Ardea Biosciences

A member of the AstraZeneca Group

Lesinurad in Combination With a Xanthine Oxidase Inhibitor for Treatment of Hyperuricemia Associated With Gout

Briefing Document for the Arthritis Advisory Committee

Meeting Date: 23 October 2015

1. EXECUTIVE SUMMARY

Lesinurad is an oral selective urate-lowering therapy (ULT) that inhibits the uric acid transporter URAT1 in the kidney, resulting in increased uric acid excretion and lowering of serum uric acid (sUA). The combination of lesinurad and a xanthine oxidase inhibitor (XOI) targets both excretion and production of uric acid, thus providing a dual mechanism approach to effectively lower sUA levels.

Approval is being sought for lesinurad in combination with an XOI for the chronic treatment of hyperuricemia associated with gout in patients who have not achieved target sUA levels with an XOI alone. Of note, this proposed indication was submitted following the original New Drug Application (NDA) for lesinurad and is intended to more clearly reflect the second line population.

1.1. New Therapies Needed for Hyperuricemia in Uncontrolled Gout

Gout is a serious, chronic, and debilitating disease and is the most common type of inflammatory arthritis, more common than rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis combined.[1-3] Currently, there are an estimated 8.3 million patients diagnosed with chronic gout in the United States (US) and the prevalence is increasing.[4] The underlying cause of gout is hyperuricemia, which is typically defined as sUA greater than 6.8 mg/dL based on the solubility limit of uric acid in vitro. When sUA exceeds the solubility limit, urate crystals form and deposit in body tissues. When these crystals form in and around joints, they can manifest clinically as recurrent attacks of painful inflammatory arthritis (ie, gout flares). Eventually chronic, progressive arthropathy, including bone erosions, can occur.[5] When uric acid crystals form in the subcutaneous tissues they manifest as tophi, which can become disfiguring, painful, and infected.

Current treatment guidelines for ULTs for the treatment of hyperuricemia are designed to persistently lower sUA below the urate saturation level so new urate crystals cannot form and existing crystals can dissolve. In the absence of uric acid crystals, gout does not exist. The sUA targets recommended by the American College of Rheumatology (ACR) and European Union League Against Rheumatism (EULAR) are sUA < 6 mg/dL for all patients and sUA < 5 mg/dL for patients with greater disease severity, such as those with tophaceous gout.[6-8] Multiple studies have demonstrated the benefit of persistent sUA lowering to reduce the incidence and severity of clinical gout, as reflected by reductions in the frequency of acute gout flares[9-11] and the size and number of palpable tophi.[12-14]

Only 4 ULTs are available in the US for the treatment of gout, which can be grouped into 3 categories based on their mechanism of action: drugs that decrease uric acid production (XOIs), drugs that increase urinary uric acid excretion (probenecid), and drugs that enzymatically degrade excess circulating uric acid (pegloticase). XOIs (allopurinol and febuxostat) are first-line therapies for the majority of patients; however, approximately 40%-70% do not achieve and approximately 50%-80% of patients do not sustain recommended sUA goals in large randomized clinical trials.[15-18] Similar low response rates for allopurinol are also observed in clinical practice.[19, 20] Allopurinol is the most commonly used ULT. It was approved in 1966 with dosing instructions for uptitration from 100 mg up to a maximum of 800 mg per

day based on the severity of disease and to target sUA levels < 6 mg/dL. However, almost 50 years later, the most frequently prescribed dose in clinical practice is 300 mg daily,[19, 21] with less than 4% of patients prescribed doses > 300 mg[17, 22] despite the fact that the majority of patients receiving 300 mg do not achieve target sUA levels. Febuxostat doses of 40 mg and 80 mg once daily (qd) are approved in the US. In controlled clinical trials, the efficacy of febuxostat 40 mg was shown to be non-inferior to allopurinol 300 mg whereas febuxostat 80 mg was superior at lowering sUA to < 6 mg/dL.[17, 22] However, even with febuxostat 80 mg, 40% to 52% of patients did not achieve sUA < 6 mg/dL using a nonresponder imputation (NRI) analysis (Uloric, FDA Statistical Review, Part 1). For patients not achieving target sUA on an XOI alone, the ACR treatment guidelines recommend the addition of an agent that increases urinary uric acid excretion.[7, 8, 23]

Probenecid has been on the market since 1951, but is rarely prescribed, likely due to dosing frequency (2-4 times a day) and multiple drug-drug interactions (DDIs) with medications commonly used in the gout population (eg, NSAIDs, antibiotics, RAAS inhibitors, loop diuretics, analgesics, and muscle relaxants) (University of Washington School of Pharmacy Drug Interaction Database Website 2015; probenecid US package insert[24]). Many of these are related to inhibition of OAT1 and OAT3 (renal transporters involved in the disposition of many drugs).[24] In addition, data regarding the efficacy and safety of probenecid as a ULT in gout patients is extremely limited, particularly in randomized trials. A recent Cochrane review identified only 2 randomized controlled trials in gout comparing probenecid monotherapy with an agent not approved in the US (benzbromarone) with 35 patients in each study receiving probenecid, and one "quasi-randomized" trial with 17 patients receiving probenecid monotherapy compared to allopurinol.[25] A review of the literature showed that evaluation of probenecid in combination with an XOI in gout patients is limited to 2 small open-label studies with 20 or fewer patients receiving the combination.[26, 27]

Pegloticase is an intravenous (IV) drug for refractory gout. Its use is limited as anti-pegloticase antibodies develop in approximately 40% of patients resulting in loss of sUA lowering activity,[28, 29] and the drug has been associated with serious infusion reactions.

Effective and convenient treatment options are clearly needed for those patients who do not achieve sUA targets on available ULTs and require further sUA lowering to control their disease.

Lesinurad is a selective uric acid reabsorption inhibitor (SURI) that inhibits the uric acid transporter URAT1 in the kidney. URAT1 is responsible for reabsorbing the majority of filtered uric acid from the renal tubular lumen.[30, 31] By inhibiting URAT1, lesinurad increases uric acid excretion and thereby lowers sUA. Lesinurad also inhibits OAT4, a uric acid transporter involved in diuretic-induced hyperuricemia.[32] Lesinurad does not inhibit OAT1 or OAT3 in vivo, and has few clinically important DDIs. The combination of lesinurad and an XOI targets both excretion and production of uric acid, thus providing a dual mechanism approach to effectively lower sUA levels. This dual-mechanism approach for treating hyperuricemia for those patients who do not achieve sUA targets on an XOI is recommended by the ACR treatment guidelines for the management of gout.[7]

1.2. Lesinurad Clinical Development Program

As there are no specific regulatory guidelines for developing agents for hyperuricemia and gout, the lesinurad Phase 3 clinical development program was based on 1) key scientific literature on

treatment trials of hyperuricemia, 2) international treatment guidelines, 3) regulatory precedents for other development programs for ULTs to treat hyperuricemia in patients with gout, 4) consultation with disease experts, including the Principal Investigators, and 5) advice from the US FDA and other regulatory authorities.

The development program was large, robust, and global in scope. As of 04 November 2014, a total of 2587 patients have been exposed to lesinurad in 41 clinical studies, including 1842 patients with gout. A total of 1224 patients had been exposed to lesinurad at a dose of ≥ 200 mg qd for ≥ 24 weeks and 919 were exposed for ≥ 48 weeks.

The Phase 3 program included 4 studies: 3 pivotal 12-month combination studies and one 6-month monotherapy study. The CLEAR 1 and CLEAR 2 studies (also referred to as Studies 301 and 302, respectively) evaluated lesinurad 200 mg and 400 mg qd compared with placebo as add-on therapy to allopurinol in patients who had not achieved sUA target levels while on a physician-determined medically appropriate dose of allopurinol. CRYSTAL (Study 304) evaluated lesinurad 200 mg and 400 mg qd versus placebo in combination with febuxostat 80 mg in patients with tophaceous gout. A fourth Phase 3 study was conducted (Study 303) to evaluate lesinurad 400 mg qd monotherapy versus placebo in patients with gout who were intolerant of or had a contraindication to an XOI. Patients who completed the pivotal studies could enroll in uncontrolled extension studies.

Efficacy was demonstrated for lesinurad 400 mg monotherapy and lesinurad 400 mg in combination with an XOI in the Phase 3 studies; however, there was an increase in renal events (including renal-related adverse events [AEs] and serum creatinine [sCr] elevations) that was highest with lesinurad 400 mg monotherapy. Based on the overall benefit risk evaluation, lesinurad 200 mg is the recommended dose in combination with an XOI for the treatment of hyperuricemia associated with gout in patients who have not achieved target sUA levels with an XOI alone.

1.3. Pivotal Phase 3 Combination Therapy Studies

1.3.1. Study Design

CLEAR 1, CLEAR 2, and CRYSTAL were Phase 3, randomized, double-blind, multicenter, placebo-controlled studies in combination with an XOI in patients with uncontrolled gout.

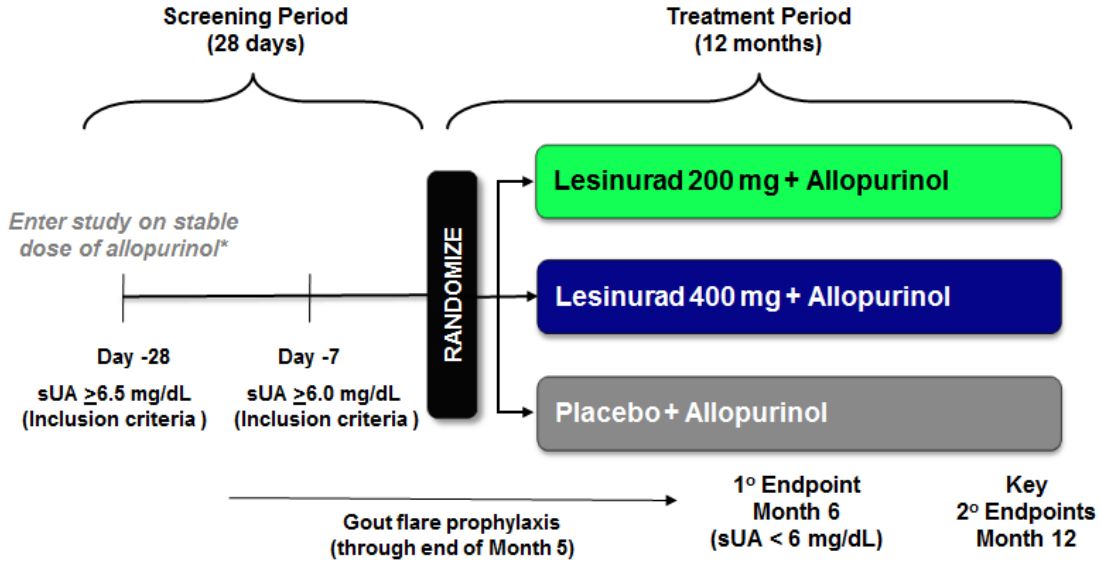
CLEAR 1 (US) and CLEAR 2 (global) were replicate studies to compare the efficacy and safety of lesinurad 200 mg and 400 mg vs. placebo when given as add-on therapy to allopurinol in patients who had not achieved sUA target levels while on a physician-determined medically appropriate dose of allopurinol, defined as a minimum of 300 mg daily (≥ 200 mg/day was permitted for patients with moderate renal impairment) and up to a maximum of 800 mg daily (in US) or 900 mg daily (in countries outside the US, depending on the local label). Patients were required to be taking a stable dose of allopurinol for ≥ 8 weeks prior to Screening and continued their individualized dose of allopurinol throughout the study. Patients were also required to have sUA levels above target at both the Screening and Day -7 Visits and ≥ 2 flares in the past year. CRYSTAL was a global study to compare the efficacy and safety of lesinurad 200 mg and 400 mg vs. placebo when given in combination with febuxostat 80 mg in patients with tophaceous gout. All patients were required to have ≥ 1 measurable target tophus and an sUA level above target at Screening. All patients initiated Sponsor-supplied febuxostat 80 mg

(highest approved dose in the US) on Day -21 and were randomized regardless of their Baseline sUA level.

In all 3 studies, patients were randomized to 1 of 3 treatment groups in a 1:1:1 ratio: lesinurad 200 mg, lesinurad 400 mg, or placebo qd plus allopurinol (CLEAR 1 and CLEAR 2) or febuxostat 80 mg (CRYSTAL) for up to 12 months. To ensure the treatment groups were balanced across medically important subgroups, randomization was stratified by Day -7 renal function (estimated creatinine clearance [eCrCl] using the Cockcroft-Gault formula ≥ 60 vs. < 60 mL/min). In CLEAR 1 and CLEAR 2, randomization was also stratified by tophus status during Screening (presence vs. absence of tophi) and in CRYSTAL, by sUA level at Day -7 (≥ 6 vs. < 6 mg/dL). Patients took lesinurad or placebo plus allopurinol (CLEAR 1 and CLEAR 2) or febuxostat (CRYSTAL) for up to 12 months. Patients also were to take gout flare prophylaxis (colchicine or a nonsteroidal anti-inflammatory drug [NSAID]) through Month 5. Patients who completed the studies had the option to enroll in an extension study, Study 306 (for CLEAR 1 and 2) or Study 307 (for CRYSTAL). Patients randomized to lesinurad plus XOI in the pivotal studies continued the same dose of lesinurad plus XOI in extension studies. Patients randomized to placebo plus XOI in the pivotal studies were randomized in a double-blind, 1:1 fashion to either lesinurad 200 mg or lesinurad 400 mg plus XOI in the extension studies. Blinding of lesinurad dose and sUA and urinary uric acid levels were maintained in the extension studies until each individual patient reached their Extension Month 12 Visit.

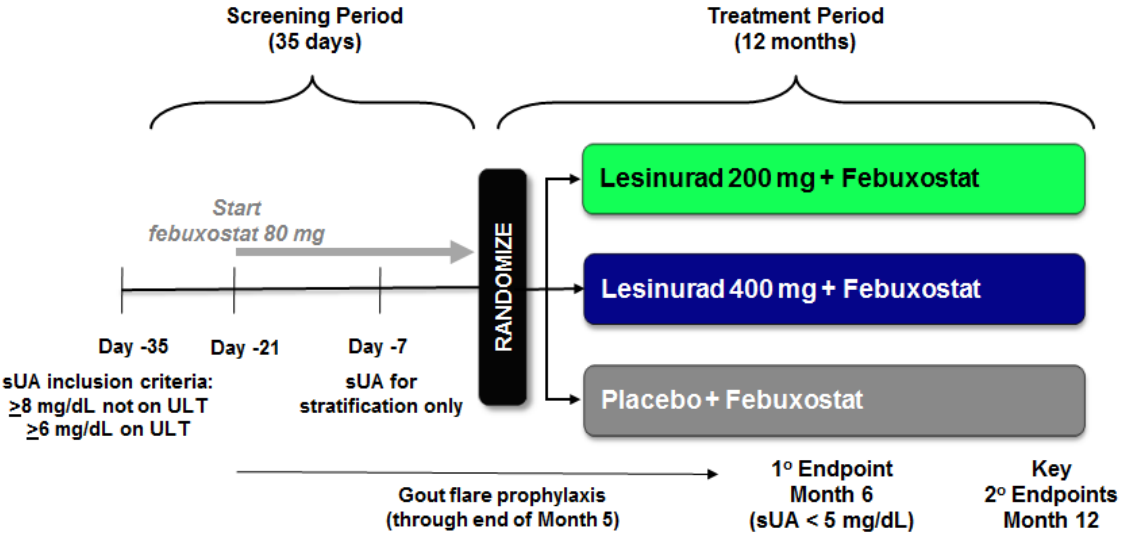
The primary endpoint was the proportion of patients with an sUA < 6 mg/dL by Month 6 for CLEAR 1 and CLEAR 2 and the proportion of patients with an sUA < 5 mg/dL by Month 6 for CRYSTAL. The sUA target levels were selected based on regulatory precedent and are in agreement with the current international treatment guidelines (including ACR and EULAR), with CRYSTAL reflecting the lower target recommended for patients with tophi. The prespecified primary method of analysis handled missing data by using the conservative NRI method, where patients who dropped out or were missing their Month 6 sUA result were analyzed as nonresponders. A gated, hierarchical testing algorithm controlled the type one error of the primary and key secondary endpoints for each trial. P values associated with analyses beyond this formal algorithm represent nominal p-values as they were not multiplicity protected. The multiplicity-protected key secondary endpoints included complete resolution (CR) of ≥ 1 target tophus (CLEAR 1, CLEAR 2, and CRYSTAL), mean gout flare rates (CLEAR 1 and CLEAR 2), and improvement in the Health Assessment Questionnaire - Disability Index (HAQ-DI), a Patient Reported Outcome (CRYSTAL). For all analyses, each lesinurad plus XOI treatment group was compared with XOI alone.

Figure 1: Study Design for CLEAR 1 and CLEAR 2 (Add-On to Allopurinol)



Abbreviations: sUA, serum uric acid.
*Patients were receiving a physician-determined medically appropriate dose of ≥ 300 mg/day and up to 800 or 900 mg/day depending on local label (≥200 mg/day was permitted for moderate renal impairment) for at least 8 weeks prior to screening.

Figure 2: Study Design for CRYSTAL (Combination With Febuxostat)



Abbreviations: sUA, serum uric acid; ULT, urate-lowering therapy.

1.3.2. Patient Disposition and Baseline Characteristics

A total of 603, 610, and 324 patients with longstanding, symptomatic gout and elevated sUA levels were treated in CLEAR 1, CLEAR 2, and CRYSTAL, respectively. In all 3 studies, over 80% of patients completed Month 6, the time of the primary endpoint assessment, and approximately 70% to 80% completed Month 12. In each study, the demographics and Baseline

disease characteristics were generally similar and well balanced across treatment groups (Appendix 1).

In CLEAR 1 and CLEAR 2, the majority of patients were male and White with a mean age of ~52 years and mean body mass index (BMI) over 33 kg/m^2. The mean duration since gout diagnosis exceeded 11 years. Over 75% of patients had at least 1 cardiovascular (CV) comorbidity or risk factor; the most common were hypertension, hyperlipidemia, and diabetes. Over half of patients had at least mild renal impairment at Baseline (eCrCl < 90 mL/min) and 14% to 22% had moderate renal impairment (eCrCl < 60 mL/min). The mean number of gout flares per patient was approximately 5.5 in the prior 12 months. The percent of patients with target tophi at Baseline was low (9% in CLEAR 1 and 16% in CLEAR 2). The mean (standard deviation [SD]) sUA level at Screening (after a minimum of 8 weeks on allopurinol before entering the study) was similar across treatment groups, ranging from 7.97 (1.47) to 8.11 (1.53) mg/dL. The majority of the patients were taking an allopurinol dose of 300 mg/day at Baseline (90% in CLEAR 1 and 84% in CLEAR 2), reflective of current medical practice.[19, 21]

In CRYSTAL, the majority of patients were also male and White. The mean age was 54 years and mean BMI was 32 kg/m^2. The mean duration since gout diagnosis exceeded 14 years. All patients were required to have ≥ 1 target tophus at Baseline. Across the treatment groups, an average of 6 to 7 gout flares per patient were reported in the prior 12 months. Similar to CLEAR 1 and 2, patients in CRYSTAL entered the study with a variety of comorbid conditions; the most common were hypertension, hyperlipidemia, and diabetes. Approximately two-thirds of patients had at least mild renal impairment and 20% to 26% had moderate renal impairment. The mean (SD) sUA ranged from 8.57 (1.76) to 8.83 (1.53) mg/dL at the Screening Visit.

1.3.3. Efficacy

The primary study endpoint for the Phase 3 studies was the proportion of patients reaching target sUA. Other clinical endpoints evaluated included gout flares requiring treatment, tophus area, and PROs.

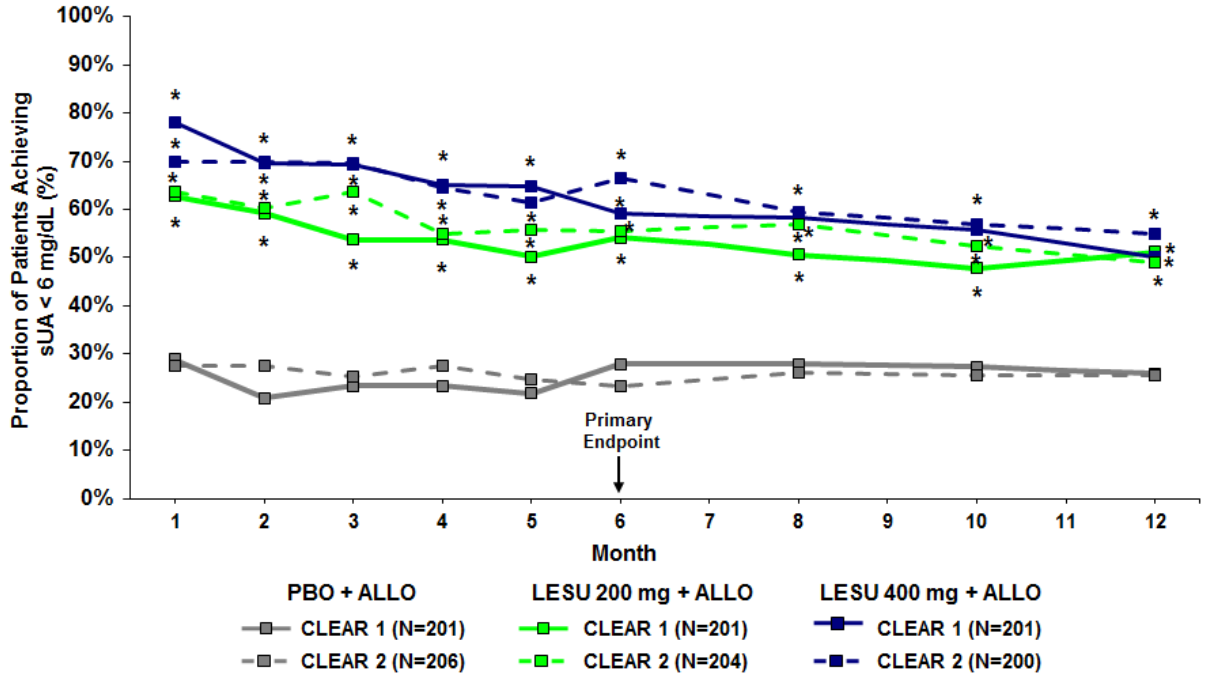
1.3.3.1. Serum Uric Acid Lowering

CLEAR 1 and CLEAR 2 Studies

The primary endpoint was met in both CLEAR 1 and CLEAR 2. When added to allopurinol, lesinurad 200 mg and 400 mg resulted in statistically significant increases in the proportion of patients who achieved the target goal of sUA < 6 mg/dL by Month 6 compared with allopurinol alone using NRI: 54.2% and 59.2% vs. 27.9% for CLEAR 1 and 55.4% and 66.5% vs. 23.3% for CLEAR 2 (Figure 3). In addition, multiple prespecified sensitivity and supportive analyses confirmed the robustness of the primary endpoint analyses.

Lesinurad plus allopurinol provided rapid, stable, and sustained sUA lowering < 6 mg/dL that was superior to allopurinol alone, resulting in a significantly greater proportion of patients achieving the recommended target sUA at all timepoints throughout each study (through Month 12).

Figure 3: Proportion of Patients Achieving Serum Uric Acid Level < 6 mg/dL by Visit in CLEAR 1 and CLEAR 2 – NRI (ITT Population)



Abbreviations: ALLO, allopurinol; ITT, intent-to-treat; LESU, lesinurad; NRI, nonresponder imputation; PBO, placebo; sUA, serum uric acid.
Note: Patients missing an sUA result were treated as nonresponders at that visit.
*p < 0.0001 vs. PBO + ALLO: multiplicity-protected at Month 6 (primary endpoint) and nominal p-values at all other months using Cochran-Mantel Haenszel test stratified by Day-7 renal function and tophus status at Screening (randomized values).

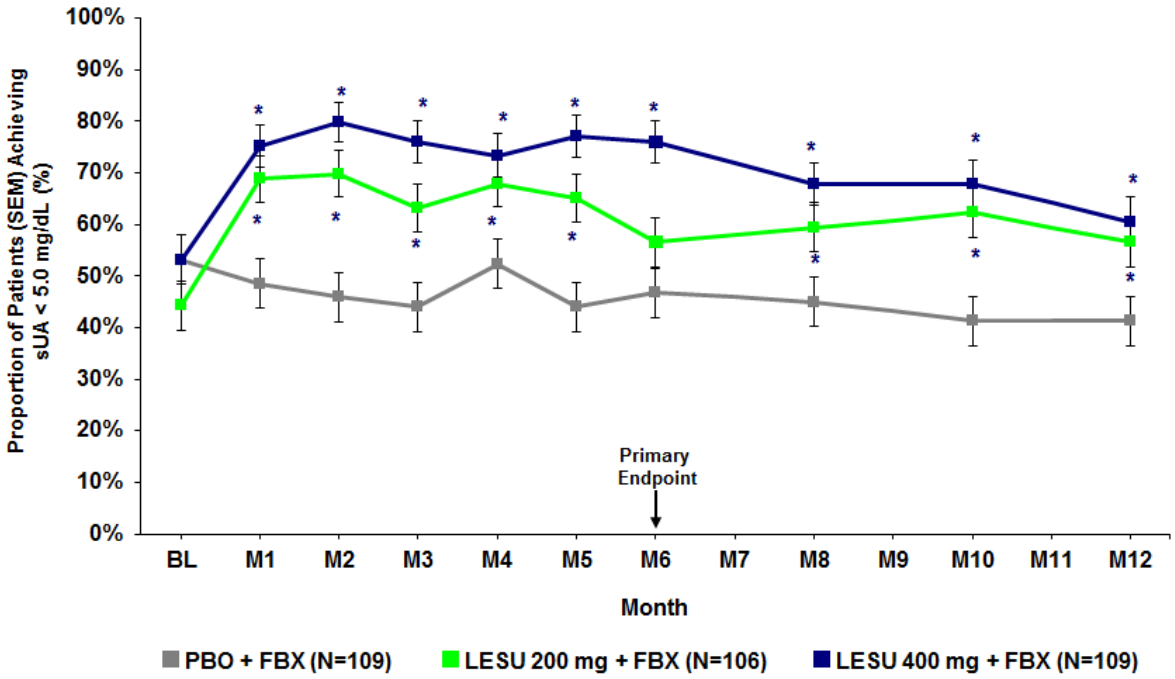
The degree of sUA lowering with the addition of lesinurad was significant and robust. At each timepoint during the 12-month treatment period, the mean percent decrease and absolute change from Baseline sUA was greater on lesinurad 200 mg plus allopurinol compared with allopurinol alone ($p < 0.0001$). At Month 6, 31% of patients in CLEAR 1 and 2 pooled demonstrated a ≥ 2 mg/dL absolute reduction in sUA. The magnitude of sUA lowering was significant as nearly 3 times as many patients in CLEAR 1 (28.9% vs. 10.4%, nominal $p < 0.0001$), and nearly 7 times as many patients in CLEAR 2 (34.8% vs. 4.9%, nominal $p < 0.0001$), treated with lesinurad 200 mg plus allopurinol achieved the more stringent sUA target < 5 mg/dL that is recommended for patients with greater disease severity.

Subgroup analyses using pooled data from CLEAR 1 and CLEAR 2 demonstrated that lesinurad plus allopurinol delivered consistent superior efficacy in clinically important subgroups, including those often difficult-to-treat patients: those with renal impairment, those with tophi, those taking thiazide diuretics, and those taking low-dose aspirin. Subgroup analyses also demonstrate that regardless of the Baseline allopurinol dose, the addition of lesinurad 200 mg resulted in consistent sUA lowering and an increase in the number of patients achieving the sUA target of < 6 mg/dL.

CRYSTAL Study

In CRYSTAL, the proportion of patients achieving the target sUA < 5 mg/dL at Month 6 (primary endpoint) was statistically significant for the lesinurad 400 mg group (76.1% vs. 46.8%; p<0.0001). The lesinurad 200 mg group did not achieve statistical significance at Month 6 compared with febuxostat alone (56.6% vs. 46.8%, p=0.1298); however, superior and clinically meaningful treatment effects were observed at all other timepoints (Months 1, 2, 3, 4, 5, 8, 10, and 12) with p-values ranging from 0.0002 to 0.0281 using NRI (Figure 4).

Figure 4: Proportion of Patients Achieving Serum Uric Acid Level < 5 mg/dL by Visit in CRYSTAL – NRI (ITT Population)



Abbreviations: FBX, febuxostat; ITT, intent-to-treat; LESU, lesinurad; NRI, nonresponder imputation; PBO, placebo; SEM, standard error of the mean; sUA, serum uric acid.
Note: Baseline reflects response rates after 3 weeks of febuxostat alone treatment during Screening. Patients missing an sUA result were treated as nonresponders at that visit.
* p < 0.0001 vs. PBO + FBX at Month 6 (multiplicity-protected primary endpoint) and nominal p-values 0.0002 to 0.0281 at all other months using Cochran-Mantel Haenszel test stratified by Day-7 renal function and Day-7 sUA level (randomized values).

As per the study design, patients were randomized in CRYSTAL after 3 weeks of febuxostat alone treatment regardless of their Baseline sUA level. At Baseline, prior to randomization, approximately 50% of patients had achieved sUA < 5 mg/dL, as expected with febuxostat alone treatment. In the prespecified subgroup of patients with a Baseline sUA ≥ 5 mg/dL, nearly twice as many patients in this subgroup achieved the target sUA < 5 mg/dL at Month 6 on lesinurad 200 mg plus febuxostat compared with febuxostat alone: 44.1% vs. 23.5% using NRI (p = 0.0243). In addition, sUA responses at Months 1 and 12 favored lesinurad combination therapy over febuxostat alone (Table 1). This is an important subgroup with the greatest need for additional treatment options because they did not achieved the target sUA level while on the highest dose of febuxostat approved in the US, and is the intended population to be treated.

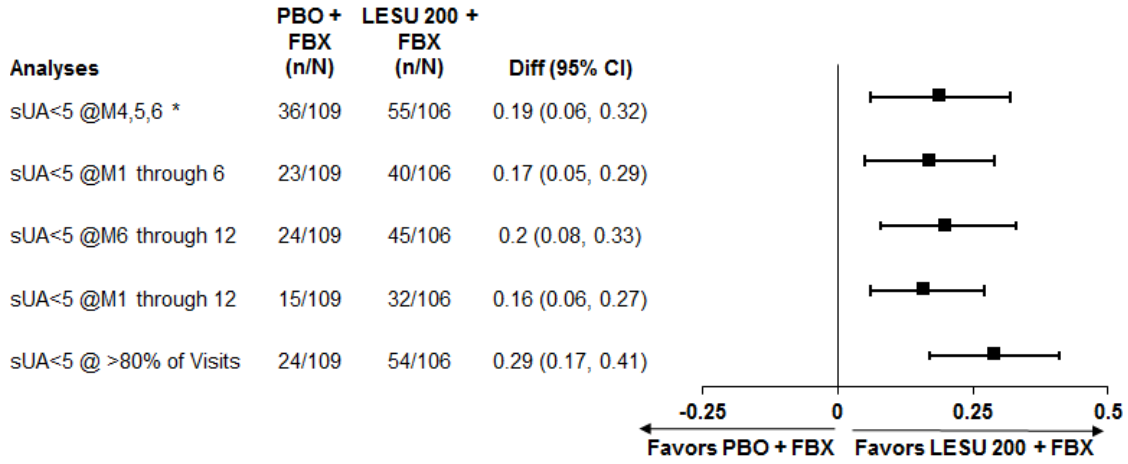
Table 1: Proportion of Patients Achieving an sUA < 5 mg/dL in the Subgroup of Patients With a Baseline sUA ≥ 5 mg/dL in CRYSTAL (ITT Population)

	PBO + FBX 80 mg	LESU 200 mg + FBX 80 mg	LESU 400 mg + FBX 80 mg
Proportion of Patients With an sUA < 5 mg/dL by Visit(s) (NRI)			
Month 1, n/N (%)	9/51 (17.6)	31/59 (52.5)	33/51 (64.7)
Difference in proportions vs. PBO + FBX 80 mg		0.35	0.47
(95%CI)		(0.18, 0.51)	(0.30, 0.64)
p-value[a]		0.0002	<0.0001
Month 6, n/N (%)	12/51 (23.5)	26/59 (44.1)	36/51 (70.6)
Difference in proportions vs. PBO + FBX 80 mg		0.21	0.47
(95%CI)		(0.03, 0.38)	(0.30, 0.64)
p-value[a]		0.0243	<0.0001
Month 12, n/N (%)	12/51 (23.5)	27/59 (45.8)	24/51 (47.1)
Difference in proportions vs. PBO + FBX 80 mg		0.22	0.24
(95%CI)		(0.05, 0.39)	(0.06, 0.42)
p-value[a]		0.0136	0.0137

Abbreviations: CI, confidence interval; FBX, febuxostat; ITT, intent-to-treat; LESU, lesinurad; NRI, nonresponder imputation; PBO, placebo; sUA, serum uric acid.
[a] Cochran-Mantel Haenszel test stratified by Day -7 renal function (eCrCl ≥ 60 vs. < 60 mL/min) and by Day -7 sUA level (≥ 6 vs. < 6 mg/dL), randomized values.

Because it is important to consistently maintain low sUA levels throughout the treatment period, additional prespecified and sensitivity analyses were conducted with measures of sustained response using NRI for the entire CRYSTAL population (Figure 5). Clinically meaningful differences favoring the lesinurad 200 mg plus febuxostat group vs. febuxostat alone were observed ($p \leq 0.0055$) for all of the analyses. In particular, more than twice as many patients in the lesinurad 200 mg plus febuxostat group reached the most stringent definition of achieving target at all timepoints (Months 1 through 12) compared with febuxostat alone.

Figure 5: Measures of Sustained Response: Lesinurad 200 mg Plus Febuxostat vs. Febuxostat Alone in CRYSTAL – NRI (ITT Population)



Abbreviations: FBX, febuxostat; ITT, intent-to-treat; LESU, lesinurad; M, month; NRI, nonresponder imputation; PBO, placebo; sUA, serum uric acid.
*Prespecified analysis.

1.3.3.2. Gout Flare Reduction

The mean rate of gout flares requiring treatment for the 6-month period from the end of Month 6 to the end of Month 12 was a key secondary endpoint in CLEAR 1 and CLEAR 2. This time period was selected because patients were to be off gout flare prophylaxis. A significant difference favoring lesinurad was not observed. In CRYSTAL, lesinurad 400 mg plus febuxostat demonstrated a 50% reduction in the mean rate of gout flares compared with febuxostat alone ($p < 0.05$).

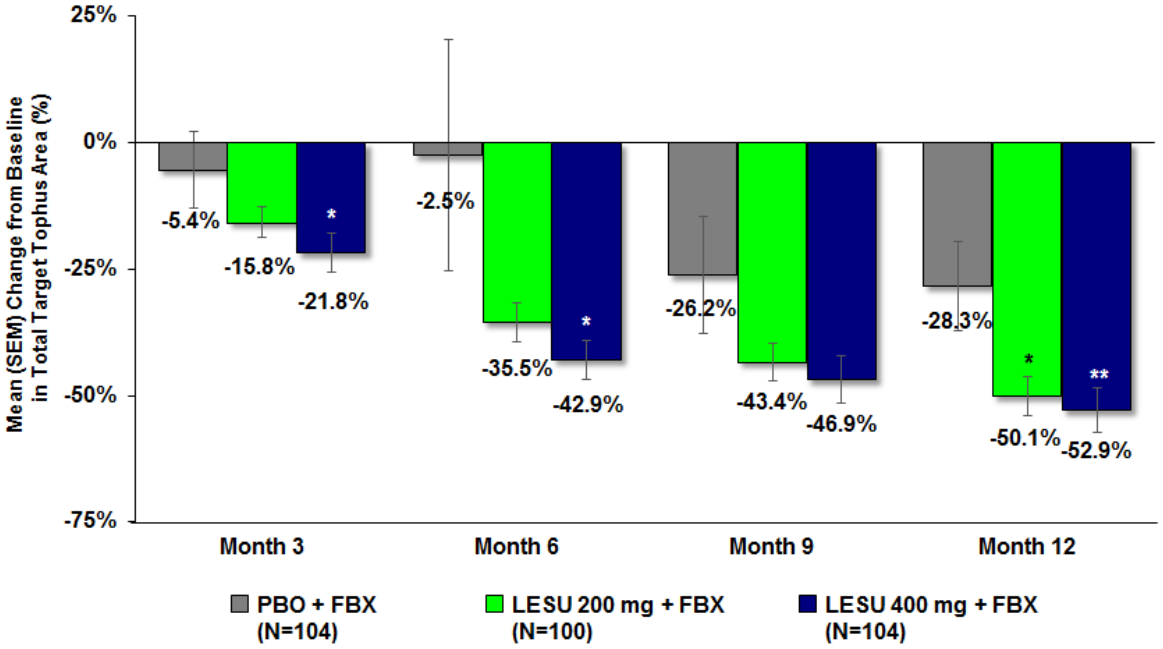
As expected with the initiation of ULT, patients treated with lesinurad tended to have increased flares during the first month on the pivotal study. The proportion of patients requiring treatment for a gout flare generally declined over time in all 3 treatment groups in the pivotal studies.

1.3.3.3. Tophus Reduction

Tophi, subcutaneous deposition of uric acid crystals, are the cardinal manifestation of persistent hyperuricemia and uncontrolled gout. Tophi resolution is dependent on both the degree and duration of sUA lowering.[33] In all 3 pivotal studies, a key secondary endpoint was the proportion of patients with ≥ 1 target tophus at Baseline who experienced a CR of ≥ 1 target tophus by Month 12. CRYSTAL also evaluated the proportion of patients with a CR or partial resolution (PR, ≥ 50% reduction) by Month 12 as a key secondary endpoint. An additional secondary endpoint in each study was the mean percent change from Baseline in the sum of the areas for all target tophi at Months 3, 6, 9, and 12. Up to 5 target tophi were followed, which were defined as measurable tophi on the hands/wrists and/or feet/ankles ≥ 5 mm and ≤ 20 mm in the longest diameter.

The proportion of patients with ≥ 1 target tophus at Baseline who experienced CR or either a CR or PR of ≥ 1 target tophus by Month 12 did not significantly favor lesinurad in any of the studies. In CRYSTAL, in which all patients had tophaceous gout, there was a dose-dependent trend favoring lesinurad for patients with a CR at Month 12: 25.5% and 30.3% for lesinurad 200 and 400 mg plus febuxostat vs. 21.1% for febuxostat alone. In addition, the mean percent reduction from Baseline to Month 12 in total target tophus area for lesinurad 200 mg and 400 mg plus febuxostat was nearly twice that of febuxostat alone (50.1% and 52.9% vs. 28.3% using last observation carried forward [LOCF]; $p = 0.0134$ and 0.0052, respectively, Figure 6). Similar results were demonstrated using the prespecified observed cases analysis and other sensitivity analyses, including mixed models repeated measure (MMRM) models.

Figure 6: Percent Change in Sum of the Areas for All Target Tophi (mm^2) by Visit in CRYSTAL - LOCF Imputation (ITT Population)



Abbreviations: FBX, febuxostat; ITT, intent-to-treat; LESU, lesinurad; LOCF, last observation carried forward; PBO, placebo; SEM, standard error of the mean.
Note: Figure depicts arithmetic means; statistical significance is based on difference in least square means.
*p < 0.05 vs. PBO + FBX, **p < 0.01 vs. PBO + FBX.

1.3.4. Safety

The proposed regimen of lesinurad 200 mg qd in combination with an XOI was generally well tolerated. The safety profile was similar to that of the XOI alone, with the exception of an increased incidence of transient or reversible sCr elevations. The incidence of renal events (ie, sCr elevations and renal-related AEs) was higher with lesinurad 400 mg plus XOI than with lesinurad 200 mg plus XOI, and highest with lesinurad 400 mg as monotherapy.

The safety assessment was based primarily on pooled data from the 12-month pivotal Phase 3 combination therapy studies (CLEAR 1, CLEAR 2, and CRYSTAL). Data from the ongoing extension studies (up to more than 2.5 years of exposure to lesinurad) have not revealed any new safety signals.

1.3.4.1. Overall Summary of Adverse Events

The AE profile of lesinurad 200 mg plus XOI was generally comparable to that of an XOI alone, whereas for each category of AEs, the incidence was higher for lesinurad 400 mg plus XOI (Table 2). Most AEs were mild or moderate in severity and resolved while continuing therapy. The number and type of events were similar whether lesinurad was combined with allopurinol or febuxostat.

Table 2: Incidence of Adverse Events by Category (CLEAR 1, CLEAR 2, and CRYSTAL Combined)

Adverse Event Category	PBO + XOI (N=516) n (%)	LESU 200 mg + XOI (N=511) n (%)	LESU 400 mg + XOI (N=510) n (%)
Any AE	363 (70.3)	386 (75.5)	407 (79.8)
AE with RCTC toxicity Grade 3 or 4	48 (9.3)	52 (10.2)	67 (13.1)
AE leading to discontinuation of PBO or LESU	28 (5.4)	32 (6.3)	48 (9.4)
Serious AE	29 (5.6)	24 (4.7)	44 (8.6)
Deaths	0	2 (0.4)	3 (0.6)

Abbreviations: AE, adverse event; LESU, lesinurad; PBO, placebo; RCTC, Rheumatology Common Toxicity Criteria; XOI, xanthine oxidase inhibitor (allopurinol/febuxostat).
Note: For each category, patients are included only once, even if they experienced multiple events in that category.

AEs with an incidence on lesinurad 200 mg or lesinurad 400 mg plus XOI that was ≥ 2% and ≥ 1 percentage point higher than on an XOI alone are shown in Table 3.

Table 3: Adverse Events With an Incidence on Lesinurad 200 mg or 400 mg Plus XOI ≥ 2% and ≥ 1 Percentage Point Higher Than on an XOI Alone (CLEAR 1, CLEAR 2, and CRYSTAL Pooled)

Preferred Term	PBO + XOI (N=516) n (%)	LESU 200 mg + XOI (N=511) n (%)	LESU 400 mg + XOI (N=510) n (%)
Upper respiratory tract infection	44 (8.5)	46 (9.0)	57 (11.2)
Hypertension	25 (4.8)	31 (6.1)	35 (6.9)
Headache	21 (4.1)	27 (5.3)	30 (5.9)
Influenza	14 (2.7)	26 (5.1)	16 (3.1)
Blood creatine phosphokinase increased	25 (4.8)	23 (4.5)	30 (5.9)
Blood creatinine increased	12 (2.3)	22 (4.3)	40 (7.8)
Sinusitis	13 (2.5)	17 (3.3)	20 (3.9)
Gastrooesophageal reflux disease	4 (0.8)	14 (2.7)	7 (1.4)
Myalgia	11 (2.1)	13 (2.5)	17 (3.3)
Dizziness	7 (1.4)	8 (1.6)	14 (2.7)

Abbreviations: LESU, lesinurad; PBO, placebo; XOI, xanthine oxidase inhibitor (allopurinol/febuxostat).
Note: Adverse events are coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 14.0. For each preferred term (PT), patients are included only once, even if they experienced multiple events in that PT. Events are sorted by decreasing incidence on LESU 200 mg + XOI.

Events classified in the Medical Dictionary for Regulatory Activities (MedDRA) Investigations, Musculoskeletal and Connective Tissue Disorders and the Renal and Urinary Disorders System Organ Classes (SOCs) were the most commonly reported AEs leading to discontinuation of randomized study medication. *Blood creatinine increased* was the most common individual AE leading to discontinuation, with an incidence of 0.8% on an XOI alone, 0.8% on lesinurad 200 mg plus XOI, and 1.8% on lesinurad 400 mg plus XOI.

Although the incidence of the preferred term (PT) *hypertension* was higher in the lesinurad plus XOI groups, evaluation of the broader list of hypertension events in the MedDRA Hypertension Standardised MedDRA Query (SMQ), which includes terms such as *blood pressure increased* and *blood pressure systolic increased*, provides evidence that lesinurad 200 mg was not associated with an increased risk of hypertension: 6.2% incidence on an XOI alone, 6.5% on lesinurad 200 mg plus XOI, and 7.8% on lesinurad 400 mg plus XOI. In addition, mean and median values for systolic and diastolic blood pressure (BP) were similar to Baseline values and comparable across treatment groups, and the incidence of clinically relevant abnormalities in systolic and diastolic BP was low and comparable across treatment groups.

Events classified in the Cardiac Disorders, Infections and Infestations, and Renal and Urinary Disorders SOCs were the most frequently reported SAEs. The most common individual SAEs were *pneumonia* (0.4%, 0.4%, and 0.2% incidence for an XOI alone, lesinurad 200 mg plus XOI, and lesinurad 400 mg plus XOI, respectively) and *coronary artery disease* (0%, 0.6%, and 0.4%, respectively).

The deaths in the clinical program were primarily CV-related, consistent with the patient population demographic and the patients' medical histories (Section 9.4.4). Five deaths occurred in lesinurad-treated patients during the randomized treatment periods of the pivotal studies.

Overall, increased duration of exposure to lesinurad 200 mg plus an XOI during the extension studies did not change the AE profile. When compared to the pivotal studies, there was a decrease in exposure-adjusted AE incidence rates in the combined pivotal and extension studies.

1.3.4.2. Clinical Laboratory Tests

No clinically relevant mean changes from Baseline or individual patient shifts from Baseline were observed for lesinurad 200 mg plus XOI with respect to any hematology or clinical chemistry parameters, with the exception of renal parameters. There was no evidence of hepatic toxicity associated with the use of lesinurad alone or in combination with an XOI. Renal laboratory parameters are discussed under Renal Safety below (Section 1.3.4.4).

1.3.4.3. Cardiovascular Safety

CV safety was a topic of special interest because of the well-documented prevalence of CV comorbidities in the gout population. Adverse CV effects were not expected with lesinurad based on its mechanism of action as a URAT1 inhibitor. In addition, in vitro and in vivo CV safety pharmacology and repeat dose studies in animals demonstrated no impact on platelet aggregation and no other effects suggesting potential adverse CV consequences at relevant human exposures. Lesinurad did not alter the QT interval or other electrocardiogram (ECG) parameters in a human thorough QT study.

In addition to standard review of AEs, blood lipids, BP, and ECG data by the Sponsor, an independent, external Cardiovascular Endpoints Adjudication Committee (CEAC), blinded to study treatment, assessed whether potential CV events met criteria for a major adverse CV event (MACE; ie, CV death, non-fatal myocardial infarction [MI]), or non-fatal stroke) or a non-MACE CV AE (eg, arrhythmias, hospitalization for heart failure, or unstable angina).

In the pivotal studies, the incidence of CV AEs was generally comparable across treatment groups. In addition, based on assessment of vital signs, lesinurad did not significantly alter BP. Clinical laboratory data analyses demonstrated that lesinurad did not alter serum lipid levels.

The number of potential CV events in the pivotal studies sent for adjudication by the CEAC was similar across treatment groups: 28 for an XOI alone, 32 for lesinurad 200 mg plus XOI, and 28 for lesinurad 400 mg plus XOI. There were a total of 17 MACE in 15 patients (1 patient on an XOI alone and 1 patient on lesinurad 400 mg plus XOI each had 2 MACE). The incidence of MACE was comparable for an XOI alone (3 patients) and lesinurad 200 mg plus XOI (4 patients), and the 95% CIs for the exposure-adjusted MACE rates for all 3 treatment groups were overlapping (Table 4). There was a numerically higher incidence for lesinurad 400 mg plus XOI (8 patients), which was due primarily to a higher incidence of nonfatal MIs in this treatment group. 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. There were no cases of unstable angina reported.

Table 4: Incidence of Adjudicated Major Adverse Cardiovascular Events (CLEAR 1, CLEAR 2, and CRYSTAL Pooled)

Event Category	PBO + XOI (N=516) (PYE = 421.2) n (%)	LESU 200 mg + XOI (N=511) (PYE = 414.6) n (%)	LESU 400 mg + XOI (N=510) (PYE = 413.0) n (%)
Incidence of CEAC-adjudicated MACE	3 (0.6)	4 (0.8)	8 (1.6)
Cardiovascular death	0	2 (0.4)	2 (0.4)
Nonfatal myocardial infarction	1 (0.2)	2 (0.4)	7 (1.4)
Nonfatal stroke	3 (0.6)	0	0
Exposure-adjusted incidence of MACE (95% CI)	0.71 (0.23, 2.21)	0.96 (0.36, 2.57)	1.94 (0.97, 3.87)

Abbreviations: AE, adverse event; CEAC, Cardiovascular Endpoints Adjudication Committee; CI, confidence interval; LESU, lesinurad; MACE, major adverse cardiovascular event; PBO, placebo; PYE, person-years of exposure; XOI, xanthine oxidase inhibitor (allopurinol/febuxostat).

1.3.4.4. Renal Safety

Lesinurad was not nephrotoxic following chronic dosing in monkeys or in rats, except at very high doses in rats (600 mg/kg/day [exposure 93 times the 200 mg dose in humans]. The no observed effect level (NOEL) was 300 mg/kg/day (exposure 43 times the 200 mg dose in humans). However, based on its mechanism of action, lesinurad may increase the risk of adverse effects related to increased uric acid excretion and potential associated sequelae in patients with gout. Therefore, a thorough assessment of renal safety data was conducted, including creation of prespecified comprehensive lists of renal-related and kidney stone AEs, and review of clinical laboratory data (including sCr, eCrCl [calculated using the Cockcroft-Gault formula], and urine protein–creatinine [Pr-Cr] ratio).

The incidence of renal-related AEs was comparable between an XOI alone and lesinurad 200 mg plus XOI, and higher for lesinurad 400 mg plus XOI (Table 5). The incidences of renal-related AEs leading to discontinuation and renal-related SAEs were low across treatment groups and again highest on lesinurad 400 mg plus XOI. The most common renal-related PT was blood

creatinine increased, with a 2.3% incidence on an XOI alone, 4.3% on lesinurad 200 mg plus XOI, and 7.8% on lesinurad 400 mg plus XOI.

The proportion of patients with a kidney stone AE was low and comparable across treatment groups.

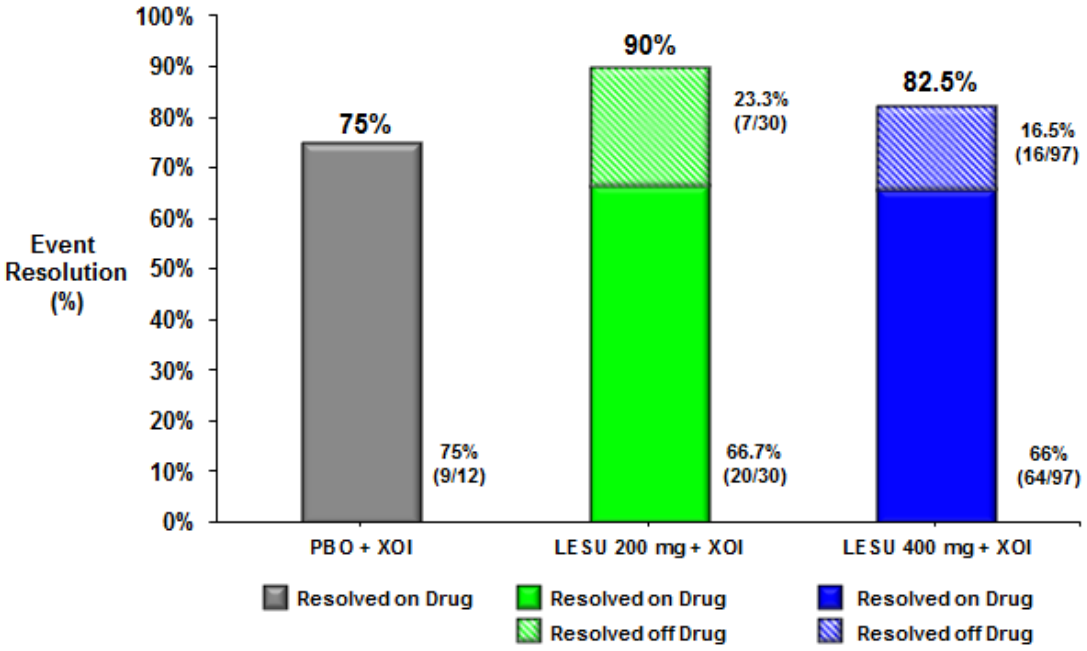
Table 5: Incidence of Renal Events by Category (CLEAR 1, CLEAR 2, and CRYSTAL Pooled)

Event Category [n (%)]	PBO + XOI (N=516)	LESU 200 mg + XOI (N=511)	LESU 400 mg +XOI (N=510)
Any renal-related AE	23 (4.5)	29 (5.7)	60 (11.8)
Renal-related AE leading to discontinuation of PBO or LESU	5 (1.0)	6 (1.2)	17 (3.3)
Renal-related SAE	2 (0.4)	0	5 (1.0)
Any kidney stone AE	9 (1.7)	3 (0.6)	13 (2.5)
Kidney stone AE leading to discontinuation of PBO or LESU	3 (0.6)	1 (0.2)	1 (0.2)
Kidney stone SAE	1 (0.2)	0	3 (0.6)
sCr elevation ≥ 1.5 x Baseline[a]	12 (2.3)	29 (5.7)	73 (14.3)
sCr elevation ≥ 2.0 x Baseline	0	9 (1.8)	34 (6.7)
sCr elevation ≥ 3.0 x Baseline	0	4 (0.8)	12 (2.4)

Abbreviations: AE, adverse event; LESU, lesinurad; PBO, placebo; SAE, serious adverse event; sCr, serum creatinine; XOI, xanthine oxidase inhibitor (allopurinol/febuxostat).
[a] Elevation categories are nested; ie, the ≥ 1.5 x Baseline category includes all elevations ≥ 1.5, ≥ 2.0, or ≥ 3.0 x Baseline, and the ≥ 2.0 x Baseline category includes all elevations ≥ 2.0 or ≥ 3.0 x Baseline.
Note: Adverse events were classified as renal-related or kidney stone adverse events as prespecified by the Sponsor. Baseline sCr was defined as the highest sCr value recorded ≤ 14 days prior to the first dose of randomized study medication.

There was no notable change in renal function within any treatment group, based on mean changes from Baseline to Last Value in sCr and eCrCl, and lesinurad in combination with an XOI did not increase the risk of proteinuria. Evaluation of individual patients who experienced sCr elevations showed that the incidence of elevations ≥ 1.5 x, 2.0 x, and 3.0 x Baseline was higher on lesinurad 200 mg and 400 mg plus XOI than on an XOI alone (Table 5). Most (27/30 or 90.0%) of the elevations on lesinurad 200 mg resolved (ie, returned to ≤ 1.2 x Baseline), and 66.7% resolved with continued lesinurad treatment (Figure 7). The majority of the elevations that resolved had resolved by the next study assessment (20/27 on lesinurad 200 mg plus XOI). The proportion of the overall safety population with a sCr elevation in a pivotal study that did not resolve, including extension study follow-up, was 3/516 for an XOI alone, 1/511 for lesinurad 200 mg plus XOI, and 10/510 for lesinurad 400 mg plus XOI.

Figure 7: Resolution of Serum Creatinine Elevations



Abbreviations: LESU, lesinurad; PBO, placebo; XOI, xanthine oxidase inhibitor (allopurinol/febuxostat).

Across the clinical development program, 2 patients required chronic renal replacement therapy. Both patients had CKD Stage III at Baseline (Baseline eCrCl 54 mL/min and 51 mL/min, respectively), were randomized to lesinurad 200 mg plus XOI, and completed the pivotal study with stable renal function. Both patients had progression of chronic kidney disease (CKD) after enrolling in an uncontrolled extension study. One of the patients discontinued the extension study after initiating chronic renal replacement therapy. The other patient required acute renal replacement therapy 11 months after discontinuing lesinurad, and initiated chronic renal replacement therapy 16 months after discontinuing lesinurad. One additional patient, who had Baseline eCrCl 32 mL/min and was receiving lesinurad 200 mg plus XOI in an uncontrolled extension study, required acute renal replacement therapy following cardiac arrest; his renal function had recovered to Baseline levels at the time of hospital discharge.

In the 6-month Phase 3 monotherapy study (Study 303), compared with placebo, lesinurad 400 mg was associated with a higher incidence of renal-related AEs (17.8% vs. 0%), renal-related SAEs (4.7% vs. 0%), and sCr elevations ≥ 1.5 x Baseline (24.3% vs. 0%). The higher rate of renal events observed with lesinurad monotherapy is likely due to excessive urinary uric acid excretion leading to intratubular uric acid precipitation. Lesinurad should only be used in combination with an XOI because the combination reduces the amount of uric acid available for excretion and decreases the risk of renal-related events.

1.3.4.5. Safety in Subgroups

Although elderly patients tended to have a higher overall incidence of AEs and a higher incidence of renal events, this was consistently observed across all treatment groups. Similarly, the incidences of AEs and renal-related AEs tended to increase with decreasing Baseline renal function; this result was observed for all 3 treatment groups. Renal impairment at Baseline was

not associated with an increased incidence of sCr elevations 1.5 x Baseline, and the mean change in eCrCl from Baseline to Last Value generally increased with decreasing Baseline renal function.

Overall, the treatment relationships with respect to the number or type of AEs, renal-related AEs, and sCr elevations were consistent across subgroups, including subgroups defined by:

- Demographic and disease characteristics: sex, age (< 65, ≥ 65, and ≥75 years), ethnicity (Hispanic or Latino/Not Hispanic or Latino), race (White/Non-White), BMI (< 30 kg/m^2 and ≥ 30 kg/m^2), presence of tophi at Baseline, comorbidity of diabetes, comorbidity of hypertension.
- Baseline renal function (eCrCl category [≥ 90, < 90, and < 60 mL/min]). Patients with severe renal impairment (< 30 mL/min) were excluded from the Phase 3 studies and severe renal impairment is a contraindication in the proposed label (lesinurad may not be effective in these patients).
- Geographic region (North America, South Africa, Europe, and Australia/New Zealand).
- Allopurinol dose > 300 mg daily.

Within the subgroup of patients with moderate renal impairment (eCrCl < 60 mL/min), there are a limited number of patients in the subset with eCrCl < 45 mL/min; in this subset, there were no clear or consistent treatment-dependent relationships with respect to the number or type of AEs, renal-related AEs, or sCr elevations.

1.3.5. Benefit-Risk Profile of Lesinurad 200 mg in Combination With an XOI

Approval is being sought for the use of lesinurad 200 mg qd in combination with an XOI, allopurinol or febuxostat, for the chronic treatment of hyperuricemia associated with gout in patients who have not achieved target sUA levels with an XOI alone.

Unfortunately, many patients do not achieve the recommended sUA target treatment goals with an XOI alone, leaving them uncontrolled and at risk for progression of urate crystal deposition and painful recurrent gout flares, disfiguring tophi, and destructive gouty arthritis.

Lesinurad is the first non-XOI, oral ULT developed in the US in over 60 years and if approved, will be the only oral ULT specifically developed as a second-line treatment option for patients unable to achieve target sUA with an XOI alone. Lesinurad, unlike probenecid, is a SURI. Lesinurad does not inhibit the renal transporters OAT1 and OAT3 in humans and therefore its use is not limited by the multiple OAT1- and OAT3-mediated DDIs of probenecid. Of note, nearly 40% of the patients in the lesinurad Phase 3 pivotal studies received a concurrent medication that has a known DDI with probenecid. Moreover, in contrast to probenecid where there are no published, large, randomized, controlled clinical trials in combination with an XOI, the safety and efficacy of lesinurad is well characterized with use in approximately 1800 patients with gout, including more than 1500 patients treated with lesinurad in combination with an XOI in Phase 3 studies. The recommended dose of lesinurad 200 mg in combination with an XOI has a safety profile comparable to an XOI alone with the exception of transient and reversible sCr elevations. The results of 3 randomized, placebo-controlled trials confirm that the combination

of lesinurad and an XOI results in superior sUA lowering, enabling significantly more patients to achieve and maintain target sUA goals.

The effect of lesinurad on sUA is rapid, evident within hours after the first dose, and sustained with continued qd dosing. The magnitude of sUA lowering observed when lesinurad is added to an XOI is significant and clinically relevant. In patients with sUA repeatedly above target on allopurinol, the addition of lesinurad 200 mg to allopurinol resulted in a doubling of the proportion of patients achieving the sUA target goal of < 6 mg/dL at Month 6 compared with allopurinol alone (primary endpoint, $p < 0.0001$). Lesinurad 200 mg in combination with febuxostat 80 mg also resulted in a significantly greater proportion of patients with tophaceous gout achieving sUA < 5 mg/dL at all timepoints through Month 12 except Month 6, which was the timepoint for the primary endpoint. Importantly, in the subgroup of patients not achieving sUA < 5 mg/dL at Baseline while on febuxostat 80 mg alone, the addition of lesinurad 200 mg nearly doubled the proportion of patients who achieved the target sUA < 5 mg/dL compared with febuxostat alone at all timepoints, including Month 6.

The urate-lowering efficacy of lesinurad in combination with an XOI is consistently observed across important patient subgroups, including patients on doses of allopurinol > 300 mg daily and difficult-to-manage patients such as those with mild or moderate renal impairment, those taking thiazide and thiazide-like diuretics, and those with pre-existing tophi.

A statistically significant difference between treatments was not observed for the key secondary endpoints of CR of ≥ 1 target tophus or mean flare rates. This was not unexpected as no ULT has convincingly demonstrated a statistically significant reduction in gout flares during the controlled study period. Sustained sUA lowering will reverse the deposition of uric acid from the tissues; however, this process may require more than 12 months of treatment. Reduction in flares and resolution of tophi have been observed with continued treatment in the open-label extension trial with febuxostat.[10, 34] Similarly, reduction of flares and resolution of tophi were observed with continued treatment with lesinurad plus an XOI in our extension studies.

Lesinurad 200 mg in combination with an XOI demonstrated a safety profile that was comparable to that of an XOI alone, with the exception of an increase in transient sCr elevations, most of which resolved without interruption of lesinurad. In the lesinurad 200 mg plus XOI and XOI alone groups, a small and comparable number of patients had unresolved sCr elevations at the end of the pivotal studies (n = 3 in both groups; of note, 2 of the 3 in the lesinurad 200 mg plus XOI group resolved with continued dosing in an extension study). There was no notable change in renal function within any treatment group, based on mean changes from Baseline to Last Value in sCr and eCrCl, and lesinurad in combination with an XOI did not increase the risk of proteinuria. There was also no increased risk of CKD progression, based on a modification of Kidney Disease Improving Global Outcomes (KDIGO) risk categories. Events suggestive of acute uric acid nephropathy have been reported on lesinurad 200 mg and lesinurad 400 mg plus XOI; however, serious events were infrequent and sCr returned to Baseline values for most patients. The frequency of sCr elevations is not increased in any particular subset of patients, including patients with mild or moderate renal impairment.

Patients with hyperuricemia associated with gout have multiple cardiac comorbidities and are at an increased risk for MACE compared to patients without gout. The incidence of MACE was low with a comparable event rate for an XOI alone and lesinurad 200 mg plus XOI. 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.

Although a CV signal with lesinurad has not been identified, a post-approval prospective observational cohort study is proposed to assess the potential risk for CV events. A secondary objective of the study will be to further characterize the renal safety of lesinurad.

