CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207988Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Application Number	207988
Priority or Standard	Standard
Submit Date	December 29, 2014
Received Date	December 29, 2014
PDUFA Goal Date	December 29, 2015
Division / Office	Division of Pulmonary, Allergy and Rheumatology Products (DPARP)/ODEII
Reviewer Name	Rosemarie Neuner, MD, MPH
Review Completion Date	September 14, 2015
Established Name	Lesinurad
(Proposed) Trade Name	Zurampic®
Therapeutic Class	Uricosuric Agent
Applicant	Ardea Biosciences, Inc.
Formulation	Oral
Dosing Regimen	200 mg once daily in the morning
Indication	Treatment of hyperuricemia associated with gout
Intended Populations	Adults

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

This clinical reviewer recommends approval of this new drug application for lesinurad as a treatment of hyperuricemia associated with gout in adults in combination with a xanthine oxidase inhibitor (XOI) provided no issues are identified during the pending site inspection of the Applicant. The data contained in this application is sufficient to support a finding of efficacy and safety for lesinurad when administered as a dosing regimen of 200 mg once daily with a concomitant XOI.

1.2 Risk Benefit Assessment

The efficacy of lesinurad as a treatment of hyperuricemia associated with gout in combination with a xanthine oxidase inhibitor (XOI) was assessed in three, adequate and well controlled dose comparison trials 301, 302 and 304. These were multiregional, randomized, double-blind, placebo-controlled, parallel group studies in 1,537 patients who failed to achieve target serum uric acid (sUA) levels despite treatment with a minimum of 8 weeks of allopurinol (at least 300 mg/day or 200 mg /day in subjects with eCrCl $\geq$45-60 mL/min) for Studies 301 and 302 or despite treatment with a "medically appropriate" dose of allopurinol or febuxostat for Study 304. These trials evaluated the urate lowering effect of 200 mg and 400 mg doses of lesinurad administered once daily with a concomitant XOI (allopurinol or febuxostat). In Studies 301 and 302, a greater proportion of patients achieved the primary endpoint (sUA <6 mg/dL at Month 6) in the lesinurad 200 mg + allopurinol treatment groups and the lesinurad 400 mg + allopurinol treatment groups as compared to placebo + allopurinol but a dose-response effect between the two lesinurad +allopurinol groups versus placebo + allopurinol was only demonstrated in Study 302. The results from multiple sensitivity analyses were generally supportive of the findings from the primary efficacy analysis. Over the 12-month courses of both studies, these differences in treatment responses between the lesinurad + allopurinol groups versus placebo + allopurinol were consistently maintained and support the durability of lesinurad's urate lowering effects. However, the magnitude of lesinurad's urate lowering effect was modest in both of these trials ranging from 1.01-1.09 mg/dL at Month 6 to 0.89-0.93 mg/dL at Month 12 for the lesinurad 200 mg + allopurinol treatment groups versus 1.23-1.36 mg/dL at Month 6 to 1.18 to 1.25 mg/dL at Month 12 for the lesinurad 400 mg + allopurinol treatment groups versus their respective PBO + ALLO groups.

The results from the third trial, Study 304, were less robust. In this study, higher proportions of patients achieved the primary endpoint (sUA <5 mg/dL at Month 6) in a dose dependent manner in the lesinurad 200 mg + febuxostat and lesinurad 400 mg +

febuxostat treatment groups as compared to the placebo + febuxostat group. A statistically significant difference in response to study treatment was only noted for the lesinurad 400 mg + febuxostat group as compared to placebo in this trial. However, statistically significant differences in the proportions of patients treated with lesinurad 200 mg + febuxostat who achieved a sUA <5 mg/dL were observed at the Month 5, Month 8 and later time points as compared to the placebo + febuxostat group, which suggests that this dose does provide additional urate lowering effect. The differences in treatment responses between both lesinurad + febuxostat groups versus placebo + febuxostat were steadily maintained over the 12-months of Study 304 and lend support to the durability of lesinurad's urate lowering effect. The magnitude of lesinurad's urate lowering effect was also modest in this trial with the adjusted differences in mean change from baseline in sUA for the lesinurad 200 mg + febuxostat arm versus PBO + FBX arm at the Months 6 and 12 time points being similar to than that observed with allopurinol in Studies 301 and 302 (0.79 mg/dL and 1.06 mg/dL, respectively) while the adjusted differences in mean change from baseline in sUA for the lesinurad 400 mg + FBX group versus PBO + FBX group at these time points were higher to that observed with allopurinol (ranging from 1.88 mg/dL at Month 6 to 1.66 mg/dL at Months 12).

Since the primary endpoints for the pivotal studies were based on serum uric acid, additional support for a clinical benefit for treatment with lesinurad was to have been derived from a number of clinical major secondary endpoints that assessed gout flares and tophus resolution. No significant additional clinical benefit in terms of decreasing gout flares or the resolution or size of tophi was demonstrated with either the 200 mg or 400 mg lesinurad treatment groups in these three studies. There was also no improvement in the assessments for disability that were conducted in these studies, but this was probably due to the low level of disability at baseline for the patient populations in these trials.

Specific safety concerns raised during the review of safety included a higher rate of deaths, a higher rate of MACE events, a higher rate of serious adverse events and a higher rate of serious and non-serious renal-related adverse events. The dose-dependent higher incidences of serious and serious renal-related adverse events observed with LESU400 mg + XOI correlated with safety findings from the LESU400 mg monotherapy dose evaluated separately in a 6-month, randomized, placebo-controlled trial (Study 303).

There was a consistent overall numeric imbalance against lesinurad in deaths that occurred during the controlled portions of the pivotal, phase 3, lesinurad +XOI trials (301, 302 and 304). Overall, the types of deaths were consistent with the risks related to the underlying and concomitant medical conditions (e.g., hypercholesterolemia, hypertension, diabetes mellitus, chronic kidney disease and cardiovascular disease) reported by these subjects. However, the exposure-adjusted incidence rates for death in the lesinurad groups were low overall, with highly overlapping confidence intervals, making it difficult to draw definitive conclusions.

MACE events were seen in all study arms, including the PBO + XOI arm. The incidence rates for the number of subjects with MACE events and the overall number of MACE events for both the PBO + XOI and the LESU200 mg + XOI group were comparably low, but the risk for subjects with MACE events as well as the overall number of MACE events was nearly double for the LESU400 mg + XOI treatment group. This was also reflected in the numeric imbalances in the various types of MACE events, with higher rates of cardiovascular deaths and non-fatal MI particularly for the LESU400 mg +XOI group. When examined separately by XOI, the exposure-adjusted incidence in all treatment groups for MACE events was higher in the lesinurad + febuxostat Study 304 which was limited by the size of the study and the small numbers of adjudicated events. Once again, the overall small numbers of these types of events along with the highly overlapping confidence intervals make it difficult to draw definitive conclusions. Although some reassurance was provided by similarities observed in the MACE rate from a 6-month, open-label, prospective safety study of 1,732 patients with gout treated with allopurinol and from the literature, it does not explain the dose-dependent increase in MACE events observed in the LESU400 mg + XOI treatment group or the apparent increase in MACE events when co-administered with febuxostat whose current USPI carries a cardiovascular warning.

A higher proportion of patients in the LESU400 mg +XOI group experienced serious adverse events during the three pivotal studies as compared to the PBO + XOI and LESU200 mg + XOI treatment groups. Similarly, a much higher proportion of serious adverse events was also reported by subjects in the LESU400 mg group as compared to placebo in the 6-month monotherapy study (303). Numerical imbalances in the number of serious adverse events were noted with higher incidences in the LESU400 mg + XOI treatment group versus PBO + XOI in the following system organ classes: Cardiac Disorders, Renal and Urinary disorders, and Metabolism and Nutrition Disorders. In the 6-month monotherapy study, the imbalance in serious adverse events was primarily due to the number of serious adverse events listed under the Renal and Urinary Disorders system organ class for LESU400 mg treated subjects. The higher rates of serious adverse events under the Metabolism and Nutritional Disorder system organ class were due to the number of cases of serious gout attacks experienced by subjects in the LESU400 mg + XOI group. This is not an unexpected finding due to the increase in risk for gout flares as a result of fluctuations in serum uric acid associated with urate lowering therapy.

The population in the lesinurad phase 3 studies had multiple risk factors for renal adverse events including chronic kidney disease (CKD), diabetic nephropathy, hypertension and congestive heart failure as well as the use of concomitant medications such as colchicine, NSAIDs, diuretics and ACE inhibitors. The risk for lesinurad-associated renal toxicity is best evidenced by safety data from the monotherapy Study 303. In this study, treatment with the drug is clearly associated with a marked increase in risk for renal adverse events, including reversible and non-reversible creatinine

elevations and serious renal-related adverse events including acute and chronic renal failure as there were no cases of renal adverse events observed in the placebo group. This risk appears to be dose-dependent, as a higher rate of renal adverse events was observed in subjects treated with LESU400 mg + XOI as compared to LESU200 mg +XOI and PBO + XOI in the three, pivotal lesinurad + XOI studies. A dose-dependent rate of renal adverse events was also seen when these data were examined by concomitant use of allopurinol (Studies 301 and 302). However, this phenomenon was not observed in Study 304 in which both lesinurad + febuxostat treatment groups had higher rates of renal adverse events than placebo. All of the serious renal adverse events (acute and chronic renal failure) that occurred in the lesinurad + XOI treatment groups of Studies 301, 302 and 304 were experienced by patients treated with LESU400 mg + XOI. However, the two patients who developed acute renal failure that required hemodialysis in the safety database submitted in support of lesinurad were taking LESU200 mg +XOI in the extension studies. Unanswered questions remain regarding the true extent of the reversibility of drug's nephrotoxicity particularly since some patients continued to have serum creatinine elevations more than 84 days after discontinuing lesinurad. Results of a cystatin C study suggest that the changes in serum creatinine that occurred are likely to represent a change in GFR rather than a change related to some other factor such as proximal tubule secretion of creatinine. Unfortunately, the results of renal biopsies from patients who developed acute renal failure following exposure to lesinurad failed to provide clarification regarding the etiology of these patients' renal failure.

A dose dependent risk for kidney stones was also seen as more subjects in the LESU400 mg + XOI group as compared to the LESU200 mg + XOI group developed kidney stones while participating in the pivotal phase 3 studies. A similar pattern was also observed for the occurrence of serious kidney stones in these trials.

In the past, the administration of uricosuric agents like lesinurad was reserved for hyperuricemic patients who were classified as under-excretors of uric acid based on the results from a 24-hour urine collection. Due to the difficulties associated with obtaining adequate 24-urine collections and the ease of administering xanthine oxidase inhibitors, this practice has lost favor in clinical practice. If the Applicant had identified potential study subjects who were under-excretors of uric acid and designed their pivotal trials around this subpopulation it is possible that the risk-benefit profile of lesinurad might have been more favorable. As such, lesinurad treatment is clearly associated with an increased risk of renal adverse events, including reversible and non-reversible creatinine elevations and serious renal-related adverse events. The risk appears to be dose-dependent, with the highest risk associated with use of lesinurad as monotherapy, without a concomitant xanthine oxidase inhibitor, which is why the Applicant is not pursuing a monotherapy indication for this drug.

However, when evaluating the safety concerns specific to the proposed regimen of lesinurad 200 mg daily in combination with a xanthine oxidase inhibitor, the risk of

adverse events does not consistently appear to be increased relative to the control group. Therefore, in contrast with higher doses or monotherapy use, the risk/benefit profile of the 200 mg daily dose of lesinurad in combination with XOI is adequately favorable, despite modest efficacy.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

The Applicant submitted a RISK Evaluation Minimization Strategy (REMS) for lesinurad in their original submission and a revised REMS in an amendment dated April 9, 2015 based on an information request contained in the agency's 74-day filing communication letter. Based on accruing experience with communication plan-only REMS, the Division of Risk Management (DRISK) has determined that communication plan-only REMS should be limited to scenarios where the safety concern is sufficiently worrisome that escalation of mitigation strategies (such as "Elements to Assure Safe Use"/restricted distribution) would be warranted if the communication plan is not meeting its objectives. Therefore, based on current information, DRISK believes that labeling may be adequate to address the renal and cardiovascular safety concerns and no REMS is required at this time. However, a REMS may be reconsidered if future postmarketing evidence identifies a safety risk that may not be managed adequately by labeling.

1.4 Recommendations for Postmarket Requirements and Commitments

As per provisions of the Pediatric Research Equity Act (PREA), the Applicant submitted a request for a full waiver not to conduct studies in birth to 18 years of age in pediatric patients with gout and hyperuricemia since such studies would be impossible or highly impractical. Based on discussions held at the July 8, 2105 meeting of the Pediatric Review Committee (PeRC), it was agreed that the Applicant's proposed request for a full pediatric waiver was acceptable.

At the present, no need for conducting postmarketing requirements and/or commitments for lesinurad has been identified. This issue will be discussed at the pending Arthritis Advisory Committee meeting scheduled for October 23, 2015.

2 Introduction and Regulatory Background

2.1 Product Information

The established name of the subject drug of this application is lesinurad and the proposed trade name is Zurampic®. The established name will be used in this review to

refer to the drug. Lesinurad is provided as immediate release, blue, oval, film-coated tablets containing 200 mg of the active pharmaceutical ingredient, lesinurad, as the free-acid and the following inactive ingredients: lactose monohydrate, microcrystalline cellulose, hypromellose, crospovidone, and magnesium stearate.

Lesinurad is a uric acid reabsorption inhibitor and a uricosuric agent. It inhibits the urate transporters URAT1 and OAT4 located in the proximal renal tubule. URAT1 is responsible for the majority of the reabsorption of filtered uric acid from the renal tubular lumen. OAT4 is a uric acid transporter involved in diuretic induced hyperuricemia. Inhibition of URAT1 and OAT4 theoretically should result in increased uric acid excretion and lower serum uric acid (sUA) levels.

The proposed indication for lesinurad is the treatment of chronic hyperuricemia associated with gout in adult patients when administered in combination with a xanthine oxidase inhibitor (XOI). The proposed dosing regimen is 200 mg of lesinurad once daily in the morning taken at the same time with one of the marketed XOIs (allopurinol or febuxostat) with food and water. Patients taking lesinurad need to be well hydrated to minimize the risk of renal calculi (stones).

2.2 Tables of Currently Available Treatments for Proposed Indications

Table 1 lists the currently approved small molecule products as well as therapeutic biologic treatments for the management of hyperuricemia.

Table 1 – Treatments for the Management of Hyperuricemia

Product	Year of Approval	Indication
Xanthine Oxidase Inhibitors (XOIs)		
Allopurinol	1966	Management of patients with signs and symptoms or primary or secondary gout (i.e., acute attacks, tophi, joint destruction, uric acid lithiasis, and/or nephropathy
Febuxostat	2009	Chronic management of hyperuricemia in patients with gout
Uricosuric Agents[1]		
Probenecid	1951	Treatment of the hyperuricemia associated with gout and gouty arthritis
Sulfinpyrazone	1959 (Removed from market 2002)	Treatment of chronic gouty arthritis and intermittent gouty arthritis
Uricase		
Rasburicase	2002	Initial management of plasma uric acid levels in pediatric patients with leukemia, lymphoma, and sold tumor malignancies who are receiving anti-cancer therapy expected to result in tumor lysis and subsequent elevation of plasma uric acid
Pegloticase	2010	Treatment of chronic gout in adult patients refractory to conventional therapy

[1]Benzbromarone is a uricosuric agent that was never marketed in the U.S. but is available in other countries.

2.3 Availability of Proposed Active Ingredient in the United States

This product is an unapproved new molecular entity under development for marketing by the Applicant.

2.4 Important Safety Issues With Consideration to Related Drugs

Several alternatives to this product that lower sUA are available and are listed in **Table** 1 above. The xanthine oxidase inhibitors (XOI), allopurinol and febuxostat, are the agents most commonly used as first-line urate lowering therapy in patients with gout and in those with a history of nephrolithiasis (renal stones). The effectiveness of allopurinol is limited by a number of issues including the need to use lower doses in patients with renal insufficiency, and an adverse event profile that includes gastrointestinal, hepatic, renal, hematological and skin toxicities that occur in approximately 20% of patients who take this drug. In addition, hypersensitivity reactions occur in 2-4% of patients that in some instances have been fatal. Febuxostat's safety profile is similar to that of allopurinol but it does not require renal adjustment in dosing in patients with a creatinine clearance > 30 ml/minute. However, its current label carries

warnings for both cardiovascular events and hepatotoxicity some of which have resulted in fatalities. Benzbromarone, sulfinpyrazone and probenecid comprise the uricosuric class of drugs which can be used in patients who are underexcretors of urate. Uricosuric agents are used as second-line therapy since their usefulness is limited by the risk for developing urate renal stones and crystalluria in patients who are overexcretors of urate, have decreased renal function (creatinine clearance of <50 mg/minute), and/or are not well hydrated to support good urine flow. Pegloticase is a pegylated formulation of recombinant porcine urate oxidase that is administered intravenously. It is reserved as tertiary therapy as a treatment for patients with severe tophaceous gout who are refractory to conventional therapy. The effectiveness of this therapeutic biologic is limited by the development of neutralizing antibodies and the occurrence of infusion reactions and anaphylaxis which requires patients to be premedicated prior to its administration. Additionally, patients with underlying congestive heart failure have to be monitored for exacerbations post-administration of pegloticase.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

An End-of-Phase 2 (EOP2) meeting for lesinurad was held in July 2011, at which time FDA and Ardea Biosciences discussed the proposals for the lesinurad/allopurinol studies 301 and 302, lesinurad monotherapy study 303, and lesinurad/febuxostat study 304. Discussion topics included:

- In light of the doubling of exposure of lesinurad in patients with renal impairment; FDA requested subgroup analyses of the trials based on degree of renal impairment
- FDA expressed concerns about calling patients who are suboptimally treated with allopurinol as “inadequate responders,” but agreed that the proposed add-on studies to typically used doses of allopurinol were acceptable.
- FDA also agreed with the proposed primary endpoint of proportion of patients achieving a serum uric acid (sUA) less than 6 mg/dL for studies 301, 302, and 303, and noted that this endpoint would also have been acceptable for study 304.
- FDA raised questions about whether the selected once-daily dosing interval was justified and whether a BID regimen would have allowed for a lower nominal dose. Ardea provided their rationale for once daily dosing, which included a longer pharmacodynamic effect than pharmacokinetic half-life, PK modeling which suggested a BID regimen would produce only a small increase in urate lowering, and their concern that dosing at night might increase the potential for crystallization due to lower urine volume at night.

In February 2014, FDA provided written feedback to questions posed by Ardea related to the results of the monotherapy Study 303, which demonstrated more renal adverse events (AEs) and serious adverse events (SAEs) in the lesinurad monotherapy group. Ardea proposed to amend the ongoing phase 2 and 3 studies of lesinurad with xanthine oxidase inhibitors to include mitigation efforts, such as urine alkalinization, mandatory withdrawal of any subjects experiencing nephrolithiasis while in the studies, requiring

patients to have a urine pH ≥6.5 at 6 to 8 hours post lesinurad dosing with mandatory monitoring and recording of urine pH, requiring calculation of creatinine clearance (CrCl) monthly for the initial 12 months and then every 2 months thereafter, and amending the management algorithm for subjects based on serum creatinine (sCr) and estimated CrCl to provide additional withdrawal guidelines and follow-up visits until sCr changes have resolved. FDA stated the proposed changes were acceptable, but noted that if intensive safety monitoring and mitigation efforts were necessary to ensure safe use of lesinurad that this would be a consideration in the overall risk-benefit assessment.

A pre-NDA meeting was held in September 2014. FDA highlighted the previously identified issues of dosing frequency, renal and cardiovascular safety, adequacy of data on patients taking more than 300 mg/day of concomitant allopurinol, and the ability to assess the impact of the renal safety-related protocol amendments implemented during the ongoing studies. FDA noted that it was unclear whether Risk Evaluation and Mitigation Strategies (REMS) would be sufficient to address the identified concerns, and that the need for REMS would be a review issue.

2.6 Other Relevant Background Information

The development of lesinurad was initially conducted by Ardea Biosciences, Inc. which has subsequently become a wholly owned subsidiary of AstraZeneca PLC. It is currently not marketed in any foreign countries.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

Ardea Biosciences' submission was appropriately organized to allow information to be reviewed in an acceptable manner. Multiple amendments were submitted to the application by Ardea Biosciences on February 5, 2015, February 25, 2015 and April 28, 2015 that contained corrected datasets for the integrated summaries of efficacy and safety analyses, and for Study 304.

3.2 Compliance with Good Clinical Practices

According to statements included in the reports for the phase 3 trials (301, 302, and 304) the Applicant certified that these studies were conducted in compliance with the following: Good Clinical Practice standards as outlined in the Declaration of Helsinki or the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines, with the institutional review board regulations as per 21 CFR (56), and the informed consent regulation as per 21 CFR (50).

Internal site audits by the Applicant conducted prior to unblinding discovered data integrity issues at 2 sites participating in three phase 3 trials (301, 303, and 304) that would have potentially impacted on the outcomes of these studies. As a result of these findings, all data from these three sites were denoted for exclusion from the analyses of these trials prior to the locking of their databases as follows: 25 screened patients (6 randomized) from Study 301, 1 screened patient (none randomized) in Study 303, and 22 screened patients (2 randomized) in Study 304. (b) (4) the Applicant conducted the primary and key secondary efficacy endpoint analyses for this trial with and without data from this site while the safety analyses included the safety data from the patients at this site. According to the Applicant, no impact on the results from the efficacy analyses for Study 302 conducted with or without data from that site was observed.

At the time this review was written, the Division of Scientific Investigation (DSI) had completed their inspection of three clinical U.S. sites (Sites 05335, 05185, and 05394) that had participated in the pivotal Studies 301 and 302. These sites were selected for inspection based on the large number of patients they had enrolled and significant variability in responder rate to study treatment that may have an impact on treatment efficacy. Although DSI did not find any regulatory violations over the course of their audit at one site (Sites 05335), minor regulatory violations were noted at the remaining two sites (Sites 05185 and 05394). However, the DSI medical officer who conducted these inspections stated in his report that these violations were unlikely to have had an impact on date integrity and patient safety. The final conclusion by the inspecting DSI medical officer was that the data generated by these inspected sites appears to be reliable to support this application. The audit of the Applicant is tentatively scheduled for the end of September 2015 after this review has been finalized.

3.3 Financial Disclosures

The financial disclosure information for this application is discussed under Section 10.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

A the time this review was written, review of the data contained in the Chemistry, Manufacturing and Controls (CMC) section of the application was still ongoing by Dr.

Arthur Shaw of the Office of Pharmaceutical Quality (OPQ)/Office of New Drug Products (ONDP)/ Division of New Drug Products II (NDPII) and Dr. Sandra Suarez of the Division of Biopharmaceutics.

4.2 Clinical Microbiology

Since lesinurad is an orally administered agent, this application did not contain any microbiology product quality data for review.

4.3 Preclinical Pharmacology/Toxicology

The preclinical pharmacology/toxicology data included in this application was reviewed by Dr. Mathew Whittaker revealed no issues that would preclude approval. The established pharmacologic class (EPC) for lesinurad remains under discussion.

4.4 Clinical Pharmacology

Dr. Jianmeng Chen reviewed the clinical pharmacology data contained in this application. Dr. Chen recommends approval of this application for the proposed indication with the caveat that lesinurad should be used in gout patients whose creatinine clearance is $\geq$ 45 mL/min based on the following:

- The activity of lesinurad is dependent on the renal function of patients. There appears to be an attenuated uric acid lowering activity in patients with eCrCl $\leq$ 45 mL/min based on subgroup analysis
- Lesinurad decreased eCrCl from baseline in a dose-dependent manner in all categories of renal impairment patients that resulted in a higher rate of renal-related adverse events in patients with worse baseline renal function (e.g., worsening renal failure)

4.4.1 Mechanism of Action

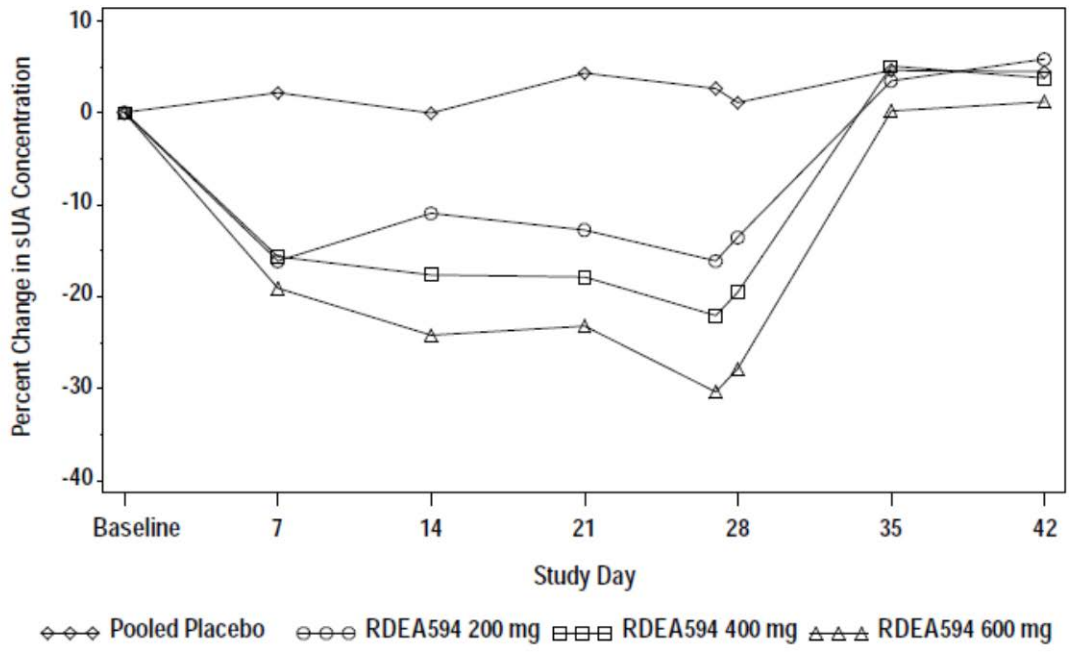
Lesinurad is proposed to act as a selective uric acid reabsorption inhibitor (SURI) that inhibits the URAT1 transporter. URAT1 is responsible for the majority of the reabsorption of filtered uric acid from the renal tubular lumen. By inhibiting URAT1, lesinurad increases urinary uric acid excretion and thereby lowers serum uric acid (sUA). Lesinurad also inhibits OAT4, a uric acid transporter involved in diuretic-induced hyperuricemia.

4.4.2 Pharmacodynamics

Phase 1 and 2 studies of lesinurad conducted by the Applicant showed a direct relationship between lesinurad dose and sUA lowering, with doses of 100 mg qd and

lower being relatively inactive and doses of 200 mg, 400 mg, and 600 mg qd showing dose-related effects on sUA and uUA. In the dose ranging study on background of allopurinol (Study 203), 3 doses of lesinurad (200 mg QD, 400 mg QD, and 600 mg QD) were compared with placebo over 28 days of treatment. The percent change from baseline in sUA following 4 weeks of treatment (primary efficacy endpoint) was statistically significant for lesinurad plus allopurinol compared with placebo plus allopurinol (Figure 1: -16.12%, -22.07%, and -30.35% in the 200 mg, 400 mg, and 600 mg dose groups, respectively, compared with +2.63% in the placebo group; $p < 0.0001$ for all comparisons). (Note: Reader is referred to Dr. Chen's review for more information.)

Figure 1 – Mean Percent Change from Baseline in sUA Concentration by Study Population (ITT Population)



Modified Sponsor's Fig.4; p. 73 CSR Study 203

4.4.3 Pharmacokinetics

Lesinurad's pharmacokinetics profile is as follows:

- Absorption: 100% bioavailability, Tmax 2-4h
  - Food effect: Cmax ↓18-52%, AUC ↔, PD effect ↑
  - Dose proportional 5-1200 mg
- Distribution:
  - 98% protein bound; mainly to albumin
  - Vss 20L

- Metabolism: mostly parent drug in plasma
  - CYP2C9 substrate (inactive metabolite)
  - CYP3A4 weak inducer
- Elimination
  - T1/2: 5 hour, longer PD effect
  - 63% urine, 32% feces, 65% dose excreted as metabolite

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

The clinical development program for lesinurad includes twenty-nine phase 1, six phase 2, and seven phase 3 studies which are summarized in **Table 2**.

Table 2 - Key Design Features of Lesinurad Trials

Study /Objectives	Study Design/ Duration/ No. Sites	Dosage Regimen/ Route of Adm.	No. of Subjects	Diagnosis/ Entry Criteria	End-points
Phase 1 Studies					
RDEA594-101:Objectives: 1. Assess the safety profile of lesinurad rising single oral doses; 2. Assess lesinurad's single dose PK; 3. Determine uricosuric effects of a single-dose lesinurad; 4. Assess food effect	1-day, single-center, R, DB, PC, single-rising dose study	Single doses of lesinurad (b) (4) 5 mg, 25 mg, 100 mg and 200 mg in fasted state and 100 mg, 400mg, and 600 mg in fed state PLO oral soln.	N=34	Healthy Male Subjects	PK/PD and safety
RDEA594-102: Objectives: 1. Assess safety and tolerability of lesinurad given as rising multiple oral doses; 2. Assess lesinurad's multiple dose PK; 3.Determine uricosuric effects of multiple-dose lesinurad: 4. Determine potential induction effect of lesinurad on urinary ration of 6-β-hydroxycortisol to free cortisol	7-10 days, R, DB, PC, 2-segment, multiple rising dose study	Multiple doses of lesinurad 100 mg (b) (4) 200 mg capsule; 200 m (b) (4) mg, and 600 mg (b) (4) capsule; 200 mg tablet in fed state. Multiple doses of lesinurad 200 mg and 400 mg capsule fasted state. PLO oral soln. and capsules	N=64	Healthy Male Subjects	PK/PD and safety

Table 2 - Key Design Features of Lesinurad Trials (cont.)

Study /Objectives	Study Design/ Duration/ No. Sites	Dosage Regimen/ Route of Adm.	No. of Subjects	Diagnosis/ Entry Criteria	End-points
Phase 1 Studies:					
RDEA594-103: Objectives: (b) (4)	1-day, single center, R, OL, 2-segment, X-over, bio-availability and bioequivalence study	Multiple, single oral doses sodium salt formulation administered in fed/fast state: 50 mg capsule; 50 mg and 200 mg (b) (4) tablet; 50 mg (b) (4) tablet; 67 mg and 200 mg (b) (4) tablet; and 200 (b) (4) formulation	N=27	Healthy Male Subjects	PK and safety
RDEA594-104: Objectives: 1. Assess PK of orally administered lesinurad in various degrees renal insufficiency; 2. Evaluate the safety profile of lesinurad in various degrees renal insufficiency; 3.Determine uricosuric effects of single-dose lesinurad in various degrees of renal insufficiency	1-day, multicenter, OL, single-dose study	Single dose of 200 mg capsule in fasted state	N=24	Male and female subjects with renal insuffici-ency excluding subjects requiring dialysis	PK/PD and safety
RDEA594-105: Objectives: 1.Compare multiple dose PK of febuxostat in the absence vs presence of lesinurad co-administration; 2. Compare the multiple dose PK of lesinurad in the absence vs presence of febuxostat co-administration	1-day,single-center, DB, PC, R, X-over drug interaction study	Multiple doses lesinurad capsules 200 mg and 400 mg qd in fed state; Multiple doses of febuxostat 40 mg qd in fed state; PLO capsules	N=36	Healthy Male and Female Subjects	PK and safety
RDEA594-106: Objectives: 1.and 2. Assess PK, safety and tolerability of multiple oral doses of (b) (4) formulation of lesinurad; 3. Determine uricosuric effects of multiple oral doses of (b) (4) formulation of lesinurad	1-day, single center, R, DB, PC, multiple single doses, X-over study	Multiple doses of lesinurad capsules 200 mg qd in fed state Multiple doses of lesinurad (b) (4) tablet 200 mg qd in fed state PLO capsules	N=8	Healthy Male Subjects	PK/PD and safety
RDEA594-107: Objectives: 1.Compare PK profiles of 2 IR dose formulations of lesinurad	1-day, single center, OL, multiple single dose, X-over study	Multiple single doses of lesinurad 200 mg capsules in fed state; Multiple single doses of lesinurad 200 mg tablet fed/fasted states	N=8	Healthy Male Subjects	PK and safety

Table 2 - Key Design Features of Lesinurad Trials (cont.)

