Running head: Lesinurad in Combination With Febuxostat in Patients with Tophaceous Gout

Lesinurad, a Selective Uric Acid Reabsorption Inhibitor, in Combination With Febuxostat in Patients With Tophaceous Gout: A Phase III Clinical Trial

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Disclosures

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ABSTRACT (249 words)

Objective. Investigate efficacy and safety of lesinurad in combination with febuxostat in patients with tophaceous gout in a 12-month, phase III trial.

Methods. Patients with serum urate (sUA) ≥8.0 mg/dl (≥6.0 mg/dl on urate-lowering therapy) and ≥1 measurable target tophus were given febuxostat 80mg daily for 3 weeks before randomization to lesinurad (200 or 400mg daily) or placebo added to febuxostat. Primary endpoint was proportion of patients achieving sUA <5.0 mg/dl (month 6). Key secondary end point was proportion of patients with complete resolution of ≥1 target tophus (month 12). Other end points included percent change in total target tophi area. Safety assessments included adverse events and laboratory data.

Results. Patients (N=324) were predominately male with mean age 54.1 years. Significantly more patients achieved sUA target by Month 6 with addition to febuxostat of lesinurad 400mg (76.1%; *P*<0.0001), but not 200mg (56.6%; *P*=0.13), versus febuxostat alone (46.8%). At all other timepoints, significantly more patients in the lesinurad 200mg group achieved sUA target. Complete tophus resolution was not different between groups. Lesinurad (200mg and 400mg) plus febuxostat reduced total target tophi area versus febuxostat alone (50.1% and 52.9% versus 28.3%, respectively, *P*<0.05). Safety was generally comparable with febuxostat alone,

except for higher rates of predominately reversible serum creatinine elevation, particularly with lesinurad 400mg.

***Conclusion*.** Lesinurad in combination with febuxostat demonstrated superior sUA lowering compared with febuxostat alone, with clinically relevant added impact on tophi and an acceptable safety profile with lesinurad 200mg in patients with tophaceous gout warranting additional therapy.

Current rheumatology guidelines for long-term treatment of gout recommend maintenance of serum urate (sUA) <6.0 mg/dl or <5.0 mg/dl in patients with greater gout disease severity through a combination of lifestyle management and pharmacotherapy (1–3). The recommended first-line urate-lowering therapy (ULT) is a xanthine oxidase inhibitor (XOI), either allopurinol or febuxostat (1,2), to inhibit urate production (4). However, in clinical trials, only about 40% of patients treated with allopurinol 300 mg daily achieved sUA <6.0 mg/dl (5–8). With febuxostat 80 mg daily, 67–75% of patients achieved sUA <6.0 mg/dl (5,7–9) , but only 48% were able to sustain it for 3 consecutive months (8). If target sUA cannot be achieved with an appropriate dose of XOI, treatment guidelines recommend combination therapy that includes an XOI with a uricosuric (1,2).

Lesinurad is a novel selective urate anion reabsorption inhibitor approved in the United States and Europe for the treatment of gout in combination with an XOI for those patients not at target on an XOI (10). Lesinurad inhibits the uric acid transporter URAT1 that is responsible for most reabsorption of urate anion from the renal tubule (11). By inhibiting URAT1, lesinurad increases excretion of uric acid and lowers sUA (12). Therefore, lesinurad in combination with an XOI provides a dual mechanism of action to lower sUA by increasing renal excretion of uric acid and reducing urate production (13,14).

A phase Ib clinical study of lesinurad plus febuxostat demonstrated greater reduction in sUA levels than febuxostat alone (12). The aims of the current phase III study (CRYSTAL) were to

examine the benefits and risks of lesinurad (200 mg or 400 mg oral, once daily) in combination with febuxostat 80 mg in patients with tophaceous gout.

PATIENTS AND METHODS

Patients. Men or women (ages 18 to 85 years; body mass index <45 kg/m^2) with a diagnosis of gout (15) were eligible. Eligible patients included those on ULT currently or in the past and those who had never taken a ULT. sUA levels were required to be ≥8.0 mg/dl for patients not taking ULT and ≥6.0 mg/dl for those on ULT. Patients were also required to have ≥1 measurable tophus on the hands/wrists and/or feet/ankles ≥5 mm and ≤20 mm in the longest diameter, measured using Vernier calipers (16).

Exclusion criteria included an estimated creatinine clearance (eCrCl) <30 ml/min calculated via Cockcroft-Gault formula using ideal body weight. History of kidney stones was not an exclusion criterion. Complete inclusion/exclusion criteria are provided in the Online Supplementary Material Table 1 and are similar to those of recent trials for the treatment of hyperuricemia and gout.

Trial design. *Treatment procedures.* The Combination Treatment Study in Subjects with Subcutaneous Tophaceous Gout with Lesinurad and Febuxostat (CRYSTAL) was a phase III, randomized, double-blind, multicenter, multinational, placebo-controlled, combination study evaluating efficacy and safety of lesinurad (200 mg or 400 mg oral) in combination with febuxostat 80 mg versus placebo in combination with febuxostat 80 mg (ClinicalTrials.gov Identifier: NCT01510769). The study, conducted in North America, Europe, Australia, and New Zealand, included an approximate 35-day screening period (including a run-in period of

approximately 21 days), a 12-month double-blind treatment period, and a follow-up period of ≤3.5 months (Supplemental Figure 1). Regardless of ULT type at screening, all patients began febuxostat 80 mg once daily as the sole ULT along with gout flare prophylaxis on Day −21. Gout flare prophylaxis consisted of colchicine (0.5 or 0.6 mg once daily, per protocol and as locally available) or a nonsteroidal antiinflammatory drug (NSAID) if patients had an intolerance /contraindication to colchicine. Gout flare prophylaxis was continued through month 5 unless patients became intolerant or developed toxicity to prophylaxis.

After 3 weeks on febuxostat 80 mg, patients were randomized 1:1:1 to placebo + febuxostat 80mg (febuxostat), lesinurad 200 mg + febuxostat 80 mg, or lesinurad 400 mg + febuxostat 80 mg. Randomization at all study sites used a centralized Interactive Voice Response System/Interactive Web Response System.

Doses of febuxostat, lesinurad, or placebo were taken once daily in the morning with food and 1 cup of water. Patients were encouraged to drink 2 liters of fluid/day and to remain well hydrated, in agreement with American College of Rheumatology guidelines for management of gout (1). Compliance with study medication was assessed by medication dispensing records, with verification of the returned medication packaging and any remaining medication during each study visit. Concomitant medication use was recorded at each study visit.

The study was conducted in accordance with Independent Ethics Committee (IEC) E6, Good Clinical Practice (GCP), the Declaration of Helsinki (October 2008), and all applicable local regulatory requirements. Patients were permitted to withdraw from treatment or study at any time. The study was conducted between February 2012 and April 2014.

Evaluations. The primary efficacy endpoint was the proportion of patients in each treatment group with an sUA <5.0 mg/dl by month 6. Secondary sUA efficacy endpoints included mean sUA levels at each visit. Prespecified sensitivity and supportive analyses included the proportion of patients with 1) sUA <5.0 mg/dl at all 3 of months 4, 5, and 6; 2) sUA levels <5.0, <4.0, and <3.0 mg/dl at each monthly visit; and 3) median sUA <5.0 mg/dl, as well as the proportion of patients with baseline sUA >5.0 mg/dl with sUA <5.0 mg/dl by month 6.

Key secondary endpoints were the proportion of patients with complete resolution (100% decrease in the area of a tophus) of ≥1 target tophus by month 12 and the proportion of patients with a best tophus response on ≥1 target tophus of complete or partial (≥50% decrease in area) resolution by month 12. An additional tophus endpoint was the mean percent change from baseline in the sum of the areas of all target tophi at each visit. Tophi were measured using digital calipers to capture both the longest diameter and longest perpendicular measurement.