Throughout the proposed product labeling for lesinurad, the risks of sCr elevations and of acute renal failure with lesinurad, particularly when used as monotherapy, are presented, including in a Boxed Warning. Emphasis is placed on the importance of co-administration with an XOI to reduce the risks. Prescribers are instructed to monitor renal function prior to initiation of lesinurad and periodically thereafter, as clinically indicated, and to interrupt lesinurad treatment if sCr increases to > 2 x the pre-treatment value or if symptoms develop that may indicate acute uric acid nephropathy, such as flank pain, nausea, or vomiting. Based on both efficacy and safety data, no dose adjustment is required in patients with mild or moderate renal impairment. Due to limited experience in patients with CrCl between 30 and 45 mL/min, caution is recommended in this subgroup. Lesinurad is contraindicated in patients with severe renal impairment (CrCl < 30 mL/min) as sufficient efficacy may not be expected in these patients, and they were excluded from the Phase 3 studies.

Patients taking lesinurad are recommended to drink 2 liters (68 ounces) of liquid a day to reduce the potential for developing nephrolithiasis and other renal events. The proposed Medication Guide to be provided to patients describes the renal-related risks and signs and symptoms to report to their doctor, and reinforces the prescribing instructions to avoid monotherapy use.

Additional proposed risk mitigation measures include a Communication Plan targeted to healthcare providers who are likely to prescribe and dispense lesinurad, and routine and expanded pharmacovigilance activities to facilitate identification and evaluation of known and potential risks, including a questionnaire to capture details on each reported case of a renal-related event.

In summary, the efficacy results provide clear evidence of significant sUA lowering with lesinurad 200 mg in combination with an XOI and support the proposed indication for the treatment of hyperuricemia associated with gout in patients who have not achieved target sUA levels with an XOI alone. The safety results indicate that lesinurad 200 mg in combination with an XOI is generally well tolerated with a consistent safety profile during extended dosing beyond 12 months. The identified risks are manageable with the proposed labeling and communication activities.

In patients unable to achieve sUA targets on an XOI alone, lesinurad 200 mg in combination with allopurinol or febuxostat has a favorable benefit-risk profile. There is a clear medical need for effective second-line treatment options with proven efficacy and safety for the management of hyperuricemia associated with gout. Lesinurad, if approved, will help to address this need and enable significantly more patients with uncontrolled gout to achieve and maintain target sUA treatment goals.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ACE	Angiotensin-converting-enzyme
ACR	American College of Rheumatology
AE	(Treatment-emergent) adverse event
AKI	Acute kidney injury
ALT	Alanine aminotransferase
ARA	American Rheumatism Association
AST	Aspartate aminotransferase
ANCOVA	Analysis of covariance
AUC	Area under the concentration-time curve
BCRP	Breast Cancer Resistance Protein
BMI	Body mass index
BP	Blood pressure
BUN	Blood urea nitrogen
CEAC	Cardiovascular Endpoints Adjudication Committee
CI	Confidence interval
CKD	Chronic kidney disease
CLEAR 1	Phase 3 study of lesinurad in combination with allopurinol (US study, also known as Study 301)
CLEAR 2	Phase 3 study of lesinurad in combination with allopurinol (global study, also known as Study 302)
C_{max}	Maximum observed concentration
CMH	Cochran-Mantel Haenszel
CR	Complete resolution
CRYSTAL	Phase 3 study of lesinurad in combination with febuxostat (global study, also known as Study 304)
CV	Cardiovascular
CYP	Cytochrome P450
DDI	Drug-drug interaction

DILI	Drug-induced liver injury
DVT	Deep venous thrombosis
ECG	Electrocardiogram
eCrCl	Estimated creatinine clearance (calculated by the Cockcroft-Gault formula using ideal body weight at Screening)
eDiary	Electronic diary
EULAR	European Union League Against Rheumatism
FDA	(United States) Food and Drug Administration
GFR	Glomerular filtration rate
HAQ	Health Assessment Questionnaire
HAQ-DI	Health Assessment Questionnaire - Disability Index
IC_{50}	50% inhibitory concentration
ICH	International Conference on Harmonisation
ITT	Intent-to-treat
IV	Intravenous
KDIGO	Kidney Disease Improving Global Outcomes
LASSO	Six-month observational study of allopurinol-treated patients (also known as ALLO-401)
LOCF	Last observation carried forward imputation
MACE	Major adverse cardiovascular event
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
MMRM	Mixed models repeated measures
n	Number of patients
NDA	New Drug Application
NOEL	No observed effect level
NRI	Nonresponder imputation
NSAID	Nonsteroidal anti-inflammatory drug
NYHA	New York Heart Association
OAT	Organic anion transporter

PD	Pharmacodynamic(s)
PGA	Patient Global Assessment
PK	Pharmacokinetic(s)
PR	Partial resolution
Pr-Cr	Urine protein-creatinine
PT	(MedDRA) preferred term
PYE	Person-years of exposure
qd	Once daily
QTcF	QT interval corrected for heart rate using Fridericia's formula
RAAS	Renin-angiotensin-aldosterone system
REAC	Renal Events Adjudication Committee
REMS	Risk Evaluation and Mitigation Strategy
SAE	Serious adverse event
sCr	Serum creatinine
SD	Standard deviation
SDS	Sheehan Disability Scale
SE	Standard error
SF-36	Short Form-36
SMQ	Standardised MedDRA Query
SOC	(MedDRA) System Organ Class
sUA	Serum uric acid (also referred to as serum urate)
SURI	Selective uric acid reabsorption inhibitor
$t_{½}$	Elimination half-life
THIN	The Health Improvement Network
TSQM	Treatment Satisfaction Questionnaire for Medication
UK	United Kingdom
ULN	Upper limit of normal
ULT	Urate-lowering therapy
URAT1	Uric acid transporter 1

US	United States
UTI	Urinary tract infection
XOI	Xanthine oxidase inhibitor

CONVENTIONS

In this document the lesinurad clinical studies are generally identified using the last 3 digits of the protocol number. For example, Study RDEA594-306 is referred to as Study 306. Studies 301, 302, and 304 are also identified by name: CLEAR 1, CLEAR 2, and CRYSTAL, respectively.

Placebo in combination with an XOI is generally referred to as "XOI alone."

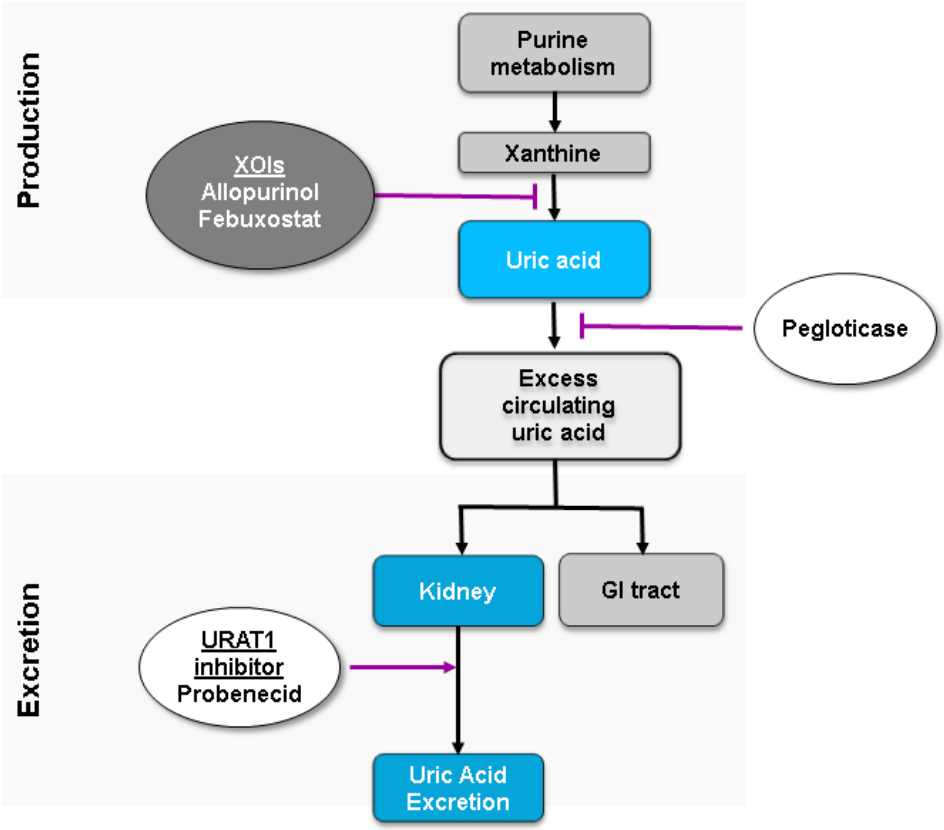
2. NEED FOR ADDITIONAL THERAPIES FOR HYPERURICEMIA IN UNCONTROLLED GOUT

Gout is a serious, chronic, and debilitating disease[1] with an estimated 8.3 million patients diagnosed in the US and the prevalence is increasing.[4] The underlying cause of gout is hyperuricemia, which is typically defined as sUA greater than 6.8 mg/dL, based on the solubility limit of uric acid in vitro. When sUA exceeds the solubility limit, urate crystals form and deposit in body tissues. When these crystals form in and around joints, they can manifest clinically as recurrent attacks of painful inflammatory arthritis (ie, gout flares). In fact, gout is the most common type of inflammatory arthritis, more common than rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis combined.[1-3] Eventually chronic, progressive arthropathy, including bone erosions, can occur.[5] When uric acid crystals form in the subcutaneous tissues, they manifest as tophi, which can become disfiguring, painful, and infected. In addition to causing pain, disability, and diminished quality of life, gout – particularly poorly controlled gout – is associated with substantial health care costs and loss of productivity. Observational studies have shown independent associations between hyperuricemia and the risk of hypertension, MI, CKD, type 2 diabetes, and metabolic syndrome (including obesity).[35-38] Gout has also been associated with an increased risk of all-cause death, as well as CV death.[39, 40] The causal relationship or the benefits of sUA lowering on these comorbid conditions or death has not been demonstrated.

Current treatment guidelines for ULTs for the treatment of hyperuricemia are designed to persistently lower sUA below the urate saturation level so new urate crystals cannot form and existing crystals can dissolve.[16, 17, 41-43] In the absence of uric acid crystals, gout does not exist. The recommended sUA target to durably improve the signs and symptoms of gout is sUA < 6 mg/dL;[6, 7, 44] a target sUA < 5 mg/dL is recommended for greater disease severity, such as patients with tophaceous gout.[6, 7] Multiple studies have demonstrated that persistent sUA lowering will in the long term lead to reductions in the frequency of acute gout flares[9-11] and the size and number of palpable tophi.[12-14]

Although diet can contribute to hyperuricemia in some patients, even a very restrictive low-purine diet is not effective at significantly lowering sUA;[45, 46] therefore, ULT remains the mainstay of gout management. Only 4 ULT agents are available in the US for the treatment of gout, which can be grouped into 3 categories based on their mechanism of action: drugs that decrease uric acid production (XOIs, allopurinol and febuxostat), drugs that increase urinary uric acid excretion (probenecid), and drugs that enzymatically degrade excess circulating uric acid (pegloticase) (Figure 8).

Figure 8: Schematic of Current Urate-Lowering Therapies



Abbreviations: GI, gastrointestinal; URAT1, uric acid transporter 1; XOI, xanthine oxidase inhibitor.
Sources: Adapted from Burns 2011[47] and the Krystexxa US package insert.[29]

XOIs (allopurinol and febuxostat) are first-line therapies for the majority of patients; however, approximately 40%-70% do not achieve and approximately 50%-80% of patients do not sustain recommended sUA goals in large randomized clinical trials and warrant additional treatment to control their disease (Table 6).[7, 8, 16-18, 22, 23, 44] Allopurinol was approved in 1966 and is the more commonly used of the 2 available XOIs. According to the US prescribing information for allopurinol, the minimal effective dosage is 100 to 200 mg daily and the maximal recommended dosage is 800 mg daily; however, the most frequently prescribed dose in clinical practice is 300 mg daily, with less than 4% of patients prescribed doses > 300 mg.[19, 21] The lack of uptitration is likely due to safety concerns with higher doses.[35, 48] In randomized controlled clinical studies in gout, approximately 60% of patients did not achieve sUA levels < 6 mg/dL and approximately 80% did not maintain these sUA levels at the last 3 consecutive visits when treated with allopurinol 300 mg daily and thus were ineffectively treated (Table 7).[17, 22] Similar low response rates are also observed in clinical practice.[19, 20, 49] Although allopurinol has been used in the treatment of gout for nearly 50 years, no data are available from adequately controlled clinical trials evaluating the efficacy and safety of allopurinol doses exceeding 300 mg. Ardea also conducted a global, open-label, 6-month interventional study of allopurinol in patients with gout, during which Investigators were encouraged to titrate allopurinol up to the highest approved dose (800 mg in the US, 900 mg in other regions) to achieve sUA < 6 mg/dL. A total of 1732 patients received at least 1 dose of allopurinol. Despite the recommendation to uptitrate allopurinol, Investigators increased the dose above 300 mg in

only 20.2% of patients, even though 67.3% of patients at daily doses of 300 mg or less were not at target. Importantly, in those patients receiving daily doses higher than 300 mg, a significant proportion (51.7%) still did not achieve target sUA < 6 mg/dL by Month 6.[50]

Febuxostat is the most recently approved XOI for the treatment of hyperuricemia in patients with gout and was studied in patients naïve to ULT or those not receiving ULT at the time of study initiation. Febuxostat doses of 40 mg and 80 mg qd are approved in the US. Compared with allopurinol 300 mg, the efficacy of febuxostat 40 mg was shown to be non-inferior whereas febuxostat 80 mg was superior; however, even with febuxostat 80 mg, 40% to 52% of patients did not achieve sUA target < 6 mg/dL using NRI (Uloric, FDA Statistical Review, Part 1).

Table 6: Proportion of Patients Who Failed to Achieve Serum Uric Acid < 6 mg/dL With Febuxostat or Allopurinol (NRI)

Phase 3 Studies	Febuxostat 80 mg qd		Allopurinol 300 mg qd	
	Month 6[a]	Last 3 Consecutive Visits[b]	Month 6[a]	Last 3 Consecutive Visits[b]
Study 1 (APEX)	52%	52%	68%	78%
Study 2 (FACT)	48%	47%	71%	79%
Study 3 (CONFIRMS)	40%	-	62%	-

[a] Uloric, FDA Statistical Review, Part 1, Table 2, nonresponder imputation analysis (of note the USPI response rates use last observation carried forward [LOCF]).
[b] Febuxostat, SmPC.

For patients not achieving target sUA levels on an XOI alone, the ACR treatment guidelines recommend the addition of an agent that increases urinary uric acid excretion.[6-8] Probenecid, an oral URAT1 inhibitor, has been on the market since 1951, but is rarely prescribed, accounting for only 2%-3% of all ULT prescriptions in the US (IMS Health, IMS Health, IMS National Prescription Audit, Sept 2015).[20] Probenecid is requires administration 2 to 4 times per day and has multiple DDIs with medications commonly used in the gout population (Table 7). Many of these DDIs are due to inhibition of OAT1 and OAT3 (renal transporters involved in the disposition of many drugs). In addition, data regarding the efficacy and safety of probenecid as ULT in gout patients is extremely limited, particularly in randomized trials. A recent Cochrane review identified only 2 randomized controlled trials in gout comparing probenecid monotherapy with an agent not approved in the US (benzbromarone) with 35 patients in each study receiving probenecid, and one "quasi-randomized" trial with 17 patients receiving probenecid monotherapy compared to allopurinol.[25] A review of the literature showed that evaluation of probenecid in combination with an XOI in gout patients is limited to 2 small open-label studies with 20 or fewer patients receiving the combination.[26, 27]

Table 7: Examples of Commonly Used Medications in Gout Population That Have Drug Interactions With Probenecid

NSAIDS	Antibiotics	RAAS Inhibitors	Loop Diuretics	Other
Indomethacin	Ciprofloxacin and norfloxacin	Captopril	Furosemide	Acetominophen
Naproxen	Penicillin and other beta-lactams	Olmesartan	Bumetanide	Baclofen
Ketoprofen	Cephalosporins (eg, ceftriaxone, cefazolin, cefaclor)	Enalapril		Lorazepam
				Famotidine

Abbreviations: NSAIDs, nonsteroidal anti-inflammatory drug; RAAS, renin-angiotensin-aldosterone system.
Sources: University of Washington School of Pharmacy Drug Interaction Database Website 2015, probenecid US package insert.[24]

Pegloticase was approved in 2010 for gout that is refractory to conventional therapy. Although efficacious, pegloticase requires IV administration and anti-pegloticase antibodies develop in approximately 40% of patients, resulting in loss of sUA lowering activity and an increased risk of anaphylactic reactions, which limit its use.[28, 29]

Effective and convenient treatment options are clearly needed for those patients who do not achieve sUA targets on available ULTs and require further sUA lowering to control their disease.

3. MECHANISM OF ACTION OF LESINURAD

Uric acid is freely filtered in the kidney at the glomerulus and enters the proximal tubule where more than 90 % is reabsorbed back into the blood stream through the uric acid transporter URAT1.[30, 31] Any uric acid that is not reabsorbed moves to the distal part of the nephron and is excreted in the urine. In the majority of patients with gout, hyperuricemia is caused by inefficient renal excretion of uric acid.[51] Lesinurad is a selective uric acid reabsorption inhibitor (SURI) that inhibits the uric acid transporter URAT1. By inhibiting URAT1, lesinurad increases uric acid excretion and thereby lowers sUA (Figure 9). Lesinurad also inhibits OAT4, a uric acid transporter involved in diuretic-induced hyperuricemia.[32] In contrast to probenecid, lesinurad does not inhibit the common drug transporters OAT1 and OAT3 in vivo (Figure 10). XOIs (allopurinol and febuxostat) act by reducing the production of uric acid, primarily in the liver and intestine. The combination of lesinurad and an XOI targets both excretion and production of uric acid, thus providing a dual mechanism approach to effectively lower sUA levels. This approach is in line with treatment guidelines for gout, which recommend combination therapy to target uric acid production and excretion for patients who do not achieve sUA targets on an XOI alone and in patients with uncontrolled gout evident by continuing disease activity (ACR international guidelines for hyperuricemia,[7] EULAR treatment recommendations[6, 8]).

Figure 9: Schematic of Lesinurad's Mechanism of Action

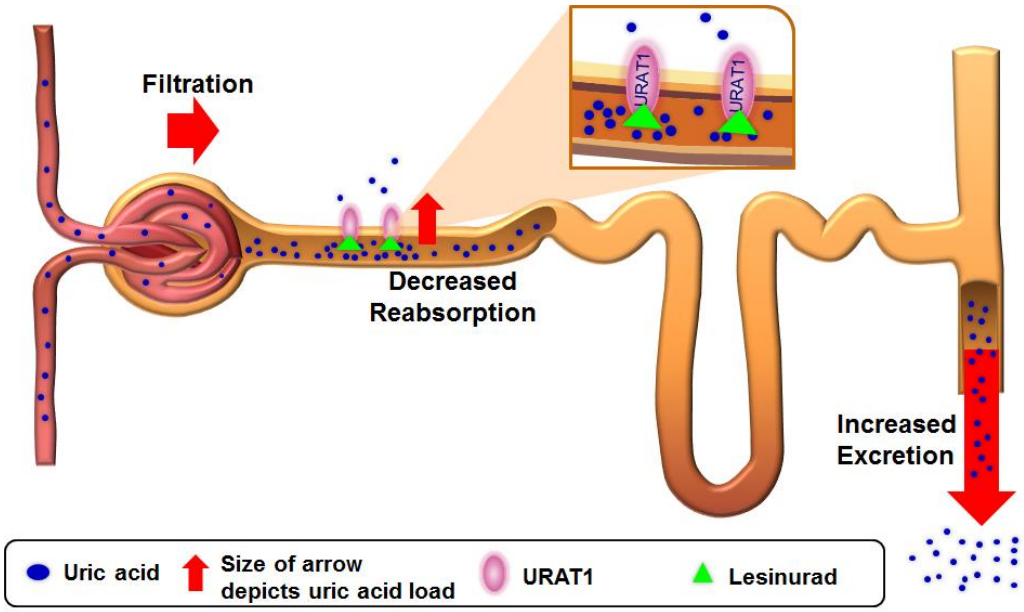
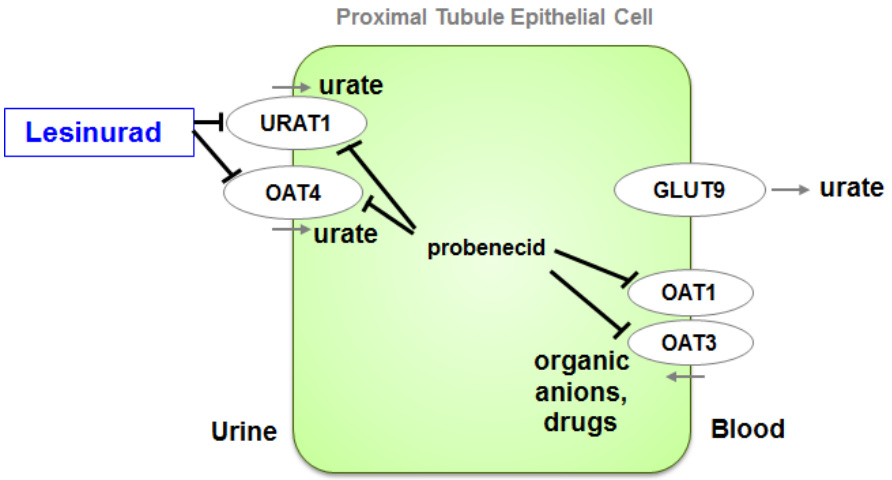


Figure 10: Targets of Lesinurad, a Selective Uric Acid Reabsorption Inhibitor (SURI)



Abbreviations: GLUT, glucose transporter, OAT, organic anion transporter; URAT1, uric acid transporter 1.

4. SUMMARY OF NONCLINICAL FINDINGS

4.1. General

The nonclinical safety profile of lesinurad was characterized in a comprehensive program of pharmacology, pharmacokinetic (PK), and toxicology studies. Lesinurad is a pharmacologically active URAT1 inhibitor that is rapidly absorbed after oral administration. Although no animal models are available to test lesinurad's uric acid lowering effect in vivo, lesinurad demonstrated inhibition of URAT1 in in vitro transporter assays at clinically relevant concentrations. Exposures to lesinurad were generally at least dose-proportional in rats and monkeys, and

generated C_{max} and AUC values that were large multiples compared with exposure in humans at a dose of 200 mg. Variability in the nonclinical exposures in animals relative to human exposure is due to dose, duration, and species evaluated.

The completed toxicology program provides a well-characterized toxicity profile. Lesinurad is not genotoxic. Lesinurad is neither a carcinogen nor a reproductive hazard. In toxicology studies after repeated doses of lesinurad at exposures higher than the human exposures at the proposed human daily dose (200 mg), target organs were the gastrointestinal tract (GI; mice, rats, monkeys), kidney (mice and rats), liver (mice, rats, and monkeys), and thyroid (rats). For each target organ, the margin of safety is considered to be adequate for chronic human oral doses of lesinurad at 200 mg qd. No synergistic, additive, or new toxicity was observed when lesinurad was coadministered with allopurinol or febuxostat.

Following chronic administration of lesinurad to humans, 2 organ systems are of particular interest: the CV system, because there are numerous reports of CV comorbidity in patients with gout,[39, 52-55] and the renal system, due to the mechanism of action of lesinurad. Both are discussed below. No clinically relevant adverse findings pertaining to the nonclinical target organs of liver or thyroid were observed, and gastroesophageal reflux disease was the only pertinent GI finding.

4.2. Nonclinical Cardiovascular Results

Based on the nonclinical results from a series of in vitro and in vivo studies, lesinurad did not affect cardiac conduction or impact thrombosis at relevant human concentrations (Table 8) Additionally, 2 different in vitro platelet aggregation assays (rabbit thromboxane and rabbit adenosine diphosphate) were conducted with lesinurad in both agonist and antagonist mode; neither showed activity with lesinurad. Thus, lesinurad was not expected to affect either of these in humans.

Table 8: Exposures of Lesinurad and Safety Margins Relative to Human in Safety Pharmacology and Repeat Dose Toxicity Studies

In Vitro		
Study	**Concentration (µg/mL)**	**Margin**
hERG IC_{50}	80	12 (578 x based on free drug at C_{max})
NOEL; APD Rabbit Purkinje Fibers with Human Serum Albumin	64	9.2

In Vivo					
Study	**NOEL/NOAEL (mg/kg)**	**C_{max} (µg/mL)**	**Margin[a]**	**AUC_{0-24h} (µg•hr/mL)**	**Margin[a]**
CV in Telemetrized Monkeys	300	146[b]	21	1060[b]	38
1 Year Monkey[c]	600	84	12	645	23

Abbreviations: APD, action potential duration; AUC, area under the concentration-time curve; C_{max}, maximum observed concentration; CV, cardiovascular; hERG, human ether-a-go-go-related gene; IC_{50}, half maximal inhibitory concentration; NOAEL, no observed adverse effect level; NOEL, no observed effect level.
[a] Margin calculated based on human C_{max} of 6.92 µg/mL and AUC of 28.0 µg•hr/mL at the MRHD.
[b] Based on Day 1 toxicokinetic data in male monkeys in the 12-month toxicology study.
[c] Parameters evaluated were electrocardiographic, coagulation, organ weight, and histopathological examinations.

4.3. Nonclinical Renal Results

Lesinurad was not nephrotoxic in monkeys following 12 months of dosing at doses up to 600 mg/kg/day with exposures 23 times the human exposure at the 200 mg dose. Lesinurad was also not nephrotoxic in rats except at very high doses (600 mg/kg/day; exposure 93 times the 200 mg dose in humans). The NOEL in rats was 300 mg/kg/day (exposure 43 times the 200 mg dose in humans).

It is important to note that lower concentrations of sUA are observed in most animal species due to the presence of uricase, an enzyme that breaks down uric acid. This is also true for the animal species used in nonclinical safety assessments. Therefore, translation of the nonclinical toxicology results may be limited because the degree of pharmacodynamic (PD) effects of increased uric acid excretion and the resultant decrease in sUA observed in humans cannot be duplicated in animals.

A renal safety pharmacology study in rats was conducted to evaluate the safety of lesinurad. Minimal dose-dependent increases in urinary uric acid excretion were observed after single high doses (≥ 300 mg/kg; exposure 101 times the 200 mg dose in humans) along with changes in renal function parameters, including elevated sCr. After repeated doses ≥ 600 mg/kg/day (exposure 93 times the 200 mg dose in humans), renal toxicity was the cause of death in some rats. Tubular degeneration and/or single cell necrosis of tubular epithelium were observed microscopically and elevated sCr and blood urea nitrogen (BUN) levels were noted in these animals. Transient increases in mean sCr in male rats at doses of 100 and 300 mg/kg/day were observed only on Day 14 of a 28-day study. The magnitude of the increases in sCr was small and did not correlate with gross or microscopic change in the kidneys. No renal toxicity was observed after 6 months of dosing in male and female rats at 300 mg/kg/day (exposure 43 times the 200 mg dose in humans).

Allopurinol and febuxostat were evaluated in combination with lesinurad in rats. Both XOIs caused high levels of xanthine resulting in xanthine crystal formation and significant renal toxicity, consistent with a previous study of XOIs.[56] When lesinurad was administered in combination with allopurinol and febuxostat, no synergistic, additive, or new toxicity was observed.

In a 2-year (lifetime) carcinogenicity study in rats, non-neoplastic renal papillary lesions were observed with 200 mg/kg/day exposure (exposure 52 times the 200 mg dose in humans). Because rats are a monopapillary species and more prone to developing papillary necrosis than multipapillary species, such as humans, this effect poses a low risk in humans.[57]

In a 12-month study in monkeys, the only observed renal effect was increased organ weight. In many instances, increased organ weight is considered a functional alteration or adaptive response to a physiological alteration brought about by administration of high doses of active pharmaceutical agents.[58] No functional or histological changes were identified.

5. CLINICAL PHARMACOLOGY

5.1. Pharmacokinetics

Lesinurad is rapidly absorbed following single dosing, with C_{max} achieved at 1.5 hours without food and 2.0 hours in the presence of food. Lesinurad has a low clearance (5.98 L/hr) and limited extravascular distribution (volume of distribution of 20.3 L). Lesinurad is highly protein bound (~98%) and has a $t_{½}$ of ~5 hours. Lesinurad plasma exposures (C_{max} and AUC) exhibited dose proportionality up to a dose of 1200 mg. Following qd dosing, there was no accumulation.

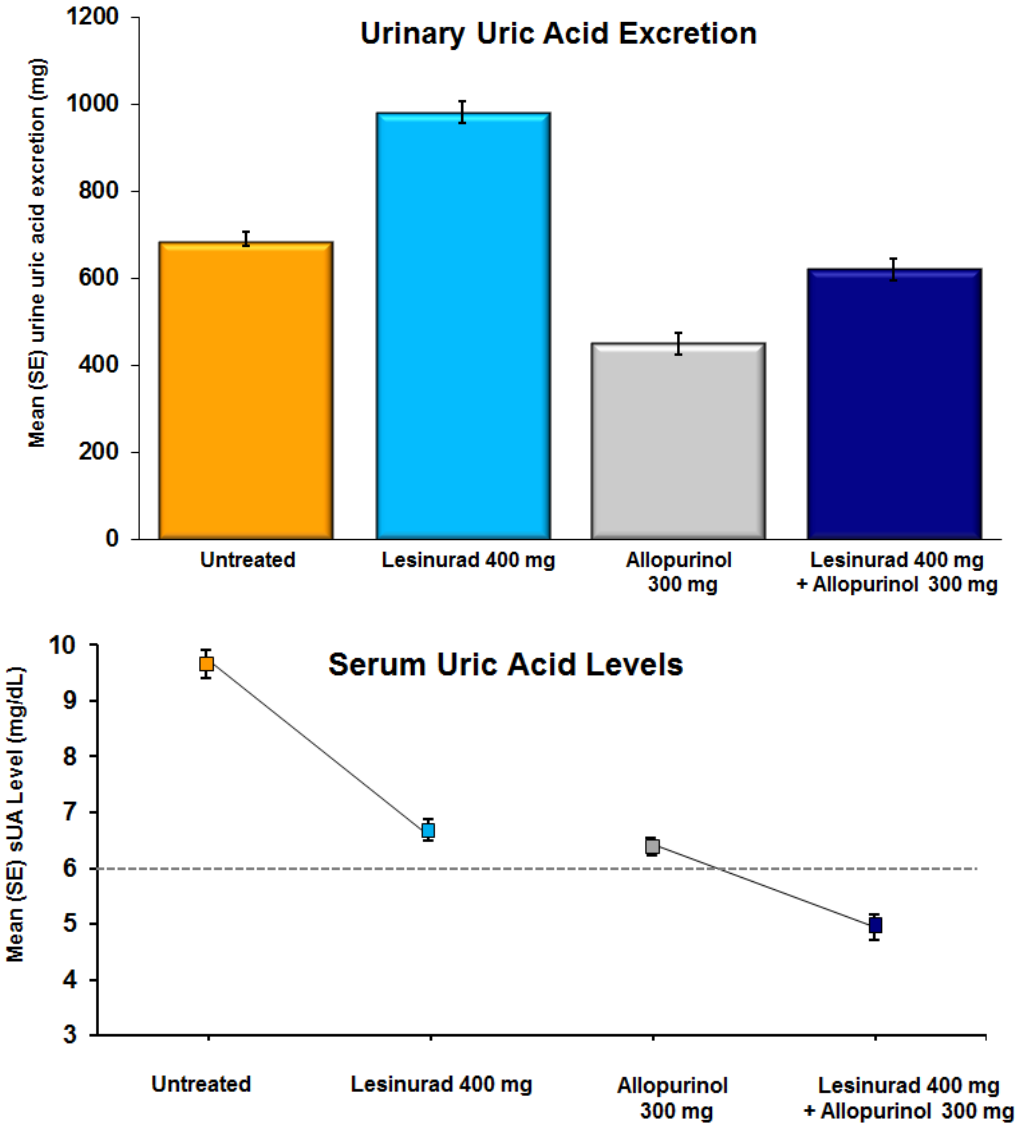
In a human study using radiolabeled lesinurad, approximately 60% of total circulating radioactivity over 24 hours was unchanged lesinurad, with no major circulating metabolites and no metabolites unique to humans. The majority of the dose was recovered in urine (mean of 63.4%), of which almost half was unchanged lesinurad. Metabolites accounted for the majority (64.1%) of the total radioactivity in the excreta, and approximately half of the oral dose is cleared via CYP2C9 metabolism.

5.2. Pharmacodynamics

Phase 1b and 2 studies of lesinurad in patients with gout showed a direct relationship between lesinurad dose, lesinurad exposure, urinary uric acid excretion, and sUA reduction. Although the plasma elimination $t_{½}$ of lesinurad is relatively short, substantial reductions in sUA are maintained at 24 hours postdose for doses 200 mg and above (≥ 70% of maximum sUA reduction).

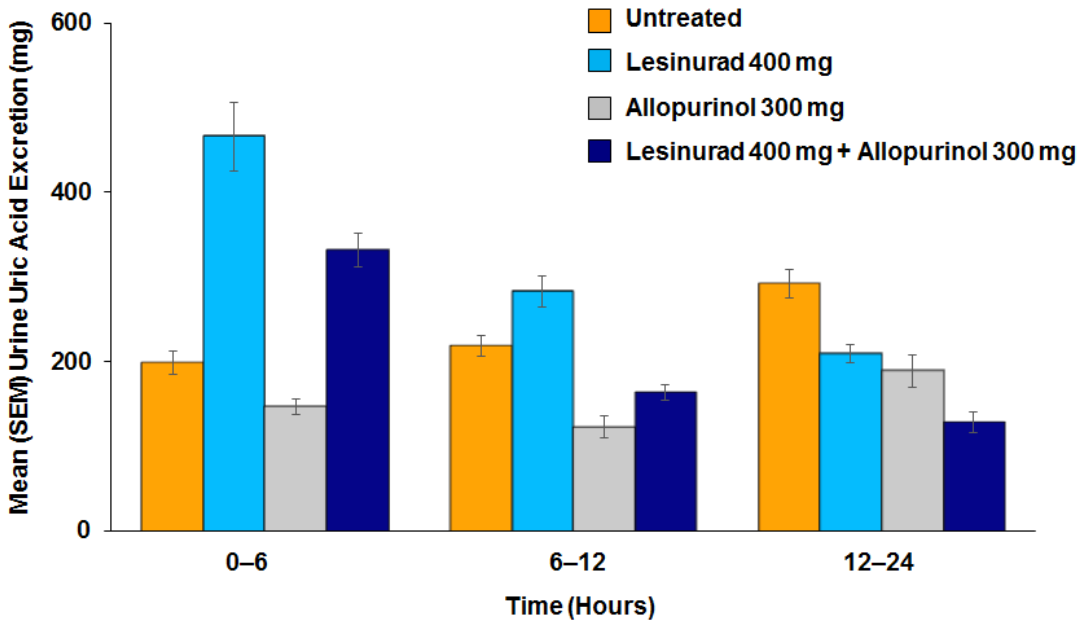
Increases in urinary uric acid excretion result in decreases in sUA levels. When lesinurad is used as monotherapy, there is an increase in urinary uric acid excretion that results in a decrease in sUA levels relative to Baseline (Figure 11). When allopurinol is used as monotherapy, there is a decrease in uric acid production, which results in a decrease in sUA and a reduction in urinary uric acid excretion. When lesinurad is added to allopurinol, there is a relative increase in urinary uric acid excretion compared with allopurinol monotherapy resulting in a further lowering of sUA. A similar relative increase in urinary uric acid excretion was observed when lesinurad 200 mg was added to febuxostat 40 mg in a Phase 1 healthy volunteer study (Study 105). Of note, with combination treatment, the total 24-hour urinary acid excretion is comparable to that observed in untreated gout patients (Figure 11).

Figure 11: Effect of Lesinurad and Allopurinol on Urinary Uric Acid Excretion and Serum Uric Acid Levels in Patients With Gout (Study 110)



Increasing urinary uric acid excretion could result in urinary uric acid concentrations that exceed the supersaturation limit, thereby causing uric acid crystals to form within the renal tubules or renal collecting system. Uric acid precipitation within the renal tubules could manifest clinically as altered renal function, as seen with acute uric acid nephropathy, while precipitation within the collecting system could present as nephrolithiasis. Uric acid precipitation is more likely to occur when the urine pH is low and the uric acid concentration is high because the solubility of uric acid is dependent upon these 2 factors. Lesinurad when used as monotherapy increases the total uric acid excretion above that observed at Baseline in the first 12 hours after administration, providing conditions that are more likely to result in uric acid precipitation. XOIs decrease urinary uric acid excretion relative to Baseline, and combination treatment with lesinurad and an XOI results in higher urinary uric acid excretion only in the first 6 hours after dose administration (Figure 12).

Figure 12: Mean Urinary Uric Acid Excretion Over Time in Patients With Gout (Study 110)



5.3. Effect of Intrinsic Factors on the Pharmacokinetics and Pharmacodynamics of Lesinurad

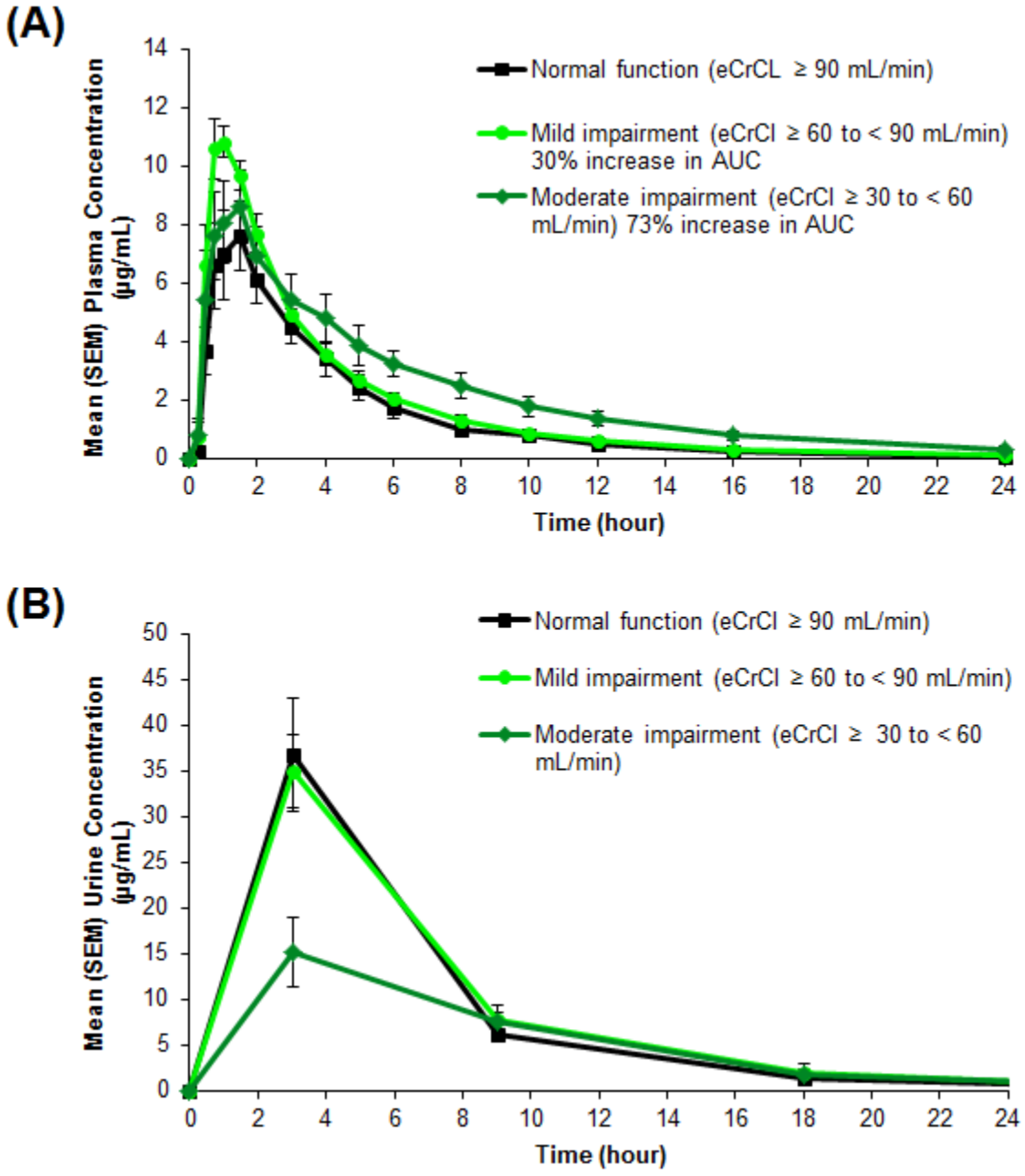
Body weight, age, gender, and race/ethnicity were not found to be significant covariates in population PK analysis.

A Phase 1 study (Study 118) evaluated lesinurad in patients with hepatic impairment and demonstrated that mild hepatic impairment did not affect lesinurad PK. Moderate hepatic impairment increased AUC by 33% with no effect on C_{max}. The sUA lowering effect of lesinurad was not impacted in patients with mild or moderate hepatic impairment compared with healthy volunteers; therefore, no dose adjustments are recommended for patients with mild or moderate hepatic impairment.

Two studies were conducted to assess lesinurad PK in patients with renal impairment as classified using the Cockcroft-Gault formula. In both studies, renal impairment did not have an effect on C_{max}.

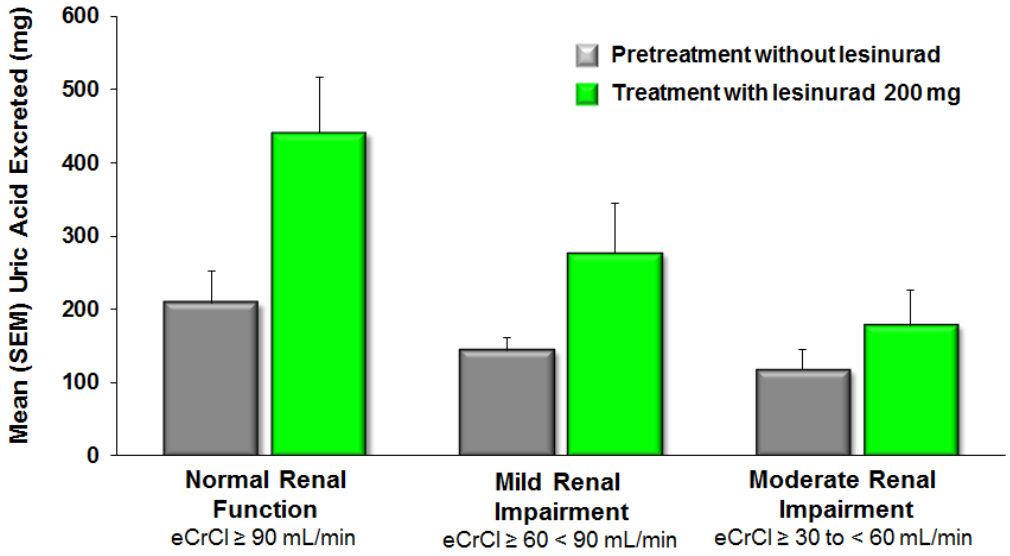
A single-dose study (Study 104) evaluating the PK of lesinurad 200 mg was conducted in patients with mild (eCrCl 60 to < 90 mL/min) and moderate renal impairment (eCrCl 30 to < 60 mL/min), as well as in healthy volunteers (eCrCl ≥ 90 mL/min). Plasma AUC of lesinurad was increased by approximately 30% and 73% in patients with mild (N=8) and moderate (N=10) renal impairment, respectively, when compared with healthy volunteers (N=6) (Figure 13). Lesinurad urine concentrations, however, were decreased in patients with moderate renal impairment (Figure 13). Pretreatment urinary uric acid excretion was lower in patients with impaired renal function and increased following administration of lesinurad (Figure 14).

Figure 13: Lesinurad Plasma and Urine Concentrations by Renal Function Category (Lesinurad 200 mg, Study 104)



Abbreviations: AUC, area under the concentration-time curve; eCrCl, estimated creatinine clearance; SEM, standard error of the mean.

Figure 14: Mean Uric Acid Excretion by Renal Function Category (0-6 Hours; Study 104)



Abbreviations: eCrCl, estimated creatinine clearance; SEM, standard error of the mean.

The second study (Study 120) was a single-dose evaluation of the PK of lesinurad 400 mg in patients with moderate (eCrCl 30 to < 60 mL/min) and severe renal impairment (eCrCl < 30 mL/min) compared with healthy volunteers. The plasma AUC of lesinurad was increased by approximately 50% and 113% in patients with moderate (N=6) and severe (N=6) renal impairment, respectively, versus healthy patients (N=6). The lesinurad urine concentrations and urinary uric acid excretion were reduced further in the severe renal impairment group relative to the moderate impairment group.

Based on these findings, the following recommendations are made regarding lesinurad dosing in renal impairment. In patients with severe renal impairment (eCrCl < 30 mL/min), lesinurad dosing is not recommended as sufficient clinical benefit may not be expected and has not been studied. In patients with moderate renal impairment (eCrCl 30 and < 60 mL/min), lesinurad is recommended without dose adjustment. The efficacy and safety from the pivotal Phase 3 studies support the dosing of lesinurad 200 mg in combination with XOI in patients with moderate renal impairment.

5.4. Drug-Drug Interactions

Lesinurad is associated with few clinically relevant DDIs. DDI studies were performed to evaluate the effect of coadministered drugs on lesinurad (Figure 15) and lesinurad on other drugs (Figure 16). The majority of DDI studies were conducted with lesinurad 400 mg.

Lesinurad is primarily metabolized by CYP2C9. It is recommended to use caution when lesinurad is administered with moderate CYP2C9 inhibitors (eg, fluconazole, amiodarone) or in CYP2C9 poor metabolizers and to monitor for reduced efficacy of lesinurad when used with moderate CYP2C9 inducers.

Lesinurad is a weak to moderate CYP3A inducer depending on the sensitivity of the substrate and dose of lesinurad; therefore, 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.

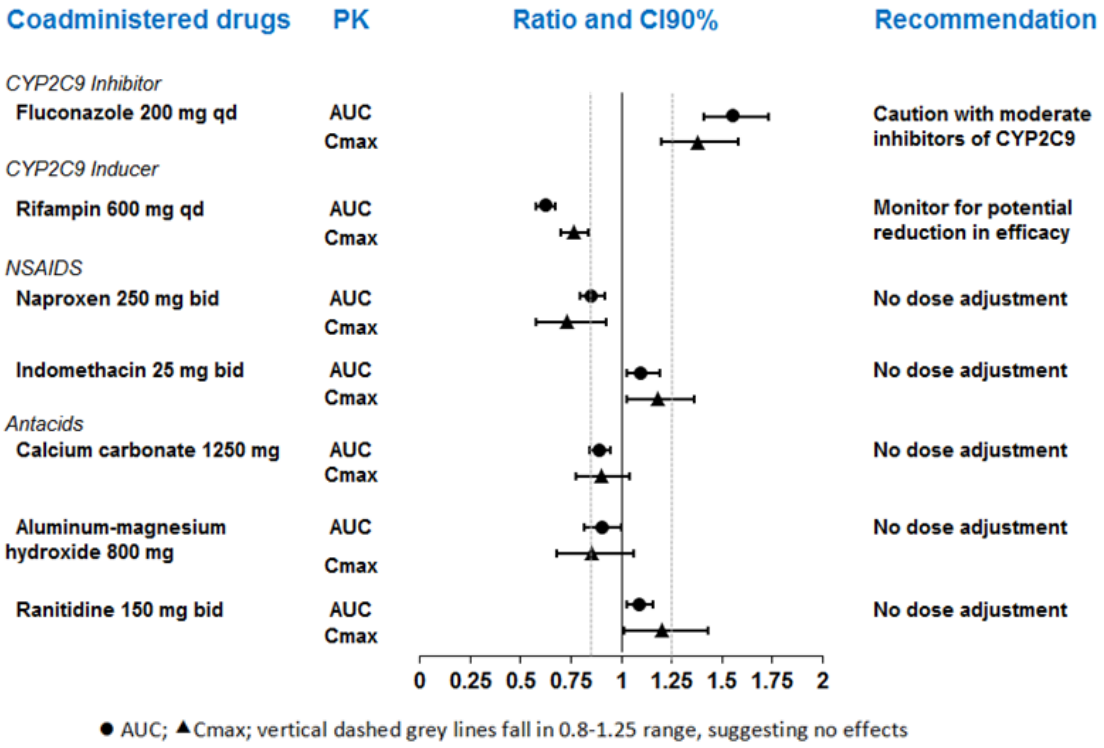
Lesinurad has no relevant effect on any other CYP enzyme for induction or inhibition.

Aspirin at doses of 325 mg or less per day (ie, for cardiovascular protection) does not decrease the efficacy of lesinurad and can be coadministered with lesinurad. Aspirin at doses higher than 325 mg per day has not been studied, but may decrease the efficacy of lesinurad.

Exposure to oxypurinol, a major active metabolite of allopurinol that is transported by URAT1, was decreased by ~26% in the presence of lesinurad (400 mg qd), but allopurinol exposure was not affected. Febuxostat exposure was unchanged with concomitant lesinurad administration (200 mg qd). Lesinurad does not have clinically significant interactions with colchicine or NSAIDs.

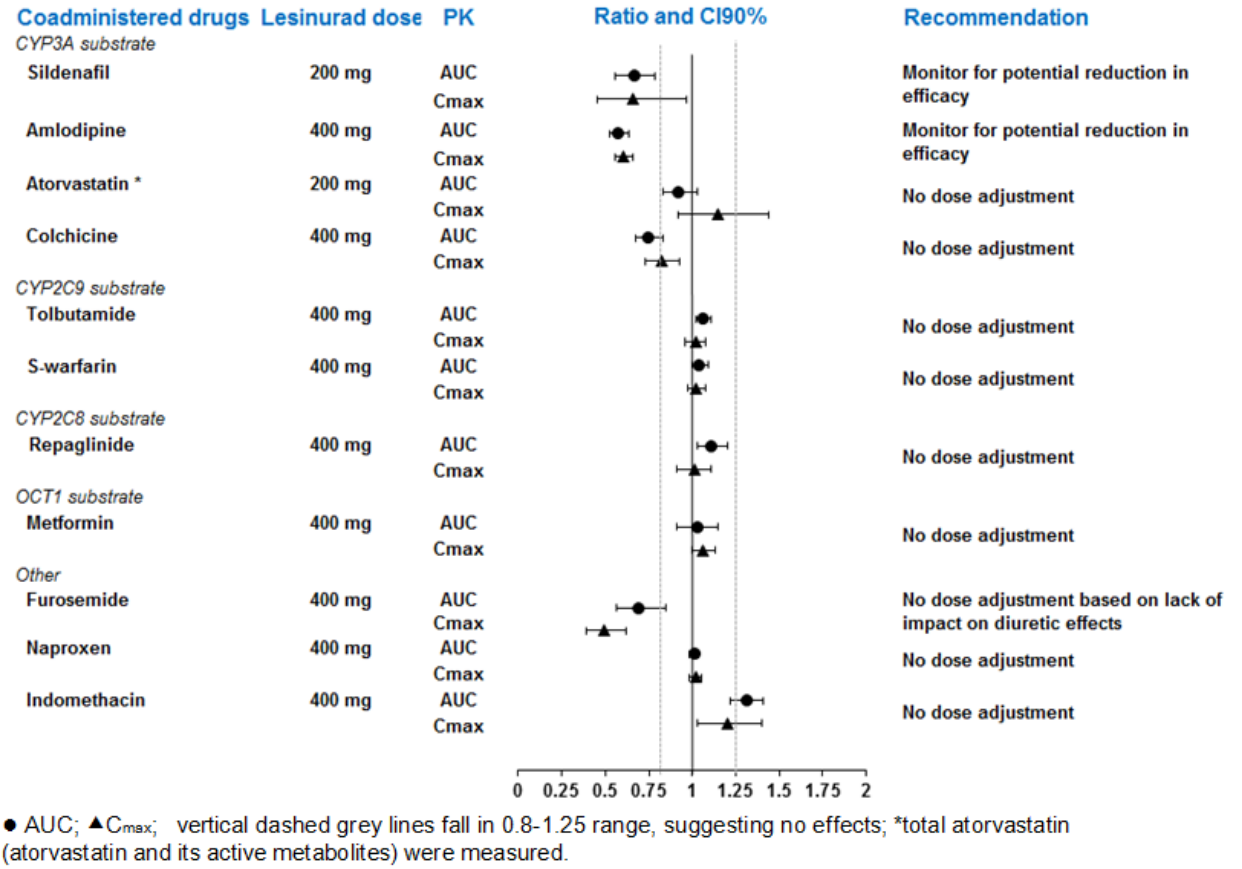
Lesinurad has no relevant effect on major drug transporters such as P-glycoprotein, organic anionic or cationic transporters, including OAT1 and OAT3.

Figure 15: Effect of Coadministered Drugs on Pharmacokinetics of Lesinurad



Note: Geometric mean ratio and 90% confidence interval (CI90%) are presented. Sources: Clinical Studies 122, 126, 127, 130.

Figure 16: Effect of Lesinurad on the Pharmacokinetics of Coadministered Drugs



● AUC; ▲C_{max}; vertical dashed grey lines fall in 0.8-1.25 range, suggesting no effects; *total atorvastatin (atorvastatin and its active metabolites) were measured.

Note: Geometric mean ratio and 90% confidence interval (CI90%) are presented. Sources are Clinical Studies 108, 110, 113, 114, 115, 116, 123, 126, 128.

6. LESINURAD CLINICAL DEVELOPMENT PROGRAM

6.1. Regulatory History

As there are no specific regulatory guidelines for developing agents for hyperuricemia and gout, the lesinurad Phase 3 clinical development program was based on 1) key scientific literature on treatment trials of hyperuricemia, 2) international treatment guidelines, 3) regulatory precedents for other development programs for ULTs to treat hyperuricemia in patients with gout, 4) consultation with disease experts, including the Principal Investigators, and 5) advice from the US FDA and other regulatory authorities. Table 9 provides a summary of the key agreements with the FDA.

Ardea submitted an NDA for lesinurad in December 2014. This briefing book includes data from the original NDA, the 4-Month Safety Update, and subsequent amendments to the NDA.

Table 9: Summary of Key Regulatory Agreements With the FDA

Topic	Agreements With FDA
Phase 3 Clinical Study Designs	The study designs for the pivotal studies of lesinurad as add-on therapy to allopurinol (Study 301 [CLEAR 1] and Study 302 [CLEAR 2]) would support a claim for the chronic treatment of hyperuricemia associated with gout in combination with allopurinol. The doses of allopurinol - a minimum daily dose of 300 mg (200 mg in patients with renal impairment) and a maximum daily dose of 800 mg or 900 mg, depending on local labels - were acceptable. One pivotal study of lesinurad in combination with febuxostat in patients with tophaceous gout (Study 304 [CRYSTAL]) was acceptable to support the proposed broader indication to include febuxostat.
Primary Endpoint in Phase 3 Registrational Studies	sUA lowering was a valid surrogate marker for clinical benefit and the 6-month primary endpoints, including target sUA levels of < 6 mg/dL for CLEAR 1 and CLEAR 2, were acceptable to address an unmet need, and sUA < 5 mg/dL for CRYSTAL was acceptable to demonstrate added benefit.
Phase 3 Doses	The doses of lesinurad 200 mg and 400 mg for the Phase 3 studies were acceptable and the FDA stated that qd dosing may result in an unfavorable risk/benefit if there is an increase in gout flares following gout flare prophylaxis discontinuation.
Safety Analyses	The analysis approach for sCr elevations was acceptable including the categorization of sCr elevations, the definition for Baseline sCr, and the definition for resolution of sCr elevations.

6.2. Overview of Clinical Development Program

The lesinurad clinical development program was designed to evaluate the safety and efficacy of lesinurad in patients with gout who had uncontrolled disease and warranted additional therapy.

The development program was large, robust, and global in scope. A total of 2587 patients and healthy volunteers have been exposed to lesinurad in 41 clinical studies, including 1842 patients with gout. The Phase 3 program included 4 randomized, placebo-controlled, double-blind, multicenter studies in 3 different patient populations (Table 10). Patients who completed the studies could enroll in an extension study.

Table 10: Brief Overview of Phase 3 Studies

CLEAR 1 & CLEAR 2 (Lesinurad + Allopurinol) (N=603 and 610 per study) 12-month studies	CRYSTAL (Lesinurad + Febuxostat) (N=324) 12-month study	Study 303 (Lesinurad Monotherapy) (N=214) 6-month study
Lesinurad plus allopurinol in gout patients who had an inadequate response to allopurinol	Lesinurad plus febuxostat 80 mg in patients with tophaceous gout	Lesinurad monotherapy in gout patients with an intolerance or contraindication to an XOI
Study Population		
• sUA > 6.5 mg/dL on stable dose of allopurinol between 300 and 900 mg (200 mg acceptable for moderate renal impairment) • ≥2 flares in prior 12 months	• Hyperuricemia (Screening sUA level ≥ 6.0 mg/dL for patients on ULT and ≥ 8 mg/dL for patients not taking ULT) • ≥ 1 target tophus	• sUA ≥ 6.5 mg/dL • Intolerance or contraindication to XOI (eg, hypersensitivity, intolerance, or toxicity)
Primary Endpoints		
Proportion of patients with sUA< 6 mg/dL by Month 6	Proportion of patients with sUA < 5 mg/dL by Month 6	Proportion of patients with sUA < 6 mg/dL by Month 6
Key Secondary Endpoints Protected for Multiplicity		
• Mean rate of gout flares requiring treatment from end of Month 6 to end of Month 12 • Complete resolution of ≥ 1 target tophus by Month 12	• Complete resolution of ≥ 1 target tophus by Month 12 • Complete or partial (≥50% reduction) resolution of ≥ 1 target tophus by Month 12 • Improvement from Baseline in HAQ-DI of at least 0.25 at Month 12	

Abbreviations: HAQ-DI, Health Assessment Questionnaire - Disability Index; sUA, serum uric acid; ULT, urate-lowering therapy; XOI, xanthine oxidase inhibitor.

In addition, the lesinurad clinical development program included 24 Phase 1 studies in healthy volunteers, 5 Phase 1/2a studies in special populations and special situations (3 studies in renal impairment, 1 study in hepatic impairment, and 1 study in Japanese healthy volunteers), 3 Phase 1b/2a studies in patients with gout, 1 Phase 2b study in patients with gout in combination with an XOI, and 1 Phase 2b monotherapy study in patients with gout (see Table 11).

Lesinurad 200 mg was not studied in a Phase 3 monotherapy study. The Phase 3 study of lesinurad 400 mg monotherapy (Study 303) demonstrated significant sUA lowering compared with placebo; however, based on the incidence of serious renal-related adverse reactions in this study, a monotherapy indication is not being pursued (see Section 6.3.1 and Appendix 10). Therefore, the focus of this briefing book is on combination therapy.

Table 11: Studies in the Lesinurad Clinical Development Program

Type of Study	Studies Included
Phase 1 Studies in Healthy Volunteers	101, 102, 103, 105, 106, 107, 108, 109, 112, 113, 114, 115, 116, 117, 121, 122, 123, 126, 127, 128, 129, 130, 131, 132
Phase 1 and 2a Studies in Special Populations and Special Situations	104, 120, and 204 (renal impairment), 118 (hepatic impairment), Study 125 (Japanese healthy volunteers)
Phase 1b and 2a Studies in Patients with Gout	110 (monotherapy and with ALLO), 111 (with FBX), 201 (monotherapy and with ALLO)
Phase 2b Studies in Patients with Gout	202 (monotherapy) and 203 (with ALLO) with extension periods for both studies
Phase 3 Monotherapy Study	303
Phase 3 Monotherapy Extension Study	305
Phase 3 Pivotal Combination Studies	301 and 302 (with ALLO), 304 (with FBX)
Phase 3 Combination Extension Studies	306 (with ALLO), 307 (with FBX)

Abbreviations: ALLO, allopurinol; FBX, febuxostat.
Note: All studies are complete with the exception of Studies 203, 306, and 307. Studies 301 and 302 are referred to as CLEAR 1 and CLEAR 2; Study 304 is referred to as CRYSTAL.

6.2.1. Clinical Endpoints

6.2.1.1. Serum Uric Acid

Serum uric acid is an accepted primary clinical trial endpoint for the basis of approval for ULTs for the treatment of hyperuricemia associated with gout. Hyperuricemia is the root cause of gout. It leads to uric acid crystal deposition, which results in clinical manifestations of gout, including gout flares and tophi. By lowering sUA below the level of urate saturation, new uric acid crystals cannot form and existing crystals can dissolve.

It is understood with the use of a surrogate endpoint that direct demonstration of the associated clinical benefit may not be feasible in the timeframe of a 12-month placebo-controlled Phase 3 study. This is reflected by the fact that no ULTs have convincingly demonstrated a statistically significant reduction in gout flares during the controlled study period. However, longer-term extension studies have demonstrated that sustained sUA reduction will result in gout flare reduction.[10, 34] As such, the pivotal Phase 3 studies for lesinurad and other ULTs to treat gout have relied upon achieving sUA targets with the expectation that longer-term extension studies will demonstrate those expected benefits over time.

Target levels of sUA for the primary endpoint in the pivotal Phase 3 studies were selected based on regulatory precedent and are in agreement with the current treatment guidelines. An sUA target level < 6 mg/dL in the CLEAR 1 and CLEAR 2 studies is recommended for most gout patients with hyperuricemia. Febuxostat and pegloticase were approved by the FDA and included sUA < 6 mg/dL in their primary endpoints. The lower sUA target of < 5 mg/dL in the CRYSTAL study is recommended for patients with greater disease severity and uric acid burden, such as those with tophi.[6, 7]

The FDA endorsed the use of sUA level targets at Month 6 as the primary endpoint in the lesinurad Phase 3 clinical program.

6.2.1.2. Gout Flares Requiring Treatment

Gout flares are an inflammatory response to uric acid crystals and are expected to occur until uric acid crystals are completely eliminated. Gout flares have been challenging to assess in clinical trials, and no approved ULT has demonstrated a significant reduction in flares in controlled studies. Currently, there is no standard validated method for assessing flares in clinical trials, including the definition, collection, or analysis. Furthermore, lowering sUA with ULTs is associated with a paradoxical initial increase in gout flares (thought to be caused by urate crystal mobilization)[59] requiring the use of gout flare prophylaxis, both of which confound the ability to demonstrate an overall reduction in the gout flares over the duration of a study. Long-term treatment may be required before clinical benefit can be observed. This was reported in the febuxostat registrational studies where no significant differences in flares were observed during the controlled study period.[10, 34]

In the lesinurad Phase 3 studies, patients were provided an eDiary for daily reporting of all gout flares; daily responses to the question, "Have you had a gout attack (flare)?" were required. Only clinically relevant gout flares, defined as gout flares which required treatment (patient-reported gout flares that required the use of colchicine, analgesics, and/or anti-inflammatory medication, which included corticosteroids), were included in the analyses. All patients were to receive gout flare prophylaxis (colchicine or NSAIDs) through Month 5. The mean rate of gout flares requiring treatment from the end of Month 6 to the end of Month 12 was a key secondary endpoint in CLEAR 1 and CLEAR 2 and a secondary endpoint in CRYSTAL. The time period of the end of Month 6 to the end of Month 12 was selected because patients were to be off gout flare prophylaxis.