Study /Objectives	Study Design/ Duration/ No. Sites	Dosage Regimen/ Route of Adm.	No. of Subjects	Diagnosis/ Entry Criteria	End-points
Phase 1 studies (cont.):					
RDEA594-108: Objectives; 1.Assess effect of lesinurad multiple doses on single dose PK of sildenafil and its pharmacologically active N-desmethyl metabolite; 2. Assess effect of lesinurad with allopurinol on single dose PK of sildenafil and its pharmacologically active N-desmethyl metabolite	1-day, single center, OL, 2-way, multiple single dose, drug-drug interaction study	Multiple single doses of lesinurad 200 mg, 400mg and 600 mg qd capsules in fed state Multiple doses of allopurinol 300 mg qd in fed state Single doses of sildenafil 50 mg in fed/fasted state	N=45	Healthy Male Subjects	PK and safety
RDEA594-109: Objectives: 1.Assess single dose PK profile and relative bioavailability of lesinurad free acid dose and IR formulations; 2. Assess effect of low-fat meal on PK profile of lesinurad formulations	1-day, single center, OL, multiple single doses relative bioavailability, X-over study	Single 200 mg dose lesinurad crystalline free acid tablet in fed state Single 400 mg and 600 mg doses lesinurad crystalline free acid tablet fed/fasted state Single doses of 400 mg and 600 mg lesinurad capsules in fed/fasted state; and 600 mg capsule in fed state	N=23	Healthy Male Subjects	PK and safety
RDEA594-110; Objectives: 1.and 2. Assess multiple dose plasma PK and urinary excretion of allopurinol and oxypurinol alone and in combination with lesinurad; 2. Assess multiple dose plasma PK of colchicine alone and in combination with lesinurad, allopurinol or both allopurinol and lesinurad	21-days, MC, OL, multiple dose, drug interaction study	Multiple doses of 400 mg and 600 mg lesinurad capsules qd in fed state Multiple doses allopurinol 300 mg qd in fed state Multiple doses colchicine 0.6 mg qd in fed state	N=21	Hyper-uricemic, gout subjects	PK and safety

Table 2 - Key Design Features of Lesinurad Trials (cont.)

Study /Objectives	Study Design/ Duration/ No. Sites	Dosage Regimen/ Route of Adm.	No. of Subjects	Diagnosis/ Entry Criteria	End-points
Phase 1 Studies (cont.):					
RDEA594-111; Objectives: 1.Assess multiple dose plasma PK of febuxostat alone and in combination with lesinurad; 2. Assess multiple dose plasma PK and urinary excretion of lesinurad in combination with febuxostat: 3. Assess multiple dose plasma PK of colchicine alone and in combination with febuxostat or both febuxostat and lesinurad	21-day, MC, OL, multiple dose, drug interaction study	Multiple doses of 400 mg and 600 mg lesinurad capsules qd in fed state Multiple doses febuxostat 40 mg and 80 mg qd in fed state Multiple doses colchicine 0.6 mg qd in fed state	N=24	Hyper-uricemic, gout subjects	PK and safety
RDEA594-112; Objectives: 1.and 2. Assess PK, absorption, metabolic profile, and excretion of a single oral 600 mg dose of [^{14}C]lesinurad	1-day, single-center, OL, single dose study	(b) (4) 600 mg/45mL with 500 µCi [^{14}C]lesinurad (sodium salt); single oral dose of 600 mg [^{14}C]lesinurad containing 500 µCi of radioactivity in fed state	N=6	Healthy Male Subjects	PK and safety
RDEA594-113: Objective: 1.and 2. Assess potential inhibitory/induction effects of lesinurad on single dose PK of atorvastatin	16-day, single center, OL, multiple single dose study	Multiple doses of 200 mg and 400 mg lesinurad crystalline free acid tablets qd in fed state Single doses of atorvastatin 40 mg in fed state	N=28	Healthy Male Subjects	PK and safety
RDEA594-114; Objectives: Evaluate the potential CYP3A4 induction effect of multiple doses of lesinurad on the steady-state PK of amlodipine	28-day, single center, OL, multiple dose study	Multiple doses of 400 mg lesinurad crystalline free acid tablet qd in fed state Multiple doses of amlodipine 5 mg qd in fed state	N=14	Healthy Male Subjects	PK and safety
RDEA594-115; Objectives: 1.and 2. Assess potential inhibitory/induction effects of lesinurad on single dose PK of tolbutamide	16-day, single center, OL, multiple dose study	Multiple doses of 400 mg lesinurad crystalline free acid tablet qd in fed state Multiple doses of tolbutamide 500 mg qd in fed state	N=14	Healthy Male and Female Subjects	PK and safety

Table 2 - Key Design Features of Lesinurad Trials (cont.)

Study /Objectives	Study Design/ Duration/ No. Sites	Dosage Regimen/ Route of Adm.	No. of Subjects	Diagnosis/ Entry Criteria	End-points
Phase 1 studies (cont.):					
RDEA594-116; Objectives: 1.and 2. Assess potential inhibitory/induction effects of lesinurad on single dose PK of repaglinide (acute inhibition and induction of CYP2C8)	15-day, single center, OL, multiple dose study	Multiple doses of 400 mg lesinurad crystalline free acid tablet qd in fed state Single doses of repaglinide 0.5 mg qd in fed state	N=14	Healthy Male and Female Subjects	PK and safety
RDEA594-117; Objectives: 1.and 2. Evaluate safety, tolerability, PK/PD of lesinurad following single doses up to 2000 mg; 3. Identify a supratherapeutic dose for thorough QT portion of study; 4. Evaluate ECG effects of therapeutic an supratherapeutic doses of lesinurad vs placebo with moxifloxacin as active comparator	1-day, single center, DB, R, X-over, thorough QT study	Single doses of 400 mg lesinurad crystalline free acid tablet: 400 mg, 800 mg, 1200 mg and 1600 mg in fed state PLO tablet Single doses of moxifloxacin 400 mg in fed state	N=89	Healthy Male and Female Subjects	PK/PD, and safety
RDEA594-118; Objectives: 1.and 2. Assess PK and safety of single-dose lesinurad in various degrees of hepatic impairment;3. Assess ↓sUA of single-dose lesinurad in various degrees of hepatic impairment	1-day, OL, single-dose study	Single dose of 400 mg lesinurad crystalline free acid tablets in fasted state	N=24	Healthy Males or Males with Mild/Mod. Hepatic Impairment	PK/PD and safety
RDEA594-120; Objectives: 1.and 2. Evaluate PK and safety of single-dose lesinurad in moderate and severe renal impairment	1-day, single dose study	Single dose of 400 mg lesinurad crystalline free acid tablets in fasted state	N=18	Healthy Male Subjects	PK and safety
RDEA594-121; Objectives: 1.and 2. Determine effect of a high fat/high calorie meal on PK/PD of lesinurad; 3.Determine effect of antacids on PK/PD of lesinurad	1-day, multiple, X-over periods, study	Single dose of 400 mg lesinurad crystalline free acid tablets in fed and fasted state Single dose of Tums Ultra Strength 1000 in fasted state Single dose of Maalox Advanced Maximum Strength in fasted state	N=16	Healthy Male Subjects	PK/PD and safety

Table 2 - Key Design Features of Lesinurad Trials (cont.)

Study /Objectives	Study Design/ Duration/ No. Sites	Dosage Regimen/ Route of Adm.	No. of Subjects	Diagnosis/ Entry Criteria	End-points
Phase 1 Studies (cont.):					
RDEA594-122; Objectives: 1. and 2. Assess effects of CYP2C9 inhibitor fluconazole and CYP2C9 inducer rifampin on lesinurad's PK	17-day, single dose study	Single doses of 400 mg lesinurad crystalline free acid tablets in fasted state Multiple doses of 200 mg and single doses of 400 mg fluconazole in fasted state Multiple doses of 600 mg rifampin qd	N=27	Healthy Male Subjects	PK and safety
RDEA594-123; Objectives: 1. Determine the effect of lesinurad on the PK of warfarin	28-day, OL, multiple dose, drug-drug interaction study	Multiple doses of 400 mg lesinurad crystalline free acid tablets in fed state Single doses of warfarin 25 mg in fed state	N=18	Healthy Male Subjects	PK and safety
RDEA594-125; Objectives: 1. and 2. Assess the safety. Tolerability, and PK/PD of lesinurad when administered as single and multiple doses	12-day R, DB, PC, single and multiple dose study	Single doses of 50 mg and 100 mg lesinurad crystalline free acid tablets in fasted state Multiple doses of 50 mg and 100 mg lesinurad in fed/fasted states Single doses of 200 mg, 400mg and 600 mg lesinurad crystalline free acid tablets in fasted state Multiple doses of 200 mg and 400mg qd lesinurad in fed/fasted states PBO tablets	N=40	Healthy Japanese Male Subjects	PK/PD and safety

Table 2 - Key Design Features of Lesinurad Trials (cont.)

Study /Objectives	Study Design/ Duration/ No. Sites	Dosage Regimen/ Route of Adm.	No. of Subjects	Diagnosis/ Entry Criteria	End-points
Phase 1 Studies (cont.):					
RDEA594-126; Objectives: 1. and 2.Determine effects of multiple doses of naproxen and indomethacin on lesinurad's single-dose PK; 3. and 4.Determine effects of multiple doses of lesinurad on naproxen's and indomethacin's multiple-dose PK	14-day, single and multiple dose, drug interaction study	Single and multiple doses of 400 mg qd lesinurad crystalline free acid tablets in fed state Multiple doses of naproxen 250 mg bid in fed state Multiple doses of indomethacin 25 mg bid in fed state	N=21	Healthy Male Subjects	PK and safety
RDEA594-127; Objectives: 1. Assess effect of ranitidine on lesinurad's single dose PK	3-day, OL, drug interaction study	Single doses of 400 mg lesinurad crystalline free acid tablets in fasted state Multiple doses of ranitidine 150 mg bid in fasted state	N=16	Healthy Male Subjects	PK and safety
RDEA594-128; Objectives: 1. and 2 Determine effect of single dose of lesinurad on the single-dose PK of metformin and furosemide	1-day, single dose, multiple X-over study	Single doses of 400 mg lesinurad crystalline free acid tablets in fasted state Single doses of metformin 850 mg in fasted state Single doses of furosemide 40 mg in fasted state	N=23	Healthy Male Subjects	PK and safety
RDEA594-129; Objectives: 1.Determine relative bioavailability of lesinurad tablets from 2 different sites in fed/fasted states based on PK	1-day, single dose, multiple X-over study	Single doses of 400 mg lesinurad crystalline free acid tablets in fed/fasted states	N=73	Healthy Male Subjects	PK and safety

Table 2 - Key Design Features of Lesinurad Trials (cont.)

Study /Objectives	Study Design/ Duration/ No. Sites	Dosage Regimen/ Route of Adm.	No. of Subjects	Diagnosis/ Entry Criteria	End-points
Phase 1 Studies (cont.):					
RDEA594-130; Objectives: 1.and 2. Determine effect of a calcium carbonate containing antacid and a magnesium hydroxide and aluminum hydroxide containing antacid on lesinurad's PK/PD under fed condition	1-day, R, OL, single dose, multiple X-over drug interaction study	Single doses of 400 mg lesinurad crystalline free acid tablets in fed state Single doses of one 500mg Tums Regular Strength tablet and one Tums Extra Strength 750 mg tablet in fed state Single doses of Mintox 10 mL in fed state	N=24	Healthy Male Subjects	PK and safety
RDEA594-131; Objectives: 1. Determine absolute bioavailability of single oral dose of lesinurad; 2. Assess PK parameters of lesinurad and [^{14}lesinurad]	1-day, OL, single dose, bioavailability study	Single dose of 400 mg lesinurad crystalline free acid tablets in fasted state [^{14}C]lesinurad crystalline free acid IV sol'n 10µ/mL, 80nCi/mL Single, 15-minute infusion of [^{14}C]lesinurad IV sol'n (10µg/mL, 80nCi/mL)	N=10	Healthy Male Subjects	PK and safety
RDEA594-132; Objectives: 1.Evaluate bioequivalence of lesinurad tablets from 2 different sites in fasted state based on PK	1-day, R, OL, 2-sequence, 2-period, single dose X-over bioequivalence study	Single dose of 400 mg lesinurad crystalline free acid tablets in fasted state	N=54	Healthy Male Subjects	PK and safety

Table 2 - Key Design Features of Lesinurad Trials (cont.)

Study /Objectives	Study Design/ Duration/ No. Sites	Dosage Regimen/ Route of Adm.	No. of Subjects	Diagnosis/ Entry Criteria	End-points
Phase 2 Studies:					
RDEA594-201; Objectives: 1.Evaluate proportion of subjects whose sUA <6.0 mg/dL after 2 wks continuous treatment with lesinurad vs allopurinol and placebo (Cohort1); 2. Assess percent ↓from baseline in sUA following 2 wks continuous treatment with lesinurad in combination with allopurinol (Cohort 2)	2-wk, MC, R, DB, PC, pilot study with two cohorts	Multiple doses of 200 mg and 400 mg qd lesinurad sodium salt 50 mg and 100 mg capsules in fed state Placebo capsules Multiple doses of 300 mg qd allopurinol tablets in fed state Multiple doses of 0.6 mg qd colchicine in fed state	N=28	Healthy Male Subjects	
RDEA594-202; Objectives: Determine proportion of subjects whose sUA level <6.0 mg/dL following 4 wks of dosing by treatment group	4-wk, DB, PC, dose response study	Multiple doses of 200 mg, 400 mg and 600 mg qd lesinurad sodium salt 100 mg capsule in fed state Placebo capsules Multiple doses of 0.6 mg qd colchicine in fed state	N=123	Subjects with gout and hyper-uricemia (sUA≥ 8.0 mg/dL)	Safety and Efficacy
RDEA594-203; Objectives: Evaluate the percent reduction in sUA levels following 4 wks continuous treatment with lesinurad in combination with allopurinol vs allopurinol alone	4-wk, R, DB, PC combination study	Multiple doses of 200 mg, 400 mg and 600 mg qd lesinurad sodium salt 100 mg capsule in fed state Placebo capsules Multiple daily doses of 200-600 mg allopurinol in fed state Multiple doses of 0.6 mg qd colchicine in fed state	N=208	Subjects with gout and an inadequate hypo-uricemic response to standard of care allopurinol	Safety, Efficacy and PK

Table 2 - Key Design Features of Lesinurad Trials (cont.)

Study /Objectives	Study Design/ Duration/ No. Sites	Dosage Regimen/ Route of Adm.	No. of Subjects	Diagnosis/ Entry Criteria	End-points
Phase 2 Studies (cont.):					
RDEA594-203 (DB extension); Objectives: 1.and 2. Determine proportion of subjects whose sUA level <6.0 mg/dL and <5 mg/dL; 3. Assess absolute and percent reduction from baseline in sUA at each visit; 4. Assess incidence of gout flares; 5. Assess safety and tolerability of lesinurad in combination with allopurinol in pts with gout	11-month, MC, R, DB, PC combination study	Multiple doses of 200 mg, 400 mg and 600 mg qd lesinurad sodium salt 100 mg capsule in fed state Placebo capsules Multiple daily doses of 200-600 mg allopurinol in fed state Multiple doses of 0.6 mg qd colchicine in fed state	N=126	Males and Females with Gout and an inadequate hypo-uricemic response to standard of care allopurinol	Safety and Efficacy
RDEA594-203 (OLE); Objectives: 1.and 2. Determine proportion of subjects whose sUA level <6.0 mg/dL and <5 mg/dL; 3. Assess absolute and percent reduction from baseline in sUA at each visit; 4. Assess incidence of gout flares; 5. Assess safety and tolerability of lesinurad in combination with allopurinol in pts with gout	Long-term, OL, extension, combination study	Multiple doses of 200 mg, 400 mg and 600 mg qd lesinurad sodium salt 100 mg capsule in fed state Multiple daily doses of 200-600 mg allopurinol in fed state Multiple doses of 0.6 mg qd colchicine in fed state	N=87	Subjects with gout with an inadequate hypo-uricemic response to standard of care allopurinol	Safety and Efficacy (Ongoing)
RDEA594-204; Objectives: 1.and 2. Assess the safety and PK of lesinurad administered alone, or as an add-on to ongoing allopurinol therapy; 3. Asses the uricosuric effects of lesinurad administered alone, or as add-on to ongoing allopurinol therapy	5-day, MC, OL, multiple dose, 2-part study	Multiple doses of 100 mg and 200 mg qd lesinurad sodium salt 100 mg capsule in fed state Multiple daily doses of 100-200 mg allopurinol in fed state Multiple doses of 0.6 mg qd colchicine in fed state	N=4	Subjects with Moderate Renal Insuff. Not on Dialysis	Safety, Efficacy and PK Study Terminated

Table 2 - Key Design Features of Lesinurad Trials (cont.)

Study /Objectives	Study Design/ Duration/ No. Sites	Dosage Regimen/ Route of Adm.	No. of Subjects	Diagnosis/ Entry Criteria	End-points
Phase 3 Studies:					
RDEA594-301; Objectives: Evaluate lesinurad's efficacy at Month 6 when used in combination with allopurinol compared to allopurinol monotherapy	12-month, MC, R, DB, PC, combination study	Multiple doses of 200 mg and 400 mg qd lesinurad crystalline free acid tablets in fed state Multiple daily doses of 100-800 mg allopurinol in fed state Colchicine 0.5-0.6 mg qd or NSAID ± PPI in fed state	N=603	Subjects with gout with an inadequate hypo-uricemic response to standard of care allopurinol	Efficacy and Safety
RDEA594-302; Objectives: Evaluate lesinurad's efficacy at Month 6 when used in combination with allopurinol compared to allopurinol monotherapy	12-month, MC, R, DB, PC, combination study	Multiple doses of 200 mg and 400 mg qd lesinurad crystalline free acid tablets in fed state Multiple daily doses of 100-900 mg allopurinol in fed state Colchicine 0.5-0.6 mg qd or NSAID ± PPI in fed state	N=610	Subjects with gout with an inadequate hypo-uricemic response to standard of care allopurinol	Efficacy and Safety
RDEA594-303; Objectives: Evaluate the efficacy and safety of lesinurad monotherapy at Month 6 versus placebo	6-Month, MC, R, DB, PC, monotherapy study	Multiple doses of 400 mg qd lesinurad crystalline free acid tablets in fed state Placebo tablets Colchicine 0.5-0.6 mg qd or NSAID ± PPI in fed state	N=214	Subjects with gout and Intolerance or Contra-Indication to a XOI	Efficacy and Safety
RDEA594-304; Objectives: Evaluate lesinurad's efficacy at Month 6 when used in combination with febuxostat compared to febuxostat monotherapy	12-month, MC, R, DB, PC combination study	Multiple doses of 200 mg and 400 mg qd lesinurad crystalline free acid tablets in fed state Multiple daily doses of 80 mg qd febuxostat in fed state Colchicine 0.5-0.6 mg qd or NSAID ± PPI in fed state	N=324	Subjects with Tophaceous Gout	Efficacy and Safety

Table 2 - Key Design Features of Lesinurad Trials (cont.)

Study /Objectives	Study Design/ Duration/ No. Sites	Dosage Regimen/ Route of Adm.	No. of Subjects	Diagnosis/ Entry Criteria	End-points
Phase 3 Studies (cont.):					
RDEA594-305; Objectives: Evaluate the long-term efficacy and safety of lesinurad monotherapy	Long-term, uncontrolled, OL extension study for subjects	Multiple doses of 200 mg and 400 mg qd lesinurad crystalline free acid tablets in fed state Colchicine 0.5-0.6 mg qd or NSAID ± PPI in fed state	N=143	Subjects with Gout	Efficacy and Safety
RDEA594-306; Objectives: Evaluate the long-term efficacy and safety of lesinurad in combination with allopurinol	Long-term, uncontrolled, OL extension study for subjects who completed Studies 301 and 302	Multiple doses of 200 mg and 400 mg qd lesinurad crystalline free acid tablets in fed state Multiple daily doses of 100-900 mg allopurinol in fed state Colchicine 0.5-0.6 mg qd or NSAID ± PPI in fed state	N=714	Subjects with Gout	Efficacy and Safety (Ongoing)
RDEA594-307; Objectives: Evaluate the long-term efficacy and safety of lesinurad in combination with febuxostat	Long-term, uncontrolled, OL extension study for subjects who completed Study 304	Multiple doses of 200 mg and 400 mg qd lesinurad crystalline free acid tablets in fed state Multiple daily doses of 80 mg qd febuxostat in fed state Colchicine 0.5-0.6 mg qd or NSAID ± PPI in fed state	N=196	Subjects with Gout	Efficacy and Safety (Ongoing)

5.2 Review Strategy

The Applicant conducted three adequate and well controlled phase 3 trials, 301, 302 and 304, in support of this application which were reviewed for efficacy. Additionally, the Applicant submitted the completed results from one phase 3 study of lesinurad monotherapy (303) and the interim results from two ongoing extension trials (306 and 307). This medical officer reviewed the results from the Applicant's pivotal studies (301, 302, and 304) for efficacy. The other trials (303, 306 and 307) were not reviewed in support of lesinurad's ability to treat hyperuricemia associated with gout in combination with a xanthine oxidase inhibitor for the following reasons: 303 evaluated only the 400

mg dose of lesinurad administered as monotherapy, which is not under consideration for marketing; and 306 and 307 were not designed to evaluate efficacy (the interim reports for these trials contained only safety data related to chronic administration of the drug).

The safety database included all subjects who participated in the pivotal phase 3 trials (301, 302 and 304) and the monotherapy Study 303 as well as safety data collected from the phase 1 and 2 studies and the ongoing extension studies 306 and 307. This review focuses primarily on the data for the proposed administration of lesinurad with a xanthine oxidase inhibitor. Safety data will be discussed in section 7.

5.3 Discussion of Individual Studies/Clinical Trials

Lesinurad's efficacy as a uricosuric agent in hyperuricemic gout patients despite concomitant XOI therapy was evaluated by the Applicant in three phase 3 clinical efficacy trials, 301, 302 and 304. These studies differed in the target populations they evaluated as well as in their primary and major secondary endpoints. Studies 301 and 302 were replicate studies in gout patients with or without tophaceous disease who had an inadequate hypouricemic response to standard of care allopurinol (e.g., a dose of at least 300 mg/day or 200 mg/day in subjects with eCrCl $\geq$ 45-60 mL/min). Study 304 evaluated tophaceous gout patients who were concomitantly taking 80 mg of febuxostat a day with lesinurad to support a broader XOI indication. The primary endpoint for studies 301 and 302 was the proportion of patients who achieved a sUA $\leq$6 mg/dL by Month 6. In addition to being used as a surrogate endpoint in the regulatory setting to evaluate other urate lowering agents, a sUA level $\leq$ 6 mg/dL is also the standard of care for individuals with symptomatic hyperuricemia and gout as per treatment guidelines published by the American College of Rheumatology[1]. Long term urate lowering at this level is expected to result in fewer clinical manifestations of hyperuricemia such as recurrent gout attacks. Although a sUA level of $\leq$ 5 mg/dL has not been required as a primary endpoint in clinical trials, this lower threshold of sUA is the recommended clinical target for patients with refractory, chronic gout and/or high urate burden (tophaceous deposits)[1].

The major secondary endpoints in these studies, assessment of gout flares, tophi reduction, and improvement in disease-related disability, are intended to provide clinical support of the benefit associated with the degree of urate lowering associated with the administration of lesinurad. The gout flare and tophi reduction assessments used in these pivotal trials are considered clinically appropriate endpoints in evaluating response to urate lowering therapy and have been used in the regulatory setting to evaluate other urate lowering agents. The Vernier calipers method used to measure tophi diameter in these studies has been found to be a reliable, sensitive and

[1] Khanna D, Fitzgerald JD, Khanna PP, et al. 2012 American College of Rheumatology guidelines for management of gout, part 1: systematic nonpharmacologic and pharmacologic therapeutic approaches to hyperuricemia. Arthritis Care Res. 2012;64(10):1431-1446.

reproducible methodology by the Outcomes Measures in Rheumatology (OMERACT) 10[2].

The Health Assessment Questionnaire Disability Index (HAQ-DI), HAQ Visual Analogue Scale (VAS) Pain Score, Patient Global Assessment (PGA) and the physical component SF-36 are patient reported outcome (PRO)[3] instruments for assessment of disability and pain in gout patients that have also been used in the clinical development programs of other urate lowering therapies submitted for regulatory review. The Sheehan Disability Score for productivity and the Treatment Satisfaction Questionnaire for Medication (TSQM) were also assessed in the trials but have not been previously accepted by FDA for gout trials.

Since Studies 301 and 302 utilized identical study protocols, the design of their common protocol will be presented first followed by a discussion of the individual reports for these trials, the study report for 304, and an interim combined report of the ongoing extension Studies 306 and 307 which also utilized a common protocol. An abbreviated study report for 303 that evaluated lesinurad monotherapy may be found in Section 10.

Review of the common protocol utilized in Studies 301 and 302:

Title: A Phase 3 Randomized, Double-Blind, Multicenter, Placebo-Controlled, Combination Study to Evaluate the Efficacy and Safety of Lesinurad and Allopurinol Compared to Allopurinol Alone in Subjects with Gout Who Have Had an Inadequate Hypouricemic Response to Standard of Care Allopurinol.

Dates Conducted:

1. Study 301 was started on February 8, 2012 and completed on July 1, 2014. Database lock was August 2, 2014.
2. Study 302 was started on December 16, 2011 and completed on July 3, 2014. Database lock was July 20, 2014.

Objectives:

Primary Objective:

- Assess the efficacy of lesinurad by Month 6 when used in combination with allopurinol as compared to allopurinol monotherapy

Secondary Objectives:

- Assess the efficacy of lesinurad by Month 12 when used in combination with allopurinol as compared to allopurinol monotherapy

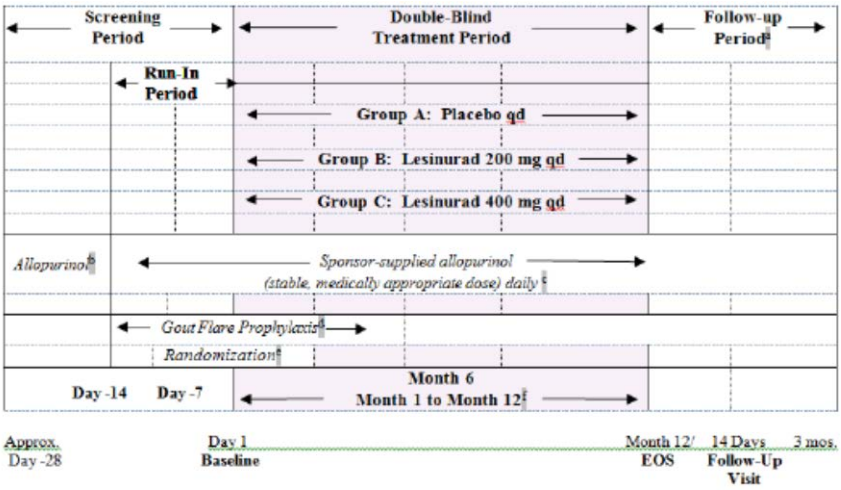
[2] Dalbeth N, McQueen FM, Singh JA, et al. Tophus measurement as an outcome measure for clinical trials of chronic gout: progress and research priorities. J Rheum 2011;38(7):1458-1461.
[3] Singh JA, Taylor WJ, Simon LS, Khanna PP, et al. Patient-Reported Outcomes in Chronic Gout: A Report from OMERACT 10. J Rheum. 2011; 38(7):1452-1457.

- Evaluate the safety of lesinurad over 6 months and 12 months when used in combination with allopurinol
- Evaluate via population analysis the influence of intrinsic factors (age, sex, race, body weight, renal function, concomitant medication use) on oral clearance of lesinurad
- Assess the effect of lesinurad when used in combination with allopurinol on Health-Related Quality of Life and physical function

Overall Design:

Studies 301 and 302 were to have been 12-month, multicenter, randomized, double-blind, placebo-controlled, three-arm, parallel group, phase 3 replicate trials in gout patients who had an inadequate hypouricemic response to standard of care allopurinol (e.g., a dose of at least 300 mg/day or 200 mg/day in subjects with eCrCl $\geq$ 45-60 mL/min). The trials were comprised of three parts: an initial 28-day screening period (which included a run-in period of approximately 14 days) followed by a 12-month, double-blind treatment period and a 14-day follow-up period. However, the common protocol was amended to include more frequent monitoring of subjects and extend the follow-up period for to 3.5 months as a result of a nephrotoxicity safety signal observed in the monotherapy trial 303 (**Figure 2**).

Figure 2 - Design Scheme for Studies 301 and 302



Abbreviations: EOS, End of Study; mos., month; NSAID, nonsteroidal anti-inflammatory drug; PPI, proton pump inhibitor; qd, once daily.

[a] Subjects 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. Subjects who completed the study and did not continue into an extension study, or who withdrew from the study for any reason other than consent withdrawn and had a serum creatinine (sCr) value > 0.1 mg/dL above their Baseline value were followed until their sCr value was ≤ 0.1 mg/dL of their Baseline value or until 3 monthly assessments after their Follow-Up Visit took place, whichever came first.

[b] Subjects were required to be receiving prescription allopurinol as the sole ULT indicated for the treatment of gout for at least 8 weeks prior to the Screening Visit at a stable, medically appropriate dose, as determined by the Investigator, of at least 300 mg/day (at least 200 mg/day for subjects with moderate renal impairment) and up to 800 mg/day. Subjects continued allopurinol until eligibility was confirmed and then were provided Sponsor-supplied allopurinol beginning on Day -14.

[c] Sponsor-supplied allopurinol was administered at the subject's same Screening dose.

[d] Prophylactic treatment for gout flare consisted of colchicine 0.5 to 0.6 mg qd or NSAID ± PPI through Month 5.

[e] Subjects whose sUA was ≥ 6.5 mg/dL at the Screening Visit and ≥ 6.0 mg/dL at the Day -7 Visit were randomized and continued to receive Sponsor-supplied allopurinol for the duration of the study.

[f] Study visits at Week 2 and monthly beginning at Month 1 through Month 12 (or early termination).

Adapted Sponsor's Figure 1; p. 37-38; Study 301 CSR

During the run-in period of the screening phase, study candidates were to have initiated prophylactic gout therapy and switched to comparable doses of sponsor-provided allopurinol therapy. Patients who successfully completed the screening process were to have been randomized via a 1:1:1 ratio stratified by renal function (estimated creatinine clearance > 60 ml/min versus < 60 ml/min) and tophi (presence or absence) to one of three treatment groups:

- Placebo QD plus allopurinol
- Lesinurad 200 mg QD plus allopurinol
- Lesinurad 400 mg QD plus allopurinol

All gout flare prophylaxis regimens were to have been discontinued at Month 5. Patients who completed these studies were to have the option of continuing to receive active treatment with lesinurad by enrolling in a 12-month, open-label extension trial (Study 306). Subjects who did not enter the OLE study were to have been seen for safety within 14 days of completing the double-blind portion of these trials. Following the implementation of Protocol Amendment 4, subjects with a serum creatinine (sCR) >0.1 mg/dL above their baseline value at the follow-up visit were required to return to the site

monthly for further assessment until the subject's sCr value was ≤0.1 mg/dL of their baseline value or until 3 monthly assessments after their follow-up visit took place.

Eligibility:

Table 3 summarizes the major inclusion and exclusion criteria for Studies 301 and 302:

Table 3 – Tabular Summary of Major Inclusion and Exclusion Criteria for Studies 301 and 302

Major Inclusion Criteria: 1. Males and females between 18 and 85 years of age 2. Diagnosis of gout as per the American Rheumatism Association Criteria for the Classification of Acute Arthritis of Primary Gout 3. Taking allopurinol as the sole urate-lowering therapy indicated for the treatment of gout for at least 8 weeks prior to the Screening visit at a stable, medically appropriate dose, as determined by the investigator, of at least 300 mg/day (at least 200 mg/day for subjects with moderate renal impairment) 4. Able to take gout flare prophylaxis with colchicine or an NSAID (including Cox-2 selective NSAID) with or without proton pump inhibitor 5. Serum uric acid (sUA) level ≥ 6.5 mg/dL at the screening visit and Day -7 visit 6. Experienced at least 2 gout flares in the prior 12 months 7. Female subjects of childbearing potential had to agree to use a non-hormonal method of contraception
Major Exclusion Criteria: 1. Acute gout flare that had not resolved at least 7 days before the baseline visit (Day 1) 2. History of (H/O) hypersensitivity or allergy to allopurinol 3. Taking any other approved urate-lowering medication that is indicated for the treatment of gout other than allopurinol (e.g., another xanthine oxidase inhibitor [XOI] or uricosuric agent) within 8 weeks of the screening visit 4. Previous treatment with pegloticase 5. Pregnant or breastfeeding 6. Consumed 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. H/O myositis/myopathy or rhabdomyolysis 8. H/O human immunodeficiency virus (HIV) infection 9. Positive test for active hepatitis B or C infection 10. Unstable angina, New York Heart Association (NYHA) class III or IV heart failure, myocardial infarction, stroke or deep venous thrombosis (DVT) within the last 12 months; or subjects currently receiving anticoagulants 11. Uncontrolled hypertension (defined as a systolic pressure > 160 mm Hg or diastolic pressure > 95 mm Hg) on repeated measurements on 2 separate visits during the screening period 12. Estimated creatinine clearance <30 mL/min calculated via the Cockcroft-Gault formula using ideal body weight 13. Hemoglobin < 10 g/dl (males) or < 9 g/dL (females) during the screening period 14. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 2.0 x upper limit of normal (ULN) during the screening period 15. Gamma glutamyl transferase (GGT) >3 x ULN during the screening period 16. Creatinine kinase (CK) >2.5 x ULN during the screening period 17. Active peptic ulcer disease requiring treatment 18. H/O xanthinuria, active liver disease, or hepatic dysfunction

Treatment:
Study medication was to have been supplied as 200 mg and 400 mg tablets of lesinurad or matching placebo. The common protocol mandated that all subjects were to have received concomitant therapy with at least 300 mg/day of allopurinol. Patients with moderate renal impairment (eCrCl ≥ 45-60 mL/min) were to have received at least 200 mg/day of allopurinol. Concomitant allopurinol was to have been provided by the sponsor as 100 mg and 300 mg tablets. Patients were to have been instructed to take their study medications as a single, oral dose in the morning with food and one cup (8oz.; 240 mL) of water along with their morning dose of allopurinol. Missed doses of study medication or concomitant allopurinol were not to have been made up on the following day. Compliance was to have been assessed by the number of study medication tablets returned.