Other secondary endpoints included the proportion of patients with gout flares requiring treatment at each month and the mean rate of gout flares from the end of month 6 to the end of month 12. Gout flares were reported on a daily electronic patient diary (e-diary) that elicited duration and extent of pain, presence of warmth, swelling, and tenderness, and any change in medication to treat the flare.

Patients were assessed at baseline (day 1), week 2 and months 1–6, 8, 10, and 12 for sUA and every 3 months for tophi measurements.

Safety assessments included treatment-emergent adverse events (TEAEs; coded by the Medical Dictionary for Regulatory Activities [MedDRA] version 14.0), clinical laboratory data, physical examination, electrocardiogram (ECG), and vital signs. Adverse events (AEs) of special interest included renal and cardiovascular (CV) safety. Renal safety assessments were included because renal impairment is a common comorbidity in patients with gout (17). Renal safety is also of special interest due to the increased uric acid excretion that lesinurad causes. Increases in urinary uric acid excretion have the potential to induce microcrystallization of uric acid in renal tubules and/or the urinary system (18), which could manifest clinically as kidney stones and/or changes in kidney function. Assessments of renal safety included renal-related and kidney stone TEAEs (Online Supplementary Table 2), and clinical laboratory data including serum creatinine (sCr), urine protein to creatinine ratio (PCR), and eCrCl.

Review of CV safety was conducted by an independent Cardiovascular Events Adjudication Committee (CEAC). AEs were routinely assessed for potential CV relationship, with categorization into major adverse CV event (MACE) and non-MACE endpoints (Online Supplementary Table 3) (19).

Patients who completed the double-blind treatment were eligible to enroll in an extension study of lesinurad plus febuxostat. Patients who did not enter the extension study completed a follow-up visit within 14 days of completing the double-blind treatment.

Statistical analyses. The study consisted of a 12-month treatment period, with the primary endpoint evaluated at month 6 and key secondary endpoints evaluated at month 12. The primary endpoint was the proportion of patients with sUA <5.0 mg/dl by month 6. All

randomized patients who received ≥1 dose of randomized study medication were included in the intent-to-treat (ITT) population, the primary population for efficacy and safety assessments. Comparisons of response rates based on sUA levels between each lesinurad group and the placebo group were performed using the Cochran-Mantel Haenszel (CMH) test statistic, stratified by day –7 renal function (eCrCl ≥60 ml/min versus <60 ml/min) and sUA level at day -7 (≥6.0 versus <6.0 mg/dl). A Bonferroni correction was used for the primary endpoint for each of the 2 treatment comparisons with placebo at an alpha level of 0.025. Results for sUA response were expressed as proportions, corresponding adjusted 95% confidence intervals (CIs) of the difference between response rates, and *P*-values. Nonresponder imputation (NRI) analysis was the primary analysis method where patients who were missing their month 6 sUA result were considered nonresponders.

If the null hypothesis for the primary endpoint for 1 dose was rejected at the 0.025 level, hierarchical testing of the key secondary endpoints for the surviving dose was performed at an alpha level of 0.025.

All other efficacy endpoints were evaluated at α=0.05 (nominal *P*-value), 2-sided without multiplicity adjustment. For the primary analyses of response rates at each level, NRI was used for all visits. Secondary endpoints were analyzed by negative binomial regression (gout flares) or CMH test (tophus response). Mean rates of gout flares were adjusted for day –7 renal function and sUA level and length of exposure to randomized study medication.

Safety data were listed by treatment group and not subjected to statistical hypothesis testing. TEAEs were coded by system organ class and preferred term and listed according to incidence, severity, relation to study medication, and relation to discontinuation. Baseline sCr was defined as the highest value within 14 days prior to first dose of study medication. Relative increase in sCr (i.e., ≥1.5x and ≥2.0x the baseline level at any time) was selected as the most clinically relevant assessment (20,21). Resolution of sCr elevation was defined as an sCr value returned to ≤1.2x baseline.

Approximately 315 patients were planned to be recruited, for an allocation of approximately 105 to each treatment group. This sample size was calculated to provide >90% power to detect a difference in response rate between treatment groups if the placebo group had a 40% response rate and the lesinurad groups had response rates as low as 65% using Fisher's exact test, adjusting for multiplicity with an alpha level of 0.025, 2-sided, for each test.

RESULTS

Patient disposition. Of 1,045 patients screened, 330 were randomized at 102 sites (Figure 1). The remaining 715 patients were withdrawn prior to randomization, including 667 screen failures and 48 patients who withdrew consent. Of the screen failures, 443 were related to inclusion criteria, 168 to exclusion criteria, 48 to both inclusion/exclusion criteria, and 8 to other. A total of 324 patients received ≥1 dose of randomized study medication. There were 74 patients (22.8%) who withdrew from the study prior to completion: febuxostat (20.2%), lesinurad 200mg + febuxostat (25.5%), and lesinurad 400mg + febuxostat (22.9%). The most

common reasons were TEAEs (10.5%) and noncompliance/protocol violation (9.0%). Study medication was completed by 86.2%, 82.1%, and 80.7% of patients at 6 months and 76.1%, 71.7%, and 69.7% at 12 months, respectively.

Baseline demographics and clinical history. Demographics and baseline disease characteristics were similar between treatment groups (Table 1). Patients were predominately male (95.4%) and white (79.9%), with a mean (SD) age of 54.1 (11.0) years and time since gout diagnosis of 14.7 (10.9) years. sUA levels were 8.7 (1.6) mg/dl at screening and 5.3 (1.6) mg/dl at randomization (baseline) after 3 weeks on febuxostat 80 mg. At baseline, mean (SD) number of tophi was 1.8 (1.2) and area of target tophi was 293.6 (234.6) mm^2. Patients self-reported a mean (SD) of 6.7 (8.2) gout flares in the 12 months prior to study entry.

Study medications. Overall proportions of patients exhibiting ≥80% compliance with study medications were 99.1%, 97.2%, and 92.7% in the febuxostat, lesinurad 200 mg + febuxostat, and lesinurad 400 mg + febuxostat groups, respectively.

Efficacy assessments. *Primary endpoint of sUA response and secondary sUA endpoints.* The proportion of patients who achieved sUA <5.0 mg/dl by month 6 was 46.8% in the febuxostat group, 56.6% in the lesinurad 200 mg + FBX and 76.1% in the lesinurad 400 mg + febuxostat (Figure 2). Significantly more patients treated with lesinurad 400 mg + febuxostat achieved the primary endpoint compared with febuxostat ($P < 0.0001$), while the difference was not significant for the lesinurad 200 mg + febuxostat group ($P = 0.13$).

Although the difference was not statistically different for the lesinurad 200 mg + febuxostat group by Month 6, superior treatment effects were observed for this group at all other time

points (Months 1, 2, 3, 4, 5, 8, 10, and 12; *P*-values ≤0.0281). In addition, prespecified sensitivity and supportive analyses showed differences favoring lesinurad 200 mg + febuxostat versus febuxostat alone (Supplemental Figure 2). These included achieving sUA <5.0 mg/dL for each of 3 consecutive months (Months 4, 5 and 6), a median sUA <5.0 mg/dL, and an sUA <4.0 and <3.0 mg/dl (Figure 2 shows months 6 and 12).