6.2.1.3. Tophus Reduction

Tophi are subcutaneous deposits of uric acid crystals and are a cardinal sign of persistent hyperuricemia and uncontrolled gout. Tophi resolution occurs when sUA levels are lowered sufficiently to enable dissolution of the uric acid crystals. The rate of resolution is dependent on both the degree and duration of sUA lowering.[13] The endpoint of complete resolution of tophi has not been achieved by any oral ULT, likely due to many factors including persistence of fibrous and inflammatory tissue; methods of tophi measurement, clinical detection, and differentiation; and the length of time that may be necessary for complete resolution. The lesinurad Phase 3 studies used Vernier calipers method to measure the area (longest diameter multiplied by longest width perpendicular to longest diameter) of subcutaneous tophi.

A key secondary endpoint in each of the Phase 3 pivotal studies was the proportion of patients with ≥ 1 target tophus at Baseline who experienced complete resolution (CR; 100% resolution) of ≥ 1 target tophus by Month 12. In CRYSTAL where all patients had tophaceous gout, an additional key secondary endpoint was the proportion of patients who experienced a CR or partial resolution (PR), defined as $\geq 50\%$ reduction in area of ≥ 1 target tophus by Month 12. Target tophi were defined as measurable tophi on the hands/wrists and/or feet/ankles ≥ 5 mm and ≤ 20 mm in the longest diameter. An additional secondary endpoint in each study was the mean percent change from Baseline in the sum of areas for all target tophi at Months 3, 6, 9, and 12.

6.2.1.4. Patient-Reported Outcomes

Patient-reported outcomes for disability, pain, and health-related quality of life were evaluated in the Phase 3 combination therapy studies as secondary endpoints using several tools (HAQ-DI, PGA, SF-36, SDS, and TSQM). The proportion of patients with an improvement from Baseline in HAQ-DI of ≥ 0.25 (minimum clinically important difference) at Month 12 was a key secondary endpoint in CRYSTAL.

6.3. Dosing Regimen Evaluated in Phase 3 Clinical Program

Lesinurad doses of 200 mg and 400 mg in combination with an XOI, allopurinol or febuxostat, were evaluated in the pivotal Phase 3 combination therapy studies. Lesinurad 400 mg was evaluated in a Phase 3 monotherapy study. Lesinurad was administered qd in the morning with food and water.

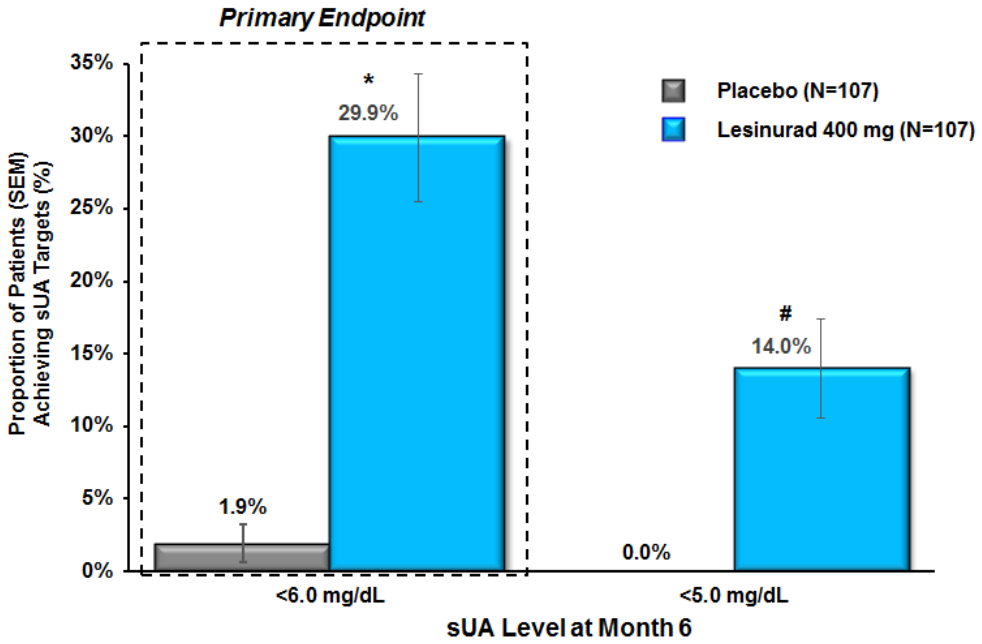
6.3.1. Dose Selection

Single and multiple doses of lesinurad were initially studied in healthy volunteers. In a Phase 1 single ascending dose study (Study 101), no sUA lowering effect was observed for doses ≤ 25 mg, and the 100 mg single dose did not result in sustained sUA reductions over 24 hours. Single doses of 200, 400, and 600 mg resulted in dose-dependent reductions in sUA with effects maintained at 24 hours postdose and beyond. In a Phase 1 multiple ascending dose study (Study 102), the effect of lesinurad versus placebo on sUA lowering was considered relatively inactive at 100 mg qd, whereas potentially clinically relevant effects were observed for lesinurad 200 mg qd. Based on these results, lesinurad doses < 200 mg were not tested in subsequent studies in patients with gout because they were not expected to result in sufficient sUA lowering.

Lesinurad doses of 200, 400, and 600 mg qd were studied as monotherapy (Study 202) and in combination with allopurinol (Study 110, Study 203) or febuxostat 40 or 80 mg (Study 111) in patients with gout. In the Phase 2b monotherapy study, lesinurad doses of 400 and 600 mg resulted in a significantly higher proportion of patients achieving sUA target < 6 mg/dL compared with placebo, whereas lesinurad 200 mg did not. In the Phase 1 and 2 combination studies, all 3 lesinurad doses were efficacious; however, the 600 mg dose was only marginally greater than 400 mg with respect to the proportion of patients achieving target sUA levels. Based on these results, lesinurad 400 mg was selected for the Phase 3 monotherapy study (Study 303) and lesinurad 200 mg and 400 mg were selected for the Phase 3 combination therapy studies (CLEAR 1, CLEAR 2, and CRYSTAL).

The Phase 3 study of lesinurad 400 mg monotherapy (Study 303) demonstrated significant sUA lowering compared with placebo (Figure 17); however, the proportion of patients with AEs, SAEs, and renal events (including renal-related AEs and sCr elevations) was higher for lesinurad-treated patients than for those treated with placebo (Table 12). This is likely due to lesinurad monotherapy causing excessive urinary uric acid excretion leading to intratubular uric acid precipitation and resulting in an unfavorable benefit-risk profile. As such, lesinurad monotherapy is not recommended. For more information on lesinurad monotherapy safety, see Appendix 10.

Figure 17: Proportion of Patients Achieving Serum Uric Acid Targets At Month 6 in Lesinurad Monotherapy Study 303 – NRI (ITT Population)



Abbreviations: ITT, intent-to-treat; NRI, nonresponder imputation; sUA, serum uric acid.
*p<0.0001 vs. placebo; #nominal p<0.0001 vs. placebo.

Table 12: Summary of Safety With Lesinurad 400 mg Monotherapy in Study 303 (Safety Population)

	PBO (N=107)	LESU 400 mg (N=107)
Adverse event category, n patients (%)		
Any AE	70 (65.4)	83 (77.6)
Serious AEs	4 (3.7)	9 (8.4)
Any renal-related AE	0	19 (17.8)
Serious renal-related AEs	0	5 (4.7)
Kidney stone AEs	0	1 (0.9)
Serum creatinine elevations, n patients (%)		
sCr ≥ 1.5 x Baseline	0	26 (24.3)
sCr ≥ 2.0 x Baseline	0	9 (8.4)
sCr ≥ 3.0 x Baseline	0	4 (3.7)

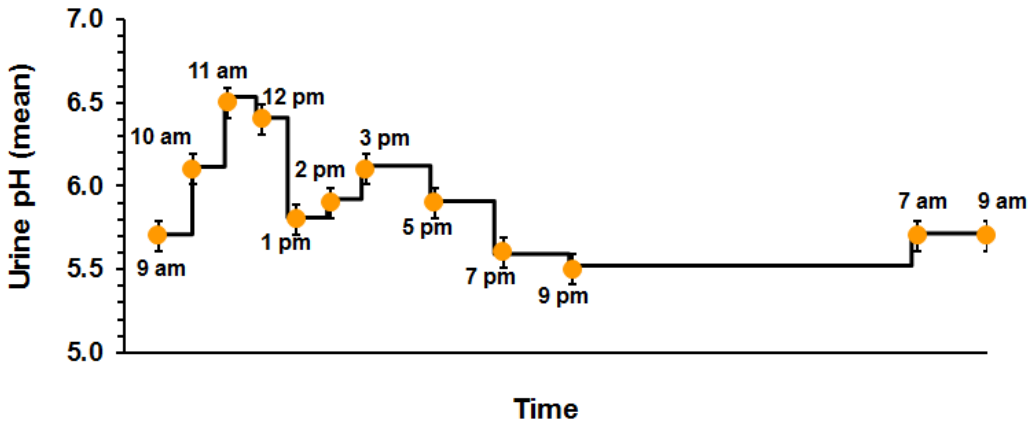
Abbreviations: AE, adverse event; LESU, lesinurad; PBO, placebo; sCr, serum creatinine.
Note: Baseline sCr was defined as the highest sCr value recorded ≤ 14 days prior to the first dose of randomized study medication. Elevation categories are nested; ie, the ≥ 1.5 x Baseline category includes all elevations ≥ 1.5, ≥ 2, or ≥ 3 x Baseline, and the ≥ 2 x Baseline category includes all elevations ≥ 2 or ≥ 3 x Baseline.

6.3.2. Dosing Frequency Selection

Lesinurad is recommended to be taken once daily in the morning based on its pharmacodynamics. Lesinurad increases urinary uric acid excretion with maximal excretion within the first 6 hours following administration (Figure 12). As a result, qd dosing of lesinurad in the morning is recommended to avoid high concentrations of urinary uric acid during the nighttime, when urine pH and urine volume is lowest, thereby reducing the risk of urinary uric

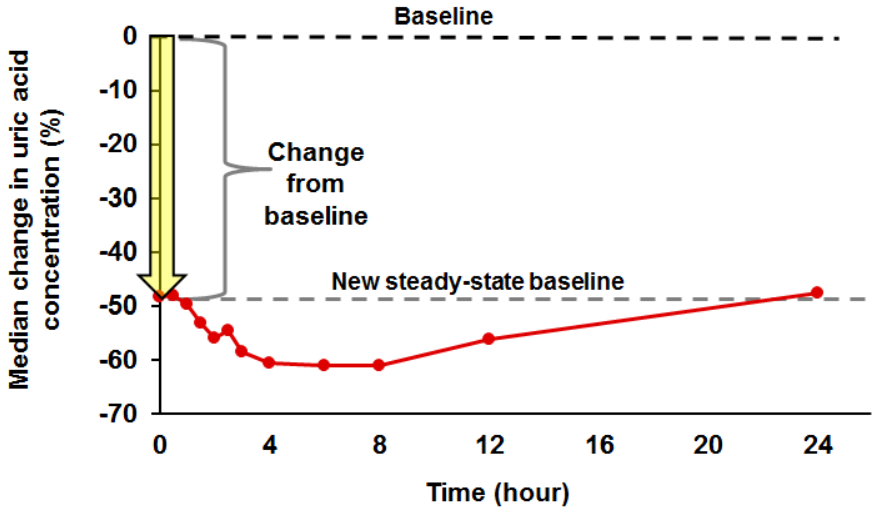
acid precipitation and kidney stone formation. A study of the circadian rhythm of urinary pH in humans showed urine pH was lowest between 11 PM and 6 AM.[60] Because uric acid solubility is highly dependent upon urine pH, the nightly drop in urinary pH to below 5.5 poses a substantial risk of uric acid precipitation if uric acid concentrations are high.[61] Once-daily morning dosing is also supported by a study of diurnal variations in urine flow and uric acid excretion, which concluded that administration of either probenecid or benzbromarone during the afternoon would increase the risk of uric acid precipitation in the urine at night.[62] We have also demonstrated that this diurnal variation in urine pH exists in gout patients, with a morning alkaline tide and lower urine pH at night (Figure 18).

Figure 18: Daily Changes in Urine pH



Once-daily morning dosing of lesinurad is also supported by the PD profile of sUA lowering. Although the $t_{½}$ of lesinurad is ~5 hours, substantial reductions in sUA are still maintained at 24 hours postdose and beyond. In Study 110, when lesinurad 400 mg was administered alone, approximately 70% of the maximum effect was maintained at 24 hours. Likewise, in Study 111, when lesinurad 400 mg qd was administered with febuxostat 40 mg or 80 mg qd, approximately 85% of the maximal reduction in sUA observed at 6 hours postdose was maintained at 24 hours postdose. When lesinurad 400 mg was dosed with allopurinol 300 mg, maximal lowering of plasma uric acid during steady state administration occurs 6 to 8 hours postdose with approximately 78% of the peak change from Baseline in sUA lowering maintained at 24 hours postdose (Figure 19).

Figure 19: Median Change in Plasma Uric Acid Concentration vs. Time After 7 Days of Lesinurad 400 mg + Allopurinol 300 mg (Study 110)



7. PROPOSED INDICATION AND DOSAGE AND ADMINISTRATION

7.1. Proposed Indication

Following the original NDA submission for lesinurad, the indication was revised to more clearly reflect the intended second line population. The proposed indication is as follows:

> *Lesinurad in combination with a xanthine oxidase inhibitor is indicated for the chronic treatment of hyperuricemia associated with gout in patients who have not achieved target serum uric acid levels with a xanthine oxidase inhibitor alone.*
>
> *Limitations of Use:*
>
> *Lesinurad is not recommended for the treatment of asymptomatic hyperuricemia.*
>
> *Lesinurad should not be used as monotherapy.*

As with all ULTs, lesinurad should not be used in patients with asymptomatic hyperuricemia. Its use is limited to combination therapy with an XOI based on the high rate of serious renal-related adverse reactions when lesinurad 400 mg was given as monotherapy (4.7%; Appendix 10).

7.2. Proposed Dosage and Administration

The recommended dose of lesinurad is 200 mg administered qd in combination with a xanthine oxidase inhibitor, including allopurinol or febuxostat.

Although efficacy was demonstrated for both lesinurad 200 mg and 400 mg doses in the pivotal Phase 3 combination studies, there was an increase in renal events observed with lesinurad 400 mg in combination with an XOI (allopurinol or febuxostat). Based on the overall benefit risk evaluation, lesinurad 200 mg in combination with an XOI was chosen as the recommended dose regimen.

Lesinurad has been studied in combination with febuxostat 80 mg once daily and in combination with allopurinol at daily doses of at least 300 mg, and 200 mg in patients with moderate renal impairment. Lesinurad in combination with allopurinol at daily doses less than 200 mg has not been studied and is not recommended.

7.2.1. Other Dosing Recommendations

It is recommended that lesinurad tablets be taken in the morning with food and water at the same time as an XOI, allopurinol or febuxostat.

Phase 1 studies with various formulations (Studies 102, 103, and 109) suggested that there was enhanced sUA lowering when lesinurad was taken fed compared with fasting. This enhanced PD activity was generally observed with a decrease in C_{max} and no change in AUC. Similar findings were observed in the pivotal food effect study (Study 121).

Patients taking lesinurad are recommended to stay well hydrated (eg, 2 liters [68 oz] of liquid per day) to reduce the potential for developing nephrolithiasis and other renal events. The hydration recommendations in the proposed lesinurad label are aligned with the recent 2012 ACR Guidelines for Management of Gout.[7] Hydration recommendations are also aligned with allopurinol's approved label, which recommends a fluid intake sufficient to yield a daily urinary output of at least 2 liters.

8. EFFICACY FINDINGS FOR LESINURAD IN COMBINATION WITH XANTHINE OXIDASE INHIBITORS

Summary of Efficacy

Lesinurad in combination with an XOI, allopurinol or febuxostat, results in superior sUA lowering by targeting both uric acid excretion and production, thereby enabling more patients with sUA levels above target on a XOI alone to achieve and maintain the recommended target treatment goals.

Primary and Secondary sUA Endpoints

The CLEAR 1 and CLEAR 2 studies evaluated lesinurad as add-on therapy to allopurinol in patients who had not achieved target sUA levels while on a physician-determined medically appropriate dose of allopurinol.

- Approximately twice as many patients receiving lesinurad 200 mg plus allopurinol achieved the sUA target goal of < 6 mg/dL by Month 6 compared with allopurinol alone (primary endpoint): 54.2% vs. 27.9% for CLEAR 1 and 55.4% vs. 23.3% for CLEAR 2; $p < 0.0001$ for each comparison.
- Using the more stringent sUA target of < 5 mg/dL recommended for patients with a greater disease severity, nearly 3 times as many patients in CLEAR 1 (28.9% vs. 10.4%, $p < 0.0001$), and nearly 7 times as many patients in CLEAR 2 (34.8% vs. 4.9%, $p < 0.0001$), treated with lesinurad 200 mg plus allopurinol achieved an sUA < 5 mg/dL at Month 6 compared with allopurinol alone.
- The sUA lowering response was rapid (by Month 1), stable, and sustained at all

timepoints (through Month 12).

- Multiple subgroup analyses showed similar efficacy to the overall ITT Population, including, but not limited to, patients taking thiazide diuretics, patients on low-dose aspirin, patients on allopurinol doses > 300 mg, patients with mild or moderate renal impairment, and patients with tophi.

The CRYSTAL study evaluated lesinurad in combination with febuxostat 80 mg in patients with tophaceous gout.

- More patients achieved sUA < 5 mg/dL than with febuxostat alone. Although statistical significance was not achieved at Month 6 with lesinurad 200 mg plus febuxostat compared with febuxostat alone:
  - A greater proportion of patients receiving lesinurad 200 mg achieved sUA < 5 mg/dL at all other timepoints through Month 12 (p-values ranging from 0.0002 to 0.0281 using NRI).
  - More importantly, in the prespecified analysis of the subset of patients with a Baseline sUA ≥ 5 mg/dL (ie, those not at target after 3 weeks of febuxostat alone), the addition of lesinurad 200 mg enabled more patients to achieve target sUA < 5 mg/dL at all timepoints through Month 12, including Month 6 (44.1% vs. 23.5% using NRI; p = 0.0243). This is a clinically meaningful result because this is the group of patients with the greatest need for additional treatment options as they failed to respond to febuxostat 80 mg, the highest dose of febuxostat approved in the US.
  - Additional prespecified and supportive analyses further demonstrated the added benefit provided by lesinurad 200 mg because more patients maintained target sUA < 5 mg/dL for longer durations of time than with febuxostat alone (eg, 3 consecutive months [Months 4, 5, and 6], Months 1-6, Months 6-12, and Months 1-12; p-values < 0.025 for all).

Other Clinical Endpoints

Other clinical endpoints evaluated included gout flares requiring treatment, tophus area, and PROs.

- A statistically significant difference favoring lesinurad was not observed in the key secondary endpoints of CR of ≥ 1 target tophus (CLEAR1, CLEAR 2, and CRYSTAL), mean flare rates (CLEAR1 and CLEAR 2), or HAQ-DI improvement (CRYSTAL). This is likely attributable to a combination of the duration of the controlled studies, the overall low flare rate, and the low HAQ-DI scores at Baseline.
- In exploratory analyses, which included all of the pivotal studies combined, a positive association was noted between lower sUA levels and less likelihood of having a gout flare and greater resolution of target tophus area.

8.1. Study Design

CLEAR 1, CLEAR 2, and CRYSTAL were Phase 3, randomized, double-blind, multicenter, placebo-controlled studies. CLEAR 1 and CLEAR 2 were replicate studies to compare the efficacy and safety of lesinurad 200 mg and lesinurad 400 mg versus placebo when given as add-on therapy to allopurinol in patients who warranted additional therapy. CLEAR 1 was conducted in the US; CLEAR 2 was a global study conducted in North America, Europe, South Africa, and Australia/New Zealand. CRYSTAL was designed to compare the efficacy and safety of lesinurad 200 mg and lesinurad 400 mg vs. placebo when given in combination with febuxostat in patients with tophaceous gout. CRYSTAL was also a global study and was conducted in North America, Europe, and Australia/New Zealand. Across the 3 pivotal studies, approximately 75% of patients were from the US.

All 3 studies included male and female patients, ≥ 18 and ≤ 85 years of age, with gout, per the American Rheumatism Association (ARA) Criteria for the Classification of Acute Arthritis of Primary Gout.[63] Key exclusion criteria included eCrCl < 30 mL/min (calculated by the Cockcroft Gault formula using ideal body weight); an ALT or AST > 2.0 x upper limit of normal (ULN) at any time during the Screening Period; patients with unstable angina, New York Heart Association (NYHA) class III or IV heart failure, MI, stroke, or deep venous thrombosis (DVT) within the last 12 months; or patients receiving anticoagulants.

In CLEAR 1 and CLEAR 2, patients warranted additional therapy because they had not achieved sUA target levels while on a physician-determined medically appropriate dose of allopurinol, defined as a minimum of 300 mg daily (≥ 200 mg/day was permitted for patients with moderate renal impairment) and up to a maximum of 800 mg daily (in US) or 900 mg daily (in countries outside the US, depending on the local label). Patients were required to be taking a stable dose of allopurinol for ≥ 8 weeks prior to Screening and continued their individualized dose of allopurinol throughout the study. Patients were also required to have sUA levels above target at both the Screening (≥ 6.5 mg/dL) and Day -7 (≥ 6 mg/dL), and be symptomatic (reporting ≥ 2 gout flares in the past year).

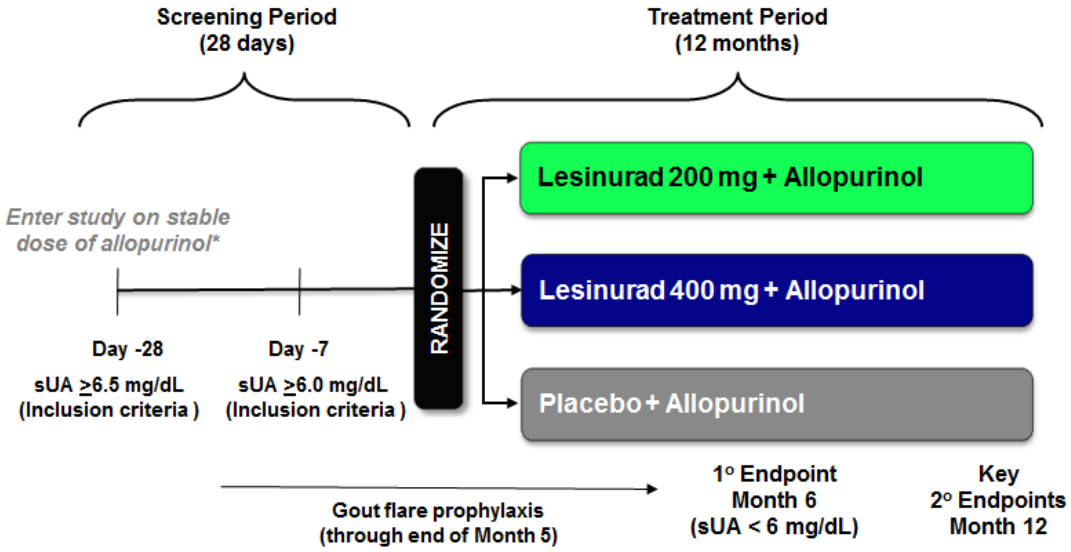
In CRYSTAL, all patients were required to have ≥ 1 measurable target tophus on the hands/wrists and/or feet/ankles (≥ 5 and ≤ 20 mm in the longest diameter) and an sUA level above target at Screening. Patients taking ULT were required to have an sUA ≥ 6 mg/dL at the Screening Visit; patients not receiving ULT had to have an sUA level ≥ 8 mg/dL. All patients initiated Sponsor-supplied febuxostat 80 mg qd at Day -21. The CRYSTAL study was designed to use the most potent dose of febuxostat approved in the US for patients with tophaceous gout (80 mg). Because of febuxostat's limited use, it was not feasible to enroll enough patients taking febuxostat 80 mg monotherapy who failed to achieve target sUA; therefore, all patients in CRYSTAL were administered febuxostat alone for 3 weeks in the Screening period. All patients were then randomized on Day 1 regardless of their Baseline sUA as powering of the 1^{o} endpoint took into account an expected 40% response (powered at 90%).

In each study, patients were randomized to 1 of 3 treatment groups in a 1:1:1 ratio: lesinurad 200 mg, lesinurad 400 mg, or placebo. To ensure the treatment groups were balanced across medically important subgroups, randomization was stratified by Day -7 renal function (eCrCl ≥ 60 vs. < 60 mL/min). In CLEAR 1 and CLEAR 2, randomization was also stratified by tophus

status during Screening (presence vs. absence of tophi) and in CRYSTAL, by sUA level at Day -7 (≥ 6 vs. < 6 mg/dL).

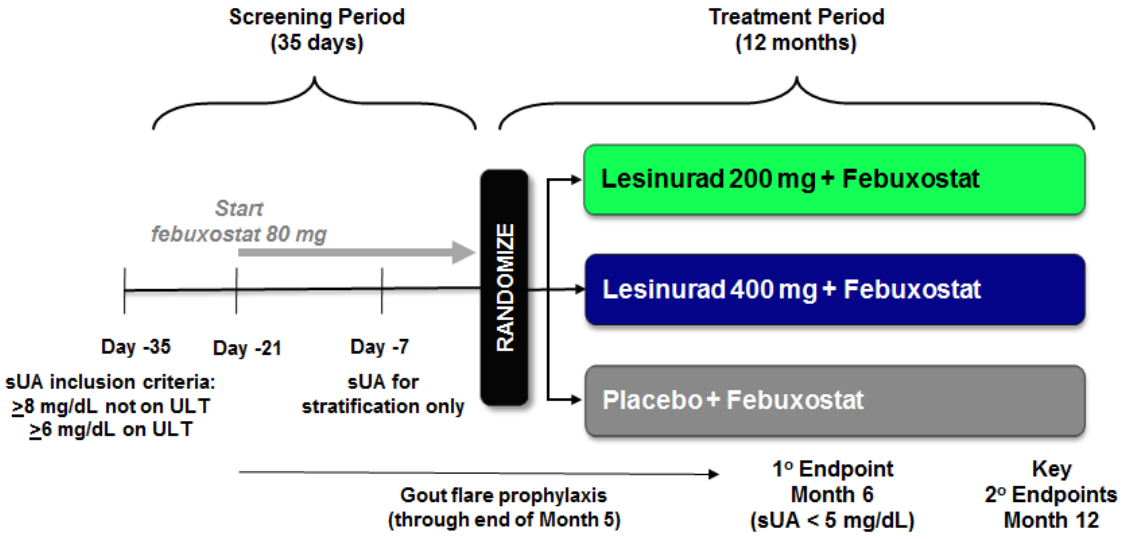
Patients took randomized study medication qd plus allopurinol (CLEAR 1 and CLEAR 2) or febuxostat 80 mg (CRYSTAL) for up to 12 months. Patients also were to take gout flare prophylaxis through Month 5.

Figure 20: Study Design for CLEAR 1 and CLEAR 2 (Add-On to Allopurinol)



Abbreviations: sUA, serum uric acid.
*Patients were receiving a physician-determined medically appropriate dose of ≥ 300 mg/day and up to 800 or 900 mg/day depending on local label (≥200 mg/day was permitted for moderate renal impairment) for at least 8 weeks prior to screening.

Figure 21: Study Design for CRYSTAL (Combination With Febuxostat)



Abbreviations: sUA, serum uric acid; ULT, urate-lowering therapy.

Patients who completed the pivotal studies had the option to enroll in an extension study, Study 306 (for CLEAR 1 and 2) or Study 307 (for CRYSTAL). Patients who had been randomized to lesinurad plus XOI in the pivotal studies continued the same dose of lesinurad plus XOI in the extension studies. Patients who were randomized to placebo plus XOI in the pivotal studies were randomized in a double-blind, 1:1 fashion to either lesinurad 200 mg or 400 mg plus XOI in the extension studies. Blinding of lesinurad dose and sUA and urinary uric acid levels were maintained in the extension studies until each individual patient reached their Extension Month 12 Visit.

8.1.1. Study Endpoints

The primary endpoint was the proportion of patients with an sUA < 6 mg/dL by Month 6 for CLEAR 1 and CLEAR 2 and the proportion of patients with an sUA < 5 mg/dL by Month 6 for CRYSTAL. The sUA target levels were selected based on regulatory precedent and are in agreement with the current international treatment guidelines (including ACR and EULAR), with CRYSTAL reflecting the lower target recommended for patients with greater disease severity and urate burden, such as those with tophi).[6, 7, 44]

A key secondary endpoint protected for multiplicity in all 3 pivotal studies was the proportion of patients with ≥ 1 target tophus at Baseline who experienced CR of ≥ 1 target tophus by Month 12. Additional key secondary endpoints protected for multiplicity included the mean rate of gout flares requiring treatment from the end of Month 6 to the end of Month 12 (CLEAR 1 and CLEAR 2), and the proportion of patients who experienced either complete or partial resolution (CR or PR) of ≥ 1 target tophus by Month 12 and the proportion of patients with at least 0.25 improvement in the HAQ-DI at Month 12 (CRYSTAL).

8.1.2. Statistical Analysis

In CLEAR 1 and 2, approximately 600 patients with gout (200 per treatment group) were to be randomized in each study. The sample size provided greater than 90% power to detect a difference in sUA response rates for the primary endpoint if the placebo plus allopurinol group had a 30% response rate and the lesinurad plus allopurinol groups had response rates as low as 48% using Fisher's exact test adjusting for multiplicity with $\alpha = 0.025$ (two-sided) for each test.

In CRYSTAL, approximately 315 patients were to be randomized (105 patients per treatment group). Based on previous studies of lesinurad plus febuxostat, it was conservatively assumed that the proportion of patients with sUA < 5 mg/dL after 6 months of treatment would be ≤ 40% in the placebo plus febuxostat group and ≥ 65% in the lesinurad plus febuxostat groups. Detecting a significant treatment effect under these assumptions with approximately 90% power and $\alpha = 0.025$ (two-sided) required 105 patients per treatment group using Fisher's exact test.

All randomized patients who received at least 1 dose of randomized study medication were included in the ITT Population, which was used as the primary population for efficacy analyses.

The difference in sUA response rates between the placebo group and each lesinurad group was tested using Cochran-Mantel Haenszel (CMH) methodology, using the randomization stratification factors. The analysis of covariance (ANCOVA) models for mean change and mean percent change from Baseline included the Baseline sUA value as a covariate and treatment group and the randomization stratification variables in the model. The key secondary variables

measured on a binomial scale were analyzed using the CMH method described above and the analysis of flare rates was conducted using negative binomial methods. For all analyses, each lesinurad plus XOI treatment group was compared with XOI alone.

The primary method for handling missing data for the primary dichotomous endpoint was to assign a non-response to all missing data points (NRI method). NRI is conservative at the patient level and in the presence of equal levels of missing data between treatment groups is conservative at the treatment effect level as well. The use of NRI results in an effectiveness estimand and represents an estimate of the efficacy of the entire patient population randomized to the study.

The LOCF method for handling missing data is a protocol defined sensitivity analysis. This method results in an efficacy estimand and provides information on the expected performance of the treatment had all patients remained on treatment. Missing data are imputed assuming the level of efficacy would remain constant had patients remained on treatment. In endpoints, such as tophus resolution, which are irreversible or slow to reverse once treatment is stopped, LOCF is an appropriate imputation method.

Observed cases data sets have been used in selected analyses and the resulting estimates provide information on the efficacy in that set of patients who could tolerate the treatment and chose to remain in the study.

Additional sensitivity analyses to evaluate the robustness of treatment effects to missing data were conducted using MMRM methods and control based imputation. Consistent results were observed using methodology that rely on a range of missing data assumptions.

The overall type one error in each pivotal study was controlled using a gated hierarchical testing procedure. The 2 primary comparisons, each lesinurad dose plus XOI vs. XOI alone, were to be tested at a Bonferroni adjusted alpha level of 0.025. If both comparisons were significant then the key secondary variables were tested in a predetermined order at an α level of 0.05. At any point in the hierarchical testing a p-value was > 0.05, the formal hypothesis testing was to stop.

If only 1 of the primary comparisons was significant at α level of 0.025, then the key secondary variables within that dose were to be tested at α of 0.025.

P values associated with analyses beyond this formal algorithm represent nominal p-values as they were not multiplicity protected.

8.2. Patient Disposition

A total of 603 and 610 patients received randomized study medication in CLEAR 1 and CLEAR 2, respectively (Table 13), and 324 patients received randomized study medication in CRYSTAL (Table 14). In all 3 studies, over 80% of patients completed 6 months of treatment, the time of the primary endpoint assessment. Approximately 70% to 80% completed 12 months of treatment, the final study visit. The most common reasons for early treatment discontinuation in CLEAR 1 and 2 were noncompliance/protocol violation, consent withdrawn, patient lost to follow-up, and AEs. The most common reasons in CRYSTAL were AEs and noncompliance/protocol violation.

Table 13: Patient Disposition in CLEAR 1 and CLEAR 2 (ITT Population)

	CLEAR 1			CLEAR 2		
Variable, n (%)	PBO + ALLO (N=201)	LESU 200 mg + ALLO (N=201)	LESU 400 mg + ALLO (N=201)	PBO + ALLO (N=206)	LESU 200 mg + ALLO (N=204)	LESU 400 mg + ALLO (N=200)
Completed 6 months of treatment with randomized study medication	174 (86.6)	163 (81.1)	163 (81.1)	175 (85.0)	175 (85.8)	171 (85.5)
Completed 12 months of treatment with randomized study medication	149 (74.1)	140 (69.7)	141 (70.1)	154 (74.8)	162 (79.4)	145 (72.5)
Discontinued randomized study medication dosing early	52 (25.9)	61 (30.3)	60 (29.9)	52 (25.2)	42 (20.6)	55 (27.5)
Adverse event	7 (3.5)	15 (7.5)	14 (7.0)	12 (5.8)	6 (2.9)	18 (9.0)
Non-compliance/protocol violation	27 (13.4)	22 (10.9)	18 (9.0)	14 (6.8)	9 (4.4)	14 (7.0)
Consent withdrawn	8 (4.0)	9 (4.5)	12 (6.0)	11 (5.3)	15 (7.4)	12 (6.0)
Lost to follow-up	9 (4.5)	13 (6.5)	16 (8.0)	11 (5.3)	5 (2.5)	7 (3.5)
Required treatment with protocol prohibited or contraindicated medication	1 (0.5)	1 (0.5)	0	2 (1.0)	4 (2.0)	3 (1.5)
Gout flare	0	0	0	2 (1.0)	3 (1.5)	1 (0.5)
Death	0	1 (0.5)	0	0	0	0

Abbreviations: ALLO, allopurinol; ITT, intent-to-treat; LESU, lesinurad; PBO, placebo.

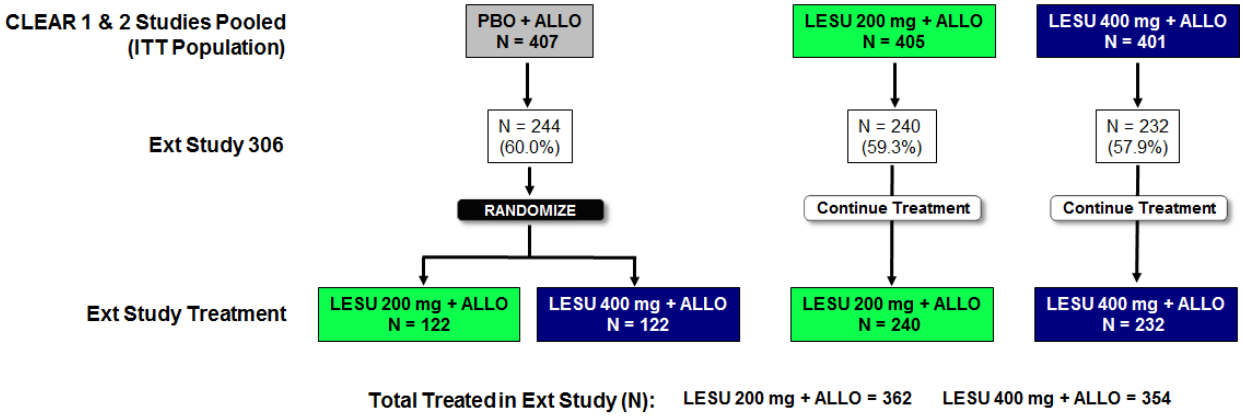
Table 14: Patient Disposition in CRYSTAL (ITT Population)

	CRYSTAL		
Variable, n (%)	PBO + FBX 80 mg (N=109)	LESU 200 mg + FBX 80 mg (N=106)	LESU 400 mg + FBX 80 mg (N=109)
Completed 6 months of treatment with randomized study medication	94 (86.2)	87 (82.1)	88 (80.7)
Completed 12 months of treatment with randomized study medication	83 (76.1)	76 (71.7)	76 (69.7)
Discontinued randomized study medication dosing early	26 (23.9)	30 (28.3)	33 (30.3)
Adverse event	9 (8.3)	10 (9.4)	15 (13.8)
Non-compliance/protocol violation	9 (8.3)	11 (10.4)	9 (8.3)
Consent withdrawn	3 (2.8)	2 (1.9)	4 (3.7)
Lost to follow-up	4 (3.7)	5 (4.7)	1 (0.9)
Required treatment with protocol prohibited or contraindicated medication	0	0	0
Gout flare	1 (0.9)	1 (0.9)	4 (3.7)
Death	0	1 (0.9)	0

Abbreviations: FBX, febuxostat; ITT, intent-to-treat; LESU, lesinurad; PBO, placebo.

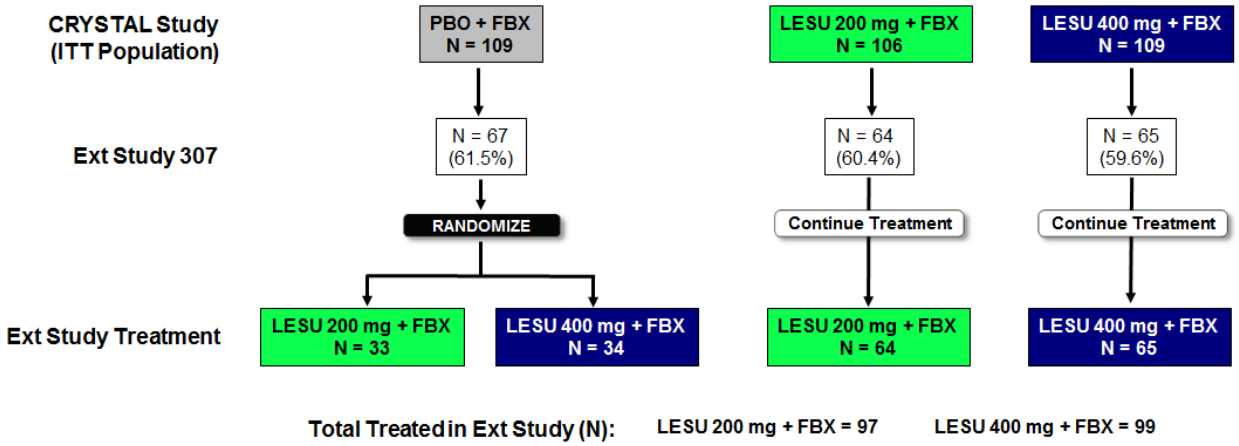
Of the 891 patients who completed CLEAR 1 and CLEAR 2, 716 (80.4%) were treated in the extension study (Study 306). Of the 235 patients who completed CRYSTAL, 196 (83.4%) were treated in the extension study (Study 307). Figure 22 and Figure 23 shows a summary of patients who continued in Extension Studies 306 and 307 and the treatment they received in the pivotal studies.

Figure 22: Patient Enrollment Into Uncontrolled Extension Study 306 (Add on to Allopurinol)



Abbreviations: ALLO, allopurinol; ITT, intent-to treat; LESU, lesinurad; PBO, placebo.

Figure 23: Patient Enrollment Into Uncontrolled Extension Study 307 (Combination With Febuxostat)



Abbreviations: FBX, febuxostat; ITT, intent-to treat; LESU, lesinurad; PBO, placebo.

8.3. Demographics and Baseline Characteristics

Patients generally had longstanding, symptomatic gout with elevated sUA levels. In each study, the treatment groups were generally similar with regard to Baseline demographics and disease characteristics.

In the 3 pivotal studies, the majority of patients were male and White with a mean age of approximately 52 years and a mean BMI over 31 kg/m^2. A summary of key Baseline disease characteristics and comorbidities for each study is included in Table 15. A full list of demographics and baseline characteristics is provided in Appendix 1.

In CLEAR 1 and 2, the mean sUA level at Screening (after a minimum of 8 weeks on allopurinol before entering the study) was approximately 8 mg/dL. The majority of patients were taking an allopurinol dose of 300 mg qd at Baseline (90.5% in CLEAR 1 and 84.1% in CLEAR 2),

reflective of current medical practice.[19, 21] Over 75% of patients had at least 1 CV comorbidity or risk factor. Differences noted between treatment groups included prior MI and kidney stones. Over half of patients had mild or moderate renal impairment (eCrCl < 90 mL/min) and approximately 20% had moderate renal impairment (eCrCl < 60 mL/min) at Baseline. Few patients had eCrCl < 45 mL/min (~8% in CLEAR 1 and ~4% in CLEAR 2). The proportion of patients with target tophi was low (9.0% in CLEAR 1 and 15.9% in CLEAR 2).

In CRYSTAL, the mean sUA at the Screening Visit was 8.71 mg/dL. After 3 weeks on febuxostat 80 mg qd, the mean sUA at Baseline had decreased to 5.27 mg/dL, and approximately 50% of patients had an sUA ≥ 5 mg/dL. Over 70% had at least 1 prespecified CV comorbidity or risk factor. The mean number of target tophi across all treatment groups was 1.8 (maximum permitted to be followed was 5). Some treatment group differences were noted including NSAID use for gout flare prophylaxis and Baseline renal impairment.

Table 15: Summary of Key Baseline Characteristics for the 3 Pivotal Studies (ITT Population)

	CLEAR 1			CLEAR 2			CRYSTAL		
Variable	PBO + ALLO (N=201)	LESU 200 mg + ALLO (N=201)	LESU 400 mg + ALLO (N=201)	PBO + ALLO (N=206)	LESU 200 mg + ALLO (N=204)	LESU 400 mg + ALLO (N=200)	PBO + FBX (N=109)	LESU 200 mg + FBX (N=106)	LESU 400 mg + FBX (N=109)
Duration since gout diagnosis (years)									
Mean (SD)	11.59 (8.75)	12.76 (10.04)	11.16 (9.23)	11.31 (9.38)	12.25 (9.76)	11.02 (8.59)	15.17 (10.90)	15.82 (11.00)	13.15 (10.64)
Number of gout flares in the past 12 months									
Mean (SD)	4.8 (4.09)	4.8 (3.16)	4.9 (3.49)	5.8 (4.92)	6.7 (7.01)	6.1 (5.65)	6.1 (5.1)	6.9 (11.2)	7.0 (7.4)
Target tophi at Baseline									
Patients with Target Tophi, N	17	18	19	33	35	29	109	106	109
Mean number of target tophi (SD)	1.8 (1.47)	1.8 (1.06)	2.1 (1.45)	2.2 (1.36)	2.0 (1.34)	2.5 (1.53)	1.9 (1.3)	1.8 (1.3)	1.8 (1.2)
Renal function at Baseline [n (%)]									
eCrCl < 90 mL/min	123 (61.2)	117 (58.2)	124 (61.7)	133 (64.6)	124 (60.8)	114 (57.0)	78 (71.6)	69 (65.1)	67 (61.5)
eCrCl < 60 mL/min	40 (19.9)	45 (22.4)	41 (20.4)	40 (19.4)	29 (14.2)	29 (14.5)	25 (22.9)	28 (26.4)	22 (20.2)
eCrCl < 45 mL/min	20 (10.0)	12 (6.0)	15 (7.5)	10 (4.9)	6 (2.9)	6 (3.0)	4 (3.7)	8 (7.5)	8 (7.3)
sUA level at Screening (mg/dL)									
Mean (SD)	8.11 (1.53)	7.97 (1.47)	8.01 (1.47)	8.00 (1.46)	8.02 (1.52)	8.08 (1.56)	8.83 (1.53)	8.71 (1.58)	8.57 (1.76)
Type of gout flare prophylaxis at Baseline [n (%)]									
Colchicine	166 (82.6)	170 (84.6)	168 (83.6)	159 (77.2)	181 (88.7)	167 (83.5)	87 (79.8)	95 (89.6)	94 (86.2)
NSAID	34 (16.9)	28 (13.9)	33 (16.4)	51 (24.8)	23 (11.3)	36 (18.0)	26 (23.9)	10 (9.4)	20 (18.3)
Allopurinol dose at Baseline [n (%)]									
< 300 mg/day	12 (6.0)	5 (2.5)	12 (6.0)	15 (7.3)	14 (6.9)	11 (5.5)	NA	NA	NA

Table 15: Summary of Key Baseline Characteristics for the 3 Pivotal Studies (ITT Population)

Variable	CLEAR 1			CLEAR 2			CRYSTAL		
	PBO + ALLO (N=201)	LESU 200 mg + ALLO (N=201)	LESU 400 mg + ALLO (N=201)	PBO + ALLO (N=206)	LESU 200 mg + ALLO (N=204)	LESU 400 mg + ALLO (N=200)	PBO + FBX (N=109)	LESU 200 mg + FBX (N=106)	LESU 400 mg + FBX (N=109)
= 300 mg/day	176 (87.6)	187 (93.0)	183 (91.0)	176 (85.4)	168 (82.4)	169 (84.5)	NA	NA	NA
> 300 mg/day	13 (6.5)	9 (4.5)	6 (3.0)	15 (7.3)	22 (10.8)	20 (10.0)	NA	NA	NA
Most Common Comorbidities[a] [n (%)]									
Hypertension	134 (66.7)	129 (64.2)	142 (70.6)	141 (68.4)	131 (64.2)	121 (60.5)	65 (59.6)	70 (66.0)	62 (56.9)
Hyperlipidemia	99 (49.3)	102 (50.7)	98 (48.8)	76 (36.9)	86 (42.2)	93 (46.5)	46 (42.2)	42 (39.6)	50 (45.9)
Diabetes mellitus	35 (17.4)	44 (21.9)	38 (18.9)	28 (13.6)	31 (15.2)	26 (13.0)	17 (15.6)	21 (19.8)	14 (12.8)
Kidney stones	38 (18.9)	20 (10.0)	22 (10.9)	28 (13.6)	23 (11.3)	18 (9.0)	16 (14.7)	15 (14.2)	11 (10.1)
Myocardial infarction	7 (3.5)	11 (5.5)	6 (3.0)	5 (2.4)	10 (4.9)	9 (4.5)	7 (6.4)	5 (4.7)	7 (6.4)

Abbreviations: ALLO, allopurinol; FBX, febuxostat; eCrCl, estimated creatinine clearance; ITT, intent-to-treat; LESU, lesinurad; PBO, placebo; SD, standard deviation; sUA, serum uric acid.
[a] Includes events recorded on the Comorbidity Summary Case Report Form using a list of predefined comorbidities.

8.4. Efficacy Results

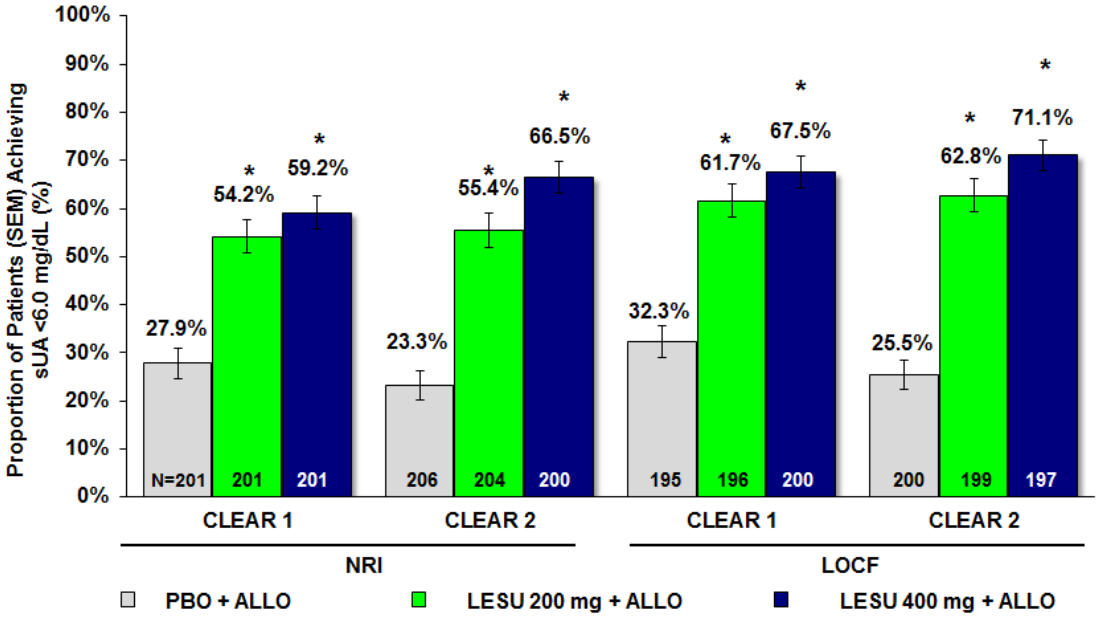
8.4.1. Serum Uric Acid Lowering

8.4.1.1. Lesinurad in Combination With Allopurinol (CLEAR 1 and CLEAR 2)

8.4.1.1.1. Primary Endpoint: Proportion of Patients With sUA < 6 mg/dL by Month 6

The primary endpoint was met for both dose levels in both CLEAR 1 and CLEAR 2 (Figure 24). The proportion of patients who achieved the target goal of sUA < 6 mg/dL by Month 6 was significantly greater for lesinurad 200 mg and lesinurad 400 mg plus allopurinol compared with placebo plus allopurinol using NRI as the primary imputation method: 54.2% and 59.2% vs. 27.9%, respectively, in CLEAR 1, and 55.4% and 66.5% vs. 23.3% in CLEAR 2; $p < 0.0001$ for each comparison. This was statistically significant after adjusting for multiple testing at $p < 0.025$. Similar results were demonstrated using other methods to handle missing data: LOCF (prespecified analysis) as well as control-based and missing at random imputation models (post hoc analyses).

Figure 24: Primary Endpoint: Proportion of Patients Achieving Serum Uric Acid < 6.0 mg/dL by Month 6 in CLEAR 1 and CLEAR 2 (ITT Population)



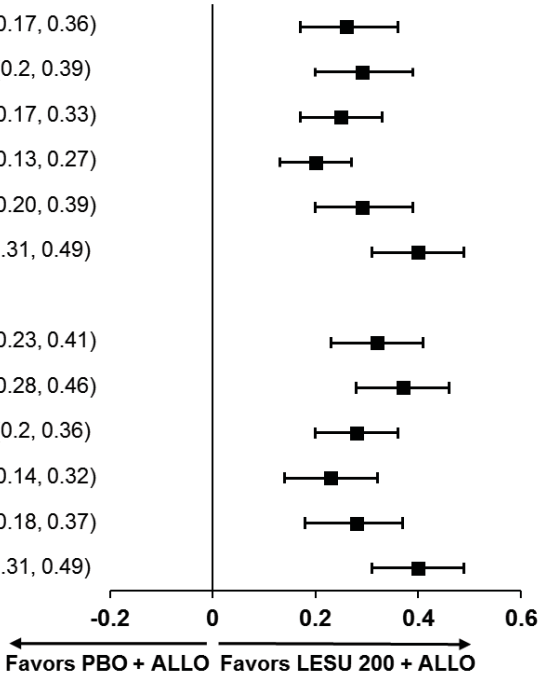
Abbreviations: ALLO, allopurinol; ITT, intent-to-treat; LESU, lesinurad; LOCF, last observation carried forward imputation; NRI, nonresponder imputation; PBO, placebo; sUA, serum uric acid.
Note: For NRI, patients missing an sUA result at Month 6 were treated as nonresponders.
*p-value <0.0001 vs. PBO + ALLO.

Prespecified Sensitivity Analyses

Multiple prespecified sensitivity analyses confirmed the robustness of the primary endpoint demonstrating superior sUA reduction for lesinurad 200 mg and lesinurad 400 mg plus allopurinol ($p < 0.0001$ for all comparisons compared with allopurinol alone). A summary of the primary and prespecified sensitivity analyses for lesinurad 200 mg plus allopurinol is presented in Figure 25.

Figure 25: Primary and Prespecified Sensitivity Analyses of sUA: Lesinurad 200 mg Plus Allopurinol vs. Placebo Plus Allopurinol in CLEAR 1 and CLEAR 2 (ITT Population)

Prespecified Analyses	PBO + ALLO (n/N)	LESU 200 + ALLO (n/N)	Diff (95% CI)
CLEAR 1			
sUA<6 @M6 (NRI)	56/201	109/201	0.26 (0.17, 0.36)
sUA<6 @M6 (LOCF)	63/195	121/196	0.29 (0.2, 0.39)
sUA<6 @M4,5,6 (NRI)	21/201	71/201	0.25 (0.17, 0.33)
sUA<6 @M12 (NRI)	15/201	55/201	0.20 (0.13, 0.27)
sUA<6 @M12 (LOCF)	63/195	121/196	0.29 (0.20, 0.39)
Median sUA<6	54/191	131/191	0.4 (0.31, 0.49)
CLEAR 2			
sUA<6 @M6 (NRI)	48/206	113/204	0.32 (0.23, 0.41)
sUA<6 @M6 (LOCF)	51/200	125/199	0.37 (0.28, 0.46)
sUA<6 @M4,5,6 (NRI)	27/206	84/204	0.28 (0.2, 0.36)
sUA<6 @M12 (NRI)	53/206	100/204	0.23 (0.14, 0.32)
sUA<6 @M12 (LOCF)	58/200	113/199	0.28 (0.18, 0.37)
Median sUA<6	57/199	135/198	0.4 (0.31, 0.49)



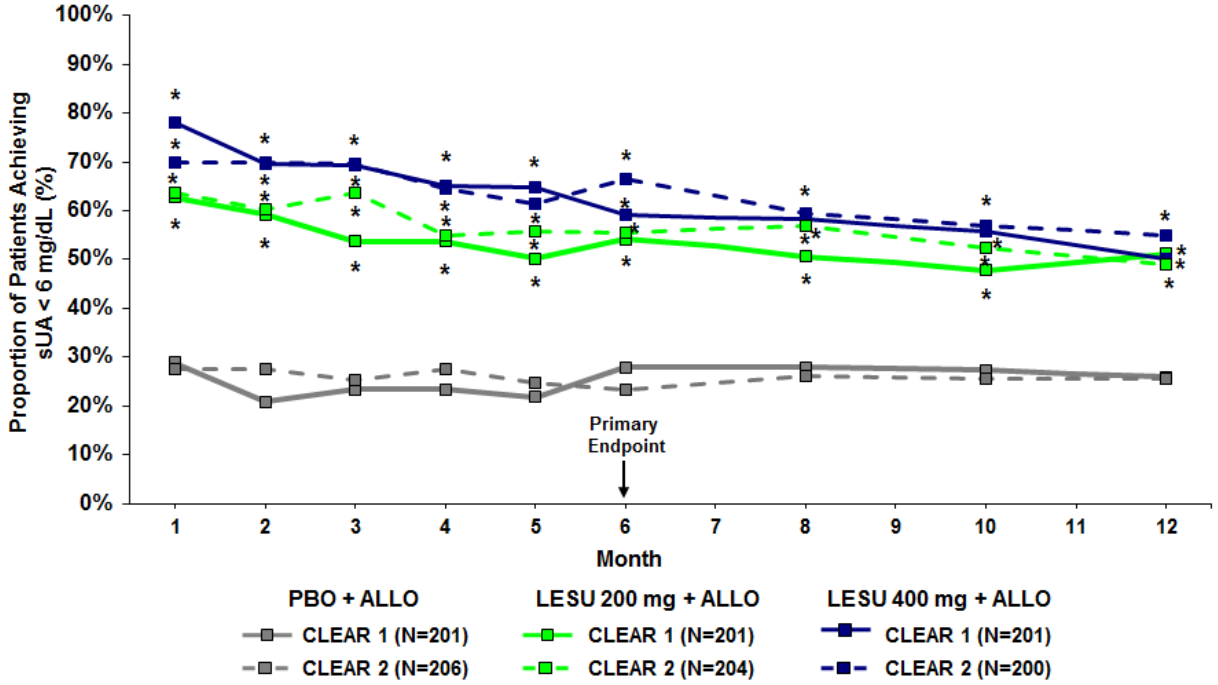
Abbreviations: ALLO, allopurinol; CI, confidence intervals; Diff, difference (LESU 200 mg + ALLO) – (PBO + ALLO); ITT, intent-to-treat; LESU, lesinurad; LOCF, last observation carried forward imputation; M; Month, Median sUA, median on-treatment sUA; NRI, nonresponder imputation analyses; PBO, placebo; sUA, serum uric acid.

8.4.1.1.2. Additional Prespecified sUA Analyses

Proportion of Patients Achieving sUA < 6 mg/dL Over Time

Efficacy was rapid, stable, and sustained with a substantially greater proportion of patients achieving sUA < 6 mg/dL for lesinurad 200 mg and lesinurad 400 mg plus allopurinol compared with allopurinol alone at all timepoints (Months 1, 2, 3, 4, 5, 6, 8, 10, and 12; $p < 0.0001$ for all comparisons in both studies using NRI; Figure 26). By Month 12, like Month 6, nearly twice the proportion of patients in the lesinurad 200 mg and lesinurad 400 mg plus allopurinol groups compared with allopurinol alone were at target sUA using NRI.

Figure 26: Proportion of Patients Achieving Serum Uric Acid Level < 6 mg/dL by Visit in CLEAR 1 and CLEAR 2 – NRI (ITT Population)

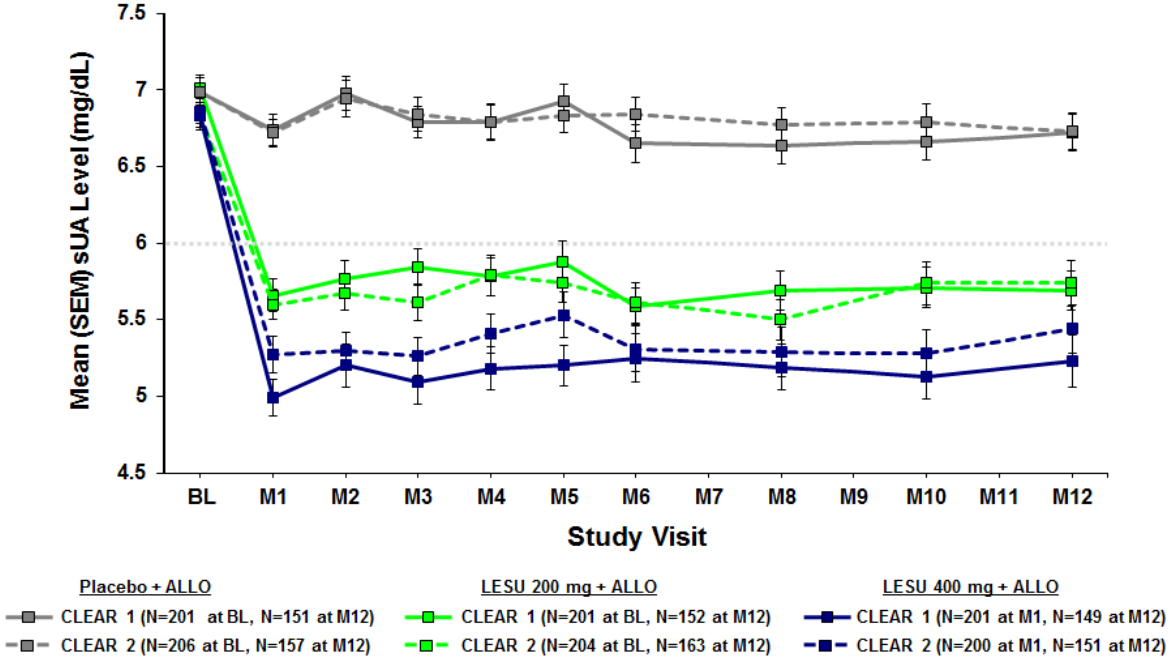


Abbreviations: ALLO, allopurinol; ITT, intent-to-treat; LESU, lesinurad; NRI, nonresponder imputation; PBO, placebo; sUA, serum uric acid.
Note: Patients missing an sUA result were treated as nonresponders at that visit.
*$p < 0.0001$ vs. placebo + allopurinol: multiplicity-protected at Month 6 (primary endpoint) and nominal p-values at all other months using Cochran-Mantel Haenszel test stratified by Day-7 renal function and tophus status at Screening (randomized values).

Mean sUA and Changes Over Time

Mean sUA levels were analyzed by visit (Figure 27). Serum uric acid was also assessed by absolute and percent changes from Baseline. Changes in sUA from Baseline were rapid (observed at Month 1), stable, and sustained (similar at each monthly assessment for the duration of the 12-month treatment) for both lesinurad dose levels in both studies. The degree of sUA lowering with the addition of lesinurad was significant and robust. At each timepoint during the 12-month treatment period, the mean percent and absolute change from Baseline sUA was greater on lesinurad 200 mg plus allopurinol compared with allopurinol alone ($p < 0.0001$). At Month 6, 31% of patients in CLEAR 1 and 2 pooled demonstrated a ≥ 2 mg/dL absolute reduction in sUA.