The protocol permitted the temporary stopping of study medication, allopurinol and/or gout prophylaxis due to suspected drug toxicity or clinically meaningful increases in serum creatinine. Resumption of the same dose of study medications (e.g., lesinurad or matching placebo) was to have occurred when medically appropriate or when the patient's serum creatinine had returned to within 0.2 mg/dL of its level prior to elevation. Additionally, subjects who had temporally discontinued study medication due to an increase in serum creatinine were to have been instructed to increase their daily fluid intake to at least 2 liters/day and start a urine alkalinization regimen (e.g., sodium bicarbonate at 650 mg once or twice daily or potassium citrate 30-40 mEq/day) in order to increase the solubility of urinary uric acid. Restarting concomitant allopurinol at a lower dose was permitted provided it was increased to the original dose. Patients who were medically unable to increase their allopurinol to the original dose were allowed to continue taking the drug at a minimum of ≥ 100 mg per day.

Concomitant Medications:
Concomitant administration of the following medications was prohibited during the study: urate lowering medications other than allopurinol, systemic immunosuppressive or immunodulatory agents, chronic treatment with > 325 mg/day of salicylate, and known inhibitors of epoxide hydrolase (e.g., valpromide, progabide, and valproic acid). Initiation of drugs with secondary uricosuric effects such as fenofibrate, losartan, and chronic guaifenesin during the trial was also not permitted. Subjects taking these medications were to have remained on stable doses for the duration of the study. Due to the increased risk for drug-drug interactions with colchicine, the concomitant use of P-gp or strong CYP3A4 inhibitors were also contraindicated in patients with renal or hepatic impairment who were taking colchicine prophylaxis. Subjects taking medications cleared by the CYP3A4 metabolic pathway were to have been monitored for possible decreases in the therapeutic effectiveness of these drugs since lesinurad has been shown to be a mild inducer of this isozyme. All concomitant medications were to have been recorded at each visit in each subject's case report form.

Gout Flare Treatment:
Patients who experienced an acute gout flare during the study were to have been treated with an individualized anti-inflammatory regimen that included colchicine (acute flare regimen), a NSAID with a PPI, or corticosteroids administered via the intra-articular or oral route.

Removal of Patients from Treatment or Assessment:
Subjects were to have been withdrawn from these trials if they discontinued study medication or concomitant allopurinol for longer than a continuous 6-week period, experienced an adverse event that would have precluded further exposure, required treatment with prohibited or contraindicated medications, were noncompliant, withdrew consent, became pregnant or due to an administrative reason. However, following the implementation of Protocol amendment 4, subjects who discontinued the use of lesinurad/placebo could continue allopurinol alone and continue protocol-specific procedures. Subjects who permanently discontinued allopurinol had to discontinue lesinurad/placebo and were to have been removed from the study.

Study Procedures:
The following **Table 4 - 6** are tabular flow charts of the scheduled study visits and protocol specified procedures and evaluations that were to have been completed. [Note: These flow charts have been updated to include additional safety measures that were implemented as per amendments 3 (June 14, 2013) and 4 (January 2, 2014) to the common study protocol as a result of the SAE reports of acute kidney failure and kidney stones in the ongoing phase 3 studies. For additional information regarding these safety changes refer to the **Study Conduct** subsection below.]

Table 4 – Schedule of Procedures and Evaluations for Studies 301 and 302

Assessment/Procedure	Screening Period			Baseline (Day 1)	Double-Blind Treatment Period**				Follow-Up***	
	Screening Visit –Day -28*	Run-In Period: Day -14	Run-In Period: Day -7		Week 2	Months 1 -6	Months 7 - 11	Month 12/Early Termination Visit	Follow-up	Post-Follow Up Visits[a]
Informed consent	√									
Review eligibility	√									
Record demographics	√									
Record Baseline characteristics of gout, including flares	√									
Record medical & surgical history (including comorbidities)	√									
Record prior ULTs	√									
Record concomitant medications	√	√	√	√	√	√	√	√	√	
Patient Reported Outcomes[b]				√		Month 3 & 6	Month 9	√		
Assess AEs		√	√	√	√	√	√	√	√	
Assess compliance with gout flare prophylaxis			√	√	√	Month 1-5				

Adapted Sponsor's Table 1 p.41-45; Study 301 CSR

Table 5 - Schedule of Procedures and Evaluations for Studies 301 and 302 (cont.)

Assessment/Procedure	Screening Period			Baseline (Day 1)	Double-Blind Treatment Period**				Follow-Up***	
	Screening Visit –Day -28*	Run-In Period: Day -14	Run-In Period: Day -7		Week 2	Months 1 -6	Months 7 - 11	Month 12/Early Termination Visit	Follow-up	Post-Follow Up Visits[a]
Assess compliance with allopurinol			√	√	√	√	√	√		
Assess gout flares			√	√	√	√	√	√	√	
Provide eDiary and training				√						
Assess compliance with eDiary					√	√	√	√		
Assess compliance with lesinurad/placebo and review dosing instructions[c]					√	√	√	√		
Physical examination		√						√[d]		
Vital signs	√	√	√	√	√	√	√	√	√	
12-lead ECG (triplicate)			√	√		Month 6		√		
Tophus measurement[e]				√		Month 3 & 6	Month 9	√		
Tophus photographs[e]				√		Month 6		√		
Confirm eligibility		√	√	√						

Adapted Sponsor's Table 1 p.41-45; Study 301 CSR

Table 6 - Schedule of Procedures and Evaluations for Studies 301 and 302 (cont.)

Assessment/Procedure	Screening Period				Double-Blind Treatment Period**				Follow-Up***	
		Run-In Period								
	Screening Visit –Day -28*	Day -14	Day -7	Baseline (Day 1)	Week 2	Months 1 -6	Months 7 - 11	Month 12/Early Termination Visit	Follow-up	Post-Follow Up Visits[a]
Randomize				√						
Urinalysis	√			√		√	√	√	√	
Urine biomarkers				√		√	Month 8 & 10	√		
Spot urine				√		Month 3 & 6		√		
Hematology	√			√		√	√	√	√	
Blood biochemistry[f] (includes sUA, pregnancy test[g], CK[h], and eCrCl[i])	√		√	√		√	√	√	√	√[j]
Record patient responses to muscle assessment questions				√		√	√	√	√	
Plasma sample for PK and biomarkers			√	√		√	Month 8 & 10	√		
Genetic testing (OPTIONAL single sample collection)				√						
Initiate gout flare prophylaxis[k]		√								

Adapted Sponsor's Table 1 p.41-45; Study 301 CSR

Table 7 - Schedule of Procedures and Evaluations for Studies 301 and 302 (cont.)

Assessment/Procedure	Screening Period				Double-Blind Treatment Period**				Follow-Up***	
	Screening Visit –Day -28*	Run-In Period: Day -14	Run-In Period: Day -7	Baseline (Day 1)	Week 2	Months 1-6	Months 7 - 11	Month 12/Early Termination Visit	Follow-up	Post-Follow Up Visits[a]
Dispense/re-dispense Sponsor-supplied allopurinol		√[k]	√[k]	√	√	√	√			
Dispense lesinurad/placebo				√	√	√	√			

Abbreviations: AE, adverse event; CK, creatine kinase; ECG, electrocardiogram; eCrCl, estimated creatinine clearance; eDiary, electronic diary; PK, pharmacokinetics; sUA, serum urate; ULT, urate-lowering therapy.

* Screening started approximately 28 days (Day -28) prior to Baseline (Day 1) and was performed no more than 2 weeks prior to start of Sponsor-supplied allopurinol and initiation of gout flare prophylaxis by Day -14. There was a ±1 day window around the Run-in Period Visits (Day -14 and Day -7).

**There was a ± 7 day window around the Double-Blind Treatment Period Visits, except Week 2 which was ± 4 days. A clinical month was considered to be 28 days. All scheduled visits were referenced to Day 1.

***Subjects who did not enter an extension study completed a safety Follow-Up Visit within approximately 14 days of completing the Double-Blind Treatment Period.

[a] Serum creatinine values collected at the Follow-Up Visit had to be evaluated by the Investigator. Subjects who had a serum creatinine elevation at the Follow Up Visit, defined as a value > 0.1 mg/dL above their Baseline serum creatinine value, were required to return to the site monthly for blood biochemistry assessment. Upon receipt of those laboratory results, Investigators had to schedule additional visits with the subject to continue to assess serum creatinine until the subject's serum creatinine value was ≤ 0.1 mg/dL of their Baseline value or until 3 monthly assessments after their Follow Up Visit had taken place, whichever came first.

[b] Patient Reported Outcome assessments included Short Form-36, Sheehan Disability Scale, Patient Global Assessment of Disease Activity, HAQ-DI, and TSQM (at Month 12 or Early Termination Visit only).

[c] All doses of lesinurad/placebo were taken in the morning with food and 1 cup (8 oz; 240 mL) of water. Subjects were instructed to drink 2 liters (68 oz) of liquid a day. For example, another 3 cups (24 oz; 720 mL) of liquid during the 3 to 4 hours after taking the study medication were encouraged, and then the subject was to remain well hydrated (an additional 4 cups [32 oz; 960 mL] of liquid) throughout the day. It was required that the morning dose of allopurinol be taken at the same time as lesinurad. If the dose of allopurinol was interrupted, the subject was not to take their dose of lesinurad/placebo until allopurinol was resumed.

[d] Excluding height measurement and waist circumference.

[e] For subjects with target tophi on hands/wrists and feet/ankles, digital caliper measurements and photographs were taken at the specific timepoints indicated and at resolution of any target tophi.

[f] Hepatitis C virus and hepatitis B virus were only evaluated during Screening and at Baseline (Day 1) to confirm study eligibility.

[g] Serum pregnancy test was conducted only on female subjects of childbearing potential.

[h] Additional information regarding potential causes of CK elevations (muscle assessments) were collected from all subjects at every scheduled visit beginning at Baseline where blood biochemistry assessments were performed.

[i] Sites could calculate eCrCl (using the Cockcroft-Gault formula and IBW) at scheduled visits where sCr was assessed; however, calculations were performed by the central laboratory for all subjects for the Day -7 Visit. After implementation of Protocol Amendment 4, the central laboratory also calculated eCrCl for all other scheduled visits where sCr was assessed.

[j] Serum creatinine measurement only.

[k] Investigator confirmed eligibility prior to prescribing prophylaxis or dispensing Sponsor-supplied allopurinol.

Adapted Sponsor's Table 1 p.41-45; Study 301 CSR

Outcome Measures:

The following efficacy assessments were to have been performed:

Primary efficacy endpoint:

The primary efficacy variable for these trials was:

- Proportion of patients with sUA <6 mg/dL by Month 6
  - Subjects' sUA levels were to have been measured via a validated bioanalytical assay at a central lab on blood samples collected at study visits scheduled during screening and at baseline, and thereafter at Months 1-6, 8, 10 and 12. To prevent unblinding, these measurements were not to have been disclosed to study investigators (after the Day -7 visit) or to the Applicant (after the baseline visit). Data generated from the serial measurement of sUA were to have been used in determining clinical outcomes that evaluated reduction in sUA over the course of these trials.

Secondary efficacy endpoints:

These studies had a number of secondary endpoints. The key secondary variables for these trials were:

- Proportion of subjects requiring treatment for a gout flare during the time period from Month 6 to Month 12
    - Clinically relevant gout flares were defined by the common protocol as subject reported gout flares that required the use of prescribed or over the counter colchicine, analgesics, and/or anti-inflammatory medication (including corticosteroids). Patients self-record each gout flare including duration, severity (pain score at rest via an 11-point numerical rating scale [0= no pain and 10= worst imaginal pain]), symptoms (presence of warmth, swelling, and tenderness of the most severely involved joint), treatment and healthcare resource utilization via an eDiary, which asked subjects daily "Have you had a gout attack (flare)?" This information was used in the determination of clinical outcomes that assessed gout flares and treatment over the course of these studies.
- Proportion of subjects with $\geq$ 1 target tophus at baseline who experienced complete resolution of at least 1 target tophus by Month 12
    - The diameters of subcutaneous tophi were to have been measured via the Vernier calipers method. This process required investigators trained in this methodology to use digital calipers to capture both the longest diameter and longest perpendicular measurement (i.e., $\geq$ 5 mm and $\leq$ 20 mm) of up to 5 target tophi located on the hands/wrists and feet/ankles of patients with tophi in these studies. Draining, acutely inflamed, or tophi that had been previously infected were not selected for this assessment. These measurements including photographs to aid in identification of selected tophi were to have been performed at baseline and the Month 12 visit. The collected data were to have used in the determination of the clinical outcomes that assessed reduction in tophus burden in these studies.

Other secondary efficacy variables for these trials were:

- Mean percent change from baseline in the sum of the areas for all target tophi at each visit
- Proportion of subjects with an improvement from baseline in the Health Assessment Questionnaire – Disability Index (HAQ-DI) of at least 0.25 at Month 12
    - This is a self-reported functional status instrument that was used to measures disability over the 12 months of treatment as assessed by 8 domains of functionality. The highest scores from the 8 domains (range: 0-24) are summed and divided by 8 to yield a Functional Disability Index (range: 0-3 with higher scores indicative of increased functional disability). The minimum clinically important difference (MCID) for the HAQ-DI score is -0.22 in rheumatoid arthritis (RA). In determining this assessment, the Applicant is using a HAQ-DI score of -0.25 since it is the closest actual score above the minimum clinically

important difference. However, it should be noted that the study population were not required to have chronically active gout, therefore using the MCID for RA may not be considered relevant to these gout study populations.

- Mean change from baseline to Month 12 in the physical component scale of the Short Form-36 (SF-36)
    - The SF-36 is a validated, 36-item, self-reported questionnaire comprised of 8 subdomains that was used to calculate the 2 summary scores: physical component summary (PCS) and mental component summary (MCS). Average scores in healthy normal population age 55-64 for males and females combined are 47 for PCS and 52 for MCS. Higher scores represent better mental and physical quality of life. The same concerns raised above regarding the HAQ-DI also apply to this outcome measure.
- Total Treatment Satisfaction Question for Medication Score (TSQM)
    - The TSQM is a self-reported questionnaire comprised of four domains: efficacy, convenience, side effects, and overall satisfaction with the medication. It is used to evaluate patient's satisfaction with a medication.
- Mean change from baseline in the Sheehan Disability Scale (SDS)
    - The SDS is a self-reported questionnaire that measures functional impairment in 3 domains: work/school impairment, social impairment, and impairment of family life/home responsibilities. A total disability score is calculated based on the sum total of the disability scores for each question. Unproductive days or days lost from work during the previous week are also calculated. Higher scores are associated with greater impairment. The same concerns raised above regarding the HAQ-DI also apply to this outcome measure.
- Mean change from baseline in Patient Global Assessment (PGA) of Disease Activity
    - The PGA is a validated patient-rated instrument that is comprised of a single item, a100 mm visual analogue scale (VAS). It is used to assess overall disease activity. Higher scores are associated with greater disease impairment.
- Proportion of subjects whose sUA level is <6.0 mg/dL, <5.0 mg/dL and <4.0 mg/dL at each visit
- Absolute and percent change from baseline in sUA levels at each visit
- Proportion of subjects requiring treatment for a gout flare at monthly intervals between Month 6 and Month 12

Statistical Design, Definitions of Analyzed Populations and Analysis Plan:
The sample size calculation for these studies was based on the efficacy and safety data generated from the Applicant's phase 2b study of lesinurad in combination with allopurinol. With projected enrollment of 600 patients (200 patients per treatment arm),

these studies were to have greater than 90% power to demonstrate a 18% difference between the lesinurad groups and placebo plus allopurinol in the proportion of subjects achieving a sUA <6 mg/dL at Month 6 assuming a placebo response rate of 30% using Fisher's exact test adjusting for multiplicity at a significance level of 0.025 (2-sided) for each test. To ensure that adequate numbers of subjects were enrolled in to the safety database and that the key secondary endpoint of the gout flares was adequately powered, the sample size for these trials was based on the key secondary endpoint of mean rate of gout flares requiring treatment between Months 6 and 12. Based on a clinically meaningful 50% reduction in the rate of gout flares requiring treatment and a coefficient of variation of 2.0 or less, the proposed sample size of 200 patients provided greater than 80% power to detect this difference in gout flares between the lesinurad arms compared to placebo using a Wilcoxon Rank-Sum test at a significance level of 0.025 (2-sided).

Three populations were to have been used for analysis. They were defined as follows:

1. Intent-to-Treat (ITT) Population: was to have consisted of all randomized patients who had received at least 1 dose of study drug.
2. Per-Protocol Population: was to have consisted of subjects in the ITT population who had no major deviations from the study protocol.
3. Safety Population: was to have consisted of all subjects who received at least 1 dose of the randomized study medication.

Efficacy Evaluation:

The statistical analysis plan (SAP) stipulated that a Bonferroni correction was to have been used in analyzing the primary endpoint (alpha level =0.025) and hierarchical testing was to have been performed on the key secondary endpoints in order to control for multiplicity. If the null hypothesis for the primary endpoint for both doses was rejected at the 0.025 level, then the key secondary endpoints were to have been tested in the following order at an alpha level of 0.05:

- Mean rate of gout flares requiring treatment for the 6-month period from the end of Month 6 to the end of Month 12, lesinurad 400 mg + allopurinol versus placebo + allopurinol
- Mean rate of gout flares requiring treatment for the 6-month period from the end of Month to the end of Month 12, lesinurad 200 mg + allopurinol versus placebo + allopurinol
- Proportion of subjects with $\geq$ 1 target tophus at baseline who experience complete response of $\geq$ 1 target tophus by Month 12, lesinurad 400 mg + allopurinol versus placebo + allopurinol
- Proportion of subjects with $\geq$ 1 target tophus at baseline who experience complete response of $\geq$ 1 target tophus by Month 12, lesinurad 200 mg + allopurinol versus placebo + allopurinol

Testing of the key secondary endpoints was to have been stopped if there was a failure to reject the null hypothesis. If only one of the primary endpoint dose contrasts was shown to be significant, then an alpha level of 0.025 was to be used for each key

secondary endpoint within the surviving dose. The order of testing within the surviving dose group was to have been the gout flare endpoint, and if significant, the tophi resolution endpoint. All other secondary efficacy endpoints were to have been tested at the alpha=0.05 level without correction for multiplicity.

The primary efficacy analyses were to be conducted via the Cochran-Mantel-Haenszel (CMH) test stratified for Day -7 renal function and tophus status at screening using the ITT population with nonresponder methodology to account for missing data. Sensitivity analyses of the primary endpoint results were to have included using last observation carried forward (LOCF) as well as conducting a completers analysis. Serum uric acid response rates were to have been analyzed via a logistic regression model testing for an association between the response rate and treatment arm while controlling for Day -7 renal function and tophus status during screening.

The two key secondary endpoints were to have been analyzed with the CMH test adjusted for the Day -7 renal function and tophus status for the gout flare endpoint and by the Day-7 renal status for the tophi resolution endpoint. Sensitivity analyses for the gout flare endpoint were to have been conducted that included counting patients who discontinued the study at any time due to a gout flare as having had a gout flare requiring treatment during Month 12, and counting subjects who discontinued the study at any time due to a gout flare after stopping gout flare prophylaxis as having had a gout flare requiring treatment during Month 12. Sensitivity analyses for the tophi resolution endpoint were to have included LOCF and a completers analysis.

Due to the possibility of a reduced sample size at the Month 12 time point, the SAP also stipulated that a pooled analysis of gout flare and tophi resolution data generated from the replicate Studies 301 and 302 was to have been conducted. This pooled analysis was to have been also conducted on the ITT population using the CMH test adjusted for study, Day -7 renal function, and tophus status at screening for the gout flare endpoint analysis, and by study and tophus status at screening for the tophi endpoint analysis. A Hochberg testing procedure dependent on the testing outcome of the primary endpoints from the individual studies was to have been applied to control for type-1 error during the pooled analysis.

Analysis of the remaining continuous secondary efficacy endpoints were to have been conducted via ANCOVA while all categorical response endpoints were to be done via a CMH model. These analyses were to have been adjusted for Day -7 renal function and/or tophus status at screening.

Safety Evaluation:
The analysis of safety assessment was to have been conducted on the safety population. Descriptive statistics were to have been used to summarize safety assessment data which was to have included treatment emergent adverse events (TEAEs), treatment-emergent serious adverse events (SAEs), clinical lab data, physical

exam findings and vital signs. All TEAEs were to have been coded using the Medical Dictionary for Regulatory Affairs (MedDRA) coding dictionary (Version 13.1). The incidences of TEAEs were to have been summarized by system organ class (SOC) and preferred term by overall and treatment group. TEAE of interest such as renal-related adverse events such as kidney stones and clinical lab data such as serum creatinine (sCr), estimated creatinine clearance (eCrCl), and spot urine protein to creatinine ratio were to have been presented separately. The common protocol defined elevations in sCr as values $\geq$ 1.5, 2.0 and 3.0 x the baseline value and was considered to be resolved when a subsequent value was $\leq$ 1.2 x baseline. Renal events were adjudicated by a post hoc renal event advisory committee (REAC). Similarly, cardiac events were adjudicated by a cardiovascular event advisory committee (CEAC).

Clinical lab data results for hematology, serum chemistry and urinalysis testing as well as vital signs, physical exam and EKGs were to have been reviewed and summarized for within treatment changes and for changes from baseline for each treatment group using descriptive statistics.

Study Conduct:

Four protocol amendments were made to the common protocol for Studies 301 and 302:

1. Amendment 1 (implemented on March 8, 2012)
   Minor changes to provide clarification to study investigators regarding:
   - Eligibility criteria, lab instructions, rescreening instructions, timing of follow-up serious adverse event (SAE) reporting, process for obtaining and distributing informed consent forms (ICFs)
2. Amendment 2 (implemented on August 28, 2012)
   Major changes to the protocol included:
   - Revised sUA eligibility criteria to $\geq$ 6.5 mg/dL at the screening visit and $\geq$ 6.0 mg/dL at the Day -7 Visit
   - Revised the eligibility criteria to exclude the morbidly obese who have an inherent increased risk for death and other SAEs
   - Changed the secondary endpoint from “proportion of subjects requiring treatment for a gout flare during Month 12” to “mean rate of gout flares requiring treatment for the 6 month period from the end of Month 6 to the end of Month 12” and associated changes in the SAP
   - Addition of the definition of gout flares for the purpose of the key secondary gout flare endpoint analysis and to describe the data collection process for recording gout flares
   - Reduction in the sample size from 750 to 600 total randomized subjects and from 250 to 200 randomized subjects per treatment group
   - Removal of the statistical analysis of safety data at Month 6 and removal of the interim analysis for safety

- Revision of the dosing guidelines for colchicine, intra-articular steroids, and oral steroids to encompass the range of dosing regimens and various regional standards of care for acute gout flares
- Revision of the definition of an SAE to also exclude planned hospitalization for an elective medical/surgical procedure, scheduled treatments, or routine check-ups, or a hospitalization lasting <24 hrs
- Required subjects to discontinue study medication following emergency unblinding

Minor changes to the protocol included:

- Specifying that trial would be conducted in the U.S. rather than North America; subjects in the safety population who received an incorrect study medication from that which was randomized would be summarized according to their intended randomization treatment group; how subjects missing their Month 12 tophus measurement would be categorized for efficacy response; and all lab retests including sUA retests during the screening period and safety lab retests to assess clinical significance should be performed in the fasted state prior to taking the morning dose of any medication to avoid any immediate influence of food or medications on the results
- Clarification of the circumstances where a retest of sUA is permitted; subjects who discontinued lesinurad/placebo could continue allopurinol alone (with protocol-specified procedures) but subjects who permanently discontinued use of allopurinol would be removed from the study; timing of the interpretation of ECGs by the investigator; for the use of the Rheumatology CTC v2.0 criteria for grading severity of AEs; only serious CV events and all deaths should be collect at Month 6 and Month 12 after treatment is discontinued; muscle assessment questions included in the list of procedures to be performed and at which time points as well as type of information for potential causes of CK elevations; procedures for subjects who discontinue study medication but who remain in study; procedures for subjects who withdraw from the study; and the process for obtaining signatures on ICFs and providing copies to subjects
- Correction of the reference for SAE reporting instructions
- Provide revised definition of overdose
- Possibility of extending the screening period for a total of 6 weeks
- Removal of language regarding not including some ITT subjects in the primary endpoint analysis to ensure that the primary analysis included all of the defined ITT population

3. Amendment 3 (implemented on June 14, 2013)
   Major changes to the protocol included additional safety measures as a result of the SAE reports of acute kidney failure and SAEs of kidney stones in the ongoing phase 3 studies. These changes were reviewed and agreed by the Independent Data Monitoring Committee (IDMC) overseeing these studies.

- Expanded guidance on subject hydration (e.g., subjects were to have been instructed to drink 2 liters of liquid per day in order to maintain adequate hydration).
- Expanded the management algorithm if a subject experiences an elevated sCr or kidney stone:
  - Subjects with sCr elevations $\geq$ 1.5 x baseline value were to have retesting of serum creatinine, BUN, and urinalysis and evaluated for potential contributing factors. Investigators were to consider temporarily stopping concomitant medications known to increase sCr including study medication.
  - Subjects with sCr elevations $\geq$ 3 x baseline value were to have study medication temporarily stopped. Once sCr had returned to within 0.2 mg/dL of the subject's baseline sCr value, randomized study medication was to have been resumed. Subjects were to have been re-instructed to drink 1 cup of water when taking study medication and 2 liters of fluid a day to maintain adequate hydration.
  - If a subject experienced 3 episodes of elevated sCr $\geq$ 2 x baseline sCr value or a kidney stone, a mid-morning urine pH assessment was to have been performed at the site and if the urine pH was <6.5, the investigator was to prescribe either sodium bicarbonate or potassium citrate, if not medically contraindicated, to be taken once in the morning prior to administration of lesinurad or placebo, at a dosage compatible with the local product label with the goal of raising urine pH to $\geq$ 6.5 for or 6 to 8 hours after dosing
  - If a kidney stone was passed, it was to have been collected and submitted to pathology for a kidney stone analysis.
- Added assessments of renal events of potential medical importance by an independent Renal Adjudication Adverse Event Committee (REAC)
- Inclusion of a review of dosing instructions in the schedule of events
- Inclusion of a new appendix to provide guidance to sites in reviewing AEs and potential contributing factors in subjects who experience a sCr elevation $\geq$ 1.5 x baseline sCr value

4. Amendment 4 (implemented on January 2, 2014)
   Major changes to the common protocol included additional safety measures as a result of the safety data from the phase 3 placebo controlled lesinurad monotherapy study 303 which showed a higher incidence of nephrotoxic AE in patients who received lesinurad 400 mg qd as compared to placebo. These changes were reviewed and agreed by the IDMC overseeing these studies.
   - Addition of calculated creatinine clearance using the Cockcroft-Gault formula and IBW at all scheduled visits where sCr is assessed
   - Required morning dose of allopurinol be taken at the same time as lesinurad and subjects to interrupt their dose of lesinurad/placebo if their dose of allopurinol is interrupted

- Required subjects who permanently discontinue use of allopurinol to discontinue use of lesinurad/placebo immediately and be removed from the study
- Any subject who experiences a kidney stone during the study must be withdrawn from treatment
- Increased frequency of subject monitoring
- Amendment of the management algorithm for subjects based on sCr and eCrCl, and to provide additional withdrawal from treatment guidelines:
  - If a subject experienced a sCr value that was elevated ≥ 2 x their baseline creatinine value, or an absolute sCr >3.0 mg/dL, study medication was to have been temporarily stopped and a retest of sCr was to have been performed within 7 days. Once the sCr had returned to ≤ 0.1 mg/dL of the subject's baseline sCr value, study drug may have been resumed.
  - If a subject experienced a sCr value that was elevated ≥ 3 x their baseline creatinine value, or an absolute sCr >4.0 mg/dL, or a CrCl of < 30 mL/min, study medication was to have been temporarily stopped and a retest of sCr was to be performed within 7 days. If the repeat sCr value confirmed that the sCr value was elevated ≥ 3 x the subject's baseline creatinine value, or sCr >4.0 mg/dL, or a CrCl of < 30 mL/min, the subject was to have been withdrawn from treatment. Additionally, subjects were to have been followed and evaluated at least weekly until their sCr returns to <2 x their baseline sCr value.
  - In all instances with a sCr ≥ 1.5 x baseline, including ≥ 2 x baseline:
    - Subjects were to have been reminded to drink a cup of water when they took their study medications and drink 2 liters of liquid a day to maintain adequate hydration
    - Investigators should consider temporarily stopping concomitant medications that are known to increase sCr or impact renal function as medically appropriate
    - If a subject had a urine pH <6.5, investigators were to consider initiation of a urinary alkalinizing medication, such as sodium bicarbonate or potassium citrate, to be taken once daily with lesinurad/placebo at a dose approved per local product label with the goal of achieving a urine pH ≥ measured 6 to 8 hours after dosing with lesinurad
    - If a study developed a kidney stone they were to be withdrawn from study treatment.
- Addition of continued follow-up of all subjects who completed the study and to not continue into an extension study, or who withdraw from treatment or from the study until sCr is ≤0.1 mg/dL of their baseline value or for 3 months

- Clarification that the vendor responsible for analyzing the population PK data will be unblinded to the subject's treatment for analysis purposes
- Clarification that no interim analyses were planned
- Removal of the review by the IDMC of the analysis of the primary endpoint at Month 6, which had been previously removed from the IDMC Charter

Results from Study 301:

Disposition:
This study was conducted at 181 centers located in the United States. Of the 2,377 potential patients screened for this study, 607 were randomized to study treatment (**Table 8**). (Note: Data from 26 subjects screened for this study was censored and not included in the final analysis due to the following reasons: 1 subject due to missing informed consent and 25 subjects due to GCP noncompliance at 2 sites.) Four randomized subjects withdrew prior to receiving study medication: 2 due to noncompliance/protocol deviations and violations and 2 due withdrawal of consent. A total of 603 subjects received one dose of study medication (ITT population) in this study: 201 patients in the placebo + allopurinol group (PBO +ALLO), 201 patients in the lesinurad 200 mg + allopurinol group (LESU200 + ALLO) and 201 patients to the lesinurad 400 mg + allopurinol group (LESU400 + ALLO). Overall, the proportion of patients who completed the study with or without completing treatment with randomized study medication was balanced across the three treatment groups (75%). Higher proportions of subjects completed treatment with randomized study medication at the 6-month and 12 month-time points in the PBO + ALLO group as compared to the two lesinurad treatment groups. The higher rates of early discontinuation from study medication treatment in the two lesinurad + ALLO groups at the 6- and 12-month time points were primarily due to subjects experiencing an adverse event, lost to follow-up and non-compliance/protocol violation. Fewer patients in the PBO +ALLO group prematurely discontinued study medications due to an adverse event but more subjects in this group discontinued study treatment early due to non-compliance/protocol violations as compared to the two lesinurad treatment groups at these study time points.

