAC, blinded to treatment group and serum uric acid (sUA) levels, will assess the likelihood that potential contributing factors, including IP, contributed to the event.

An independent Cardiovascular Endpoints Adjudication Committee (CEAC) will routinely adjudicate all SAEs and other prospectively-defined AEs for CV-related events in a blinded

fashion using MACE and non-MACE CV criteria. The CEAC will also operate under a written, detailed CEAC Charter. The incidences of MACE (CV death, nonfatal myocardial infarction, and nonfatal stroke), MACE+ (MACE or hospitalization for unstable angina), and the individual components of MACE+ will be reported by treatment.

The AEs of special interest are defined as renal events (eg, renal-related AEs and kidney stone AEs) that are serious or lead to permanent discontinuation of IP, and all potential CV events.

The amended text regarding AEs of special interest can be found in the following sections of the protocol:

- Synopsis (Methodology section)
- Synopsis (Safety Endpoints section)
- Section 3.1. Overall Study Design and Plan
- Section 3.2.1. Safety Endpoints
- Section 6.11.1.1. Adverse Events of Special Interest
- Section 9.4.2.2. Renal-Related Outcomes
- Section 9.4.2.3. Cardiovascular Outcomes
- 11.8.2. Renal Events Adjudication Committee
- 11.8.3. Cardiovascular Endpoints Adjudication Committee.

2.12. Gout Flare Assessments

Subject-reported gout flare severity (mild/moderate/severe) will be assessed, in addition to start and stop dates, and any treatment for the flare. Investigators are directed to the concomitant medications case report form (CRF) to record medications used for gout flare treatment.

This is reflected in the following sections of the protocol:

- Section 6.10.4. Gout Flares
- Section 11.6.3. Source Data and Source Documents.

2.13. Centralized Data Checking Tool

A new section was added: Section 11.7.3. Centralized Data Check System.

2.14. Updated Lesinurad Exposure Information

Updated, cumulative lesinurad exposure data is now provided in Section 1.2.1. Known and Potential Benefits and Risks With Lesinurad in Combination With Xanthine Oxidase Inhibitors.

RDEA594-401 (PMR) protocol amendment 1

rdea594-401-protocol-amend1.docx

Clinical Study Protocol

20Mar2017 02:41:08 PM GMT-08:00

ELECTRONIC SIGNATURES

Signed By	Signature Meaning	Outcome	Date
[redacted]	Medical	Approve	20Mar2017 02:41:08 PM GMT-08:00
[redacted]	Medical	Approve	20Mar2017 02:28:41 PM GMT-08:00

CLINICAL STUDY PROTOCOL: RDEA594-401
AMENDMENT 2

Protocol Title:	A Phase 4, Randomized, Double-Blind, Multicenter, Placebo-Controlled Study to Evaluate the Safety and Efficacy of Lesinurad 200 mg in Combination With a Xanthine Oxidase Inhibitor (XOI), Compared With an XOI Alone, in Subjects With Gout and Estimated Creatinine Clearance 30 to <60 mL/min Who Have Not Achieved Target Serum Uric Acid Levels on an XOI Alone
Brief Title:	Lesinurad in Subjects With Gout and Moderate Renal Impairment
Study Number:	RDEA594-401
Phase:	4
Investigational Product:	Lesinurad
Population/Indication:	Gout with estimated creatinine clearance 30 to <60 mL/min
Sponsor:	Ironwood Pharmaceuticals, Inc.
Sponsor Medical Monitor:	[redacted]
Amendment Number:	2
Amendment Date:	21 June 2017

Protocol Sign-Off Sheet

Protocol RDEA594-401 Amendment 2

A Phase 4, Randomized, Double-Blind, Multicenter, Placebo Controlled Study to Evaluate the Safety and Efficacy of Lesinurad 200 mg in Combination With a Xanthine Oxidase Inhibitor (XOI), Compared With an XOI Alone, in Subjects With Gout and Estimated Creatinine Clearance 30 to <60 mL/min Who Have Not Achieved Target Serum Uric Acid Levels on an XOI Alone

Reviewed and approved by the Sponsor:

The electronic signature is appended.