Included in the prespecified analyses was the subgroup of patients with sUA ≥5.0 mg/dl after 3 weeks on febuxostat (n=161, 49.7%). In this subgroup, 23.5% of patients were at goal by month 6 with febuxostat alone, 44.1% with lesinurad 200 mg + febuxostat, and 70.6% with lesinurad 400 mg + febuxostat (*P*=0.024 and <0.0001 versus febuxostat alone). The proportion of patients who achieved sUA <5.0 mg/dl was greater in both lesinurad + febuxostat groups than in the febuxostat alone group at all time points (Supplemental Figure 3). Also, more patients achieved sUA <4.0 mg/dl by month 6 with lesinurad 200 mg + febuxostat (28.8%, *P*=0.005) and lesinurad 400 mg + febuxostat (56.9%, *P*<0.0001) than with febuxostat (7.8%).

Key secondary and secondary endpoints: tophus resolution. The proportion of subjects with complete resolution of ≥1 target tophus was numerically greater in both the lesinurad 200 mg + febuxostat (25.5%) and lesinurad 400 mg + febuxostat (30.3%) groups compared with the febuxostat group (21.1%) although the differences were not statistically significant (*P*=0.45 and *P*=0.11, respectively). The proportion of patients with complete or partial resolution of ≥1 target tophus also was numerically greater in the lesinurad 200 mg + febuxostat (49.1%) and lesinurad 400 mg + febuxostat (51.4%) groups compared with the febuxostat group (45.9%) at month 12, but the differences were not significant.

At months 3, 6, 9, and 12 when tophi were measured, the lesinurad 200 mg + febuxostat and lesinurad 400 mg + febuxostat groups had a higher mean percent reduction from baseline for the sum of the areas for all target tophi when compared with the febuxostat group (Figure 4). At month 12, a 50.1% and 52.9% reduction in target tophi area was observed with the lesinurad 200 mg + febuxostat and lesinurad 400 mg + febuxostat groups compared with febuxostat alone (28.3%), *P*-values of 0.01 and 0.005, respectively.

Secondary endpoint: gout flares requiring treatment. The mean (SD) rates of gout flares requiring treatment over the 6-month period from end of month 6 to end of month 12 were 1.2 (2.7), 1.4 (2.5), and 0.7 (1.2) per patient per 6 months in the febuxostat, lesinurad 200 mg + febuxostat, and lesinurad 400 mg + febuxostat groups, respectively (*P*=0.55 and 0.04 versus febuxostat alone).

The proportion of patients with gout flares requiring treatment at the end of month 1 was higher in both lesinurad + febuxostat groups (200 mg, 25.5%; 400 mg, 35.8%) than the febuxostat group (17.4%). The proportion of patients with gout flares requiring treatment generally declined throughout the study, with lowest proportions at the end of month 11 to the end of month 12 (febuxostat, 9.2%; lesinurad 200 mg + febuxostat, 10.1%; lesinurad 400 mg + febuxostat, 6.0%).

Safety assessments. *Adverse events.* The proportion of patients with TEAEs throughout the study was 72.5% in the febuxostat group, 82.1% in the lesinurad 200 mg + febuxostat group, and 82.6% in the lesinurad 400 mg + febuxostat group (Table 2). The majority of patients in each group had TEAEs with maximum severity of grade 1 or 2, based on Rheumatology

Common Toxicity Criteria (22). TEAEs led to discontinuation of study medication in 8.3%, 8.5%, and 13.8% of patients in the febuxostat, lesinurad 200 mg + febuxostat, and lesinurad 400 mg + febuxostat groups, respectively. The most common individual TEAEs in the febuxostat, lesinurad 200 mg + febuxostat, and lesinurad 400 mg + febuxostat groups, respectively, were nasopharyngitis (8.3%, 9.4%, 13.8%), hypertension (7.3%,5.7%, 11.0%), headache (7.3%, 9.4%, 5.5%), extremity pain (3.7%, 5.7%, 8.3%), and back pain (4.6%, 7.5%, 5.5%).

Serious TEAEs were reported in 9.2% of patients in the febuxostat group, 5.7% in the lesinurad 200 mg + febuxostat group, and 8.3% in the lesinurad400 mg + febuxostat group (Table 2). No single serious TEAE occurred in >1 patient. One death was reported in the lesinurad 200 mg + febuxostat group due to cardiac arrest and one in the lesinurad 400 mg + febuxostat group due to congestive heart failure.

Renal safety analyses (Table 2). Renal-related TEAEs occurred in 5.5% of patients in the febuxostat group, 8.5% in the lesinurad 200 mg + febuxostat group, and 10.1% in the lesinurad 400 mg + febuxostat group. No patients in the lesinurad 200 mg + febuxostat group had a renal-related serious AE, while 2 patients in the lesinurad 400 mg + febuxostat group (renal failure acute; renal failure chronic) and 1 patient (0.9%) in the febuxostat group (renal failure acute) had renal-related serious AEs. All were considered by the investigator to be unlikely related or unrelated to study medication. Kidney stone TEAEs were reported by 0.9%, 1.8%, and 3.7%, respectively.

Elevation of sCr ≥1.5x baseline occurred in 2.8% (n=3), 4.7% (n=5), and 10.1% (n=11) of patients in the febuxostat, lesinurad 200 mg + febuxostat, and lesinurad 400 mg + febuxostat

groups, respectively. A total of 100%, 60%, and 85.7% of cases resolved without interruption in study medication. sCr elevation ≥2.0x baseline occurred in 0.0%, 2.8% (n=3), and 5.5% (n=6), respectively. There was only 1 unresolved elevation in both the lesinurad 200 mg + febuxostat and lesinurad 400 mg + febuxostat groups at last study assessment.

Changes in mean (SD) sCr between baseline and last value were 0.00 (0.19), 0.03 (0.18), and –0.09 (0.21) mg/dl in the febuxostat, lesinurad 200 mg + febuxostat, and lesinurad 400 mg + febuxostat groups, respectively. There were no clinically meaningful changes in mean eCrCl or PCR (Supplemental Material Table 4).

Cardiovascular safety analyses. TEAEs classified as CV events were reported in 1.8%, 5.7%, and 3.7% of patients in the febuxostat, lesinurad 200 mg + febuxostat, and lesinurad 400 mg + febuxostat groups, respectively, with serious CV events in 0.9%, 2.8%, and 3.7%. All patients with CV events had ≥1 baseline CV comorbidity and/or CV disease history.

The CEAC determined that criteria for MACE were met by 1 patient (1 event) in the febuxostat group, 2 patients (2 events) in the lesinurad 200 mg + febuxostat, and 2 patients (4 events) in the lesinurad 400 mg + febuxostat. Non-MACE CV endpoints were reported in 0, 2 patients (2 events), and 2 patients (3 events), respectively. There were no notable changes from baseline in ECG parameters in any group.

Other clinical laboratory tests and vital signs. Clinical laboratory test results, including hematology, serum chemistry parameters (excluding renal laboratory results reported above), and urinalysis, assessed over time, demonstrated no notable differences between treatment

groups. There were no notable changes from baseline during the study in vital signs, including blood pressure, in any group.

DISCUSSION

CRYSTAL investigated the efficacy and safety of lesinurad in combination with febuxostat in patients with tophaceous gout. Lesinurad 200 mg or 400 mg, in combination with febuxostat 80mg, increased the proportions of patients achieving sUA <5.0 mg/dl by month 6 (the primary endpoint) compared with febuxostat alone. The difference in proportions was significant only for the lesinurad 400 mg group. However, additional prespecified analyses showed that lesinurad 200 mg + febuxostat was effective in getting more patients to target sUA.

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 sUA <5 mg/dL at all timepoints through Month 12, including Month 6. 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 United States.

Some patients in the study achieved sUA <3 mg/dL. The clinical benefits and risks of these very low serum urate levels are currently uncertain. Although both clinical trial data and observational studies have shown benefit in flare reduction and tophus regression with very low serum urate concentrations (16,23), EULAR has recommended against urate lowering to these levels for more than several years (2).