Table 8 – Subject Disposition by for Study 301

	PBO + ALLO (N=201)	LESU200 mg + ALLO (N=201)	LESU400 mg + ALLO (N=201)	Total (N=603)
Number of Patients Randomized:	**202**	**202**	**203**	**607**
Subjects Withdrawn Prior to Receiving Randomized Medications	1	1	2	4
Intent-To-Treat (ITT) Population	**201**	**201**	**201**	**603**
Safety Population	**201**	**201**	**201**	**603**
Per Protocol (PP) Population	**186**	**183**	**175**	**544**
Pts. Completed Study (W/O Completing Randomized Medication Treatment):	**152 (76%)**	**151 (75%)**	**150 (75%)**	**453 (75%)**
Adverse Event	5 (2%)	7 (3%)	8 (4%)	20 (3%)
Consent Withdrawn	10 (5%)	9 (4%)	12 (6%)	31 (55)
Death	0	1 (<1%)	0	1 (<1%)
Gout Flare	0	1 (<1%)	0	1 (<1%)
Lost to Follow-Up	9 (45)	13 (6%)	16 (8%)	38 (6%)
Noncompliance/Protocol Violation	22 (11%)	17 (8%)	15 (7%)	54 (9%)
Sponsor Terminated Study	2 (<1%)	2 (<2%)	0	4 (<1%)
Pts. Completed 6 Months of Randomized Study Medication Treatment:	**174 (87%)**	**163 (81%)**	**163 (81%)**	**500 (83%)**
Adverse Event	4 (2%)	10 (5%)	10 (5%)	24 (4%)
Consent Withdrawn	4 (2%)	6 (3%)	9 (4%)	19 (3%)
Lost to Follow-Up	4 (2%)	9 (4%)	9 (4%)	22 (4%)
Noncompliance/Protocol Violation	14 (7%)	13 (6%)	10 (5%)	37 (6%)
Required Treatment with Prohibited/ Contraindicated Medication	1(<1%)	0	0	1 (<1%)
Pts. Completed 12 Months of Randomized Study Medication Treatment:	**149 (74%)**	**140 (70%)**	**141 (70%)**	**430 (71%)**
Adverse Event	7 (3%)	15 (7%)	14 (7%)	36 (6%)
Consent Withdrawn	8 (4%)	9 (4%)	12 (6%)	29 (5%)
Death	0	1 (<1%)	0	1 (<1%)
Lost to Follow-Up	9 (4%)	13 (6%)	16 (8%)	38 (6%)
Noncompliance/Protocol Violation	27(13%)	22 (11%)	18 (9%)	67 (11%)
Required Treatment with Prohibited/ Contraindicated Medication	1 (<1%)	1 (<1%)	0	2 (<1%)

Table courtesy of Dr. Jade Wang, Staff Statistician

Protocol Deviations and Violations:
A total of 59 patients incurred one or more protocol deviations and violations over the course of this 52-week trial as shown in **Table 9**. A higher rate of protocol deviations/violations occurred in the LESU400 + ALLO group as compared to the LESU200 + ALLO and PBO + ALLO groups which were comparable. Imbalances are noted in the two lesinurad treatment groups (8%) due to noncompliance with study medications >20% of time while on randomized study medications and missed the Month 6 visit (2%) as compared to the PBO + ALLO group (4% and 0%, respectively).

Table 9 – Summary of Subjects with a Major Protocol Deviation by Randomized Treatment Group for Study 301

	PBO + ALLO (N=201)	LESU200 mg + ALLO (N=201)	LESU400 mg + ALLO (N=201)	Total (N=603)
Number of Subjects with Protocol Deviations/Violations	**15 (8%)**	**18 (9%)**	**26 (13%)**	**59 (10%)**
Failure to Meet Incl/Excl. Criteria	1 (1%)	1 (1%)	1 (1%)	3 (1%)
Taking <300 mg of Allopurinol (or < 200 mg if Moderate Renal Insufficiency) at Randomization	4 (2%)	0	6 (3%)	10 (2%)
Received Prohibited ULT	2 (1%)	0	2 (1%)	4 (1%)
Noncompliance with Study Meds >20%	8 (4%)	15 (8%)	15 (8%)	38 (6%)
Missed > 2 Study Visits	0	1 (1%)	0	1 (<1%)
Missed Month 6 Visit	0	4 (2%)	4 (2%)	8 (1%)

Adapted Sponsor's Table 14.1.1.4, p. 257-258 Study 301 CSR

Demographics:

As summarized by the following tables (**Table 10** and **Table 11**), the treatment groups within Study 301 were generally well balanced with respect to baseline demographics, disease characteristics and activity.

The subjects who participated in this trial were overwhelmingly Caucasian males with a mean age 52 years (**Table 10**). These patients were also overweight as evidenced by a mean body mass index (BMI) of 35 kg/m^2 which is consistent with the fact that obesity is a risk factor for gout. The majority (98%) of subjects did not report a history of alcoholism, another risk factor for gout.

Table 10 – Baseline Demographic Characteristics of Subjects Enrolled in Study 301

Demographic Characteristic	PBO + ALLO (N=201)	LESU200 mg + ALLO (N=201)	LESU400 mg + ALLO (N=201)	Total (N=603)
Age (years)				
Mean (SD)	52 (12)	52 (11)	52 (11)	52 (11)
Gender				
Male	189 (94%)	192 (96%)	186 (93%)	567 (94%)
Female	12 (6%)	9 (5%)	15 (8%)	36 (6%)
Race:				
American Indian/Alaska Native	1 (1%)	2 (1%)	0	3 (1%)
Asian	10 (5%)	9 (5%)	7 (4%)	26 (4%)
Black/African American	29 (14%)	31 (15%)	30 (15%)	90 (15%)
Maori	0	0	0	0
Native Hawaiian/other Pacific Islander	5 (3%)	4 (2%)	5 (3%)	14 (2%)
White	153 (76%)	151 (75%)	156 (78%)	460 (76%)
Other	3 (2%)	4 (2%)	3 (2%)	10 (2%)
Ethnicity (Hispanic/Latino)				
Yes	19 (10%)	27 (13%)	31 (15%)	77 (13%)
No	182 (91%)	174 (87%)	170 (85%)	526 (87%)
Weight (Kg)				
Mean (SD)	109 (24)	110 (21)	110 (24)	110 (23)
Height (cm)				
Mean (SD)	178 (8)	177 (8)	177 (9)	177 (8)
Body Mass Index (BMI) [kg/m^2]				
Mean (SD)	34 (6)	35 (6)	35 (7)	35 (7)
History of Alcoholism:				
Yes	2 (1%)	1 (1%)	3 (2%)	6 (1%)
No	197 (98%)	198 (99%)	197 (98%)	592 (98%)

Adapted Sponsor's Tables 14.1.2.1 and 14.1.2.4, p. 259-260 and 257-258 Study 301 CSR

The overall mean duration of disease since the first gout attack was 12 years for the study population who also reported having a mean number of 5 gout attacks per year over the last 12 months (**Table 11**). The treatment groups within the trial were also generally well balanced with respect to baseline disease status and treatment with the following exceptions. Differences in the three treatment groups were observed for crystal proven gout, mean total area of target tophi and concomitant doses of allopurinol > 300 mg/day. More patients randomized to the PBO + ALLO (15%) and the LESU400 + ALLO (14%) groups had crystal proven gout as compared to the LESU20 + ALLO group (10%). The mean total area of target tophi at baseline was also higher in the PBO + ALLO (322 mm^2) and LESU200 + ALLO (325 mm^2) groups versus the LESU400 + ALLO group (254 mm^2). A higher proportion of patients in the PBO +ALLO group were taking >300 mg/day allopurinol (17%) as compared to the LESU200 + ALLO (5%) and LESU400 + ALLO (3%) groups.

Following at least 10 weeks on a medically appropriate stable dose of allopurinol, the study population had a baseline mean sUA 6.94 mg/dL with approximately 19% having a baseline sUA <6 mg/dL (**Table 11**). A total of 21% of the patients had mild to moderate impairment as assessed by an estimated creatinine clearance (eCrCl) of <60 ml/min at baseline with 8% having moderate to severe renal impairment (eCrCl < 45 ml/min). Overall, the study population who participated in this trial was representative of patients who continued to have symptomatic hyperuricemia despite urate lowering therapy and could potentially benefit from treatment with lesinurad.

Table 11 – Summary of Subject's Gout History, Disease Status, and Treatment at Baseline by Randomized Treatment Group for Study 301

	PBO + ALLO (N=201)	LESU200 mg + ALLO (N=201)	LESU400 mg + ALLO (N=201)	Total (N=603)
American Rheumatism Association Diagnostic Criteria	**200(99.5%)**	**200(99.5%)**	**201(100%)**	**601 (99.7%)**
Presence of MSU Crystals in Jt. Fluid	31 (15%)	20 (10%)	29 (14%)	80 (13%)
Number of Years Since Gout Dx:				
Mean (SD)	12 (9)	13 (10)	11 (9)	12 (9)
Number of Gout Flares in Past 12 Months				
Mean (SD)	5 (4)	5 (3)	5 (3)	5 (3.6)
Tophi				
Yes	27 (13%)	30 (14%)	31 (15%)	87 (14%)
No	174 (87%)	172 (86%)	170 (85%)	516 (86%)
Baseline Presence of ≥1 Target Tophus (≥5 mm and ≤20 mm in diam.)				
Yes	17 (9%)	18 (9%)	19 (10%)	54 (9%)
No	184 (92%)	183 (91%)	182 (91%)	549 (91%)
Mean Number of Target Tophi (SD)	**1.8 (1.5)**	**1.8 (1.1)**	**2.1 (1.5)**	**1.9 (1.3)**
Total Area of Target Tophi at Baseline (mm^2)				
Mean (SD)	322 (281)	335 (201)	254 (165)	302 (210)
Baseline sUA (mg/dL)				
Mean (SD)	**6.99 (1.25)**	**7.01 (1.32)**	**6.83 (1.24)**	**6.94 (1.27)**
<6.0	31 (15%)	36 (18%)	45 (22%)	112 (19%)
6.0 -<7.0	82 (41%)	76 (38%)	72 (36%)	230 (38%)
7.0 -<8.0	52 (26%)	52 (26%)	52 (26%)	156 (26%)
8.0 - <10.0	32 (16%)	31 (15%)	28 (14%)	91 (15 %)
>10.0	4 (2%)	6 (3%)	4 (2%)	14 (2%)
Baseline Renal Function (ml/min)				
eCrCl ≥90	77 (38%)	83 (41%)	76 (38%)	236 (39%)
eCrCl <90	123 (61%)	117 (58%)	124 (62%)	364 (60%)
eCrCl ≥60	**160 (80%)**	**155 (77%)**	**159 (79%)**	**474 (79%)**
eCrCl <60	**40 (20%)**	**45 (22%)**	**41 (20%)**	**128 (21%)**
eCrCl ≥ 45	180 (90%)	188 (94%)	185 (92%)	553 (92%)
eCrCl < 45	20 (10%)	12 (6%)	15 (8%)	47 (8%)
Prior ULT				
Allopurinol	4 (2%)	8 (4%)	4 (2%)	16 (3%)
Febuxostat	5 (3%)	3 (2%)	5 (3%)	13 (2%)
Probenecid	3 (2%)	2 (1%)	2 (1%)	7 (1%)
Other	1 (1%)	0	2 (1%)	3 (1%)

Adapted Sponsor's Table 14.1.2.3, p. 263-268 Study 301 CSR

Table 11 – Summary of Subject's Gout History, Disease Status, and Treatment at Baseline by Randomized Treatment Group for Study 301 (cont.)

	PBO + ALLO (N=201)	LESU200 mg + ALLO (N=201)	LESU400 mg + ALLO (N=201)	Total (N=603)
Gout Flare Prophylaxis				
Colchicine	166 (83%)	170 (85%)	168 (84%)	504 (84%)
NSAID	34 (17%)	28 (14%)	33 (16%)	95 (16%)
Both	1 (1%)	2 (1%)	3 (2%)	6 (1%)
Other or Missing	2 (1%)	5 (3%)	3 (3%)	10 (2%)
Allopurinol Dose at Baseline (mg/d)				
Mean (SD)	310 (70)	310 (60)	300 (47)	307 (60)
Allopurinol Dose at Baseline (mg/d)				
<300	**12 (6%)**	**5 (3%)**	**12 (6%)**	**29 (5%)**
=300	**176 (88%)**	**187 (93%)**	**183 (91%)**	**546 (91%)**
>300	**13 (7%)**	**9 (5%)**	**3 (2%)**	**28 (5%)**
400-<500	3 (2%)	1 (1%)	3 (2%)	7 (1%)
500-<600	1 (1%)	1 (1%)	0	2 (<1%)
≥600	9 (5%)	7 (4%)	3 (2%)	19 (3%)

Adapted Sponsor's Table 14.1.2.3, p. 263-268 Study 301 CSR

As summarized in **Table 12**, the majority (82%) of the subjects who participated in Study 301 reported having ≥ 1 comorbid condition associated with hyperuricemia. Comorbid conditions with a high prevalence in this study population that increased the risk for metabolic syndrome and/or hyperuricemia included hypertension (67%), hyperlipidemia (50%), hypertriglyceridemia (23%), diabetes mellitus (19%) and kidney stones (13%). The three treatment groups were generally similar with respect to the occurrence of co-morbid conditions except for kidney stones. More patients with kidney stones were randomized to the PBO + ALLO group as compared to the LESU200 + ALLO and LESU400 + ALLO groups. The overall rate of CV comorbidity and/or CV disease history was also very high (80%) in this study population.

Table 12 – Summary of Comorbid Medical Conditions Reported by Subjects by Randomized Treatment Group in Study 301

	PBO + ALLO (N=201)	LESU200 mg + ALLO (N=201)	LESU400 mg + ALLO (N=201)	Total (N=603)
≥1 Comorbidity	167 (83%)	161 (80%)	167 (83%)	495 (82%)
≥2 Comorbidity	101 (50%)	106 (53%)	111 (55%)	318 (53%)
≥3 Comorbidity	60 (30%)	63 (31%)	54 (27%)	177 (29%)
Types of Comorbidities				
Hypertension	134 (67%)	129 (64%)	142 (71%)	405 (67%)
Hyperlipidemia	**99 (49%)**	**102 (51%)**	**98 (49%)**	**299 (50%)**
Hypercholesterolemia	90 (45%)	90 (45%)	83 (41%)	263 (44%)
Hypertriglyceridemia	40 (20%)	51 (25%)	45 (22%)	136 (23%)
Diabetes Mellitus	35 (17%)	44 (22%)	38 (19%)	117 (19%)
Kidney Stones	38 (19%)	20 (10%)	22 (11%)	80 (13%)
Myocardial Infarction	7 (4%)	11 (6%)	6 (3%)	24 (4%)
Heart Failure	4 (2%)	12 (6%)	6 (3%)	22 (4%)
Angina Pectoris	3 (2%)	5 (3%)	7 (4%)	15 (3%)
Transient Ischemic Attack	3 (2%)	3 (2%)	3 (2%)	9 (2%)
Stroke	3 (2%)	1 (1%)	3 (2%)	7 (1%)
Peripheral Vascular Disease	1 (1%)	3 (2%)	2 (1%)	6 (1%)
Any CV Comorbidity and/or CV Disease History	**158 (79%)**	**159 (79%)**	**164 (82%)**	**481 (80%)**

Adapted Sponsor's Tables 14.1.3.1 and 14.1.3.3; p. 273 and 274 Study 301 CSR

Information regarding concomitant medications used by more than 10% of the study population was also examined (**Table 13**). The most commonly reported concomitant non-gout classes of medications were drugs acting on the renin-angiotensin system, analgesics, lipid-modifying agents, antibacterials and beta-blockers. This information is consistent with what is typically seen in gout patients since this disease is commonly associated with chronic disorders such as hypertension, diabetes mellitus, hyperlipidemia and cardiovascular disease.

Table 13 - Concomitant Medications Taken by ≥ 10% of Subjects in Study 301 by Treatment Group (Safety Population)

ATC Class and WHO Drug Dictionary Preferred Term	PBO + ALLO (N=201)	LESU200 mg + ALLO (N=201)	LESU400 mg + ALLO (N=201)
Any Concomitant Medication	**201 (100%)**	**201 (100%**	**200 (100%)**
Anti-Gout Preparations	**168 (84%)**	**171 (85%)**	**173 (86%)**
Colchicine	168 (84%)	171 (85%)	173 (86%)
Anti-Inflammatory and Anti-Rheumatic Products	**123 (61%)**	**108 (54%)**	**122 (61%)**
Ibuprofen	55 (27%)	38 (19%)	49 (24%)
Indomethacin	38 (19%)	44 (22%)	29 (14%)
Naproxen	24 (12%)	19 (10%)	26 (13%)
Naproxen Sodium	16 (8%)	16 (8%)	10 (10%)
Drugs Acting on Renin-Angiotensin System	**95 (47%)**	**91 (45%)**	**108 (54%)**
Lisinopril	45 (22%)	51 (25%)	56 (28%)
Analgesics	**96 (48%)**	**72 (36%)**	**72 (36%)**
Vicodin	26 (13%)	17 (9%)	22 (11%)
Paracetamol	26 (13%)	11 (6%)	15 (8%)
Lipid Modifying Agents	**89 (44%)**	**90 (45%)**	**70 (35%)**
Simvastatin	31 (15%)	25 (12%)	18 (9%)
Fish Oil	26 (13%)	14 (7%)	15 (8%)
Vitamins	**51 (25%)**	**49 (24%)**	**56 (28%)**
Multivitamin	26 (13%)	20 (10%)	29 (14%)
Antibacterials for Systemic Use	**42 (21%)**	**43 (21%)**	**54 (27%)**
Beta-Blocking Agents	**50 (25%)**	**50 (25%)**	**54 (27%)**
Metoprolol	19 (10%)	16 (8%)	20 (10%)
Drugs for Acid-Related Disorders	**41 (20%)**	**35 (17%)**	**49 (24%)**
Omeprazole	17 (9%)	16 (8%)	22 (11%)
Antithrombotic Agents	**51 (25%)**	**45 (22%)**	**42 (21%)**
Acetylsalicylic Acid	49 (24%)	41 (20%)	40 (20%)
Corticosteroids for Systemic Use	**28 (14%)**	**24 (12%)**	**40 (20%)**
Prednisone	15 (8%)	13 (7%)	20 (10%
Calcium Channel Blockers	**34 (17%)**	**30 (15%)**	**38 919%)**
Amlodipine	24 (12%)	16 (8%)	19 (10%)
Psycholeptics	**26 (13%)**	**25 (12%)**	**38 (19%)**
Diuretics	**40 (20%)**	**45 (22%)**	**36 (18%)**
Furosemide	21 (10%)	22 (11%)	14 (7%)
Hydrochlorothiazide	8 (4%)	19 (10%)	14 (7%)
Drugs Used in Diabetes	**31 (15%)**	**41 (20%)**	**35 (17%)**
Metformin	17 (9%)	26 (13%)	25 (12%)
Antihistamines for Systemic Use	**27 (13%)**	**26 (13%)**	**30 (15%)**
Psychoanaleptics	**29 (14%)**	**31 (15%)**	**29 (14%)**
Drugs for Obstructive Airway Diseases	**17 (9%)**	**23 (11%)**	**25 (12%)**
Mineral Supplements	**29 (15%)**	**23 (11%)**	**19 (10%)**
Vaccines	**18 (9%)**	**12 (6%)**	**19 (10%)**

Adapted Sponsor's Table 14.4.3.a; p. 321-358 Study 301 CSR

Examination of the data in **Table 13** revealed that study participants in each treatment group were taking concomitant medications (e.g., beta-blockers, acetylsalicylic acid,

diuretics, amlodipine, and losartan) that are known to interfere with uric acid metabolism. Overall, the use of these medications appears to be similar across the treatment groups. The following table (**Table 14**) summarizes concomitant usage of thiazide and thiazide-like diuretics by more than 2% of subjects who participated in Study 301. More subjects randomized to the LESU400 + ALLO group as compared to LESU200 + ALLO and PBO + ALLO groups were taking concomitant thiazide and thiazide-like diuretics and renin-angiotensin drugs. Both of these drug classes can affect the urinary excretion of uric acid and could potentially impact on the study's outcome.

Table 14 - Concomitant Thiazide and Thiazide-Like Diuretics by ≥2% of Subjects by Treatment Group During Study 301 (Safety Population)

ATC Class and WHO Drug Dictionary Preferred Term	PBO + ALLO (N=201)	LESU200 mg + ALLO (N=201)	LESU400 mg + ALLO (N=201)
Any Concomitant Thiazide and Thiazide-Like Diuretic	**32 (16%)**	**37 (18%)**	**46 (23%)**
Agents Acting on Renin-Angiotensin System	**14 (7%)**	**11 (6%)**	**23 (11%)**
Zestoretic (lisinopril/hydrochlorothiazide)	9 (5%)	7 (4%)	7 (4%)
Benicar HCT (olmesartan medoxomil/HCTZ)	0	0	3 (2%)
Co-Diovan (valsartan/HCTZ)	1 (1%)	1 (1%)	3 (2%)
Hydrochlorothiazide(HCTZ)/Losartan	2 (1%)	1 (1%)	3 (2%)
Diuretics	**17 (9%)**	**26 (13%)**	**20 (10%)**
Hydrochlorothiazide	8 (4%)	19 (10%)	14 (7%)
Dyazide	4 (2%)	1 (1%)	3 (2%)
Chlorthalidone	0	3 (2%)	2 (1%)
Beta-Blocking Agents	**1 (1%)**	**2 (1%)**	**3 (2%)**

Adapted Sponsor's Table 14.1.4.5.1; p. 385-386 Study 301 CSR

The protocol permitted patients to take medications to treat gout flares they experienced over the course of the study. This information is summarized in **Table 15**. The usage of gout flare medications during this trial appears to be generally similar for the three treatment groups.

Table 15 - Gout Flare Medications Taken by ≥ 2% of Subjects by Treatment Group in Study 301 (Safety Population)

WHO Drug Dictionary Preferred Term	PBO + ALLO (N=201)	LESU200 mg + ALLO (N=201)	LESU400 mg + ALLO (N=201)
Any Concomitant Medication Used to Treat Gout Flares	**83 (41%)**	**87 (43%)**	**76 (38%)**
Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)	**51 (25%)**	**51 (25%)**	**46 (23%)**
Indomethacin	28 (14%)	31 (15%)	24 (12%)
Ibuprofen	18 (9%)	14 (7%)	16 (8%)
Naproxen Sodium	1 (1%)	2 (1%)	7 (4%)
Naproxen	4 (2%)	5 (3%)	2 (1%)
Anti-Gout Drugs	**33 (16%)**	**44 (22%)**	**35 (17%)**
Colchicine	33 (16%)	44 (22%)	35 (17%)
Corticosteroids	**18 (9%)**	**15 (8%)**	**23 (11%)**
Prednisone	9 (5%)	9 (5%)	12 (6%)
Methylprednisolone	6 (3%)	6 (3%)	8 (4%)
Non-NSAID Analgesics	**11 (6%)**	**11 (6%)**	**15 (8%)**
Vicodin (hydrocodone/acetaminophen)	6 (3%)	2 (1%)	5 (3%)
Oxycocet (oxycodone/acetaminophen)	1 (1%)	1 (1%)	3 (2%)
Paracetamol	1 (1%)	2 (1%)	3 (2%)

Adapted Sponsor's Table 14.1.4.7; p. 406-407 Study 301 CSR

Treatment Compliance:

The common protocol specified that patients' compliance with study medication was to have been assessed by pill counts performed on the returned study medication kits which contained a 40-day supply of randomized medication. Overall mean compliance was high for all three treatment groups (≥95%) with 13% of the subjects reporting greater than 100% compliance with study medication (**Table 16**).

Table 16 – Compliance With Randomized Study Medication for Subjects by Randomized Treatment Group in Study 301

	PBO + ALLO (N=201)	LESU200 mg + ALLO (N=201)	LESU400 mg + ALLO (N=201)
Overall Compliance (Baseline to Month 12 or Early Discontinuation)			
Mean (SD)	**95% (9)**	**96% (18)**	**95% (8)**
Min, Max	47, 131	27, 300	53, 115
Compliance Category			
<80%	10 (5%)	13 (7%)	14 (7%)
80-100%	162 (81%)	164 (82%)	160 (80%)
>100%	29 (14%)	24 (12%)	27 (13%)

Note: Overall Compliance was calculated by the Applicant as follows: [Total number of small and large tablets taken]/[2 x total days on randomized medication] x 100% where total days on randomized study medication is calculated as follows: (last randomized study medication dose date – first randomized study medication dose date + 1)

Adapted Sponsor's Table 14.1.6; p. 411 Study 301 CSR

Efficacy:

Primary Endpoint

As discussed in the preceding common protocol section, the primary efficacy parameter for Study 301 was the proportion of patients with sUA less than 6 mg/dL by Month 6. As shown in **Table 17**, greater proportions of patients treated with both LESU400 + ALLO and LESU200 + ALLO showed a response to therapy as compared to patients treated with PBO + ALLO. The differences between each of the treatment groups and the placebo group were statistically significant (p<0.0001). A dose response between the two lesinurad + ALLO groups was not clearly demonstrated for this parameter.

Table 17 – Month 6 Primary Endpoint Results (ITT Population) for Study 301

	PBO + ALLO (N=201)	LESU200 mg + ALLO (N=201)	LESU400 mg + ALLO (N=201)
Proportion with sUA <6.0 mg/dL by Month 6	56 (28%)	109 (54%)	119 (59%)
Difference vs PBO + ALLO (95% CI)		0.26 (0.17, 0.36)	0.31 (0.22, 0.41)
P-Value[a]		<0.0001	<0.0001

CI = Confidence interval
Cochran-Mantel Haenszel test stratified by Day-7 renal function (eCrCl≥ 60 mL/min) and tophus status during screening (presence vs absence), randomization stratification values using nonresponder imputation for subjects missing Month 6 sUA.
Table Courtesy Dr. Jade Wang

The Applicant provided the results from six sensitivity analyses for the primary efficacy endpoint that were prespecified in the SAP (e.g., last observation carried forward [LOCF] analysis; observed case analysis; reached target sUA <5 mg/dL at each Month 4, 5, and 6; reached target sUA <6 mg/dL logistic regression analysis, a CMH test stratified by Day -7 renal function and tophus status using actual values for these variables rather than stratification factor values; and the per protocol population analysis) which were generally supportive of the findings of the primary efficacy analysis. (Note: Reader is referred to the statistical review of this application by Dr. Jade Wang for further information regarding these sensitivity analyses and the results of additional sensitivity analyses that she conducted as part of her review of this application.)

Secondary Endpoints:

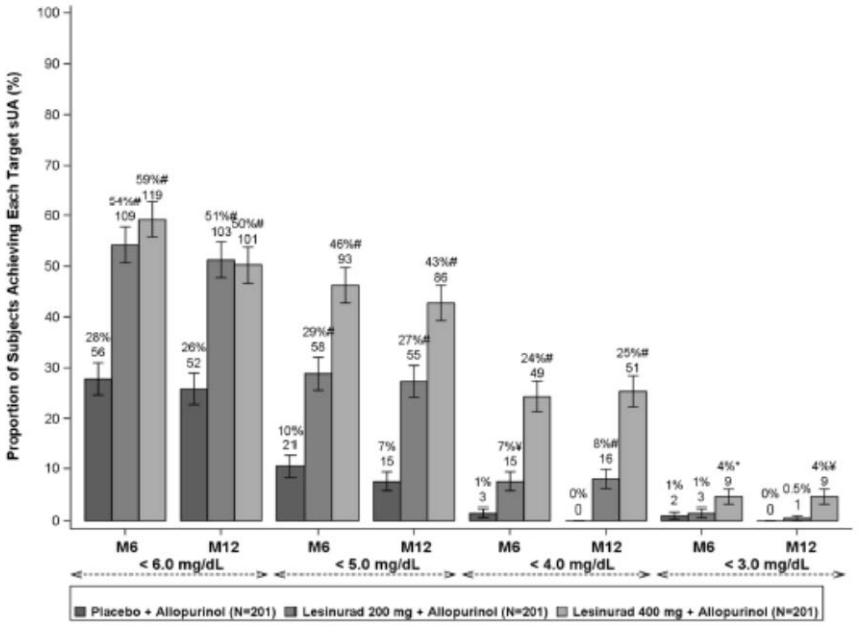
There were two major and multiple ancillary secondary endpoints for this trial that were assessed in order to determine if a clinical benefit (e.g., gout flare and resolution of tophi) was associated with the administration of lesinurad. These secondary assessments are presented below by corresponding assessment area. In order to control for multiplicity, the statistical analysis plan mandated the major secondary endpoints for this study to be analyzed via a sequential procedure in a prespecified descending order following testing of the primary endpoint. Due to the statistically non-

significant finding for the major secondary endpoint analysis for gout flares for the LESU400 + ALLO treatment group, no further testing was to have been performed. For completeness, the results of the secondary endpoint analyses are being presented in this review. However, findings from the major secondary endpoints should not be considered statistically significant due to the hierarchical testing method used for multiple endpoints. Declaring statistical significance of the ancillary secondary endpoints using unadjusted p-values may be inappropriate due to multiplicity concerns.

sUA Reduction:

- Proportion of subjects whose sUA level is <6.0 mg/dL, <5.0 mg/dL and <4.0 mg/dL at each visit: Lesinurad's urate lowering capability was also assessed by examining different threshold response levels than that explored by the primary endpoint. As shown in **Figure 3**, higher proportions of patients randomized to the two lesinurad + ALLO treatment groups achieved sUA levels <6.0, <5.0, < 4.0, and <3.0 mg/dL as compared to the PBO + ALLO group at the Months 6 and 12 time points. The differences between each of the treatment groups and the placebo group were statistically significant. Overall, the response appears to be dose-dependent, particularly at lower sUA level targets.

Figure 3 - Subjects Achieving sUA <6.0, <5.0, <4.0, and <3.0 at Months 6 and 12 in Study 301 (NRI) (ITT Population)



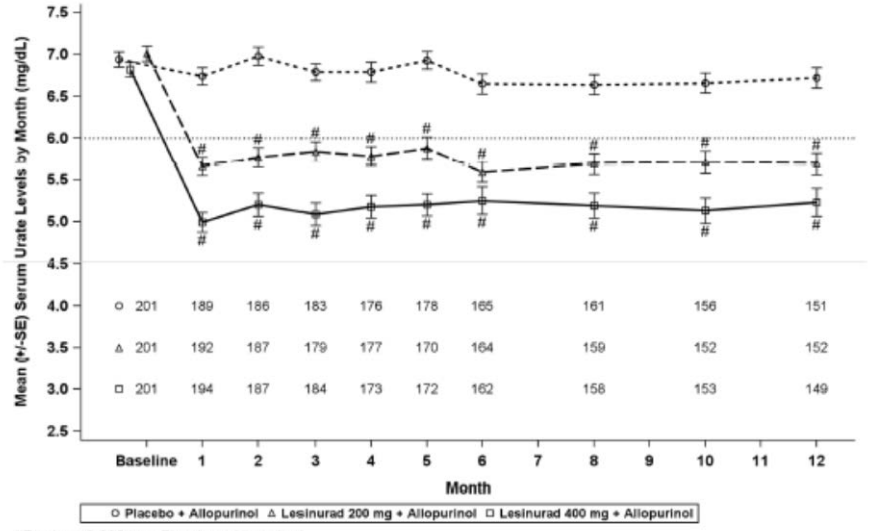
*P-value <0.05 vs. Placebo + Allopurinol; ¥P-value <0.01 vs. Placebo + Allopurinol
#P-value <0.0001 vs. Placebo + Allopurinol

Abbreviations: ITT, intent-to-treat; M, month; NRI, nonresponder imputation; sUA, serum urate.
Note: Numbers in the figure refer to % of subjects who achieved the target sUA at either Month 6 or Month 12 (M6 or M12) and the number of subjects in that group that achieved target. The targets are listed below the x-axis (< 6.0, < 5.0, < 4.0, and < 3.0 mg/dL). Proportions and standard errors are noted in the figure.
Source: Study 301 CSR Table 14.2.1.7, Table 14.2.1.8, Table 14.2.1.9, Table 14.2.1.10.

Adapted Sponsor's Fig. 11; p. 89 Summary of Clinical Efficacy

- Absolute and percent change from baseline in sUA levels at each visit: **Figure 4** graphically depicts the mean sUA level profiles for the three treatment groups. The maximum change related to lesinurad treatment appears to be in the first month of treatment; approximately 1 mg/dL decrease for the 200 mg dose and approximately 2 mg/dL for the 400 mg dose. The decrease appears to be consistent over time through Month 12. The PBO + ALLO group's baseline mean sUA remains essentially unchanged over the course of the study. At each visit, the mean changes in sUA levels over baseline for both lesinurad + ALLO groups were significantly different as compared to PBX + ALLO (p<0.0001).

Figure 4 - Mean Serum Urate Levels by Visit in Study 301 (Observed Cases; ITT Population)



Abbreviations: ITT, intent-to-treat; SE, standard error.
Numbers indicate the number of subjects contributing data at each timepoint. Dotted line indicates target sUA (< 6.0 mg/dL). Statistical significance is based on the difference in least square mean percent change from Baseline.
Note: Months 7, 9, and 11 data are excluded because the timing of the last protocol amendment (Protocol Amendment 4), which added sUA assessments at these timepoints, resulted in minimal data collection at these timepoints for analysis.
Source: Study 301 CSR Table 14.2.1.22.