Name [redacted]
Function [redacted]
Ironwood Pharmaceuticals, Inc.

Name [redacted]
Function [redacted]
Ardea Biosciences, Inc.

Investigator Protocol Agreement
Protocol RDEA594-401 Amendment 2

I have read the protocol described above. I agree to the following:

- To assume responsibility for the proper conduct of this clinical study at this site and to conduct the study in compliance with this protocol, any future amendments, and with any other study conduct procedures provided by the Sponsor.
- That I am aware of, and will comply with, the internationally recognized code of Good Clinical Practices (GCP) and all other applicable regulatory requirements to obtain written and dated approval from the Ethics Committee (eg, Institutional or Central Review Board [IRB] or Independent Ethics Committee [IEC]) for the study protocol, written informed consent, consent-form updates, subject-recruitment procedures (eg advertisements), and any other written information to be provided to the subjects before initiating this clinical study.
- Not to implement any changes to, or deviations from the protocol without prior agreement from the Sponsor and review and documented approval from the EC, except to eliminate an immediate hazard to the study subjects, or when change(s) involves only logistical or administrative aspect of the clinical study.
- To permit direct monitoring and auditing by the Sponsor or Sponsor's representatives and inspection by the appropriate regulatory authority(ies).
- That I am thoroughly familiar with the appropriate use of the investigational product(s) and other study medication(s) (if applicable), as described in this protocol, and any other information provided by the Sponsor or designee, including, but not limited to, the current Investigator's Brochure or equivalent document and marketed prescription information (if applicable).
- To provide sufficient time and adequate numbers of qualified staff and facilities for the foreseen duration of the clinical study to conduct the study properly, ethically and safely.
- To ensure that all persons assisting in this study are adequately informed about the protocol, investigational product(s), and their clinical study-related duties and functions.

Signed:_____ Date:_____

Printed Name:_____
enter name and credentials

TABLE OF CONTENTS

Clinical Study Protocol

Protocol RDEA594-401 Amendment 2

A Phase 4, Randomized, Double-Blind, Multicenter, Placebo Controlled Study to Evaluate the Safety and Efficacy of Lesinurad 200 mg in Combination With a Xanthine Oxidase Inhibitor (XOI), Compared With an XOI Alone, in Subjects With Gout and Estimated Creatinine Clearance 30 to <60 mL/min Who Have Not Achieved Target Serum Uric Acid Levels on an XOI Alone

1. RATIONALE FOR AMENDMENT

The primary purpose of this amendment is to address a request from the United States Food and Drug Administration (FDA) to omit "Investigator decision" and "Sponsor's decision" from the list of possible reasons for early discontinuation from the study (comments from the Division of Pulmonary, Allergy, and Rheumatology Drug Products, dated 25 May 2017, on Amendment 1 of the protocol).

The FDA also requested revisions to the charter of the Renal Events Adjudication Committee (REAC), and protocol language related to the responsibilities of the REAC has been amended to reflect those revisions.

In addition, minor editorial changes have been made to improve clarity and consistency with respect to the following:

- Treatment "discontinuation" and study "withdrawal"
- Subjects who prematurely discontinue investigational product (IP)
- Referencing study visits to the Baseline Visit, rather than to Day 1
- Destruction of unused XOI and colchicine
- Recording of overdoses
- Dispensing of XOI at the Month 24 Visit
- Vital status assessment at the End of Study Visit.

2. SUMMARY OF CHANGES

Revisions are presented below in order of their appearance in the protocol. Revisions are indicated by **bold** font, with deleted text as **~~strikethrough~~** and new text **<u>underlined</u>**.

2.1. Protocol Synopsis, Methodology Section

. . .