Figure 27: Mean Serum Uric Acid Levels by Visit in CLEAR 1 and CLEAR 2 – Observed Cases (ITT Population)

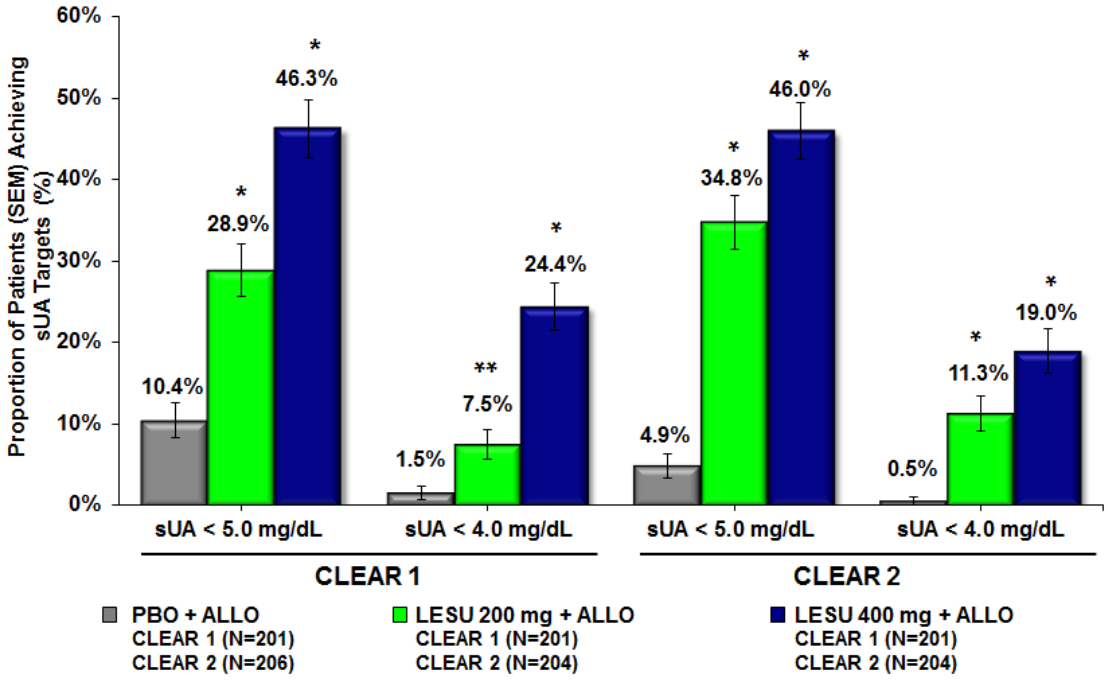


Abbreviations: ALLO, allopurinol; BL, Baseline; ITT, intent-to-treat; LESU, lesinurad; M, month; SEM, standard error of the mean; sUA, serum uric acid.
Note: Dotted line indicates target sUA (< 6 mg/dL). Nominal p-values <0.0001 vs. PBO + ALLO for all study months. p-values are based on the treatment difference in least square mean percent change from Baseline, ANCOVA.

Proportion of Patients Achieving sUA < 5 mg/dL Over Time

Because sUA levels of < 5 mg/dL are recommended for patients with greater disease severity,[23, 44] the proportion of patients achieving lower sUA levels was also assessed. In both CLEAR 1 and CLEAR 2, substantially more patients in the lesinurad 200 mg and lesinurad 400 mg plus allopurinol groups compared with the allopurinol alone group achieved an sUA level < 5 mg/dL and < 4 mg/dL at each monthly visit, starting at Month 1 and continuing through Month 12 (p-values ranging from < 0.0001 to < 0.0066 for all comparisons). Results at Month 6 are presented in Figure 28. Four times as many patients receiving lesinurad 200 mg plus allopurinol achieved the target sUA < 5 mg/dL at Month 6 compared with allopurinol alone when averaged across both the CLEAR 1 and 2 studies (31.9% vs. 7.7%, respectively) and nearly 9 times as many for sUA < 4 mg/dL (9.4% vs. 1.1%, respectively).

Figure 28: Proportion of Patients Achieving Serum Uric Acid Levels < 5 mg/dL and < 4 mg/dL At Month 6 in CLEAR 1 and CLEAR 2 – NRI (ITT Population)



Abbreviations: ALLO, allopurinol; ITT, intent-to-treat; LESU, lesinurad; NRI, nonresponder imputation; PBO, placebo; SEM, standard error of the mean; sUA, serum uric acid.
Note: Patients missing an sUA result at Month 6 were treated as nonresponders.
*Nominal p-values < 0.0001 vs. PBO + ALLO; ** nominal p-value < 0.01 vs. PBO + ALLO.

Subgroup Analysis

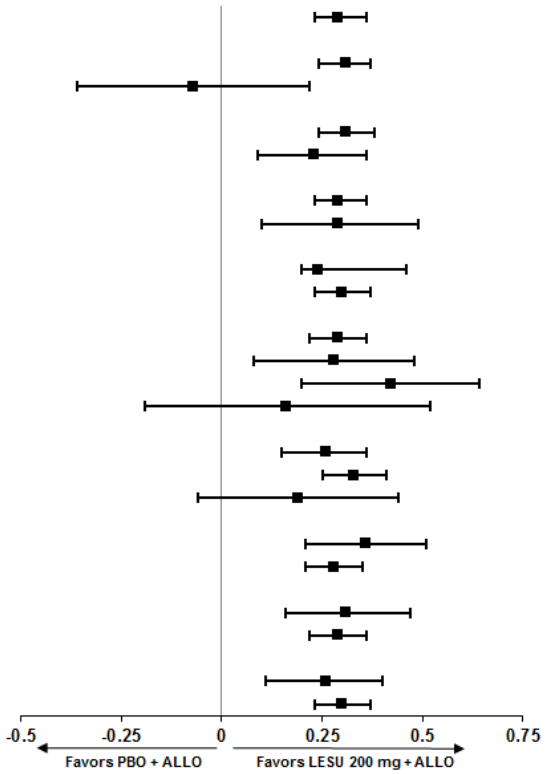
Subgroup analyses of the proportion of patients with sUA < 6 mg/dL by Month 6 (primary endpoint) were performed for demographics, relevant Baseline disease factors, and select concomitant medications. The studies were not powered to independently assess the proportion of responders within subgroups; therefore, to increase the sensitivity of these analyses, data from CLEAR 1 and CLEAR 2 were pooled.

When given with allopurinol, the magnitude of efficacy of lesinurad 200 mg and lesinurad 400 mg in reducing sUA was generally similar to the ITT Population for all subgroups with point estimates > 0 (favoring lesinurad). Notable subgroups with similar efficacy to the overall ITT Population included, but were not limited to patients on allopurinol doses > 300 mg patients taking thiazide diuretics, patients on low-dose aspirin, and patients with tophi. In the female subgroup, the point estimate was < 0; however, the analysis was limited due to the small sample size (n=38) and the results had wide confidence intervals. PK-PD studies showed similar systemic exposure and reductions in sUA for males and females; therefore, no notable differences are expected for females regarding efficacy. Of note, when analyzed by individual study, the point estimate for females in CLEAR 2 was > 0 (favoring lesinurad) for both lesinurad 200 and 400 mg. In CLEAR 1, the point estimate for the female subgroup was > 0 only for lesinurad 400 mg.

Results for key subgroups for lesinurad 200 mg plus allopurinol vs. allopurinol alone are presented in Figure 29.

Figure 29: Subgroup Analyses of Difference from Placebo in Proportion of Patients on Lesinurad 200 mg Achieving sUA < 6 mg/dL by Month 6 – NRI (ITT Population, CLEAR 1 and CLEAR 2 Pooled)

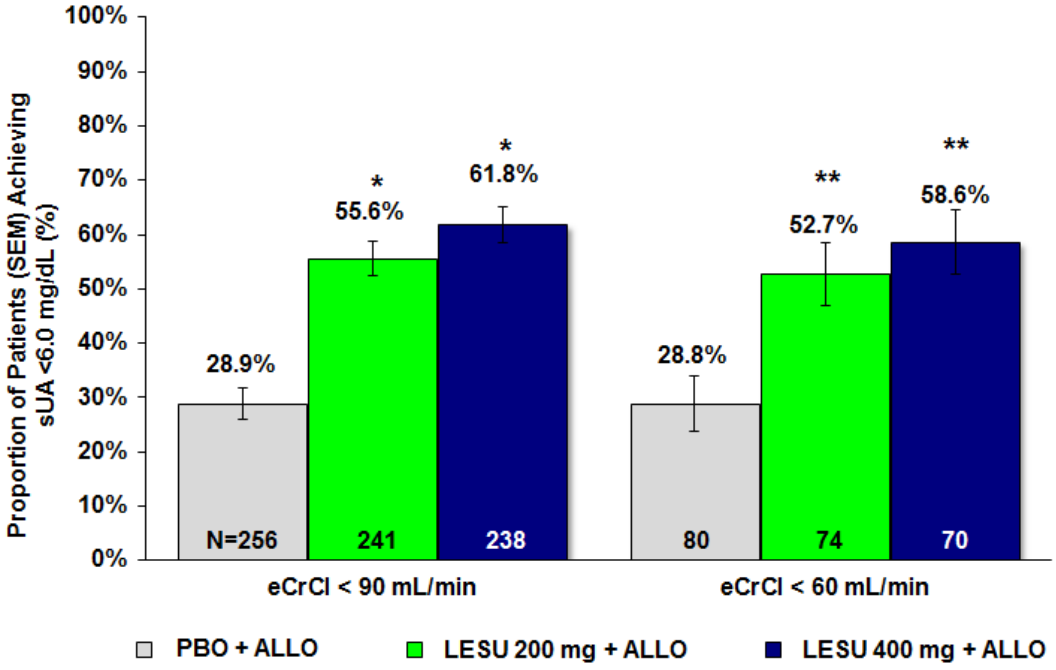
Subgroup	PBO + ALLO (n/N)	LESU 200 mg + ALLO (n/N)	Diff (95% CI)
Overall	104/407	222/405	0.29 (0.23, 0.36)
Sex			
Male	97/385	218/389	0.31 (0.24, 0.37)
Female	7/22	4/16	-0.07 (-0.36, 0.22)
Race			
White	82/308	183/318	0.31 (0.24, 0.38)
Non-White	22/99	39/87	0.23 (0.09, 0.36)
Age			
<65	89/354	199/365	0.29 (0.23, 0.36)
≥65	15/53	23/40	0.29 (0.1, 0.49)
Ethnicity			
Hispanic/Latino	5/26	16/37	0.24 (0.2, 0.46)
Not-Hispanic/Latino	99/381	206/368	0.3 (0.23, 0.37)
Region			
North America	83/320	173/316	0.29 (0.22, 0.36)
Europe	11/43	23/43	0.28 (0.08, 0.48)
South Africa	7/33	19/30	0.42 (0.2, 0.64)
Australia/New Zealand	3/11	7/16	0.16 (-0.19, 0.52)
Weight			
≤100 kg	61/177	92/153	0.26 (0.15, 0.36)
>100 kg	43/227	130/252	0.33 (0.25, 0.41)
BL Allo > 300	10/28	17/31	0.19 (-0.06, 0.44)
BL Aspirin			
Yes	20/82	38/63	0.36 (0.21, 0.51)
No	84/325	184/341	0.28 (0.21, 0.35)
BL Thiazides & Thiazide like			
Yes	19/64	48/79	0.31 (0.16, 0.47)
No	85/343	174/326	0.29 (0.22, 0.36)
Screening Presence of Tophi			
Yes	16/75	37/79	0.26 (0.11, 0.4)
No	88/332	185/326	0.3 (0.23, 0.37)



Abbreviations: ALLO, allopurinol (subgroup dose > 300 mg); BL, baseline; CI, confidence interval; Diff, difference (LESU 200 mg + ALLO) – (PBO + ALLO); ITT, intent-to-treat; LESU, lesinurad; NRI, nonresponder imputation; PBO, placebo; sUA, serum uric acid.
Note: BL Thiazide and Thiazide like indicates use of thiazide or thiazide-like diuretics at Baseline. Patients missing the Month 6 sUA value were treated as non-responders.

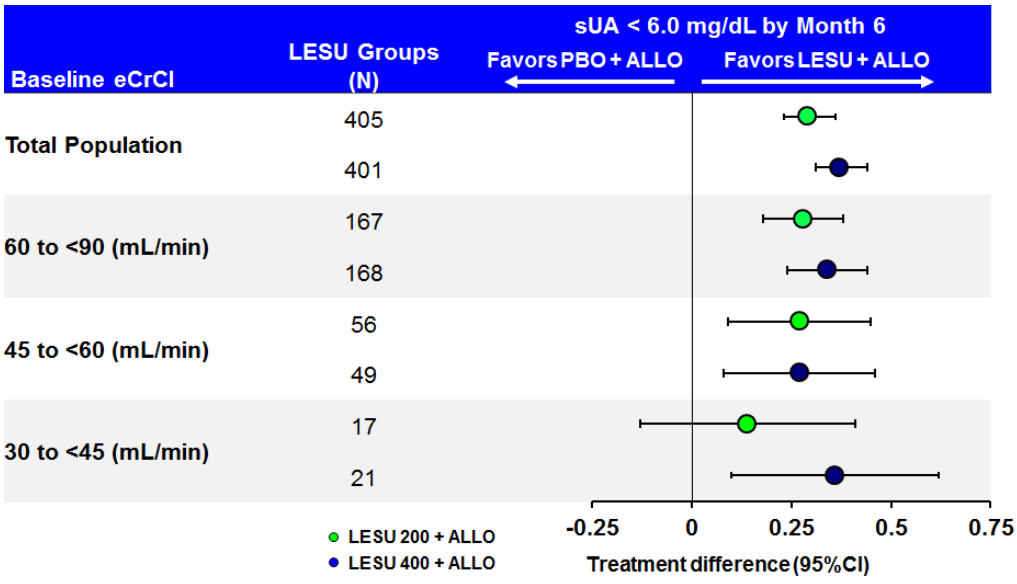
Efficacy by Baseline renal function was also evaluated. Patients with mild or moderate renal impairment (< 90 mL/min) and those with only moderate (< 60 mL/min) demonstrated response rates consistent with the overall population (Figure 30). Looking more closely at discrete renal impairment categories, patients with eCrCl 60 to < 90 mL/min or eCrCl 45 to < 60 mL/min showed similar efficacy to the overall ITT Population (Figure 31). For the lesinurad plus allopurinol groups, the point estimate of the treatment effect for the eCrCl 30 to < 45 mL/min subgroup was slightly less than that observed in patients with eCrCl 45 to < 60 mL/min. This is likely a reflection of the small sample size of this subgroup, as the lower point estimate was not noted for the 400 mg lesinurad dose.

Figure 30: Proportion of Patients With sUA < 6 mg/dL At Month 6 in Patients With Baseline Mild or Moderate Renal Impairment – NRI (ITT Population, CLEAR 1 and CLEAR 2 Pooled)



Abbreviations: ALLO, allopurinol; eCrCl, estimated creatinine clearance; ITT, intent-to-treat; LESU, lesinurad; NRI, nonresponder imputation; PBO, placebo; SEM, standard error of the mean; sUA, serum uric acid.
*p<0.0001 vs. PBO + ALLO; **p<0.005 vs. PBO + ALLO.

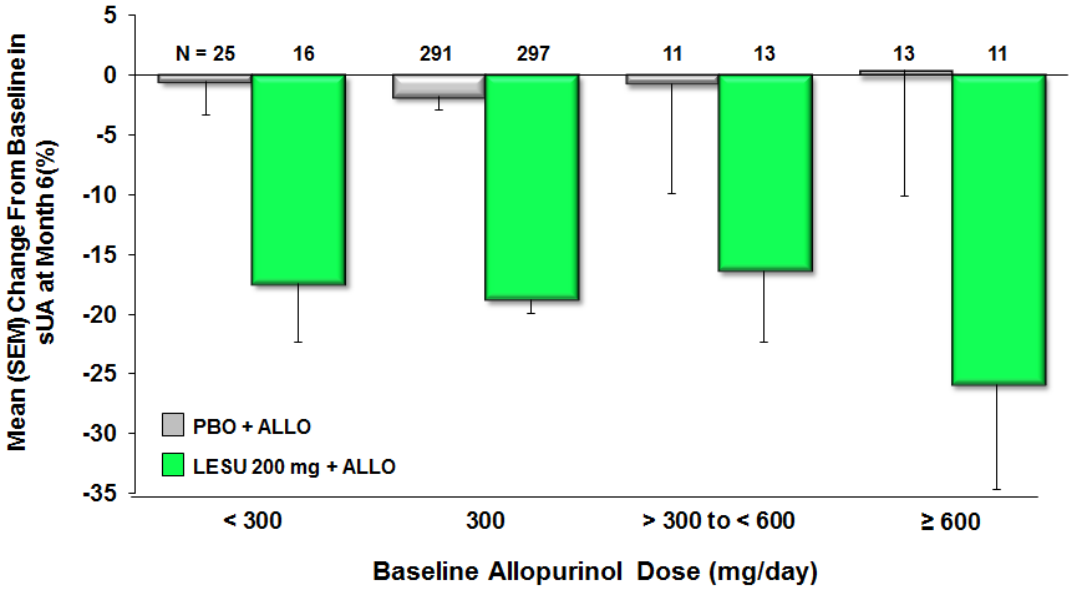
Figure 31: Subgroup Analyses by Baseline Renal Function – NRI (ITT Population, CLEAR 1 and CLEAR 2 Pooled)



Abbreviations: ALLO, allopurinol; CI, confidence interval; eCrCl, estimated creatinine clearance; ITT, intent-to-treat; LESU, lesinurad; NRI, nonresponder imputation; PBO, placebo; sUA, serum uric acid.

In addition, subgroup analyses demonstrated that regardless of the Baseline allopurinol dose, the addition of lesinurad 200 mg resulted in a consistent sUA lowering across allopurinol doses. Figure 32 shows the percent change in sUA from Baseline for all Baseline allopurinol dose levels (< 300 mg, 300 mg, > 300 mg to < 600 mg, and ≥ 600 mg) at Month 6. Similar results were seen at other timepoints through Month 12. In addition, across these baseline allopurinol doses, when lesinurad was added to any allopurinol dose level, the number of patients achieving the sUA target of < 6 mg/dL was higher compared with allopurinol alone.

Figure 32: Percent Change from Baseline to Month 6 in Serum Uric Acid Levels by Baseline Allopurinol Dose - Observed Cases (ITT Population, CLEAR 1 and CLEAR 2 Pooled)



Abbreviations: ALLO, allopurinol; ITT, intent-to-treat; LESU, lesinurad; PBO, placebo; SEM, standard error of the mean; sUA, serum uric acid.

8.4.1.2. Lesinurad in Combination With Febuxostat (CRYSTAL)

8.4.1.2.1. Primary Endpoint: Proportion of Patients With sUA < 5 mg/dL by Month 6

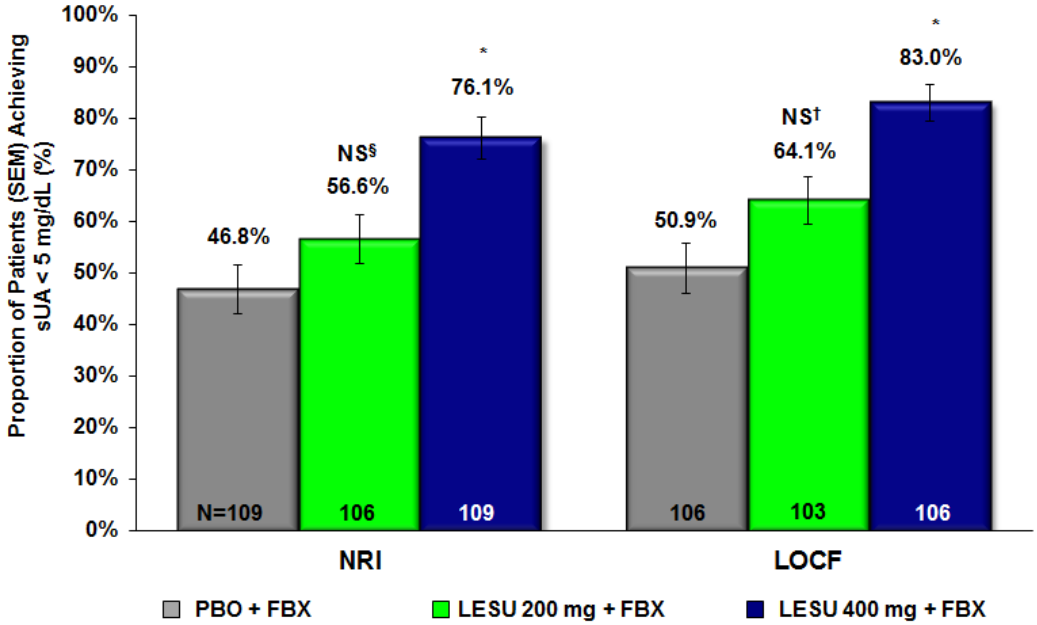
When given in combination with febuxostat, both the lesinurad 200 mg and lesinurad 400 mg groups had a higher proportion of patients with an sUA < 5 mg/dL by Month 6 (primary endpoint) compared with febuxostat alone (Figure 33). Using NRI, the response rate was statistically significant for the lesinurad 400 mg group (76.1% vs. 46.8%; $p < 0.0001$), but not for the lesinurad 200 mg group (56.6% vs. 46.8%; $p = 0.1298$).

The high rate of response in the febuxostat alone group was expected because all patients were included in CRYSTAL after 3 weeks of febuxostat alone treatment regardless of their Baseline sUA level and approximately 95% of patients enrolled in the study were febuxostat-naïve. The response rate was consistent with other febuxostat clinical trials.[16, 22]

Using LOCF, the response rate was 64.1% vs. 50.9% ($p = 0.0377$) for lesinurad 200 mg plus febuxostat vs. febuxostat alone and 83.0% vs. 50.9% ($p < 0.0001$) for lesinurad 400 mg plus febuxostat vs. febuxostat alone. Additional analyses using alternate methods to address missing

data were conducted and resulted in treatment effects at Month 6 that were consistent with the analyses using NRI and LOCF.

Figure 33: Primary Endpoint: Proportion of Patients Achieving Serum Uric Acid < 5 mg/dL by Month 6 in CRYSTAL (ITT Population)

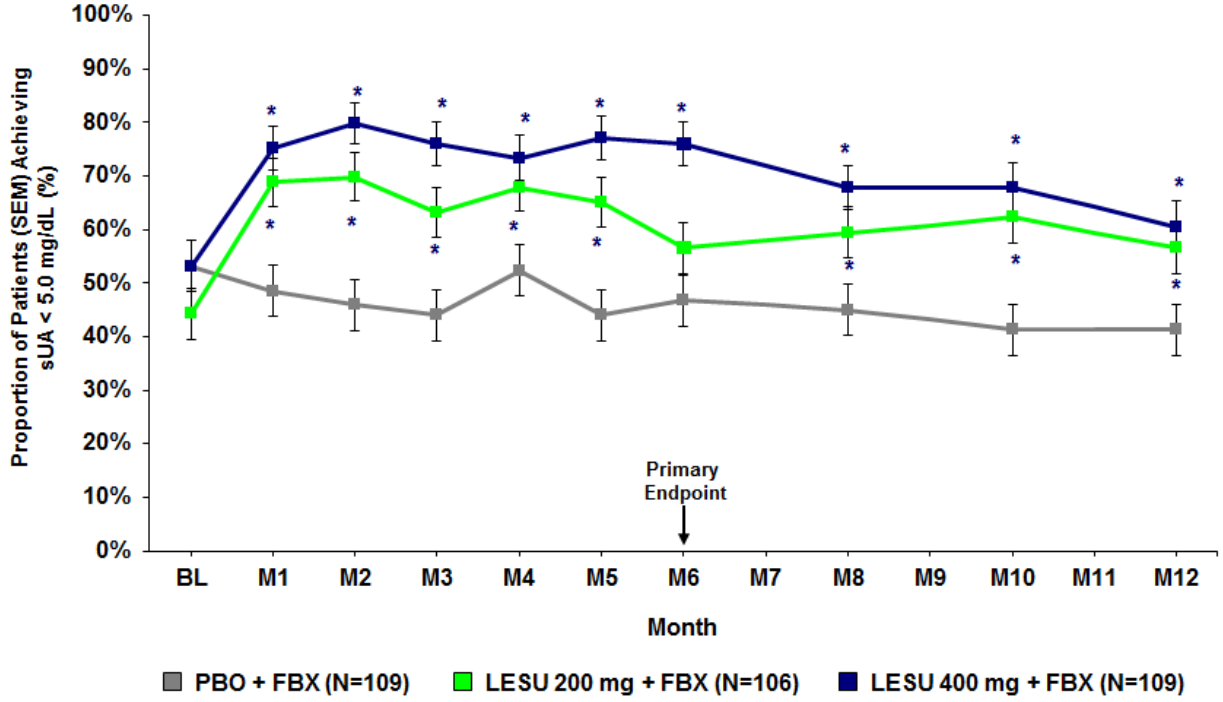


Abbreviations: FBX, febuxostat; ITT, intent-to-treat; LESU, lesinurad; LOCF, last observation carried forward imputation; NRI, nonresponder imputation; NS, not statistically significant; PBO, placebo; sUA, serum uric acid.
Note: Patients missing an sUA result at Month 6 were treated as nonresponders using NRI. Nominal p-values are presented for LOCF.
*p<0.0001 vs. PBO + FBX. †p=0.0377 vs. PBO + FBX. §p=0.1298 vs. PBO + FBX.

Prespecified Sensitivity and Prespecified Supportive Analyses

Although the difference was not statistically different for the lesinurad 200 mg plus febuxostat group by Month 6, superior treatment effects were observed at all other timepoints (Months 1, 2, 3, 4, 5, 8, 10, and 12; p-values ranging from 0.0002 to 0.0281 using NRI) for both the lesinurad 200 mg and lesinurad 400 mg plus febuxostat groups (Figure 34).

Figure 34: Proportion of Patients Achieving Serum Uric Acid Level < 5 mg/dL by Visit in CRYSTAL – NRI (ITT Population)

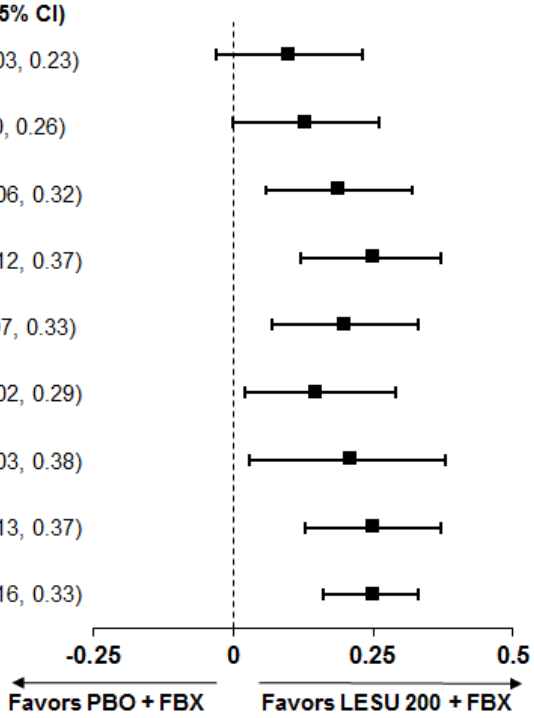


Abbreviations: FBX, febuxostat; ITT, intent-to-treat; LESU, lesinurad; NRI, nonresponder imputation; PBO, placebo; SEM, standard error of the mean; sUA, serum uric acid.
Note: Baseline reflects response rates after 3 weeks of febuxostat alone treatment during Screening. Patients missing an sUA result were treated as nonresponders at that visit.
*p < 0.0001 vs. PBO + FBX at Month 6 (multiplicity-protected primary endpoint) and nominal p-values 0.0002 to 0.0281 (not protected for multiplicity) at all other months using Cochran-Mantel Haenszel test stratified by Day-7 renal function and Day-7 sUA level (randomized values).

Additional prespecified sensitivity and supportive analyses demonstrated that lesinurad 200 mg plus febuxostat was superior to febuxostat alone in sUA lowering and achieving a target sUA < 5 mg/dL for each of 3 consecutive months, (Months 4, 5, and 6) as well as achieving a median target sUA < 5 mg/dL (Figure 35). Superior efficacy was also observed for lower sUA targets (< 4 and < 3 mg/dL).

Figure 35: Primary and Prespecified Sensitivity Analyses of Serum Uric Acid: Lesinurad 200 mg Plus Febuxostat vs. Placebo Plus Febuxostat in CRYSTAL (ITT Population)

Prespecified Analyses	PBO + FBX (n/N)	LESU 200 + FBX (n/N)	Diff (95% CI)
sUA<5 @M6 (NRI)	51/109	60/106	0.1 (-0.03, 0.23)
sUA<5 @M6 (LOCF)	54/106	66/103	0.13 (0, 0.26)
sUA<5 @M4,5,6 (NRI)	36/109	55/106	0.19 (0.06, 0.32)
Median sUA<5	54/105	76/100	0.25 (0.12, 0.37)
sUA<5 @M1 (NRI)	53/109	73/106	0.2 (0.07, 0.33)
sUA<5 @M12 (NRI)	45/109	60/106	0.15 (0.02, 0.29)
Baseline ≥ 5 with sUA<5 @M6 (NRI)	12/51	26/59	0.21 (0.03, 0.38)
sUA<4 @M6 (NRI)	21/109	47/106	0.25 (0.13, 0.37)
sUA<3 @M6 (NRI)	2/109	28/106	0.25 (0.16, 0.33)



Abbreviations: BL ≥ 5 mg/dL indicates a Baseline sUA ≥ 5 mg/dL; CI, confidence intervals; Diff, difference (LESU 200 mg + FBX) – (PBO + FBX); FBX, febuxostat; ITT, intent-to-treat; LESU, lesinurad; LOCF, last observation carried forward; M, Month; NRI, nonresponder imputation; PBO, placebo; sUA, serum uric acid.

Exploratory Analyses of Month 6 sUA Results

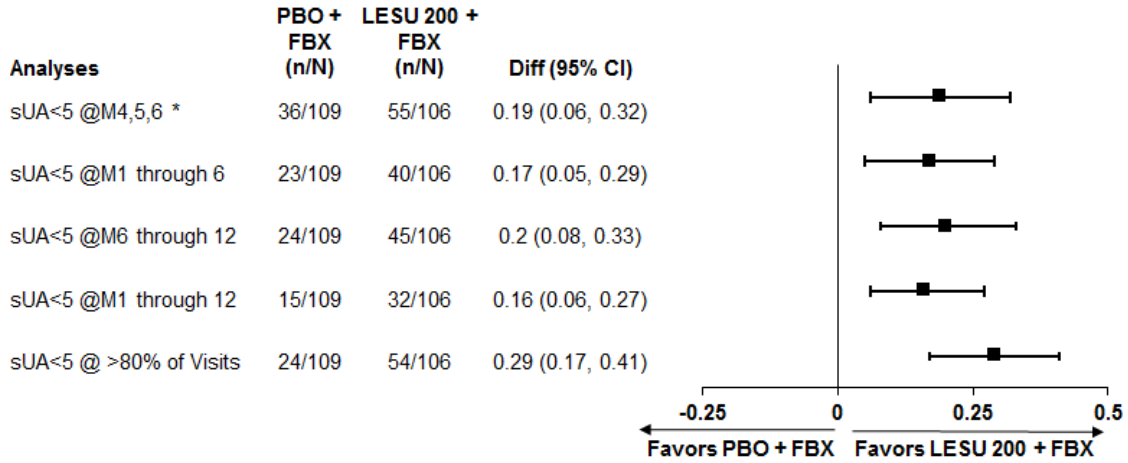
To investigate the inconsistent treatment effect at Month 6 for the lesinurad 200 mg group, data from patients with a response that was not uniform across Months 5, 6, and 8 were reviewed for potential confounding factors that could prohibit patients from achieving the primary endpoint (eg, lack of compliance, gout flares, AEs). There was no clinical evidence to account for the inconsistent result at Month 6 for the lesinurad 200 mg group.

Prespecified and Sensitivity Analyses of Sustained Response

Additional prespecified and sensitivity analyses were conducted to evaluate the effectiveness of the combination to achieve a sustained response (Figure 36). Each analysis used NRI, where patients who dropped out or were missing any of the required visits were considered nonresponders. Differences favoring the lesinurad 200 mg plus febuxostat group vs. febuxostat alone were observed ($p \leq 0.0055$) for all of the analyses. In particular, more than twice as many patients in the lesinurad 200 mg group reached the most stringent definition of achieving target at all timepoints (Months 1 through 12) compared with febuxostat alone.

A post hoc analysis of the sUA response across 12 months resulted in an odds ratio of 3.24 (95% CI [2.06, 5.09]); the lesinurad 200 mg group had more than 3 times the odds of achieving an sUA response than placebo.

Figure 36: Measures of Sustained Response: Lesinurad 200 mg Plus Febuxostat vs. Placebo Plus Febuxostat in CRYSTAL – NRI (ITT Population)



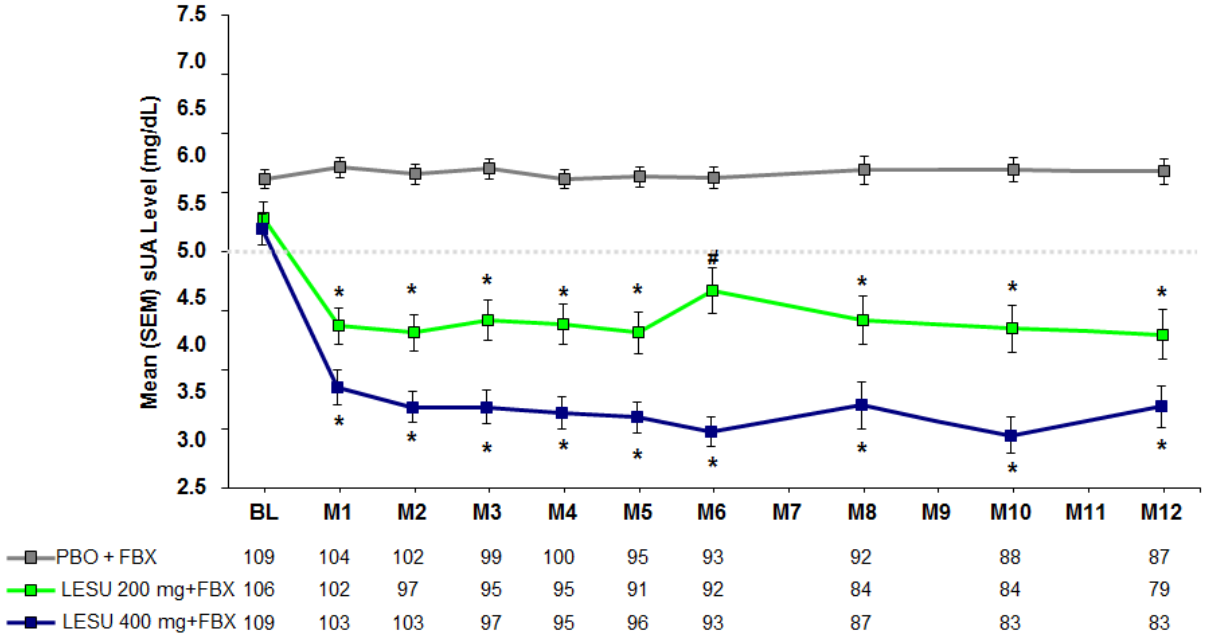
Abbreviations: CI, confidence interval; Diff, difference (LESU 200 mg + FBX) – (PBO + FBX); FBX, febuxostat; ITT, intent-to-treat; LESU, M, Month; NRI, nonresponder imputation; PBO placebo; sUA, serum uric acid.
*Prespecified analysis.

8.4.1.2.2. Additional Prespecified Analysis

Mean sUA and Changes Over Time

Serum uric acid as a continuous variable was also assessed by absolute and percent changes from Baseline of sUA at each timepoint. The changes in sUA from Baseline were rapid (observed at Month 1), stable, and sustained (similar at each monthly assessment for the duration of the 12-month treatment period) for both lesinurad dose levels. At each timepoint during the 12-month treatment period, the mean sUA was lower for lesinurad 200 mg and lesinurad 400 mg plus febuxostat compared with febuxostat alone (Figure 37), with p-values ≤ 0.0004 for the mean change and mean percent change from Baseline.

Figure 37: Mean Serum Uric Acid Levels by Visit in CRYSTAL – Observed Cases (ITT Population)



Abbreviations: BL, Baseline; FBX, febuxostat; ITT, intent-to-treat; LESU, lesinurad; M, month; PBO, placebo; SEM, standard error of the mean; sUA, serum uric acid.
*Nominal p-value < 0.0001 vs. PBO + FBX. # Nominal p-value < 0.01 vs. PBO + FBX.
Notes: Numbers indicate the number of patients contributing data at each timepoint. Dotted line indicates target sUA (< 5 mg/dL). p-values are based on the treatment difference in least square mean percent change from Baseline, ANCOVA.

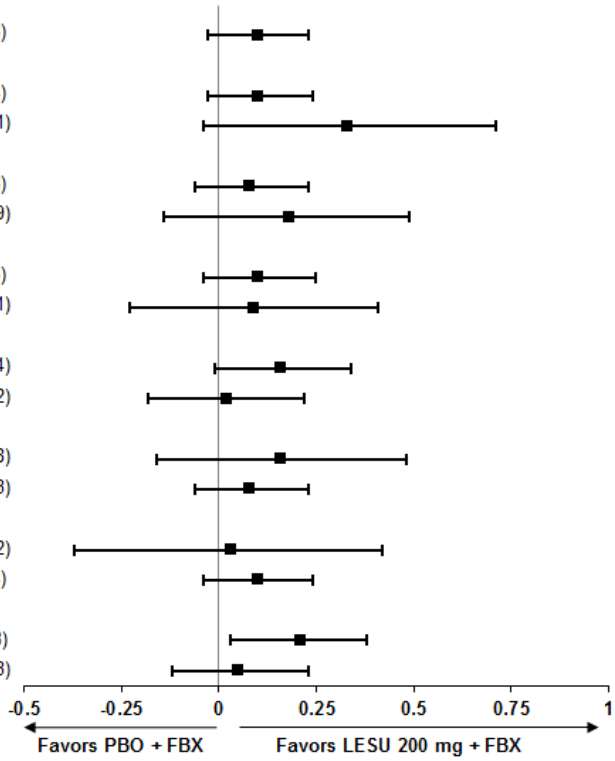
Subgroup Analysis

All Subgroups

Multiple subgroup analyses for sUA < 5 mg/dL by Month 6 (primary endpoint) showed the same trends and effectiveness of lesinurad to lower sUA as observed in the overall ITT Population. These included subgroups based on Baseline demographic information, renal impairment at Baseline, and concomitant medications of interest. Results for key subgroups for lesinurad 200 mg plus febuxostat vs. febuxostat alone are presented in Figure 38. Consistent with the primary endpoint, the point estimates were on the right, favoring lesinurad 200 mg.

Figure 38: Subgroup Analyses of Difference from Placebo in Proportion of Patients on Lesinurad 200 mg Achieving sUA < 5 mg/dL by Month 6 in CRYSTAL – NRI (ITT Population)

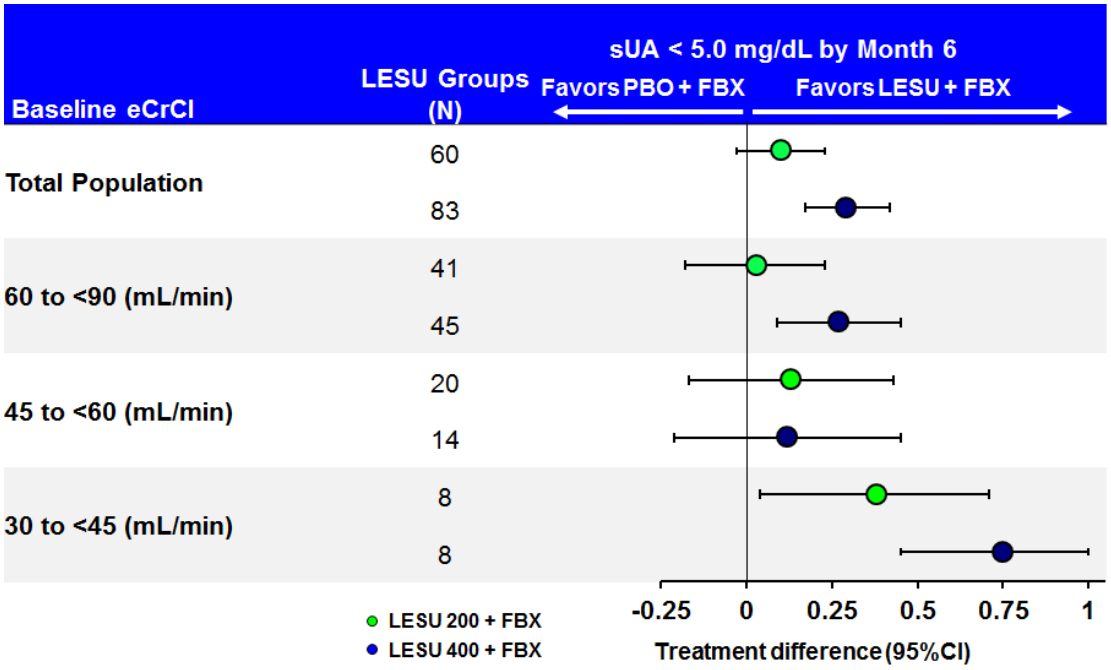
Subgroup	PBO + FBX (n/N)	LESU 200 mg + FBX (n/N)	Diff (95% CI)
Overall	51/109	60/106	0.1 (-0.03, 0.23)
Sex			
Male	51/107	58/100	0.1 (-0.03, 0.24)
Female	0/2	2/6	0.33 (-0.04, 0.71)
Race			
White	45/94	45/80	0.8 (-0.06, 0.23)
Non-White	6/15	15/26	0.18 (-0.14, 0.49)
Age			
<65	41/89	50/89	0.1 (-0.04, 0.25)
≥65	10/20	10/17	0.09 (-0.23, 0.41)
Weight			
<100 kg	29/62	36/57	0.16 (-0.01, 0.34)
≥100 kg	22/47	24/49	0.02 (-0.18, 0.22)
BL Aspirin			
Yes	9/16	13/18	0.16 (-0.16, 0.48)
No	42/93	47/88	0.08 (-0.06, 0.23)
BL Thiazides & Thiazide like			
Yes	6/9	9/13	0.03 (-0.37, 0.42)
No	45/100	51/93	0.1 (-0.04, 0.24)
BL sUA ≥5			
Yes	12/51	26/59	0.21 (0.03, 0.38)
No	39/58	34/47	0.05 (-0.12, 0.23)



Abbreviations: BL, baseline; CI, confidence interval; Diff, difference (LESU 200 mg + FBX) – (PBO + FBX); FBX, febuxostat; ITT, intent-to-treat; LESU, lesinurad; NRI, nonresponder imputation; PBO, placebo; sUA, serum urate. Age in years; BL renal impairment expressed as eCrCl in mL/min; BL Thiazide and Thiazide like indicates use of thiazide or thiazide-like diuretics at Baseline; BL sUA in mg/dL.
Note: Patients missing the Month 6 sUA value were treated as non-responders.

Efficacy by Baseline renal function was also evaluated (Figure 39). Although the sample sizes were small for most subgroups, efficacy was consistent with the overall ITT Population with point estimates > 0, favoring lesinurad. The increase in the treatment effect observed in patients with eCrCl 30 to < 45 mL/min is likely a reflection of the small sample size rather than an indication of enhanced efficacy.

Figure 39: Subgroup Analyses by Baseline Renal Function – NRI (ITT Population, CRYSTAL)

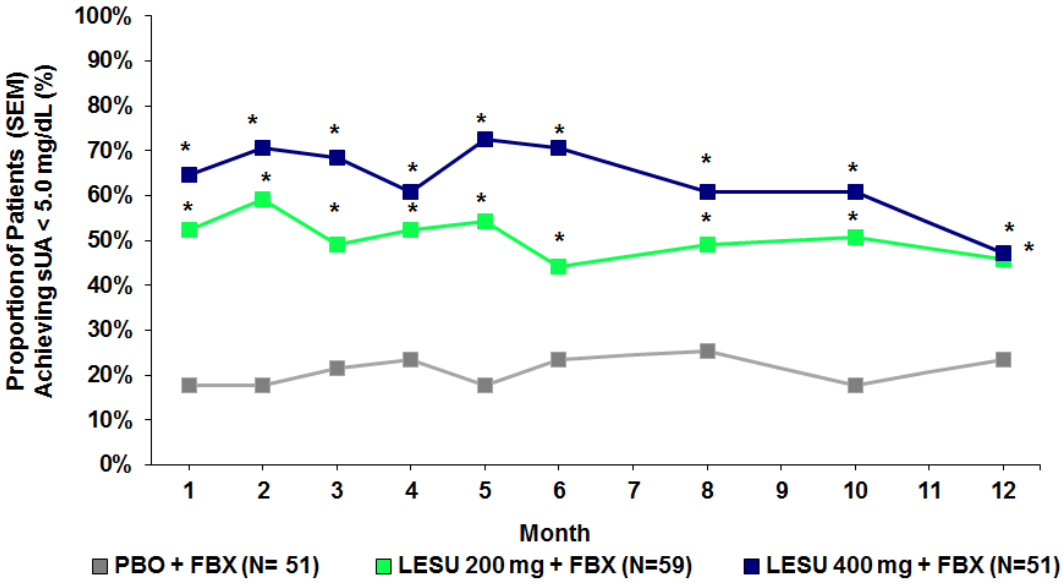


Abbreviations: CI, confidence interval; eCrCl, estimated creatinine clearance; FBX, febuxostat; ITT, intent-to-treat; LESU, lesinurad; NRI, nonresponder imputation; PBO, placebo; sUA, serum uric acid.

Subgroup of Patients Not at Target at Baseline on Febuxostat Alone

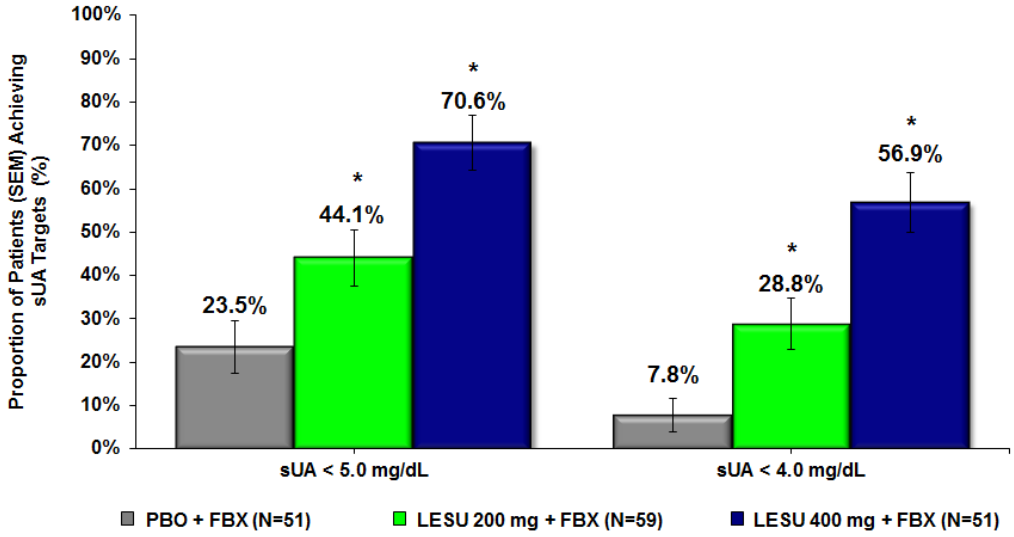
As per the study design, patients were randomized in CRYSTAL after 3 weeks of febuxostat alone treatment regardless of their Baseline sUA level. At Baseline, prior to randomization, approximately 50% of patients had achieved sUA < 5 mg/dL, as expected with febuxostat alone treatment. In the subgroup of patients with a Baseline sUA ≥ 5 mg/dL after 3 weeks of febuxostat, lesinurad 200 mg demonstrated added benefit. This is an important subgroup with the greatest need for additional treatment options because they did not achieve the target sUA level while on febuxostat 80 mg monotherapy, the highest dose of febuxostat approved in the US. This is the intended population to receive lesinurad in the proposed treatment indication. In this population of patients, a greater proportion of patients achieved the target sUA < 5 mg/dL on lesinurad 200 mg plus febuxostat compared with febuxostat alone at every visit using NRI (Figure 40). Specifically, at Month 6, nearly twice as many patients achieved the target sUA < 5 mg/dL on lesinurad 200 mg plus febuxostat compared with febuxostat alone using NRI (44.1% vs. 23.5%, p = 0.0243) and nearly four times as many achieved the target sUA < 4 mg/dL (28.8% vs. 7.8%, p = 0.0054) (Figure 41). Similar results were noted using LOCF: 47.4% vs. 26.0%, p=0.022 for sUA < 5.0 mg/dL and 29.8% vs. 8.0%, p=0.005 for sUA < 4.0 mg/dL by Month 6. Although the sample size for patients with mild or moderate renal impairment in this subgroup was small (N=38 receiving lesinurad 200 mg plus febuxostat), a numerically higher proportion of patients on lesinurad 200 mg plus febuxostat also achieved target sUA < 5.0 mg/dL: 39.5% vs. 25.7% using NRI (p=0.21) at Month 6.

Figure 40: Proportion of Patients With an sUA < 5 mg/dL by Visit in the Subgroup of Patients With Baseline sUA ≥ 5 mg/dL in CRYSTAL – NRI (ITT Population)



Abbreviations: ITT, intent-to-treat; FBX, febuxostat; LESU, lesinurad; NRI, nonresponder imputation; PBO, placebo; sUA, serum uric acid.
Note: Patients missing an sUA result were treated as nonresponders at that visit.
*Nominal p-value < 0.025 vs. PBO + FBX.

Figure 41: Proportion of Patients Achieving sUA < 5 mg/dL and < 4 mg/dL At Month 6 in the Subgroup of Patients With a Baseline sUA ≥ 5 mg/dL in CRYSTAL – NRI (ITT Population)



Abbreviations: FBX, febuxostat; LESU, lesinurad; NRI, nonresponder imputation; PBO, placebo; SEM, standard error of the mean; sUA, serum uric acid.
Note: Patients missing an sUA result at Month 6 were treated as nonresponders.
*Nominal p-value < 0.025 vs. PBO + FBX.

8.4.2. Gout Flares Requiring Treatment

The mean rate of gout flares requiring treatment for the 6-month period from the end of Month 6 to the end of Month 12 (the period after gout flare prophylaxis was to be discontinued) was a key secondary endpoint in CLEAR 1 and CLEAR 2 and a prespecified endpoint in CRYSTAL. This time period was selected to reduce the potential confounding impact of gout flare prophylaxis that was to be used through Month 5.

In CLEAR 1 and CLEAR 2, the mean rate of gout flares requiring treatment during the study was low. During the 6-month period from the end of Month 6 to the end of Month 12, only 20% to 32% of patients across all treatment groups reporting a flare requiring treatment. After adjustment for Day -7 renal function, tophus status at Screening, and length of exposure to randomized study medication, the mean rates of gout flares that required treatment during the 6-month period from the end of Month 6 through Month 12 were similar for lesinurad 200 mg or 400 mg plus allopurinol when compared with allopurinol alone, with no statistically significant differences (Table 16).

In CRYSTAL, the mean rate of gout flare requiring treatment during the 6-month period from the end of Month 6 through Month 12 was higher than the allopurinol studies (CLEAR 1 and CLEAR 2), as expected in a tophaceous gout population with greater uric acid crystal burden. The adjusted rate was similar for the lesinurad 200 mg plus febuxostat and febuxostat alone groups ($p = 0.5493$). The lesinurad 400 mg plus febuxostat group had a nearly 50% lower adjusted rate of gout flares requiring treatment compared with the febuxostat alone group ($p = 0.0401$) (Table 16).

The mean rates of gout flares requiring treatment were also examined at each monthly interval (Figure 42). The unadjusted rates of gout flares requiring treatment were higher in the lesinurad 400 mg groups during Baseline to the end of Month 1 in all 3 pivotal studies, consistent with initial increase in gout flares observed with other ULT, thought to be caused by urate crystal mobilization. After Month 2, the rates were generally similar across the 3 treatment groups.

Table 16: Mean Rate of Gout Flares Requiring Treatment Per Patient for the 6-Month Period from the End of Month 6 to the End of Month 12 in CLEAR 1, CLEAR 2, and CRYSTAL (ITT Population)

	CLEAR 1			CLEAR 2			CRYSTAL		
	PBO + ALLO (N=201)	LESU 200 mg + ALLO (N=201)	LESU 400 mg + ALLO (N=201)	PBO + ALLO (N=206)	LESU 200 mg + ALLO (N=204)	LESU 400 mg + ALLO (N=200)	PBO + FBX 80 mg (N=109)	LESU 200 mg + FBX 80 mg (N=106)	LESU 400 mg + FBX 80 mg (N=109)
Adjusted Rate of Gout Flares Requiring Treatment[a] (SE)[b]	0.58 (0.10)	0.57 (0.10)	0.51 (0.09)	0.83 (0.13)	0.73 (0.12)	0.77 (0.13)	1.3 (0.25)	1.5 (0.31)	0.7 (0.15)
Median (Min, Max)	0.0 (0, 8)	0.0 (0, 7)	0.0 (0, 8)	0.0 (0, 10)	0.0 (0, 6)	0.0 (0, 11)	0.0 (0, 19)	0.0 (0, 12)	0.0 (0, 5)
p-value of Incidence Rate Ratio[b]		0.9796	0.6125		0.5716	0.7454		0.5493	0.0401

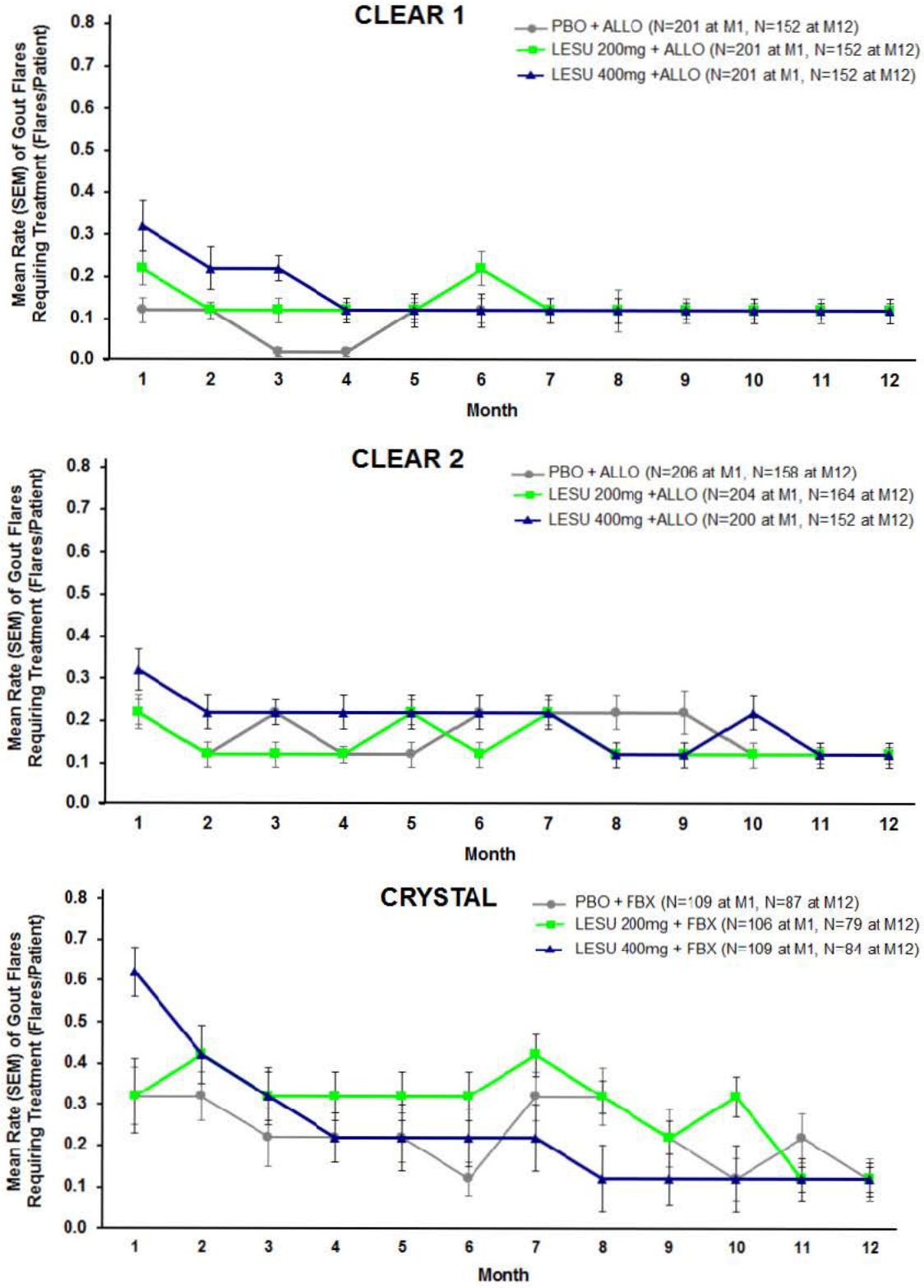
Abbreviations: ALLO, allopurinol; FBX, febuxostat; ITT, intent-to-treat; LESU, lesinurad; PBO, placebo; SE, standard error.

[a] A gout flare requiring treatment was defined as one with a protocol-specified medication recorded with indication of "Treatment for Gout Flare" beginning within 3 days prior to the start or 3 days after the end of the gout flare.

[b] Estimates obtained from Negative Binomial Regression adjusted for Day -7 renal function (eCrCl ≥ 60 vs. < 60 mL/min) and either tophus status during Screening (presence vs. absence) for CLEAR 1 and CLEAR 2 or Day -7 sUA level (sUA ≥6 vs. <6 mg/dL) for CRYSTAL, randomized values, and log follow-up time as the offset variable.

Note: The 6-month time period was selected to reduce the potential confounding impact of gout flare prophylaxis that was to be used through Month 5. The gout flare requiring treatment rate was defined as the total number of gout flares requiring treatment during the interval per patient. Summary statistics use observed data (no imputation).

Figure 42: Mean Rate of Gout Flares Requiring Treatment in the Pivotal Phase 3 Studies (ITT Population) - Observed Cases



Abbreviations: ALLO, allopurinol; FBX, febuxostat; LESU, lesinurad; ITT, intent-to-treat; PBO, placebo; SEM, standard error of the mean.

8.4.3. Tophus Reduction

In all 3 pivotal studies, the proportion of patients with ≥ 1 target tophus at Baseline who achieved a CR of ≥ 1 target tophus by the patient's last on-study visit (by Month 12) was a key secondary endpoint. A target tophus was defined as a tophus on the hands/wrists and/or feet/ankles that was ≥ 5 mm and ≤ 20 mm in the longest diameter and was measured by Vernier calipers. Up to 5 target tophi were measured by Investigators and followed during the study.

In CLEAR 1 and CLEAR 2, the power to detect treatment group differences was limited due to the low number of patients with ≥ 1 target tophus enrolled in these studies (approximately 9% in CLEAR 1 and 16% in CLEAR 2). The proportions of patients achieving these endpoints were similar among treatment groups, except for lesinurad 200 mg in CLEAR 1 where none of the 18 patients achieved a CR while on study (Table 17).

In CRYSTAL, all patients were required to have ≥ 1 target tophus. The difference between the proportions of patients who experienced CR of ≥ 1 target tophus by Month 12 was not statistically significant across treatment groups; however, a dose-dependent resolution of tophi was noted. The febuxostat alone group had the smallest proportion of patients who achieved CR (21.1%) followed by the lesinurad 200 mg plus febuxostat group (25.5%), whereas the lesinurad 400 mg plus febuxostat group had the greatest proportion (30.3%) (Table 17).

Table 17: Proportion of Patients With At Least One Target Tophus At Baseline Who Had Complete Resolution of At Least One Target Tophus by Month 12 in the Pivotal Studies – NRI (ITT Population)

Study	PBO + XOI n/N (%)	LESU 200 mg + XOI n/N (%)	Difference vs. PBO (95% CI) p-value	LESU 400 mg + XOI n/N (%)	Difference vs. PBO (95% CI) p-value
CLEAR 1	5/17 (29.4%)	0/18 (0%)	-0.29 (-0.51, -0.08) 0.0183	4/19 (21.1%)	-0.08 (-0.37, 0.20) 0.5974
CLEAR 2	11/33 (33.3%)	11/35 (31.4%)	-0.02 (-0.24, 0.20) 0.8466	8/29 (27.6%)	-0.06 (-0.29, 0.17) 0.6301
CRYSTAL	23/109 (21.1%)	27/106 (25.5%)	0.04 (-0.07, 0.16) 0.4453	33/109 (30.3%)	0.09 (-0.02, 0.21) 0.1149

Abbreviations: CI, confidence interval; ITT, intent-to-treat; LESU, lesinurad; NRI, nonresponder imputation; PBO, placebo; XOI, xanthine oxidase inhibitor.
Note: Patients who experienced a best response of CR of at least 1 target tophus at their last on-study visit (by Month 12) met the endpoint. Patients with progressive disease at their last on-study visit (by Month 12) and those who did not achieve CR by their last on-study visit (by Month 12) were treated as nonresponders.

Another key secondary endpoint in CRYSTAL was the proportion of patients with a CR or PR (≥ 50% reduction) in ≥ 1 target tophus by Month 12. More patients in the lesinurad 200 mg and 400 mg plus febuxostat groups had a CR or PR compared with febuxostat alone (56.6% and 58.7% vs. 50.5%), but the differences were not statistically significant.

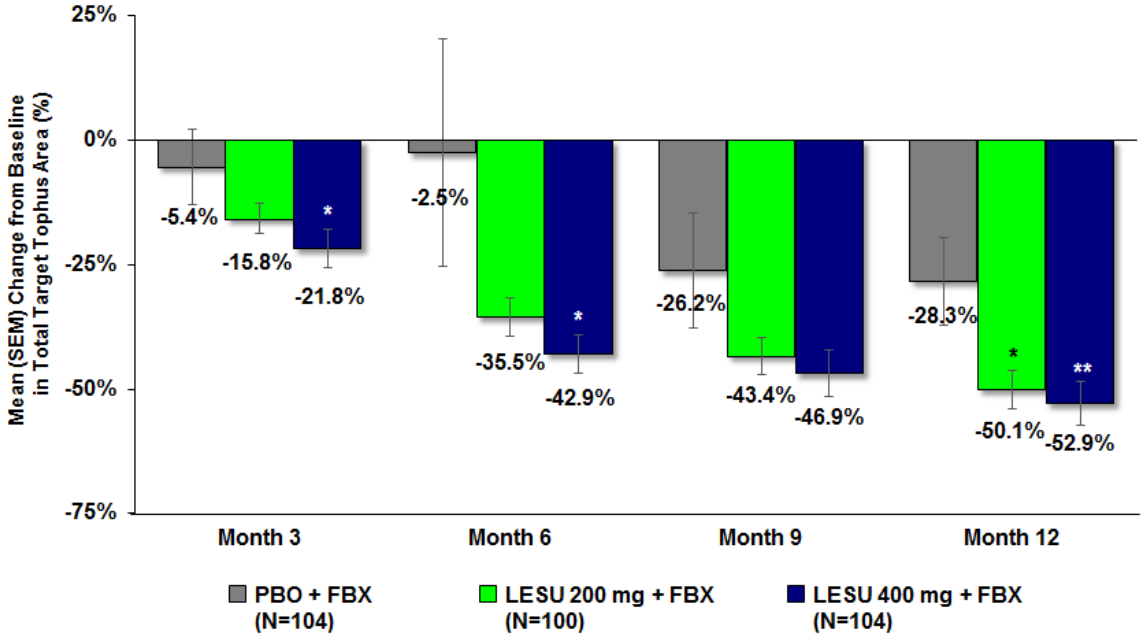
Given that up to 5 target tophi could be followed in the pivotal studies, the proportion of patients with resolution of all target tophi was also evaluated in prespecified analyses. In CLEAR 2 and CRYSTAL, more patients in the lesinurad 200 mg and 400 mg in combination with allopurinol or febuxostat groups had 100% resolution of all target tophi at Month 12: 29.6% and 23.1% vs. 10.7% for CLEAR 2 and 18.2% and 27.4% vs. 14.0% for CRYSTAL. In CLEAR 1, where few patients had target tophi in each group (~9%), this difference favoring lesinurad was only noted

in the lesinurad 400 mg dose group: 23.1% vs. 12.5% for LESU 400 mg + ALLO vs. PBO +ALLO respectively.