Adapted Sponsor's Fig. 14; p. 99 Summary of Clinical Efficacy

Gout Flares Requiring Treatment:

Initiation of urate lowering therapies in gout patients is known to be associated with an increased risk of gout flare. Theoretically, the occurrence of gout flares should decrease once a subject's sUA level is < 6mg/dL. A total of 668 gout flares requiring treatment were reported by 235 subjects over the 12- month course of this study as follows: 37% of subjects in the PBO + ALLO group, 40% of subjects in the LESU200 mg + ALLO group and 39% of subjects in the LESU400 mg + ALLO group. The majority (59%) of gout flares occurred during the time period from baseline to the end of Month 6 with numerically higher rates of gout flares observed in the LESU400 mg + ALLO (32%) and LESU200 mg + ALLO (29%) groups as compared to PBO + ALLO (21%). To prevent confounding of the gout flare assessments during Months 6 to 12, subjects were required to discontinue their gout flare prophylaxis regimens at the end of Month 5.

- Mean rate of subjects requiring treatment for a gout flare during the 6-month time period from Month 6 to Month 12: This was an unmet major secondary endpoint for both lesinurad + ALLO treatment groups in this study (**Table 18**). Overall, the adjusted mean rates of gout flares requiring treatment were low during this prespecified time period and no differences between the three treatment groups were observed for this endpoint.

Table 18 – Mean Rate of Gout Flares requiring Treatment[1] per Subject for from Month 6 to Month 12 During Study 301 (ITT Population)

	PBO + ALLO (N=201)	LESU200 mg + ALLO (N=201)	LESU400 mg + ALLO (N=201)
Adjusted Rate[2,3] of Gout Flare Requiring Treatment per Subject Months 6 to 12 (SE)	0.62 (0.11)	0.62 (0.11)	0.55 (0.10)
Incidence Rate Ratio (95% CI) vs PBO + ALLO P-value		0.99 (0.61, 1.61) 0.98	0.88 (0.54, 1.43) 0.61

[1]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 prior to the start or 3 days after the end of the gout flare.
[2]Estimates obtained from Negative Binomial Regression adjusted for Day -7 renal function (eCrCl ≥ 60 mL/min versus < 60 mL/min) and tophus status during Screening (presence versus absence), randomized values, and log follow-up time as the offset variable.
[3]Estimates of adjusted rate for each treatment group obtained from inputting empirical proportion of each stratification factor level under each study.
Table Courtesy of Dr. Jade Wang

- Proportion of subjects requiring treatment for gout flares at monthly intervals between Month 6 and Month 12: Consistent with the other flare endpoint mentioned above, the proportion of subjects requiring treatment for gout flares for each monthly interval was low and comparable between the three treatment groups. (Data not shown.)

Target Tophus Resolution:
Another clinical benefit associated with urate lowering therapy is the resolution of tophaceous deposits. At baseline, a total of 15% of the subjects had tophi that qualified as a target tophus by prespecified study criteria. This subset population was used in the analyses of tophus response assessments in this trial.

- Proportion of subjects with ≥ 1 target tophus at baseline who experienced complete resolution of at least 1 target tophus by Month 12: This was the remaining major secondary endpoint for this trial that was also unmet. As shown in **Table 19**, the proportions of patients achieving a "complete" or "best" response at Month 12 were comparable for the three treatment groups. (Note: Although the p-value appears to be significant for the comparison between the LESU200 mg + ALLO and PBO + ALLO the difference favors the PBO + ALLO group.)

Table 19 – Proportion of Subjects with ≥1 Target Tophus at Baseline Who Experienced Complete Resolution of at least 1 Target Tophus by Month 12 During Study 301 (NRI; ITT Population with at Least 1 Target Tophus at Baseline)

	PBO + ALLO (N=201)	LESU200 mg + ALLO (N=201)	LESU400 mg + ALLO (N=201)
Subjects with at Least 1 Target Tophus at Baseline (ITT Population)	17	18	19
Proportion with Best Response of CR by Month 12 [n, %]	5 (29%)	0	4 (21%)
Diff. in Proportion vs PBO + ALLO (95% CI)[1]		-0.29 (-0.51, -0.08)	-0.08 (-0.37, 0.20)
P-value[2]		0.02	0.60

[1]Binomial confidence interval for difference in proportions
[2]Cochran-Mantel Haenszel test stratified by Day -7 renal function (eCrCl ≥ 60 mL/min versus < 60 mL/min), randomized values.
Table Courtesy Dr. Jade Wang

- Mean percent change from baseline in the sum of the areas for all target tophi at each visit: As shown in **Table 20**, decreases in the mean sum area of all tophi were observed at both the Month 6 and Month 12 time points which were not significantly different on comparison between the three treatment groups.

Table 20 - Sum of the Areas of All Tophi at Month 6 and Month 12 in Subjects with at Least 1 Target Tophus at Baseline in Study 301 (Observed Cases; ITT Population – Subjects with at Least 1 Target Tophus at Baseline)

	PBO + ALLO (N=201)	LESU200 mg + ALLO (N=201)	LESU400 mg + ALLO (N=201)
Subjects with at Least 1 Target Tophus at Baseline (ITT Population)	17	18	19
Mean Area (mm^2) (SD)	322 (281)	335 (207)	254 (165)
Percent Change from Baseline to Month 6			
n	16	13	13
Mean (SD)	-17 (47)	-5.5 (49)	-23 (47)
Adjusted Differ. in Means vs PBO + ALLO (95% CI)		4.3 (-33, 41)	-11 (-47, 26)
p-value[1]		0.8132	0.5639
Percent Change from Baseline to Month 12			
n	16	13	13
Mean (SD)	33 (158)	12 (134)	-11 (116)
Adjusted Differ. in Means vs PBO + ALLO (95% CI)		-28 (-136, 79)	-57 (-164, 51)
p-value[1]		0.5985	0.2936

Diff. = Difference
Note: Only subjects with non-missing tophus measurements at a particular visit are included for that visit. End of study/early termination data are included in the appropriate visit month if no scheduled visit occurred during that visit month.
[1]p-values are from ANCOVA modes with baseline value as a covariate and treatment group and Day -7 renal function (eCrCl ≥60 ml/min vs <60 mL/min) as randomization factor values
Adapted Sponsor's Table 14.2.3.20; p779-784. Study 301 CSR

Patient Reported Outcomes (PROs):

The results from four of the six ancillary secondary PRO assessing disability and pain are listed in **Table 21**. Overall, minimal improvements are noted on review of the results for the Month 6 and Month 12 time points for these assessments that were generally similar for the three treatment groups. These are not unexpected findings, since the level of disability was not high at baseline for this study population.

Table 21 - Summary of Ancillary Secondary Patient Reported Assessments for Study 301 (Observed Cases – ITT Population)

Patient Reported Outcome Assessment	PBO + ALLO (N=201)	LESU200 mg + ALLO (N=201)	LESU400 mg + ALLO (N=201)
Proportion of Subjects with an Improvement of ≥0.25 from Baseline in HAQ-DI at:			
Month 6:			
Diff. in Proportions vs PBO + ALLO (95% CI)	35%	28%	29%
p-value[1]		-0.06 (-0.16, 0.04)	-0.05 (-0.16, 0.05)
		0.2282	0.3897
Month 12:			
Diff. in Proportions vs PBO + ALLO (95% CI)	35%	30%	29%
p-value[1]		-0.05 (-0.16, 0.06)	-0.06 (-0.17, 0.04)
		0.4120	0.2701
Mean Δ (SD) in HAQ VAS Pain Score at:			
Month 6	-4.6 (28)	-0.7 (28)	-3.9 (26)
Adj. Diff. in Means vs PBO + ALLO (95% CI)		3.6 (-1.5, 8.7)	3.5 (-1.7, 8.7)
p-value[2]		0.1682	0.1855
Month 12	-7.8 (29)	-4.7 (25)	-7.3 (25)
Adj. Diff. in Means vs PBO + ALLO (95% CI)		1.5 (-3.4, 6.5)	3.0 (-1.9, 8.0)
p-value[2]		0.5454	0.2263
Proportion of Subjects with Improvement ≥2.5 in SF-36 PCS at:			
Month 6	45%	41%	47%
Adj. Diff. in Means vs PBO + ALLO (95% CI)		-0.04 (-0.15, 0.07)	0.02 (-0.09, 0.13)
p-value[1]		0.4249	0.7379
Month 12	51%	45%	47%
Adj. Diff. in Means vs PBO + ALLO (95% CI)		-0.06 (-0.17, 0.06)	-0.03(-0.15, 0.08)
p-value		0.3206	0.6019
Mean Δ (SD) from Baseline PGA score at:			
Month 6	-14 (29)	-9.0 (28)	-9.4 (25)
Adj. Diff. in Means vs PBO + ALLO (95% CI)		4.59 (0.09, 9.10)	2.04 (-2.49, 6.57)
p-value[1]		0.0458	0.3761
Month 12	-14 (29)	-13 (27)	-9.7 (23)
Adj. Diff. in Means vs PBO + ALLO (95% CI)		-1.57 (-5.98, 2.84)	2.24 (-2.14, 6.62)
p-value[1]		0.4844	0.3153

Adj.= Adjusted; Diff.= Difference; Δ = Change
HAQ-DI assesses patient's level of functional ability with items scores ranging from 0-3 with 0 being the least disability.
HAQ VAS pain scores range from 0 (no pain) to 100 (worst pain) based on 100 mm visual analogue scale (VAS).
SF-36
PGA scores range from 0-100 with lower scores indicating a higher patient global assessment
[1]Cochran-Mantel Haenszel test stratified by Day-7 renal function (eCrCl≥ 60 mL/min) and tophus status during screening (presence vs absence), randomization stratification values
[2]ANCOVA models with baseline value as a covariate and treamtnt group, Day -7 renal function (eCrCl ≥ 60 ml/min versus <60 ml/min), and tophus status during screening (presence versus absence) as factors, randomized values
Adapted Sponsor's Tables 14.2.4.2.a, 14.2.4.4.a, 14.2.4.8.a, and 14.2.4.11.a; p. 820, Study 301 CSR

- Total Treatment Satisfaction Question for Medication Score (TSQM): No apparent differences were noted the between the two lesinurad + ALLO treatment groups and the PBO + ALLO group regarding overall satisfaction (mean scores ranging from 64 to 78), effectiveness satisfaction (mean scores ranging from 67 to 69), side effects (mean scores ranging from 58 to 67) and convenience satisfaction (mean scores ranging from 77 to 81)
- Mean change from baseline in the Sheehan Disability Scale (SDS): The mean baseline scores for each of the subscales (work/school, social life, family life/home, global function impairment, and days lost from work) comprising this assessment were all low indicating minimal impairment for all three treatment groups. Mean changes from baseline at the Month 6 and Month12 time points were similar for all three treatment groups for each of the subscales and not significantly different on comparative analysis.

Efficacy Conclusions:
Significantly greater proportions of subjects treated with LESU200 mg + ALLO and LESU400 mg + ALLO achieved a sUA < 6mg/dL at Month 6 as compared to PBO + ALLO which was sustained through the 12-month course of study treatment and were generally supported by sensitivity analyses. Results from the major and ancillary secondary endpoints that assessed clinical benefits (e.g., gout flares and tophi resolution) associated with this decrease in sUA as well as a variety of patient reported outcomes (overall disease activity, pain and patient functioning) were not robust for either of the two lesinurad + ALLO treatment groups as compared to placebo + ALLO. The findings from the major and secondary endpoints should not be considered statistically significant due to the hierarchical testing used for multiple endpoints and/or unadjusted p-values due to multiplicity concerns.

Results from Study 302:

Disposition:
This study was conducted at 152 international centers. Of the 2,199 potential patients screened for this study, 611 were randomized to study treatment. One randomized subject withdrew prior to receiving study medication due to noncompliance/protocol deviation and violation. As shown in **Table 22**, a total of 610 subjects received one dose of study medication (ITT population) in this study: 206 patients in the placebo + allopurinol group (PBO +ALLO), 204 patients in the lesinurad 200 mg + allopurinol group (LESU200 + ALLO) and 200 patients to the lesinurad 400 mg + allopurinol group (LESU400 + ALLO). The proportions of subjects who completed treatment with or without study medication as well as the 6-Month time point were comparable for the three treatment groups. More patients randomized to the LESU200 + ALLO group (79%) completed treatment with study medication at the 12-month time point compared

to the LESU200 + ALLO (73%) and PBO + ALLO (75%) groups. This imbalance was due to higher rates of subjects discontinuing study medications as a result of an adverse event (9%) and non-compliance/protocol violation (7%) in the LESU400 mg + ALLO and PBO +ALLO groups. Of note, the participation of 10 subjects in this study was terminated as a result of GCP noncompliance (3 subjects at 1 site in Canada) and due to a German regulatory agency mandated protocol restriction of recruitment of patients from that country to those who failed to respond to all other established alternative therapies as given in national and international treatment guidelines (7 subjects from 6 sites in Germany).

Table 22 - Subject Disposition by for Study 302

	PBO + ALLO (N=206)	LESU200 mg + ALLO (N=204)	LESU400 mg + ALLO (N=200)	Total (N=610)
Number of Patients Randomized:	**206**	**204**	**201**	**611**
Subject Withdrawn Prior to Receiving Randomized Medications	0	0	1	1
Intent-To-Treat (ITT)Population	**206**	**204**	**200**	**610**
Safety Population	**206**	**204**	**200**	**610**
Per Protocol (PP) Population	**194**	**182**	**181**	**557**
Pts. Completed Study (W/O Completing Randomized Medication Treatment):	**158 (77%)**	**163 (80%)**	**150 (75%)**	**471 (77%)**
Adverse Event	9 (4%)	4 (2%)	12 (6%)	25 (4%)
Consent Withdrawn	11 (5%)	16 (8%)	13 (7%)	40 (7%)
Death	0	0	1 (<1%)	1 (<1%)
Gout Flare	2 (<1%)	3 (1%)	0	5 (<1%)
Lost to Follow-Up	11 (5%)	5 (2%)	7 (4%)	23 (4%)
Noncompliance/Protocol Violation	12 (6%)	8 (4%)	15 (8%)	35 (6%)
Sponsor Terminated Study	3 (1%)	5 (2%)	2 (1%)	10 (2%)
Pts. Completed 6 Months of Randomized Study Medication Treatment:	**175 (85%)**	**175 (86%)**	**171 (86%)**	**521 (85%)**
Adverse Event	6 (3%)	6 (3%)	9 (5%)	21 (3%)
Consent Withdrawn	8 (4%)	10 (5%)	9 (5%)	27 (4%)
Gout Flare	0	2 (<1%)	1 (<1%)	3 (<1%)
Lost to Follow-Up	6 (3%)	5 (2%)	4 (2%)	15 (2%)
Noncompliance/Protocol Violation	10 (5%)	6 (3%)	5 (3%)	21 (3%)
Required Treatment with Prohibited/ Contraindicated Medication	1 (<1%)	0	1 (<1%)	2 (<1%)
Pts. Completed 12 Months of Randomized Study Medication Treatment:	**154 (75%)**	**162 (79%)**	**145 (73%)**	**461 (76%)**
Adverse Event	12 (6%)	6 (3%)	18 (9%)	36 (6%)
Consent Withdrawn	11 (5%)	15 (7%)	12 (6%)	38 (6%)
Gout Flare	2 (<1%)	3 (1%)	1 (<1%)	6 (<1%)
Lost to Follow-Up	11 (5%)	5 (2%)	7 (4%)	23 (4%)
Noncompliance/Protocol Violation	14 (7%)	9 (4%)	14 (7%)	37 (6%)
Required Treatment with Prohibited/ Contraindicated Medication	2 (<1%)	4 (2%)	3 (2%)	9 (1%)

Adapted Sponsor's Table 14.1.1.3, p. 255-256 Study 302 CSR

Protocol Deviations and Violations:
A total of 53 patients incurred one or more protocol deviations and violations over the course of this 52-week trial as shown in **Table 23**. Higher overall rates of protocol deviations/violations occurred in the LESU200 + ALLO and LESU400 + ALLO groups as compared to the PBO +ALLO group. More patients occurred protocol violations in the two lesinurad treatment groups (6%) due to noncompliance with study medications >20% of time.

Table 23 – Summary of Subjects with a Major Protocol Deviation/Violation by Randomized Treatment Group for Study 302

	PBO + ALLO (N=206)	LESU200 mg + ALLO (N=204)	LESU400 mg + ALLO (N=200)	Total (N=610)
Number of Subjects with Protocol Deviations/Violations	**12 (6%)**	**22 (11%)**	**19 (10%)**	**53 (9%)**
Failure to Meet Incl/Excl. Criteria	0	1 (1%)	0	1 (<1%)
Failure to Provide ICF by Randomization	0	1 (1%)	0	1 (<1%)
Taking <300 mg of Allopurinol (or < 200 mg if Moderate Renal Insufficiency) at Randomization	6 (3%)	5 (3%)	5 (3%)	16 (3%)
Received Prohibited ULT	0	2 (1%)	0	2 (<1%)
Noncompliance with Study Meds >20%	5 (2%)	12 (6%)	11 (6%)	28 (5%)
Missed > 2 Study Visits	0	1 (1%)	0	1 (<1%)
Missed Month 6 Visit	1 (1%)	4 (2%)	3 (2%)	8 (1%)

Adapted Sponsor's Table 14.1.1.4, p. 257-258 Study 302 CSR

Demographics:
As summarized by the following tables (**Table 24** and **Table 25**), the treatment groups within Study 302 were generally well balanced with respect to baseline demographics, disease characteristics and activity.

The subjects who participated in this trial were overwhelmingly Caucasian males with a mean age 51 years (**Table 24**). These patients were also overweight as evidenced by a mean body mass index (BMI) of 34 kg/m^2 which is consistent with the fact that obesity is a risk factor for gout. The majority (99%) of subjects did not report a history of alcoholism, another risk factor for gout. Patients who participated in this international study were predominantly from North America (55%), while the remaining patients were from Europe (22%), South Africa (16%), and Australia/new Zealand (7%).

Table 24 – Baseline Demographic Characteristics of Subjects Enrolled in Study 302

	PBO + ALLO (N=206)	LESU200 mg + ALLO (N=204)	LESU400 mg + ALLO (N=200)	Total (N=610)
Age (years)				
Mean (SD)	51 (11)	51 (11)	51 (11)	51 (11)
Gender				
Male	196 (95%)	197 (97%)	194 (97%)	587 (96%)
Female	10 (5%)	7 (3%)	6 (3%)	23 (4%)
Race:				
American Indian/Alaska Native	1 (1%)	1 (1%)	0	2 (<1%)
Asian	14 (7%)	10 (5%)	9 (5%)	33 (5%)
Black/African American	22 (11%)	15 (7%)	21 (11%)	58 (10%)
Maori	1 (1%)	4 (2%)	1 (1%)	6 (1%)
Native Hawaiian/other Pacific Islander	5 (2%)	3 (2%)	2 (1%)	10 (2%)
White	155 (75%)	167 (82%)	160 (80%)	482 (79%)
Other	8(4%)	4 (2%)	6 (3%)	18 (3%)
Missing	0	0	1 (1%)	1 (<1%)
Ethnicity (Hispanic/Latino)				
Yes	7 (3%)	10 (5%)	7 (4%)	24 (4%)
No	199 (97%)	194 (95%)	193 (97%)	586 (96%)
Weight (Kg)				
Mean (SD)	106 (21)	110 (24)	107 (24)	107 (23)
Height (cm)				
Mean (SD)	177 (8)	177 (8)	177 (8)	177 (8)
BMI (kg/m^2)				
Mean (SD)	34 (6)	35 (6)	34 (7)	34 (6)
Alcohol Consumption:				
Yes	3 (2%)	0	2 (1%)	5 (1%)
No	201 (98%)	202 (99%)	198 (99%)	601 (99%)
Missing	2 (1%)	2 (1%)	0	4 (1%)
Region and Country				
North America	119 (58%)	115 (56%)	100 (50%)	334 (55%)
Europe	43 (21%)	43 (21%)	48 (24%)	134 (22%)
South Africa	33 (16%)	30 (15%)	36 (18%)	99 (16%)
Australia/New Zealand	11 (5%)	16 (8%)	17 (9%)	44 (7%)

Adapted Sponsor's Tables 14.1.1.2, 14.1.2.1 and 14.1.2.3;, p. 246-254, 259-260 and 271-272 Study 302 CSR

The overall mean duration of disease since the first gout attack was 12 years for the study population who also reported having a mean number of 6 gout attacks per year over the last 12 months (**Table 25**). The treatment groups within the trial were also generally well balanced with respect to baseline disease status and treatment with the following exceptions. Differences in the three treatment groups were observed for mean total area of target tophi and type of gout flare prophylaxis at baseline. The mean total area of target tophi at baseline was higher in the LESU400 + ALLO group (560 mm^2) compared to the PBO + ALLO (373 mm^2) and LESU200 + ALLO (346 mm^2) groups. This baseline imbalance in the LESU400 mg + ALLO group was due primarily to one subject with a total target tophi area of 3,366 mm^2 as the result of having three out of 5

target tophi that exceeded the maximum diameter specified in the protocol (≥ 5 mm and ≤ 20 mm). Higher rates of subjects were using colchicine and nonsteroidal anti-inflammatory drugs [NSAIDs] in the PBO + ALLO group compared to the LESU200 + ALLO and LESU400 + ALLO groups.

Following at least 10 weeks on a medically appropriate stable dose of allopurinol, the study population had a baseline mean sUA 6.90 mg/dL with 19% having a baseline sUA <6 mg/dL (**Table 25**). A total of 16% of the patients had mild to moderate impairment as assessed by an estimated creatinine clearance (eCrCl) of <60 ml/min at baseline with 8% having moderate to severe renal impairment (eCrCl < 45 ml/min). Overall, the study population who participated in this trial was representative of patients who continued to have symptomatic hyperuricemia despite urate lowering therapy and could potentially benefit from treatment with lesinurad.

Table 25 – Summary of Subject's Gout History, Disease Status, and Treatment at Baseline for Study 302

	PBO + ALLO (N=206)	LESU200 mg + ALLO (N=204)	LESU400 mg + ALLO (N=200)	Total (N=610)
American Rheumatism Association Diagnostic Criteria	205(100%)	204(100%)	200(100%)	609(100%)
Presence of MSU Crystals in Jt. Fluid	16 (8%)	18 (9%)	20 (10%)	54 (9%)
Number of Years Since Gout Dx				
Mean (SD)	11 (9)	12 (10)	11 (9)	12 (9)
Number of Gout Flares in the Past 12 Months				
Mean (SD)	6 (5)	7 (7)	6 (6)	6 (6)
Tophi				
Yes	48 (23%)	49 (24%)	47 (24%)	144 (24%)
No	157 (77%)	155 (76%)	153 (77%)	466 (76%)
Baseline Presence of ≥1 Target Tophus				
Yes	33 (16%)	35 (17%)	29 (15%)	97 (16%)
No	173 (84%)	169 (83%)	171 (86%)	513 (84%)
Mean (SD)	**2.2 (1.4)**	**2.0 (1.3)**	**2.5 (1.5)**	**2.2 (1.4)**
Total Area of Target Tophi at Baseline				
Mean (SD)	373 (379)	346 (336)	560 (715)	419 (496)
Baseline sUA				
Mean (SD)	**6.99 (1.26)**	**6.84 (1.11)**	**6.86 (1.19)**	**6.90 (1.19)**
<6.0	38 (18%)	39 (19%)	39 (20%)	116 (19%)
6.0 -<7.0	80 (39%)	88 (43%)	80 (40%)	248 (41%)
7.0 -<8.0	44 (21%)	50 (25%)	45 (23%)	139 (23%)
8.0 - <10.0	39 (19%)	22 (11%)	32 (16%)	93 (15%)
>10.0	5 (2%)	5 (3%)	4 (2%)	14 (2%)
Baseline Renal Function (ml/min)				
eCrCl ≥90	72 (35%)	80 (39%)	85 (43%)	237 (39%)
eCrCl <90	133 (65%)	124 (61%)	114 (57%)	371 (61%)
eCrCl ≥60	**165 (80%)**	**175 (86%)**	**170 (85%)**	**510 (84%)**
eCrCl <60	**40 (19%)**	**29 (14%)**	**29 (15%)**	**98 (16%)**
eCrCl ≥ 45	195 (95%)	198 (97%)	193 (97%)	586 (96%)
eCrCl < 45	10 (5%)	6 (3%)	6 (3%)	22 (4%)
Prior ULT				
Allopurinol	23 (11%)	18 (9%)	28 (14%)	69 (11%)
Febuxostat	5 (2%)	4 (2%)	1 (1%)	10 (2%)
Benzbromarone	2 (1%)	0	2 (1%)	4 (1%)
Probenecid	0	2 (1%)	3 (2%)	5 (1%)
Other	4 (2%)	1 (1%)	1 (1%)	6 (1%)

Adapted Sponsor's Table 14.1.2.3, p. 263-270 Study 302 CSR

Table 25 – Summary of Subject's Gout History, Disease Status, and Treatment at Baseline for Study 302 (cont.)

	PBO + ALLO (N=206)	LESU200 mg + ALLO (N=204)	LESU400 mg + ALLO (N=200)	Total (N=610)
Gout Flare Prophylaxis				
Colchicine	159 (77%)	181 (89%)	167 (84%)	507 (83%)
NSAID	51 (25%)	23 (11%)	36 (18%)	110 (18%)
Both	8 (4%)	4 (2%)	3 (2%)	15 (3%)
Other or Missing	4 (2%)	4 (2%)	0	8 (1%)
Allopurinol Dose at Baseline (mg/d)				
Mean (SD)	309 (69)	314 (78)	315 (78)	312 (75)
Allopurinol Dose at Baseline (mg/d)				
<300	**15 (7%)**	**14 (7%)**	**11 (6%)**	**40 (7%)**
=300	**176 (85%)**	**168 (82%)**	**169 (85%)**	**513 (83%)**
>300	**15 (7%)**	**22 (11%)**	**20 (10%)**	**57 (9%)**
400-<500	5 (2%)	13 (6%)	10 (5%)	28 (5%)
500-<600	2 (1%)	3 (2%)	3 (2%)	8 (1%)
≥600	8 (4%)	6 (3%)	7 (4%)	21 (3%)

Adapted Sponsor's Table 14.1.2.3, p. 263-270 Study 302 CSR

As summarized in **Table 26**, the majority (79%) of the subjects who participated in Study 302 reported having ≥ 1 comorbid condition associated with hyperuricemia. Comorbid conditions with a high prevalence in this study population that increased the risk for metabolic syndrome and/or hyperuricemia included hypertension (64%), hyperlipidemia (42%), hypertriglyceridemia (16%), diabetes mellitus (14%) and kidney stones (11%). The three treatment groups were generally similar with respect to the presence of co-morbid conditions except for kidney stones. More patients with kidney stones were randomized to the PBO + ALLO group as compared to the lesinurad + ALLO groups. The overall rate of CV comorbidity and/or CV disease history was also very high (78%) in this study population.

Table 26 - Summary of Comorbid Medical Conditions Reported by Subjects by Randomized Treatment Group in Study 302

	PBO + ALLO (N=206)	LESU200 mg + ALLO (N=204)	LESU400 mg + ALLO (N=200)	Total (N=610)
≥1 Comorbidity	165 (80%)	158 (78%)	160 (80%)	483 (79%)
≥2 Comorbidity	94 (46%)	92 (45%)	99 (50%)	285 (47%)
≥3 Comorbidity	34 (17%)	49 (24%)	42 (21%)	125 (21%)
Types of Comorbidities				
Hypertension	141 (68%)	131 (64%)	121 (61%)	393 (64%)
Hyperlipidemia	**76 (37%)**	**86 (42%)**	**93 (47%)**	**255 (42%)**
Hypercholesterolemia	68 (33%)	73 (36%)	85 (43%)	226 (37%)
Hypertriglyceridemia	26 (13%)	39 (19%)	35 (18%)	100 (16%)
Diabetes Mellitus	28 (14%)	31 (15%)	26 (13%)	85 (14%)
Kidney Stones	28 (14%)	23 (11%)	18 (9%)	69 (11%)
Heart Failure	7 (3%)	6 (3%)	12 (6%)	25 (4%)
Myocardial Infarction	5 (2%)	10 (5%)	9 (5%)	24 (4%)
Angina Pectoris	10 (5%)	7 (3%)	6 (3%)	23 (4%)
Peripheral Vascular Disease	4 (2%)	5 (3%)	1 (1%)	10 (2%)
Transient Ischemic Attack	3 (2%)	3 (2%)	1 (1%)	7 (1%)
Stroke	3 (2%)	1 (1%)	2 (1%)	6 (1%)
Any CV Comorbidity and/or CV Disease History	**163 (79%)**	**158 (78%)**	**157 (79%)**	**478 (78%)**

Adapted Sponsor's Tables 14.1.3.1 and 14.1.3.3; p. 273 and 277 Study 302 CSR

Information regarding concomitant medications used by more than 10% of the study population was also examined (**Table 27**). The most commonly reported concomitant non-gout classes of medications were drugs acting on the renin-angiotensin system, analgesics, lipid-modifying agents, antibacterials and beta-blockers. This information is consistent with what is typically seen in gout patients since this disease is commonly associated with chronic disorders such as hypertension, diabetes mellitus, hyperlipidemia and cardiovascular disease.

Table 27 – Concomitant Medications Taken by ≥ 10% of Subjects in Study 302 by Treatment Group (Safety Population)

ATC Class and WHO Drug Dictionary Preferred Term	PBO + ALLO (N=206)	LESU200 mg + ALLO (N=204)	LESU400 mg + ALLO (N=200)
Any Concomitant Medication	**205 (100%)**	**204 (100%)**	**200 (100%)**
Anti-Gout Preparations	**164 (80%)**	**186 (91%)**	**169 (85%)**
Colchicine	164 (80%)	186 (91%)	169 (85%)
Anti-Inflammatory and Anti-Rheumatic Products	**119 (58%)**	**125 (61%)**	**130 (65%)**
Ibuprofen	29 (14%)	42 (21%)	34 (17%)
Diclofenac	27 (13%)	31 (15%)	33 (17%)
Indomethacin	23 (11%)	21 (10%)	27 (14%)
Diclofenac Sodium	14 (7%)	20 (10%)	22 (11%)
Naproxen	24 (12%)	18 (9%)	17 (9%)
Drugs Acting on Renin-Angiotensin System	**112 (54%)**	**105 (52%)**	**96 (48%)**
Lisinopril	27 (13%)	39 (19%)	27 (14%)
Analgesics	**77 (37%)**	**86 (42%)**	**81 (41%)**
Paracetamol	18 (9%)	26 (13%)	24 (12%)
Lipid Modifying Agents	**66 (32%)**	**64 (31%)**	**69 (35%)**
Simvastatin	31 (15%)	26 (13%)	21 (11%)
Fish Oil	7 (3%)	16 (8%)	12 (6%)
Antibacterials for Systemic Use	**51 (25%)**	**48 (24%)**	**51 (26%)**
Beta-Blocking Agents	**55 (27%)**	**42 (21%)**	**46 (23%)**
Corticosteroids for Systemic Use	**35 (17%)**	**54 (27%)**	**45 (23%)**
Prednisone	18 99%)	32 (16%)	27 (14%)
Drugs for Acid-Related Disorders	**38 (18%)**	**46 (23%)**	**42 (21%)**
Omeprazole	20 (10%)	23 (11%)	17 (9%)
Vitamins	**29 (14%)**	**33 (16%)**	**40 (20%)**
Antithrombotic Agents	**38 (18%)**	**38 (19%)**	**36 (18%)**
Acetylsalicylic Acid	34 (17%)	32 (16%)	31 (16%)
Calcium Channel Blockers	**33 (16%)**	**29 (14%)**	**35 (18%)**
Diuretics	**36 (18%)**	**39 (19%)**	**33 (17%)**
Drugs Used in Diabetes	**23 (11%)**	**29 (14%)**	**26 (13%)**
No Code Found	**15 (7%)**	**19 (9%)**	**26 (13%)**
Cough and Cold Preparation	**14 (7%)**	**18 (9%)**	**21 (11%)**
Drugs for Obstructive Airway Diseases	**16 (8%)**	**20 (10%)**	**21 (11%)**
Antihistamines for Systemic Use	**20 (10%)**	**19 (9%)**	**20 (10%)**
Psycholeptics	**19 (9%)**	**23 (11%)**	**20 (10%)**
Mineral Supplements	**13 (6%)**	**16 (8%)**	**19 (10%)**
Psychoanaleptics	**24 (12%)**	**23 (11%)**	**12 (6%)**

Adapted Sponsor's Table 14.1.4.3.a; p. 325-382 Study 302 CSR

Examination of the data in **Table 27** revealed that study participants in each treatment group were taking concomitant medications (e.g., beta-blockers and diuretics) that are known to interfere with uric acid metabolism. Overall, the use of these medications is similar across the treatment groups. The following table (**Table 28**) summarizes concomitant usage of thiazide and thiazide-like diuretics by more than 2% of subjects who participated in Study 302. No imbalances for the three treatment groups are noted on the use of these drugs which can affect uric acid excretion.