Subjects who complete the Treatment Period or who plan to withdraw from the study early should complete an End of Study Visit approximately 1 month after study completion/treatment ~~withdrawal~~**discontinuation**.

Subjects who permanently discontinue IP early for any reason, including inability to continue dosing with XOI, should complete an End of Treatment Visit as soon as possible followed by a Post-**End of** Treatment Visit 1 month after the End of Treatment Visit. Subjects should then continue on study and follow the protocol-defined schedule of events, including the End of Study Visit.

. . .

An independent Renal Events Adjudication Committee (REAC) will routinely evaluate **and categorize** all serious prospectively-defined renal-related and kidney stone AEs, and any additional SAEs deemed by the REAC Chair to be relevant for adjudication, ~~to~~ **and will** assess the likelihood that potential contributing factors, including IP, contributed to the event. CEAC and REAC assessments will be performed in a blinded fashion.

. . .

2.2. Section 3.1 Overall Study Design and Plan

. . .

To be eligible for the study, subjects must be on a stable, medically appropriate dose of XOI as their sole ULT indicated for the treatment of gout for at least 4 weeks prior to Screening and throughout the Screening Period. Investigators should have followed the treatment guidelines to determine the medically appropriate dose of XOI. During the Screening Period, subjects will complete 2 Screening Visits: Screening Visit 1 (approximately 1 month before ~~Day 1~~ **the Baseline Visit**) and Screening Visit 2 (3 weeks after Screening Visit 1 [±3 days]). To be eligible for the study, estimated creatinine clearance (eCrCl; calculated by the Cockcroft-Gault formula using ideal body weight) must be 25.0 to ≤65.0 mL/min at each Screening Visit and the average eCrCl of both Screening Visits must be 30.0 to <60.0 mL/min, which is the Screening eCrCl. Additionally, subjects must have an sUA level ≥6.0 mg/dL (387 µmol/L) at both Screening Visits.

. . .

Subjects who permanently discontinue IP early should complete an End of Treatment Visit as soon as possible, followed by a Post-**End of** Treatment Visit 1 month after the End of Treatment Visit where all AEs must be recorded. Subjects should then continue on study (and may remain on their study-supplied XOI) and follow the protocol-defined schedule of events, including the End of Study Visit.

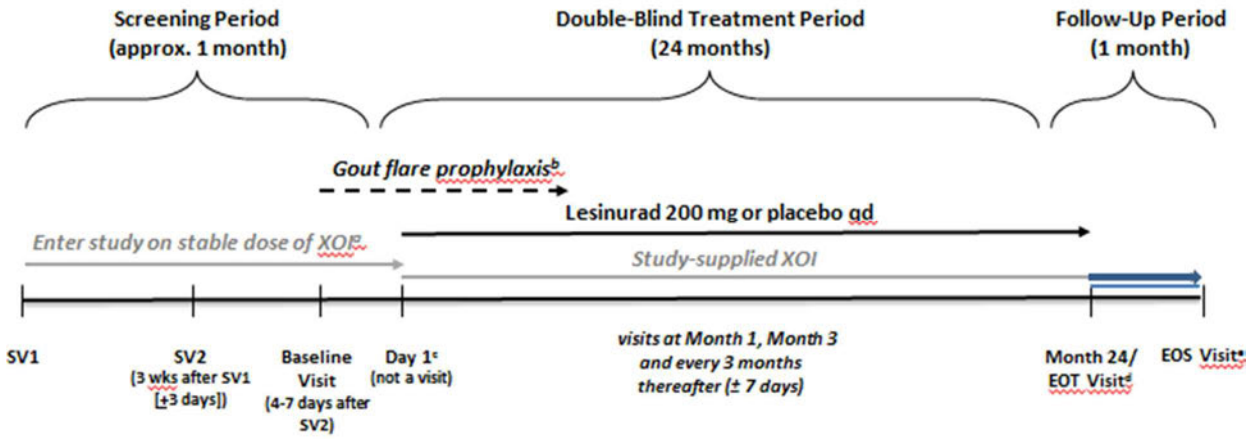
. . .