Lesinurad 200 and 400 mg in combination with febuxostat resulted in numerical increases in the proportion of patients with complete resolution of ≥1 target tophus by month 12 compared with febuxostat alone, but differences were not statistically significant. A similar positive, but not statistically significant, trend was noted for the proportion of patients with complete or partial resolution of ≥1 target tophus by month 12. However, there was an almost 50% greater reduction in target tophi area with lesinurad 200 mg + febuxostat and lesinurad 400 mg + febuxostat groups compared with febuxostat alone. This is the first study of an oral agent to show benefits in tophus regression by month 12 of therapy.

The mean rate of gout flares requiring treatment in the 6-month period from the end of month 6 through month 12 was reduced by nearly 50% in the lesinurad 400 mg + febuxostat group compared with febuxostat alone, whereas the rate with lesinurad 200 mg + febuxostat was similar to that of febuxostat alone. The proportion of patients with gout flares requiring treatment declined over 52 weeks, similar to that observed in other studies with febuxostat or allopurinol (5,6,8). Longer-term treatment may be needed to further reduce gout flares, as well as to dissolve baseline tophi, particularly to demonstrate treatment effect differences (24,25).

Lesinurad was generally well tolerated, particularly at the 200 mg dose. Although incidence of overall TEAEs was higher with lesinurad 200 mg and 400 mg in combination with febuxostat compared with febuxostat alone, the majority of events were grade 1 or 2, and incidence of serious AEs, and TEAEs that led to study withdrawal were comparable across the 3 treatment groups. Patients treated with lesinurad 400 mg in combination with febuxostat had a higher

incidence of TEAEs that led to randomized study medication discontinuation, compared with lesinurad 200 mg in combination with febuxostat or febuxostat alone.

In renal safety analyses, patients treated with lesinurad 200 mg or 400 mg in combination with febuxostat had higher incidence of renal-related TEAEs compared with those treated with febuxostat alone. sCr elevations occurred at higher rates in the lesinurad groups versus febuxostat alone, particularly with lesinurad 400 mg, which is not an approved dosage for treatment. The majority of sCr elevations resolved by the time of the next assessment; most resolved without interruption of randomized study medication and without adverse impact on renal function during the study. The mechanism underlying sCr elevation has not been completely elucidated, but may be due to increased excretion and microcrystallization of urinary uric acid in renal tubules. NSAIDs were allowed as prophylaxis for subjects not able to tolerate colchicine and use was low (approximately 17% of patients). Evaluation of CV and renal safety by this subgroup did not demonstrate notable treatment differences. The safety profile of lesinurad 200 mg daily in combination with a xanthine oxidase inhibitor is being further characterized in a randomized controlled clinical trial with a planned duration of 2 years.

Other therapies that inhibit URAT1 have been associated with development of kidney stones (18,26). Few kidney stone TEAEs were reported during the study and may be explained by the fact that febuxostat, through decreasing urate production, reduces the amount of uric acid excreted by the kidneys, as previously reported for XOI therapies (27,28).

When prescribing lesinurad, physicians should take into consideration that patients with gout typically present with comorbidities, may also be taking other renal-acting medications,

and may be poorly hydrated. The prescribing information (10) recommends patients take lesinurad with food and water and maintain appropriate hydration via daily water intake. It also states that physicians should monitor renal function before starting and during lesinurad therapy, particularly in patients with eCrCl <60 mL/min or with sCr elevations 1.5 to 2 times the starting value, and evaluate for signs and symptoms of acute uric acid nephropathy. Lesinurad should not be started in patients with eCrCl <45 mL/min.

In CV safety analyses, CV comorbidities and risk factors were present in 74% of patients at baseline, reflecting the high rates of CV disease in gout patients. Nonserious CV TEAEs were observed at low frequencies in this high CV risk population, with small increases in rates with the lesinurad treatment groups. All patients had ≥1 baseline CV comorbidity or CV disease history. Independently-adjudicated MACE occurred in 1 patient in the febuxostat group and 2 patients in each lesinurad + febuxostat group. Database analyses have indicated no change in CV risk on initiation of XOI therapy (29) and similar risks of CV AEs for allopurinol and febuxostat versus placebo (30,31).

Limitations of CRYSTAL include the small number of women in the study and the high percentage of patients who had already achieved sUA <5.0 mg/dl at randomization after 3 weeks on febuxostat. However, analysis of patients not at goal at randomization showed that lesinurad (200 or 400 mg) + febuxostat increased the percentage of patients at goal compared to febuxostat alone. The relatively short length of the study limited the amount of resolution of tophi and decline in gout flares. Previous studies with febuxostat or allopurinol showed that much longer treatment, longer than 12 months, was needed to show a treatment difference

(24,25). An extension of CRYSTAL has recently been completed that included an additional one year follow up for resolution of tophi and decline in gout flares.

For patients uncontrolled on an appropriate dose of an XOI for whom a uricosuric is recommended, there is a need for additional treatment options. Lesinurad 200 mg is a novel selective uric acid reabsorption inhibitor approved for treatment of gout in combination with an XOI for those not at target sUA on an XOI alone. Combination therapy with lesinurad and febuxostat provides a dual mechanism, addressing both uric acid excretion and urate production, and may represent a treatment option for patients with tophaceous gout on febuxostat who warrant additional therapy.

Acknowledgments

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Author contributions

- Criterion 1: a) Substantial contributions to study conception and design; and/or b) Substantial contributions to acquisition of data; and/or c) Substantial contributions to analysis and interpretation of data
- Criterion 2: Drafting the article or revising it critically for important intellectual content
- Criterion 3: Final approval of the version of the article to be published

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Tables and Figures

Table legends

Table 1. Demographic and baseline characteristics of patients – Intent-to-treat population

Table 2. Overall summary of treatment-emergent adverse events and renal-related adverse events (safety population)

Figure legends

Figure 1. Patient disposition.

LESU = lesinurad; FBX = febuxostat; PBO = placebo; qd = once daily. * Screened was defined as signing an informed consent form. † Completed the study with or without completing randomized study medication.

Figure 2. Proportion of patients achieving serum uric acid (sUA) targets of <5.0 mg/dl, <4.0 mg/dl, and <3.0 mg/dl at month 6 and month 12 (ITT population).

Primary endpoint: proportion of patients achieving sUA <5.0 mg/dl at month 6 – nonresponder imputation. PBO = placebo; LESU = lesinurad; FBX =febuxostat. *P <0.0001 versus PBO + FBX after adjustment for multiplicity; †P < 0.01; #P <0.0001 versus PBO + FBX without multiplicity adjustment.

Figure 3. Mean serum urate levels by visit – observed cases (ITT population).

B = baseline; PBO = placebo; FBX = febuxostat; LESU = lesinurad. Data are mean (SE). For the LESU + FBX groups, all time points are $P < 0.0001$ versus baseline (except month 6 for LESU200 mg + FBX, $P = 0.0002$).

Figure 4. Percent change in sum of the areas for all target tophi (mm^2) by visit – LOCF imputation (ITT Population).

Data are mean ± SE. FBX = febuxostat; ITT = intent-to-treat; LESU = lesinurad; LOCF = last observation carried forward; PBO = placebo; SE = standard error of the mean.*$P < 0.05$ vs. PBO + FBX, **$P < 0.01$ versus PBO + FBX.