Table 28 - Concomitant Thiazide and Thiazide-Like Diruretics by ≥2% of Subjects by Treatment Group During Study 302 (Safety Population)

ATC Class and WHO Drug Dictionary Preferred Term	PBO + ALLO (N=206)	LESU200 mg + ALLO (N=204)	LESU400 mg + ALLO (N=200)
Any Concomitant Thiazide and Thiazide-Like Diuretic	**43 (21%)**	**46 (23%)**	**41 (21%)**
Agents Acting on Renin-Angiotensin System	**23 (11%)**	**18 (9%)**	**18 (9%)**
Zestoretic (lisinopril/HCTZ)	13 (6%)	3 (2%)	4 (2%)
Co-Diovan (valsartan/HCTZ)	4 (2%)	5 (3%)	3 (2%)
Hyzaar (losartan/HCTZ)	2 (1%)	3 (2%)	3 (2%)
Diuretics	**18 (9%)**	**26 (13%)**	**18 (9%)**
Hydrochlorothiazide (HCTZ)	13 (6%)	17 (8%)	10 (5%)
Indapamide	2 (1%)	4 (2%)	4 (2%)
Beta-Blocking Agents	**2 (1%)**	**3 (2%)**	6 (3%)
Biselect (bisoprolol)	0	3 (2%)	2 (1%)

Adapted Sponsor's Table 14.1.4.5.1; p. 396-397 Study 302 CSR

The protocol permitted patients to take medications to treat gout flares they experienced over the course of the study. This information is summarized in **Table 29**. Higher proportions of subjects randomized to the lesinurad + ALLO groups used concomitant medications to treat gout flares during the trial as compared to the PBO + ALLO group. This imbalance is due to more subjects who reported using NSAIDs and colchicine in the lesinurad + ALLO groups versus the PBO + ALLO group.

Table 29 - Gout Flare Medications Taken by ≥ 2% of Subjects by Treatment Group During Study 302 (Safety Population)

ATC Class and WHO Drug Dictionary Preferred Term	PBO + ALLO (N=206)	LESU200 mg + ALLO (N=204)	LESU400 mg + ALLO (N=200)
Any Concomitant Medication Used to Treat Gout Flares	**88 (43%)**	**101 (50%)**	**98 (49%)**
Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)	**56 (27%)**	**68 (33%)**	**76 (38%)**
Diclofenac	17 (8%)	23 (11%)	27 (14%)
Indomethacin	15 (7%)	16 (8%)	21 (11%)
Diclofenac Sodium	11 95%)	17 (8%)	18 (9%)
Ibuprofen	6 (3%)	13 (6%)	13 (7%)
Naproxen	8 (4%)	5 (3%)	6 (3%)
Diclofenac Potassium	1 (1%)	3 (2%)	3 (2%)
Etoricoxib	1 (1%)	3 (2%)	2 (1%)
Meloxicam	0	3 (2%)	2 (1%)
Naproxen Sodium	2 (1%)	3 (2%)	2 (1%)
Anti-Gout Drugs	**42 (20%)**	**58 (28%)**	**50 (25%)**
Colchicine	42 (20%)	58 (28%)	50 (25%)
Corticosteroids	**28 (14%)**	**34 (17%)**	**29 (15%)**
Prednisone	16 (8%)	24 (12%)	21 (11%)
Dexamethasone	0	0	3 (2%)
Methylprednisolone acetate	1 (1%)	3 (2%)	2 (1%)
Prednisolone	3 (2%)	1 (1%)	2 (1%)
Non-NSAID Analgesics	**19 (9%)**	**19 (9%)**	**17 (9%)**
Paracetamol	3 (2%)	6 (3%)	5 (3%)
Myprodol (ibuprofen/paracetamol/codeine)	2 (1%)	0	4 (2%)
Supragesic (paracetamol/codeine/caffeine/meprobamate)	5 (2%)	3 (2%)	4 (2%)
Panadeine Co (paracetamol/codeine)	3 (2%)	0	3 (2%)

Adapted Sponsor's Table 14.1.4.7; p. 417-420 Study 302 CSR

Treatment Compliance:

The common protocol specified that patients' compliance with study medication was to have been assessed by pill counts performed on the returned study medication kits which contained a 40-day supply of randomized medication. Overall mean compliance was high for all three treatment groups (≥95%) with higher proportions of subjects reporting greater than 100% compliance with study medication in the LESU200 + ALLO and PBO + ALLO groups as compared to the LESU400 + ALLO group (**Table 30**).

Table 30 – Compliance With Randomized Study Medication for Subjects in Study 302

	PBO + ALLO (N=206)	LESU200 mg + ALLO (N=204)	LESU400 mg + ALLO (N=200)
Overall Compliance* (Baseline to Month 12 or Early Discontinuation)			
Mean (SD)	**97% (7%)**	**96% (11)**	95% (11)
Min, Max	44, 115	22, 116	13, 110
Compliance Category			
<80%	5 (2%)	12 (6%)	11 (6%)
80-100%	163 (79%)	150 (74%)	166 (83%)
>100%	38 (18%)	42 (21%)	23 (12%)

Note: Overall Compliance was calculated by the Applicant as follows: [Total number of small and large tablets taken]/[2 x total days on randomized medication] x 100% where total days on randomized study medication is calculated as follows: (last randomized study medication dose date – first randomized study medication dose date + 1)
Adapted Sponsor's Table 14.1.6; p. 425 Study 302 CSR

Efficacy:

Primary Endpoint:

As discussed in the preceding common protocol section, the primary efficacy parameter for Study 302 was the proportion of patients with sUA less than 6 mg/dL by Month 6. As shown in **Table 31**, greater proportions of patients treated with both LESU400 + ALLO and LESU200 + ALLO achieved sUA less than 6 mg/dL compared to patients treated with PBO + ALLO in a dose-dependent manner. The differences between each of the lesinurad + ALLO treatment groups and the PBO + ALLO group were statistically significant.

Table 31 – Month 6 Primary Endpoint Results for Study 302 (NRI; ITT Population)

	PBO + ALLO (N=206)	LESU200 mg + ALLO (N=204)	LESU400 mg + ALLO (N=200)
Proportion with sUA <6.0 mg/dL by Month 6	48 (23%)	113 (55%)	133 (67%)
Difference in Proportions vs PBO + ALLO (95% CI)*		0.32 (0.23, 0.41)	0.43 (0.34, 0.52)
P-Value**		<0.0001	<0.001

NRI = Non-responder imputation CI = Confidence interval
*Binomial confidence interval for difference in proportions
**Cochran-Mantel Haenszel test stratified by Day-7 renal function (eCrCl≥ 60 mL/min) and tophus status during screening (presence vs absence), randomization stratification values using nonresponder imputation for subjects missing Month 6 sUA.
Table courtesy Dr. Jade Wang

The Applicant provided seven sensitivity analyses for the primary efficacy endpoint (e.g., LOCF analysis; observed case analysis; reached target sUA <5 mg/dL at each Month 4, 5, and 6; reached target sUA <6 mg/dL logistic regression analysis, a CMH test stratified by Day -7 renal function and tophus status using actual values for these

variables rather than stratification factor values, the per protocol population analysis, and a ITT analysis at Month 6 that excluded subjects from Site 15006 in South Africa as a result of GCP issues at that site). (Note: Six out of these seven sensitivity analyses were conducted as planned in the SAP.) The results of these sensitivity analyses were consistent with the primary efficacy analysis. (Note: The reader is referred to the statistical review of this application by Dr. Jade Wang for further information regarding these sensitivity analyses and the results of additional sensitivity analyses that she conducted as part of her review of this application.)

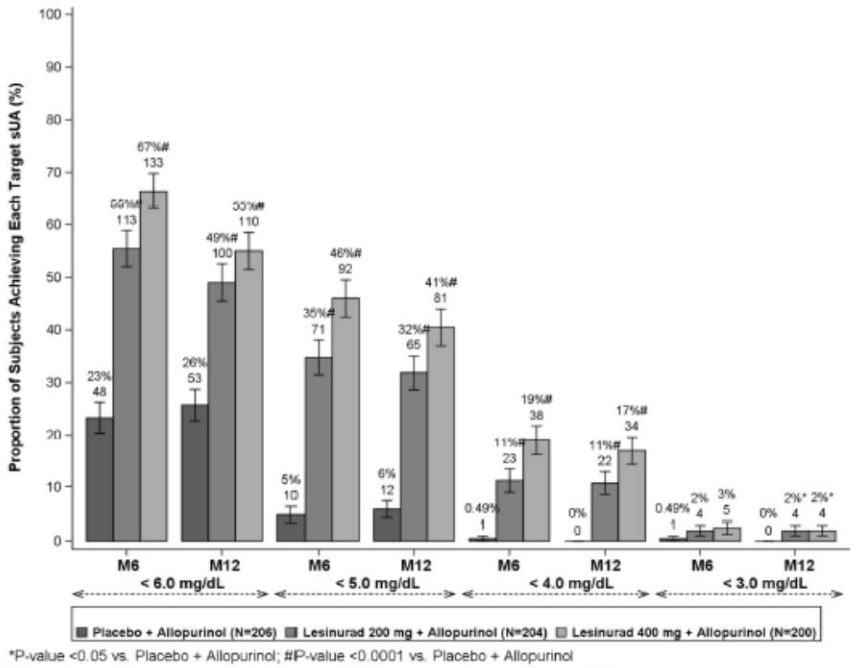
Secondary Endpoints:

There were two major and multiple ancillary secondary endpoints for this trial that were assessed in order to determine if a clinical benefit (e.g., gout flare and resolution of tophi) was associated with the administration of lesinurad. These secondary assessments are presented below by corresponding assessment area. In order to control for multiplicity, the statistical analysis plan mandated the major secondary endpoints for this study to be analyzed via a sequential procedure in a prespecified descending order following testing of the primary endpoint. Due to the statistically non-significant finding for the major secondary endpoint analysis of gout flares for the LESU400 + ALLO treatment group, no further testing was to have been performed. For completeness, the results of the secondary endpoint analyses are being presented in this review. However, findings from the major secondary endpoints should not be considered statistically significant due to the hierarchical testing method used for multiple endpoints. Declaring statistical significance of the ancillary secondary endpoints using unadjusted p-values may be inappropriate due to multiplicity concerns.

sUA Reduction:

- Proportion of subjects whose sUA level is <6.0 mg/dL, <5.0 mg/dL and <4.0 mg/dL at each visit: Lesinurad's urate lowering capability was also assessed by examining different threshold response levels other than that explored by the primary endpoint. As shown in **Figure 5**, higher proportions of patients randomized to the two lesinurad treatment groups achieved these pre-specified lower sUA threshold levels in a dose dependent manner as compared to the PBO + ALLO group at the Months 6 and 12 time points. The differences between each of the treatment groups and the placebo group were statistically significant at each time point ($p<0.0001$ and $p<0.05$).

Figure 5 – Subjects Achieving sUA <6.0 mg/dL, <5.0 mg/dL, <4.0 mg/dL, and <3.0 mg/dL at Months 6 and 12 in Study 302 (NRI) (ITT Population)



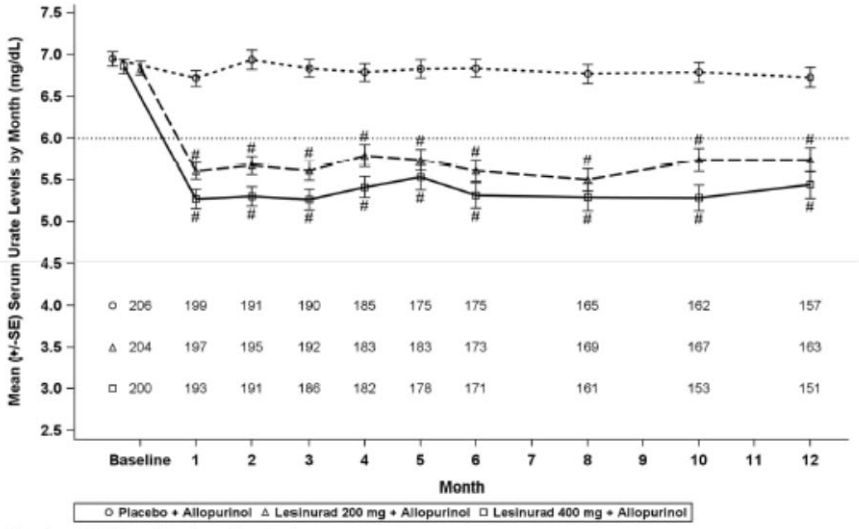
*P-value <0.05 vs. Placebo + Allopurinol; #P-value <0.0001 vs. Placebo + Allopurinol

Abbreviations: ITT, intent-to-treat; M, month; NRI, nonresponder imputation; sUA, serum urate.
Note: Numbers in the figure refer to % of subjects who achieved the target sUA at either Month 6 or Month 12 (M6 or M12) and the number of subjects in that group that achieved target. The targets are listed below the x-axis (< 6.0, < 5.0, < 4.0, and < 3.0 mg/dL). Proportions and standard errors are noted in the figure.
Source: Study 302 CSR Table 14.2.1.7, Table 14.2.1.8, Table 14.2.1.9, Table 14.2.1.10.

Adapted Sponsor's Fig. 12; p. 90 Summary of Clinical Efficacy

- Absolute and percent change from baseline in sUA levels at each visit: **Figure 6** graphically depicts the mean sUA level profiles for the three treatment groups. Mean serum urate levels in the two lesinurad + ALLO groups drop within the first month by approximately 1.5 to 2 mg/dL and remain consistent through Month 12. The PBO + ALLO group's baseline mean sUA remains unchanged over the course of treatment. The percent reduction in mean sUA levels over baseline was greater at every time point for both lesinurad + ALLO groups as compared to PBX + ALLO (p<0.0001).

Figure 6 - Mean Serum Urate Levels by Visit in Study 302 (Observed Cases; ITT Population)



Abbreviations: ITT, intent-to-treat; SE, standard error.
Numbers indicate the number of subjects contributing data at each timepoint. Dotted line indicates target sUA (< 6.0 mg/dL). Statistical significance is based on the difference in least square mean percent change from Baseline.
Note: Months 7, 9, and 11 data are excluded because the timing of the last protocol amendment (Protocol Amendment 6), which added sUA assessments at these timepoints, resulted in minimal data collection at these timepoints for NRI analysis.
Source: Study 302 CSR Table 14.2.1.22.

Adapted Sponsor's Fig. 15; p. 100 Summary of Clinical Efficacy

Gout Flares Requiring Treatment:

Initiation of urate lowering therapies in gout patients is known to be associated with an increased risk of gout flare. Theoretically, the occurrence of gout flares should decrease once a subject's sUA level is < 6mg/dL. A total of 954 gout flares requiring treatment were reported by 262 subjects over the 12- month course of this study as follows: 39% of subjects in the PBO + ALLO group, 44% of subjects in the LESU200 mg + ALLO group and 46% of subjects in the LESU400 mg + ALLO group. The majority (56%) of gout flares occurred during the time period from baseline to the end of Month 6 with numerically higher rates of gout flares observed in the LESU400 mg + ALLO (40%) and LESU200 mg + ALLO (37%) groups as compared to PBO + ALLO (29%). To prevent confounding of the gout flare assessments during Months 6 through 12, subjects were required to discontinue their gout flare prophylaxis regimens at the end of Month 5.

- Mean rate of subjects requiring treatment for a gout flare during the 6-month time period from Month 6 to Month 12: This was an unmet major secondary endpoint for both lesinurad + ALLO treatment groups in this study (**Table 32**). Overall, the adjusted mean rates of gout flares requiring treatment were low during this time period and no significant differences between the three treatment groups were observed for this endpoint on comparative analysis.

Table 32 – Mean Rate of Gout Flares requiring Treatment[1] per Subject for from Month 6 to Month 12 During Study 302 (ITT Population)

	PBO + ALLO (N=206)	LESU200 mg + ALLO (N=204)	LESU400 mg + ALLO (N=200)
Adjusted Rate[2,3] of Gout Flare Requiring Treatment per Subject Months 6 to 12 (SE)	0.89 (0.14)	0.78 (0.13)	0.83 (0.14)
Incidence Rate Ratio (95% CI) vs PBO + ALLO P-value		0.88 (0.57, 1.37) 0.57	0.93 (0.60, 1.45) 0.75

[1]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 prior to the start or 3 days after the end of the gout flare.
[2]Estimates obtained from Negative Binomial Regression adjusted for Day -7 renal function (eCrCl ≥ 60 mL/min versus < 60 mL/min) and tophus status during Screening (presence versus absence), randomized values, and log follow-up time as the offset variable.
[3]Estimates of adjusted rate for each treatment group obtained from inputting empirical proportion of each stratification factor level under each study.
Table Courtesy of Dr. Jade Wang

- Proportion of subjects requiring treatment for gout flares at monthly intervals between Month 6 and Month 12. Consistent with the other flare endpoint mentioned above, the proportion of subjects requiring treatment for gout flares for each monthly interval was low and comparable between the three treatment groups. (Data not shown.)

Target Tophus Resolution:
Another clinical benefit associated with urate lowering therapy is the resolution of tophaceous deposits. At baseline, a total of 24% of the subjects had tophi that qualified as a target tophus by prespecified study criteria. This subset population was used in the analyses of tophus response assessments in this trial.

- Proportion of subjects with ≥ 1 target tophus at baseline who experienced complete resolution of at least 1 target tophus by Month 12: This was the remaining major secondary endpoint for this trial that was also unmet. As shown in **Table 33**, the proportions of patients achieving a "complete" or "best" response at Month 12 were comparable and not significantly different for the three treatment groups.

Table 33 – Proportion of Subjects with ≥1 Target Tophus at Baseline Who Experienced Complete Resolution of at least 1 Target Tophus by Month 12 During Study 302 (NRI; ITT Population with at Least 1 Target Tophus at Baseline)

	PBO + ALLO (N=206)	LESU200 mg + ALLO (N=204)	LESU400 mg + ALLO (N=200)
Subjects with at Least 1 Target Tophus at Baseline (ITT Population)	33	35	29
Proportion with Best Response of CR by Month 12 [n, %]	11 (33%)	11 (31%)	8 (28%)
Diff. in Proportion vs PBO + ALLO (95% CI)[1]		-0.02 (-0.24, 0.20)	-0.06 (-0.29, 0.17)
P-value[2]		0.85	0.63

[1]Binomial confidence interval for difference in proportions
[2]Cochran-Mantel Haenszel test stratified by Day -7 renal function (eCrCl ≥ 60 mL/min versus < 60 mL/min), randomized values.
Table Courtesy Dr. Jade Wang

- Mean percent change from baseline in the sum of the areas for all target tophi at each visit: The imbalance in mean tophi area observed in the LESU400 mg + ALLO group at baseline was due to primarily to one subject with a total target tophi area of 3,366 mm^2 as the result of having three out of 5 target tophi that exceeded the maximum diameter specified in the protocol (≥ 5 mm and ≤ 20 mm). As shown in **Table 34**, decreases in the mean sum area of all tophi were observed at both the Month 6 and Month 12 time points that were not significantly different for the three treatment groups.

Table 34 - Sum of the Areas of All Tophi at Month 6 and Month 12 in Subjects with at Least 1 Target Tophus at Baseline in Study 302(Observed Cases; ITT Population – Subjects with at Least 1 Target Tophus at Baseline)

	PBO + ALLO (N=206)	LESU200 mg + ALLO (N=204)	LESU400 mg + ALLO (N=200)
Subjects with at Least 1 Target Tophus at Baseline (ITT Population)			
Mean Area (mm^2) (SD)	33 373 (379)	35 347 (336)	29 560 (715)
Percent Change from Baseline to Month 6			
n	31	30	24
Mean (SD)	-21 (64)	-16 (64)	-27 (39)
Adjusted Diff. in Means vs PBO + ALLO (95% CI)		3.69 (-126, 33)	-3.68 (-35, 28)
p-value[1]		0.8045	0.8176
Percent Change from Baseline to Month 12			
n	28	27	26
Mean (SD)	-39 (46)	-34 (92)	-31 (70)
Adjusted Diff. in Means vs PBO + ALLO (95% CI)		3.90 (-34, 42)	7.91 (-30, 46)
p-value[1]		0.8382	0.6817

Diff. = Difference
Note: Only subjects with non-missing tophus measurements at a particular visit are included for that visit. End of study/early termination data are included in the appropriate visit month if no scheduled visit occurred during that visit month.
[1]p-values are from ANCOVA modes with baseline value as a covariate and treatment group and Day -7 renal function (eCrCl ≥60 ml/min vs <60 mL/min) as randomization factor values
Adapted Sponsor's Table 14.2.3.20; p. Study 302 CSR

Patient Reported Outcomes (PROs):

The results from four of the six ancillary secondary PRO assessments are listed in **Table 35**. Overall, limited improvements are noted on review of the results for the Month 6 and Month 12 time points for these assessments with numerically greater improvements noted in favor of the PBO + ALLO group versus both lesinurad + ALLO groups for the mean change in HAQ VAS pain score at Months 6 and 12 as well as the Patient Global Assessment of Disease Activity (PGA) mean change scores at Months 6 and 12.(Note: Although the p-value appears to be significant for the comparisons between the LESU200 mg + ALLO and PBO + ALLO and the LESU400 + ALLO group versus PBO + ALLO, the difference favors the PBO + ALLO group for these analyses.)

Table 35 - Summary of Ancillary Secondary Patient Reported Assessments for Study 302 (Observed Cases – ITT Population)

Patient Reported Outcome Assessment	PBO + ALLO (N=206)	LESU200 mg + ALLO (N=204)	LESU400 mg + ALLO (N=200)
Proportion of Subjects with Improvement of ≥0.25 from Baseline in HAQ-DI at:			
Month 6:			
Diff. in Proportions vs PBO + ALLO (95% CI)	33%	31% -0.02 (-0.12, 0.08)	34% 0.02 (-0.09, 0.12)
p-value		0.9536	0.7539
Month 12:			
Diff. in Proportions vs PBO + ALLO (95% CI)	39%	30% -0.10 (-0.20, 0.01)	38% -0.01 (-0.12, 0.10)
p-value		0.1025	0.8201
Mean Δ (SD) in HAQ VAS Pain Score at:			
Month 6	-5.0 (30)	-2.7 (28)	-4.7 (27)
Adj. Diff. in Means vs PBO + ALLO (95% CI)		1.5 (-3.5, 6.5)	0.2 (-4.8, 5.3)
p-value		0.5604	0.9322
Month 12	-13 (27)	-5.4 (26)	-7.3 (27)
Adj. Diff. in Means vs PBO + ALLO (95% CI)		6.2 (1.4, 11.0)	5.3 (0.5, 10.1)
p-value		0.0110	0.0321
Proportion of Subjects with Improvement ≥2.5 in SF-36 PCS at:			
Month 6	53%	49%	53%
Adj. Diff. in Means vs PBO + ALLO (95% CI)		-0.04 (-0.14, 0.07)	0.0 (-0.11, 0.11)
p-value		0.5537	0.9932
Month 12	56%	52%	52%
Adj. Diff. in Means vs PBO + ALLO (95% CI)		-0.01 (-0.11, 0.09)	-0.01(-0.11, 0.09)
p-value		0.9214	0.8177
Mean Δ (SD) from Baseline PGA score at:			
Month 6	-13 (28)	-6.8 (28)	-9.4 (25)
Adj. Diff. in Means vs PBO + ALLO (95% CI)		4.59 (0.09, 9.10)	2.04 (-2.49, 6.57)
p-value		0.0458	0.3761
Month 12	-16 (29)	-8.7 (26)	-12.3 (25)
Adj. Diff. in Means vs PBO + ALLO (95% CI)		5.75 (1.30, 10.2)	2.39 (-2.13, 6.91)
p-value		0.0115	0.2999

Adj.= Adjusted; Diff.= Difference; Δ = Change
HAQ-DI assesses patient's level of functional ability with items scores ranging from 0-3 with 0 being the least disability.
HAQ VAS pain scores range from 0 (no pain) to 100 (worst pain) based on 100 mm visual analogue scale (VAS).
SF-36
PGA scores range from 0-100 with lower scores indicating a higher patient global assessment
[1]Cochran-Mantel Haenszel test stratified by Day-7 renal function (eCrCl≥ 60 mL/min) and tophus status during screening (presence vs absence), randomization stratification values
[2]ANCOVA models with baseline value as a covariate and treatment group, Day -7 renal function (eCrCl ≥ 60 ml/min versus <60 ml/min), and tophus status during screening (presence versus absence) as factors, randomized values
Adapted Sponsor's Tables 14.2.4.2.a, 14.2.4.4.a, 14.2.4.8.a, and 14.2.4.11.a; p. 838, 922-927,1532 and 1820-1824 Study 302 CSR

- Total Treatment Satisfaction Question for Medication Score (TSQM): No significant differences were noted on comparative analysis between the two lesinurad + ALLO treatment groups and the PBO + ALLO group regarding overall satisfaction (mean scores ranging 68 to 70), effectiveness satisfaction (mean scores ranging 67 to 69), and convenience satisfaction (mean scores ranging 77 to 78). However, the mean side effects score (51) was lower (meaning less satisfaction with side effects) for the LESU400 mg +ALLO group as compared to the comparable mean scores for this subscale reported by subjects in the LESU200 mg + ALLO (63) and PBO + ALLO (63) treatment groups.
- Mean change from baseline in the Sheehan Disability Scale (SDS): The mean baseline scores for each of these subscales (work/school, social life, family life/home, global function impairment, and days lost from work) comprising this assessment were all low indicating minimal impairment for all three treatment groups. Mean changes from baseline at the Month 6 and 12 time points were similar for all three treatment groups for each of the subscales which were not significantly different on comparative analysis.

Efficacy Conclusions:
Significantly greater proportions of subjects treated with LESU200 mg + ALLO and LESU400 mg + ALLO achieved a sUA < 6mg/dL at Month 6 as compared to PBO + ALLO which was sustained through the 12-month course of study treatment and supported by from multiple sensitivity analyses. Results from the endpoints that assessed clinical benefits (e.g., gout flares and tophi resolution) associated with this decrease in sUA as well as a variety of patient reported outcomes (overall disease activity, pain and patient functioning) were not robust for either of the lesinurad + ALLO treatment groups. The findings from the major and ancillary secondary endpoints should not be considered statistically significant due to the hierarchical testing used for multiple endpoints and/or unadjusted p-values due to multiplicity concerns.

Study 304 - Title: A Phase 3 Randomized, Double-Blind, Multicenter, Placebo-Controlled, Combination Study to Evaluate the Efficacy and Safety of Lesinurad and Febuxostat Compared to Febuxostat Alone at Lowering Serum Uric Acid and Resolving Tophi in Subjects with Tophaceous Gout

Dates Conducted:
Study 304 was started on February 23, 2012 and completed on April 17, 2014. Database lock was June 24, 2014.

Objectives:

Primary Objective:

- Assess the efficacy of lesinurad by Month 6 when used in combination with febuxostat as compared to febuxostat monotherapy

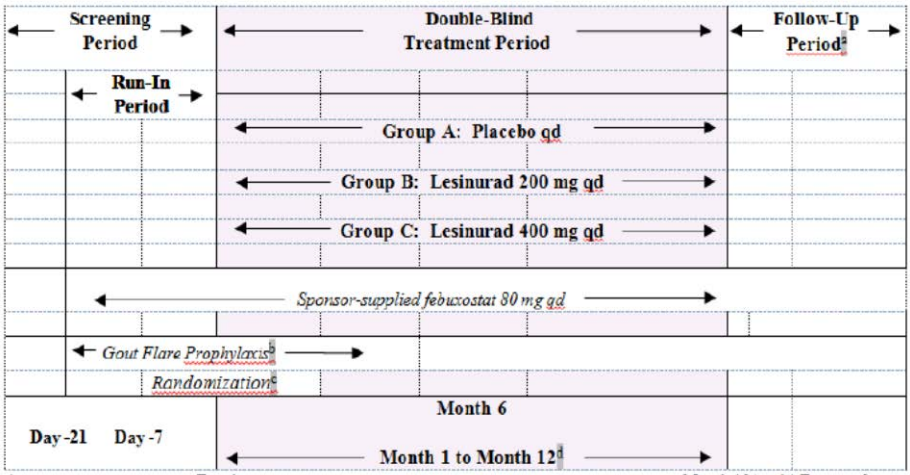
Secondary Objectives:

- Assess the efficacy of lesinurad by Month 12 when used in combination with febuxostat as compared to febuxostat monotherapy
- Evaluate the safety of lesinurad over 6 months and 12 months when used in combination with febuxostat
- Evaluate via population analysis the influence of intrinsic factors (age, sex, race, body weight, renal function, concomitant medication use) on oral clearance of lesinurad
- Assess the effect of lesinurad when used in combination with allopurinol on Health-Related Quality of Life and physical function

Overall Design:

Study 304 was to have been 12-month, multicenter, randomized, double-blind, placebo-controlled, three-arm, parallel group, phase 3 trial in tophaceous gout patients with an inadequate hypouricemic response to 80 mg of febuxostat a day. The trial was comprised of three parts: an initial 35-day screening period (which included a run-in period of approximately 21 days) followed by a 12-month, double-blind treatment period and a 14-day follow-up period. However, the study protocol was amended to include more frequent monitoring of subjects with an extension of the follow-up period for up to 3.5 months as a result of a nephrotoxicity safety signal observed in the lesinurad monotherapy trial 303 (**Figure 7**):

Figure 7 – Design Scheme for Study 304



Abbreviations: EOS, End of Study; mos., month; NSAID, nonsteroidal anti-inflammatory drug; PPI, proton pump inhibitor; qd, once daily.

[a] Subjects 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. Subjects who completed the study and did not continue into an extension study, or who withdrew from the study for any reason other than consent withdrawn and had a serum creatinine (sCr) value > 0.1 mg/dL above their Baseline value were followed until their sCr value was ≤ 0.1 mg/dL of their Baseline value or until 3 monthly assessments after their Follow-Up Visit took place, whichever came first.

[b] Prophylactic treatment for gout flare consisted of colchicine 0.5 to 0.6 mg qd or NSAID ± PPI through Month 5.

[c] Subjects who qualified for the study were randomized in a double-blind fashion to 1 of 3 treatment groups in a 1:1:1 ratio: Groups A, B, or C.

[d] Study visits at Week 2 and monthly from Month 1 through Month 12 (or early termination).

Adapted Sponsor's Fig. 1; p. 37 Study 304 CSR

During the run-in period of the screening phase, study candidates were to have initiated prophylactic gout therapy, discontinued their urate lowering therapy (if applicable) and initiated therapy with sponsor-provided febuxostat 80 mg qd. Patients who successfully completed the screening process were to have been randomized via a 1:1:1 ratio stratified by Day -7 renal function (estimated creatinine clearance > 60 ml/min versus < 60 ml/min) and sUA level at Day -7 (≥6.0 mg/dL versus <6.0 mg/dL) to one of three treatment groups:

- Placebo QD + febuxostat 80 mg qd
- Lesinurad 200 mg QD + febuxostat 80 mg qd
- Lesinurad 400 mg QD + febuxostat 80 qd

All gout prophylaxis regimens were to have been discontinued at Month 5. Patients who completed this study were to have the option of continuing to receive active treatment with lesinurad by enrolling in a 12-month, open-label extension trial (Study 305). Subjects who did not enter the OLE study were to have been seen for safety within 14 days of completing the double-blind portion of these trials. Following the implementation of Protocol Amendment 5, subjects with a serum creatinine (sCR) >0.1 mg/dL above their baseline value at the follow-up visit were required to return to the site monthly for further assessment until the subject's sCr value was ≤0.1 mg/dL of their baseline value or until 3 monthly assessments after their follow-up visit took place.

Eligibility:
In addition to utilizing the same major inclusion and exclusion criteria listed in the preceding **Table 3**, study candidates for this trial could not be hypersensitive or allergic to febuxostat and had to meet the following two key entry criteria:

1. Had ≥1 measurable tophus on the hands/wrists and/or feet/ankles ≥5 mm and ≤20 mm in the longest diameter; **and**
2. Satisfied one of the following:
    - Individuals not currently taking an approved ULT must have had a sUA level ≥ 8 mg/dL
    - Individuals taking a medically appropriate dose of febuxostat or allopurinol must have had a sUA level ≥ 6.0 mg/dL

Treatment:
Study medication was to have been supplied as 200 mg and 400 mg tablets of lesinurad or matching placebo. To maintain blind, subjects were to take 2 placebo tablets (1 large and 1 small) to match the lesinurad 400 mg and 200 mg tablets. The protocol mandated that all subjects were to have received concomitant therapy with 80 mg/day of febuxostat. Concomitant febuxostat was to have been provided by the sponsor as 80 mg tablets. Patients were to have been instructed to take their study medications as a single, oral dose in the morning with food and one cup (8oz.; 240 mL) of water along with their morning dose of febuxostat. Missed doses of study medication or concomitant febuxostat were not to have been made up on the following day. Compliance was to have been assessed by the number of study medication tablets returned.