In a prespecified secondary endpoint analysis in CRYSTAL, the mean percent reduction from Baseline to Month 12 in total target tophus area was 50.1% and 52.9% for the lesinurad 200 mg and lesinurad 400 mg plus febuxostat groups, respectively, vs. 28.3% for the febuxostat alone group using LOCF (p = 0.0134 and 0.0052, respectively; Figure 43). Similar results were noted using the prespecified observed cases analysis and other post hoc sensitivity analyses, including MMRM models.

Some studies have shown that complete resolution of tophi may require long-term therapy with oral ULT.[22] The duration of the lesinurad pivotal studies may not have been sufficient to demonstrate differences between the groups; however, a primarily positive trend favoring lesinurad was noted.

Figure 43: Percent Change in Sum of the Areas for All Target Tophi (mm^2) by Visit in CRYSTAL - LOCF Imputation (ITT Population)



Abbreviations: FBX, febuxostat; ITT, intent-to-treat; LESU, lesinurad; LOCF, last observation carried forward; PBO, placebo; SEM, standard error of the mean.
Note: Figure depicts arithmetic means; statistical significance is based on difference in least square means.
*p < 0.05 vs. PBO + FBX, **p < 0.01 vs. PBO + FBX.

8.4.4. Patient Reported Outcomes

Patient-reported outcomes for disability, pain, and health-related quality of life were evaluated in the pivotal Phase 3 combination therapy studies using HAQ-DI, HAQ Pain Scale, SF-36, PGA, SDS, and TSQM. As assessed by these tools, the patient population in these studies had only minimal or limited impairment at Baseline (eg, more than half of all patients had a Baseline HAQ-DI < 0.25), which limited the degree of improvement that could be detected during the studies. Some improvements were observed over time but the improvements were small and

generally similar across groups. In general, results for the lesinurad 200 mg and 400 mg groups were comparable to placebo when given in combination with an XOI (allopurinol or febuxostat).

The proportion of patients with an improvement from Baseline in HAQ-DI of ≥ 0.25 (minimum clinically important difference) at Month 12 was a key secondary endpoint in CRYSTAL. The proportion of patients who met the endpoint at Month 12 was greatest for the febuxostat alone group; however, this is attributed to the imbalance in Baseline HAQ-DI scores. When analyzing only patients eligible to demonstrate a benefit (ie, those with a Baseline score of ≥ 0.25), there was no difference in the proportion of patients meeting the endpoint among the 3 treatment groups (Table 18).

Table 18: Proportion of Patients Achieving Health Assessment Questionnaire – Disability Index Improvement of ≥ 0.25 At Month 12 in CRYSTAL – Observed Cases (ITT Population)

	PBO + FBX 80 mg (N=109) n/N (%)	LESU 200 mg + FBX 80 mg (N=106) n/N (%)	LESU 400 mg + FBX 80 mg (N=109) n/N (%)
Mean Baseline HAQ-DI	0.729 (0.617)	0.671 (0.618)	0.586 (0.628)
Proportion with a HAQ-DI improvement of ≥0.25 at Month 12			
All Patients	42/80 (52.5)	34/77 (44.2)	26/78 (33.3)
p-value[a]		0.3034	0.0210
Patients with Baseline HAQ-DI Score ≥ 0.25[b]	42/61 (68.9)	34/50 (68.0)	26/39 (66.7)
p-value[a]		0.9661	0.9977

Abbreviations: FBX, febuxostat; HAD-QI, Health Assessment Questionnaire - Disability Index; ITT, intent-to-treat; LESU, lesinurad; PBO, placebo; SD, standard deviation.
[a] Cochran-Mantel Haenszel test stratified by Day -7 renal function (eCrCl ≥ 60 vs. < 60 mL/min) and Day -7 sUA level (sUA ≥ 6 vs. < 6 mg/dL), randomized values.
[b] Post hoc analysis.
Note: HAQ-DI assesses a patient's level of functional ability with scores ranging from 0 to 3. 0 indicates the least disability.

8.5. Exploratory Analyses: Association of Serum Uric Acid Levels With Gout Flares and Tophi Reduction

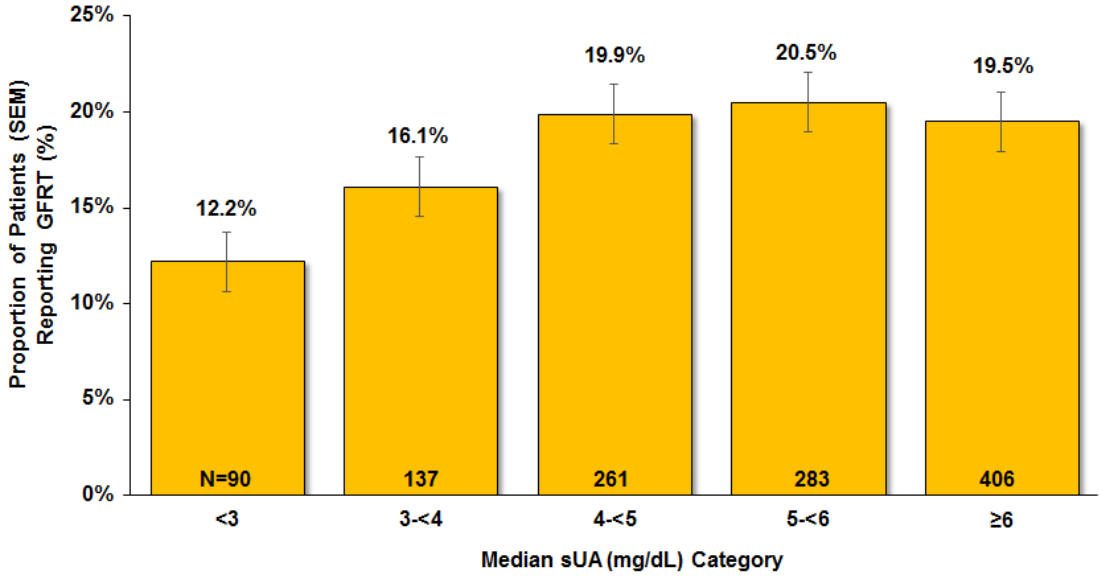
Exploratory analyses were performed to assess whether there was an association between sUA levels and gout flare or tophus reduction in a pooled analysis across the 3 studies. Because the rates of gout flares could increase initially with new ULT therapy and sustained treatment may be required for quantifiable benefits, the proportions of patients with a gout flare requiring treatment were assessed in the last quarter of study treatment (end of Month 9 to end of Month 12). Consistent with previously published reports,[9-14] results of the pooled analysis demonstrate that patients, regardless of treatment group, who achieved the lowest median on-study sUA levels were less likely to have a gout flare requiring treatment. During this last quarter, 12.2% with median sUA < 3 mg/dL experienced a gout flare requiring treatment compared with 20.5% with median on-study sUA of 5 to < 6 mg/dL (Figure 44).

Similarly, in patients with ≥ 1 target tophi at Baseline in the pooled 3 pivotal studies, patients with the lowest median sUA levels over the course of treatment achieved the greatest reduction in total target tophus area (Figure 45). Patients with median sUA < 3 mg/dL had an almost 60%

mean reduction in tophus area at Month 12 compared with a 28% mean reduction for patients with median sUA of 5 to < 6 mg/dL.

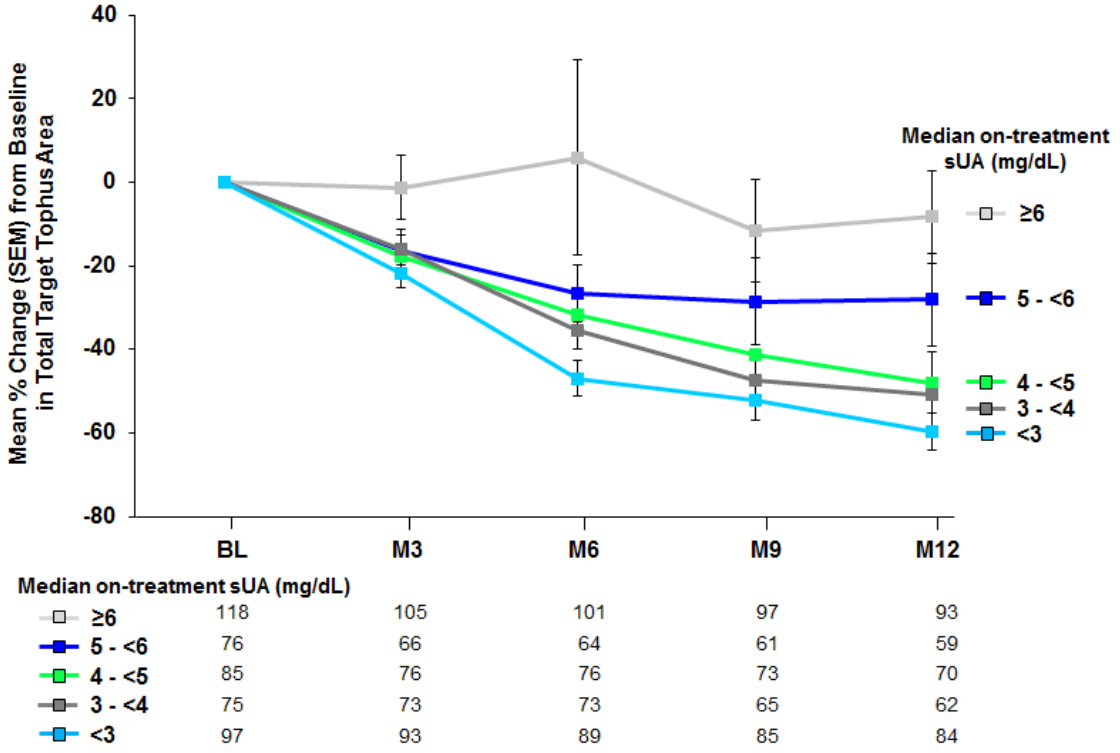
These findings suggest that the lower sUA levels over time are associated with less gout flares and more tophus reduction.

Figure 44: Proportion of Patients With ≥ 1 Gout Flare Requiring Treatment from Month 9 to Month 12 by Median On-Treatment sUA Level in Pivotal Studies - Observed Cases (ITT Population, All Treatment Groups Pooled)



Abbreviations: ITT, intent-to-treat; sUA, serum uric acid; SEM, standard error of the mean.
Note: A gout flare requiring treatment is defined as one with a protocol-specified medication recorded with indication of "Treatment for Gout Flare" beginning within 3 days before the start or 3 days after the end of the gout flare. Patients with ≥ 1 gout flare requiring treatment in the period are counted only once in each sUA category.

Figure 45: Mean Percent Change in Total Tophus Area by Median On-Treatment sUA Levels in Pivotal Studies - Observed Cases (ITT Population, All Treatment Groups Pooled)



Median on-treatment sUA (mg/dL)	BL	M3	M6	M9	M12
≥6	118	105	101	97	93
5 - <6	76	66	64	61	59
4 - <5	85	76	76	73	70
3 - <4	75	73	73	65	62
<3	97	93	89	85	84

Abbreviations: BL, Baseline; ITT, intent-to-treat; M, month; SEM, standard error of mean; sUA, serum uric acid.
Notes: Numbers indicate the number of patients contributing data at each timepoint.

8.6. Clinical Benefits of Extended Treatment

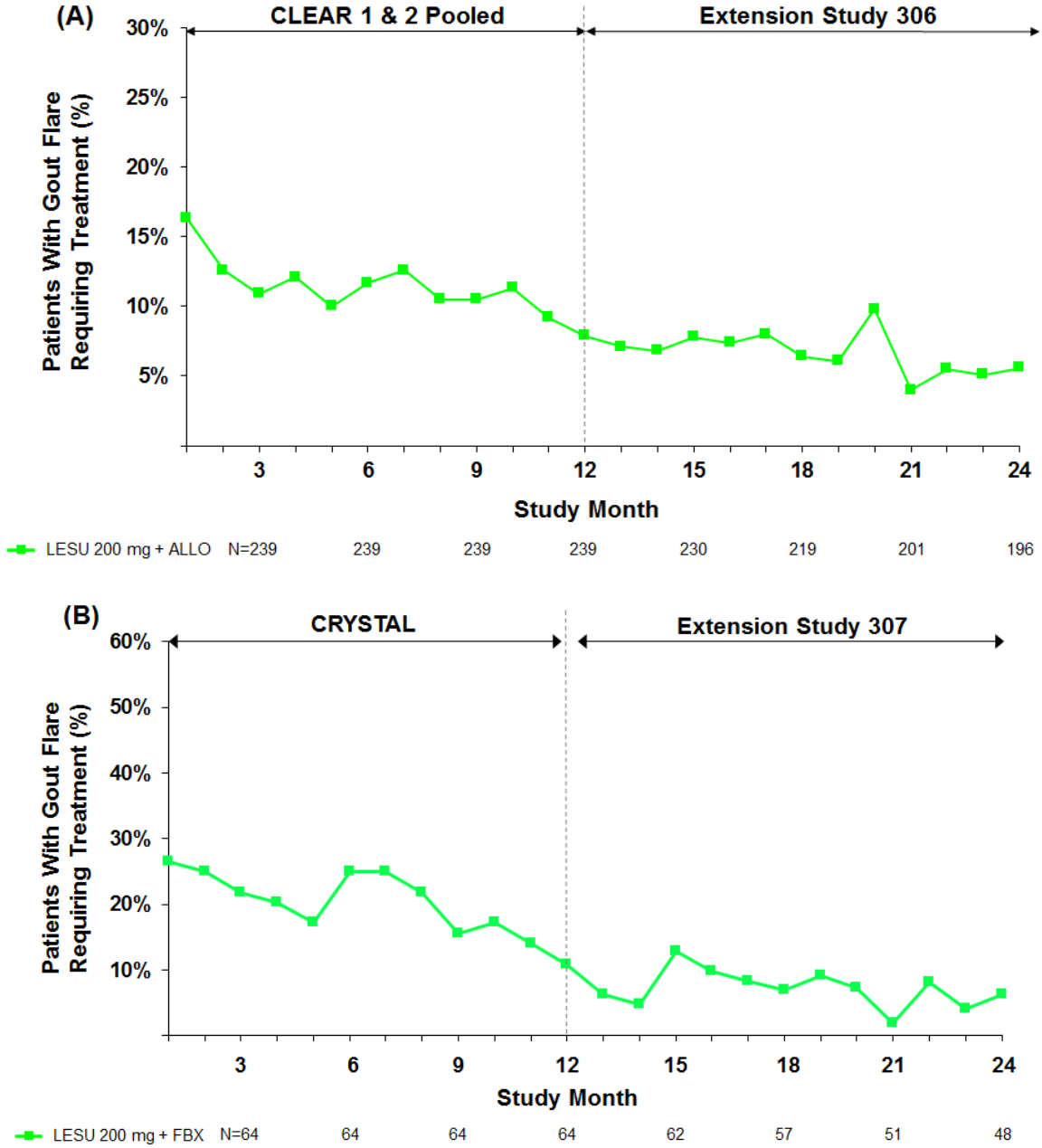
Patients who completed the 12-month pivotal studies were eligible to enroll in extension studies where all patients received either lesinurad 200 or 400 mg plus allopurinol (Study 306) or febuxostat (Study 307). See Figure 22 and Figure 23. These extension studies remain ongoing.

From CLEAR 1 and 2 (combination with allopurinol), 240 patients in the lesinurad 200 mg and 232 in the lesinurad 400 mg groups enrolled into Extension Study 306. For the allopurinol alone group, 244 patients enrolled in Study 306; 122 were randomized to lesinurad 200 mg and 122 to lesinurad 400 mg plus allopurinol. From CRYSTAL (combination with febuxostat), 64 patients in the lesinurad 200 mg and 65 in the lesinurad 400 mg groups enrolled into Extension Study 307. For the febuxostat alone group, 67 patients enrolled in Study 307; 33 were randomized to lesinurad 200 mg and 34 to lesinurad 400 mg plus febuxostat.

The clinical response of target tophi and gout flares requiring treatment were evaluated over time. Of the patients who received lesinurad 200 mg plus XOI for up to 24 months (12 months in the pivotal study and up to 12 months in the extension study), the proportion who experienced a gout flare requiring treatment continued to decline over time. Figure 46 demonstrates the decline in the proportion of patients with a gout flare requiring treatment by monthly interval through the 24 month period, and Figure 47 demonstrates the proportion of patients who experienced a CR of ≥ 1 target tophus that continued to increase over time. Similar results were

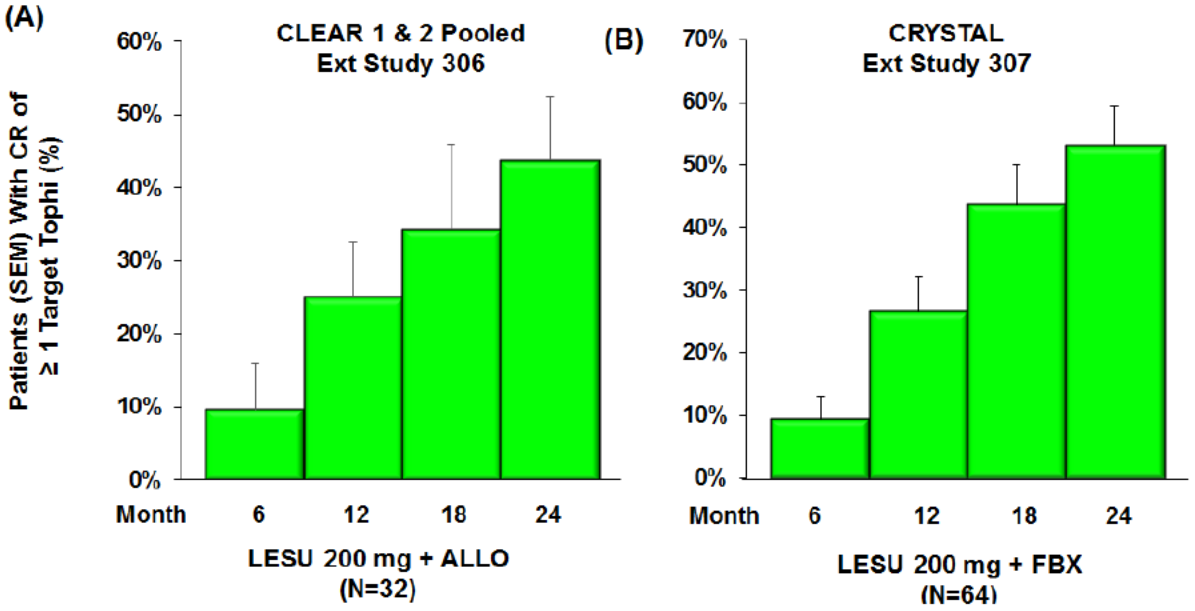
observed in patients receiving lesinurad 400 mg + XOI. Given the inherent limitations of optional uncontrolled extension studies, these results do not claim superiority of lesinurad in these endpoints. Rather, these results provide additional supportive evidence that continued treatment and maintenance of target sUA levels over time results in fewer flares and more tophus reduction.

Figure 46: Proportion of Patients With Gout Flares Requiring Treatment Over Time in Patients Who Received Lesinurad 200 mg Plus an XOI in the Pivotal Studies and Continued Into the Uncontrolled Extension Studies (ITT Population, Observed Cases)



Abbreviations: ALLO, allopurinol; FBX, febuxostat; LESU, lesinurad; PBO, placebo.

Figure 47: Proportion of Patients With Complete Resolution of ≥ 1 Target Tophus Over Time in Patients Who Received Lesinurad 200 mg Plus an XOI in the Pivotal Studies and Continued Into the Uncontrolled Extension Studies (ITT Population, LOCF)



Abbreviations: ALLO, allopurinol; FBX, febuxostat; ITT, intent-to-treat; LESU, lesinurad; LOCF, last observation carried forward; SEM, standard error of the mean; XOI, xanthine oxidase inhibitor.
Note: The bar graphs present LOCF data. The number of patients with target tophi who reached Month 24 was 27 in Study 306 and 47 in Study 307.

9. CLINICAL SAFETY ACROSS LESINURAD DEVELOPMENT

Summary of Safety

Lesinurad is recommended for use with an XOI. Lesinurad 200 mg qd in combination with an XOI was generally well tolerated. The safety profile was similar to that of the XOI alone (ie, placebo in combination with an XOI), with the exception of an increased incidence of transient or reversible sCr elevations. Lesinurad 400 mg qd plus XOI was associated with a higher incidence of sCr elevations and renal-related SAEs. Rates were highest when lesinurad was used as monotherapy (see Section 6.3.1).

The global lesinurad clinical development program included 3010 patients, 2587 of whom received at least 1 dose of lesinurad. The primary safety evaluation is based on pooled data from the 12 month pivotal combination therapy Studies 301 (CLEAR 1), 302 (CLEAR 2), and 304 (CRYSTAL) (N = 1537 [1021 exposed to lesinurad]). The ongoing Phase 3 extension studies (Studies 306 [CLEAR 1 and CLEAR 2 extension] and 307 [CRYSTAL extension]) provide supportive data regarding longer exposure to lesinurad in combination with an XOI; in these studies, 910 patients have received lesinurad, including 311 patients who received an XOI alone in a pivotal study.

The key safety findings from the combination therapy studies are summarized below.

Key General Safety Findings

- Whether combined with allopurinol or febuxostat, the safety findings were similar.
- The incidences of AEs, AEs leading to discontinuation of randomized study medication, and SAEs were generally comparable for lesinurad 200 mg plus XOI and an XOI alone, and higher for lesinurad 400 mg plus XOI.
- There were no notable treatment differences, nor any notable mean changes from Baseline within any treatment group, for any clinical laboratory parameter, with the exception of transient sCr elevations.
- There was no evidence of hepatic toxicity with the use of lesinurad alone or in combination with an XOI.
- There were no new safety findings with extended treatment (for up to more than 2.5 years[1]).
- The deaths in the clinical program (n = 20) were primarily CV-related, consistent with the patient population demographic and the patients' medical histories. There were 7 deaths in the pivotal studies: 2 during the 1-month screening period (when patients were on an XOI alone), 0 on an XOI alone during the randomized treatment period, 2 on lesinurad 200 mg plus XOI, and 3 on lesinurad 400 mg plus XOI.

Key Cardiovascular Safety Findings

- Nonclinical studies did not identify signals to suggest adverse CV consequences of lesinurad treatment.
- In clinical studies, overall rates of adjudicated MACE and of Investigator-reported CV-related AEs, AEs leading to discontinuation, and SAEs were low across all treatment groups. The incidence of MACE was comparable for lesinurad 200 mg plus XOI (4 patients) and an XOI alone (3 patients), and numerically higher for lesinurad 400 mg plus XOI (8 patients). 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.

Key Renal Safety Findings

- Lesinurad was associated with an increased proportion of patients with sCr elevations $\geq$ 1.5 x Baseline (2.3% on XOI alone, 5.7% on lesinurad 200 mg plus XOI, and 14.3% on lesinurad 400 mg plus XOI). In the lesinurad 200 mg plus XOI group, most (27/30 or 90.0%) of the elevations resolved and 66.7% resolved with continued lesinurad treatment. The proportion of the overall safety population with a sCr elevation in a pivotal study that did not resolve, including extension study follow-up, was 3/516 for an XOI alone, 1/511 for lesinurad 200 mg plus XOI, and 10/510 for lesinurad 400 mg plus XOI.
- There was no clinically meaningful change in the mean eCrCl from Baseline to Last Value for lesinurad 200 mg plus XOI, and the mean change in eCrCl from Baseline to the off-treatment follow-up visit was comparable for lesinurad 200 mg plus XOI and an XOI alone.

- The incidences of renal-related AEs, AEs leading to discontinuation, and SAEs were comparable for lesinurad 200 mg plus XOI and an XOI alone, and higher for lesinurad 400 mg.
- Lesinurad did not increase the incidence of kidney stone AEs.

Drug-Drug Interaction

- Lesinurad is a mild to moderate CYP3A inducer and the possibility of reduced efficacy of concomitant drugs that are CYP3A substrates (eg, simvastatin, amlodipine) should be considered and their efficacy (eg, cholesterol and BP levels) should be monitored.

Subgroup Analyses

- There was no apparent interaction between factors of sex, age (< 65 and ≥ 65 years), ethnicity (Hispanic or Latino/Not Hispanic or Latino), race (White/Non-White), renal function (eCrCl ≥90, < 90, < 60, and < 45 mL/min), or BMI (< 30 kg/m^2 and ≥ 30 kg/m^2) and the relative occurrence across treatment groups of AEs or other safety parameters evaluated.
- The safety profile of lesinurad in patients with higher allopurinol exposures (ie, patients taking > 300 mg/day) was comparable to that in the overall safety population.

9.1. Safety Analysis Populations

The primary analysis of safety is focused on the pooled, randomized, placebo-controlled, pivotal 12-month Phase 3 studies of lesinurad in combination with an XOI (CLEAR 1, CLEAR 2, and CRYSTAL); ie, the "pivotal" studies. All patients who received at least 1 dose of randomized study medication were included in the safety analyses.

Data from the combination therapy extension studies (Studies 306 and 307) of the pivotal studies are considered supportive. Patients who received lesinurad 200 mg or 400 mg plus XOI in the core studies continued on the same treatment for at least the initial 12 months of the extension studies, and patients who received an XOI alone in the core studies were re-randomized to lesinurad 200 mg or 400 mg plus XOI in the extension studies. Most of the data presentations use a data cutoff date of 04 November 2014, the cutoff date for the 4-Month Safety Update Report. For deaths and MACE, updated analyses including additional data from the ongoing extension studies have been provided to the FDA in response to an information request; these updated analyses are included in this document.

Data from the Phase 2b (Study 203) of lesinurad and allopurinol combination therapy study were not pooled with data from Phase 3 studies due to differences in study design.

There was 1 Phase 2b monotherapy study (Study 202) and 2 Phase 3 monotherapy studies (6-month core Study 303 [lesinurad 400 mg vs. placebo] and extension Study 305 [lesinurad 400 mg]), conducted in patients with an intolerance or contraindication to XOIs. Study 305 was terminated early based on the renal safety profile for lesinurad 400 mg as monotherapy observed in Study 303. A monotherapy indication for lesinurad is not being sought at this time. The safety profile of lesinurad as monotherapy is summarized in Section 6.3.1 and Appendix 10.

9.2. Extent of Exposure

The extent of exposure to lesinurad in the clinical development program exceeded International Conference on Harmonisation (ICH) guidelines for minimal patient exposure to investigational product in a clinical program for the treatment of a chronic disease. A total of 2587 patients have been exposed to lesinurad in completed or ongoing clinical studies (Table 19), including 687 healthy volunteers, 100 patients in special populations, and 1842 patients with gout (1800 in the Phase 2/3 program).

Table 19: Total Number of Unique Patients Exposed to Lesinurad by Dose

	LESU < 200 mg	LESU 200 mg	LESU 400 mg	LESU > 400 mg	LESU Any Dose
Total number of patients	**74**	**1086**	**1614**	**296**	**2587**
Phase 2 studies	**0**	**283**	**219**	**133**	**283**
Phase 3 studies	**0**	**666**	**851**	**0**	**1517**
Combination with an XOI	0	666	666	0	1332
12- month pivotal study	0	511	510	0	1021
Extension study (additional unique patients [placebo plus XOI crossovers] only)	0	155	156	0	311

Abbreviations: LESU, lesinurad; XOI, xanthine oxidase inhibitor (allopurinol or febuxostat).
Note: Patients may be presented in > 1 treatment column if they received > 1 different dose. In the column "Total Patients," each patient is counted only once. In the Extension Studies/Periods (202 Extension Period, 203 Extension Period, and Studies 305, 306, and 307) only unique patients (ie, those randomized to placebo plus XOI during the double-blind treatment who then switched to lesinurad plus XOI during Extension) are counted toward the total.

There were nearly 2000 person-years of exposure to lesinurad in patients with gout as of 04 November 2014, the cutoff date for the 4-Month Safety Update Report (Table 20).

Table 20: Lesinurad Exposure in Patients With Gout: Phase 2 and 3 Studies

	Patients	Person-Years of Exposure
Total	**1800**	**1939.2**
Duration of exposure (weeks)		
≥ 24	1328	
≥ 48	974	
≥ 96	297	
≥ 144	54	
Exposure by dose		
200 mg	949	855.8
400 mg	1070	953.2
600 mg	133	129.7

Note: Included are Study 201, Study 202, Study 203, CLEAR 1, CLEAR 2, Study 303, CRYSTAL, Study 305, Study 306, and Study 307.

9.3. Gout Flares

In the Phase 3 studies, gout flares were considered an efficacy endpoint and were not captured on the AE case report form. Gout flares that met the definition of an SAE were to be reported as SAEs.

Gout flares are known to paradoxically increase with the initiation of effective ULT (Section 6.2.1.2). In all 3 pivotal combination therapy studies, the unadjusted rates of gout flares requiring treatment were higher from Baseline to the end of Month 1 for lesinurad 400 mg plus XOI than for lesinurad 200 mg plus XOI and an XOI alone (Section 8.4.2). After Month 2, the rates were generally similar across the 3 treatment groups.

9.4. Adverse Events

Overall, the proposed dose of lesinurad 200 mg in combination with an XOI was generally well tolerated with an AE profile similar to that of an XOI alone, while the incidence of AEs was higher for lesinurad 400 mg plus XOI (Table 21). Most AEs were mild or moderate in severity and resolved while continuing lesinurad therapy. When evaluated by XOI (allopurinol vs. febuxostat), the number and type of AEs were similar to those observed in the pooled XOI population.

Table 21: Incidence of Adverse Events by Category (CLEAR 1, CLEAR 2, and CRYSTAL Pooled)

Adverse Event Category	PBO + XOI (N=516) n (%)	LESU 200 mg + XOI (N=511) n (%)	LESU 400 mg + XOI (N=510) n (%)
Any AE	363 (70.3)	386 (75.5)	407 (79.8)
AE with RCTC toxicity Grade 3 or 4	48 (9.3)	52 (10.2)	67 (13.1)
AE leading to discontinuation of randomized study medication (lesinurad or placebo)	28 (5.4)	32 (6.3)	48 (9.4)
Serious AE	29 (5.6)	24 (4.7)	44 (8.6)
Fatal AE	0	2 (0.4)	3 (0.6)

Abbreviations: AE, adverse event; LESU, lesinurad; PBO, placebo; RCTC, Rheumatology Common Toxicity Criteria; XOI, xanthine oxidase inhibitor (allopurinol/febuxostat).
Note: For each category, patients are included only once, even if they experienced multiple events in that category.

9.4.1. Common Adverse Events

The most commonly reported PTs (incidence ≥ 5% on any treatment) were *upper respiratory tract infection*, *nasopharyngitis*, *arthralgia*, and *back pain*. Incidences of the most common AEs were generally comparable for an XOI alone and lesinurad 200 mg plus XOI. When evaluated separately by XOI (allopurinol or febuxostat), the findings were similar.

AEs with an incidence on lesinurad 200 mg or lesinurad 400 mg plus XOI that was ≥ 2% and ≥ 1 percentage point higher than on an XOI alone are shown in Table 22.

Table 22: Adverse Events With an Incidence on Lesinurad 200 mg or 400 mg Plus XOI ≥ 2% and ≥ 1 Percentage Point Higher Than on an XOI Alone (CLEAR 1, CLEAR 2, and CRYSTAL Pooled)

Preferred Term	PBO + XOI (N=516) n (%)	LESU 200 mg + XOI (N=511) n (%)	LESU 400 mg + XOI (N=510) n (%)
Upper respiratory tract infection	44 (8.5)	46 (9.0)	57 (11.2)
Hypertension	25 (4.8)	31 (6.1)	35 (6.9)
Headache	21 (4.1)	27 (5.3)	30 (5.9)
Influenza	14 (2.7)	26 (5.1)	16 (3.1)
Blood creatine phosphokinase increased	25 (4.8)	23 (4.5)	30 (5.9)
Blood creatinine increased	12 (2.3)	22 (4.3)	40 (7.8)
Sinusitis	13 (2.5)	17 (3.3)	20 (3.9)
Gastrooesophageal reflux disease	4 (0.8)	14 (2.7)	7 (1.4)
Myalgia	11 (2.1)	13 (2.5)	17 (3.3)
Dizziness	7 (1.4)	8 (1.6)	14 (2.7)

Abbreviations: LESU, lesinurad; PBO, placebo; XOI, xanthine oxidase inhibitor (allopurinol/febuxostat).
Note: Adverse events are coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 14.0. For each preferred term (PT), patients are included only once, even if they experienced multiple events in that PT. Events are sorted by decreasing incidence on LESU 200 mg + XOI.

9.4.2. Adverse Events Leading to Discontinuation of Randomized Study Medication

In the pivotal combination therapy studies, the incidence of AEs leading to discontinuation was comparable for an XOI alone and lesinurad 200 mg plus XOI, and higher for lesinurad 400 mg plus XOI (5.4%, 6.3%, and 9.4%, respectively) (Table 21). Events classified in the Investigations, Musculoskeletal and Connective Tissue Disorders and the Renal and Urinary Disorders SOCs were the most commonly reported AEs leading to discontinuation. *Blood creatinine increased* was the most common individual PT leading to discontinuation, with an incidence of 0.8% on an XOI alone, 0.8% on lesinurad 200 mg plus XOI, and 1.8% on lesinurad 400 mg plus XOI. When evaluated by type of XOI, the number and type of AEs leading to discontinuation were similar to those observed in the pooled XOI population.

9.4.3. Serious Adverse Events

Overall, the incidence of SAEs was comparable for an XOI alone (5.6%) and lesinurad 200 mg plus XOI (4.7%), and higher for lesinurad 400 mg plus XOI (8.6%), in the pivotal combination therapy studies (Table 21). Events classified in the Cardiac Disorders, Infections and Infestations, and Renal and Urinary Disorders SOCs were the most frequently reported SAEs

(Appendix 2). Similar results were observed when SAE incidences were adjusted for exposure or when evaluated by type of XOI treatment (allopurinol or febuxostat). For further discussion of SAEs in the Cardiac Disorders and Renal and Urinary Disorders SOCs, see Section 9.8.1.3 and Section 9.8.2.1, respectively.

The most common individual SAE PTs were *pneumonia* (0.4%, 0.4%, and 0.2% incidence for an XOI alone, lesinurad 200 mg plus XOI, and lesinurad 400 mg plus XOI, respectively) and *coronary artery disease* (0%, 0.6%, and 0.4%, respectively) (Appendix 2).

9.4.4. Deaths in the Lesinurad Clinical Development Program

There have been a total of 20 deaths across the entire lesinurad clinical development program, including 7 deaths in the pivotal studies: 2 after screening and before the first dose of randomized study medication (while patients were on an XOI alone), 2 following treatment with lesinurad 200 mg plus XOI, and 3 following treatment with lesinurad 400 mg plus XOI (see Table 23 and Appendix 3). Of the 17 deaths that occurred after the first dose of lesinurad, 14 were adjudicated by the CEAC as death due to CV causes and are discussed in Section 9.8.1.4 and Section 9.8.1.5. The 3 remaining deaths were due to suicide (2 patients: 1 patient following participation in a Phase 1 study [lesinurad 400 mg] and 1 patient in Study 306 [lesinurad 400 mg with allopurinol]) and gastric cancer (1 patient in Study 306 [lesinurad 400 mg with allopurinol]).

Table 23: Summary of All Deaths in the Lesinurad Clinical Development Program

	Total	Lesinurad 200 mg	Lesinurad 400 mg
Lesinurad development program	20		
Phase 1	1	0	1[a]
Phase 2			
Screening	1	NA	NA
Controlled	0	0	0
Extension	1[b]	0	0
Phase 3 monotherapy			
Controlled	1	NA	1
Uncontrolled extension	1	NA	1
Phase 3 combination therapy			
Screening	2	NA	NA
Controlled	5	2	3
Uncontrolled extension	8	4	4

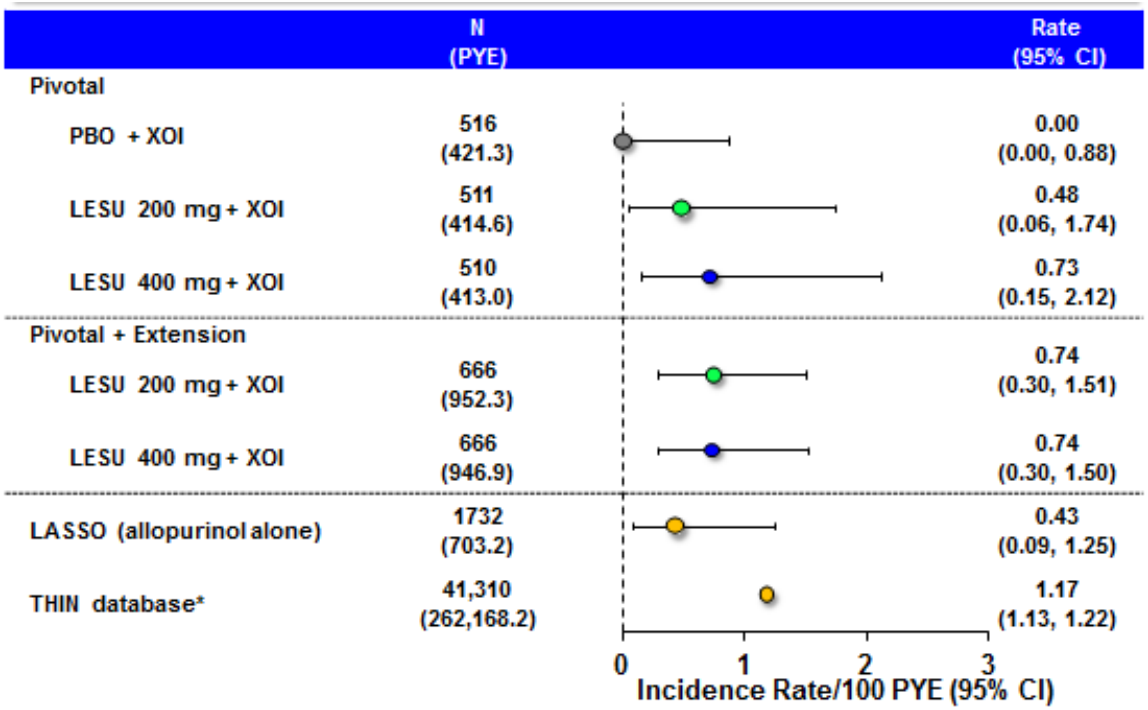
Abbreviations: LESU, lesinurad; NA, not applicable.
[a] Single dose.
[b] Lesinurad 600 mg plus allopurinol in a controlled extension period.
Note: Based on new analyses including additional data from the ongoing extension studies, Study 306 and Study 307, with data cutoff dates of 15 May 2015 and 12 March 2015, respectively.

The exposure-adjusted incidence of death for the population of lesinurad-treated patients was similar to that observed among 1732 allopurinol-treated patients who were followed for 6 months in the LASSO study (also known as ALLO-401), which had similar entry criteria; and also to that observed in an analysis of gout patients in The Health Improvement Network (THIN)

database in the United Kingdom (UK), which was performed by an independent epidemiologist (Hyon K. Choi MD, Dr.PH; data on file) (Figure 48). In this latter analysis, patients (N = 41,310) were matched for age, gender, and other key entry criteria that were used in the pivotal Phase 3 combination therapy studies. Patients with a malignancy within the previous 5 years and patients with a history of angina pectoris, MI, stroke, DVT or pulmonary embolism, or anticoagulant use within the previous year were excluded from the analysis. The mean (SD) age of these patients was 52.7 (11.6) years and most of the patients were men (95.4%).

Overall, the rate of fatal SAEs with lesinurad was low and consistent with this population demographic and the individual patients' medical histories.

Figure 48: Death Rates Among Gout Patients (Lesinurad Phase 3 Combination Therapy Studies, LASSO Study, and THIN Database)



Abbreviations: CI, confidence interval; LASSO, Study ALLO-401 (allopurinol alone); LESU, lesinurad; PYE, person years of exposure; PYE, person-years of exposure; THIN, The Health Improvement Network; XOI, xanthine oxidase inhibitor.
*Patients in the United Kingdom with gout ≥ 18 and ≤ 85 years of age, male or female. Matched to lesinurad trial program age and sex distribution. Excluding patients with a malignancy within the past 5 years; patients with a history of angina, MI, stroke, deep vein thrombosis, or pulmonary embolism; and patients with anticoagulant use within the past year. Data on file.
Note: Lesinurad Pivotal + Extension results based on new analyses including additional data from the ongoing extension studies, Study 306 and Study 307, with data cutoff dates of 15 May 2015 and 12 March 2015, respectively.

9.5. Laboratory Findings

The following are the main findings for hematology and nonrenal chemistry:

- No clinically relevant mean changes from Baseline or individual patient shifts from Baseline were observed for lesinurad 200 mg plus XOI with respect to any hematology or nonrenal clinical chemistry parameters. Renal laboratory parameters are discussed in Section 9.8.2.2.

- Based upon the known hepatic toxicities associated with XOIs, extensive evaluations throughout the lesinurad clinical development program were performed and showed no evidence of hepatic toxicity associated with the use of lesinurad alone or in combination with an XOI. The incidence of elevations in AST and/or ALT > 3 x ULN was low (≤ 2%) and comparable across treatment groups. No patient met the Hy's law definition of hepatic toxicity at any timepoint in the Phase 3 or Phase 2b studies; thus, no signal of a potential for drug-induced liver injury (DILI) was observed.

Urinalysis results are described in Section 9.8.2.2.3.

9.6. Safety in Special Groups and Situations

In the pivotal combination therapy studies, the treatment relationships with respect to the number or type of AEs, renal-related AEs, and sCr elevations were generally consistent across subgroups, including subgroups defined by:

- Demographic and disease characteristics: sex, age (< 65, ≥ 65, and ≥75 years), ethnicity (Hispanic or Latino/Not Hispanic or Latino), race (White/Non-White), BMI (< 30 kg/m^2 and ≥ 30 kg/m^2), presence of tophi at Baseline (Yes/No), comorbidity of diabetes (Yes/No), comorbidity of hypertension (Yes/No).
- Baseline renal function (eCrCl category [≥ 90, < 90, and < 60 mL/min]).
- Geographic region (North America, South Africa, Europe, and Australia/New Zealand).
- Allopurinol dose > 300 mg daily.

Within the subgroup of patients with moderate renal impairment (eCrCl < 60 mL/min), there are a limited number of patients in the subset with eCrCl < 45 mL/min; in this subset, there were no clear or consistent treatment-dependent relationships with respect to the number or type of AEs, renal-related AEs, or sCr elevations.

9.6.1. Overall Incidence of Adverse Events by Subgroup

Across subgroups defined by age, sex, ethnicity, race, BMI, tophus status at Screening, and renal function at Baseline, the overall incidence of AEs was generally consistent with that observed in the overall safety population (Table 24).

Table 24: Incidence of Any Adverse Event by Subgroup (CLEAR 1, CLEAR 2, and CRYSTAL Pooled)

Total Patients with ≥ 1 TEAE	PBO + XOI		LESU 200 mg + XOI		LESU 400 mg + XOI	
	n/N	(%)	n/N	(%)	n/N	(%)
All Patients	**363/516**	**(70.3)**	**386/511**	**(75.5)**	**407/510**	**(79.8)**
Sex						
Male	346/492	(70.3)	367/489	(75.1)	385/482	(79.9)
Female	17/24	(70.8)	19/22	(86.4)	22/28	(78.6)
Age						
<65 years	308/443	(69.5)	338/454	(74.4)	349/433	(80.6)
≥65 years	55/73	(75.3)	48/57	(84.2)	58/77	(75.3)
≥75 years	8/9	(88.9)	11/12	(91.7)	6/8	(75.0)
Ethnicity						
Hispanic or Latino	23/35	(65.7)	36/44	(81.8)	29/43	(67.4)
Not Hispanic or Latino	340/481	(70.7)	350/467	(74.9)	378/467	(80.9)
Race						
White	282/402	(70.1)	301/398	(75.6)	321/401	(80.0)
Non-White	81/114	(71.1)	85/113	(75.2)	85/108	(78.7)
BMI						
< 30 kg/m²	111/165	(67.3)	91/132	(68.9)	128/163	(78.5)
≥ 30 kg/m²	251/348	(72.1)	295/379	(77.8)	279/346	(80.6)
≥ 40 kg/m²	70/89	(78.7)	76/94	(80.9)	73/84	(86.9)
Presence of Tophi						
Yes	140/183	(76.5)	140/184	(76.1)	152/185	(82.2)
No	223/333	(67.0)	246/327	(75.2)	255/325	(78.5)
eCrCl						
≥ 90 mL/min	124/180	(68.9)	153/200	(76.5)	162/203	(79.8)
< 90 mL/min	239/334	(71.6)	232/310	(74.8)	244/305	(80.0)
< 60 mL/min	79/105	(75.2)	89/102	(87.3)	75/92	(81.5)
< 45 mL/min	24/34	(70.6)	24/26	(92.3)	22/29	(75.9)
Diabetes						
Yes	54/80	(67.5)	83/96	(86.5)	58/78	(74.4)
No	309/436	(70.9)	303/415	(73.0)	349/432	(80.8)
Hypertension						
Yes	225/340	(66.2)	257/330	(77.9)	263/325	(80.9)
No	138/176	(78.4)	129/181	(71.3)	144/185	(77.8)

Abbreviations: BMI, body mass index; eCrCl, estimated creatinine clearance; LESU, lesinurad; PBO, placebo; TEAE, treatment-emergent adverse event; XOI, xanthine oxidase inhibitor (allopurinol/febuxostat).

9.6.2. Safety in Patients With Renal Impairment

Lesinurad has an altered PK/PD relationship in patients with renal impairment. Despite higher lesinurad plasma concentrations with renal impairment (see Section 5), there is a decrease in the amount urinary uric acid excreted compared to that observed in patients with normal renal function. This decrease in PD activity is a result of a combination of decreased delivery of lesinurad to the site of action (the proximal renal tubule) and an intrinsic decrease in urinary uric acid excretion associated with decreasing renal function. The clinical relevance of the increased exposure and altered PK/PD relationship of lesinurad with decreasing renal function was assessed in the Phase 3 studies of lesinurad. The studies confirm that lesinurad 200 mg in combination with an XOI demonstrates a consistent safety profile irrespective of renal function.

There was no consistent effect of Baseline renal function on the treatment difference in the incidence of AEs in the pivotal combination therapy studies (Table 25). In the pivotal

combination therapy studies, the subgroup of patients with moderate renal impairment at Baseline (eCrCl < 60 mL/min) was more likely to experience an AE compared to the overall safety population. This was consistently observed across treatment groups. In this subgroup, as in the overall safety population, the incidence of AEs was comparable for an XOI alone and lesinurad 200 mg plus XOI. When evaluated separately by XOI (allopurinol or febuxostat), the findings were similar to those observed in the pooled XOI population.

Within the subgroup of patients with moderate renal impairment (eCrCl < 60 mL/min), there are a limited number of patients in the subset with eCrCl < 45 mL/min; in this subset, there were no clear or consistent treatment-dependent relationships.

For an assessment of renal safety parameters in patients with renal impairment at Baseline, see Section 9.8.2.4.

Table 25: Incidence of Adverse Events by Category and Baseline Renal Function Subgroup (CLEAR 1, CLEAR 2, and CRYSTAL Pooled)

AE category/ Baseline eCrCl	PBO +XOI n/N (%)	LESU 200 mg +XOI n/N (%)	LESU 400 mg +XOI n/N (%)
Any AE			
All patients	363/516 (70.3)	386/511 (75.5)	407/510 (79.8)
≥ 90 mL/min	124/180 (68.9)	153/200 (76.5)	162/203 (79.8)
60 to < 90 mL/min	160/229 (69.9)	143/208 (68.8)	169/213 (79.3)
< 60 mL/min	79/105 (75.2)	89/102 (87.3)	75/92 (81.5)
45 to < 60 mL/min	55/71 (77.5)	65/76 (85.5)	53/63 (84.1)
< 45 mL/min	24/34 (70.6)	24/26 (92.3)	22/29 (75.9)
Any AE leading to discontinuation of PBO or LESU			
All patients	28/516 (5.4)	32/511 (6.3)	48/510 (9.4)
≥ 90 mL/min	5/180 (2.8)	6/200 (3.0)	13/203 (6.4)
60 to < 90 mL/min	12/229 (5.2)	14/208 (6.7)	26/213 (12.2)
< 60 mL/min	11/105 (10.5)	12/102 (11.8)	9/92 (9.8)
45 to < 60 mL/min	5/71 (7.0)	6/76 (7.9)	7/63 (11.1)
< 45 mL/min	6/34 (17.6)	6/26 (23.1)	2/29 (6.9)
Any SAE			
All patients	29/516 (5.6)	24/511 (4.7)	44/510 (8.6)
≥ 90 mL/min	4/180 (2.2)	6/200 (3.0)	8/203 (3.9)
≥ 60 to < 90 mL/min	11/229 (4.8)	7/208 (3.4)	16/213 (7.5)
< 60 mL/min	14/105 (13.3)	11/102 (10.8)	20/92 (21.7)
45 to < 60 mL/min	10/71 (14.1)	8/76 (10.5)	14/63 (22.2)
< 45 mL/min	4/34 (11.8)	3/26 (11.5)	6/29 (20.7)

Abbreviations: AE, adverse event; LESU, lesinurad; PBO, placebo; SAE, serious adverse event; XOI, xanthine oxidase inhibitor (allopurinol/febuxostat).

9.7. Lesinurad Safety Profile During Extended Treatment

Additional exposure to lesinurad in combination with an XOI did not result in an increase in exposure-adjusted incidence rates of AEs, AEs leading to discontinuation of lesinurad, or SAEs (Table 26). In order to focus on the effects of exposure beyond 12 months, the integrated pivotal + extension data shown are from only those patients who received lesinurad plus XOI in a

pivotal study (4-Month Safety Update cutoff). When evaluated separately by XOI (allopurinol or febuxostat), the findings were similar to those observed in the pooled XOI population. Similar results were observed for CV and renal safety parameters (see Section 9.8.1.5 and Section 9.8.2.6, respectively).

Table 26: Exposure-Adjusted Incidence Rates for Adverse Events by Category, Excluding Patients Who Received an XOI Alone in the Pivotal Study

	LESU 200 mg + XOI		LESU 400 mg + XOI	
Event Category	Pivotal[a] (N=511) (PYE=396.3) n (Rate)	Pivotal + Extension[b] (N=511) (PYE=641.8) n (Rate)	Pivotal[a] (N=510) (PYE=390.5) n (Rate)	Pivotal + Extension[b] (N=510) (PYE=635.7) n (Rate)
Any AE	386 (97.4)	412 (64.2)	407 (104.2)	429 (67.5)
AE leading to discontinuation of LESU	32 (8.1)	52 (8.1)	48 (12.3)	64 (10.1)
Serious AE	24 (6.1)	43 (6.7)	44 (11.3)	56 (8.8)

Abbreviations: AE, adverse event; LESU, lesinurad; PYE, person-years of exposure; XOI, xanthine oxidase inhibitor (allopurinol/febuxostat).
[a] CLEAR 1, CLEAR 2, and CRYSTAL pooled.
[b] CLEAR 1, CLEAR 2, CRYSTAL, and Studies 306 and 307 combined. Based on a data cutoff date of 04 November 2014, the cutoff date for the 4-Month Safety Update Report. In order to focus on the effects of exposure beyond 12 months, the pivotal + extension data shown here include data for only those patients who received lesinurad plus XOI in a pivotal study; ie, not those who received XOI alone in a pivotal study.
Note: For each category, patients are included only once, even if they experienced multiple events in that category. Exposure-adjusted incidence rates are expressed as patients with events per 100 person-years.

The most common AEs and their exposure-adjusted incidence rates were also comparable in the combined pivotal + extension studies vs. the pivotal studies. *Blood creatinine increased* was the most common AE leading to discontinuation; the incidence rate was 1.6 per 100 person-years of exposure (PYE) for lesinurad 200 mg plus XOI and 2.2/100 PYE for lesinurad 400 mg plus XOI in the pivotal + extension dataset. Overall, increased exposure to lesinurad plus XOI did not change the SAE profile from that presented in the pivotal studies.

Finally, there was no evidence of an increase in the exposure-adjusted incidence rate of clinical laboratory abnormalities with increased duration of exposure to lesinurad plus XOI.

9.8. Safety Topics of Special Interest

9.8.1. Cardiovascular Safety

Gout is associated with a broad range of comorbidities, particularly CV disorders. Epidemiologic studies have reported an increased risk of CV death, MI, and stroke with higher sUA levels and in patients with gout.[39, 52-55, 64-66] Therefore, CV safety was a topic of special interest in the lesinurad development program.

Because lesinurad is a selective inhibitor of uric acid reabsorption in the kidney, it would not be expected to have adverse CV consequences based on its mechanism of action. A review of nonclinical data and data obtained in Phase 1 and Phase 2 studies with lesinurad did not identify signals to suggest adverse CV consequences of lesinurad treatment (see Section 4.2). In the in vitro and in vivo CV safety pharmacology studies, lesinurad demonstrated no impact on platelet aggregation or other effects suggesting potential adverse CV consequences.

A placebo-controlled thorough QT study with positive moxifloxacin control (Study 117) showed no QT interval effects following lesinurad doses up to 8 times the 200 mg dose and 10 times the exposure observed at 200 mg. The effect of lesinurad on cardiac repolarization using an optimized QT interval correction for individual heart rates (QTcI) and the PK-PD relationships showed no effect for either the 400 mg dose or the 1600 mg supratherapeutic dose. There was no effect on heart rate, or on AV conduction or cardiac depolarization as measured by PR interval and QRS complex duration. In addition, there were no clinically relevant morphological ECG changes.

The Phase 2 and 3 studies included standard safety assessments of reported AEs, BP, blood lipids (total cholesterol and triglycerides), and ECG data. In addition, all deaths and potential CV events (serious and nonserious) identified by Investigators or the CEAC chair from Phase 3 studies, and all deaths and serious CV events from Phase 2 studies, were adjudicated by the CEAC, which comprised 3 independent external CV experts blinded to randomized study treatment. A list of events that were to be adjudicated by the CEAC, as well as events to be sent to the CEAC Chair to determine whether additional cases should be adjudicated, is provided in Appendix 4. If considered to be CV in cause, the CEAC classified events into MACE (ie, CV death, nonfatal MI, or nonfatal stroke) and non-MACE CV categories using standard criteria and prespecified definitions to eliminate inherent variation.

9.8.1.1. Baseline Cardiovascular Risk in the Study Population

Patients were excluded from the Phase 3 studies if they were currently receiving anticoagulants (other than low-dose aspirin) or had any of the following conditions within the last 12 months prior to Screening: hospitalization for acute coronary syndromes (MI, unstable angina), NYHA class III or IV heart failure, stroke or transient ischemic attack, or venous thromboembolic disorders (pulmonary embolism or deep venous thrombosis). Patients were also excluded if they had uncontrolled hypertension (systolic BP > 160 mmHg or diastolic BP > 95 mm Hg on repeat measurements at 2 separate visits during the Screening Period).

In the pivotal combination therapy studies, 78.0% of the patients had ≥ 1 CV comorbidity or CV risk factor at Baseline and 21.4% had ≥ 3 (Table 27). The most common were hypertension (64.7%), hyperlipidemia (45.0%), and diabetes mellitus (16.5%). The 3 treatment groups were generally well balanced with respect to CV comorbidities and risk factors.

Table 27: Baseline Comorbidities and Cardiovascular Risk Factors in the Pivotal Studies (CLEAR 1, CLEAR 2, and CRYSTAL Pooled)

Comorbidity	PBO + XOI (N=516) n (%)	LESU 200 mg + XOI (N=511) n (%)	LESU 400 mg + XOI (N=510) n (%)
≥ 1 CV comorbidity or CV disease history (combined)	401 (77.5)	401 (78.5)	399 (78.2)
≥ 2 CV comorbidity or CV disease history (combined)	234 (45.3)	243 (47.6)	240 (47.1)
≥ 3 CV comorbidity or CV disease history (combined)	103 (20.0)	118 (23.1)	108 (21.2)
Hypertension	340 (65.9)	330 (64.6)	325 (63.7)
Hyperlipidemia[a]	221 (42.8)	230 (45.0)	241 (47.3)
Diabetes mellitus	80 (15.5)	96 (18.8)	78 (15.3)
eCrCl < 60 mL/min	89 (17.2)	90 (17.6)	86 (16.9)
Myocardial infarction	19 (3.7)	26 (5.1)	22 (4.3)
Heart failure	12 (2.3)	20 (3.9)	21 (4.1)
Angina pectoris	17 (3.3)	13 (2.5)	19 (3.7)
Peripheral vascular disease	7 (1.4)	9 (1.8)	4 (0.8)
Transient ischemic attack	6 (1.2)	7 (1.4)	5 (1.0)
Stroke	7 (1.4)	4 (0.8)	6 (1.2)

Abbreviations: eCrCl, estimated creatinine clearance; CV, cardiovascular; LESU, lesinurad; PBO, placebo; XOI, xanthine oxidase inhibitor (allopurinol/febuxostat).
[a] Terms for hypercholesterolemia and hypertriglyceridemia are collapsed as hyperlipidemia and counted as 1 comorbidity.
Note: The table includes events recorded on the Comorbidity Summary Case Report Form (CRF) using a list of predefined comorbidities (excluding kidney stones) and eCrCl values < 60 mg/dL on Day -7. All other CV history was recorded on the Medical History CRF.

9.8.1.2. Blood Pressure, Blood Lipids, and ECG Findings

Review of systolic BP and diastolic BP data from the pivotal combination therapy studies revealed no treatment differences. Mean and median values for systolic and diastolic BP were similar to Baseline values and comparable across treatment groups. The incidence of clinically relevant abnormalities in systolic and diastolic BP was low and comparable across treatment groups.

A review of data from the Phase 2/3 studies showed no evidence that lesinurad at doses ranging from 200 or 600 mg for up to 12 months altered total cholesterol or serum triglyceride levels. For patients participating in the pivotal and extension Phase 3 combination therapy studies, there were no notable changes in total cholesterol (non-fasting) or triglycerides (non-fasting) with longer exposure to lesinurad.

In the pivotal combination therapy studies, the incidence of ECG-associated AEs was low and comparable across treatment groups: 0.4% for an XOI alone, 0.2% for lesinurad 200 mg plus XOI, and 0.6% for lesinurad 400 mg plus XOI. No notable changes from Baseline or differences among treatment groups in QTcF were observed in any study. Electrocardiograms were not recorded in the extension studies.

9.8.1.3. Cardiovascular Adverse Events

The incidence of Investigator-reported CV AEs was generally comparable across treatment groups in the pivotal combination therapy studies (Table 28). The incidence of CV AEs leading to discontinuation was comparable across the treatment groups. Although a higher incidence of SAEs in the Cardiac Disorders SOC was observed for lesinurad 200 mg and lesinurad 400 mg plus XOI compared with an XOI alone, no individual SAE by PT occurred at an incidence ≥ 1%.

In addition to CV SAEs prespecified for adjudication by the CEAC, all SAEs were sent to the CEAC for possible adjudication (see Appendix 4). When the incidence of CV AEs was compared by type of XOI therapy (allopurinol or febuxostat), the results were similar.

Table 28: Incidence of Investigator-Reported Cardiovascular Adverse Events by Category (CLEAR 1, CLEAR 2, and CRYSTAL Pooled)

Category	PBO + XOI (N=516) n (%)	LESU 200 mg + XOI (N=511) n (%)	LESU 400 mg + XOI (N=510) n (%)
Any AE in the Cardiac Disorders SOC	20 (3.9)	17 (3.3)	22 (4.3)
Any AE in the Cardiac Disorders SOC leading to discontinuation of PBO or LESU	2 (0.4)	3 (0.6)	3 (0.6)
Any SAE in the Cardiac Disorders SOC	2 (0.4)	10 (2.0)	14 (2.7)
Any AE in the Vascular Disorders SOC	33 (6.4)	41 (8.0)	45 (8.8)
Any AE in the Vascular Disorders SOC leading to discontinuation of PBO or LESU	0	0	1 (0.2)
Any SAE in the Vascular Disorders SOC	0	0	1 (0.2)

Abbreviations: AE, adverse event; LESU, lesinurad; PBO, placebo; SAE, serious adverse event; SOC, System Organ Class; XOI, xanthine oxidase inhibitor (allopurinol/febuxostat).
Note: Adverse events are coded using Medical Dictionary for Regulatory Activities (MedDRA) version 14.0. For each preferred term (PT), patients are included only once, even if they experienced multiple events with that PT.

Hypertension

There was a numeric increase in the incidence of the AE PT *hypertension* in patients receiving lesinurad: in the pivotal combination therapy studies, the incidence was 4.8%, 6.1%, and 6.9% for an XOI alone, lesinurad 200 mg plus XOI, and lesinurad 400 mg plus XOI, respectively. However, evaluation of the Hypertension SMQ, which includes terms such as *blood pressure increased* and *blood pressure systolic increased*, revealed a comparable incidence of AEs across treatment groups: 6.2%, 6.5%, and 7.8%, respectively (Table 29). Furthermore, vital signs data revealed no differences in BP by treatment group (Section 9.8.1.2).

In addition, when the incidence of AEs in the Hypertension SMQ was evaluated in patients without the comorbidity of hypertension at Baseline, the proportion of patients who experienced events of hypertension was highest for an XOI alone (Table 29). Among patients with the comorbidity of hypertension, lesinurad plus XOI-treated patients tended to have a higher incidence of Hypertension SMQ AEs during the study than XOI alone-treated patients.

Table 29: Incidence of Hypertension SMQ Adverse Events by Comorbidity of Hypertension (CLEAR 1, CLEAR 2, and CRYSTAL Pooled)

	PBO + XOI n/N (%)	LESU 200 mg + XOI n/N (%)	LESU 400 mg + XOI n/N (%)
All Patients	**32/516 (6.2)**	**33/511 (6.5)**	**40/510 (7.8)**
Comorbidity of Hypertension: No	14/176 (8.0)	6/181 (3.3)	9/185 (4.9)
Comorbidity Hypertension: Yes	18/340 (5.3)	27/330 (8.2)	31/325 (9.5)

Abbreviations: LESU, lesinurad; PBO, placebo; SMQ, Standardised MedDRA Query; XOI, xanthine oxidase inhibitor (allopurinol/febuxostat).
Note: Adverse events are coded using Medical Dictionary for Regulatory Activities (MedDRA) version 14.0. For each SMQ, patients are included only once, even if they experienced multiple events in that SMQ.

There was no evidence of increased risk of hypertension with increased exposure to lesinurad in the extension studies (Section 9.8.1.5).

9.8.1.4. Adjudicated Cardiovascular Events

The number of events adjudicated as due to CV causes was low and comparable across treatment groups in the pivotal combination therapy studies (Table 30).