Table 1. Demographic and baseline characteristics of patients – Intent-to-treat population

	PBO + FBX n = 109	LESU200 + FBX n = 106	LESU400 + FBX n = 109	TOTAL N = 324
Age, years (SD)	54.6 (10.9)	54.2 (11.0)	53.3 (11.2)	54.1 (11.0)
Male, n (%)	107 (98.2)	100 (94.3)	102 (93.6)	309 (95.4)
Race, n (%)				
Asian	6 (5.5)	8 (7.5)	6 (5.5)	20 (6.2)
Black/African American	8 (7.3)	14 (13.2)	13 (11.9)	35 (10.8)
White	94 (86.2)	80 (75.5)	85 (78.0)	259 (79.9)
Other	1 (0.9)	4 (3.8)	5 (4.6)	10 (3.3)
Ethnicity, n (%)				
Hispanic/Latino	9 (8.3)	7 (6.6)	5 (4.6)	21 (6.5)
Not Hispanic/Latino	100 (91.7)	99 (93.4)	104 (95.4)	303 (93.5)
Body weight, kg	99.4 (21.0)	110.3 (19.5)	98.8 (21.4)	99.5 (20.6)
Body mass index, kg/m^2	32.0 (5.6)	32.4 (5.6)	31.6 (5.7)	32.0 (5.6)
Duration since gout diagnosis, years (SD)	15.2 (10.9)	15.8 (11.0)	13.2 (10.6)	14.7 (10.9)
Number of target tophi at baseline (SD)	1.9 (1.3)	1.8 (1.3)	1.8 (1.2)	1.8 (1.2)
Total area of target tophi at	291.1	310.1 (227.9)	280.3 (230.3)	293.6

baseline, mm^2 (SD)	(246.4)			(234.6)
Number of gout flares – past 12 months (SD)	6.1 (5.1)	6.9 (11.2)	7.0 (7.4)	6.7 (8.2)
Gout flare prophylaxis at baseline, n (%)				
Colchicine	87 (79.8)	95 (89.6)	94 (86.2)	276 (85.2)
NSAID	22 (20.2)	9 (8.5)	15 (13.8)	46 (14.2)
Renal function at baseline, mL/min, n (%)				
eCrCl ≥90	31 (28.4)	37 (34.9)	42 (38.5)	110 (34.0)
eCrCl 60–<90	53 (48.6)	41 (38.7)	45 (41.3)	139 (42.9)
eCrCl <60	25 (22.9)	28 (26.4)	22 (20.2)	75 (23.1)
Thiazide/thiazide-like diuretic at baseline, n (%)	11 (10.1)	15 (14.2)	18 (16.5)	44 (13.6)
sUA, mg/dl				
screening	8.8 (1.5)	8.7 (1.6)	8.6 (1.8)	8.7 (1.6)
baseline	5.2 (1.5)	5.4 (1.7)	5.3 (1.6)	5.3 (1.6)
Any CV comorbidity or CV disease history (combined)*, n (%)	80 (73.4)	81 (76.4)	79 (72.5)	240 (74.1)
Hypertension, n (%)	65 (59.6)	70 (66.0)	62 (56.9)	197 (60.8)
Hyperlipidemia, n (%)	46 (42.2)	42 (39.6)	50 (45.9)	138 (42.6)
Diabetes mellitus, n (%)	17 (15.6)	21 (19.8)	14 (12.8)	52 (16.0)

Myocardial infarction, n (%)	7 (6.4)	5 (4.7)	7 (6.4)	19 (5.9)
Kidney stones, n (%)	16 (14.7)	15 (14.2)	11 (10.1)	42 (13.0)

Data are mean (SD) or n (%)

PBO = placebo; FBX = febuxostat; LESU = lesinurad; NSAID = nonsteroidal antiinflammatory drugs; ULT = urate-lowering therapy; eCrCl = estimated creatinine clearance; sUA = serum uric acid.

*Includes hypertension, hyperlipidemia (hypercholesterolemia, hypertriglyceridemia), diabetes mellitus, kidney stones, myocardial infarction, angina pectoris, heart failure, peripheral vascular disease, stroke, and transient ischemic attack.

Table 2. Overall summary of treatment-emergent adverse events and renal-related adverse events (safety population)

Adverse event category	PBO + FBX n = 109	LESU200 + FBX n = 106	LESU400 + FBX n = 109
Any treatment-emergent adverse events (TEAE)	79 (72.5)	87 (82.1)	90 (82.6)
Any TEAE with RCTC toxicity Grade 3 or 4	13 (11.9)	11 (10.4)	11 (10.1)
Any TEAE possibly related to randomized study medication	22 (20.2)	25 (23.6)	28 (25.7)
Any serious TEAE	10 (9.2)	6 (5.7)	9 (8.3)
Any fatal TEAE	0	1 (0.9)	1 (0.9)
Any TEAE leading to randomized study medication discontinuation	9 (8.3)	9 (8.5)	15 (13.8)
Any TEAE leading to study withdrawal	4 (3.7)	7 (6.6)	7 (6.4)
Renal-related adverse events			
Any renal-related AEs	6 (5.5)	9 (8.5)	11 (10.1)
Serious renal-related AEs	1 (0.9)	0 (0)	2 (2.8)

Renal failure acute	1 (0.9)	0	1 (0.9)
Renal failure chronic	0	0	1 (0.9)
Kidney stones	4 (3.7)	1 (0.9)	2 (1.8)
sCr elevation ≥ 1.5x baseline[a]	3 (2.8)	5 (4.7)	11 (10.1)
sCr elevation cases unresolved at last study assessment[a,b]	0	1	1
sCr elevation ≥ 2.0x baseline	0 (0)	3 (2.8)	6 (5.5)
sCr elevation cases unresolved at last study assessment[b]	0	1	1

Data are n (%).

PBO = placebo; FBX = febuxostat; LESU = lesinurad; RCTC = Rheumatology Common Toxicity Criteria.

[a]All ≥ 2.0x baseline elevations captured in ≥ 1.5x elevations.

[b]sCr resolution defined as an sCr elevation returning to ≤ 1.2x baseline.