The protocol originally permitted the temporary stopping of study medication, febuxostat and/or gout prophylaxis due to suspected drug toxicity or clinically meaningful increases in serum creatinine. Resumption of the same dose of study medications (e.g., lesinurad or matching placebo) was to have occurred when medically appropriate or when the patient's serum creatinine had returned to within 0.2 mg/dL of its level prior to elevation. Additionally, subjects who had temporarily discontinued study medication due to an increase in serum creatinine were to have been instructed to increase their daily fluid intake to at least 2 liters/day and start a urine alkalinization regimen (e.g., sodium bicarbonate at 650 mg once or twice daily or potassium citrate 30-40 mEq/day) in order to increase the solubility of urinary uric acid. Restarting concomitant febuxostat at a lower dose was permitted provided it was increased to the original dose. Patients who were medically unable to increase their febuxostat to the original dose were allowed to continue taking the drug at 40 mg per day.

Concomitant Medications:
Concomitant administration of the following medications was prohibited during the study: urate lowering medications other than febuxostat, systemic immunosuppressive or immunodulatory agents, chronic treatment with > 325 mg/day of salicylate, and known inhibitors of epoxide hydrolase (e.g., valpromide, progabide, and valproic acid). Initiation of drugs with secondary uricosuric effects such as fenofibrate, losartan, and chronic guaifenesin during the trial was also not permitted. Subjects taking these medications were to have remained on stable doses for the duration of the study. Due to the increased risk for drug-drug interactions with colchicine, the concomitant use of P-gp or strong CYP3A4 inhibitors were also contraindicated in patients with renal or hepatic impairment who were taking colchicine prophylaxis. Subjects taking medications cleared by the CYP3A4 metabolic pathway were to have been monitored for possible decreases in the therapeutic effectiveness of these drugs since lesinurad has been shown to be a mild inducer of this isozyme. All concomitant medications were to have been recorded at each visit in each subject's case report form.

Gout Flare Treatment:
Patients who experienced an acute gout flare during the study were to have been treated with an individualized anti-inflammatory regimen that included colchicine (acute flare regimen), a NSAID with a PPI, or corticosteroids administered via the intra-articular (5-40 mg of methylprednisolone acetate or equivalent) or oral route. (Note: Oral corticosteroids could be used for up to 7days and were not to exceed a total weekly dose of 84 mg of methylprednisolone or 105 mg of prednisone or prednisolone or a maximal daily dose of 24 mg methylprednisolone or 30 mg of prednisone or prednisolone).The use of intramuscular injections for the treatment of acute gout flares was prohibited.

Removal of Patients from Treatment or Assessment:
Subjects were to have been withdrawn from these trials if they discontinued study medication or concomitant febuxostat for longer than a continuous 6-week period, experienced an adverse event that would have precluded further exposure, required treatment with prohibited or contraindicated medications, were noncompliant, withdrew consent, became pregnant or due to an administrative reason. However, following the implementation of Protocol 3, subjects who discontinued the use of lesinurad/placebo could continue febuxostat alone and continue protocol-specific procedures. Subjects who permanently discontinued febuxostat had to discontinue lesinurad/placebo and were to have been removed from the study.

Study Procedures:
The following tables (**Table 36 - Table 38**) are tabular flow charts of the scheduled study visits and protocol specified procedures and evaluations that were to have been

completed. [Note: These flow charts have been updated to include additional safety measures that were implemented as per amendments 3 (June 14, 2013) and 4 (January 2, 2014) to the common study protocol as a result of the SAE reports of acute kidney failure and kidney stones in the ongoing phase 3 studies. For additional information regarding these safety changes refer to the **Study Conduct** subsection below.]

Table 36 - Schedule of Procedures and Evaluations for Study 304

Assessment/Procedure	Screening				Double-Blind Treatment Period**				Follow-Up***	
	Screening Visit – Day -35*	Run-In Period: By Day -21	Run-In Period: Day -7	Day 1 (Baseline)	Week 2	Months 1 -6	Months 7 - 11	Month 12/Early Termination Visit	Follow-up	Post-Follow Up Visits*
Informed consent	√									
Review eligibility	√									
Record demographics	√									
Record Baseline characteristics of gout, including flares	√									
Record medical & surgical history (including comorbidities)	√									
Record prior ULTs	√									
Record concomitant medications	√	√	√	√	√	√	√	√	√	
Patient Reported Outcomes[b]				√		Month 3 & 6	Month 9	√		
Assess AEs		√	√	√	√	√	√	√	√	
Assess compliance with gout flare prophylaxis			√	√	√	Through Month 5				
Assess compliance with febuxostat			√	√	√	√	√	√		

Adapted Sponsor's Table 1; p. 40 CSR 304

Table 37 - Schedule of Procedures and Evaluations for Study 304 (cont.)

Assessment/Procedure	Screening				Double-Blind Treatment Period**				Follow-Up***	
	Screening Visit – Day -35*	Run-In Period: By Day -21	Run-In Period: Day -7	Day 1 (Baseline)	Week 2	Months 1 -6	Months 7 - 11	Month 12/Early Termination Visit	Follow-up	Post-Follow Up Visits *
Assess gout flares			√	√	√	√	√	√	√	
Provide eDiary and training				√						
Assess compliance with eDiary					√	√	√	√		
Assess compliance with lesinurad/placebo and review dosing instructions[c]					√	√	√	√		
Physical examination	√							√[d]		
Vital signs	√	√	√	√	√	√	√	√	√	
12-lead ECG (triplicate)			√	√		Month 6		√		
Tophus assessment for resolution				√		√	√	√		
Tophus measurement[e]				√		Month 3 & 6	Month 9	√		
Tophus photographs[e]				√		Month 6	Month 9	√		
Confirm eligibility		√	√	√						
Randomize				√						

Adapted Sponsor's Table 1; p. 41 CSR 304

Table 38 - Schedule of Procedures and Evaluations for Study 304 (cont.)

Assessment/Procedure	Screening				Double-Blind Treatment Period**				Follow-Up***	
		Run-In Period								
	Screening Visit ~ Day -35*	By Day -21	Day -7	Day 1 (Baseline)	Week 2	Months 1 -6	Months 7 - 11	Month 12/Early Termination Visit	Follow-up	Post-Follow Up Visits [a]
Urinalysis	√			√		√	√	√	√	
Urine biomarkers				√		√	Month 8 & 10	√		
Spot urine				√		Month 3 & 6		√		
Hematology	√			√		√	√	√	√	
Blood biochemistry[f] (includes sUA, pregnancy test[g], creatine kinase, and eCrCl[h])	√		√	√		√	√	√	√	√[i]
Record patient responses to muscle assessment questions				√		√	√	√	√	
Plasma sample for PK and biomarkers				√		√	Month 8 & 10	√		
Genetic testing (OPTIONAL single sample collection)				√						
Initiate gout flare prophylaxis[j]		√								
Dispense/re-dispense Sponsor-supplied febuxostat[k]		√[j]	√[j]	√	√	√	√			
Dispense lesinurad/placebo				√	√	√	√			

Abbreviations: CK, creatine kinase; ECG, electrocardiogram; eCrCl, estimated creatinine clearance; PK, pharmacokinetics; sUA, serum urate; ULT, urate-lowering therapy.

* Screening started approximately 35 days (Day -35) prior to Baseline (Day 1) and was performed no more than 2 weeks prior to start of Sponsor-supplied febuxostat and initiation of gout flare prophylaxis by Day -21. There was a ± 1 day window around the Run-In Period Visits (Day -21 and Day -7).

**There was a ± 7 day window around the Double-Blind Treatment Period Visits, except Week 2 which was ± 4 days. A clinical month was considered to be 28 days. All scheduled visits were referenced to Day 1.

***Subjects who did not enter an extension study completed a safety Follow-Up Visit within approximately 14 days of completing the Double-Blind Treatment Period.

[a] Serum creatinine values collected at the Follow-Up Visit had to be evaluated by the Investigator. Subjects who had a sCr (serum creatinine) elevation at the Follow Up Visit, defined as a value > 0.1 mg/dL above their Baseline sCr value, were required to return to the site monthly for blood biochemistry assessment. Upon receipt of those laboratory results, Investigators had to schedule additional visits with the subject to continue to assess sCr until the subject's sCr value was ≤ 0.1 mg/dL of their Baseline value or until 3 monthly assessments after their Follow Up Visit had taken place, whichever came first.

[b] Patient Reported Outcome assessments included Short Form-36, Sheehan Disability Scale, Patient Global Assessment, Health Assessment Questionnaire - Disability Index, and Treatment Satisfaction Questionnaire for Medicine (at Month 12 and Early Termination Visit only).

[c] All doses of lesinurad/placebo were taken in the morning with food and 1 cup (8 oz; 240 mL) of water. Subjects were instructed to drink 2 liters (68 oz) of liquid a day. For example, another 3 cups (24 oz; 720 mL) of liquid during the 3 to 4 hours after taking the study medication was encouraged, and then the subject was to remain well hydrated (an additional 4 cups [32 oz; 960 mL] of liquid) throughout the day. It was required that the morning dose of febuxostat be taken at the same time as lesinurad. If the dose of febuxostat was interrupted, the subject was not to take their dose of lesinurad/placebo until febuxostat was resumed.

[d] Excluded height measurement and waist circumference.

[e] Hands/wrists and feet/ankles, digital caliper measurements and photographs were taken at the specific timepoints indicated and at resolution of any measurable tophi.

[f] Hepatitis C virus and hepatitis B virus were only evaluated during Screening and at Baseline (Day 1) to confirm study eligibility.

[g] Serum pregnancy test was conducted only on female subjects of childbearing potential.

[h] Sites could calculate eCrCl (using the Cockcroft-Gault formula and IBW) at scheduled visits where sCr was assessed; however, calculations were performed by the central laboratory for all subjects for the Day -7 Visit. After implementation of Protocol Amendment 5, the central laboratory also calculated eCrCl for all other scheduled visits where sCr was assessed.

[i] Serum creatinine measurement only.

[j] Investigator confirmed eligibility prior to prescribing prophylaxis or febuxostat.

[k] On Day -21, Day 1 (Baseline), and at all monthly visits up to and including Month 11, febuxostat was dispensed. On Day -7 and Week 2, subjects returned febuxostat for drug accountability and the remaining tablets were redispensed.

Sponsor's Table 1; p. 42 CSR 304

Outcome Measures:

The following efficacy assessments were to have been performed:

Primary efficacy endpoint:

The primary efficacy variable for these trials was:

- Proportion of patients with sUA <5 mg/dL by Month 6

- Subjects' sUA levels were to have been measured via a validated bioanalytical assay at a central lab on blood samples collected at study visits scheduled during screening and at baseline, and thereafter at Months 1-6, 8, 10 and 12. To prevent unblinding, these measurements were not to have been disclosed to study investigators (after the Day -7 visit) or to the Applicant (after the baseline visit). Data generated from the serial measurement of sUA were to have been used in determining clinical outcomes that evaluated reduction in sUA over the course of these trials.

Secondary efficacy endpoints:

These studies had a number of secondary endpoints. The key secondary variables for these trials were:

- Proportion of subjects who experienced complete resolution of at least 1 target tophus by Month 12
  - The diameters of subcutaneous tophi were to have been measured via the Vernier calipers method. This process required investigators trained in this methodology to use digital calipers to capture both the longest diameter and longest perpendicular measurement (i.e., $\geq$ 5 mm and $\leq$ 20 mm) of up to 5 target tophi located on the hands/wrists and feet/ankles of patients with tophi in these studies. Draining, acutely inflamed, or previously infected tophi were not selected for this assessment. These measurements including photographs to aid in identification of selected tophi were to have been performed at baseline and the Month 12 visit. The collected data were to have used in the determination of the clinical outcomes that assessed reduction in tophus burden in these studies.
- Proportion of subjects with a best tophus response on at least 1 target tophus of complete or partial resolution by Month 12
- Proportion of subjects with an improvement from baseline in the Health Assessment Questionnaire – Disability Index (HAQ-DI) of at least 0.25 at Month 12
  - This is a self-reported functional status instrument that was used to measures disability over the 12 months of treatment as assessed by 8 domains of functionality. The highest scores from the 8 domains (range: 0-24) are summed and divided by 8 to yield a Functional Disability Index (range: 0-3 with higher scores indicative of increased functional disability). The minimum clinically important difference (MCID) for the HAQ-DI score is -0.22 in rheumatoid arthritis (RA) populations. In determining this assessment, the Applicant is using a HAQ-DI score of -0.25 since it the closest actual score above the minimum clinically important difference; however it is not clear whether the MCID for RA is applicable to the gout population in this study.

Other secondary efficacy variables for these trials were:

- Mean percent change from baseline in the sum of the areas for all target tophi at each visit

- Mean rate of gout flares requiring treatment for a gout flare during the time period from Month 6 to Month 12
  - Clinically relevant gout flares were defined by the common protocol as subject reported gout flares that required the use of prescribed or over the counter colchicine, analgesics, and/or anti-inflammatory medication (including corticosteroids). Patients self-record each gout flare including duration, severity (pain score at rest via an 11-point numerical rating scale [0= no pain and 10= worst imaginal pain]), symptoms (presence of warmth, swelling, and tenderness of the most severely involved joint), treatment and healthcare resource utilization via an eDiary, which asked subjects daily "Have you had a gout attack (flare)?" This information was used in the determination of clinical outcomes that assessed gout flares and treatment over the course of these studies.
- Mean change from baseline to Month 12 in the physical component scale of the Short Form-36 (SF-36)
  - The SF-36 is a 36-item, self-reported questionnaire comprised of 8 subdomains that was used to calculate the 2 summary scores: physical component summary (PCS) and mental component summary (MCS). Average scores in healthy normal population age 55-64 for males and females combined are 47 for PCS and 52 for MCS. Higher scores represent better mental and physical quality of life. The same concerns raised above regarding the HAQ-DI also apply to this outcome measure.
- Total Treatment Satisfaction Question for Medication Score (TSQM)
  - The TSQM is a self-reported questionnaire comprised of four domains: efficacy, convenience, side effects, and overall satisfaction with the medication. It is used to evaluate patient's satisfaction with a medication.
- Mean change from baseline in the Sheehan Disability Scale (SDS)
  - The SDS is a self-reported questionnaire that measures functional impairment in 3 domains: work/school impairment, social impairment, and impairment of family life/home responsibilities. A total disability score is calculated based on the sum total of the disability scores for each question. Unproductive days or days lost from work during the previous week are also calculated. Higher scores are associated with greater impairment.
- Mean change from baseline in Patient Global Assessment (PGA) of Disease Activity
  - The PGA is a patient-rated instrument that is comprised of a single item, a100 mm visual analogue scale (VAS). It is used to assess overall disease activity. Higher scores are associated with greater disease impairment.
- Proportion of subjects whose sUA level is <6.0 mg/dL, <5.0 mg/dL and <4.0 mg/dL at each visit

- Absolute and percent change from baseline in sUA levels at each visit
- Proportion of subjects requiring treatment for a gout flare at monthly intervals between Month 6 and Month 12

Statistical Design, Definitions of Analyzed Populations and Analysis Plan:
The sample size calculation for these studies was based on the efficacy and safety data generated from the Applicant's phase 2 study of lesinurad in combination with febuxostat. With projected enrollment of 315 patients (105 patients per treatment arm), the study was to have approximately 90% power to demonstrate a 25% difference between the lesinurad groups and placebo plus febuxostat in the proportion of subjects achieving a sUA <5 mg/dL at Month 6 assuming a placebo response rate of 40% using using a 2-sided test at a significance level of 0.025 for each test.

Three populations were to have been used for analysis. They were defined as follows:

1. Intent-to-Treat (ITT) Population: was to have consisted of all randomized patients who had received at least 1 dose of study drug.
2. Per-Protocol Population: was to have consisted of subjects in the ITT population who had no major violations or deviations from the study protocol.
3. Safety Population: was to have consisted of all subjects who received at least 1 dose of the randomized study medication.

Efficacy Evaluation:
The statistical analysis plan (SAP) stipulated that a Bonferroni correction was to have been used in analyzing the primary endpoint and a gated, ranked, endpoint-level step-down procedure was to have been used to analyze the key secondary endpoints in order to control for multiplicity. If the null hypothesis for the primary endpoint for both doses was rejected at the 0.025 level, then the key secondary endpoints were to have been tested in the following order at an alpha level of 0.05:

- Mean rate of gout flares requiring treatment for the 6-month period from the end of Month 6 to the end of Month 12, lesinurad 400 mg + allopurinol versus placebo + allopurinol
- Mean rate of gout flares requiring treatment for the 6-month period from the end of Month to the end of Month 12, lesinurad 200 mg + allopurinol versus placebo + allopurinol
- Proportion of subjects with $\geq$ 1 target tophus at baseline who experience complete response of $\geq$ 1 target tophus by Month 12, lesinurad 400 mg + allopurinol versus placebo + allopurinol
- Proportion of subjects with $\geq$ 1 target tophus at baseline who experience complete response of $\geq$ 1 target tophus by Month 12, lesinurad 200 mg + allopurinol versus placebo + allopurinol

Testing of the key secondary endpoints was to have been stopped if there was a failure to reject the null hypothesis. If only one of the primary endpoint dose contrasts was shown to be significant, then an alpha level of 0.025 was to be used for each key secondary endpoint within the surviving dose. The order of testing within the surviving

dose group was to have been the gout flare endpoint, and if significant, the tophi resolution endpoint. All other secondary efficacy endpoints were to have been tested at the alpha=0.05 level without correction for multiplicity.

The primary efficacy analyses were to be conducted via the Cochran-Mantel-Haenszel (CMH) test stratified for Day -7 renal function and tophus status at screening using the ITT population with nonresponder methodology to account for missing data. Sensitivity analyses of the primary endpoint results were to have included using last observation carried forward (LOCF) as well as conducting a completers analysis. Serum uric acid response rates were to have been analyzed via a logistic regression model testing for an association between the response rate and treatment arm while controlling for Day -7 renal function and tophus status during screening.

The two key secondary endpoints were to have been analyzed with the CMH test adjusted for the Day -7 renal function and tophus status for the gout flare endpoint and by the Day-7 renal status for the tophi resolution endpoint. Sensitivity analyses for the gout flare endpoint were to have been conducted that included counting patients who discontinued the study at any time due to a gout flare as having had a gout flare requiring treatment during Month 12, and counting subjects who discontinued the study at any time due to a gout flare after stopping gout flare prophylaxis as having had a gout flare requiring treatment during Month 12. Sensitivity analyses for the tophi resolution endpoint were to have included LOCF and a completers analysis.

Analysis of the remaining continuous secondary efficacy endpoints were to have been conducted via ANCOVA while all categorical response endpoints were to be done via a CMH model. These analyses were to have been adjusted for Day -7 renal function and/or tophus status at screening.

Safety Evaluation:
The analysis of safety assessment was to have been conducted on the safety population. Safety assessment was to have included treatment emergent adverse events (TEAEs), treatment-emergent serious adverse events (SAEs), clinical lab data, physical exam findings and vital signs. All TEAEs were to have been coded using the Medical Dictionary for Regulatory Affairs (MedDRA) coding dictionary (Version 13.1). The incidences of TEAEs were to have been summarized by system organ class (SOC) and preferred term by overall and treatment group. TEAE of interest such as renal-related adverse events such as kidney stones and clinical lab data such as serum creatinine (sCr), estimated creatinine clearance (eCrCl), and spot urine protein to creatinine ratio were to have been presented separately. The common protocol defined elevations in sCr as values $\geq$ 1.5, 2.0 and 3.0 x the baseline value and was considered to be resolved when a subsequent value was $\leq$ 1.2 x baseline. Renal events were adjudicated by a post hoc renal event advisory committee (REAC). Similarly, cardiac events were adjudicated by a cardiovascular event advisory committee (CEAC).

Clinical lab data results for hematology, serum chemistry and urinalysis testing as well as vital signs, physical exam and EKGs were to have been reviewed and summarized for within treatment changes and for changes from baseline for each treatment group.

Study Conduct:

Four protocol amendments were made to the protocol for Study 304:

1. Amendment 1 (implemented on December 9, 2011)
   Major changes to the protocol included:
   - Number of study sites was increased to approximately 160 sites in order to enroll patients with tophaceous gout
   - Addition of South Africa and Latin America as potential study sites
   - Clarify approved dosing of febuxostat in the US and globally
   - Provide guidance regarding the collection of serious adverse events 30 days after the last dose of study medication for subjects who do not continue in an extension study, withdraw from the study, or are withdrawn from study treatment and refuse further follow-up in the study
2. Amendment 2 (implemented on March 8, 2012)
   Minor changes to provide clarification to study investigators regarding"
   - Eligibility criteria, lab instructions, rescreening instructions, and timing of follow-up SAEs reporting
   - Remove Latin America from list of study locations and revise the number of sites accordingly
3. Amendment 3 (implemented on July 20, 2012)
   Major changes to the protocol included:
   - Revised sUA eligibility criteria to $\geq$ 10 mg/dL to $\geq$ 8 mg/dL for subjects currently not taking an approved ULT
   - Provide a conversion factor for screening sUA
   - Changed the secondary endpoint from "proportion of subjects requiring treatment for a gout flare during Month 12" to "mean rate of gout flares requiring treatment for the 6 month period from the end of Month 6 to the end of Month 12"
   - Addition of the definition of gout flares for the purpose of the key secondary gout flare endpoint analysis and to describe the data collection process for recording gout flares
   - Revised the eligibility criteria to exclude the morbidly obese who have an inherent increased risk for death and other SAEs
   - Correct guidance on confirmation of eligibility
   - Removal of the statistical analysis of safety data at Month 6 and removal of the interim analysis for safety
   - Provide revised definition of overdose
   - Revision of the dosing guidelines for colchicine, intra-articular steroids, and oral steroids to encompass the range of dosing regimens and various regional standards of care for acute gout flares

- Revision of the definition of an SAE to also exclude planned hospitalization for an elective medical/surgical procedure, scheduled treatments, or routine check-ups, or a hospitalization lasting <24 hrs
- Required subjects to discontinue study medication following emergency unblinding
- Require that repeat assessment of potentially clinically significant lab abnormalities should be performed with the subject in the fasted state to avoid any influence of food on the results
- Clarification of the circumstances where a retest of sUA is permitted; that subjects who discontinued lesinurad/placebo could continue febuxostat alone (with protocol-specified procedures) but subjects who permanently discontinued use of febuxostat would be removed from the study; timing of the interpretation of ECGs by the investigator; for the use of the Rheumatology CTC v2.0 criteria for grading severity of AEs; only serious CV events and all deaths should be collect at Month 6 and Month 12 after treatment is discontinued; muscle assessment questions included in the list of procedures to be performed and at which time points as well as type of information for potential causes of CK elevations; procedures for subjects who discontinue study medication but who remain in study; procedures for subjects who withdraw from the study; and the process for obtaining signatures on ICFs and providing copies to subjects
- Removal of plasma collection for pharmacology sampling at Day -7
- Specify that for the safety population, subjects who receive an incorrect study medication from that which was randomized will be summarized according to the intended randomized treatment group
- Removal of language regarding not including some ITT subjects in the primary endpoint analysis to ensure that the primary analysis includes all of the defined ITT subjects
- Specify how subjects who are missing their Month 12 tophus measurements will be categorized for efficacy response

4. Amendment 4 (implemented on June 14, 2013)
   Major changes to the protocol included additional safety measures as a result of the SAE reports of acute kidney failure and SAEs of kidney stones in the ongoing phase 3 studies. These changes were reviewed and agreed by the IDMC overseeing these studies.
   - Expanded guidance on subject hydration
   - Expanded the management algorithm if a subject experiences an elevated sCr or kidney stone
     - Subjects with sCr elevations > 1.5 x baseline value were to have retesting of serum creatinine, BUN, and urinalysis and evaluated for potential contributing factors. Investigators were to consider temporarily stopping concomitant medications known to increase sCr including study medication.

- Subjects with sCr elevations > 3 x baseline value were to have study medication temporarily stopped. Once sCr had returned to within 0.2 mg/dL of the subject's baseline sCr value, randomized study medication was to have been resumed. Subjects were to have been re-instructed to drink 1 cup of water when taking study medication and 2 liters of fluid a day to maintain adequate hydration.
- If a subject experienced 3 episodes of elevated sCr > 2 x baseline sCr value or a kidney stone, a mid-morning urine pH assessment was to have been performed at the site and if the urine pH was <6.5, the investigator was to prescribe either sodium bicarbonate or potassium citrate, if not medically contraindicated, to be taken once in the morning prior to administration of lesinurad or placebo, at a dosage compatible with the local product label with the goal of raising urine pH to > 6.5 for or 6 to 8 hours after dosing
- If a kidney stone was passed, it was to have been collected and submitted to pathology for a kidney stone analysis.

- Provide guidance on the management of subjects who report symptoms that may indicate liver injury
- Added assessments of renal events of potential medical importance by an independent Renal Adjudication Adverse Event Committee (REAC)
- Inclusion of a review of dosing instructions in the schedule of events
- Inclusion of a new appendix to provide guidance to sites in reviewing AEs and potential contributing factors in subjects who experience a sCr elevation $\geq$ 1.5 x baseline sCr value

5. Amendment 5 (implemented on January 2, 2014)
   Major changes to the common protocol included additional safety measures as a result of the safety data from the phase 3 placebo controlled lesinurad monotherapy study 303 which showed a higher incidence of nephrotoxic AE in patients who received lesinurad 400 mg qd as compared to placebo. These changes were reviewed and agreed by the IDMC overseeing these studies.
   - Addition of calculated creatinine clearance using the Cockcroft-Gault formula and IBW at all scheduled visits where sCr is assessed
   - Required morning dose of febuxostat be taken at the same time as lesinurad and subjects to interrupt their dose of lesinurad/placebo if their dose of febuxostat is interrupted
   - Required subjects who permanently discontinue use of allopurinol to discontinue use of lesinurad/placebo immediately and will be removed from the study
   - Any subject who experiences a kidney stone during the study must be withdrawn from treatment
   - Increased frequency of subject monitoring

- Amendment of the management algorithm for subjects based on sCr and eCrCl, and to provide additional withdrawal from treatment guidelines:
  - If a subject experienced a sCr value that was elevated > 2 x their baseline creatinine value, or an absolute sCr >3.0 mg/dL, study medication was to have been temporarily stopped and a retest of sCr was to have been performed within 7 days. Once the sCr had returned to < 0.1 mg/dL of the subject's baseline sCr value, study drug may have been resumed.
  - If a subject experienced a sCr value that was elevated > 3 x their baseline creatinine value, or an absolute sCr >4.0 mg/dL, or a CrCl of < 30 mL/min, study medication was to have been temporarily stopped and a retest of sCr was to be performed within 7 days. If the repeat sCr value confirmed that the sCr value was elevated > 3 x the subject's baseline creatinine value, or sCr >4.0 mg/dL, or a CrCl of < 30 mL/min, the subject was to have been withdrawn from treatment. Additionally, subjects were to have been followed and evaluated at least weekly until their sCr returns to <2 x their baseline sCr value.
  - In all instances with a sCr > 1.5 x baseline, including > 2 x baseline:
    - Subjects were to have been reminded to drink a cup of water when they took their study medications and drink 2 liters of liquid a day to maintain adequate hydration
    - Investigators should consider temporarily stopping concomitant medications that are known to increase sCr or impact renal function as medically appropriate
    - If a subject had a urine pH <6.5, investigators were to consider initiation of a urinary alkalinizing medication, such as sodium bicarbonate or potassium citrate, to be taken once daily with lesinurad/placebo at a dose approved per local product label with the goal of achieving a urine pH > measured 6 to 8 hours after dosing with lesinurad
    - If a study developed a kidney stone they were to be withdrawn from study treatment.
- Addition of continued follow-up of all subjects who completed the study and to not continue into an extension study, or who withdraw from treatment or from the study until sCr is $\leq$0.1 mg/dL of their baseline value or for 3 months
- Clarification that the vendor responsible for analyzing the population PK data will be unblinded to the subject's treatment for analysis purposes
- Clarification that no interim analyses were planned
- Removal of the review by the IDMC of the analysis of the primary endpoint at Month 6, which had been previously removed from the IDMC Charter

Results from Study 304:

Disposition:
This study was conducted at 141 international centers. Of the 1,045 potential patients screened for this study, 330 were randomized to study treatment. Six randomized subjects withdrew prior to receiving study medication: three subjects due to pretreatment adverse events (e.g., arthralgia, sinus tachycardia and atrial fibrillation) while receiving febuxostat and gout flare prophylaxis during the run-in period, 1 subject due to noncompliance/protocol deviation and violation, 2 subjects as a result of study termination by the Applicant at that site. As shown in **Table 39**, a total of 324 randomized subjects received one dose of study medication (ITT population) in this trial: 109 patients in the placebo + febuxostat 80 mg group (PBO + FBX), 106 patients in the lesinurad 200 mg + febuxostat 80 mg group (LESU200 + FBX) and 109 patients to the lesinurad 400 mg + febuxostat 80 mg group (LESU400 + FBX). The proportions of subjects who completed the study with or without completing randomization study medication were comparable for the three treatment groups. Fewer patients randomized to the LESU400 + FBX group and LESU200 + FBX group completed treatment with study medication at the 6- and 12-month time points compared to the PBO + FBX group. The higher rates of premature discontinuation of study medication in the LESU400 + FBX group were due to adverse events, non-compliance/protocol violation and gout flares. More patients in the LESU200 + FBX group prematurely stopped study medication due to non-compliance/protocol violation, experiencing an adverse event and lost to follow-up. A similar pattern of premature withdrawals was observed for the PBO + FBX subjects.

Table 39 - Subject Disposition for Study 304

	PBO + FBX 80 mg	LESU200 + FBX 80 mg	LESU400 + FBX 80 mg	Total
Number of Patients Randomized:	**111**	**109**	**110**	**330**
Subject withdrawn Prior to Receiving Randomized Medication	2	3	1	6
Intent-To-Treat (ITT)Population	**109**	**106**	**109**	**324**
Safety Population	**109**	**106**	**109**	**324**
Per Protocol (PP) Population	**106**	**102**	**99**	**307**
Pts. Completed Study (W/O Completing Randomized Medication Treatment):	**87 (80%)**	**79 (75%)**	**84 (77%)**	**250 (77%)**
Adverse Event	4 (4%)	7 (7%)	6 (6%)	17 (5%)
Consent Withdrawn	3 (3%)	3 (3%)	4 (4%)	10 (3%)
Death	0	1 (<1%)	1 (<1%)	2 (<1%)
Gout Flare	1 (<1%)	0	3 (3%)	4 (1%)
Lost to Follow-Up	5 (5%)	5 (5%)	1 (<1%)	11 (3%)
Noncompliance/Protocol Violation	9 (8%)	11 (10%)	10 (9%)	30 (9%)
Pts Completed 6 Months of Randomized Study Medication Treatment:	**94 (86%)**	**87 (82%)**	**88 (81%)**	**269 (83%)**
Adverse Event	5 (5%)	7 (7%)	11 (10%)	23 (7%)
Consent Withdrawn	1 (<1%)	1 (<1%)	2 (2%)	4 (1%)
Death	0	1 (<1%)	0	1 (<1%)
Gout Flare	0	1 (<1%)	3 (3%)	4 (1%)
Lost to Follow-Up	4 (4%)	3 (3%)	0	7 (2%)
Noncompliance/Protocol Violation	5 (5%)	6 (6%)	5 (5%)	16 (5%)
Pts Completed 12 Months of Randomized Study Medication Treatment:	**83 (76%)**	**76 (72%)**	**76 (70%)**	**235 (73%)**
Adverse Event	9 (8%)	10 (9%)	15 (14%)	34 (10%)
Consent Withdrawn	3 (3%)	2 (2%)	4 (4%)	9 (3%)
Death	0	1 (1%)	0	1 (<1%)
Gout Flare	1 (<1%)	1 (<1%)	4 (4%)	6 (2%)
Lost to Follow-Up	4 (4%)	5 (5%)	1 (<1%)	10 (3%)
Noncompliance/Protocol Violation	9 (8%)	11 (10%)	9 (8%)	29 (9%)

Table courtesy Dr. Jade Wang

Protocol Deviations and Violations:
A total of 17 patients incurred one or more protocol deviations and violations over the course of this 52-week trial as shown in **Table 40**. Higher overall rates of protocol deviations/violations occurred in the LESU400 + FBX group as compared to the LESU200 + FBX and PBO +ALLO groups. The higher rate of overall protocol violations in the LESU400 + FBX group was primarily due to noncompliance with study medications >20% of time while on randomized study medications (7%).