The small number of MACE observed in the pooled analysis of data from the pivotal studies places limitations on assessment of treatment associated differences in MACE risk. There were a total of 17 MACE events that occurred in 15 patients: 3 on an XOI alone (1 of whom had 2 MACE), 4 on lesinurad 200 mg, and 8 on lesinurad 400 mg plus XOI (1 of whom had 2 MACE) (Table 30). The higher incidence on lesinurad 400 mg plus XOI was primarily due to a higher incidence of nonfatal MI. Exposure-adjusted MACE rates were low across treatment groups with considerable overlap of the 95% CI (Figure 50)

Results were similar in the allopurinol combination studies and in the febuxostat combination study.

Additional MACE in the lesinurad clinical development program included 9 patients in extension Studies 306 or 307 (see Section 9.8.1.5), 1 patient on lesinurad 600 mg with allopurinol in Study 203, 1 patient on lesinurad 400 mg alone in Study 303, and 2 patients on lesinurad 400 mg alone in Study 305.

Key information regarding all adjudicated MACE in the lesinurad Phase 3 combination therapy studies (as of 20 January 2015) is provided in Appendix 5 and narratives are provided in Appendix 6.

Table 30: Incidence of Adjudicated Cardiovascular Adverse Events by Category (CLEAR 1, CLEAR 2, and CRYSTAL Pooled)

Category	PBO + XOI (N=516) n [no. events]	LESU 200 mg + XOI (N=511) n [no. events]	LESU 400 mg + XOI (N=510) n [no. events]
Patients with events sent for adjudication	**28 [38]**	**32 [44]**	**28 [47]**
Number of patients with adjudicated events classified as CV event	**15 [17]**	**18 [21]**	**15 [24]**
MACE	**3 [4]**	**4 [4]**	**8 [9]**
CV death	0	2	2
Nonfatal myocardial infarction	1 [1]	2 [2]	7 [7]
Nonfatal stroke	3 [3]	0	0
Non-MACE CV events			
Other CV event[a]	2 [2]	8 [9]	6 [10]
Congestive heart failure with hospitalization	1 [1]	1 [1]	3 [4]
Venous and peripheral arterial thromboembolic event	1 [1]	2 [2]	0
Arrhythmia not associated with ischemia	7 [7]	4 [5]	1 [1]
Transient ischemic attack	1 [2]	0	0
Unstable angina with urgent coronary revascularization	0	0	0
Urgent cerebral revascularization (non-elective)	0	0	0

Abbreviations: CV, cardiovascular; LESU, lesinurad; MACE, major adverse cardiovascular event; PBO, placebo; XOI, xanthine oxidase inhibitor (allopurinol/febuxostat).
[a] For example, hospitalization for angina without revascularization, elective coronary revascularization, or syncope.
Note: Patients with multiple adjudicated events can be counted in ≥ 1 category.

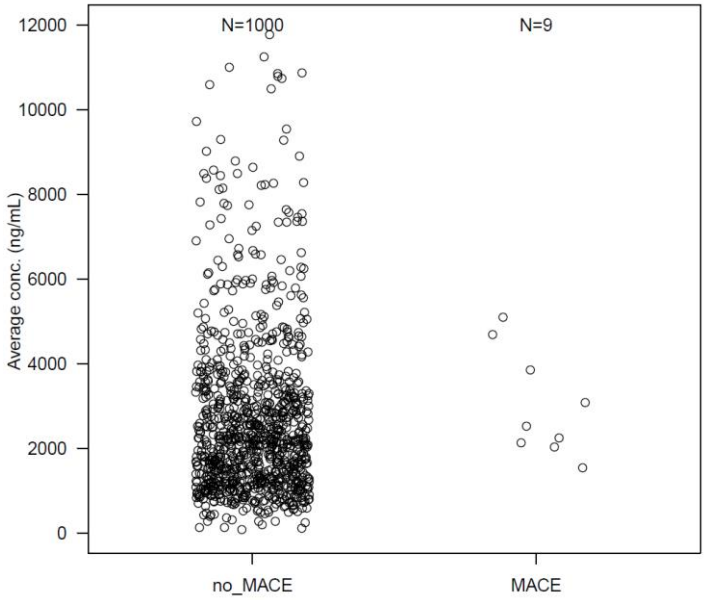
The CEAC had insufficient information to adjudicate the events in a total of 15 patients (4 on an XOI alone, 10 on lesinurad 200 mg plus XOI, and 1 on lesinurad 400 mg plus XOI). All of these events were nonserious (and therefore had minimal source documentation), were mild or moderate in severity, and had resolved by the end of the pivotal study. The verbatim terms for the events with insufficient information were as follows:

- XOI alone: exacerbation of chest pain (type unknown), faint, intermittent angina pectoris, atrial fibrillation.
- Lesinurad 200 mg plus XOI: non-cardiac chest pain and chest pain (type unknown) in 1 patient, dyspnea, fainted, positive treadmill test, unk[nown] chest pain, worsening cardiac chest pain, worsening of hypertension, patient reported loss of consciousness, vasovagal syncope, dyspnea on exertion.
- Lesinurad 400 mg plus XOI: angina pectoris.

Lesinurad Exposure and MACE

There was no apparent difference in lesinurad plasma concentrations between patients who experienced a MACE compared with those who did not experience a MACE, based on data from a Phase 3 population PK analysis that was performed using a population PK sampling method (Figure 49). The PK samples were obtained in a total of 1009 lesinurad-treated patients (1000 patients who did not experience a MACE, 9 patients who experienced a MACE).

Figure 49: Lesinurad Average Concentration Based on Population Pharmacokinetics in Patients Who Did or Did Not Experience MACE



Abbreviations: MACE, major adverse cardiovascular event.

9.8.1.5. CV Safety During Extended Treatment

There was no increase in the exposure-adjusted incidence rates of Investigator-reported CV AEs, AEs leading to discontinuation of lesinurad, or SAEs associated with increased duration of exposure to lesinurad in combination with an XOI (Table 31 [4-Month Safety Update cutoff]). In order to focus on the effects of exposure beyond 12 months, the integrated pivotal + extension data shown are from only those patients who received lesinurad plus XOI in a pivotal study.

Table 31: Exposure-Adjusted Incidence Rates for Cardiovascular Adverse Events by Category, Excluding Patients Who Received XOI Alone in the Pivotal Study

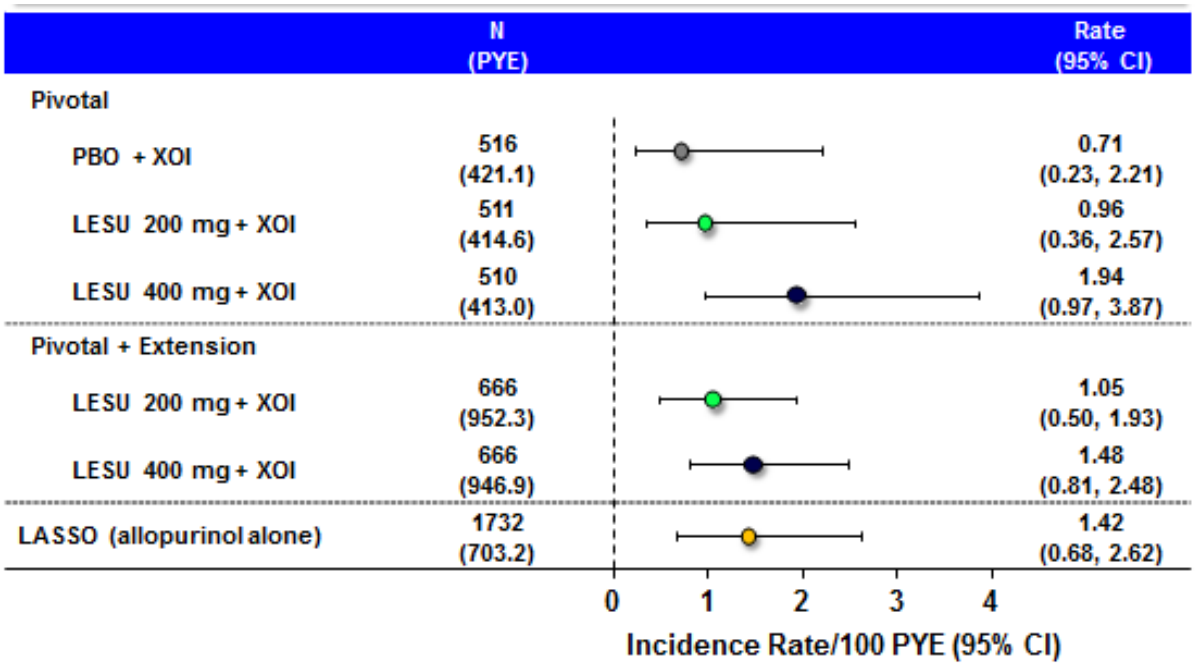
	LESU 200 mg + XOI		LESU 400 mg + XOI	
Event Category	Pivotal[a] (N=511) (PYE=396.3) n (Rate)	Pivotal + Extension[b] (N=511) (PYE=641.8) n (Rate)	Pivotal[a] (N=510) (PYE=390.5) n (Rate)	Pivotal + Extension[b] (N=510) (PYE=635.7) n (Rate)
Cardiac Disorders AEs	17 (4.3)	21 (3.3)	22 (5.6)	25 (3.9)
Cardiac Disorders AEs leading to discontinuation of LESU	3 (0.8)	4 (0.6)	3 (0.8)	3 (0.5)
Cardiac Disorders SAEs	10 (2.5)	14 (2.2)	14 (3.6)	14 (2.2)
Vascular Disorders AEs	41 (10.3)	51 (7.9)	45 (11.5)	62 (9.8)
Vascular Disorders AEs leading to discontinuation of LESU	0	1 (0.2)	1 (0.3)	2 (0.3)
Vascular Disorders SAEs	0	1 (0.2)	1 (0.3)	3 (0.5)

Abbreviations: AE, adverse event; LESU, lesinurad; PYE, person-years of exposure; SAE, serious adverse event; XOI, xanthine oxidase inhibitor (allopurinol/febuxostat).
[a] CLEAR 1, CLEAR 2, and CRYSTAL pooled.
[b] CLEAR 1, CLEAR 2, CRYSTAL, and Studies 306 and 307 combined. Based on a data cutoff date of 04 November 2014, the cutoff date for the 4-Month Safety Update Report. In order to focus on the effects of exposure beyond 12 months, the pivotal + extension data shown here include data for only those patients who received lesinurad plus XOI in a pivotal study; ie, not those who received XOI alone in a pivotal study.
Note: For each category, patients are included only once, even if they experienced multiple events in that category. Exposure-adjusted incidence rates are expressed as patients with events per 100 person-years of exposure.

Similarly, exposure-adjusted MACE rates did not increase with increased duration of exposure to lesinurad (Figure 50 [data cutoff dates of 15 May 2015 and 12 March 2015 for ongoing extension Studies 306 and 307, respectively]). The rate for the population of lesinurad plus XOI-treated patients was similar to the observed MACE rate among 1732 patients treated with allopurinol alone and followed for 6 months in the LASSO study (Figure 50). This observational study had similar entry criteria and utilized prospective adjudication of MACE by the same CEAC that was used in the lesinurad Phase 3 program.

Thus, the rate of MACE observed in the Phase 3 combination therapy studies was in the range expected for a population with gout and multiple CV comorbidities.

Figure 50: Exposure-Adjusted MACE Rates (Lesinurad Phase 3 Combination Therapy Studies and LASSO Study)



Abbreviations: CI, confidence interval; LASSO, Study ALLO-401; LESU, lesinurad; MACE, major adverse cardiovascular event; PBO, placebo; PYE, person-years of exposure; XOI, xanthine oxidase inhibitor.
Note: Pivotal + Extension results based on new analyses including additional data from the ongoing extension studies, Study 306 and Study 307, with data cutoff dates of 15 May 2015 and 12 March 2015, respectively.

For patients who received lesinurad in combination with an XOI in a pivotal study, a comparison of the exposure-adjusted incidence rates for the AE of hypertension on lesinurad 200 mg plus XOI and lesinurad 400 mg plus XOI in the combined pivotal + extension studies (6.5 and 7.7 events/100 PYE, respectively) with those in the pivotal studies (7.8 and 8.9 events/100 PYE, respectively) demonstrated no increased risk of hypertension with increased exposure of lesinurad. In addition, changes in systolic and diastolic BP in the pivotal + extension dataset were small and comparable to those in the pivotal studies. Overall, there were no notable increases in systolic or diastolic BP with longer exposure to lesinurad.

9.8.2. Renal Safety

Nonclinical toxicology studies were performed in mice, rats, and monkeys (see Section 4.2). Renal toxicity was observed in mice and rats but only at exposures that are substantially higher than human exposure following a dose of lesinurad 200 mg (> 97-fold and > 43-fold higher exposures, respectively). Renal toxicity was not observed in monkeys. When lesinurad was combined with either allopurinol or febuxostat, no additive, synergistic, or overlapping renal toxicity was observed. The ability to correlate observations of renal toxicity with lesinurad in the nonclinical species to humans is limited by the presence of uricase in mice, rats, and monkeys; nevertheless, the data would support the conclusion that lesinurad is not a renal toxicant at exposures in nonclinical species that are relevant to human exposures. Regarding off-target pharmacology, it was concluded that neither lesinurad nor its major metabolite (M4) has NSAID-like properties, and neither inhibits creatinine transport.

Patients with gout are at increased risk for kidney stones and many patients with gout have significant comorbid illnesses, including CKD, diabetes, hypertension, and heart failure[4, 67-76] that put them at risk for adverse effects related to the kidney. Lesinurad inhibits uric acid reabsorption, resulting in increased urinary uric acid excretion. Based on the physicochemical properties of uric acid, the physiology of renal uric acid excretion, and the PD properties of lesinurad, patients with gout who are being treated with lesinurad may be at increased risk for adverse effects related to the kidney. Therefore, a comprehensive assessment of renal safety, particularly with regard to changes in renal function and the risk for nephrolithiasis was conducted.

AE data (including the incidence of prespecified renal-related and kidney stone AEs) and clinical laboratory data (including sCr, eCrCl, and Pr-Cr ratio) were analyzed. An independent, external Renal Events Adjudication Committee (REAC), blinded to randomized study medication, reviewed predefined renal events (AEs in the Acute Renal Failure SMQ that were serious or led to discontinuation of randomized study medication, as well as all increases in sCr $\geq$ 1.5 x the Baseline Visit value). The REAC provided an assessment of the relative potential contribution to the event of the patient's medical history, concomitant medications, and AEs/procedures.

9.8.2.1. Renal Adverse Events

9.8.2.1.1. Renal-Related Adverse Events

To enable a broad and comprehensive analysis of potential AEs that could reflect a decline in renal function, a custom list of renal-related PTs was selected from the MedDRA Renal and Urinary Disorders SOC, the Investigations SOC, and the Acute Renal Failure MedDRA SMQ (see Appendix 7).

In the pivotal combination therapy studies, the proportion of patients with renal-related AEs was comparable for an XOI alone and lesinurad 200 mg plus XOI, and higher for lesinurad 400 mg plus XOI (4.5% and 5.7% vs. 11.8%) (Table 32). The most common renal-related PT was *blood creatinine increased*, for which the incidence was dose-ordered.

The incidence of renal-related AEs leading to discontinuation of randomized study medication (placebo or lesinurad) was comparable for an XOI alone and lesinurad 200 mg plus XOI, and slightly higher for lesinurad 400 mg plus XOI. Across treatment groups, *blood creatinine increased* was the most common AE leading to discontinuation.

The incidence of renal-related SAEs was low and comparable across treatment groups. There were no renal-related SAEs on lesinurad 200 mg plus XOI. A listing of patients in the Phase 3 combination therapy studies with renal-related SAEs is provided in Appendix 8 and narratives are provided in Appendix 9.

Table 32: Incidence of Renal-Related Adverse Events (CLEAR 1, CLEAR 2, and CRYSTAL Pooled)

Category/ Preferred Term	PBO + XOI (N=516) n (%)	LESU 200 mg + XOI (N=511) n (%)	LESU 400 mg + XOI (N=510) n (%)
Any renal-related AE	**23 (4.5)**	**29 (5.7)**	**60 (11.8)**
Blood creatinine increased	12 (2.3)	22 (4.3)	40 (7.8)
Blood urea increased	3 (0.6)	7 (1.4)	7 (1.4)
Renal failure	6 (1.2)	4 (0.8)	6 (1.2)
Renal impairment	0	1 (0.2)	5 (1.0)
Renal failure acute	2 (0.4)	0	4 (0.8)
Renal failure chronic	3 (0.6)	1 (0.2)	2 (0.4)
Urine output decreased	0	0	3 (0.6)
Acute prerenal failure	0	0	2 (0.4)
Creatinine renal clearance decreased	0	0	2 (0.4)
Any renal-related AE leading to discontinuation of PBO or LESU	**5 (1.0)**	**6 (1.2)**	**17 (3.3)**
Blood creatinine increased	4 (0.8)	4 (0.8)	9 (1.8)
Renal failure	0	2 (0.4)	3 (0.6)
Renal failure acute	0	0	2 (0.4)
Renal impairment	0	0	2 (0.4)
Acute prerenal failure	0	0	1 (0.2)
Renal failure chronic	1 (0.2)	0	1 (0.2)
Any renal-related SAE	**2 (0.4)**	**0**	**5 (1.0)**
Renal failure acute	2 (0.4)	0	2 (0.4)
Renal failure	0	0	1 (0.2)
Renal failure chronic	0	0	1 (0.2)
Renal impairment	0	0	1 (0.2)

Abbreviations: AE, adverse event; LESU, lesinurad; PBO, placebo; SAE, serious adverse event; XOI, xanthine oxidase inhibitor (allopurinol/febuxostat).
Note: Adverse events are coded using Medical Dictionary for Regulatory Activities (MedDRA) version 14.0. For each preferred term (PT), patients are included only once, even if they experienced multiple events with that PT.

No renal-related AEs were reported as having an outcome of death. There were 2 patients in the lesinurad clinical development program who had ongoing renal-related AEs at the time of their deaths: Patient 302-15003-210 (lesinurad 400 mg with allopurinol) and Patient 304-05056-401 (lesinurad 400 mg with febuxostat) (narratives are provided in Appendix 5).

9.8.2.1.2. Kidney Stone Adverse Events

Because patients with gout are known to be at increased risk of developing kidney stones, and kidney stones have been reported with drugs that increase urinary uric acid excretion (Section 9.8.2), a custom list of kidney stone PTs was selected from the Renal and Urinary Disorders SOC, the Investigations SOC, and the Surgical and Medical Procedures SOC (see Appendix 7).

There was no evidence that lesinurad increased the incidence of kidney stones. In the pivotal combination therapy studies, the proportion of patients with kidney stone AEs, AEs leading to discontinuation of randomized study medication (placebo or lesinurad), and SAEs was low and

comparable across treatment groups (Table 33). Across treatment groups, 10.0% to 15.9% of the patients had a reported history of kidney stones at Baseline. Among the patients with kidney stone AEs, 8 of 9 on an XOI alone, 2 of 3 on lesinurad 200 mg plus XOI, and 3 of 13 on lesinurad 400 mg plus XOI had a reported history of kidney stones.

Table 33: Incidence of Kidney Stone Adverse Events (CLEAR 1, CLEAR 2, and CRYSTAL Pooled)

Category/ Preferred Term	PBO + XOI (N=516) n (%)	LESU 200 mg + XOI (N=511) n (%)	LESU 400 mg + XOI (N=510) n (%)
Any kidney stone AE	**9 (1.7)**	**3 (0.6)**	**13 (2.5)**
Nephrolithiasis	9 (1.7)	3 (0.6)	11 (2.2)
Calculus ureteric	0	0	3 (0.6)
Calculus urinary	0	0	1 (0.2)
Stag horn calculus	0	0	1 (0.2)
Any kidney stone AE leading to discontinuation of PBO or LESU	**3 (0.6)**	**1 (0.2)**	**1 (0.2)**
Nephrolithiasis	3 (0.6)	1 (0.2)	1 (0.2)
Any kidney stone SAE	**1 (0.2)**	**0**	**3 (0.6)**
Nephrolithiasis	1 (0.2)	0	2 (0.4)
Calculus ureteric	0	0	1 (0.2)
Stag horn calculus	0	0	1 (0.2)

Abbreviations: AE, adverse event; LESU, lesinurad; PBO, placebo; SAE, serious adverse event; XOI, xanthine oxidase inhibitor (allopurinol/febuxostat).
Note: Adverse events are coded using Medical Dictionary for Regulatory Activities (MedDRA) version 14.0. For each preferred term (PT), patients are included only once, even if they experienced multiple events with that PT.

9.8.2.2. Renal Laboratory Parameters

9.8.2.2.1. Serum Creatinine

Serum creatinine is a widely accepted marker of renal function because its clearance is predominantly through glomerular filtration. In addition to filtration, creatinine clearance also occurs via tubular secretion. Several organic cation transporters are responsible for creatinine secretion and inhibition of these transporters can result in increases in sCr. In vitro assays have demonstrated that neither lesinurad nor its major metabolite inhibits transporters of creatinine secretion, including hOCT2, MATE-1, and MATE-2K. In addition, no inhibition of cyclooxygenase or prostaglandin receptors involved with glomerular filtration was observed.

Elevations in sCr meeting predefined criteria are described in this section. The following definitions of sCr Baseline, sCr elevation categories, and resolution of a sCr elevation were proposed by the REAC and subsequently agreed to by the FDA:

- sCr Baseline: the highest sCr value recorded ≤ 14 days prior to the first dose of randomized study medication.
- sCr elevation categories: ≥ 1.5, ≥ 2.0, and ≥ 3.0 x Baseline. Note that elevation categories are nested; ie, the ≥ 1.5 x Baseline category includes all elevations ≥ 1.5, ≥ 2.0, or ≥ 3.0 x Baseline, and the ≥ 2.0 x Baseline category includes all elevations ≥ 2.0 or ≥ 3.0 x Baseline.

- sCr elevation resolution: a value ≤ 1.2 x Baseline following an elevation.

For mean changes in renal function, see the eCrCl results in Section 9.8.2.2.2. Because eCrCl was calculated using baseline age, baseline ideal body weight, and sCr value at the time of the study visit, any change in eCrCl was due to a change in sCr.

Incidence of Serum Creatinine Elevations

As shown in Table 34, the incidences of sCr elevations ≥ 1.5, ≥ 2.0, and ≥ 3.0 x Baseline were lesinurad dose-ordered in the pivotal combination therapy studies. The incidence of elevations was similar whether patients were receiving allopurinol or febuxostat.

Table 34: Incidence of Serum Creatinine (mg/dL) Elevations by Category (CLEAR 1, CLEAR 2, and CRYSTAL Pooled)

Elevation Category[a]	PBO + XOI (N=516) n (%)	LESU 200 mg + XOI (N=511) n (%)	LESU 400 mg + XOI (N=510) n (%)
sCr ≥ 1.5 x Baseline	12 (2.3)	29 (5.7)	73 (14.3)
sCr ≥ 2.0 x Baseline	0	9 (1.8)	34 (6.7)
sCr ≥ 3.0 x Baseline	0	4 (0.8)	12 (2.4)

Abbreviations: LESU, lesinurad; PBO, placebo; sCr, serum creatinine; XOI, xanthine oxidase inhibitor (allopurinol/febuxostat).
[a] Elevation categories are nested; ie, the ≥ 1.5 x Baseline category includes all elevations ≥ 1.5, ≥ 2.0, or ≥ 3.0 x Baseline, and the ≥ 2.0 x Baseline category includes all elevations ≥ 2.0 or ≥ 3.0 x Baseline.
Note: Baseline is defined as the highest sCr value recorded ≤ 14 days prior to the first dose of randomized study medication.

The number of patients with 2 separate sCr elevation events ≥ 1.5 x Baseline was 0 for an XOI alone, 1 for lesinurad 200 mg plus XOI, and 18 for lesinurad 400 mg plus XOI; 3 patients on lesinurad 400 mg plus XOI had 3 separate elevation events. Six patients, all on lesinurad 400 mg plus XOI (5/401 on allopurinol and 1/109 on febuxostat), had 2 separate sCr elevation events ≥ 2.0 x Baseline; no patient had > 2 events.

The rate of new sCr elevations ≥ 1.5 x Baseline and ≥ 2.0 x Baseline remained stable over time (Figure 51). Throughout the studies, lesinurad 400 mg plus XOI had a higher cumulative incidence of sCr elevations ≥ 1.5 and ≥ 2.0 x Baseline than lesinurad 200 mg plus XOI, which had a higher cumulative incidence than an XOI alone.

There was no apparent association between sCr elevations and AEs of *hyperkalemia* or shifts in potassium. A total of 7 patients in the pivotal combination therapy studies (1 on an XOI alone, 2 on lesinurad 200 mg plus XOI, and 4 on lesinurad 400 mg plus XOI) experienced both a sCr elevation and an AE of hyperkalemia and/or a potassium value > ULN. There was a temporal association between the sCr elevations and increased potassium levels in 3 patients (1 on allopurinol alone and 2 on lesinurad 400 mg with allopurinol). The elevated potassium value was 5.9 mmol/L in the patient on an XOI alone and 5.6 mmol/L in both lesinurad 400 mg plus XOI-treated patients (normal range 3.4 to 5.4 mmol/L).

Duration of Serum Creatinine Elevations

In the pivotal combination therapy studies, the majority of the sCr elevations had resolved by the end of the study, most without interruption of lesinurad. For lesinurad 200 mg, 27 (90.0%) of the 30 elevations ≥ 1.5 x Baseline resolved by the end of the study, 20/30 (66.7%) without

interruption of lesinurad. The number of patients with unresolved sCr elevations at the end of the pivotal studies was small: n = 3 for an XOI alone (none entered the extension study), n = 3 for lesinurad 200 mg plus XOI (2 entered the extension study, where 2/2 elevations resolved), and n = 17 for lesinurad 400 mg plus XOI (10 entered the extension study, where 7/10 elevations resolved).

The reported resolution date of each sCr elevation is in part a reflection of the study visit schedule (Months 1, 2, 3, 4, 5, 6, 8, 10, and 12). Of the elevations that resolved, most had resolved by the next study assessment following the initial report of the elevation: 55.6% for an XOI alone, 74.1% for lesinurad 200 mg plus XOI, and 56.3% for lesinurad 400 mg plus XOI. The median duration of sCr elevations ≥ 1.5 x Baseline was 58 days for an XOI alone, 29 days for lesinurad 200 mg plus XOI, and 29 days for lesinurad 400 mg plus XOI.

The median duration of sCr elevations ≥ 2.0 x Baseline was 13 days for lesinurad 200 mg plus XOI, and 29 days for lesinurad 400 mg plus XOI. For lesinurad 200 mg plus XOI, 8/9 (88.9%) resolved during the study (all within 3 months), 6/9 (66.7%) without interruption of lesinurad. The proportion of the overall treatment group with an elevation ≥ 2.0 x Baseline ongoing at the end of a pivotal study was 1/511 for lesinurad 200 mg plus XOI and 8/510 for lesinurad 400 mg plus XOI.

9.8.2.2.2. Creatinine Clearance

Overall, lesinurad had no persistent effect on renal function, as measured by mean change from Baseline to Last Value in eCrCl in each treatment group.

In the Phase 2b and Phase 3 studies, eCrCl was calculated by the Cockcroft-Gault formula using ideal body weight. In the pivotal combination therapy studies, there was a mean decrease in eCrCl values from Baseline to Month 1 for lesinurad 200 mg and 400 mg plus XOI that remained stable to Month 12 (Month 12 values provided in Table 35), as compared with a mean increase for an XOI alone. However, there was no mean change in eCrCl from Baseline to Last Value (on or off lesinurad) for lesinurad 200 mg plus XOI. While there was a small mean decrease for lesinurad 400 mg plus XOI, there was evidence of reversibility after patients discontinued lesinurad therapy: across treatment groups, there were similar mean increases in eCrCl from Baseline to the off-treatment Follow-Up Visit scheduled for the subset of patients who did not enter an extension study.

Table 35: Change from Baseline in Estimated Creatinine Clearance (eCrCl, mL/min) (CLEAR 1, CLEAR 2, and CRYSTAL Pooled)

	PBO + XOI (N=516)	LESU 200 mg + XOI (N=511)	LESU 400 mg + XOI (N=510)
Baseline Visit			
N	514	510	508
Mean (SD)	81.06 (24.52)	83.61 (25.91)	84.05 (25.20)
Median	80.22	82.74	83.22
Min, Max	21.03, 152.50	29.59, 168.78	31.81, 173.39
Change from Baseline to Month 12			
N	394	392	384
Mean (SD)	3.97 (9.48)	-0.38 (10.55)	-2.85 (11.48)
Median	3.54	-0.21	-2.36
Min, Max	-35.51, 35.74	-37.80, 38.75	-74.29, 33.23
Change from Baseline to Last Value[a]			
N	500	497	501
Mean (SD)	3.72 (9.63)	0.55 (10.36)	-1.99 (13.78)
Median	3.19	0.50	-1.62
Min, Max	-34.52, 42.72	-37.80, 38.75	-84.46, 147.61
Change from Baseline to the Post-Treatment Follow-up Visit[b]			
N	96	98	103
Mean (SD)	3.03 (11.91)	2.54 (9.93)	2.41 (17.42)
Median	1.80	3.63	1.25
Min, Max	-28.67, 42.72	-31.73, 26.71	-24.43, 147.61

Abbreviations: LESU, lesinurad; Max, maximum; Min, minimum; PBO, placebo; SD, standard deviation; XOI, xanthine oxidase inhibitor (allopurinol/febuxostat).
[a] Last value on or off randomized study treatment.
[b] Patients who did not enter an extension study were required to attend a Follow-Up Visit within approximately 14 days of completing the Double-Blind Treatment Period.

9.8.2.2.3. Urinalysis Results

No notable findings for urinalysis parameters were observed. In the pivotal combination therapy studies, consistent with lesinurad's mechanism of action, there were mean increases from Baseline in urine uric acid for lesinurad 200 mg and 400 mg plus XOI, and the proportion of patients with uric acid crystals detected in urine was higher than for an XOI alone. Because urine samples were stored at room temperature for up to 72 hours before testing, the presence of uric acid crystals in samples from lesinurad-treated patients could reflect the expected increased uric acid excretion followed by ex vivo precipitation.

Based on Pr-Cr ratio data, there was no suggestion of long-term proteinuria, either in patients with sCr elevations or in patients without sCr elevations. A Pr-Cr ratio of ≥ 0.2 mg/mg is potentially clinically meaningful if proteinuria persists.[77] There were no notable treatment differences for changes in Pr-Cr ratio in the pivotal lesinurad studies. The mean change from Baseline to Last Value was 0.03 mg/mg for each of the treatment groups and the mean change from Baseline to maximum post-Baseline value range from 0.16 to 0.17 mg/mg across treatment

groups. Thus, treatment with lesinurad does not appear to be associated with the development of proteinuria.

In addition, patients with sCr elevations were not more likely than patients without elevations to experience proteinuria. The results for mean change from Baseline in Pr-Cr ratio across subgroups defined by presence/absence of sCr elevations ≥ 1.5 or ≥ 2.0 x Baseline during the study were similar to those in the overall Safety Population: the mean change from Baseline in Pr-Cr ratio was comparable for all treatment groups over the course of the studies. For example, the mean changes from Baseline to maximum post-Baseline Pr-Cr ratio for patients with a sCr elevation ≥ 1.5 x Baseline and those without an elevation were 0.12 vs. 0.16, respectively, for an XOI alone; 0.30 vs. 0.16, respectively, for lesinurad 200 mg plus XOI; and 0.11 vs. 0.17, respectively, for lesinurad 400 mg plus XOI.

Shifts from Baseline to maximum Pr-Cr ratio were summarized by category (< 0.2, ≥ 0.2 to <1.0, and ≥ 1.0 mg/mg) for patients with/without a sCr elevation ≥ 1.5 x Baseline during the study and for patients with/without sCr elevation ≥ 2.0 x Baseline during the study. Two patients (1 on lesinurad 200 mg plus XOI and 1 on lesinurad 400 mg plus XOI) who shifted from a Baseline value < 0.2 mg/mg to a maximum post-Baseline value ≥ 1.0 mg/mg had a Pr-Cr ratio > 1.0 mg/mg, which occurred at the same visit at which a sCr elevation ≥ 2.0 x Baseline elevation was observed. Overall, across all 4 subgroups, there were no notable treatment differences with respect to the proportion of patients with shifts in Pr-Cr ratio category from a Baseline value < 0.2 mg/mg to a maximum post-Baseline value ≥ 0.2 mg/mg. The results were also similar for patients with a sCr elevation ≥ 1.5 x Baseline and those without an elevation.

9.8.2.3. REAC-Adjudicated Events

The REAC is described in Section 9.8.2. Based on the REAC review of sCr elevations ≥ 1.5 x Baseline and AEs in the MedDRA Acute Renal Failure SMQ that were serious or led to discontinuation of randomized study medication, over 97% of all adjudicated events in the pivotal combination therapy studies were associated with at least 1 potential contributing factor (medical history, concomitant medication, or AE/procedure). The proportion of events judged to be confounded by at least 1 potential contributing factor with a moderate or high likelihood of having contributed to the event was 8/18 (44.4%) for an XOI alone, 13/36 (36.1%) for lesinurad 200 mg plus XOI, and 32/96 (33.3%) for lesinurad 400 mg plus XOI.

The most common individual contributing factors with a moderate or high level of contribution were CKD and dehydration for an XOI alone; CKD, gout flare, and infection for lesinurad 200 mg plus XOI; and CKD, NSAID use, and infection for lesinurad 400 mg plus XOI. Although there were multiple contributory factors in many adjudicated cases, CKD was identified as a moderate or high contributory factor in a number of adjudicated cases across all treatment groups.

9.8.2.4. Renal Safety in Special Groups and Situations

9.8.2.4.1. Renal-Related Adverse Events by Subgroup

In the pivotal combination therapy studies, as was observed for overall AE rates (Section 9.6.2), within all subgroups defined by age (< 65, ≥ 65 years), sex, and Baseline renal function (eCrCl category), the relative treatment differences in the incidence of renal-related AEs were similar to

those that had been observed in the overall safety population; ie, the proportion of patients who had a renal-related AE was generally comparable for an XOI alone and lesinurad 200 mg plus XOI, and higher for lesinurad 400 mg plus XOI (Table 36). Within each treatment, the incidence was generally higher in elderly patients and in those with lower Baseline renal function.

Table 36: Incidence of Renal-Related Adverse Events by Subgroup (CLEAR 1, CLEAR 2, and CRYSTAL Pooled)

	PBO + XOI		LESU 200 mg + XOI		LESU 400 mg + XOI	
Subgroup	**n/N**	**(%)**	**n/N**	**(%)**	**n/N**	**(%)**
All patients	23/516	(4.5%)	29/511	(5.7%)	60/510	(11.8%)
Age						
< 65 years	15/443	(3.4%)	23/454	(5.1%)	50/433	(11.5%)
≥ 65 years	8/73	(11.0%)	6/57	(10.5%)	10/77	(13.0%)
Sex						
Male	23/492	(4.7%)	28/489	(5.7%)	55/482	(11.4%)
Female	0/24	--	1/22	(4.5%)	5/28	(17.9%)
Baseline eCrCl category[a]						
≥ 90 mL/min	1/180	(0.6%)	8/200	(4.0%)	18/203	(8.9%)
< 90 mL/min	22/334	(6.6%)	21/310	(6.8%)	41/305	(13.4%)
< 60 mL/min	14/105	(13.3%)	13/102	(12.7%)	15/92	(16.3%)
< 45 mL/min	6/34	(17.6%)	6/26	(23.1%)	6/29	(20.7%)

Abbreviations: eCrCl, estimated creatinine clearance; LESU, lesinurad; PBO, placebo; sCr, serum creatinine; XOI, xanthine oxidase inhibitor (allopurinol/febuxostat).
[a] Baseline eCrCl is calculated using the highest sCr value recorded ≤ 14 days prior to the first dose of randomized study medication.

9.8.2.4.2. Evaluation of Potential Risk Factors for Serum Creatinine Elevations

Despite an extensive evaluation of potential factors that might be predictive of sCr elevations ≥ 1.5 x Baseline, no subgroup of patients in the pivotal combination therapy studies was determined to be at increased risk of experiencing a sCr elevation during treatment with lesinurad.

There was no apparent association between the incidence of sCr elevations and Baseline renal function, or the incidence of sCr elevations and gout flare prophylaxis medication (colchicine/NSAID), based on subgroup analyses (Table 37).

Table 37: Incidence of Serum Creatinine (mg/dL) Elevations ≥ 1.5 x Baseline by Subgroup (CLEAR 1, CLEAR 2, and CRYSTAL Pooled)

	PBO + XOI		LESU 200 mg + XOI		LESU 400 mg + XOI	
Subgroup	**n/N**	**(%)**	**n/N**	**(%)**	**n/N**	**(%)**
All patients	12/516	(2.3%)	29/511	(5.7%)	73/510	(14.3%)
Baseline eCrCl category[a]						
≥ 90 mL/min	7/180	(3.9%)	11/200	(5.5%)	25/203	(12.3%)
< 90 mL/min	5/334	(1.5%)	18/310	(5.8%)	48/305	(15.7%)
< 60 mL/min	2/105	(1.9%)	5/102	(4.9%)	10/92	(10.9%)
< 45 mL/min	0/34	(0%)	1/26	(3.8%)	5/29	(17.2%)
Gout flare prophylaxis						
Colchicine	8/412	(1.9%)	26/446	(5.8%)	57/429	(13.3%)
NSAID	4/111	(3.6%)	3/61	(4.9%)	17/89	(19.1%)

Abbreviations: eCrCl, estimated creatinine clearance; LESU, lesinurad; NSAID, nonsteroidal anti-inflammatory drug; PBO, placebo; XOI, xanthine oxidase inhibitor (allopurinol/febuxostat).
[a] Baseline eCrCl is calculated using the highest sCr value recorded ≤ 14 days prior to the first dose of randomized study medication.

Similarly, inspection of Baseline characteristics showed that the patients with sCr elevations were comparable to the overall safety population with respect to demographic characteristics, Baseline disease and treatment characteristics, and comorbidities.

Among the 300 parameters (including Baseline laboratory values and BP, all AEs, concomitant medications, questionnaire scores, physical examination results, medical history, ECG data, presence/absence of tophi, and gout flare data) evaluated in a multivariate analysis using virtual twins methodology, no association was strong enough to be of practical importance in either predicting sCr elevations or in identifying a subgroup of patients with increased risk.

Finally, concomitant use of NSAIDs, diuretics, and/or agents acting on the renin-angiotensin system had no apparent effect on the proportion of patients with sCr elevations ≥ 1.5 x Baseline.

9.8.2.5. Risk for Progression of Chronic Kidney Disease

An analysis was conducted to assess whether patients exposed to lesinurad were at increased risk for progression of CKD based on risk categories defined by the KDIGO working group.[78] The risk for CKD progression is classified based on GFR category and albuminuria category. Although albumin-to-creatinine ratios are considered the preferred test for evaluation of urinary protein excretion, Pr-Cr ratio is also suggested and considered to be clinically relevant. Therefore, given that albumin data were not available, the Sponsor modified the KDIGO risk classification framework as shown below, using patients' Baseline and Last Value for eCrCl and Pr-Cr ratio to interpret the risk of CKD progression in patients in the pivotal Phase 3 studies.

		Urine Protein-Creatinine Ratio (mg/mg)		
		< 0.2	≥ 0.2 to < 0.5	≥ 0.5
Estimated Creatinine Clearance (mL/min)	≥ 90	Low	Low	Intermediate
	≥ 60 to < 90	Low	Intermediate	Intermediate
	≥ 30 to < 60	Intermediate	High	High
	< 30	Intermediate	High	High

Based on this analysis, there were few patients at high risk for CKD progression in the safety population and the risk of CKD progression after 1 year of treatment with an XOI alone was comparable to the risk observed with lesinurad plus XOI (Table 38).

Table 38: Incidence of Risk of Chronic Kidney Disease Progression by Risk Category and Treatment (CLEAR 1, CLEAR 2, and CRYSTAL Pooled)

	PBO + XOI (N=405)		LESU 200 mg + XOI (N=410)		LESU 400 mg + XOI (N=410)	
	Baseline	Last Value	Baseline	Last Value	Baseline	Last Value
Low risk	74.1%	77.0%	76.1%	76.1%	75.1%	72.2%
Intermediate risk	21.2%	18.3%	18.3%	18.0%	22.4%	23.2%
High risk	4.9%	4.7%	5.6%	5.9%	2.4%	4.6%

Abbreviations: eCrCl, estimated creatinine clearance; LESU, lesinurad; PBO, placebo; Pr-Cr, urine protein-creatinine ratio; XOI, xanthine oxidase inhibitor (allopurinol/febuxostat).
Note: The denominators are the number of patients who reported both eCrCl and Pr-Cr data at the same visit. Baseline for Pr-Cr is defined as the last observation prior to the first dose of study drug. Baseline for sCr (which is used to determine Baseline eCrCl) is defined as the highest scheduled or unscheduled sCr value recorded ≤ 14 days prior to the first dose of study drug.

9.8.2.6. Renal Safety During Extended Treatment

Longer exposure to lesinurad in combination with an XOI did not result in an increase in exposure-adjusted incidence rates of renal-related AEs, renal-related AEs leading to discontinuation of lesinurad, or renal-related SAEs; kidney stone AEs, kidney stone AEs leading to discontinuation of lesinurad, or kidney stone SAEs; or sCr elevations (Table 39). In order to focus on the effects of exposure beyond 12 months, the integrated pivotal + extension data shown are from only those patients who received lesinurad plus XOI in a pivotal study (4-Month Safety Update cutoff).

Table 39: Exposure-Adjusted Incidence Rates for Renal Events by Category, Excluding Patients Who Received XOI Alone in the Pivotal Study

Category	LESU 200 mg + XOI		LESU 400 mg + XOI	
	Pivotal[a] (N=511) (PYE=396.3) n (Rate)	Pivotal + Extension[b] (N=511) (PYE=641.8) n (Rate)	Pivotal[a] (N=510) (PYE=390.5) n (Rate)	Pivotal + Extension[b] (N=510) (PYE=635.7) n (Rate)
Renal-related AEs	29 (7.3)	54 (8.4)	60 (15.4)	89 (14.0)
Renal-related AEs leading to discontinuation of LESU	6 (1.5)	15 (2.3)	17 (4.4)	24 (3.8)
Renal-related SAEs	0	4 (0.6)	5 (1.3)	8 (1.3)
Kidney stone AEs	3 (0.8)	6 (0.9)	13 (3.3)	16 (2.5)
Kidney stone AEs leading to discontinuation of LESU	1 (0.3)	3 (0.5)	1 (0.3)	3 (0.5)
Kidney stone SAEs	0	0	3 (0.8)	5 (0.8)
sCr elevation ≥ 1.5 x Baseline[c]	29 (7.3)	54 (8.4)	73 (18.7)	109 (17.1)
≥ 2.0 x Baseline	9 (2.3)	16 (2.5)	34 (8.7)	41 (6.4)
≥ 3.0 x Baseline	4 (1.0)	6 (0.9)	12 (3.1)	16 (2.5)

Abbreviations: AE, adverse event; LESU, lesinurad; PYE, person-years of exposure; SAE, serious adverse event; sCr, serum creatinine; XOI, xanthine oxidase inhibitor (allopurinol/febuxostat).
[a] CLEAR 1, CLEAR 2, and CRYSTAL pooled.
[b] CLEAR 1, CLEAR 2, CRYSTAL, and Studies 306 and 307 combined. Based on a data cutoff date of 04 November 2014, the cutoff date for the 4-Month Safety Update Report. In order to focus on the effects of exposure beyond 12 months, the pivotal + extension data shown here include data for only those patients who received lesinurad plus XOI in a pivotal study; ie, not those who received XOI alone in a pivotal study.
[c] Elevation categories are nested; ie, the ≥ 1.5 x Baseline category includes all elevations ≥ 1.5, ≥ 2.0 or ≥ 3.0 x Baseline, and the ≥ 2.0 x Baseline category includes all elevations ≥ 2.0 or ≥ 3.0 x Baseline.
Note: For each category, patients are included only once, even if they experienced multiple events in that category. Exposure-adjusted incidence rates are expressed as patients with events per 100 person-years.

Two patients who experienced SAEs on lesinurad 200 mg plus XOI went on to require chronic renal replacement therapy due to progression of CKD that was present at Baseline. Both patients were randomized to lesinurad 200 mg plus XOI in the pivotal study, and completed the pivotal study with stable renal function. One of the 2 patients experienced acute renal failure in the setting of bilateral lower extremity cellulitis and decompensated heart failure, and discontinued the extension study after initiating chronic renal replacement therapy. The other patient was at risk for CKD progression due to a history of chronic renal failure, acute on chronic renal failure, and proteinuria, and required acute renal replacement therapy 11 months after discontinuing lesinurad. He subsequently initiated chronic renal replacement therapy 16 months after discontinuing lesinurad. In addition, 1 patient, who was receiving lesinurad 200 mg plus XOI in an extension study, required acute renal replacement therapy following cardiac arrest; his renal function had recovered to Baseline levels at the time of hospital discharge. Additional information is provided in the narratives in Appendix 9 (Patients 306-08001-204, 306-05095-109, and 307-17002-408).

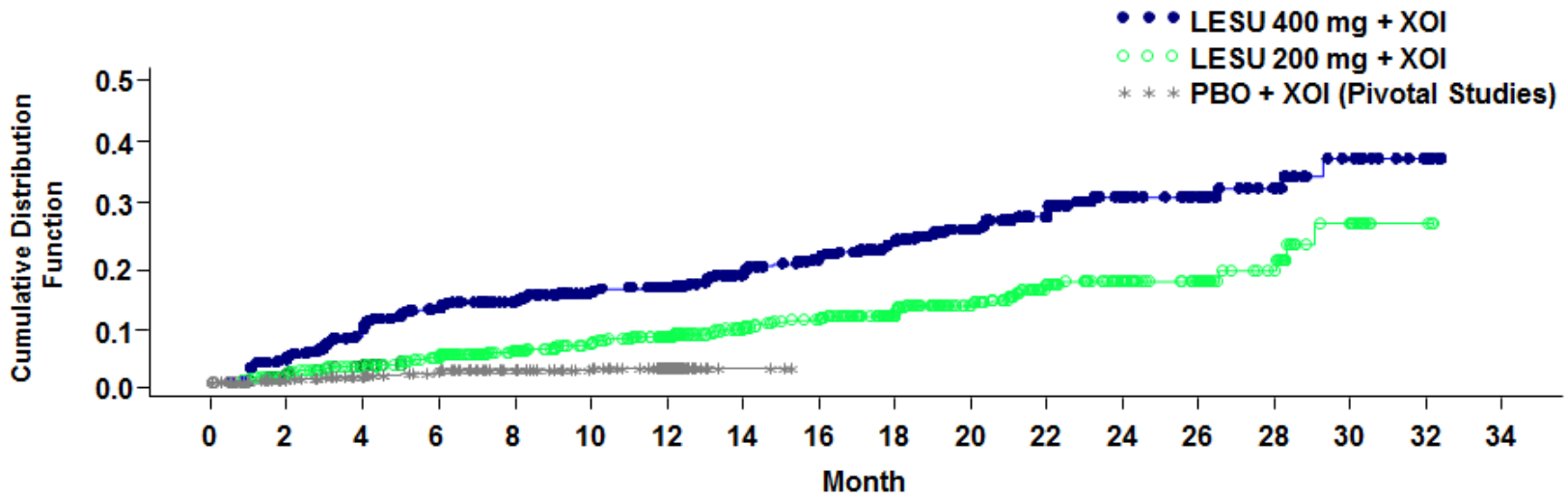
For patients who received lesinurad 200 mg in a pivotal study, the renal-related PTs with the highest exposure-adjusted incidence rates (per 100 PYE) in the pivotal + extension integrated dataset were *blood creatinine increased* (6.4), *blood urea increased* (1.2), and *renal failure* (0.8).

The rate of patients having a first sCr elevation ≥ 1.5 x Baseline remained stable over the pivotal + extension studies (Figure 51). Note that the sample size decreases over time and data points

after 26 months represent data from a small number of patients. When analyzed by 3-month time intervals, the incidence of sCr elevations also appeared stable over time.

Figure 51: Cumulative Incidence of Serum Creatinine Elevations ≥ 1.5 x Baseline (CLEAR 1, CLEAR 2, and CRYSTAL, and Studies 306, and 307 Combined)

LESU 400 mg + XOI	AR	666	620	555	500	451	403	365	282	253	210	159	118	79	61	38	19	7	0
	E (C)		26 (20)	54 (57)	76 (90)	82 (133)	90 (173)	94 (207)	102 (282)	111(302)	119(337)	124(383)	128(420)	133(454)	133(472)	134(494)	136(511)	136(523)	136(530)
LESU 200 mg + XOI	AR	666	632	593	545	484	446	395	308	284	227	179	125	97	70	43	20	3	0
	E (C)		8 (26)	17 (56)	28 (93)	33 (149)	38 (182)	44 (227)	48 (310)	53 (329)	55 (384)	59 (428)	65 (476)	66 (503)	66 (530)	67 (556)	70 (576)	70 (593)	70 (596)
PBO + XOI	AR	516	488	468	453	425	406	313	3	0									
	E (C)		2(26)	5(43)	9 (54)	11 (80)	11 (99)	12 (191)	12 (501)	12 (504)									



Abbreviations: LESU, lesinurad; PBO, placebo; XOI, xanthine oxidase inhibitor.
Note: Based on a data cutoff date of 04 November 2014, the cutoff date for the 4-Month Safety Update Report. Baseline is defined as the highest serum creatinine value recorded ≤14 days prior to the first dose of lesinurad in either the pivotal study or the extension study. For patients who received PBO + XOI during a pivotal study and enrolled in an extension study, their pivotal study data are included in the Pivotal PBO + XOI curve and their extension study data are included in the appropriate LESU + XOI curve (with "Month 0" = extension study baseline).

Of the elevations that had resolved by the time of the 4-Month Safety Update data cutoff, most had resolved by the next study assessment following the initial report of the elevation: 56.5% for lesinurad 200 mg plus XOI and 55.3% for lesinurad 400 mg plus XOI.

Mean sCr, eCrCl, and Pr-Cr ratio were stable in patients who had received lesinurad for 12 months in a pivotal study and continued into an extension study. Analyses to assess renal function on and off lesinurad treatment demonstrated small changes in renal function over time. No meaningful differences in sCr from Baseline to Last Value were observed for patients who did not experience a sCr elevation during the pivotal + extension studies and who discontinued lesinurad. In this population, the mean (SD) change in sCr from Baseline to the last value on treatment was 0.02 (0.16) mg/dL for lesinurad 200 mg plus XOI and 0.05 (0.15) mg/dL for lesinurad 400 mg plus XOI; and the mean (SD) change in sCr from Baseline to the last value off treatment was -0.03 (0.16) mg/dL for lesinurad 200 mg plus XOI and -0.02 (0.18) mg/dL for lesinurad 400 mg plus XOI. In all patients who discontinued lesinurad and had a follow-up sCr assessment ≥ 7 days later, there was no mean change from Baseline to the lowest post-discontinuation sCr value.

An analysis of the mean change in sCr for the small population of patients who experienced a sCr elevation ≥ 1.5 x Baseline was confounded by a small number of outlier patients. Twenty-one patients on lesinurad 200 mg plus XOI and 51 on lesinurad 400 mg plus XOI experienced a sCr elevation ≥ 1.5 x Baseline and discontinued treatment for any reason in the pivotal study or extension study. Of these, 3/21 patients on lesinurad 200 mg plus XOI and 7/51 patients on lesinurad 400 mg plus XOI had a change in sCr value ≥ 0.3 mg/dL from Baseline to last value off-treatment. For comparison, analysis of the 12 patients on an XOI alone (placebo plus XOI) in the pivotal study who had a sCr elevation ≥ 1.5 x Baseline and discontinued placebo demonstrated that 3/12 patients had a change in sCr ≥ 0.3 mg/dL from Baseline to Last Value.

10. PROPOSED POST-APPROVAL RISK MANAGEMENT AND PHARMACOVIGILANCE ACTIVITIES

A comprehensive risk management program has been proposed to minimize risks through labeling and communication activities and to facilitate timely identification and evaluation of changes in the safety profile of lesinurad therapy through enhanced pharmacovigilance activities.

10.1. Labeling

The proposed labeling addresses the identified and potential risks for lesinurad, as described below.

- A Boxed Warning is proposed to warn prescribers of the increased risk of acute renal failure with monotherapy use and the importance of co-administration with an XOI.
- Renal Events: The proposed labeling warns of and describes the higher incidence of sCr elevations and renal-related adverse reactions with lesinurad, including serious adverse reactions of acute renal failure observed with lesinurad 400 mg, with the highest incidence on lesinurad 400 mg as monotherapy. Prescribers are instructed to monitor renal function prior to initiation of lesinurad and periodically thereafter, as

clinically indicated, and to interrupt lesinurad treatment if sCr increases to > 2 x the pre-treatment value or if symptoms develop that may indicate acute uric acid nephropathy, including flank pain, nausea, or vomiting.

- Avoidance of Monotherapy Use: The proposed labeling indicates that lesinurad should not be used as monotherapy due to the increased risk for serious renal events. It emphasizes the importance of co-administration with an XOI, and instructs prescribers that if treatment with the XOI is interrupted, lesinurad should also be interrupted.
- Renal Impairment: The proposed labeling includes a Contraindication for severe renal impairment (CrCl < 30 mL/min), end-stage renal disease, and patients on dialysis. It is recommended that patients discontinue treatment if CrCl is persistently < 30 mL/min. Experience with lesinurad in patients with a CrCl < 45 mL/min is limited; therefore, it is recommended that lesinurad be used with caution in these patients.
- Cardiovascular Events: The proposed labeling warns of and describes the types and incidences of MACE although a causal relationship with lesinurad has not been established.

10.2. Communication Program

Ardea proposed a communication program to inform healthcare professionals and patients of the risks of AKI with lesinurad, and the importance of co-administration of lesinurad 200 mg with an XOI due to the increase in the risk of AKI with monotherapy use at twice the recommended dose. The program includes:

- A patient Medication Guide dispensed with each lesinurad prescription.
- A Communication Plan targeted to health care providers who are likely to prescribe and dispense lesinurad.
- A website for more information.

10.3. Pharmacovigilance Activities

Routine and enhanced pharmacovigilance activities are planned. The routine activities include the collection and analysis of all individual AE cases for expedited and periodic reporting, and signal identification and review of the risk on an ongoing basis for aggregate safety reporting. The following enhanced activities are proposed by Ardea to identify and evaluate potential changes in the safety profile:

- Targeted Questionnaire on Renal-Related Events: A Targeted Follow-up Questionnaire will be sent to each healthcare professional when a renal-related event is reported post-approval. The questionnaire captures specific symptoms of AKI (eg, flank pain, nausea, dehydration), need for temporary or chronic renal replacement therapy, other potentially nephrotoxic medications taken by the patient (eg, NSAIDs, angiotensin-converting-enzyme [ACE] inhibitors), and laboratory data and tests (eg, sCr, urinalysis, renal biopsy).

- Ongoing Clinical Trials: Long-term open-label extension studies will continue to assess renal and CV safety and monitor for any unidentified risks.
- Pharmacoepidemiology Study: In the lesinurad pivotal Phase 3 combination therapy studies, there was a low rate of MACE across treatment groups, which places limitations on assessment of treatment-associated differences in MACE risk. There was a higher incidence of renal events including AKI on lesinurad in combination with an XOI than on an XOI alone, and renal events are considered an important identified risk for lesinurad. Uncontrolled extension studies and standard pharmacovigilance activities may not be sufficient for signal detection; therefore, this prospective observational cohort study is proposed to assess the potential risk for CV events with lesinurad and to further characterize the renal safety of lesinurad in a real-world setting. This study will compare the risk of CV events between gout patients who are new users of lesinurad in combination with an XOI and those who are continuing users of an XOI as monotherapy, and will also compare the rates of hospitalization for AKI.
  - Primary objective: Compare lesinurad in combination with an XOI to XOI monotherapy with respect to the event rates of the composite MACE-plus, which comprises CV death, nonfatal MI, nonfatal stroke, and hospitalization for unstable angina.
  - Secondary objectives: Compare lesinurad in combination with an XOI to XOI monotherapy with respect to the event rates for hospitalization for AKI including renal failure.

11. BENEFIT-RISK PROFILE OF LESINURAD 200 MG IN COMBINATION WITH A XANTHINE OXIDASE INHIBITOR

Approval is being sought for lesinurad 200 mg qd as a second-line treatment option for use in combination with an XOI, allopurinol or febuxostat, for the chronic treatment of hyperuricemia associated with gout in patients who have not achieved target sUA levels with an XOI alone.

Recent ACR treatment guidelines indicate that the therapeutic goal in the management of gout is to lower sUA levels sufficiently to durably improve the signs and symptoms of gout with a target sUA of < 6 mg/dL at minimum;[6, 7] a target sUA of < 5 mg/dL is recommended for greater disease severity such as in patients with tophi.[6, 7]. Unfortunately, approximately 40%-70% of patients do not achieve, and approximately 50%-80% of patients do not sustain, recommended sUA goals in large randomized clinical trials.[15-18] For patients not achieving target sUA levels on an XOI alone, the ACR treatment guidelines recommend the addition of an agent that increases urinary uric acid excretion.[6-8]

Summary of Benefits

Lesinurad is the first non-XOI, oral ULT developed in the US since the approval of probenecid over 60 years ago. Lesinurad, if approved, will be the only oral ULT specifically developed as a second-line treatment option for patients unable to achieve target sUA with an XOI alone. Unlike probenecid, lesinurad is a SURI. It does not inhibit the drug transporters OAT1 and OAT3 in humans and therefore its use is not limited by the multiple OAT1- and OAT3-mediated

DDIs of probenecid. Of note, nearly 40% of the patients in the lesinurad pivotal Phase 3 studies received a concurrent medication that has a known DDI with probenecid. Moreover, in contrast to probenecid where there are no published, large, randomized, controlled clinical trials in combination with an XOI, the safety and efficacy of lesinurad is well characterized with use in approximately1800 patients with gout, including more than 1500 patients treated with lesinurad in combination with an XOI in Phase 3 studies.

The sUA-lowering effect of lesinurad is rapid, evident within hours after the first dose, and sustained with continued qd dosing. In patients with sUA repeatedly above target on allopurinol, the addition of lesinurad 200 mg to allopurinol resulted in significant and clinically meaningful sUA lowering, with approximately twice as many patients achieving the sUA target goal of < 6 mg/dL at Month 6 compared with allopurinol alone (primary endpoint, $p < 0.0001$; Figure 25). The magnitude of sUA lowering was also significant. At each timepoint during the 12-month treatment period, the mean percent and absolute change from Baseline sUA was greater on lesinurad 200 mg plus allopurinol compared with allopurinol alone ($p < 0.0001$). This degree of sUA reduction achieved with the addition of lesinurad is clinically relevant as evidenced not only by the significant increase in the proportion of patients able to achieve target sUA of <6 mg/dL, but also by the significant increase in the proportion of patients able to achieve the more stringent sUA target of < 5 mg/dL recommended for those patients with greater disease severity (Figure 28).[7] The addition of lesinurad 200 mg resulted in a consistent sUA lowering regardless of allopurinol dose.

When used in combination with febuxostat 80 mg, lesinurad 200 mg resulted in a significantly greater proportion of patients with tophaceous gout achieving the sUA target goal of < 5 mg/dL at all timepoints through Month 12 except Month 6, which was the timepoint for the primary endpoint (Figure 34). Of clinical relevance is the ability of ULTs to not only achieve sUA target levels, but to sustain those levels over time. In this regard, lesinurad 200 mg in combination with febuxostat was superior to febuxostat alone over all treatment intervals (Figure 36). Importantly, the results in the subgroup of patients with sUA ≥ 5 mg/dL at Baseline demonstrate that nearly twice as many patients achieved the target sUA of < 5 mg/dL on lesinurad 200 mg plus febuxostat compared with febuxostat alone at all timepoints, including Month 6 (Figure 40). This is clinically relevant as these are the patients in greatest need of additional treatment options and the patients whom lesinurad is intended to treat.

The urate-lowering efficacy of lesinurad in combination with an XOI is consistently observed across important patient subgroups, including difficult-to-manage patients such as those with mild or moderate renal impairment, those taking thiazide and thiazide-like diuretics, and those with pre-existing tophi.

Lesinurad, when added to allopurinol or febuxostat, demonstrated consistent efficacy in patients with mild or moderate renal impairment (Figure 30). This is clinically relevant given the prevalence of renal impairment in patients with gout as well as the limited options to effectively manage these patients. In the lesinurad pivotal studies, 61.7% of the patients had eCrCl < 90 mL/min); 19.5% had eCrCl < 60 mL/min. In patients taking thiazide diuretics, which are known to increase sUA levels, lesinurad in combination with an XOI was equally as effective as it was in patients not taking a thiazide diuretic. This may be a result of lesinurad's inhibition of OAT4, a uric acid transporter involved in diuretic-induced hyperuricemia.

No ULT has convincingly demonstrated a statistically significant reduction in gout flares during the controlled study period. A statistically significant difference between treatments was not observed for the key secondary endpoints in the lesinurad pivotal studies, including mean flare rates and CR of ≥ 1 target tophus. Potential reasons for this include the low rate of flares in the studies, the paradoxical increase in flares with the initiation of effective ULT, and the lack of a validated method to report flares. Another important factor impacting these clinical endpoints is the duration of the clinical trials. Sustained sUA lowering will reverse the deposition of uric acid from the tissues; however, this process may require more than the 12 month duration of the clinical trials. This is supported by the observation of the reduction in flares and resolution of tophi observed with continued treatment in the open label extension trial with febuxostat.[10, 34] Similarly, reduction of flares and resolution of tophi were observed with continued treatment with lesinurad plus an XOI in our extension studies.

In summary, the 3 pivotal studies confirm that lesinurad 200 mg in combination with an XOI provides meaningful sUA lowering resulting in a significant increase in the proportion of patients able to achieve and maintain the sUA target treatment goals. These results clearly support the proposed indication for the chronic treatment of hyperuricemia associated with gout in patients who have not achieved target sUA levels with an XOI alone.

Summary of Risks

Following extensive safety data collection and analysis, robust prospective adjudication processes, and comprehensive review of patient-level data, the only confirmed safety signal for lesinurad is an increase in renal-related events. The incidence of renal-related events was higher with lesinurad 400 mg and an XOI, and highest with 400 mg monotherapy. The events are likely due to excessive urinary uric acid excretion leading to intratubular uric acid precipitation. As a result of the renal safety profile, an indication is sought only for lesinurad 200 mg in combination with an XOI.

Lesinurad 200 mg in combination with an XOI demonstrated a safety profile that was comparable to that of an XOI alone, with the exception of an increase in transient sCr elevations, most of which resolved without interruption of lesinurad. In the lesinurad 200 mg plus XOI and XOI alone groups, a small and comparable number of patients had unresolved sCr elevations at the end of the pivotal studies (n = 3 in both groups, 2 of the 3 in the lesinurad 200 mg group resolved with continued dosing in the extension study). There was no notable change in renal function within any treatment group, based on mean changes from Baseline to Last Value in sCr and eCrCl, and lesinurad in combination with an XOI did not increase the risk of proteinuria. There was also no increased risk of CKD progression, based on a modification of KDIGO risk categories. Events suggestive of serious acute uric acid nephropathy have been reported on lesinurad 200 mg plus XOI and lesinurad 400 mg plus XOI; however, serious events were infrequent and sCr returned to Baseline values in most patients.