Figure 1

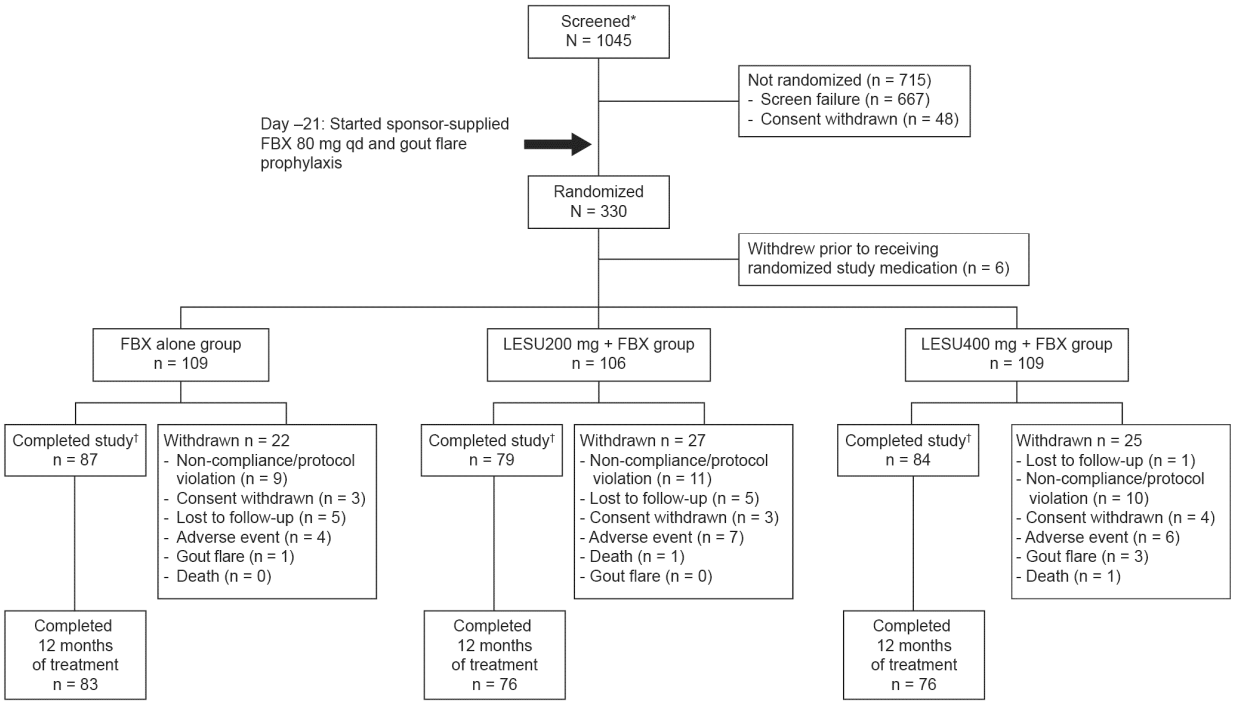


Figure 2

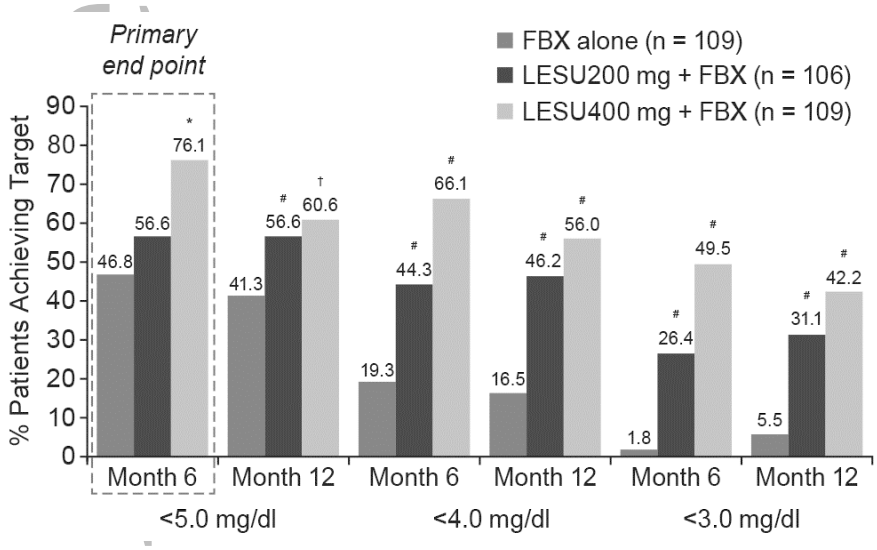


Figure 3

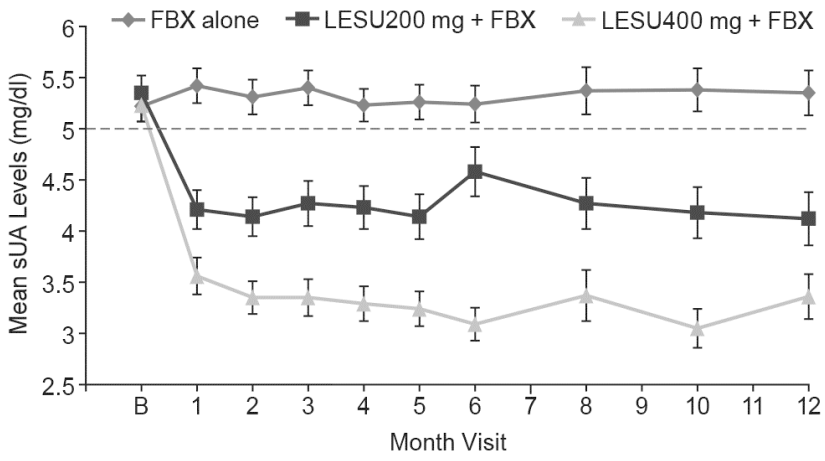
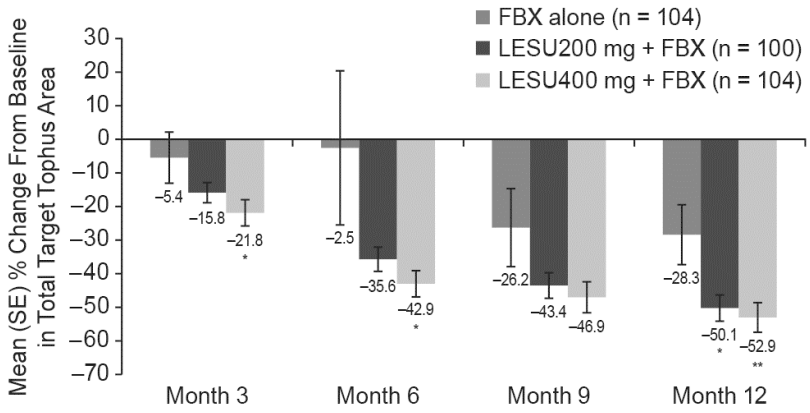


Figure 4



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PBO = placebo; FBX = febuxostat; LESU = lesinurad; RCTC = Rheumatology Common Toxicity Criteria.

[a]All ≥ 2.0x baseline elevations captured in ≥ 1.5x elevations.

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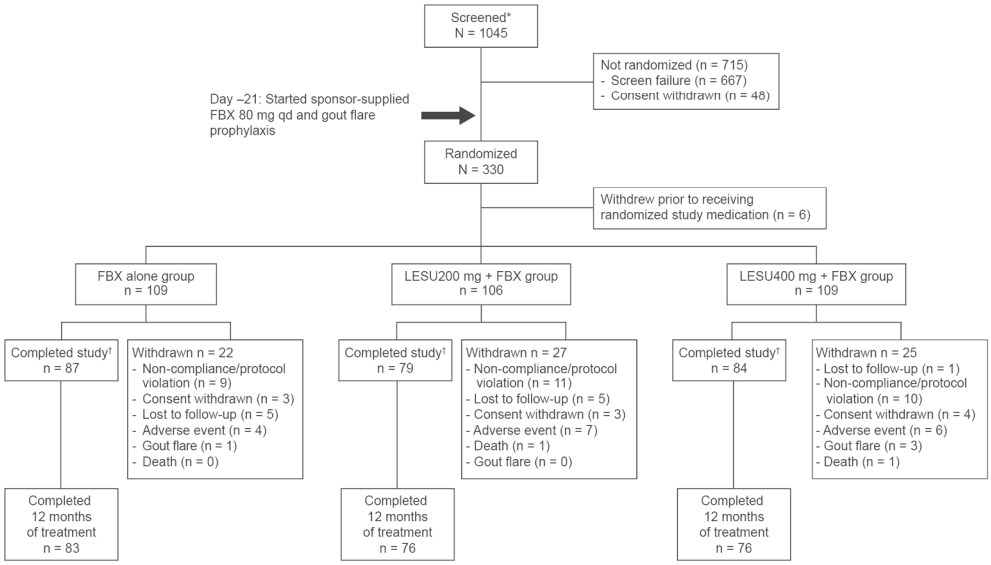