An independent Renal Events Adjudication Committee (REAC) will routinely evaluate **and categorize** all serious prospectively-defined renal-related and kidney stone AEs, and any

additional SAEs deemed by the REAC Chair to be relevant for adjudication, ~~to~~ **and will** assess the likelihood that potential contributing factors, including IP, contributed to the event.

. . .

Figure 1:Overview of Study Design Scheme



Abbreviations: EOS, End of Study; EOT, End of Treatment; qd, once daily; SV, Screening Visit; wk, week; XOI, xanthine oxidase inhibitor.

Note: A clinical month is considered to be 28 days.
[a] Subjects will enter the study on a stable, medically appropriate dose of XOI (allopurinol or febuxostat) for at least 4 weeks prior to Screening and throughout the Screening Period and will continue this dose (study-supplied after Baseline) throughout the study.
[b] Gout flare prophylaxis, colchicine, will be taken through the Month 6 study visit as tolerated. If low-dose corticosteroids are used as gout flare prophylaxis, the course may be through the Month 3 study visit.
[c] Subjects will start investigational product (lesinurad/placebo) and study-supplied XOI on Day 1 (1 day after the Baseline Visit). Day 1 is not a study visit. Gout flare prophylaxis may be started at the Baseline Visit.
[d] Subjects who permanently discontinue lesinurad/placebo early should complete an EOT Visit as soon as possible followed by a Post-**End of** Treatment Visit 1 month later. Subjects should then continue to follow the protocol-defined schedule of events.
[e] Subjects who complete the study or plan to withdraw from the study early should complete an EOS Visit approximately 28 days after study treatment completion or ~~**withdrawal**~~ **discontinuation**.

. . .

2.3. Section 5.3.2.1.2. Other Reasons, and Procedures, for Permanent Discontinuation of Investigational Product

. . .

Subjects who permanently discontinue IP early should complete an End of Treatment Visit (Section 8.3.3) as soon as possible followed by a Post-End of Treatment Visit (Section 8.4.1) 1 month after the End of Treatment Visit. Subjects should then continue on study and follow the protocol-defined schedule of events, through Month 24. ~~**If the subject discontinues IP, the scheduled study visits, data collection, and procedures should continue through Month 24.**~~ The subject has the option to continue on study-supplied XOI during this time. Although all assessments are encouraged, at a minimum, it is requested that collection of AEs and collection of a blood sample for Analytes 1 (see Table 1) occur. Alternatively, if the subject does not agree to this option, a modified follow-up including, eg, regular telephone

contacts or a contact at ~~study closure~~ **Month 24**, should be arranged, if agreed to by the subject and in compliance with local data privacy laws/practices. **Subjects who do not wish to continue on study after discontinuing IP should complete an End of Study Visit (Section 8.4.2) 1 month after treatment discontinuation.**

If IP is permanently discontinued prior to the Month 6 study visit, then gout flare prophylaxis should also be discontinued.

~~**Subjects who permanently discontinue IP early should complete an End of Treatment Visit (Section 8.3.3) as soon as possible followed by a Post-Treatment Visit (Section 8.4.1) 1 month after the End of Treatment Visit. Subjects should then continue on study and follow the protocol-defined schedule of events, including the End of Study Visit.**~~

2.4. Section 5.8 Study-Supplied Medications Receipt, Storage, Accountability, and Returns

The Investigator must maintain accurate records of all IP, XOI, and colchicine administered as per protocol, including date received, number of units received, and lot number. The Investigator must also ensure that all study-supplied medications are kept secured and accounted for with access limited to only those individuals authorized by the Investigator. The Investigator, his/her designee, or the pharmacist must also maintain adequate records of distribution~~,~~ **and** dispensing~~, and return~~ of all study-supplied medications**, as well as return of IP to the Drug Depot and destruction of all other study-supplied medications,** to be able to reconcile their records (ie, accountability or dispensing logs) periodically throughout the study.