Two lesinurad-treated patients, both of whom had CKD at Baseline and additional confounding medical conditions, required chronic renal replacement therapy; one of these patients initiated chronic renal replacement therapy more than 16 months after discontinuation of lesinurad.

Patients with gout are known to be at increased risk of kidney stones. Patients with a history of kidney stones were included in the pivotal combination therapy studies. The incidence of kidney

stones with lesinurad in combination with an XOI was low and comparable to that seen with an XOI alone.

Lesinurad plasma exposure is higher in patients with moderate renal impairment; however, there were no overall treatment-related differences in the renal AE profile or in the incidence of sCr elevations in patients with mild or moderate renal impairment. This is because the amount of uric acid available for excretion and the amount of lesinurad that reaches its site of action is dependent upon renal function. As renal function decreases, urinary uric acid excretion also decreases. As a result, the total amount of urinary uric acid excreted in patients with moderate renal impairment following lesinurad treatment is similar to the amount excreted in untreated gout patients with normal renal function. Also, despite higher plasma levels, the concentration of lesinurad at the active site in the proximal tubule lumen is less, as reflected by the decrease in lesinurad urine concentration. Based on these data, lesinurad 200 mg qd in combination with an XOI can be used in patients with mild or moderate renal impairment.

The overall incidence of MACE in the lesinurad clinical development program was low, with comparable rates for lesinurad 200 mg in combination with an XOI and an XOI alone. The rate was also low, but numerically higher, with lesinurad 400 mg; no causal relationship has been established. There was no apparent relationship between lesinurad plasma exposure and MACE. Patients with hyperuricemia associated with gout have multiple cardiac comorbidities and are at an increased risk for MACE compared to patients without gout. 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.

Although a CV signal with lesinurad has not been identified, a post-approval prospective observational cohort study is proposed to assess the potential risk for CV events. A secondary objective of the study will be to further characterize the renal safety of lesinurad.

In summary, lesinurad 200 mg in combination with an XOI demonstrated a safety profile that was comparable to that of an XOI alone, with the exception of an increase in transient sCr elevations, most of which resolved without interruption of lesinurad. The safety profile was consistent with extended dosing and the treatment relationships were consistent across subgroups, including subgroups defined by demographic and disease characteristics, Baseline renal function, geographic region, and allopurinol dose.

Risk Management Strategy

Throughout the proposed product labeling for lesinurad, the risks of sCr elevations and of acute renal failure, particularly when used as monotherapy, are presented, including in a Boxed Warning. Emphasis is placed on the importance of co-administration with an XOI to reduce the risks. The Warnings and Precautions highlight the higher risk with twice the recommended dose (ie, 400 mg in combination with an XOI), and instruct prescribers to 1) monitor renal function prior to initiation of lesinurad and periodically thereafter, as clinically indicated, and 2) interrupt lesinurad treatment if sCr increases to > 2 x the pre-treatment value or if symptoms develop that may indicate acute uric acid nephropathy, such as flank pain, nausea, or vomiting. It is recommended that patients taking lesinurad drink 2 liters (68 ounces) of liquid a day to reduce the potential for developing nephrolithiasis and other renal events. Due to the limited experience in patients with eCrCl < 45 mL/min, caution is proposed in these patients. Lesinurad has not been studied in gout patients with eCrCl < 30 mL/min and efficacy may not be expected in this

population based on limited data from Phase 1 healthy volunteers; as a result, lesinurad is contraindicated for use in severe renal impairment, ESRD, and in patients on dialysis in the proposed label.

A proposed Medication Guide for patients describes the renal-related risks and signs and symptoms to report to their doctor, and reinforces the prescribing instructions to avoid monotherapy use. Although a CV signal with lesinurad has not been identified, the CV outcomes are presented in the Warnings and Precautions section to inform prescribers.

Additional proposed risk mitigation measures include a Communication Plan targeted to healthcare providers who are likely to prescribe and dispense lesinurad, and routine and expanded pharmacovigilance activities to facilitate identification and evaluation of known and potential risks, including a questionnaire to capture details on each reported case of a renal-related event.

Benefit-Risk Conclusions

In summary, the efficacy results provide clear evidence of significant sUA lowering with lesinurad 200 mg in combination with an XOI and support the proposed indication for the treatment of hyperuricemia associated with gout in patients who have not achieved target sUA levels with an XOI alone. The safety results indicate that lesinurad 200 mg in combination with an XOI is generally well tolerated with a consistent safety profile during extended dosing beyond 12 months. The identified risks are manageable with the proposed labeling and communication activities.

In patients unable to achieve sUA targets on an XOI alone, lesinurad 200 mg in combination with allopurinol or febuxostat has a favorable benefit-risk profile. There is a clear medical need for effective second-line treatment options with proven efficacy and safety for the management of hyperuricemia associated with gout. Lesinurad, if approved, will help to address this need and enable significantly more patients with uncontrolled gout to achieve and maintain target sUA treatment goals.

12. CONCLUSIONS

There is a clear need for additional treatment options for patients with gout who are unable to achieve and sustain recommended sUA levels with currently available therapies. Lesinurad is a SURI that inhibits the uric acid transporter URAT1. By inhibiting URAT1, lesinurad increases uric acid excretion and thereby lowers sUA. Lesinurad also inhibits OAT4, a uric acid transporter involved in diuretic-induced hyperuricemia. Lesinurad when used in combination with an XOI (allopurinol or febuxostat) targets both aspects of sUA regulation - production and excretion - providing a dual mechanism approach to more effectively lower sUA.

The results of the lesinurad clinical program substantiate the conclusion that the proven benefits outweigh the documented risks for lesinurad 200 mg in combination with an XOI and support its use as a chronic treatment for hyperuricemia associated with gout in patients who have not achieved target sUA on an XOI alone.

- Lesinurad 200 mg in combination with an XOI results in clinically significant lowering of sUA levels, allowing substantially more patients to achieve and maintain target treatment goals.
- The efficacy of lesinurad in combination with an XOI is consistently observed across important patient subgroups, including patients with mild or moderate renal impairment and those taking thiazide and thiazide-like diuretics.
- Lesinurad 200 mg in combination with an XOI has a manageable safety profile that is similar to that of an XOI alone, with the exception of an increased risk of transient sCr elevations, most of which resolved without interruption of lesinurad.
- The overall incidence of MACE was low, with comparable rates for lesinurad 200 mg in combination with an XOI and an XOI alone. The rate was also low, but numerically higher, with lesinurad 400 mg; no causal relationship has been established.
- Risk management activities will be undertaken to facilitate the safe and effective use of lesinurad and to maintain vigilance for any potential unidentified risks, including a post-approval pharmacoepidemiology study designed primarily to assess the potential risk for CV events and also to further characterize the risk for renal events in a real-world setting.
- Overall, lesinurad 200 mg in combination with an XOI has a favorable benefit-risk profile in patients with hyperuricemia associated with gout and offers an important new therapeutic option for uncontrolled gout.

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14. APPENDICES

APPENDIX 1. DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Table 40: Demographics and Baseline Characteristics for Phase 3 Combination Therapy Pivotal Studies

	Study 301 (CLEAR 1)			Study 302 (CLEAR 2)			Study 304 (CRYSTAL)		
Variable	**PBO + ALLO (N=201)**	**LESU 200 mg + ALLO (N=201)**	**LESU 400 mg + ALLO (N=201)**	**PBO + ALLO (N=206)**	**LESU 200 mg + ALLO (N=204)**	**LESU 400 mg + ALLO (N=200)**	**PBO + FBX (N=109)**	**LESU 200 mg + FBX (N=106)**	**LESU 400 mg + FBX (N=109)**
Sex [n (%)]									
Male	189 (94.0)	192 (95.5)	186 (92.5)	196 (95.1)	197 (96.6)	194 (97.0)	107 (98.2)	100 (94.3)	102 (93.6)
Female	12 (6.0)	9 (4.5)	15 (7.5)	10 (4.9)	7 (3.4)	6 (3.0)	2 (1.8)	6 (5.7)	7 (6.4)
Race [n (%)]									
White	153 (76.1)	151 (75.1)	156 (77.6)	155 (75.2)	167 (81.9)	160 (80.0)	94 (86.2)	80 (75.5)	85 (78.0)
Non-White (or missing)	48 (23.9)	50 (24.9)	45 (22.4)	51 (24.8)	37 (18.1)	40 (20.0)	15 (13.8)	26 (24.5)	24 (22.0)
Age (years)									
Mean (SD)	51.7 (11.70)	51.6 (10.69)	52.3 (11.47)	51.4 (10.56)	51.0 (11.11)	51.3 (11.08)	54.6 (10.87)	54.2 (11.04)	53.3 (11.16)
Median (Min, Max)	52.0 (22, 81)	52.0 (25, 77)	53.0 (23, 77)	52.0 (21, 80)	51.0 (21, 82)	52.0 (18, 80)	54.0 (27, 77)	54.0 (28, 80)	53.0 (28, 82)
Body mass index (kg/m^2)									
Mean (SD)	34.31 (6.44)	35.02 (6.17)	34.96 (7.33)	33.87 (6.19)	34.67 (6.43)	33.81 (6.68)	32.00 (5.55)	32.41 (5.61)	31.56 (5.68)
Min, Max	15.91, 50.99	17.79, 59.38	15.77, 83.65	21.91, 56.27	22.55, 55.63	22.76, 69.36	21.50, 51.67	19.23, 45.73	19.73, 50.50
Duration since gout diagnosis (years)									
Mean (SD)	11.59 (8.75)	12.76 (10.04)	11.16 (9.23)	11.31 (9.38)	12.25 (9.76)	11.02 (8.59)	15.17 (10.90)	15.82 (11.00)	13.15 (10.64)
Min, Max	0.2, 40.4	0.2, 45.2	0.0, 43.0	0.2, 53.0	0.5, 45.0	0.0, 47.4	0.3, 51.0	0.2, 49.2	0.0, 53.1
Presence of ≥ 1 target tophus at Baseline [n (%)]									
Yes	17 (8.5)	18 (9.0)	19 (9.5)	33 (16.0)	35 (17.2)	29 (14.5)	109 (100.0)	105 (99.1)	109 (100.0)

Table 40: Demographics and Baseline Characteristics for Phase 3 Combination Therapy Pivotal Studies

	Study 301 (CLEAR 1)			Study 302 (CLEAR 2)			Study 304 (CRYSTAL)		
Variable	**PBO + ALLO (N=201)**	**LESU 200 mg + ALLO (N=201)**	**LESU 400 mg + ALLO (N=201)**	**PBO + ALLO (N=206)**	**LESU 200 mg + ALLO (N=204)**	**LESU 400 mg + ALLO (N=200)**	**PBO + FBX (N=109)**	**LESU 200 mg + FBX (N=106)**	**LESU 400 mg + FBX (N=109)**
Number of target tophi at Baseline									
N	17	18	19	33	35	29	109	106	109
Mean (SD)	1.8 (1.47)	1.8 (1.06)	2.1 (1.45)	2.2 (1.36)	2.0 (1.34)	2.5 (1.53)	1.9 (1.3)	1.8 (1.3)	1.8 (1.2)
Median (Min, Max)	1.0 (1, 5)	1.5 (1, 5)	1.0 (1, 5)	2.0 (1, 5)	1.0 (1, 5)	2.0 (1, 5)	1.0 (1, 5)	1.0 (0, 5)	1.0 (1, 5)
Total area of target tophi at Baseline (mm^2)									
N	17	18	19	33	35	29	109	105	109
Mean (SD)	321.85 (281.49)	334.95 (207.27)	254.19 (165.19)	373.04 (378.95)	346.63 (335.78)	559.69 (715.27)	291.08 (246.36)	310.12 (227.85)	280.34 (230.28)
Median	273.48	282.70	230.55	294.84	246.03	351.42	220.40	241.57	210.60
Min, Max	60.60, 1162.37	75.65, 852.68	56.25, 632.56	23.92, 1795.66	31.62, 1643.15	54.00, 3365.82	11.52, 1352.68	12.10, 1172.85	37.40, 1233.56
Number of gout flares in the past 12 months									
Mean (SD)	4.8 (4.09)	4.8 (3.16)	4.9 (3.49)	5.8 (4.92)	6.7 (7.01)	6.1 (5.65)	6.1 (5.1)	6.9 (11.2)	7.0 (7.4)
Median (Min, Max)	3.0 (2, 36)	4.0 (2, 20)	4.0 (2, 20)	4.0 (2, 30)	4.0 (2, 50)	4.0 (2, 48)	4.0 (2, 24)	4.0 (0, 104)	4.0 (0, 50)
Renal function at Baseline [n (%)]									
eCrCl < 90 mL/min	123 (61.2)	117 (58.2)	124 (61.7)	133 (64.6)	124 (60.8)	114 (57.0)	78 (71.6)	69 (65.1)	67 (61.5)
eCrCl < 60 mL/min	40 (19.9)	45 (22.4)	41 (20.4)	40 (19.4)	29 (14.2)	29 (14.5)	25 (22.9)	28 (26.4)	22 (20.2)
eCrCl < 45 mL/min	20 (10.0)	12 (6.0)	15 (7.5)	10 (4.9)	6 (2.9)	6 (3.0)	4 (3.7)	8 (7.5)	8 (7.3)
sUA level at Screening (mg/dL)									
Mean (SD)	8.11 (1.53)	7.97 (1.47)	8.01 (1.47)	8.00 (1.46)	8.02 (1.52)	8.08 (1.56)	8.83 (1.53)	8.71 (1.58)	8.57 (1.76)
Median (Min, Max)	5.5, 14.4	4.7, 12.7	5.6, 13.2	4.8, 13.0	4.9, 12.5	4.7, 12.1	5.5, 12.4	4.8, 13.3	4.5, 13.2

Table 40: Demographics and Baseline Characteristics for Phase 3 Combination Therapy Pivotal Studies

	Study 301 (CLEAR 1)			Study 302 (CLEAR 2)			Study 304 (CRYSTAL)		
Variable	**PBO + ALLO (N=201)**	**LESU 200 mg + ALLO (N=201)**	**LESU 400 mg + ALLO (N=201)**	**PBO + ALLO (N=206)**	**LESU 200 mg + ALLO (N=204)**	**LESU 400 mg + ALLO (N=200)**	**PBO + FBX (N=109)**	**LESU 200 mg + FBX (N=106)**	**LESU 400 mg + FBX (N=109)**
sUA category at Baseline (mg/dL) [n (%)]									
< 5.0	NA	NA	NA	NA	NA	NA	58 (53.2)	47 (44.3)	58 (53.2)
5.0 - < 6.0	NA	NA	NA	NA	NA	NA	19 (17.4)	28 (26.4)	23 (21.1)
< 6.0	31 (15.4)	36 (17.9)	45 (22.4)	38 (18.4)	39 (19.1)	39 (19.5)	77 (70.6)	75 (70.8)	81 (74.3)
6.0 - < 7.0	82 (40.8)	76 (37.8)	72 (35.8)	80 (38.8)	88 (43.1)	80 (40.0)	16 (14.7)	14 (13.2)	11 (10.1)
7.0 - < 8.0	52 (25.9)	52 (25.9)	52 (25.9)	44 (21.4)	50 (24.5)	45 (22.5)	12 (11.0)	9 (8.5)	8 (7.3)
8.0 - < 10.0	32 (15.9)	31 (15.4)	28 (13.9)	39 (18.9)	22 (10.8)	32 (16.0)	4 (3.7)	6 (5.7)	8 (7.3)
≥ 10.0	4 (2.0)	6 (3.0)	4 (2.0)	5 (2.4)	5 (2.5)	4 (2.0)	0	2 (1.9)	1 (0.9)
sUA level at Baseline (mg/dL)									
Mean (SD)	6.99 (1.25)	7.01 (1.32)	6.83 (1.24)	6.99 (1.26)	6.84 (1.11)	6.86 (1.19)	5.22 (1.53)	5.35 (1.72)	5.23 (1.64)
Median (Min, Max)	6.70 (3.8, 12.2)	6.80 (3.8, 13.3)	6.70 (3.6, 12.2)	6.80 (3.4, 11.3)	6.75 (4.0, 11.3)	6.80 (3.8, 11.0)	4.90 (2.2, 9.6)	5.10 (2.0, 11.6)	4.80 (1.4, 10.0)
Type of gout flare prophylaxis at Baseline [n (%)]									
Colchicine	166 (82.6)	170 (84.6)	168 (83.6)	159 (77.2)	181 (88.7)	167 (83.5)	87 (79.8)	95 (89.6)	94 (86.2)
NSAID	34 (16.9)	28 (13.9)	33 (16.4)	51 (24.8)	23 (11.3)	36 (18.0)	26 (23.9)	10 (9.4)	20 (18.3)
Both	1 (0.5)	2 (1.0)	3 (1.5)	8 (3.9)	4 (2.0)	3 (1.5)	4 (3.7)	1 (0.9)	5 (4.6)
Other or Missing	2 (1.0)	5 (2.5)	3 (1.5)	4 (1.9)	4 (2.0)	0	0	2 (1.9)	0
Allopurinol dose at Baseline [n (%)]									
< 300 mg/day	12 (6.0)	5 (2.5)	12 (6.0)	15 (7.3)	14 (6.9)	11 (5.5)	NA	NA	NA
= 300 mg/day	176 (87.6)	187 (93.0)	183 (91.0)	176 (85.4)	168 (82.4)	169 (84.5)	NA	NA	NA
> 300 mg/day	13 (6.5)	9 (4.5)	6 (3.0)	15 (7.3)	22 (10.8)	20 (10.0)	NA	NA	NA

Table 40: Demographics and Baseline Characteristics for Phase 3 Combination Therapy Pivotal Studies

	Study 301 (CLEAR 1)			Study 302 (CLEAR 2)			Study 304 (CRYSTAL)		
Variable	**PBO + ALLO (N=201)**	**LESU 200 mg + ALLO (N=201)**	**LESU 400 mg + ALLO (N=201)**	**PBO + ALLO (N=206)**	**LESU 200 mg + ALLO (N=204)**	**LESU 400 mg + ALLO (N=200)**	**PBO + FBX (N=109)**	**LESU 200 mg + FBX (N=106)**	**LESU 400 mg + FBX (N=109)**
Most Common Comorbidities[a] [n (%)]									
≥ 1 comorbidity	167 (83.1)	161 (80.1)	167 (83.1)	165 (80.1)	158 (77.5)	160 (80.0)	82 (75.2)	82 (77.4)	78 (71.6)
Hypertension	134 (66.7)	129 (64.2)	142 (70.6)	141 (68.4)	131 (64.2)	121 (60.5)	65 (59.6)	70 (66.0)	62 (56.9)
Hyperlipidemia	99 (49.3)	102 (50.7)	98 (48.8)	76 (36.9)	86 (42.2)	93 (46.5)	46 (42.2)	42 (39.6)	50 (45.9)
Diabetes mellitus	35 (17.4)	44 (21.9)	38 (18.9)	28 (13.6)	31 (15.2)	26 (13.0)	17 (15.6)	21 (19.8)	14 (12.8)
Kidney stones	38 (18.9)	20 (10.0)	22 (10.9)	28 (13.6)	23 (11.3)	18 (9.0)	16 (14.7)	15 (14.2)	11 (10.1)
Myocardial infarction	7 (3.5)	11 (5.5)	6 (3.0)	5 (2.4)	10 (4.9)	9 (4.5)	7 (6.4)	5 (4.7)	7 (6.4)

Abbreviations: ALLO, allopurinol; FBX, febuxostat; eCrCl, estimated creatinine clearance; ITT, intent-to-treat; LESU, lesinurad; Max, maximum; Min, minimum; NSAID, nonsteroidal anti-inflammatory drugs; PBO, placebo; SD, standard deviation; sUA, serum uric acid.
a Includes events recorded on the Comorbidity Summary Case Report Form using a list of predefined comorbidities.

APPENDIX 2. SERIOUS ADVERSE EVENTS BY SYSTEM ORGAN CLASS AND PREFERRED TERM IN THE PHASE 3 COMBINATION THERAPY STUDIES

Table 41: Incidence of Serious Adverse Events by System Organ Class and Preferred Term in the Pivotal Studies (CLEAR 1, CLEAR 2, and CRYSTAL Pooled)

System Organ Class Preferred Term	PBO + XOI (N=516) n (%)	LESU 200 mg + XOI (N=511) n (%)	LESU 400 mg + XOI (N=510) n (%)
Any adverse event	29 (5.6)	24 (4.7)	44 (8.6)
Infections and infestations	6 (1.2)	4 (0.8)	6 (1.2)
Pneumonia	2 (0.4)	2 (0.4)	1 (0.2)
Bronchopneumonia	0	0	1 (0.2)
Cellulitis	1 (0.2)	0	1 (0.2)
Empyema	0	1 (0.2)	0
Escherichia infection	0	0	1 (0.2)
Influenza	0	1 (0.2)	0
Pyelonephritis chronic	0	0	1 (0.2)
Sinobronchitis	0	1 (0.2)	0
Vulval abscess	0	0	1 (0.2)
Vulval cellulitis	0	0	1 (0.2)
Abscess limb	2 (0.4)	0	0
Appendicitis	1 (0.2)	0	0
Diverticulitis	1 (0.2)	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3 (0.6)	2 (0.4)	5 (1.0)
Basal cell carcinoma	0	0	2 (0.4)
Gastric cancer	0	0	1 (0.2)
Metastatic neoplasm	0	0	1 (0.2)
Ovarian adenoma	0	1 (0.2)	0
Parathyroid tumour benign	0	1 (0.2)	0
Prostate cancer	1 (0.2)	0	1 (0.2)
Lung neoplasm malignant	1 (0.2)	0	0
Pancreatic neuroendocrine tumour	1 (0.2)	0	0
Metabolism and nutrition disorders	0	2 (0.4)	5 (1.0)
Gout	0	0	4 (0.8)
Dehydration	0	1 (0.2)	1 (0.2)
Type 2 diabetes mellitus	0	1 (0.2)	0
Psychiatric disorders	1 (0.2)	1 (0.2)	1 (0.2)
Depression	0	1 (0.2)	0
Dissociative disorder	0	0	1 (0.2)
Suicide attempt	1 (0.2)	0	0
Nervous system disorders	6 (1.2)	0	0
Cerebrovascular accident	2 (0.4)	0	0
Subarachnoid haemorrhage	1 (0.2)	0	0
Transient ischaemic attack	1 (0.2)	0	0
Vascular dementia	1 (0.2)	0	0
Vocal cord paralysis	1 (0.2)	0	0
Ear and labyrinth disorders	1 (0.2)	0	1 (0.2)
Vertigo	1 (0.2)	0	1 (0.2)

Table 41: Incidence of Serious Adverse Events by System Organ Class and Preferred Term in the Pivotal Studies (CLEAR 1, CLEAR 2, and CRYSTAL Pooled)

System Organ Class Preferred Term	PBO + XOI (N=516) n (%)	LESU 200 mg + XOI (N=511) n (%)	LESU 400 mg + XOI (N=510) n (%)
Cardiac disorders	2 (0.4)	10 (2.0)	14 (2.7)
Acute myocardial infarction	0	1 (0.2)	4 (0.8)
Coronary artery disease	0	3 (0.6)	2 (0.4)
Cardiac failure congestive	0	1 (0.2)	3 (0.6)
Myocardial infarction	1 (0.2)	0	3 (0.6)
Angina pectoris	0	1 (0.2)	1 (0.2)
Atrial fibrillation	0	2 (0.4)	0
Atrial flutter	0	0	1 (0.2)
Cardiac arrest	0	1 (0.2)	0
Cardiac failure acute	0	0	1 (0.2)
Intracardiac thrombus	0	0	1 (0.2)
Myocardial ischaemia	0	1 (0.2)	0
Pulseless electrical activity	0	1 (0.2)	0
Arrhythmia	1 (0.2)	0	0
Vascular disorders	0	0	1 (0.2)
Hypertensive crisis	0	0	1 (0.2)
Respiratory, thoracic and mediastinal disorders	1 (0.2)	0	1 (0.2)
Pulmonary oedema	0	0	1 (0.2)
Chronic obstructive pulmonary disease	1 (0.2)	0	0
Gastrointestinal disorders	2 (0.4)	2 (0.4)	2 (0.4)
Duodenal ulcer haemorrhage	1 (0.2)	0	1 (0.2)
Gastritis	0	1 (0.2)	0
Gastrointestinal haemorrhage	0	1 (0.2)	0
Pancreatitis acute	0	0	1 (0.2)
Alcoholic pancreatitis	1 (0.2)	0	0
Hepatobiliary disorders	0	2 (0.4)	1 (0.2)
Cholecystitis acute	0	1 (0.2)	1 (0.2)
Bile duct stone	0	1 (0.2)	0
Musculoskeletal and connective tissue disorders	2 (0.4)	3 (0.6)	4 (0.8)
Osteoarthritis	2 (0.4)	0	2 (0.4)
Arthralgia	0	1 (0.2)	0
Back pain	0	1 (0.2)	0
Flank pain	0	1 (0.2)	0
Intervertebral disc degeneration	0	0	1 (0.2)
Spinal column stenosis	0	0	1 (0.2)
Joint contracture	1 (0.2)	0	0
Renal and urinary disorders	4 (0.8)	0	8 (1.6)
Nephrolithiasis	1 (0.2)	0	2 (0.4)
Renal failure acute	2 (0.4)	0	2 (0.4)
Calculus ureteric	0	0	1 (0.2)
Renal failure	0	0	1 (0.2)
Renal failure chronic	0	0	1 (0.2)
Renal impairment	0	0	1 (0.2)
Stag horn calculus	0	0	1 (0.2)
Urinary retention	1 (0.2)	0	0

Table 41: Incidence of Serious Adverse Events by System Organ Class and Preferred Term in the Pivotal Studies (CLEAR 1, CLEAR 2, and CRYSTAL Pooled)

System Organ Class Preferred Term	PBO + XOI (N=516) n (%)	LESU 200 mg + XOI (N=511) n (%)	LESU 400 mg + XOI (N=510) n (%)
General disorders and administration site conditions	2 (0.4)	2 (0.4)	1 (0.2)
Non-cardiac chest pain	2 (0.4)	2 (0.4)	0
Adverse drug reaction	0	1 (0.2)	0
Systemic inflammatory response syndrome	0	0	1 (0.2)
Injury, poisoning and procedural complications	3 (0.6)	3 (0.6)	1 (0.2)
Coronary artery restenosis	0	0	1 (0.2)
Laceration	0	1 (0.2)	0
Multiple drug overdose	0	1 (0.2)	0
Multiple injuries	0	1 (0.2)	0
Clavicle fracture	1 (0.2)	0	0
Concussion	1 (0.2)	0	0
Facial bones fracture	1 (0.2)	0	0
Femur fracture	1 (0.2)	0	0
Subdural haematoma	1 (0.2)	0	0

Abbreviations: LESU, lesinurad; PBO, placebo; XOI, xanthine oxidase inhibitor (allopurinol/febuxostat).
Note: Adverse events are using MedDRA version 14.0. For each system organ class (SOC) and preferred term (PT), patients are included only once, even if they experienced multiple events in that SOC or PT.

Table 42: Incidence of Serious Adverse Events by System Organ Class and Preferred Term in the Uncontrolled Extension Studies (Studies 306 and 307 Pooled)

System Organ Class Preferred Term	LESU 200 mg + XOI (N=460) n (%)	LESU 400 mg + XOI (N=453) n (%)
Any serious adverse event	32 (7.0)	33 (7.3)
Infections and infestations	8 (1.7)	5 (1.1)
Pneumonia	3 (0.7)	1 (0.2)
Cellulitis	1 (0.2)	1 (0.2)
Diverticulitis	1 (0.2)	0
Gastroenteritis viral	0	1 (0.2)
Osteomyelitis chronic	1 (0.2)	0
Ovarian infection	1 (0.2)	0
Post procedural sepsis	1 (0.2)	0
Pyelonephritis	0	1 (0.2)
Sepsis	1 (0.2)	0
Urosepsis	0	1 (0.2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3 (0.7)	2 (0.4)
Prostate cancer	2 (0.4)	1 (0.2)
Neuroendocrine carcinoma	1 (0.2)	0
Renal cell carcinoma	0	1 (0.2)
Blood and lymphatic system disorders	0	1 (0.2)
Coagulopathy	0	1 (0.2)
Metabolism and nutrition disorders	2 (0.4)	1 (0.2)
Dehydration	1 (0.2)	0
Gout	1 (0.2)	0
Hypovolaemia	0	1 (0.2)
Psychiatric disorders	1 (0.2)	2 (0.4)
Completed suicide	0	1 (0.2)
Delusional disorder, unspecified type	1 (0.2)	0
Depression	0	1 (0.2)
Nervous system disorders	4 (0.9)	6 (1.3)
Cerebrovascular accident	1 (0.2)	1 (0.2)
Subarachnoid haemorrhage	2 (0.4)	0
Syncope	0	2 (0.4)
Transient ischaemic attack	0	2 (0.4)
Carotid artery stenosis	0	1 (0.2)
Cerebral infarction	0	1 (0.2)
Hemiparesis	1 (0.2)	0
Ischaemic stroke	0	1 (0.2)
Migraine	1 (0.2)	0
Cardiac disorders	8 (1.7)	2 (0.4)
Atrial fibrillation	3 (0.7)	0
Acute myocardial infarction	2 (0.4)	0
Cardiac failure congestive	1 (0.2)	1 (0.2)
Angina pectoris	1 (0.2)	0
Angina unstable	1 (0.2)	0
Aortic valve stenosis	0	1 (0.2)
Cardiac failure	1 (0.2)	0
Coronary artery disease	0	1 (0.2)
Ischaemic cardiomyopathy	1 (0.2)	0
Myocarditis	1 (0.2)	0
Vascular disorders	2 (0.4)	3 (0.7)

Table 42: Incidence of Serious Adverse Events by System Organ Class and Preferred Term in the Uncontrolled Extension Studies (Studies 306 and 307 Pooled)

System Organ Class Preferred Term	LESU 200 mg + XOI (N=460) n (%)	LESU 400 mg + XOI (N=453) n (%)
Hypertension	0	2 (0.4)
Aortic aneurysm	0	1 (0.2)
Deep vein thrombosis	1 (0.2)	0
Femoral arterial stenosis	1 (0.2)	0
Hypertensive crisis	0	1 (0.2)
Iliac artery stenosis	1 (0.2)	0
Jugular vein thrombosis	0	1 (0.2)
Respiratory, thoracic and mediastinal disorders	2 (0.4)	2 (0.4)
Pulmonary embolism	0	2 (0.4)
Dyspnoea	1 (0.2)	0
Respiratory failure	1 (0.2)	0
Gastrointestinal disorders	4 (0.9)	4 (0.9)
Diarrhoea	0	1 (0.2)
Diverticular perforation	1 (0.2)	0
Gastrointestinal haemorrhage	1 (0.2)	0
Pancreatitis acute	0	1 (0.2)
Peptic ulcer	0	1 (0.2)
Peritonitis	1 (0.2)	0
Small intestinal obstruction	1 (0.2)	0
Umbilical hernia	0	1 (0.2)
Umbilical hernia, obstructive	1 (0.2)	0
Hepatobiliary disorders	0	2 (0.4)
Cholecystitis acute	0	1 (0.2)
Cholelithiasis	0	1 (0.2)
Skin and subcutaneous tissue disorders	0	1 (0.2)
Skin ulcer	0	1 (0.2)
Musculoskeletal and connective tissue disorders	2 (0.4)	2 (0.4)
Joint destruction	0	1 (0.2)
Knee deformity	1 (0.2)	0
Lumbar spinal stenosis	0	1 (0.2)
Spinal column stenosis	1 (0.2)	0
Renal and urinary disorders	5 (1.1)	10 (2.2)
Renal failure acute	3 (0.7)	8 (1.8)
Calculus ureteric	1 (0.2)	0
Nephrolithiasis	0	1 (0.2)
Nephropathy	0	1 (0.2)
Renal impairment	1 (0.2)	0
Stag horn calculus	0	1 (0.2)
Reproductive system and breast disorders	0	1 (0.2)
Prostatitis	0	1 (0.2)
Injury, poisoning and procedural complications	3 (0.7)	1 (0.2)
Injury	1 (0.2)	0
Spinal fracture	1 (0.2)	0
Tendon rupture	1 (0.2)	0
XIIth nerve injury	0	1 (0.2)

Abbreviations: LESU, lesinurad; XOI, xanthine oxidase inhibitor (allopurinol/febuxostat).
Note: Adverse events that start on or after the first exposure of extension lesinurad are displayed and are coded using MedDRA version 14.0. For each system organ class (SOC) and preferred term (PT), patients are included only once, even if they experienced multiple events with that SOC or PT.

APPENDIX 3. LISTINGS OF ALL POST-RANDOMIZATION DEATHS IN THE LESINURAD CLINICAL STUDY PROGRAM

Table 43: Fatal Adverse Events Occurring After Receipt of Randomized/Assigned Study Medication in the Pivotal Phase 3 Studies (CLEAR 1, CLEAR 2, and CRYSTAL)

Patient ID	Age/Sex	Study Treatment	MedDRA Preferred Term	Study Day[a]	Days Since Last Dose of LESU	CEAC-Adjudicated Category
301-05376-103	48/M	LESU 200 mg + ALLO	Cardiac arrest	233	1	MACE: CV death
304-05064-406	78/M	LESU 200 mg + FBX	Pulseless electrical activity	122	0	MACE: CV death
302-15003-210	58/M	LESU 400 mg + ALLO	Pulmonary oedema	242	59	MACE: CV death
302-17006-207	51/M	LESU 400 mg + ALLO	Gastric cancer	314 (360)	0	Non-CV Event/Death
304-05056-401	71/M	LESU 400 mg + FBX	Cardiac failure congestive	68 (78)	0	MACE: CV death

Abbreviations: ALLO, allopurinol; CEAC, Cardiovascular Events Adjudication Committee; CV, cardiovascular; FBX, febuxostat; LESU, lesinurad; M, male; MACE, major adverse cardiovascular event; MedDRA, Medical Dictionary for Regulatory Activities.
Note: Adverse events are coded using the MedDRA version 14.0.
[a] Study day at start of event, the same as death date unless otherwise noted in parentheses.

Table 44: Fatal Adverse Events Occurring After Receipt of Randomized/Assigned Study Medication in Supportive Studies in the Lesinurad Clinical Study Program

Patient ID	Age/Sex	Study Treatment[a]	MedDRA Preferred Term	Study Day[b]	Days from First/Last Dose of PBO/LESU to Death	CEAC-Adjudicated Category
118-001-009	57/M	LESU 400 mg (one dose)	Completed suicide	Post-study	45/45	N/A
203-0309-005	41/M	LESU 600 mg + ALLO (DB ext) LESU 200 & 400 mg + ALLO (Main)	Cerebral artery embolism	169	168/14	MACE: CV death
306-05395-210	62/M	LESU 200 mg + ALLO (Study 306) PBO + ALLO (CLEAR 2)	Ischaemic cardiomyopathy	386	48/42	MACE: CV death

Table 44: Fatal Adverse Events Occurring After Receipt of Randomized/Assigned Study Medication in Supportive Studies in the Lesinurad Clinical Study Program

Patient ID	Age/Sex	Study Treatment[a]	MedDRA Preferred Term	Study Day[b]	Days from First/Last Dose of PBO/LESU to Death	CEAC-Adjudicated Category
306-05285-104	51/M	LESU 200 mg + ALLO (Study 306) PBO + ALLO (CLEAR 1)	Subarachnoid hemorrhage	636 (649)	289/9	MACE: CV death
306-05185-117	65/M	LESU 200 mg + ALLO (Study 306) LESU 200 mg + ALLO (CLEAR 1)	Coronary artery disease	519	518/1	MACE: CV death
307-05192-411	53/M	LESU 200 mg + FBX (Study 307) LESU 200 mg + FBX (CRYSTAL)	Cerebrovascular accident Subarachnoid haemorrhage	373 373	372/0 372/0	Non-CV Event/Death MACE: CV death
303-05230-308	50/M	LESU 400 mg	Death	199	198/100[c]	MACE: CV death
305-05264-302	62/M	LESU 400 mg (Study 305) PBO (Study 303)	Death	Between Days 377 and 400[d]	Unknown[d]	MACE: CV death
306-05097-115	37/M	LESU 400 mg + ALLO (Study 306) PBO + ALLO (CLEAR 1)	Pulmonary embolism	376	38/9	MACE: CV death
306-03006-203	60/M	LESU 400 mg + ALLO (Study 306) LESU 400 mg + ALLO (CLEAR 2)	Ischaemic stroke	460 (463)	459/3	MACE: CV death
306-05110-113	53/M	LESU 400 mg + ALLO (Study 306) PBO + ALLO (CLEAR 1)	Completed suicide	553	222/0	Non-CV Event/Death
306-10005-216	76/M	LESU 400 mg + ALLO (Study 306) LESU 400 mg + ALLO (CLEAR 2)	Cerebrovascular accident	652 (655)	651/1	MACE: CV death

Abbreviations: ALLO, allopurinol; DB, double-blind; ext, extension; FBX, febuxostat; LESU, lesinurad; M, male; MACE, major adverse cardiovascular event; MedDRA, Medical Dictionary for Regulatory Activities; N/A, not applicable; PBO, placebo.
Note**:** Adverse events are coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 14.0.
[a] Study medication in prior core/pivotal study also provided for patients who completed the corresponding core/pivotal study.
[b] Study day at start of event, the same as death date unless otherwise noted in parentheses.
[c] The last patient contact was on Day 99 when a 40 day supply of randomized study medication was dispensed. The patient was subsequently lost to follow-up.
[d] The last patient contact was on Day 352. A neighbor reported on Day 400 that the patient had died between Day 377 and Day 400.
Note: This table includes data from the ongoing extension studies, Study 306 and Study 307, with data cutoff dates of 15 May 2015 and 12 March 2015, respectively.

APPENDIX 4. ADJUDICATION OF POTENTIAL CARDIOVASCULAR EVENTS

The CEAC, which comprised 3 independent external CV experts, prospectively reviewed and adjudicated AEs in a blinded fashion. The CEAC used standard criteria and prespecified definitions during adjudication to eliminate inherent variation. All deaths and potential CV events (serious and nonserious) identified by Investigators or the CEAC chair from Phase 3 studies and all deaths and serious CV events from Phase 2 were adjudicated and if considered to be CV in cause, were classified into MACE (ie, CV death, nonfatal MI, or nonfatal stroke) and non-MACE CV categories. A list of events that were to be adjudicated by the CEAC, as well as events to be sent to the CEAC Chair to determine whether additional cases should be adjudicated, is provided in Table 45.

Table 45: Potential Cardiovascular Events for Adjudication

Adjudicated by CEAC

- All deaths (Phase 2b and Phase 3)
- SAEs that met the following predefined CV criteria (Phase 2b and Phase 3):
  - Nonfatal myocardial infarction.
  - Nonfatal stroke.
  - Unstable angina requiring urgent coronary revascularization.
  - Cerebral ischemia requiring revascularization (elective and non-elective).
  - Congestive heart failure requiring hospitalization.
  - Arrhythmias not associated with ischemia.
  - Venous and peripheral arterial vascular thrombotic events (eg, pulmonary embolism, deep venous thrombosis, arterial dissection, thrombosis and peripheral arterial ischemia).
  - Transient ischemic attack.
- All AEs (serious and nonserious) identified by Investigators as potential CV events (Phase 3).

Sent to CEAC chair for possible adjudication (excluding events that met the criteria for adjudication)

- AEs in the clinical database coded to the following SMQ terms for CV and cerebrovascular events (Phase 3):
  - Cardiac arrhythmias.
  - Cardiac failure.
  - Cardiomyopathy.
  - Cerebrovascular disorders.
  - Embolic and thrombotic events.
  - Hypertension.
  - Ischaemic heart disease.
  - Pulmonary hypertension.
  - Renovascular disorders.
  - Shock.
  - Torsade de pointes/QT prolongation.
- Line listings of SAEs (Phase 2b and Phase 3)

Abbreviations: AE, adverse event; CEAC, Cardiovascular Endpoints Adjudication Committee; CV, cardiovascular; SAE, serious adverse event; SMQ, Standardised MedDRA Query.
Note: Investigators were asked to make an assessment of resolution of any SAE with or without sequelae. If the SAE was considered resolved with sequelae, then the sequelae were captured as a nonserious AE. For the purposes of CEAC adjudication, both the potential CV SAE and the nonserious potential CV AE sequelae were sent to the CEAC as separate events for adjudication. The CEAC then determined if these were 2 distinct and separate CV events or only 1 event.

APPENDIX 5. LISTINGS OF PATIENTS WITH ADJUDICATED MAJOR ADVERSE CARDIOVASCULAR EVENTS IN THE PHASE 3 COMBINATION THERAPY STUDIES

Table 46: Patients With Adjudicated Major Adverse Cardiovascular Events in the Pivotal Studies (CLEAR 1, CLEAR 2, and CRYSTAL)

Patient ID	Age/ Sex	Study Treatment	Major CV Risk Factors[a]	Baseline eCrCl (mL/min)[b]	Screening sUA (mg/dL)	Last sUA prior to event (mg/dL)	CEAC-Adjudicated Category	MedDRA Preferred Term	Study Day	Days from Last Dose of PBO/ LESU	Rand. Study Med. Action Taken[c]
301-05156-108	60/M	PBO + ALLO	1,2	66.38	6.5	7.2	Non-fatal stroke	Cerebrovascular accident	29	0	2
301-05345-105	65/M	PBO + ALLO	2,3	40.46	7.3	5.9	Non-fatal MI	MI	39	0	2
							Non-fatal stroke	Cerebrovascular accident	44	5	1
304-03016-402	67/M	PBO + FBX	2,4	56.74	8.3	6.0	Non-fatal stroke	Subdural haematoma	78	0	2
301-05111-114	62/M	LESU 200 mg + ALLO	1,2,3	52.31	8.4	7.2	Non-fatal MI	Acute MI	196	0	5
301-05376-103	48/M	LESU 200 mg + ALLO	1,2,3	29.59	8.7	9.0	CV death	Cardiac arrest	233	1	2
304-05064-406	78/M	LESU 200 mg + FBX	1,2	46.98	9.0	2.5	CV death	Pulseless electrical activity	122	0	2
304-16011-406	69/M	LESU 200 mg + FBX	4	49.23	7.6	2.8	Non-fatal MI	Angina pectoris	256	0	1
301-05019-111	45/M	LESU 400 mg + ALLO	3	89.57	6.6	5.0	Non-fatal MI	Acute MI	40	1	5
301-05206-106	73/M	LESU 400 mg + ALLO	2,3	42.83	10.9	9.0	Non-fatal MI	Acute MI	24	4	5
301-05367-107	65/M	LESU 400 mg + ALLO	2,3	52.08	7.1	4.7	Non-fatal MI	Acute MI	61	0	2
302-05125-202	68/M	LESU 400 mg + ALLO	1,2,3	63.03	6.7	6.9	Non-fatal MI	MI	209	33	1
302-05137-209	53/M	LESU 400 mg + ALLO	None	100.57	6.4	3.4	Non-fatal MI	MI	36	0	2
302-15003-210	58/M	LESU 400 mg + ALLO	2	67.62	8.1	5.4	Non-fatal MI	Myocardial infarction	191	8	1
						12.9	CV death	Pulmonary oedema	242	59	1
304-05056-401	71/M	LESU 400 mg + FBX	2,3	51.66	7.8	3.8	CV death	Cardiac failure congestive	68	0	2
304-17002-412	63/M	LESU 400 mg + FBX	2,3	51.44	4.5	2.4	Non-fatal MI	Acute MI	296	0	1

Table 46: Patients With Adjudicated Major Adverse Cardiovascular Events in the Pivotal Studies (CLEAR 1, CLEAR 2, and CRYSTAL)

Patient ID	Age/ Sex	Study Treatment	Major CV Risk Factors[a]	Baseline eCrCl (mL/min)[b]	Screening sUA (mg/dL)	Last sUA prior to event (mg/dL)	CEAC-Adjudicated Category	MedDRA Preferred Term	Study Day	Days from Last Dose of PBO/ LESU	Rand. Study Med. Action Taken[c]

Abbreviations: ALLO, allopurinol; CEAC, Cardiovascular Endpoints Adjudication Committee; CV, cardiovascular; eCrCl, estimated creatinine clearance; FBX, febuxostat; LESU, lesinurad; M, male; MACE, major adverse cardiovascular event; Med, medication; MedDRA, Medical Dictionary for Regulatory Activities; MI, myocardial infarction; Rand, randomizated; sUA, serum uric acid.
[a] Major CV risk factors (from comorbidity case report form) includes 1=diabetes mellitus, 2=hypertension, 3=hypercholesterolemia, 4=current smoking.
[b] Baseline eCrCl is calculated using the highest serum creatinine value recorded ≤ 14 days prior to the first dose of randomized study medication.
[c] Action taken with randomized study medication: 1=None; 2=Drug withdrawn; 5=Dose interrupted.
Note: Creatinine clearance values include local laboratory-reported values that are not in the clinical study database.

Table 47: Patients With Adjudicated Major Adverse Cardiovascular Events in the Uncontrolled Extension Studies (Studies 306 and 307)

Patient ID	Age/ Sex	Study Treatment in Extension (and Pivotal if Different)	Major CV Risk Factors[a]	Baseline eCrCl (mL/min)[b]	Screening sUA (mg/dL)	Last sUA prior to event (mg/dL)	CEAC Category	MedDRA Preferred Term	Study Day[c]	Days from First/Last Dose of LESU[d]	Rand. Study Med. Action Taken[e]
306-04001-205	42/M	LESU 200 mg + ALLO	3	90.89	10.5	7.2	Non-fatal MI	Acute MI	614	613/0	5
306-05395-210	62/M	LESU 200 mg + ALLO (PBO + ALLO)	1,2,3	59.07	7.0	5.7	Non-fatal MI	Acute MI	350	12/6	1
						5.7	CV death	Ischaemic cardiomyopathy	386	48/42	1
307-05192-411	53/M	LESU 200 mg + FBX (LESU 200 mg + FBX)	2	39.05	6.8	2.1	CV death	Subarachnoid haemorrhage	373	372/0	2
306-05097-115	37/M	LESU 400 mg + ALLO (PBO + ALLO)	None	128.0	7.8	8.2	CV death	Pulmonary embolism	376	38/9	2
306-03006-203	60/M	LESU 400 mg + ALLO	1,2,3	91.39	8.6	9.5	CV death	Ischaemic stroke	460	459/3	1
306-05285-104	51/M	LESU 200 mg + ALLO (PBO + ALLO)	4	102.37	10.5	8.6	CV death	Subarachnoid haemorrhage	636	289/9	2
306-10005-216	76/M	LESU 400 mg + ALLO	2	46.49	6.8	5.0	CV death	Cerebrovascular accident	652	651/1	2
306-05079-101	61/M	LESU 400 mg + ALLO PBO + ALLO	2,3,4	70.89	6.6	4.4	Non-fatal stroke	Cerebral infarction	752	420/0	5
306-05395-213	55/M	LESU 400 mg + ALLO (PBO + ALLO)	2	50.89	9.2	11.5	Non-fatal stroke	Transient ischaemic attack	445	106/0	1
306-05185-117	65/M	LESU 200 mg + ALLO	2	84.19	7.0	2.4	CV death	Coronary artery disease	519	518/0	2
307-05276-406	39/M	LESU 400 mg + FBX	3	70.57	9.3	2.7	Non-fatal MI	MI	617	617/0	5

Abbreviations: ALLO, allopurinol; CEAC, Cardiovascular Endpoints Adjudication Committee; CV, cardiovascular; eCrCl, estimated creatinine clearance; FBX, febuxostat; LESU, lesinurad; M, male; MACE, major adverse cardiovascular event; Med, medication; MedDRA, Medical Dictionary for Regulatory Activities; MI, myocardial infarction; Rand, randomized; sUA, serum uric acid.

[a] Major CV risk factors (from comorbidity case report form) includes 1=diabetes mellitus, 2=hypertension, 3=hypercholesterolemia, 4=current smoking.

[b] Baseline eCrCl is calculated using the highest serum creatinine value recorded ≤ 14 days prior to the first dose of lesinurad.

[c] Date of Randomization in pivotal study was used for pivotal or extension patients who received lesinurad in pivotal study; date of first dose in extension study was used for extension patients who received placebo in pivotal study.

[d] Date for first dose of randomized drug was used for patients in pivotal study; date of first dose of the lesinurad was used for patients in extension study.

[e] Action taken with randomized study medication: 1=None; 2=Drug withdrawn; 5=Dose interrupted.

Note: The cutoff date for this table is 30 January 2015. Creatinine clearance values include local laboratory-reported values that are not in the clinical study database.

APPENDIX 6. BRIEF NARRATIVES FOR ALL PATIENTS WITH ADJUDICATED MAJOR ADVERSE CARDIOVASCULAR EVENTS THROUGH 30 JANUARY 2015

MACE Event: CV Death

Patient 301-05376-103, a 48-year-old African American male with a history of heart failure, hypertension, hypercholesterolemia, and diabetes mellitus receiving **lesinurad 200 mg with allopurinol,** experienced a Grade 4 SAE of cardiac arrest on Day 233. During transportation to the emergency room, advanced cardiac life support measures were performed including chest compressions, intubation, defibrillation, and oxygen via automated ventilation. In response to the event, resuscitation was performed, and the patient was treated with epinephrine. Cardiac life support measures were unsuccessful, and the patient died that same day. An autopsy was not performed. The Investigator considered the event of cardiac arrest not related to lesinurad. According to the death certificate, the cardiac arrest was attributed to natural cause and was the immediate cause of death.

Patient 302-15003-210, a 58-year-old Asian male with a history of coronary artery disease, angina pectoris, and hypertension receiving **lesinurad 400 mg with allopurinol,** had a nonserious Grade 1 AE of angina pectoris on Day 155. Treatment with lesinurad and allopurinol was not interrupted at that time, and the patient continued in the study. On Day 159, the AE of angina pectoris was reportedly resolved; however, that same day, the patient was diagnosed with a nonserious Grade 1 AE of left ventricular dysfunction. On Days 173 to 242, the patient received carvedilol 25 mg qd and isosorbide mononitrate 20 mg qd for treatment of angina. On Day 174, treatment with lesinurad and allopurinol was interrupted due to a Grade 1 AE of blood creatinine increased that occurred. On Day 191, the patient experienced a Grade 4 SAE of MI and was hospitalized. It was determined that the patient was not a candidate for coronary artery bypass grafting. The patient was discharged from the hospital on Day 195. The SAE of MI was reportedly resolved that same day. On Days 197 to 242, the patient received furosemide 40 mg qd and 80 mg qd for treatment of hypertension and coronary artery disease. On Day 242, the patient presented to the emergency room with chest pain and difficulty breathing. Vital signs included a gasping respiratory rate, no pulse, no BP, and he was cold to touch. The patient was diagnosed with a Grade 4 SAE of pulmonary oedema. Treatment of the SAE of pulmonary oedema included cardiopulmonary resuscitation, epinephrine 3 mg, atropine 0.5 mg, and intubation, which failed. The outcome of the SAE of pulmonary oedema was death. The cause of death was determined to be cardiorespiratory failure due to pulmonary edema, hypertension, and previous bypass surgery that was 22 years prior. No autopsy was performed. The Investigator considered the event of cardiac failure not related to lesinurad.

Patient 304-05056-401, a 71-year-old White male with a history of congestive heart failure, atrial fibrillation, MI, irregular heartbeat, blood clot in kidney, and bilateral lower extremity edema receiving **lesinurad 400 mg with febuxostat,** was hospitalized on Day 61 after previously experiencing increasing abdominal swelling, lower extremity swelling, a 24-pound weight gain, and dizziness. The patient was diagnosed with a Grade 3 SAE of acute cardiac failure and with a nonserious Grade 2 AE of angina pectoris. Lesinurad treatment was temporarily interrupted from Day 61 to Day 66; no action was taken with febuxostat. The

patient received treatment with morphine 5 mg q3hr prn, glyceryltrinitrate 0.4 mg prn, ocuvite 1 tablet bid, ascriptin 125 mg qd, carvedilol 6.25 bid, dabigatran etexilate mesilate 150 mg bid, heparin 5000 units tid, paracetamol 1300 mg prn, and furosemide 160 mg bid. On Day 66, the patient was discharged from the hospital and the outcome of the SAE of acute cardiac failure was reported as resolved with sequelae. On Day 68, the patient was hospitalized again for a Grade 3 SAE of cardiac failure congestive following mental status changes, edema, weakness, abdominal bloating, leg cramps, malaise, and shortness of breath. That same day, the patient experienced AEs of liver injury and acute prerenal failure. In response to the SAE of cardiac failure congestive and the AEs of liver injury and acute prerenal failure, treatment with randomized study medication was discontinued. On Day 78, the patient died. An autopsy was not performed. The outcome of the AE of angina pectoris was reported as unknown. The Investigator considered the event of cardiac failure congestive not related to lesinurad.

Patient 304-05064-406, a 78-year-old White male with a history of stroke, diabetes mellitus, hypertension, thrombophlebitis, and pulmonary embolism receiving **lesinurad 200 mg with febuxostat,** died of a Grade 4 SAE of pulseless electrical activity on Day 122 after collapsing. The patient was treated with CPR prior to arriving at the hospital by emergency staff. At the hospital, the patient was treated with epinephrine and CPR with no resulting cardiac activity on ultrasound. Prior to the event, the patient reported experiencing dyspnea on exertion that resolved with rest, but no chest pain. Based upon available evidence, the etiology of the death was unclear and the cause of death could include cardiac arrest, cardiac dysrhythmia, head trauma, head bleed, and pulmonary embolism. No autopsy was performed. The Investigator considered the event of pulseless electrical activity unlikely to be related to lesinurad.

Patient 306-05097-115, a 37-year-old White male with a history of morbid obesity receiving **lesinurad 400 mg with allopurinol,** experienced a Grade 4 SAE of cardiac arrest due to pulmonary embolism on Day 39. This patient received placebo with allopurinol in the pivotal study CLEAR 1. Prior to the event, the patient did not feel well and stopped taking lesinurad and allopurinol on Day 30 by his own decision. During transportation to the emergency room, cardiopulmonary resuscitation was performed. At the hospital, the patient was treated with multiple doses of epinephrine (dose and frequency unknown) and vasopressin (dose and frequency unknown). Attempts at resuscitation were unsuccessful, and the patient died that same day. The cause of death was determined to be pulmonary thromboembolism with morbid obesity as a contributory factor. The Investigator considered the event of pulmonary embolism not related to lesinurad.

Patient 306-03006-203, a 60-year-old White male with a history of myocardial ischemia, diabetes mellitus, hypertension, hypercholesterolemia, and laryngeal cancer receiving **lesinurad 400 mg with allopurinol,** was hospitalized on Day 119 and diagnosed with a Grade 4 SAE of ischaemic stroke. This patient received lesinurad 400 mg plus allopurinol in the pivotal study CLEAR 1. Three days prior to the event, the patient did not feel well and stopped taking lesinurad and allopurinol by his own decision. A CT scan performed on Day 120 revealed an extensive ischemic stroke. The patient's condition continued to deteriorate and the patient died on Day 122. The cause of death was determined to be ischemic stroke, circulatory and respiratory failure, and respiratory and cardiac arrest. No autopsy was performed. The Investigator considered the event of ischemic stroke not related to lesinurad.

Patient 306-05395-210, a 62-year-old White male with a history of coronary artery disease and MI receiving **lesinurad 200 mg with allopurinol** was brought to the ER on Day 8 and hospitalized on Day 8 for a Grade 3 SAE of sepsis. This patient received placebo with allopurinol in the pivotal study CLEAR 2. In response to the event of sepsis, lesinurad, allopurinol, and naproxen were withdrawn on Day 7. On Day 13, the patient was transferred to the ICU and intubated. Following a CT scan, chest x-ray, and ECG, the patient was diagnosed with a Grade 3 SAE of acute MI concurrent with a nonserious Grade 3 AE of cardiac failure congestive. A chest x-ray also showed mild cardiomegaly and a nonserious Grade 3 AE of pulmonary oedema with no pneumothorax. Treatment included aggressive diuresis and clopidogrel (dose and frequency unknown), and the events were reported as resolved. On Day 31, the patient was diagnosed with a nonserious Grade 2 AE of cardiomyopathy. On Day 36, an echocardiogram was performed, and the patient was diagnosed with a Grade 4 SAE of ischaemic cardiomyopathy. On Day 49, the patient was found cyanotic, unresponsive and with no pulse, and CPR attempts were discontinued upon confirmation of the patient's DNR order. The outcome of the SAE of acute on ischaemic cardiomyopathy was reported as fatal. The Investigator considered the event of ischaemic cardiomyopathy not related to lesinurad.

Patient 307-05192-411, a 53-year-old African American male with a history of peripheral edema and transient ischemic attack receiving **lesinurad 200 mg with febuxostat** experienced Grade 4 SAEs of cerebrovascular accident and subarachnoid hemorrhage on Day 41. This patient received lesinurad 200 mg in the pivotal study CRYSTAL. Treatment for the events included the following medications with unknown dose and frequency: atropine, bicarbonate, dextrose 50%, and dopamine. The patient was determined to be brain dead and was removed from life support. The outcome of the SAEs was reported to be death on Day 41. No autopsy was performed. The Investigator considered the event of subarachnoid hemorrhage not related to lesinurad.

Patient 303-05230-308, a 50-year-old Puerto Rican male with a history of hypercholesterolemia and hypertriglyceridemia receiving **lesinurad 400 mg** died suddenly of unknown causes on Day 199. The last study visit prior to his death was on Day 99 when a 40-day supply of randomized study medication was dispensed. The patient missed subsequent visits and informed the site that he did not want to continue in the study due to personal reasons. Multiple attempts were made to contact the patient to return for an Early Termination Visit. The site was informed by the patient's emergency work number that the patient had died. An autopsy report and a death certificate were requested from the medical examiner's office, but were not released. Based upon the available evidence, the cause of death is unknown. The Investigator considered the death not related to lesinurad.

Patient 305-05264-302, a 62-year-old White male with a history of atrioventricular block, hypercholesterolemia, and hypertension receiving **lesinurad 400 mg,** presented to the primary care physician's clinic on Day 47 with complaints of several months of left hip pain, and was found to be hypertensive. This patient received placebo in the core study (Study 303). The patient was hospitalized that same day due to a Grade 2 SAE of atrioventricular block complete. On Day 48, a transthoracic echocardiogram revealed mild concentric left ventricular hypertrophy with basal septal hypertrophy, left ventricular ejection fraction of 65-70%, intermittent atrioventricular block, mild-moderate mitral annular calcification, mild thickening of the mitral valve, and trivial stenosis. In response to the SAE of atrioventricular block complete, lesinurad treatment was interrupted on Day 47 and resumed on Day 99, and the patient continued in the

study. On Day 50, the patient was discharged from the hospital in stable condition and was advised to follow-up with a cardiologist. The SAE of atrioventricular block complete was reportedly resolved that same day without sequelae. On Day 400, the site was contacted by the patient's neighbor who reported that on an unknown date in (b) (6) the patient died in his home due to unknown causes. Based upon the available evidence, the cause of death is unknown. Of note, on Day 90, a computed tomography angiography of the heart with 3D image showed evidence of coronary artery disease. On Day 169, electrocardiogram results showed artificial pacemaker with prolonged QTC, which could not be confirmed with the patient's medical history and records. The last phone contact with the patient was on Day 352. The Investigator considered the death unlikely to be related to lesinurad.

Patient 203-0309-005, a 41-year-old White male with a history of avascular necrosis of right and left hip with a total hip replacement hyperlipidemia, hypertension, and obesity receiving **lesinurad 600 mg with allopurinol 200 mg** at the time of the event experienced a Grade 5 SAE of cerebral artery embolism on Day 86 of the blinded extension period and was found dead by his wife. Prior to the SAE of cerebral artery embolism, the patient had received treatment with lesinurad 600 mg from Days 57 through 72 of the extension period. An autopsy was performed. The patient's wife verbally reported that the autopsy result reported the cause of the death as cerebral embolism. The Investigator considered the event of cerebral artery embolism not related to lesinurad.

Patient 306-05185-117 was a 65-year-old White male with a history of MI, heart failure, cardiac murmur, and hypertension. The patient received **lesinurad 200 mg with allopurinol** in the pivotal study CLEAR 1 and in extension Study 306. After the 4MSU data cutoff date on Day 519, the patient was hospitalized for a Grade 4 SAE of worsening coronary artery disease, which led to lesinurad and allopurinol discontinuation. Treatment for the event included furosemide, carvedilol, and rosuvastatin. The patient died on Day 519. The Investigator considered the event of worsening coronary artery disease unlikely to be related to lesinurad.

Patient 306-05285-104 was a 51-year-old White male with a history of hypertension and hyperlipidemia. The patient also reported a family history of cerebral aneurysm. The patient received placebo with allopurinol in the pivotal study CLEAR 1 and **lesinurad 200 mg with allopurinol** in extension Study 306. During the pivotal study, the patient was diagnosed with the nonserious and ongoing Grade 1 events of hypertension on Day 257 and hypertriglyceridemia on Day 285. For these respective ongoing events, the patient was treated with lisinopril and fenofibrate. On Day 636, the patient was hospitalized for a Grade 4 SAE of subarachnoid haemorrhage (289 days after starting lesinurad), leading to discontinuation of lesinurad and allopurinol. The patient was treated with nicardipine hydrochloride for the event. The patient died on Day 649. The death certificate reported a stroke as the immediate cause of death resulting from total occlusion of left internal carotid artery (ICA) due to ICA thrombosis. The Investigator considered the event not related to lesinurad.

Patient 306-10005-216 was a 76-year-old White male with a history of MI, angina pectoris, and hypertension. The patient received **lesinurad 400 mg with allopurinol** in the pivotal study CLEAR 2 and in extension Study 306. On Day 652, the patient was hospitalized for a Grade 4 SAE of cerebrovascular accident, which led to lesinurad discontinuation. The patient died on Day 655. An autopsy revealed the direct cause of death to be cerebral infarction due to

thrombosis of the pre-cerebral arteries. The Investigator considered the event unlikely to be related to lesinurad.

MACE Event: Nonfatal Myocardial Infarction

Patient 301-05111-114, a 62-year-old White male with a history of coronary artery disease, MI, heart failure, peripheral vascular disease, transient ischemic attack, and deep vein thrombosis receiving **lesinurad 200 mg with allopurinol**, was hospitalized on Day 196 due to a Grade 3 SAE of acute MI. An echocardiogram showed severe global hypokinesis of the left ventricle, apical akinesis, and ejection fraction of <25%. In response to the event, the patient was treated with enoxaparin (dose and frequency unknown) and potassium chloride 40 mEq qd. Treatment with lesinurad and allopurinol was interrupted on Day 197 and resumed on Day 199, and the patient continued in the study. The patient was discharged from the hospital on Day 198, and the SAE of acute MI was reportedly resolved that same day without sequelae. The Investigator considered the event not related to lesinurad.