Patient disposition

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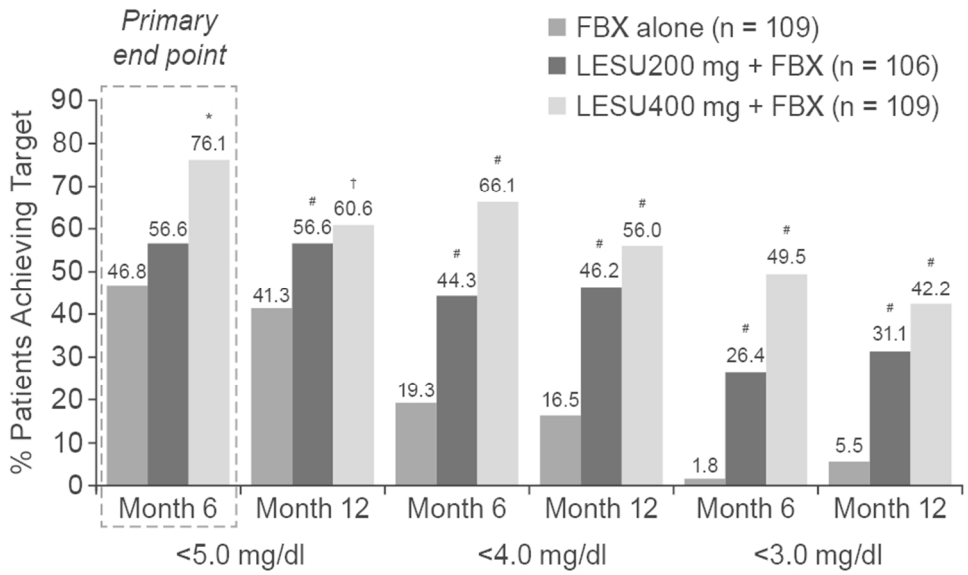
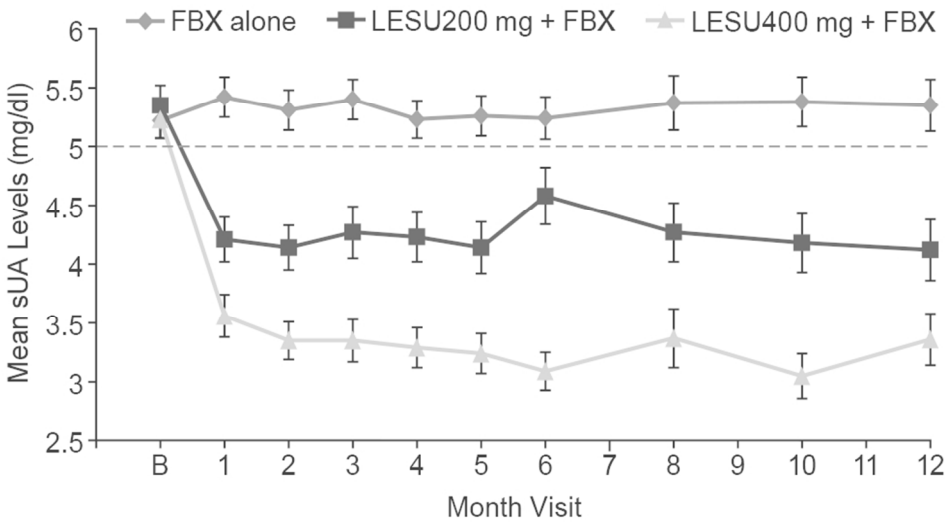


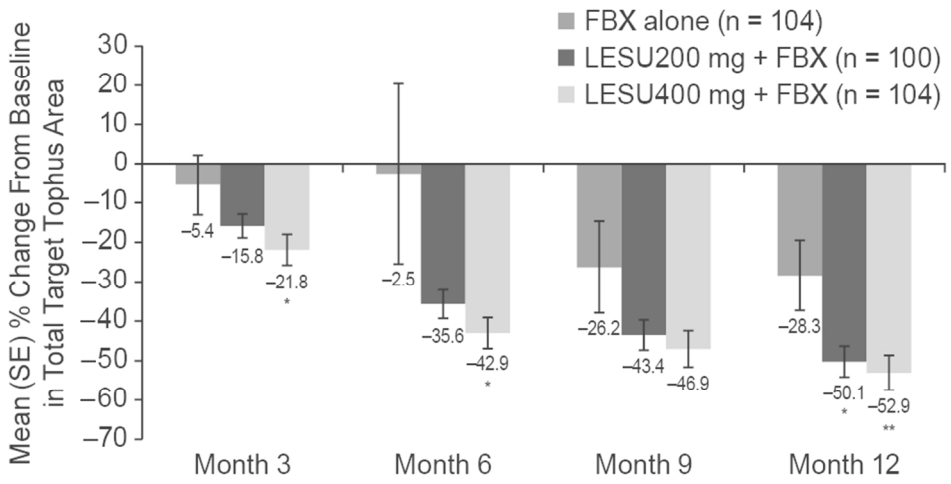
Proportion of patients achieving serum uric acid (sUA) targets of <5.0 mg/dl, <4.0 mg/dl, and <3.0 mg/dl at month 6 and month 12 (ITT population)

86x50mm (300 x 300 DPI)



Mean serum urate levels by visit – observed cases (ITT population)

87x46mm (300 x 300 DPI)



Percent change in sum of the areas for all target tophi (mm^2) by visit – LOCF imputation (ITT Population)

88x45mm (300 x 300 DPI)

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Online Supplemental Material

Supplemental Table 1. Complete inclusion/exclusion criteria for CRYSTAL

Inclusion criteria

1. Able to understand the study procedures, the risks involved and willing to provide written informed consent before the first study related activity.

2. Willing to adhere to the visit/protocol schedules.

3. Is ≥18 years and ≤85 years of age.

4. Is male or female; female of childbearing potential who agrees to use non-hormonal contraception.

5. Meets the diagnosis of gout as per the American Rheumatism Association Criteria for the Classification of Acute Arthritis of Primary Gout.

6. Meets one of the following criteria:

- Not currently taking an approved ULT must have an sUA value ≥8 mg/dL.
- Entering the study on a medically appropriate dose of febuxostat orallopurinol must have an sUA value ≥6.0 mg/dL.

7. Able to take gout flare prophylaxis with colchicine or NSAID (including Cox-2 selective NSAID) ± PPI.

8. With ≥1 measurable tophus on the hands/wrists and/or feet/ankles ≥5 mm and ≤20 mm in the longest diameter.

9. Body mass index (BMI) < 45 kg/m^2.

Exclusion criteria

1. Known hypersensitivity or allergy to febuxostat
2. Taking any approved urate-lowering medication other than allopurinol or febuxostat that is indicated for the treatment of gout (e.g., uricosuric agent) within 8 weeks of the screening visit.
3. Previously received pegloticase
4. Previously participated in a clinical study involving lesinurad (RDEA594) or RDEA806 and received active treatment or placebo
5. Pregnant or breastfeeding
6. Consumes more than 14 drinks of alcohol per week (e.g., 1 drink = 5 oz [150 ml] of wine, 12 oz [360 ml] of beer, or 1.5 oz [45 ml] of hard liquor)
7. History or suspicion of drug abuse within the past 5 years
8. History of myositis/myopathy or rhabdomyolysis
9. Requires or may require systemic immunosuppressive or immunomodulatory treatment (e.g., azathioprine, 6-mercaptopurine, cyclosporine)
10. Known or suspected human immunodeficiency virus (HIV) infection
11. Positive test for active hepatitis B or hepatitis C infection

12. History of malignancy within the previous 5 years with the exception of non-melanoma skin cancer that has been treated with no evidence of recurrence, treated cervical dysplasia or treated in situ Grade 1 cervical cancer
13. Unstable angina, New York Heart Association (NYHA) class III or IV heart failure, myocardial infarction, stroke, or deep venous thrombosis (DVT); or subjects currently receiving anticoagulants in last 12 months
14. Uncontrolled hypertension (systolic pressure above 160 or diastolic pressure above 95 mmHg on repeat measurements on two separate visits during the screening period)
15. An estimated creatinine clearance < 30 ml/min calculated by the Cockcroft-Gault formula using ideal body weight
16. Hemoglobin < 10 g/dl (males) or < 9 g/dl (females) at any time during the Screening Period
17. An alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >2.0 x upper limit of normal (ULN) at any time during the Screening Period
18. Gamma glutamyl transferase (GGT) >3 x ULN at any time during the Screening Period
19. Creatine kinase >2.5 x ULN at any time during the Screening Period
20. Active peptic ulcer disease requiring treatment
21. History of xanthinuria; subject with active liver disease or hepatic dysfunction
22. Receiving chronic treatment with more than 325 mg of salicylates per day
23. Taking valpromide, progabide, valproic acid, or other known inhibitors of epoxide hydrolase