All records must be readily available for inspection by the site monitor and/or auditor. No medications may be returned to the Sponsor or designee **(IP)** or disposed of at the study site **(XOI and colchicine)** until the site monitor has verified the accuracy of the records at the study site. All returns, disposals, or destruction must be approved by the Sponsor.

For more complete information ~~for~~ **regarding** study-supplied medication receipt, storage, accountability, ~~and~~ return~~s~~ **(IP), and destruction (XOI and colchicine)**, refer to the Study Reference Manual.

2.5. Section 5.8.6 Destruction of XOI/Colchicine

After accountability has been verified by the site monitor, returned supplies of XOI and colchicine will be destroyed per the study site's process. The destruction will be documented within the source documentation and processed by the site monitor.

2.6. Section 6.15. Overdose

An overdose is defined as a daily dose of IP more than 200 mg (>1 tablet).

AEs associated with an overdose should be recorded on the appropriate AE CRF; however, all overdoses, including those not associated with an AE, should be recorded on the **appropriate** CRF~~s~~. ~~**An overdose should be reported even if it does not result in an AE.**~~

2.7. Section 6.16. Premature ~~Discontinuation~~ Withdrawal From the Study

. . .

Possible reasons for early ~~discontinuation~~**withdrawal** of subjects from the study include the following:

- Subject withdraws consent
- Death
- Lost to follow up
- ~~**Investigator decision**~~
- ~~**Sponsor's decision**~~

. . .

For subjects who ~~discontinue~~**withdraw** early or do not have an End of Study Visit, the site or delegate should attempt to collect vital status information (dead or alive). Vital status, based on publicly available sources, may also be investigated at ~~**the scheduled study end (ie,** Month 2~~**54)** for subjects who did not complete the study.

The date and the reason must be recorded on the CRF for all subjects who ~~discontinue~~**withdraw** early from the study. See Section 8.4.1 for End of Study Visit procedures.

2.8. Section 8 STUDY ACTIVITIES

. . .

During the Double-Blind Treatment Period, all visits will occur at the end of the study month (ie, the Month 3 Visit will occur on Day 84 [±7 days]). All scheduled visits should be referenced back to ~~**Day 1 (first dose of IP)**~~**the Baseline Visit**.

. . .

2.9. Section 8.1 Screening Period (Day ~~-30~~28 to ~~Day -1~~the Baseline Visit)

2.10. Section 8.1.1 Screening Visit 1 (Approximately 28 Days Before ~~Day 1~~the Baseline Visit)

2.11. Section 8.3. Treatment Period (Day 1 Through Month 24)

Subjects must meet all of the eligibility criteria listed in Section 4.2 and Section 4.3 before being randomized and starting IP, study-supplied XOI, and colchicine (as applicable). Subjects will receive IP in combination with an XOI for up to 24 months. Subjects who permanently discontinue IP early should complete an End of Treatment Visit **(Section 8.3.3)** as soon as possible after discontinuing IP ~~**(Section 8.3.3)**~~, and a Post-End of Treatment Visit **(Section 8.4.1)** 1 month after ~~**discontinuing IP (Section 8.4.1)**~~**the End of Treatment Visit**, but should remain on the study and follow the protocol-scheduled visits.