Patient 301-05019-111, a 45-year-old White male with a history of hypercholesterolemia receiving **lesinurad 400 mg with allopurinol**, experienced a Grade 4 SAE of acute MI on Day 40. Coronary angiography revealed an acute inferior MI with total occlusion of the distal right coronary artery and severe hypokinesis of the left coronary artery with ejection fraction estimated at 45-50%. Percutaneous revascularization of the distal right coronary artery was successfully performed using a combination of aspiration thrombectomy and placement of a stent. The patient continued in the study. On Day 41, the patient was discharged from the hospital, and the SAE of acute MI was reportedly resolved that same day without sequelae. The Investigator considered the event not related to lesinurad.

Patient 301-05206-106, a 73-year-old White male with a history of coronary artery disease and angina pectoris receiving **lesinurad 400 mg with allopurinol** was hospitalized on Day 24 due to a Grade 4 SAE of acute MI. Cardiac catheterization revealed multi-vessel coronary artery disease. An ECG performed that same day revealed a Grade 2 nonserious AE of atrial fibrillation. Treatment for the events included angioplasty with stent placement, ceftriaxone 1 g, enoxaparin sodium 100 mg, atorvastatin/amlodipine 10 mg qd, hydrochlorothiazide 25 mg qd, clopidogrel bisulfate 75 mg qd, and dronedarone hydrochloride 400 mg BID. Treatment with lesinurad and allopurinol had been previously interrupted on Day 20 but was restarted on Day 28, 1 day after the patient was discharged from the hospital. The patient continued in the study. The SAE of acute MI was reportedly resolved on Day 27 without sequelae. At the time of this report, the AE of atrial fibrillation was ongoing. The Investigator considered the event of acute MI not related to lesinurad.

Patient 301-05367-107, a 65-year-old White male with a history of coronary artery bypass surgery, hypertension and hypercholesterolemia receiving **lesinurad 400 mg with allopurinol**, was hospitalized on Day 61 due to a Grade 3 SAE of acute MI. The patient underwent cardiac catheterization, which revealed severe left main and 3-vessel coronary artery disease, severe left ventricular dysfunction, and occluded saphenous vein grafts, with ejection fraction estimated at 25%. An infra-aortic balloon pump was implanted for support due to the subtotal occlusion in the bypass graft. Angioplasty successfully treated the severely stenosed saphenous vein and a bare-metal stent resolved the stenosis of the right coronary artery. In response to the event, treatment with lesinurad was withdrawn on Day 61 but allopurinol was not interrupted, and the patient continued in the study. On Day 65, the patient was discharged from the hospital, and the

SAE of acute MI was reportedly resolved that same day without sequelae. On Day 78, the patient completed the early termination visit. The Investigator considered the event of acute MI not related to lesinurad.

Patient 302-05125-202, a 68-year-old White male with a history of type II diabetes mellitus, hypertension, and hypercholesterolemia receiving **lesinurad 400 mg with allopurinol**, was hospitalized on Day 209 after experiencing chest pain for 2 days and nausea. Prior to the event, lesinurad was discontinued due to a nonserious Grade 2 AE of elevated creatinine on Day 169, which resolved without sequelae on Day 269; no action was taken with allopurinol. On Day 209, the patient was diagnosed with a Grade 3 SAE of MI based on symptoms of unstable angina, a subtle ST-segment elevation in the inferior leads of the ECG, and an elevated troponin level. In addition, a left heart catheterization with left ventriculography and coronary angiography performed on Day 210 revealed multi-vessel coronary artery disease with severely stenosed left anterior descending proximal and mid circumflex and right coronary arteries. On Day 212, the patient underwent coronary artery bypass grafting times five. On Day 218, the SAE of MI was reported as resolved without sequelae. On Day 219, the patient was stable and was discharged from the hospital with instructions to follow-up with the cardiac surgeon. At the time of the event, the patient continued in the study. The Investigator considered the event of MI not related to lesinurad.

Patient 302-05137-209, a 53-year-old White male receiving **lesinurad 400 mg with allopurinol**, was hospitalized on Day 36 after collapsing at the gym and subsequently being treated with CPR by emergency staff. The emergency staff found the patient in cardiac arrest, pulseless, and with cardiac rhythm in ventricular fibrillation. The patient was diagnosed with a Grade 4 SAE of MI after cardiac catheterization revealed a totally occluded left anterior descending (LAD) artery with anterior wall and apical akinesis and an estimated ejection fraction of 35%. The patient was also diagnosed with a Grade 2 AE of ventricular fibrillation, which resolved without sequelae the same day. Treatment of the SAE of MI included placement of an intra-aortic balloon pump during cardiac catheterization, a successful angioplasty of the LAD artery, and placement of 2 drug-eluting stents in the mid and distal LAD. In response to the SAE of MI, lesinurad was discontinued on Day 36 and the patient was withdrawn from the study on Day 48. Allopurinol and colchicine were interrupted on Day 36 and restarted on Day 38. The SAE of MI resolved on Day 39 without sequelae and the patient was discharged from the hospital in stable condition. The Investigator considered the event of MI not related to lesinurad.

Patient 304-16011-406, a 69-year-old White male with a history of MI receiving **lesinurad 200 mg with febuxostat**, reportedly experienced a Grade 2 AE of angina pectoris on Day 256 that was treated with glyceryl triniate and acetylsalicylic acid. The AE was reported to have resolved without sequelae 1 day later. On Day 313, the patient was hospitalized after presenting with angina pectoris, which was subsequently diagnosed as a Grade 3 SAE of coronary artery disease following cardiac catheterization. The catheterization revealed severe right coronary artery disease that was distal to a stent placed over 10 years prior and proximal to 30% in stent-restenosis. Treatment included a coronary angiogram and percutaneous transluminal coronary angioplasty for insertion of cardiac stent (promus drug eluting stent); stenosis post deployment was noted to be 0%. Randomized study medication, febuxostat, and indomethacin were discontinued 1 day prior to the event (Day 312), but the patient continued in the study. On Day 315, the patient was discharged from the hospital later and the outcome of the SAE of

coronary artery disease was reported as resolved. The Investigator considered the event of angina pectoris not related to lesinurad.

Patient 304-17002-412, a 63-year-old native Hawaiian or other Pacific Islander male with a history of transient ischemic attack, hypertension, hypercholesterolemia and hypertriglyceridemia receiving **lesinurad 400 mg with febuxostat**, was hospitalized on Day 296 due to chest pain subsequently diagnosed as a Grade 4 SAE of acute MI. On Day 306, a left heart catheterization was performed and revealed significant coronary artery disease, proximal right coronary artery (RCA) 60% stenosis, and circumflex obtuse marginal with 50% stenosis. Treatment included aspirin 100 mg orally qd, atorvastatin 40 mg orally qd, and clopidogrel 75 mg orally qd. In response to this event, treatment with lesinurad and febuxostat was not interrupted, and the patient continued in the study. On Day 310, the patient was discharged from the hospital with recommendation for medical management and a further outpatient cardiac MRI scan to rule out myocarditis. The SAE of acute MI was reported as resolved without sequelae on Day 310. The Investigator considered the event of acute MI not related to lesinurad.

Patient 306-04001-205, a 42-year-old Asian male with a history of hypercholesterolemia receiving **lesinurad 200 mg with allopurinol**, was hospitalized on Day 278 and diagnosed with a Grade 3 SAE of acute MI. This patient received lesinurad 200 mg in the pivotal study CLEAR 2. Treatment for this event included angioplasty with stent placement. Treatment with lesinurad and allopurinol was interrupted Day 278, and the patient continued in the study without restarting lesinurad or allopurinol. On Day 283, the patient was discharged from the hospital, and the SAE of acute MI was reportedly resolved. On Day 329, the patient was hospitalized and diagnosed with a Grade 3 SAE of angina unstable. Treatment for this event included aspirin (dose and frequency unknown), enoxaparin 0.3 mL bid, and glyceryl trinitrate 0.4 mg prn. On Day 333, the patient was discharged from the hospital, and the SAE of angina unstable was reportedly resolved and the patient continued in the study. On Day 334, the patient experienced a nonserious Grade 1 AE of angina pectoris with worsening chest pain and was diagnosed with a nonserious Grade 2 AE of angina unstable on Day 362. On Day 364, the patient was hospitalized and diagnosed with a Grade 2 SAE of angina unstable. On Day 367, the patient was discharged from the hospital and the patient continued in the study, and the SAE of angina unstable was reportedly resolved and the patient continued in the study. The Investigator considered the event of acute MI not related lesinurad.

Patient 305-05047-304, a 52-year-old White male receiving **lesinurad 400 mg,** began experiencing waxing and waning chest pain on Day 117. On the morning of Day 120, the patient experienced tightness in the chest and shortness of breath and was hospitalized for a Grade 4 SAE of MI. Coronary angiography showed single vessel disease with a total occlusion of the mid LAD that was successfully recanalized with a combination of catheter aspiration thrombectomy and placement of a single drug-eluting stent with restoration of normal blood flow. Lesinurad was interrupted on Day 120 due to a nonserious AE of blood creatinine increased that started on Day 113 and restarted on Day 144. On Day 122, the patient was discharged from the hospital and the SAE of MI was reportedly resolved without sequelae. The Investigator considered the event of MI not related to lesinurad.

Patient 307-05276-406 was a 39-year-old White male with a history of hyperlipidemia. The patient received **lesinurad 400 mg with febuxostat** in the pivotal study CRYSTAL and in extension Study 307. After the 4MSU data cutoff date on Day 617, the patient was hospitalized

for a Grade 4 SAE of MI. As a result of the event, an emergency angioplasty with stent placement from origin to distal IOM, and origin to mid-D2 was performed. Treatment for the event also included metoprolol, acetylsalicylic acid, prasugrel hydrochloride, amlodipine, and nitro patch. Treatment with lesinurad and febuxostat was interrupted and restarted on Day 636 and Day 660, respectively. The event resolved on Day 618 and the patient continued in the study. The following day, the patient was discharged from the hospital. The Investigator considered the event of MI unlikely to be related to be lesinurad.

Patient 203-0536-004 was a 49-year-old White male with no known CV risk factors who received **lesinurad 600 mg with allopurinol** in the main, double-blind extension, and open-label extension periods. On Day 1328, the patient was hospitalized for a Grade 3 SAE of MI and diagnosed with moderate coronary artery disease. On Day 1329, the patient underwent a left heart catheterization, which revealed 95% mid left anterior descending (LAD) artery thrombotic stenosis in proximal to mid vessel with atherosclerotic change. A small thrombus was aspirated and angiographic improvement was seen. Two boluses of eptifibatide were administered and a drug eluting stent was placed in the mid-LAD artery. Treatment for the event also included losartan, amlodipine, atorvastatin calcium, carvedilol, clopidogrel, and nitroglycerin. In response to the event, lesinurad and allopurinol were discontinued on Day 1328. The patient was discharged from the hospital on Day 1330 and the event was reported as resolved. On Day 1366, the patient was withdrawn from the study. The Investigator considered the MI not related to lesinurad.

Patient 203-0401-121 was a 57-year-old White male with a history of hypertension and diabetes mellitus who received **lesinurad 600 mg with allopurinol** in the main, double-blind extension, and open-label extension periods. The patient experienced an SAE before the 4MSU data cutoff date of (b) (6), which was previously recorded as acute coronary syndrome. Updated medical records were received after the 4MSU data cutoff date, and the information in this brief narrative describing the date of the SAE, preferred term for SAE, and action taken due to the SAE is based on these updates. On Day 1373 after the 4MSU data cutoff date, the patient was reported to have been hospitalized for a non-fatal Grade 3 SAE of MI. The patient was transferred to another hospital where he received 2 drug-eluting stents in his left anterior descending artery. On Day 1374, he had a staged percutaneous coronary intervention with 1 drug-eluting stent in his right coronary artery. On Day 1375, he was transferred back to the first hospital and admitted. An ECG showed sinus rhythm, first degree AV block, left axis deviation, anteroseptal infarction with unknown duration, and T-wave changes in the lateral leads, which may have been ischemic prolonged QT interval. On Day 1377, the event of MI was reported as resolved, the patient was discharged from the hospital. Treatment for the event of MI included perindopril, clopidogrel, bisoprolol, atorvastatin, acetyl salicylic acid, and nitroglycerin spray. Treatment with lesinurad and allopurinol was not interrupted and the patient continued in the study. On Day 1395, the patient experienced a Grade 1 AE of ECG T-wave inversion. On Day 1401, a follow-up ECG was again abnormal with inverted T waves. The Investigator considered the MI not related to lesinurad.

MACE Event: Nonfatal Stroke

Patient 301-05156-108, a 60-year-old Native Hawaiian or Other Pacific Islander male with a history of diabetes mellitus and hypertension receiving **placebo with allpurinol** was hospitalized on Day 29 due to a Grade 4 SAE of stroke. Treatment with placebo and allopurinol was

withdrawn on Day 29; however, the patient continued treatment with allopurinol. The patient continued in the study. On Day 31, the patient was discharged from the hospital, and the SAE of stroke was reportedly resolved that same day without sequelae. On Day 62, the patient withdrew consent due to the event.

Patient 301-05345-105, a 65-year-old White male with a history of hypercholesterolemia, hypertriglyceridemia, and hypertension receiving **placebo with allopurinol**, was hospitalized on Day 39 due to a Grade 4 SAE of MI. On Day 39, treatment with lesinurad was withdrawn and allopurinol was interrupted, and the patient continued in the study. Treatment with allopurinol was resumed on an unknown date. On Day 40, the patient underwent cardiac catheterization, which revealed a left ventricular ejection fraction visually estimated at 60%. On Day 43, the SAE of MI was reportedly resolved without sequelae. That same day the patient was diagnosed with a Grade 3 nonserious AE of coronary artery disease and underwent a 4-vessel coronary artery bypass graft. The patient continued in the study. The AE of coronary artery disease was reportedly ongoing at the time of reporting. On Day 44, the patient experienced a Grade 4 SAE of cerebrovascular accident that extended the hospitalization but was reportedly resolved that same day with sequelae. The patient continued in the study. The patient was discharged from the hospital to a convalescent hospital on Day 58, then moved to an inpatient rehabilitation center on Day 108, and eventually discharged home on Day 124. The patient completed the early termination visit on Day 176.

Patient 304-03016-402, a 67 year old White male with a history of peripheral vascular disease receiving **placebo with febuxostat**, was hospitalized on Day 78 after presenting with slow slurred speech, progressive deterioration of his general condition, and right upper and lower extremity weakness lasting a few days. The patient was diagnosed with a Grade 4 SAE of subdural haemotoma after emergency CT scan revealed a left-sided subdural haematoma confirmed to be life-threatening. On Day 80, the haematoma was surgically removed by double burr hole trepanation. As a result of the event, colchicine, placebo, and febuxostat were discontinued on Day 78, and the patient was withdrawn from the study. On Day 87, the patient was stable and discharged from the hospital and the outcome of the SAE of subdural haematoma was reported as resolved with sequelae of hemiparesis and aphasia.

Patient 306-05079-101 was a 61-year-old White male with a history of coronary artery disease, pulmonary hypertension, deep vein thrombosis, hypertension, hypercholesterolemia, and hyperlipidemia. The patient received placebo with allopurinol in the pivotal study CLEAR 1 and **lesinurad 400 mg with allopurinol** in extension Study 306. Prior to the current reporting period for this 4MSU on Day 752 (420 days after starting lesinurad), the patient was hospitalized for a Grade 4 SAE of cerebral infarction, which led to interruption of treatment with lesinurad. Treatment for the event included clopidogrel bisulfate and warfarin. During hospitalization on Day 754, the patient was diagnosed with a Grade 3 AE of carotid artery stenosis. A right carotid artery endarterectomy was planned. The event of cerebral infarction resolved on Day 760 and the patient was discharged from the hospital. The events of cerebral infarction and carotid artery stenosis were considered not related to lesinurad. The Investigator considered the events of cerebral infarction and carotid artery stenosis not related to lesinurad. The events of cerebral infarction and carotid artery stenosis were adjudicated during the current reporting period as a non-fatal stroke (MACE) and non-cardiovascular event, respectively.

Patient 306-05395-213 was a 55-year-old White male with a history of heart failure and hypertension. The patient received placebo with allopurinol in the pivotal study CLEAR 2 and **lesinurad 400 mg with allopurinol** in extension Study 306. On Day 445 (106 days after starting lesinurad), the patient was hospitalized with a Grade 3 SAE of transient ischaemic attack and a nonserious Grade 2 AE of cardiac failure congestive. Treatment for these events included a heparin infusion, apixaban, acetylsalicylic acid, digoxin, atorvastatin, lisinopril, carvedilol, and bumetanide. Treatment with lesinurad and allopurinol was not interrupted, and the patient continued in the study. On Day 447, the event of transient ischaemic attack was reported as resolved. The event of cardiac failure congestive had not resolved at the time of reporting. The events of transient ischaemic attack and cardiac failure congestive were considered by the Investigator not related to lesinurad and were adjudicated by the CEAC as non-fatal stroke (MACE) and congestive heart failure with hospitalization (non-MACE), respectively.

APPENDIX 7. DEFINITIONS OF RENAL-RELATED AND KIDNEY STONE ADVERSE EVENTS

Custom list of renal-related preferred terms:

- Acute prerenal failure
- Anuria
- Azotaemia
- Blood creatinine abnormal
- Blood creatinine increased
- Blood urea abnormal
- Blood urea increased
- Blood urea nitrogen/creatinine ratio increased
- Creatinine renal clearance abnormal
- Creatinine renal clearance decreased
- Cystatin C abnormal
- Cystatin C increased
- Glomerular filtration rate abnormal
- Glomerular filtration rate decreased
- Hypercreatininaemia
- Inulin renal clearance abnormal
- Inulin renal clearance decreased
- Nephropathy
- Nephropathy toxic
- Obstructive uropathy
- Oliguria
- Postrenal failure
- Renal cortical necrosis
- Renal failure
- Renal failure acute
- Renal failure chronic
- Renal function test abnormal
- Renal impairment
- Renal injury
- Renal papillary necrosis
- Renal tubular atrophy
- Renal tubular disorder
- Renal tubular necrosis
- Urate nephropathy
- Urea renal clearance decreased
- Urine output decreased

Custom list of kidney stone preferred terms:

- Calculus bladder
- Calculus ureteric
- Calculus urethral
- Calculus urinary
- Nephrolithiasis
- Renal stone removal
- Stag horn calculus
- Ureteric calculus removal
- Ureterolithotomy
- Urinary calculus removal
- Urinary stone analysis

APPENDIX 8. LISTINGS OF PATIENTS WITH SERIOUS RENAL-RELATED ADVERSE EVENTS IN THE PHASE 3 COMBINATION THERAPY STUDIES

Table 48: Patients With Serious Renal-Related Adverse Events in the Pivotal Studies (CLEAR 1, CLEAR 2, and CRYSTAL)

Patient Number	Age/ Sex	Study Treatment	Baseline eCrCl (mL/min)[a]	Lowest eCrCl (mL/min)	Final eCrCl (mL/min)	Screening sUA (md/dL)	Last sUA prior to event (mg/dL)	MedDRA Preferred Term	Study Day at Onset	Out-come[b]	Rand. Study Med. Action Taken[c]	Contri-buting Factors[d]
302-05349-204	70/M	PBO + ALLO	54.74	32.22	33.44	7.1	7.0	Renal failure acute	17	1	5	Dehydra-tion, CKD
304-05164-405	54/M	PBO + FBX	45.54	44.61	63.36	10.3	6.3	Renal failure acute	128	1	1	CKD
301-05115-108	47/M	LESU 400 mg + ALLO	99.25	47.68	90.90	6.8	8.2	Renal failure	9	1	2	Bladder outlet obstruction
302-15003-210	58/M	LESU 400 mg + ALLO	67.62	20.56	21.02	8.1	13.4	Renal impairment	211	3	1	MI, CKD
302-15010-216	43/M	LESU 400 mg + ALLO	104.68	92.64	116.31	9.1	3.2	Renal failure acute	203	3	2	Gout flare, NSAID
304-03016-406	70/M	LESU 400 mg + FBX	33.58	26.60	33.39	9.8	4.5	Renal failure chronic	65	3	1	NA
304-05151-401	43/M	LESU 400 mg + FBX	96.92	29.80	89.94	10.3	3.3	Renal failure acute	255	3	1	None

Abbreviations: ALLO, allopurinol; CKD, chronic kidney disease; eCrCl, estimated creatinine clearance; FBX, febuxostat; LESU, lesinurad; M, male; Med, medication; MedDRA, Medical Dictionary for Regulatory Activities; MI, myocardial infarction; NA, not available; NSAID, nonsteroidal anti-inflammatory drug; Rand, randomized; sUA, serum uric acid.
[a] Baseline eCrCl is calculated using the highest sCr value recorded ≤ 14 days prior to the first dose of randomized study medication.
[b] Outcome: 1=Recovered; 2=Not recovered; 3=Recovered with sequelae; 4=Fatal; 5=Unknown.
[c] Action taken with randomized study medication: 1=None; 2=Drug withdrawn; 5=Dose interrupted.
[d] Factors for which the likelihood of having contributed to the renal event was rated moderate or high by the Renal Events Adjudication Committee.
Note: Adverse events are coded using MedDRA version 14.0. Creatinine clearance values include local laboratory-reported values that are not in the clinical study database.

Table 49: Patients With Serious Renal-Related Adverse Events in the Uncontrolled Extension Studies (Studies 306 and 307)

Patient Number	Age/ Sex	Study Treatment in Extension (and pivotal if different)	Baseline eCrCl (mL/min)[a]	Lowest eCrCl (mL/min)	Final eCrCl (mL/min)	Screening sUA (md/dL)	Last sUA prior to event (mg/dL)	MedDRA Preferred Term	Study Day at Onset	Days from First/Last Dose of LESU	Out-come[b]	Rand. Study Med. Action Taken[c]	Contributing Factors[d]
306-05095-109	46/M	LESU 200 mg + ALLO	54.22	10.77	15.73	7.0	4.9	Renal failure acute	561	560/0	2	2	CKD, Diabetes mellitus
306-05074-219	54/M	LESU 200 mg + ALLO	41.19	23.79	37.56	6.6	5.3	Renal failure acute	623	622/0	1	5	CKD
306-08001-204	62/M	LESU 200 mg + ALLO	32.03	28.50	28.50	7.8	5.7	Renal failure acute	391	390/9	1	1	Myocarditis, congestive heart failure, arrhythmia; CKD
307-17002-408	34/M	LESU 200 mg + FBX	51.20	29.07	29.07	11.6	7.6	Renal impairment	400	399/0	2	2	CKD
306-05097-106	40/M	LESU 400 mg + ALLO	90.21	29.25	81.80	8.4	7.3	Renal failure acute	401	400/0	3	2	None
306-05185-108	38/F	LESU 400 mg + ALLO	48.79	23.28	38.80	8.1	3.7	Nephropathy	551	550/0	1	5	NA
							3.7	Renal failure acute	551	550/0	3	5	Infection, CKD, Other
306-05207-119	73/M	LESU 400 mg + ALLO (PBO + ALLO)	52.24	35.00	35.00	10.5	7.2	Renal failure acute	599	261/0	1	5	Infection, CKD, Other
306-05306-110	56/M	LESU 400 mg + ALLO (PBO + ALLO)	79.74	61.75	84.39	7.9	7.0	Renal failure acute	499	162/0	1	2	Gout flare
306-05421-201	50/F	LESU 400 mg + ALLO (PBO + ALLO)	42.22	11.45	47.61	9.3	15.4	Renal failure acute	527	201/2	1	5	Dehydration, CKD
306-15015-210	63/M	LESU 400 mg + ALLO (PBO + ALLO)	49.37	19.09	51.7	9.1	8.6	Renal failure acute	465	119/4	1	2	CKD, NSAID
307-05285-413	49/M	LESU 400 mg + FBX	89.44	39.42	92.1	9.0	1.5	Renal failure acute	549	548/1	1	5	Dehydration, NSAID
307-05287-413	42/M	LESU 400 mg + FBX (PBO + FBX)	105.06	41.62	95.76	12.0	9.9	Renal failure acute	378	34/1	1	2	None

Abbreviations: ALLO, allopurinol; CKD, chronic kidney disease; eCrCl, estimated creatinine clearance; F, female; FBX, febuxostat; LESU, lesinurad; M, male; Med, medication; MedDRA, Medical Dictionary for Regulatory Activities; NA, not available; NSAID, nonsteroidal anti-inflammatory drug; Rand, randomization; sUA, serum uric acid.

[a] Baseline eCrCl is calculated using the highest sCr value recorded ≤ 14 days prior to the first dose of randomized study medication.

[b] Outcome: 1=Recovered; 2=Not recovered; 3=Recovered with sequelae; 4=Fatal; 5=Unknown.

[c] Action taken with randomized study medication: 1=None; 2=Drug withdrawn; 5=Dose interrupted.

[d] Factors for which the likelihood of having contributed to the renal event was rated moderate or high by the Renal Events Adjudication Committee.

Note: Cutoff date 30 January 2015. Adverse events are coded using MedDRA version 14.0. Creatinine clearance values include local laboratory-reported values that are not in the clinical study database.

APPENDIX 9. BRIEF NARRATIVES FOR PATIENTS WITH RENAL-RELATED SERIOUS ADVERSE EVENTS IN THE PHASE 3 COMBINATION THERAPY STUDIES AS OF 30 JANUARY 2015

Renal-Related SAEs During the Pivotal Studies

Patient 301-05098-116 was a 48-year-old White male who was enrolled in CLEAR 1, but **had not been randomized** to blinded study medication at the time of the renal SAE. His relevant medical history included gastroesophageal reflux disease, obesity, hypertension, cholelithiasis, current smoker, and gout. On Day -14, the patient presented to the emergency room with severe diarrhea, nausea and vomiting, and dehydration. The patient complained of a 3-day history of watery diarrhea and crampy abdominal pain and stated that he had not had anything to eat or drink for 3 days. The patient was diagnosed as having AKI secondary to dehydration due to gastroenteritis. He was placed in the intensive care unit for severe hypotension. On Day -10, the patient was discharged from the hospital with all symptoms resolved. At the time of discharge the laboratory results of WBC, BUN, sCr, sodium, and chloride were within normal ranges; glucose remained elevated. Treatment for the events included ciprofloxacin, metronidazole (Flagyl), multiple boluses of fluids, lisinopril, and dopamine. In response to the event, no action was taken with the blinded therapy since it was never initiated and no action was taken with allopurinol or prophylaxis medication. The Investigator considered the event not related to study drug. The Sponsor considered the event as unexpected and not applicable to study drug. In the opinion of the REAC, the contributing AEs resulting in AKI were highly related to dehydration and consistent with a diagnosis of pre-renal azotemia.

Patient 302-05349-204 was a 70-year-old Black male who was enrolled in CLEAR 2 and randomized to **placebo with allopurinol**. His relevant medical history included chronic renal disease, chronic umbilical hernia, hypertension, angina pectoris, MI, cardiac by-pass surgery in 2000, hypercholesterolemia, degenerative joint disease, joint pain, and gout. (Of note, prior to study enrollment the patient had elevated sCr results of 1.50 mg/dL [Oct 2010], 1.60 mg/dL [Apr 2007], and 1.70 mg/dL [Jul 2005]). The Baseline sCr was 1.40 mg/dL. On Day 14, the patient was admitted to hospital telemetry unit with left upper quadrant abdominal pain of unknown cause, AKI, severe dehydration, worsening hypertension, and elevated troponin. Abnormal laboratory test results included sCr 2.52 mg/dL, BUN 29 mg/dL, troponin T 0.026 ng/mL, and creatinine kinase (CK) 179 IU/L. On Day 16 the SAE acute on chronic renal failure was reported as resolved and the patient was discharged from the hospital. The Investigator considered the event not related to the investigational drug. The Sponsor considered the event possibly related to randomized study medication (placebo).

Patient 304-05164-405 was a 54-year-old White male who was enrolled in CRYSTAL and randomized to **placebo with febuxostat**. He had a relevant medical and surgical history of chronic renal insufficiency, and hypertension, with a sCr 1.92 mg/dL at Baseline. On Day 127 the patient developed AKI and was hospitalized. The patient presented to the hospital with lightheadedness for 10 days and diarrhea 2-3 times per day. Upon admission the patient's BP was 135/69 mm Hg, sCr was 2.61 mg/dL, GFR 26 mL/min. The patient was found to have dehydration and orthostatic hypotension. No action was taken with study medication. The patient was treated with fluids and potassium chloride/sodium chloride. Lisinopril and

hydrochlorothiazide were stopped temporarily and amlodipine besylate (Norvasc) was started. On Day 129, the patient was discharged from the hospital with creatinine of 1.30 mg/dL. The Investigator considered the event unlikely to be related to placebo. The Sponsor considered the event as possibly related to placebo.

Patient 301-05115-108 was a 47-year-old White male who was enrolled in CLEAR 1 and randomized to **lesinurad 400 mg with allopurinol 300 mg**. The patient had a past medical history of lithium overdose; renal failure related to lithium, urinary retention, hypertension, bipolar disorder, hypercholesterolemia, and benign prostatic hyperplasia and had a Baseline sCr of 0.98 mg/dL. Relevant concomitant medications included aspirin, divalproex sodium (Depakote), doxepin, fluoxetine, propranolol, ziprasidone, lisinopril, doxazosin mesilate (Cardura), and ezetimibe/simvastatin (Inegy). He was admitted to the hospital on Day 8 with complaints of lethargy, back pain, and other non-specific symptoms and was diagnosed with renal failure with a sCr of 13.78 mg/dL. He was admitted for treatment of volume depletion. The patient had initiated divalproex sodium (a protocol prohibited/ exclusionary concomitant medication) for bipolar disorder a couple of days prior to the hospitalization. At the time of hospital admission, his creatine kinase was as high as 266 and CKMB as high as 13.46; troponin was unremarkable. The patient was seen in consultation by a urologist who considered the underlying causes to include "long-standing" bladder outlet obstruction with urinary retention (presumably multifactorial, with a possible contribution of the antihypertensive medication, investigational product, and urinary tract infection [UTI]). He was treated for back pain possibly from urinary obstruction and myalgia, and a UTI that was found on Day 16. The outcome of the renal failure was reported as recovered and he was discharged from the hospital on Day 18. The patient was withdrawn from the study on Day 21. The sCr subsequently resolved to 1.07 mg/dL on Day 50. The SAE of acute renal failure was considered possibly related to lesinurad by the Sponsor but not by the Investigator. The REAC considered the combination of bladder outlet obstruction and UTI to be potential contributing factors along with hypertension, ACE inhibitor, and colchicine.

Patient 302-15003-210 was a 58-year-old Asian male who was enrolled in CLEAR 2 and randomized to **lesinurad 400 mg with allopurinol 300 mg**. The patient's past medical history was significant for angina pectoris, coronary artery disease, hypertension, and prior tobacco use; the baseline sCr was 1.11 mg/dL. On Day 156, the patient was hospitalized for an SAE of coronary artery disease, diagnosed with inoperable triple vessel disease, and discharged on Day 160. On Day 183 lesinurad was discontinued due an AE of raised sCr of 1.97 mg/dL on Day 177. The patient was re-hospitalized with an MI on Day 191. Hospital course included radiographic contrast use for angiograms and the patient was discharged on Day 195. From Day 211-216, an SAE of renal impairment was reported, followed by an AE renal impairment from Day 217. His sCr had reached a maximum of 3.65 mg/dL on Day 207. The treating nephrologist reported that renal impairment during the hospitalization from Day 211-216 was due to right-sided renal artery stenosis, hypertension, ischemic heart disease, and dilated left ventricle and left ventricular dysfunction with low ejection fraction (30%) in addition to a possible relation to study medication. Administration of radiographic contrast for 2 coronary angiograms may have been a risk factor for renal impairment. The patient was discharge from the hospital on Day 216. At a follow up visit on Day 225, sCr was 3.57 mg/dL. On Day 242, the patient experienced chest pain and difficulty breathing and presented to the ER during which time he experienced a cardio-respiratory arrest. Attempts at resuscitation failed and the patient

died as a result of pulmonary edema on Day 242. An autopsy was not done. The death certificate listed the immediate cause of death as cardiorespiratory failure due to pulmonary edema, hypertension, and previous bypass surgery 22 years ago. The SAE of renal impairment was considered possibly related to lesinurad by the Sponsor and the Investigator, and not related to allopurinol or colchicine. The REAC considered the MI to be a potential contributing factor (also hypertension, CKD, and colchicine use). The REAC Chair's comments on the SAE stated that the major AE was an acute MI and that the decline in renal function (judged by comparing the eGFR vs. days of observation) proceeded in a linear fashion (R2 = 0.9025) and most likely was related to underlying, intrinsic renal disease accentuated by the severe ischemic heart disease. The REAC commented that there was no evidence that blinded study medication influenced the decline in renal function.

Patient 302-15010-216 was a 43-year-old White male who was enrolled in the pivotal study CLEAR 2 and randomized to **lesinurad 400 mg with allopurinol 300 mg**. The patient's past medical history was significant for hypercholesterolemia and he had a baseline sCr of 1.00 mg/dL. On Day 203, the patient was hospitalized for the SAE of AKI. The highest value of sCr reported during the hospitalization was 3.6 mg/dL. Nephrology consultation notes reported that the patient had been taking "more than 4-6 tablets" of diclofenac daily for gout. Workup for other causes of renal failure was negative. On Day 206 the outcome of the SAE was reported as resolved with sequelae (nonserious Grade 2 AE of renal failure) with sCr of 1.39 mg/dL. The patient was discharged from the hospital on the same day. In response to the SAE of renal failure acute and the AE of renal failure starting Day 206, lesinurad and allopurinol were discontinued on Day 202, and the patient withdrawn from the study on Day 208. At the end-of-study visit (Day 208), laboratory testing showed the sCr to be 1.13 mg/dL. The SAE of acute renal failure was considered possibly related to lesinurad by both the Investigator and the Sponsor. The REAC determined that the AE of gout flare and the use of NSAID medication were moderate contributing factors.

Patient 304-03016-406 was a 70-year-old White male who was enrolled in CRYSTAL and randomized to **lesinurad 400 mg with febuxostat 80 mg**. The patient's past medical history was significant for hypertension, tophi at Screening, a 40 mm cyst in the right kidney, and former tobacco use with a baseline sCr of 1.83 mg/dL. On Day 65, the patient was hospitalized for pre-planned diagnostic testing for an SAE of CKD (RCTC Grade 2), which was initially noted at Screening and determined to be chronic after having persisted for 3 months while the patient was on study. Investigations confirmed a renal cyst in the right kidney and on Day 73 the patient was discharged with the SAE resolved with sequelae of CKD. Following increases in sCr on Day 172 to 1.80 mg/dL and on Day 203 to 2.31 mg/dL, lesinurad treatment was interrupted from Day 214 to Day 234 and then withdrawn permanently on Day 255. The patient completed the study and on Day 336, at the Month 12 Visit and 131 days after withdrawal of lesinurad, the patient's sCr was 1.66 mg/dL. In the Investigator's opinion, the SAE of CKD was considered unlikely to be related to lesinurad or febuxostat. The Sponsor considered the event CKD to be not related to lesinurad or febuxostat. The REAC felt that the change in the values for sCr and GFR noted during the course of the study were most closely associated with the underlying stage 3 CKD rather than ongoing drug therapy.

Patient 304-05151-401 was a 43-year-old White male who was enrolled in CRYSTAL and randomized to **lesinurad 400 mg with febuxostat 80 mg**. The patients' past medical history was significant for coronary artery disease, ischemic cardiomyopathy, MI, cardiac stent

placement, coronary artery bypass, hypertension, deep vein thrombosis, factor V Leiden mutation, hyperlipidemia, hypercholesterolemia; the Baseline sCr was 1.03 mg/dL. On Day 255 the patient was hospitalized for a diagnostic workup of chest pain. SAEs of angina pectoris, dehydration, and renal failure acute were reported. The sCr result was 1.7 mg/dL on Day 255, 1.76 mg/dL on Day 279, and 3.35 mg/dL on Day 283. The renal failure was reported as resolved on Day 257 with sequelae of blood creatinine increased reported on Day 257. Due to this AE, lesinurad and febuxostat were permanently withdrawn on Day 285. On Day 342, the patient's sCr had decreased to 1.11 mg/dL and the AE of blood creatinine increased was reported as resolved. In the Investigator's opinion, the SAE of AKI was considered not related to lesinurad. The Sponsor considered the event to be possibly related to lesinurad. The REAC Chairman's comments on the SAE stated that the progressive rise in the sCr from Day 189 to Day 283 and the fall to Baseline values after withdrawal of the study drug were consistent with a possible study drug effect (with contributing factors being gout flare, medical history of coronary artery disease, and hypertension along with ACE inhibitor, colchicine, and NSAIDs).

Renal-Related SAEs During the Phase 3 Combination Therapy Extension Studies

Patient 306-05095-109 was a 46-year-old Native Hawaiian male who was enrolled in CLEAR 1 and randomized to lesinurad 200 mg with allopurinol 300 mg. Following completion of the pivotal study, he enrolled in extension Study 306 and continued on **lesinurad 200 mg with allopurinol 300 mg**. The patient had a past medical history of diabetic nephropathy and proteinuria, and had a Baseline sCr of 1.5 mg/dL. He was admitted to the hospital on Day 567 for evaluation of pain in both legs. He was diagnosed with cellulitis and treated with intravenous antibiotics. He was also found to have decompensated heart failure requiring treatment and was found to have a sCr of 2.93 mg/dL. Workup for his kidney failure was unrevealing, but he was found to have significant proteinuria, hematuria, and pyuria; the patient refused to undergo a recommended renal biopsy. The sCr continued to rise to 7.96 mg/dL on Day 570 and the patient ultimately required hemodialysis on Day 577. On Day 593, the patient's sCr increased to 7.52 mg/dL and lesinurad was discontinued on Day 597, and allopurinol (non-study) was also reduced to 100 mg 3 times a week after dialysis (although study-supplied allopurinol was discontinued on Day 561). The patient continued to receive hemodialysis treatments and on Day 684, the sCr was 5.17 mg/dL. On Day 691, the patient remained on chronic dialysis 3 times per week. The treating physicians considered the cause of the renal failure to be the diabetic nephropathy or potential autoimmune disease (due to reduced C3, positive SSA antibody and lupus anticoagulant). The Investigator and Sponsor both considered the SAE of AKI to be possibly related to lesinurad. The REAC determined that the AE of infection (cellulitis), medical history of CHF, CKD, diabetes mellitus, and hypertension were contributing factors, along with concomitant medications of ACE inhibitor, diuretics, and vancomycin.

Patient 306-05074-219 was a 54-year-old Asian male who was enrolled in CLEAR 2 and randomized to lesinurad 200 mg and allopurinol 300 mg. After completing the 12-month study, he enrolled in extension Study 306 and continued on **lesinurad 200 mg and allopurinol 300 mg**. The patient had a past medical history of kidney stones, chronic renal insufficiency, hypercholesterolemia, hypertriglyceridemia, hypertension, colon cancer, and gastroparesis, and had a Baseline sCr of 1.45 mg/dL. He was admitted to the hospital on study Day 280 for an SAE of AKI ("Acute on chronic kidney failure"). At that time he was found to have a sCr of 2.6 mg/dL. A nephrology consult was obtained and the etiology of the worsening renal function was believed to be related to study medication. As a result of the event, lesinurad and

allopurinol were interrupted. The outcome of the renal failure was reported as resolved (Day 295) following discharge from the hospital (Day 288). The sCr subsequently resolved to 1.57 mg /dL on Day 308. The SAE of acute kidney injury was considered possibly related to lesinurad by the Sponsor and the Investigator, and the Investigator also considered the event to be possibly related to allopurinol. The REAC considered the baseline CKD to be a potential contributing factor along with hypertension, ACE inhibitor, NSAID, and infection.

Patient 306-08001-204 was a 62-year-old White male who was enrolled in CLEAR 2 and randomized to lesinurad 200 mg with allopurinol 300 mg. After completing the 12-month pivotal study, he enrolled in the extension Study 306 and continued on **lesinurad 200 mg with allopurinol 300 mg**. The patient's past medical history included Crohn's disease, iliectomy, ileocolostomy, transient ischemic attack, stroke, monoparesis, drug hypersensitivity, pancreatitis, hypertension, proteinuria, renal failure, polyneuropathy, urethral stenosis, angioedema, urethrotomy, renal cyst, urethral stenosis. His Baseline sCr was 2.75 mg/dL. He was admitted to the hospital on Day 382 for an SAE of cardiac failure congestive with typical angina. At that time he was found to have ST segment elevations and troponin of 887 ng/L, and was diagnosed with myocarditis. His sCr was 2.8 mg/dL. Study medication was discontinued on Day 382 due to the SAE of myocarditis. On Day 391, his hospital course was complicated by pneumonia, ventricular fibrillation, and cardiac and respiratory arrest, which required resuscitation and intubation. On Day 392, an SAE of AKI was reported when the sCr was 4.8 mg/dL. The patient required acute hemodialysis for treatment of acute on chronic renal failure. Dialysis was required from Day 392 until Day 416, after which sCr was reported as elevated but stable at values between 3.5 and 4.5 mg/dL. On Day 428, the patient was discharged from the hospital to a rehabilitation facility, from where he was discharged on Day 448. He was discontinued from the study on Day 450, with a sCr of 3.09 mg/dL. The event of AKI was considered possibly related to lesinurad by the Investigator. The Sponsor considered the event not related to lesinurad due to sCr levels remaining at baseline levels until immediately after the event of ventricular fibrillation requiring resuscitation. The AKI is most likely due to hypoperfusion of the kidneys during the resuscitation. The REAC determined that the AEs of myocarditis, congestive heart failure, and arrhythmias; the medical history of CKD and hypertension; and the concomitant medications of angiotensin receptor blocker (ARB), colchicine, diuretics, and NSAID were potential contributing factors.

Patient 307-17002-408 was a 34-year-old male Native Hawaiian or other Pacific Islander who was enrolled in CRYSTAL and randomized to lesinurad 200 mg in combination with febuxostat 80 mg. Following completion of the pivotal study, he enrolled in extension Study 307 and continued on **lesinurad 200 mg with febuxostat 80 mg**. The patient's relevant medical history included chronic renal failure, acute on chronic renal failure, kidney stones (left renal pelvic stone), hypertension, chronic hyperkalemia, below the knee amputation, non-smoker, and gout. His Baseline sCr and Pr-Cr were 2.26 mg/dL and 1.89 mg/mg, respectively. On Day 399 (Day 46 of the extension study), the Investigator reported that the patient experienced the important medical event of acute on chronic renal impairment. The patient reported no symptoms; his sCr was elevated to 3.54 mg/dL and BUN was elevated to 46 mg/dL. On Day 412, sCr was 2.79 mg/dL and urine culture was positive for *Klebsiella pneumoniae*. The patient was diagnosed with a nonserious UTI and treated with norfloxacin, paracetamol, and tramadol. Lesinurad was discontinued on Day 413, and sCr was 3.14 mg/dL. On Day 458 during a visit at a renal clinic, the patient was found to have a nonserious AE of deterioration of

chronic renal failure, sCr not reported. On Day 473, the patient was withdrawn from the study due to deterioration of chronic renal failure. At the Early Termination Visit on Day 473, sCr was 3.98 mg/dL. On Day 508, as part of follow-up information, results from a local laboratory reported that sCr was 4.19 mg/dL. The patient then had several follow-up visits at a renal clinic for chronic renal failure. From Day 754 to Day 760, the patient was hospitalized for acute on chronic kidney injury and fluid overload with hyperkalemia. He underwent a sustained low efficiency dialysis in ICU during this hospitalization and 4 liters of fluid were removed. Chronic hemodialysis was initiated on Day 899 for worsening renal function and multiple episodes of renal failure (after study discontinuation and 12 months following lesinurad discontinuation). The Investigator and Sponsor considered the acute on chronic renal failure to be possibly related to lesinurad. The REAC determined that the medical history of CKD and hypertension, and use of an ACE inhibitor and colchicine potentially contributed to the patient's acute on chronic renal impairment.

Patient 306-05097-106 was a 40-year-old White male who was enrolled in CLEAR 1 and randomized to lesinurad 400 mg with allopurinol 300 mg. Following completion of the study, he enrolled in extension Study 306 and continued on **lesinurad 400 mg with allopurinol 300 mg**. The patient had a past medical history significant for drug hypersensitivity and back pain, and had a Baseline sCr of 1.07 mg/dL. He was admitted to the hospital on Day 400 for an SAE of acute renal failure with sCr 4.1 mg/dL; lesinurad was discontinued. A computed tomography (CT) of the abdomen and pelvis revealed moderate bilateral perinephric stranding and possible bilateral nephritis; however, there was no radiopaque urolithiasis or obstructive uropathy. A renal ultrasound revealed no abnormal results. The serologic assessments for possible autoimmune and infectious causes of renal failure were negative. A CT-guided renal biopsy revealed acute tubular cell injury with no evidence of primary glomerulopathy; with negative light microscopy and immunofluorescence studies. However, the epithelial tubular profile showed patchy and diffuse acute tubular cell injury with areas of sloughing and denudation of the lining epithelium. There was no evidence of tubulitis. The glomeruli at electron microscopy revealed diffuse basement membrane sclerosis with thickening and a diffuse epithelial foot process effacement. There was no evidence of immune complex deposition. The pathology report stated that this finding, although focal, may be considered suggestive of primary focal segmental glomerulosclerosis. Resolution of the SAE of renal failure was reported on Day 405. On Day 435, sCr was 1.15 mg/dL and the patient was withdrawn from the study. The SAE of acute renal failure was considered possibly related to lesinurad, allopurinol, or colchicine by the Investigator. The Sponsor considered it possibly related to lesinurad and not to allopurinol or febuxostat. The REAC noted the concomitant use of colchicine and NSAIDs were contributing factors.

Patient 306-05185-108 was a 38-year-old Africa American female who was enrolled in CLEAR 1 and randomized to lesinurad 400 mg with allopurinol 300 mg. Following completion of the study, she enrolled in extension Study 306 and continued on **lesinurad 400 mg with allopurinol 300 mg**. The patient had a past medical history significant for kidney disease, UTI, hypertension, type 2 diabetes mellitus, obesity, and anxiety. Her Baseline sCr was 1.36 mg/dL. She was admitted to the hospital on study Day 550 for an SAE of AKI, nephropathy, and pyelonephritis with a sCr of 2.19 mg/dL, along with the nonserious AE of hyperkalemia. Blood and urine cultures were positive for *Escherichia coli* and she was treated with IV antibiotics and IV fluids. Lesinurad was interrupted from Day 550 to Day 552. On Day 552 the SAE of AKI

was reported as resolved with sequelae, and the events of nephropathy and pyelonephritis were reported as resolved. A nonserious AE of chronic renal failure was reported on Day 553. The SAEs of AKI and nephropathy were considered by the Investigator unlikely related to lesinurad and allopurinol, whereas pyelonephritis was considered not related. The Sponsor considered all 3 unlikely related to lesinurad. The REAC noted the AE of infection, medical history of CKD and diabetes mellitus, Bactrim, ACE inhibitors, colchicine, and diuretics were contributing factors.

Patient 306-05207-119 was a 73-year-old White male who was enrolled in CLEAR 1 and randomized to placebo with allopurinol 300 mg. Following completion of the study, the patient enrolled in the extension Study 306 and was randomized to **lesinurad 400 mg with allopurinol 300 mg**. The patient had a past medical history significant for coronary artery disease, MI, cardiomyopathy, heart failure, cardiac valve replacement, paroxysmal atrial fibrillation, hypertension, hypercholesterolemia, hypertriglyceridemia, fluid retention, obesity, chronic obstructive pulmonary disease, sleep apnea, asthma, polymyalgia rheumatica, neuropathy, osteoarthritis, depression, and kidney stones. His Baseline sCr was 1.57 mg/dL. He was admitted to the hospital on Day 251 for an SAE of AKI, with a sCr 3.4 mg/dL. The prior week he had been hospitalized for treatment of an abdominal hematoma and abscess and prescribed a 21-day course of vancomycin. The nephrology consultation noted that vancomycin may be associated with acute tubular necrosis and, in view of no other signs and considering the patient had not been eating or drinking well, it was also noted that vasomotor effects from volume depletion, low BP, and renin-angiotensin system blockade were possible contributing factors for renal failure. In response to the event, lesinurad was interrupted for a week and the allopurinol dose was halved during hospitalization. The SAE was reported as resolved on Day 257. In response to hydration and general medical care the patient's renal function improved and the sCr was 2.4 mg/dL on Day 257 and 1.97 mg/dL on Day 392. The SAE of AKI was considered possibly related to lesinurad and vancomycin by the Investigator. The Sponsor considered it to be possibly related to lesinurad. The REAC determined that there was no evidence to implicate study medication in this episode of AKI.

Patient 306-05306-110 was a 56-year-old Africa American male who was enrolled in CLEAR 1 and randomized to placebo with allopurinol 300 mg. Following completion of the study, the patient enrolled in extension Study 306 and was randomized to **lesinurad 400 mg with allopurinol 300 mg**. The patient had a past medical history significant for drug hypersensitivity, peripheral neuropathy, back pain, depression, heart failure, hypertension, impaired glucose tolerance, obesity, hypercholesterolemia, and hypertriglyceridemia. His Baseline sCr was 1.27 mg/dL. He was admitted to the hospital on study Day 163 for an SAE of AKI, with sCr 2.6 mg/dL, along with the nonserious AE of dehydration. Lesinurad was discontinued on Day 163. The patient reported that because of his inability to ambulate due to severe pain in the knee and leg, he had not had his usual oral intake, was taking indomethacin 25 mg tid, and felt dehydrated. Ultrasound of the kidneys was negative. On Day 167, the SAE of AKI was reported as resolved, and the patient was discharged from the hospital. His sCr was 1.20 mg/dL on Day 206. The SAE of acute renal failure was considered possibly related to lesinurad, allopurinol, and colchicine by the Investigator. The Sponsor considered it possibly related to lesinurad, but not to allopurinol. The REAC noted that the dehydration, gout flare, medical history of CKD and hypertension, and the concomitant medications of ACE inhibitor, diuretics, and NSAID were contributing factors.

Patient 306-05421-201 was a 50-year-old Black female who was enrolled in CLEAR 2 and randomized to placebo with allopurinol 300 mg. Following completion of the study, she enrolled in extension Study 306 and randomized to **lesinurad 400 mg with allopurinol 300 mg**. The patient had a past medical history significant for CKD (2008), fluid retention caused by kidney disease, hypercholesterolemia, obesity (1990), gastric banding surgery (2006), diabetes mellitus, hypertension and secondary hyperparathyroidism, and had a Baseline sCr of 1.31 mg/dL. On Day 156 the patient underwent surgery to revise the gastric banding to a sleeve. On Day 183 she was admitted to hospital following poor oral intake, was found to have a sCr of 4.1 mg/dL, and an SAE of AKI was reported. In response to the event, lesinurad and allopurinol were interrupted. The SAE was considered resolved on Day 185 when the patient was discharged. On Day 199, sCr was 1.33 mg/dL. The SAE was considered not related to lesinurad by the Investigator. The Sponsor considered it possibly related to lesinurad. The REAC considered dehydration following the gastric surgery was a contributing factor for the SAE of AKI.

Patient 306-15015-210 was a 63-year-old South African black male who was enrolled in CLEAR 2 and randomized to placebo with allopurinol 300 mg. Following completion of the study he enrolled in the extension Study 306 and was randomized to **lesinurad 400 mg with allopurinol 300 mg**. The patient had a past medical history significant for mild renal impairment (2012), central obesity, osteoarthritis, bradycardia, and smoking. His Baseline sCr was 1.33 mg/dL. On Day 113 of Study 306, lesinurad was interrupted for an AE of acute on chronic renal failure with a sCr of 3.44 mg/dL. He was admitted to the hospital on Day 121 for an SAE of acute on chronic renal failure, with sCr 3.23 mg/dL. The SAE was reported as resolved on Day 129 at the time of hospital discharge, and a nonserious AE of acute on chronic renal failure started on Day 130. In response to the event, the patient was withdrawn from the study on Day 135. The acute on chronic renal failure resolved on Day 169, when the sCr returned to 1.27 mg/dL. The SAE of AKI was considered not related to lesinurad by the Investigator, and possibly related to the concomitant medications celecoxib and acetylsalicylic acid. The Sponsor considered it possibly related to lesinurad or concomitant celecoxib. The REAC determined that the AKI was not likely to be related to study medications but was significantly influenced by the presence of chronic renal failure and possibly by the extended use of celecoxib.

Patient 307-05285-413 was a 49-year-old White male who was enrolled in CRYSTAL and started lesinurad 400 mg with febuxostat 80 mg. Following completion of the study, he enrolled in extension Study 307 and continued on **lesinurad 400 mg with febuxostat 80 mg**. The patient had a past medical history significant for hypertension, poor appetite, and weight loss. His Baseline sCr was 1.04 mg/dL. He was admitted to the hospital on Day 548 for an SAE of AKI, with a sCr 2.81 mg/dL, after treatment with Amoxicillin and taking "a handful of Ibuprofen" for a headache associated with a presumed sinusitis. A bilateral renal ultrasound revealed normal kidneys with restrictive indices and moderate prostamegaly. Hospital discharge records indicated the AKI was suspected to be due to the excessive use of ibuprofen and dehydration. In response to the event, lesinurad and febuxostat were interrupted from Day 548 to 570, but the patient continued in the study. The renal failure was reported as resolved on Day 550 and the sCr had resolved to 1.06 mg/dL on Day 554. The SAE of acute renal failure was considered by the Investigator unlikely to be related to lesinurad and febuxostat. The Sponsor considered it possibly related to lesinurad, but not to febuxostat. The REAC reported that the AKI was influenced by dehydration and excessive use of an NSAID.

Patient 307-05287-413 was a 42-year-old African American male who was enrolled in CRYSTAL and randomized to placebo with febuxostat 80 mg. Following completion of the study, he enrolled in extension Study 307 and was randomized to **lesinurad 400 mg with febuxostat 80 mg**. The patient had a past medical history significant for AKI (2013) and hypertension, and had a Baseline sCr of 1.03 mg/dL. On Day 33 the patient was found to have a sCr value of 2.60 mg/dL and the patient was therefore asked to stop the study medication and go to the Emergency Room. He was admitted to the hospital on study Day 35 following 2 days of weakness and exhaustion. He was found to have a sCr of 5.87 mg/dL and an SAE of AKI was reported. A diagnostic workup found that he had microscopic hematuria and proteinuria; a renal ultrasound was negative. Treatment for the event included intravenous fluids, methylprednisolone sodium succinate, enoxaparin, and amlodipine. The SAE was reported as resolved on Day 38 and the patient was discharged from the hospital. On Day 54, the sCr had resolved to 1.13 mg/dL. The patient was withdrawn from the study on Day 61. The Investigator considered the SAE of AKI to be possibly related to lesinurad and febuxostat. The Sponsor considered the event to be possibly related to lesinurad but not to febuxostat. The REAC noted that the proteinuria and colchicine use were contributing factors, and that the increase in sCr on Day 35 was accompanied by the appearance of proteinuria, pyuria, and hematuria in association with peripheral edema. The REAC raised the possibility that the patient had transient glomerular inflammation.

APPENDIX 10. LESINURAD SAFETY IN MONOTHERAPY

There was 1 Phase 2b monotherapy study (Study 202) and 2 Phase 3 monotherapy studies (6-month core Study 303 [lesinurad 400 mg vs. placebo] and its uncontrolled extension Study 305 [lesinurad 400 mg]), conducted in patients with an intolerance or contraindication to XOIs.

Adverse Events

In Study 303, the incidence of AEs, including AEs leading to discontinuation and SAEs, was higher on lesinurad 400 mg qd than on placebo (Table 50). The higher incidence was due primarily to renal-related AEs (such as acute renal failure, renal impairment, and blood creatinine increased). Other common AEs that occurred in at least 2 patients more in the lesinurad group than the placebo group included diarrhea, nausea, constipation, and bronchitis.

One patient had a fatal AE; this event occurred in the lesinurad 400 mg group 100 days after the last 40-day supply of randomized study medication was dispensed (see Section 9.4.4 and Appendix 3).

Table 50: Number (%) of Patients With ≥ 1 Adverse Event by Category (Study 303)

Adverse Event Category	PBO (N=107) n (%)	LESU 400 mg (N=107) n (%)
Any AE	70 (65.4)	83 (77.6)
Any AE with RCTC toxicity Grade 3 or 4	4 (3.7)	18 (16.8)
Any AE leading to discontinuation	6 (5.6)	20 (18.7)
Any serious AE	4 (3.7)	9 (8.4)
Any fatal AE	0	1 (0.9)

Abbreviations: AE, adverse event; LESU, lesinurad; PBO, placebo; RCTC, Rheumatology Common Toxicity Criteria.
Note: For each category, patients are included only once, even if they experienced multiple events in that category.

Cardiovascular Safety

In Study 303, the incidence of CV AEs was low and comparable for lesinurad 400 mg and placebo (Table 51). Fewer patients on lesinurad 400 mg experienced the AE of hypertension compared with placebo (5.6% vs. 8.4%, respectively).

There was 1 CV event adjudicated as a MACE (CV death): A 50-year-old Puerto Rican male in the lesinurad 400 mg group died from unknown causes on Day 199 (100 days after his last 1-month supply of randomized study medication was dispensed). The patient had a history of hypercholesterolemia and hypertriglyceridemia and was a current smoker.

Based on vital signs and clinical laboratory results, lesinurad did not significantly alter either BP or blood lipid levels.

Table 51: Incidence of Cardiovascular Events by Category (Study 303)

Category	PBO (N=107) n (%)	LESU 400 mg (N=107) n (%)
Any AE in the Cardiac Disorders SOC	**3 (2.8)**	**2 (0.9)**
Any AE leading to discontinuation in the Cardiac Disorders SOC	1 (0.9)	0
Any SAE in the Cardiac Disorders SOC	2 (1.9)	0
Any AE in the Vascular Disorders SOC	**9 (8.4)**	**7 (6.5)**
Any AE leading to discontinuation in the Vascular Disorders SOC	0	0
Any SAE in the Vascular Disorders SOC	0	0
CEAC-adjudicated MACE	**0**	**1 (0.9)**
Cardiovascular death	0	1 (0.9)
Nonfatal myocardial infarction	0	0
Nonfatal stroke	0	0

Abbreviations: AE, adverse event; CEAC, Cardiovascular Endpoints Adjudication Committee; LESU, lesinurad; MACE, major adverse cardiovascular event; PBO, placebo; SAE, serious adverse event; SOC, System Organ Class.
Note: Adverse events are coded using Medical Dictionary for Regulatory Activities (MedDRA) version 14.0.

Renal Safety

The incidences of renal-related AEs and of sCr elevations were higher for lesinurad 400 mg than for placebo (Table 52 and Table 53).

A single patient, who was in the lesinurad 400 mg group, had kidney stone AEs (calculus ureteric, calculus urinary, and nephrolithiasis). The calculus ureteric was an SAE and led to discontinuation of lesinurad.

One patient on lesinurad 400 mg with a renal-related SAE underwent a renal biopsy. Patient 303-05042-307, a 25-year-old White male in Study 303, was also taking naproxen/esomeprazole as gout flare prophylaxis. On Day 2, he experienced abdominal pain, which radiated to his back with associated nausea and vomiting, and caused him to discontinue his study medication. Three days later, he was hospitalized with acute renal failure (admission sCr 8.86 mg/dL; Baseline sCr 0.94 mg/dL). A serologic work-up was negative and a renal biopsy revealed focal acute tubular necrosis and minimal tubulointerstitial fibrosis. There was no evidence of an acute interstitial nephritis, glomerulosclerosis, or immune complex disease. Electron microscopy revealed the presence of mild glomerular basement membrane thickening suggesting a dysmetabolic syndrome type injury. By Day 11, the sCr had decreased to 2.75 mg/dL and the SAE of acute renal failure was reported as resolved. On Day 27 the sCr had declined to 0.95 mg/dL and on Day 182 the sCr was 0.79 mg/dL.

Table 52: Incidence of Renal-Related Adverse Events (Study 303)

Category/ Preferred Term	PBO (N=107) n (%)	LESU 400 mg (N=107) n (%)
Any renal-related AE	**0**	**19 (17.8)**
Blood creatinine increased	0	9 (8.4)
Renal impairment	0	4 (3.7)[a]
Renal failure	0	3 (2.8)
Renal failure acute	0	3 (2.8)
Blood urea increased	0	2 (1.9)
Renal failure chronic	0	1 (0.9)
Any renal-related AE leading to discontinuation	**0**	**10 (9.3)**
Renal impairment	0	4 (3.7)
Renal failure	0	3 (2.8)
Blood creatinine increased	0	2 (1.9)
Renal failure acute	0	2 (1.9)
Blood urea increased	0	1 (0.9)
Any renal-related SAE	**0**	**5 (4.7)**
Renal failure	0	2 (1.9)
Renal failure acute	0	2 (1.9)
Renal impairment	0	1 (0.9)

Abbreviations: AE, adverse event; LESU, lesinurad; PBO, placebo; SAE, serious adverse event.
[a] Renal impairment was reported for 1 additional patient (303-15001-303) in the Study 303 Clinical Study Report; however, the event began on the first day of study drug dosing in the extension study (Study 305) and to avoid double-counting, is reported only under Study 305 in the Integrated Analysis of Safety.
Note: Adverse events are coded using Medical Dictionary for Regulatory Activities version 14.0. For each preferred term (PT), patients are included only once, even if they experienced multiple events with that PT.

Table 53: Incidence of Serum Creatinine Elevations (Study 303)

Variable	PBO (N=107) n (%)	LESU 400 mg (N=107) n (%)
sCr Elevation Category[a]		
sCr ≥ 1.5 x Baseline	0	26 (24.3)[b]
sCr ≥ 2.0 x Baseline	0	9 (8.4)
sCr ≥ 3.0 x Baseline	0	4 (3.7)

Abbreviations: LESU, lesinurad; PBO, placebo; sCr, serum creatinine.
[a] Elevation categories are nested; ie, the ≥ 1.5 x Baseline category includes all elevations ≥ 1.5, ≥ 2.0, or ≥ 3.0 x Baseline, and the ≥ 2.0 x Baseline category includes all elevations ≥ 2.0 or ≥ 3.0 x Baseline.
[b] There were 3 additional patients, all in the LESU 400 mg group, who had sCr elevations but are not included in the table because the elevated sCr values were reported by local laboratories and thus are not included in the clinical database. All 3 patients had SAEs in the Acute Renal Failure SMQ, which are included in the clinical database.
Note: Baseline is defined as the highest sCr value recorded ≤ 14 days prior to the first dose of randomized study medication.

Safety During Extended Treatment With Lesinurad as Monotherapy

Evaluation of data from the 185 patients who received lesinurad 400 mg as monotherapy in Study 303 and/or extension Study 305 demonstrated that extended exposure for up to 24 months (total population exposure 128.6 PYE) did not result in a change in the overall safety profile compared the observations in the 6-month core study.

One patient in extension Study 305 had a fatal AE; this event occurred at some time between Day 377 and Day 400 and was adjudicated by the CEAC as a CV death (see Section 9.4.4 and Appendix 3). One additional patient had an adjudicated nonfatal MI.