24. Received an investigational therapy within 8 weeks or 5 half-lives (whichever is longer) prior to the Screening Visit; this does not include febuxostat or locally marketed products used in clinical trials.
25. Any other medical or psychological condition, which in the opinion of the Investigator and/or Medical Monitor, might create undue risk to the patient or interfere with the patient's ability to comply with the protocol requirements, or to complete the study

Supplemental Table 2. Renal-related and kidney stone TEAEs

Renal-related TEAEs

Acute prerenal failure

Anuria

Azotemia

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

Hypercreatininemia

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

Kidney Stone TEAEs

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

Supplemental Table 3. Major and non-major adverse cardiovascular events

Major adverse cardiovascular events (MACE)

- All deaths (both CV and non-CV deaths)
- Nonfatal myocardial infarction
- Nonfatal stroke

Non-major adverse cardiovascular events (non-MACE)

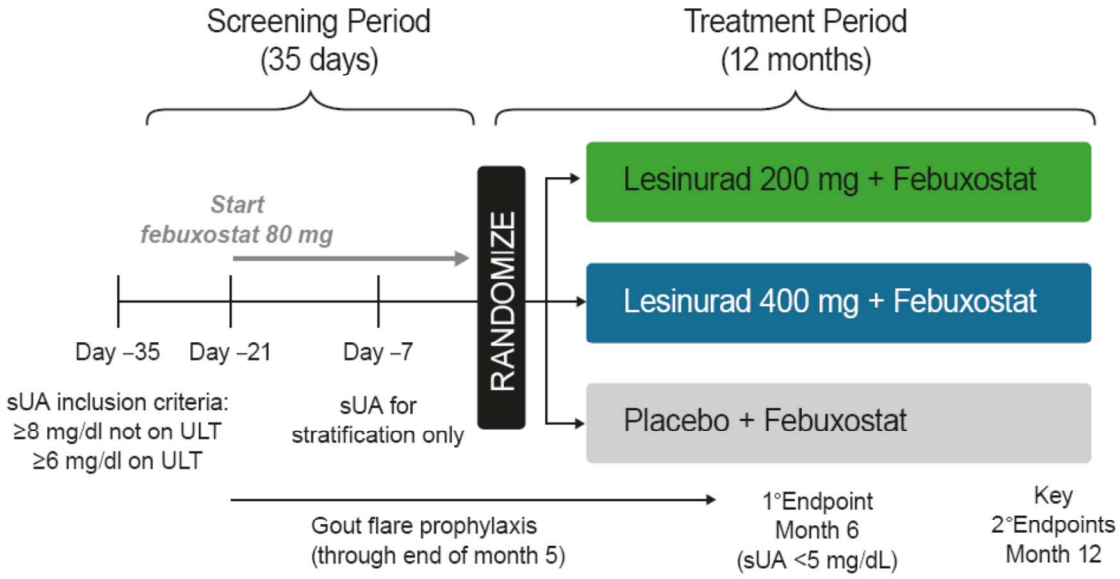
- Unstable angina with urgent coronary revascularization
- Cerebral revascularization (elective and non-elective)
- Hospitalized congestive heart failure
- Arrhythmias not associated with ischemia
- Venous and peripheral arterial vascular thrombotic events (e.g. pulmonary embolism, deep venous thrombosis, arterial dissection, thrombosis and peripheral arterial ischemia)
- Transient ischemic attack

Supplemental Table 4. Change from baseline to month 12 (or to last value) in eCrCl and change from baseline to month 12 in the urinary protein/creatinine ratio.

	PBO + FBX n = 109	LESU200 + FBX n = 106	LESU400 + FBX n = 109
	Change from baseline to month 12		
eCrCl, ml/min	5.79 (9.70) n=87	–0.34 (10.77) n=79	–0.20 (9.48) n=84
PCR, mg/mg	0.02 (0.08) n=78	0.13 (0.78) n=74	–0.01 (0.13) n=79
	Change from baseline to Last Value		
eCrCl, ml/min	4.88 (10.11) n=106	1.08 (10.49) n=103	−0.26 (9.40) n=106

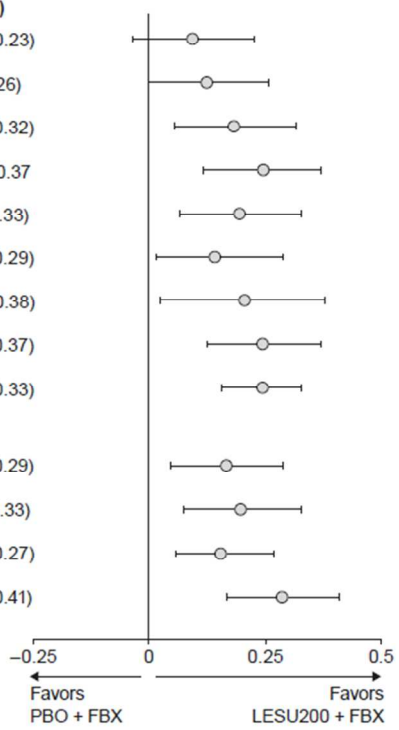
Data are mean (SD). eCrCl, estimated creatinine clearance; PCR, urinary protein to creatinine ratio.

Supplemental Figure 1. Study Design



Supplemental Figure 2. Summary of analyses showing a response that favors lesinurad 200 mg + febuxostat over placebo + febuxostat. NRI, nonresponder imputation; LOCF, last observation carried forward; sUA, serum uric acid; LESU, lesinurad; PBO, placebo; FBX, febuxostat; CI, confidence interval.

Prespecified Analyses	PBO + FBX (n/N)	LESU200 + FBX (n/N)	Diff (95% CI)
sUA <5 mg/dl at Month 6 (NRI)	51/109	60/106	0.1 (–0.03, 0.23)
sUA <5 mg/dl at Month 6 (LOCF)	54/106	66/103	0.13 (0, 0.26)
sUA <5 mg/dl at Months 4,5,6 (NRI)	36/109	55/106	0.19 (0.06, 0.32)
Median sUA <5 mg/dl	54/105	76/100	0.25 (0.12, 0.37
sUA <5 mg/dl at Month 1 (NRI)	53/109	73/106	0.2 (0.07, 0.33)
sUA <5 mg/dl at Month 12 (NRI)	45/109	60/106	0.15 (0.02, 0.29)
Baseline ≥5mg/dl with sUA <6 mg/dl at Month 6 (NRI)	12/51	26/59	0.21 (0.03, 0.38)
sUA <4 mg/dl at Month 6 (NRI)	21/109	47/106	0.25 (0.13, 0.37)
sUA <3 mg/dl at Month 6 (NRI)	2/109	28/106	0.25 (0.16, 0.33)
Additional sensitivity analyses			
sUA <5 mg/dl at Months 1–6 (NRI)	23/109	40/106	0.17 (0.05, 0.29)
sUA <5 mg/dl at Months 6–12 (NRI)	24/109	45/106	0.2 (0.08, 0.33)
sUA <5 mg/dl at Months 1–12 (NRI)	15/109	32/106	0.16 (0.06, 0.27)
sUA <5 mg/dl at Months at >80% of visits (NRI)	24/109	54/106	0.29 (0.17, 0.41)



Supplemental Figure 3. Proportion of patients with a sUA <5.0 mg/dl by visit – Nonresponder imputation (ITT population subgroup with baseline sUA ≥5.0 mg/dl). *$P \leq 0.025$ for difference in proportions versus PBO + FBX. sUA = serum uric acid; PBO = placebo; FBX = febuxostat; LESU = lesinurad.