2.12. Section 8.3.3. Month 24 (±7 Days) and/or End of Treatment Visit

The following procedures and assessments will be performed at Month 24 (for subjects who complete the Treatment Period) or as soon as possible after permanently discontinuing IP (for subjects who discontinue IP early):

- Collect reasons for discontinuing IP, if applicable.
- Administer patient-reported outcome assessments.
- Review gout flares that occurred since the last study visit.
- Take vital signs.
- Measure weight.
- Assess AEs.
- Record concomitant medications.
- Assess compliance with IP (lesinurad/placebo).
- Assess compliance with XOI.
- Measure target tophi.
- Collect blood sample for hematology.
- Collect blood sample for the following serum chemistry analyses:
  - Analytes 1.
  - Analytes 2.
  - Analytes 3.
  - Pregnancy test for females of childbearing potential.
- Collect blood sample for plasma biomarkers.
- Collect urine sample for the following analyses:
  - Urinalysis.
  - Protein-creatinine ratio.
  - Urine biomarkers.
- **Dispense XOI.**

2.13. Section 8.4. Follow-Up Period

All subjects who complete the Treatment Period will return to the site for an End of Study Visit 1 month later (Section 8.4.2).

Subjects who permanently discontinue IP early should return to the site for an End of Treatment visit (Section 8.3.3) **as soon as possible after discontinuing IP**, then a Post-End of Treatment **(Section 8.4.1)** Visit 1 month after ~~**discontinuing IP**~~ **the End of Treatment Visit** ~~**(Section 8.3.1) , and then.**~~ **They should** remain on study and follow the protocol schedule (with

the exception of dispensing and taking IP) and have an End of Study Visit **(Section 8.4.2)** at the conclusion of the**ir** study period. **Alternatively, if the subject does not agree to this option, a modified follow-up including, eg, regular telephone contacts or a contact at Month 24, should be arranged, if agreed to by the subject and in compliance with local data privacy laws/practices.** Subjects who do not wish to continue on study after discontinuing IP should complete an End of Study Visit 1 month after treatment ~~withdrawal~~ **discontinuation** (Section 8.4.1), which ~~can~~ **should** be performed in place of the Post-End of Treatment Visit.

2.14. Section 8.4.2 End of Study Visit

All subjects should complete an End of Study Visit. This visit should occur approximately 28 days after completing the Treatment Period or after **permanent** treatment ~~withdrawal~~**discontinuation** if the subject is no longer continuing in the study. Subjects should return all study supplies to the site. The following procedures and assessments will be performed:

- Collect reasons for early study ~~discontinuation~~**withdrawal** if applicable.

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2.15. Section 11.8.2. Renal Events Adjudication Committee

An independent REAC will routinely evaluate **and categorize** all serious prospectively-defined renal-related and kidney stone AEs. In addition, the REAC chair will review all other SAEs in the clinical database and determine whether any additional SAEs should be adjudicated by the REAC. The REAC, in a blinded fashion, will assess the likelihood that potential contributing factors, including IP, contributed to the event. The committee will operate under a written, detailed REAC Charter. See the REAC Charter for details.

2.16. Appendix A. Schedule of Events

Assessment/Procedure	Screening Period			Double-Blind Treatment Period[a]			Follow-Up Period	
	SV1	SV2 (3 weeks [±3 days] after SV1)	Baseline Visit (4-7 days after SV2)	Day 1 (not a visit)	M1, 3, 6, 9, 12, 15, 18, 21	Month 24/ EOT Visit	Post-EOT Visit for Subjects off IP[b]	Month 25/ EOS Visit[c]
Obtain informed consent	X							
Review eligibility criteria	X	X	X					
Record demographics	X							
Record prior ULTs, including XOI and dose	X							
Assess AEs	X	X	X		X[d]	X	X	X
Randomize in IVRS/IWRS			X[e]					
Complete medical history			X					
Record concomitant medications			X		X	X	X	X
Administer patient-reported outcomes			X		X (except at M1)	X	X	X
Vital signs	X	X	X		X	X	X	X
Physical examination			X					
Height and weight (BMI)	X					Weight only		
12-lead ECG			X					
Assess gout flares[f]			X		X	X	X	X
Measure target tophi			X		M6, 12, 18	X	X	X
Laboratory Assessments								
Hematology blood collection			X		M6, 12, 18	X	X	X

Assessment/Procedure	Screening Period			Double-Blind Treatment Period[a]			Follow-Up Period	
	SV1	SV2 (3 weeks [±3 days] after SV1)	Baseline Visit (4-7 days after SV2)	Day 1 (not a visit)	M1, 3, 6, 9, 12, 15, 18, 21	Month 24/ EOT Visit	Post-EOT Visit for Subjects off IP[b]	Month 25/ EOS Visit[c]
Serum collection for the following chemistry analyses:								
Analytes 1	X[g]	X[g]	X		X[d]	X	X	X
Analytes 2			X		X	X	X	X
Analytes 3			X		M6, 12, 18	X	X	X
Pregnancy tests[h]		X			M12	X		
Urine collection for the following analyses:								
Urinalysis		X[i]	X		X	X	X	X
Protein-creatinine ratio			X		M6, 12, 18	X	X	X
Plasma and urine samples for biomarker collection			X		M6, 12, 18	X		X
Study Medication[j]								
Dispense Study Medication (lesinurad/placebo, XOI, colchicine)[k]			X		X (except at M1)	**X (XOI only)**	X (XOI only)	
Assess compliance with XOI[l]		X	X		X	X	X	X
Assess compliance with gout flare prophylaxis[m]					M3 and 6			
Assess compliance with IP					X	X		
Vital status								**X**

Abbreviations: AE, adverse event; BMI, body mass index; ECG, electrocardiogram; EOS, End of Study; EOT, End of Treatment; IP, investigational product; IVRS, Interactive Voice Response System; IWRS, Interactive Web Response System; M, study month, SV, Screening Visit; ULT, urate-lowering therapy; XOI, xanthine oxidase inhibitor.

Note: A clinical month is considered to be 28 days. All scheduled visits should be referenced to ~~**Day 1**~~**the Baseline Visit**. See Section 6 for more information on study procedures and assessments. Additional visits will be required if subjects experience changes in renal function as outlined in Section 6.12.

[a] The visit window during the Double-Blind Treatment Period is ±7-days beginning with the Month 1 Visit.

[b] Subjects who permanently discontinue IP early but remain on study should complete a Post-End of Treatment Visit approximately 28 days after the End of Treatment Visit.

[c] All subjects should complete an End of Study Visit approximately 28 days after completing the Treatment Period or withdrawing early from the study.

[d] For subjects who have permanently discontinued IP, at a minimum AE should be assessed and blood drawn for Analyte panel 1.

[e] Investigator must confirm eligibility prior to randomization.

[f] Baseline assessment is an assessment of gout flare history and post-Baseline assessment is an assessment of gout flares since the last visit.

[g] The estimated creatinine clearance (eCrCl) for each Screening Visit and the average of both Screening Visits (the "Screening eCrCl") will be calculated by the Cockcroft-Gault formula using ideal body weight.

[h] The follicle-stimulating hormone ~~**test**~~ (FSH) test will be done at SV2 only, and only for females with 12 months of spontaneous amenorrhea who are not surgically sterile. The human chorionic gonadotropin (HCG) test will be done at SV2 for all females and again at Month 12 for all females except those who are surgically sterile or not of childbearing potential as confirmed by the SV2 FSH.

[i] Includes assessment of protein by dipstick by the central laboratory.

[j] After a subject permanently discontinues IP, dispensing and compliance are not required.

[k] Colchicine will be dispensed at Baseline Visit and Month 3 Visit as applicable.

[l] Prescription XOI compliance will be assessed from Screening to Baseline. Study-supplied XOI compliance will be assessed from Day 1 through Month 2**45/End of Study**.

[m] Corticosteroids for gout flare prophylaxis may be taken through Month 3.

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Clinical Study Protocol

21Jun2017 09:35:33 PM GMT-08:00

ELECTRONIC SIGNATURES

Signed By	Signature Meaning	Outcome	Date
[redacted]	Medical	Approve	21Jun2017 11:56:10 AM GMT-08:00
[redacted]	Medical	Approve	21Jun2017 09:35:33 PM GMT-08:00