Table 40 - Summary of Subjects with a Major Protocol Deviation/Violation by Randomized Treatment Group for Study 304

	PBO + FBX80 mg (N=109)	LESU200 + FBX 80 mg (N=106)	LESU400 + FBX 80 mg (N=109)	Total (N=324)
Number of Subjects with Protocol Deviations/Violations	3(3%)	4 (4%)	10 (9%)	17 (5%)
Failure to Meet ARA Classification Criteria of Acute Arthritis of 1° Gout	0	1 (1%)	0	1 (<1%)
Failure to have ≥ 1 measurable Tophus on Hand/Wrist and/or feet/ankles ≥5mm and ≤20 mm in longest diameter	1 (1%)	1(1%)	0	2 (1%)
Noncompliance with Study Meds >20%	1 (1%)	3 (3%)	8 (7%)	12 (4%)
Missed Month 6 Study Visit	1 (1%)	0	2 (2%)	3 (1%)

Adapted Sponsor's Table 14.1.1.4; p. 275-276 Study 304 CSR

Demographics:

As summarized by the following tables (**Table 41** and **Table 42**), the treatment groups within Study 304 were generally well balanced with respect to baseline demographics, disease characteristics and activity.

The subjects who participated in this trial were overwhelmingly Caucasian males with a mean age 54 years (**Table 41**). A higher proportion of Black/African American patients were randomized to the LESU200 mg + FBX and LEU400 mg + FBX groups as compared to the PBX + FBX group. Subjects in this trial were also overweight as evidenced by a mean body mass index (BMI) of 32 kg/m^2 which is consistent with the fact that obesity is a risk factor for gout. The majority (97%) of patients did not report a history of alcoholism, another risk factor for gout. Subjects in this international trial were predominantly from North America (81%), while the remaining subjects were from Europe (10%) and Australia/new Zealand (9%). No important imbalances in these demographic factors across treatment groups were noted in Study 304.

Table 41 - Baseline Demographic Characteristics of Subjects Enrolled in Study 304

Demographic Characteristic	PBO + FBX80 mg (N=109)	LESU200 + FBX 80 mg (N=106)	LESU400 + FBX 80 mg (N=109)	Total (N=324)
Age (years)				
Mean (SD)	55 (11)	54 (11)	53 (11)	54 (11)
Gender				
Male	107 (98%)	100 (94%)	102 (94%)	309 (95%)
Female	2 (2%)	6 (6%)	7 (6%)	15 (5%)
Race:				
American Indian/Alaska Native	0	1 (1%)	0	1 (1%)
Asian	6 (6%)	8 (8%)	6 (6%)	20 (6%)
Black/African American	8 (7%)	14 (13%)	13 (12%)	35 (11%)
Maori	0	0	3 (3%)	3 (1%)
Native Hawaiian/other Pacific Islander	0	1 (1%)	2 (2%)	3 (1%)
White	94 (86%)	80 (76%)	85 (78%)	259 (80%)
Other	1 (1%)	2 (2%)	0	3 (1%)
Ethnicity (Hispanic/Latino)				
Yes	9 (8%)	7 (7%)	5 (5%)	21 (7%)
No	100 (92%)	99 (93%)	104 (95%)	303 (94%)
Weight (Kg)				
Mean (SD)	99 (21)	100 (20)	99 (21)	99 (21)
Height (cm)				
Mean (SD)	176 (8)	176 (8)	177 (9)	176 (8)
Body Mass Index (BMI) [kg/m^2]				
Mean (SD)	32 (6)	32 (6)	32 (6)	32 96)
History of Alcoholism:				
Yes	4 (4%)	2 (2%)	3 (3%)	9 (3%)
No	104 (95%)	103 (97%)	106 (97%)	313 (97%)
Missing	1 (1%)	1 (1%)	0	2 (1%)
Region and Country				
North America	86 (78%)	93 (85%)	87 (79%)	266 (81%)
Europe	15 (14%)	8 (7%)	11 (10%	34 (10%)
Australia/New Zealand	10 (9%)	8 (7%)	12 (11%)	30 (9%)

Adapted Sponsor's Tables 14.1.1.2, 14.1.2.1 and 14.1.2.4; p. 267- 272, 277-278 and 287-288 Study 304 CSR

The overall mean duration of disease since the first gout attack was 15 years for the study population who also reported having a mean number of 7 gout attacks per year over the last 12 months (**Table 42**). The treatment groups within the trial were also generally well balanced with respect to baseline disease status and treatment with the following exceptions. Differences in the three treatment groups were observed for mean total area of target tophi, prior urate lowering therapy (ULT) and type of gout flare prophylaxis at baseline The mean total area of target tophi at baseline was higher in the LESU200 mg + FBX group (310 mm^2) compared to the PBO + FBX (291 mm^2) and LESU400 mg + FBX (280 mm^2) groups. A higher proportion of subjects in the PBO +

FBX group were taking allopurinol at baseline as compared to the two lesinurad + FBX groups. More subjects used NSAIDs at baseline for flare prophylaxis in the PBO + FBX and LESU400 mg + FBX groups compared to the LESU200 mg + FBX group. Fewer patients randomized to PBO + FBX also took colchicine at baseline to prevent gout flares as compared to patients in the LESU400 mg + FBX and LESU200 mg + FBX groups.

Following at least 21 days of treatment with febuxostat 80 mg a day, the study population had a baseline mean sUA 5.27 mg/dL with 50% having a baseline sUA <5 mg/dL (**Table 42**). A total of 23% of the patients had mild to moderate impairment as assessed by an estimated creatinine clearance (eCrCl) of <60 ml/min at baseline with 6% having moderate to severe renal impairment (eCrCl < 45 ml/min). Overall, the study population who participated in this trial was representative of patients with a high uric acid burden as manifested by their tophaceous deposits and persistent hyperuricemia despite treatment with febuxostat and could potentially benefit from treatment with lesinurad.

Table 42 - Summary of Subject's Gout History, Disease Status, and Treatment at Baseline for Study 304

	PBO + FBX80 mg (N=109)	LESU200 + FBX 80 mg (N=106)	LESU400 + FBX 80 mg (N=109)	Total (N=324)
American Rheumatism Association Diagnostic Criteria	109(100%)	106(100%)	109(100%)	324(100%)
Presence of MSU Crystals in Jt. Fluid	14 (13%)	16 (15%)	12 (11%)	42 (13%)
Number of Years Since Gout Diagnosis				
Mean (SD)	15 (11)	16 (11)	13 (11)	15 (11)
Number of Gout Flares in the Past 12 Months				
Mean (SD)	6 (5)	7(11)	7 (7)	7 (8)
Baseline Presence of ≥1 Target Tophus				
0	0	1 (1%)	0	1 (<1%)
1	56 (51%)	62 (59%)	63 (58%)	181 (56%)
2	26 (24%)	21 (20%)	26 (24%)	73 (23%)
3	14 (13%)	8 (8%)	9 (8%)	31 (10%)
4	3 (3%)	6 (6%)	4 (4%)	13 (4%)
5	10 (9%)	8 (8%)	7 (6%)	25 (8%)
Mean (SD)	**1.9 (1.3)**	**1.8 (1.3)**	**1.8 (1.2)**	**1.8 (1.2)**
Total Area of Target Tophi at Baseline				
Mean (SD)	291 (246)	310 (228)	280 (230)	293 (235)
Baseline sUA				
Mean (SD)	**5.22 (1.53)**	**5.35 (1.72)**	**5.23 (1.64)**	**5.27 (1.63)**
<5.0	58 (53%)	47 (44%)	58 (53%)	163 (50%)
5.0 - <6.0	19 (17%)	28 (26%)	23 (21%)	70 (22%)
6.0 - <7.0	16 (15%)	14 (13%)	11 (10%)	41 (13%)
7.0 - <8.0	12 (11%)	9 (9%)	8 (7%)	29 (9%)
8.0 - <10.0	4 (4%)	6 (6%)	8 (7%)	18 (6%)
>10.0	0	2 (2%)	1 (1%)	3 (1%)
Baseline Renal Function (ml/min)				
eCrCl ≥90	31 (28%)	37 (35%)	42 (39%)	110 (34%)
eCrCl <90	78 (72%)	69 (65%)	67 (62%)	214 (66%)
eCrCl ≥60	**84 (77%)**	**78 (74%)**	**87 (80%)**	**249 (77%)**
eCrCl <60	**25 (23%)**	**28 (26%)**	**22 (20%)**	**75 (23%)**
eCrCl ≥ 45	105 (96%)	98 (93%)	101 (93%)	304 (94%)
eCrCl < 45	4 (4%)	8 (8%)	8 (7%)	20 (6%)
Prior ULT				
Allopurinol	38 (35%)	26 (25%)	28 (26%)	92 (28%)
Febuxostat	4 (4%)	2 (2%)	6 (6%)	12 (4%)
Benzbromarone	1 (1%)	1 (1%)	0	2 (1%)
Probenecid	2 (2%)	2 (2%)	1 (1%)	5 (2%)
Other	0	0	1 (1%)	1 (<1%)
Baseline Gout Flare Prophylaxis				
Colchicine	87 (80%)	95 (90%)	94 (86%)	276 (85%)
NSAID	26 (24%)	10 (9%)	20 (18%)	56 (17%)
Both	4 (4%)	1 (1%)	5 (5%)	10 (3%)
Other or Missing	0	2 (2%)	0	2 (1%)

Adapted Sponsor's table 14.1.2.3; p. 281-287 Study 304 CSR

As summarized in **Table 43**, the majority (75%) of the subjects who participated in Study 304 reported having ≥ 1 comorbid condition associated with hyperuricemia. Comorbid conditions with a high prevalence in this study population that increased the risk for metabolic syndrome and/or hyperuricemia included hypertension (61%), hyperlipidemia (43%), hypertriglyceridemia (15%), diabetes mellitus (16%) and kidney stones (13%). The three treatment groups were generally similar with respect to the presence of co-morbid conditions with the following exceptions. Differences in the three treatment groups were observed for hypertension, diabetes mellitus, kidney stones and angina pectoris. A higher rate of hypertension was reported by patients randomized to LESU200 mg + FBX as compared to PBO + FBX and LESU400 + FBX. Fewer subjects in the LESU400 mg + FBX had diabetes mellitus as compared to the LESU400 mg + FBX and PBO + FBX. More patients with kidney stones were randomized to the PBO + FBX group and LESU200 mg + FBX groups as compared to the LESU400 mg + FBX group. Higher rates of angina pectoris were reported in the LESU400 mg + FBX and PBO + FBX groups versus the LESU200 mg + FBX. The overall rate of CV comorbidity and/or CV disease history was very high (74%) in this study population but balanced across the treatment groups.

Table 43 – Summary of Comorbid Medical Conditions Reported by Subjects by Randomized Treatment Group in Study 304

	PBO + FBX 80 mg (N=109)	LESU200 + FBX 80 mg (N=106)	LESU400 + FBX 80 mg (N=109)	Total (N=324)
≥1 Comorbidity	82 (75%)	82 (77%)	78 (72%)	242 (75%)
≥2 Comorbidity	49 (45%)	48 (45%)	43 (39%)	140 (43%)
≥3 Comorbidity	25 (23%)	27 (26%)	24 (22%)	76 (24%)
Types of Comorbidities				
Hypertension	65 (60%)	70 (66%)	62 (57%)	197 (61%)
Hyperlipidemia	46 (42%)	42 (40%)	50 (46%)	138 (43%)
Hypercholesterolemia	42 (39%)	40 (38%)	41 (38%)	123 (38%)
Hypertriglyceridemia	16 (15%)	11 (10%)	21 (19%)	48 (15%)
Diabetes Mellitus	17 (16%)	21 (20%)	14 (13%)	52 (16%)
Kidney Stones	16 (15%)	15 (14%)	11 (10%)	42 (13%)
Myocardial Infarction	7 (6%)	5 (5%)	7 (6%)	19 (6%)
Angina Pectoris	4 (4%)	1 (1%)	6 (6%)	11 (3%)
Heart Failure	1 (1%)	2 (2%)	3 (3%)	6 (2%)
Peripheral Vascular Disease	2 (2%)	1 (1%)	1 (1%)	4 (1%)
Stroke	1 (1%)	2 (2%)	1 (1%)	4 (1%)
Transient Ischemic Attack	0	1(1%)	1 (1%)	2 (1%)
Any CV Comorbidity and/or CV Disease History	80 (73%)	81 (76%)	79 (73%)	240 (74%)

Adapted Sponsor's table 14.1.3.1 and 14.1.3.3; p. 289 and 292 Study 304 CSR

Information regarding concomitant medications used by more than 10% of the study population was also examined (**Table 44**). The most commonly reported concomitant non-gout classes of medications were drugs acting on the renin-angiotensin system, analgesics, lipid-modifying agents, drugs for acid-related disorders and beta-blockers. This information is consistent with what is typically seen in gout patients since this disease is commonly associated with chronic disorders such as hypertension, diabetes mellitus, hyperlipidemia and cardiovascular disease.

Table 44 – Concomitant Medications Taken by ≥ 10% of Subjects in Study 304 by Treatment Group (Safety Population)

	PBO + FBX 80 mg (N=109)	LESU200 + FBX 80 mg (N=106)	LESU400 + FBX 80 mg (N=109)
Any Concomitant Medication	**109 (100%)**	**106 (100%)**	**109 (100%)**
Antigout Preparations	**90 (83%)**	**96 (91%)**	**98 (90%)**
Colchicine	90 (83%)	96 (91%)	98 (90%)
Anti-Inflammatory and Antirheumatic Products	**70 (64%)**	**69 (65%)**	**70 (64%)**
Ibuprofen	24 (22%)	22 (21%)	30 (28%)
Indomethacin	18 (17%)	18 (17%)	21 ((19%)
Naproxen	12 (11%)	12 (11%)	15 (14%)
Naproxen Sodium	11 (10%	17 (16%)	8 (7%)
Agents Acting on Renin-Angiotensin System	**44 (40%)**	**54 (51%)**	**46 (42%)**
Lisinopril	13 (12%)	21 (20%)	16 (15%)
Analgesics	**46 (42%)**	**39 (37%)**	**39 (36%)**
Paracetamol	10 (9%)	18 (17%)	12 (11%)
Vicodin (hydrocodone/acetaminophen)	12 (11%)	4 (4%)	9 (8%)
Corticosteroids for Systemic Use	**28 (26%)**	**29 (27%)**	**36 (33%)**
Prednisone	18 (17%)	17 (16%)	25 (23%)
Lipid Modifying Agents	**35 (32%)**	**39 (37%)**	**31 (28%)**
Fish Oil	8 (7%)	12 (11%)	4 (4%)
Drugs for Acid Related Disorders	**31 (28%)**	**19 (18%)**	24 (22%)
Omeprazole	13 (12%)	11 (10%)	11 (10%)
Beta Blocking Agents	**21 (19%)**	**22 (21%)**	**23 (21%)**
Metoprolol	9 (8%)	12 (11%)	8 (7%)
Antibacterials for Systemic Use	**26 (24%)**	**23 (22%)**	**22 (20%)**
Antithrombotic Agents	**18 (17%)**	**20 (19%)**	**21 (19%)**
Acetylsalicylic Acid	17 (16%)	19 (18%)	17 (16%)
Calcium Channel Blockers	**17 (16%)**	**19 (18%)**	**21 (19%)**
Amlodipine	9 (8%)	7 (7%)	11 (10%)
Vitamins	**18 (17%)**	**24 (23%)**	**21 (19%)**
Diuretics	**13 (12%)**	**15 (14%)**	**19 (17%)**
Drugs Used in Diabetes	**16 (15%)**	**21 (20%)**	**14 (13%)**
Metformin	8 (7%)	12 (11%)	6 (6%)
Psychoanaleptics	**10 (9%)**	**16 (15%)**	**13 912%)**
Psycholeptics	**15 (14%)**	**9 (9%)**	**13 (12%)**
Antihistamines for Systemic Use	**8 (7%)**	**19 (18%)**	**11 (10%)**
No Code Found	**10 (9%)**	**14 (13%)**	**11 (10%)**
Nasal Preparations	**11 (10%)**	**5 (5%)**	**8 (7%)**
Cough and Cold Preparations	**11 (10%)**	**10 (9%)**	**6 (6%)**
Urologicals	**8 (7%)**	**13 (12%)**	**6 (6%)**

Adapted Sponsor's Table 14.1.4.3a; p. 331-372 Study 304 CSR

Examination of the data in **Table 44** revealed that study participants in each treatment group were taking concomitant medications (e.g., lisinopril, beta-blockers, acetylsalicylic acid, amlodipine and diuretics) that are known to interfere with uric acid metabolism. The three treatment groups were generally similar with respect to the use of drugs that affect uric acid metabolism with the following exceptions. Differences in the three treatment groups were observed for the use of renin-angiotensin system drugs and diuretics. A higher proportion of subjects in the LESU200 mg + FBX group were taking renin-angiotensin drugs as compared to the LESU400 mg + FBX and PBO + FBX groups. More patients randomized to LESU400 mg + FBX reported taking concomitant diuretic therapy than in the PBO + FBX and LESU200 mg + FBX groups. The following table (**Table 45**) summarizes concomitant usage of thiazide and thiazide-like diuretics by more than 2% of subjects who participated in Study 304. Overall, higher usage rates of these types of drugs occurred in the two lesinurad treatment groups as compared to the placebo group. It is unlikely that these imbalances impacted on the trial's outcome since the study protocol mandated that the use of drugs affecting uric acid metabolism were to have been kept stable for the duration of the study.

Table 45 - Concomitant Thiazide and Thiazide-Like Diruretics by ≥2% of Subjects by Treatment Group During Study 304 (Safety Population)

ATC Class and WHO Drug Dictionary Preferred Term	PBO + FBX 80 mg (N=109)	LESU200 + FBX 80 mg (N=106)	LESU400 + FBX 80 mg (N=109)
Any Concomitant Thiazide and Thiazide-Like Diuretic	**11 (10%)**	**15 (14%)**	**18 (17%)**
Diuretics	**8 (7%)**	**10 (9%)**	**13 (12%)**
Hydrochlorothiazide (HCTZ)	7 (6%)	7 (7%)	6 (6%)
Indapamide	1 (1%)	3 (3%)	4 (4%)
Agents Acting on Renin-Angiotensin System:	**3 (3%)**	**6 (6%)**	**7 (6%)**
Hyzaar (Losartan/HCTZ)	0	0	2 (2%)
Zestoretic (Lisinopril/HCTZ)	1 (1%)	2 (2%)	2 (2%)

Adapted Sponsor's Table 14.1.4.5.1;p. 383 Study 304 CSR

The protocol permitted patients to take medications to treat gout flares they experienced over the course of the study. This information is summarized in **Table 46**. Higher proportions of subjects randomized to LESU400 mg + FBX used concomitant medications to treat gout flares during the trial as compared to the LESU200 mg + FBX and PBO + FBX groups. Imbalances are noted in the use of corticosteroids and analgesics to treat gout flares for the three treatment groups. A higher rate of patients in the LESU400 mg + FBX group used corticosteroids and analgesics to treat gout flares than patients in the LESU200 mg + FBX and PBO + FBX groups.

Table 46 - Gout Flare Medications Taken by ≥ 2% of Subjects by Treatment Group During Study 304 (Safety Population)

	PBO + FBX 80 mg (N=109)	LESU200 + FBX 80 mg (N=106)	LESU400 + FBX 80 mg (N=109)
Any Concomitant Medication Used to Treat Gout Flares	**61 (56%)**	**63 (59%)**	**69 (63%)**
Colchicine	**36 (33%)**	**37 (35%)**	**43 (39%)**
Colchicine	36 (33%)	37 (35%)	43 (39%)
NSAIDs	**37 (34%)**	**41 (39%)**	**40 (37%)**
Ibuprofen	13 (12%)	8 (8%)	14 (13%)
Indomethacin	14 (13%)	16 (15%)	13 (12%)
Diclofenac	2 (2%)	2 (2%)	7 (6%)
Naproxen Sodium	3 (3%)	10 (9%)	5 (5%)
Diclofenac Sodium	2 (2%)	1 (1%)	3 (3%)
Ketoprofen	1 (1%)	2 (2%)	2 (2%)
Naproxen	5 (5%)	6 (6%)	2 (2%)
Corticosteroids	**19 (17%)**	**22 (21%)**	**29 (27%)**
Prednisone	13 (12%)	16 (15%)	23 (21%)
Methylprednisolone	4 (4%)	6 (6%)	7 (6%)
Prednisolone	0	2 (2%)	2 (2%)
Triamcinolone Acetate	1 (1%)	0	2 (2%)
Non-NSAID Analgesics	**6 (6%)**	**9 (9%)**	**15 (14%)**
Paracetamol	2 (2%)	6 (6%)	6 (6%)
Vicodin	2 (2%)	2 (2%)	5 (5%)

Adapted Sponsor's Table 14.1.4.7; p. 397-399 Study 304 CSR

Treatment Compliance:

The common protocol specified that patients' compliance with study medication was to have been assessed by pill counts performed on the returned study medication kits which contained a 40-day supply of randomized medication. Overall mean compliance was high for all three treatment groups (≥96%) with comparable proportions achieving >100% compliance for all three treatment groups (**Table 47**).

Table 47 - Compliance With Randomized Study Medication for Subjects in Study 304

	PBO + FBX 80 mg (N=109)	LESU200 + FBX 80 mg (N=106)	LESU400 + FBX 80 mg (N=109)
Overall Compliance* (Baseline to Month 12 or Early Discontinuation)			
Mean (SD)	98% (4.4)	96% (7.6)	96% (8.4)
Min, Max	74, 114	48, 111	64, 106
Compliance Category			
<80%	1 (1%)	3 93%)	8 (7%)
80-100%	97 (89%)	89 (84%)	88 (81%)
>100%	11 (10%)	14 (13%)	13 (12%)

Note: Overall Compliance was calculated by the Applicant as follows: [Total number of small and large tablets taken]/[2 x total days on randomized medication] x 100% where total days on randomized study medication is calculated as follows: (last randomized study medication dose date – first randomized study medication dose date + 1)
Adapted Sponsor's Table 14.1.6; p. 404 Study 304 CSR

Efficacy:

Primary Endpoint

As discussed in the preceding protocol section, the primary efficacy parameter for Study 304 was the proportion of patients with sUA less than 5 mg/dL by Month 6. As shown in **Table 48**, higher proportions of patients treated with LESU200 mg + FBX and LESU400 mg + FBX achieved this level of response to study treatment in a dose dependent manner as compared to patients treated with PBO + FBX. The difference between the LESU400 mg + FBX group response versus the PBO + FBX group was statistically significant but the difference between the LESU200 mg + FBX and the PBO + FBX groups was not.

Table 48 – Month 6 Primary Endpoint Results for Study 304 (ITT Population)

	PBO + FBX80 mg (N=109)	LESU200 + FBX 80 mg (N=106)	LESU400 + FBX 80 mg (N=109)
Proportion with sUA <5.0 mg/dL by Month 6	51 (47%)	60 (57%)	83 (76%)
Diff. in Proportions vs PBO + FBX (95% CI)		0.10 (-0.03, 0.23)	0.29 (0.17, 0.42)
P-Value[a]		0.1298	<0.0001

CI = Confidence interval
Cochran-Mantel Haenszel test stratified by Day-7 renal function (eCrCl≥ 60 mL/min) and Day-7 sUA status (sUA≥ 6.0mg/dL vs <6.0 mg/dL), randomization stratification values using nonresponder imputation for subjects missing Month 6 sUA.
Table courtesy Dr. Jade Wang

The Applicant provided the results from seven sensitivity analyses for the primary efficacy endpoint (e.g., LOCF analysis; observed case analysis; reached target sUA <5 mg/dL at each Month 4, 5, and 6; per protocol population analysis; reached target sUA

<5 mg/dL at Month 6 via logistic regression; and subject's personal median sUA reached target <5 mg/dL). The results of these sensitivity analyses for the LESU400 mg + FBX treatment group were generally supportive of the findings from the primary endpoint analysis. The results for the LESU200 mg + FBX treatment group were less robust. (Note: The reader is referred to the statistical review of this application by Dr. Jade Wang for further information regarding these sensitivity analyses and the results of additional sensitivity analyses that she conducted as part of her review of this application.)

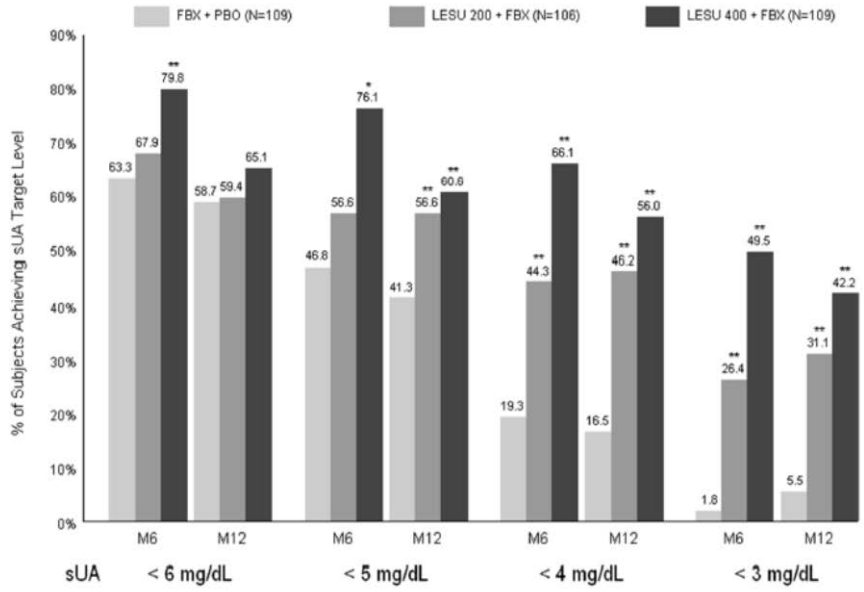
Secondary Endpoints:

There were three major and multiple ancillary secondary endpoints for this trial which were assessed in order to determine if a clinical benefit (e.g., resolution of tophi and frequency of gout flares) was associated with the administration of lesinurad. These secondary assessments are presented below by corresponding assessment area. In order to control for multiplicity, the statistical analysis plan mandated the three major secondary endpoints for this study to be analyzed via a sequential procedure in a prespecified descending order following testing of the primary endpoint. However, no multiplicity correction was implemented for the remaining secondary endpoints. Due to the statistically non-significant finding for the primary endpoint analysis for the LESU200 mg + FBX treatment group, no further testing was to have been performed. For completeness, the results of the major and ancillary secondary endpoint analyses are being presented in this review. However, findings from the major secondary endpoints should not be considered statistically significant due to the hierarchical testing used for multiple endpoints. Declaring statistical significance of the ancillary secondary endpoints using unadjusted p-values may be also inappropriate due to multiplicity concerns.

sUA Reduction:

- Proportion of subjects whose sUA level is <6.0 mg/dL, <5.0 mg/dL and <4.0 mg/dL at each visit: Lesinurad's urate lowering agent capability was also assessed by examining different threshold response levels than that explored by the primary endpoint. As shown in **Figure 8**, higher proportions of patients randomized to the two lesinurad+ FBX treatment groups achieved sUA levels <6.0, <5.0, <4.0, and < 3.0 mg/dL in a dose dependent manner as compared to the PBO + FBX group at the Months 6 and 12 time points. Significant differences in the proportions of subjects who achieved <4.0 mg/dL and <3.0 mg/dL sUA levels at both the Month 6 and Month 12 time points and <5 mg/dL at Month 12 in the LESU200 mg + FBX group were shown on comparison with the PBO + FBX group. No differences were noted on the comparisons of the LESU200 + FBX group for sUA <6.0 mg/dL at Month 6 and Month 12 and for sUA<5.0 mg/dL at Month 6 as compared with the PBO + FBX group. Significant differences between the LESU400 mg + FBX group versus the PBO + FBX group were observed at both the Month 6 and Month 12 time points for each of these prespecified threshold sUA levels.

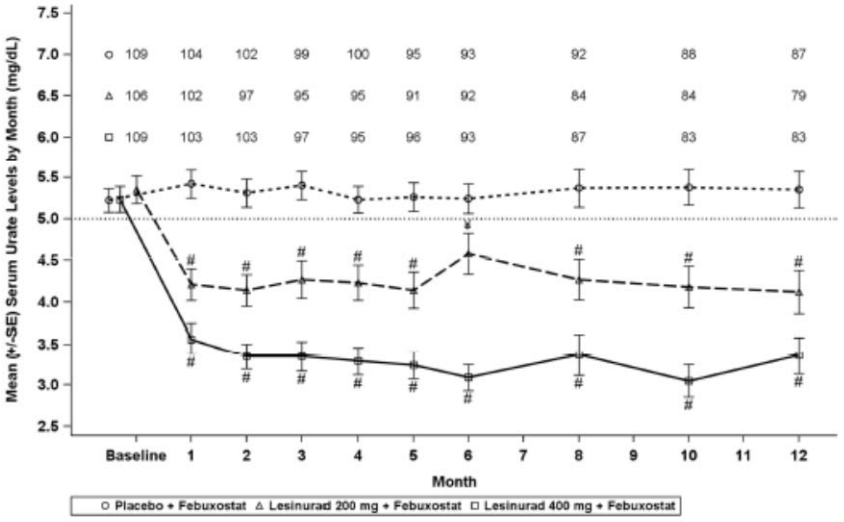
Figure 8 – Proportion of Subjects Achieving sUA < 6mg/dl, < 5 mg/dL, <4 mg/dL, and < 3.0 mg/dL at Months 6 and 12 in Study 304 ((NRI; ITT Population)



Abbreviations: FBX, febuxostat; ITT, Intent-to-treat; LESU, lesinurad; M, month; PBO, placebo; sUA, serum urate.
Note: Subjects missing an sUA result at each visit were treated as nonresponders.
* Indicates statistically significant $p < 0.025$ for LESU + FBX versus PBO + FBX using a 2-sided Cochran-Mantel Haenszel test stratified by Day-7 renal function and Day-7 sUA status (randomized values), adjusted for multiple comparisons.
** Indicates $p < 0.05$ for LESU + FBX versus PBO + FBX using a 2-sided Cochran-Mantel Haenszel test stratified by Day-7 renal function and Day-7 sUA status (randomized values), not adjusted for multiple comparisons.
Source: Table 14.2.1.1.a, Table 14.2.1.7, Table 14.2.1.8, Table 14.2.1.9, Table 14.2.1.10.
Adapted Sponsor's Fig. 6; p. 134 Study 304 CSR

- Absolute and percent change from baseline in sUA levels at each visit: **Figure 9** graphically depicts the mean sUA level profiles for the three treatment groups by visit over the 12-month course of the study. Within one month following initiation of study treatment, the two lesinurad + FBX groups separate out in a dose dependent manner from the PBO + FBX group, with a reduction in sUA of approximately 1 to 2 mg/dL. The decrease in mean sUA level remains constant for both lesinurad + FBX groups over the 12-months of study treatment. The baseline mean sUA level for the PBO + FBX group remains unchanged over the course of the study. The mean change in sUA from baseline at each visit was significantly higher in both lesinurad + FBX treatment groups as compared with the PBO + FBX group.

Figure 9 - Mean sUA Levels by Visit in Study 304 (Observed Cases; ITT Population)



¥P-value <0.01 vs. Placebo + Febuxostat; #P-value <0.0001 vs. Placebo + Febuxostat

Abbreviations: ITT, intent-to-treat; SE, standard error.
Numbers indicate the number of subjects contributing data at each timepoint. Dotted line indicates target sUA (< 5.0 mg/dL). Statistical significance is based on the difference in least square mean percent change from Baseline.
Note: Months 7, 9, and 11 data were excluded because the timing of the last protocol amendment (Protocol Amendment 5), which added sUA assessments at these timepoints, resulted in minimal data at these timepoints for analysis.
Source: Study 304 CSR Table 14.2.1.22.

Adapted Sponsor's Fig. 16; p. 101 Summary of Clinical Efficacy

Target Tophus Resolution:

The resolution of tophaceous deposits is a clinical benefit associated with urate lowering therapy in patients with symptomatic hyperuricemia and was assessed in this study by the following:

- Proportion of subjects who experienced complete resolution of at least 1 target tophus by Month 12: This was an unmet major secondary endpoint for this trial. Numeric increases in the proportions of subjects who experienced complete resolution (CR) in a target tophus following 12-months of treatment were observed for the two lesinurad + FBX groups in a dose-dependent manner, but were not significantly different as compared to the PBO + FBX group (**Table 49)**.

Table 49 - Proportion of Subjects Who Experienced Complete Resolution of at least 1 Target Tophus by Month 12 in Study 304 (NRI; ITT Population)

	PBO + FBX80 mg (N=109)	LESU200 + FBX 80 mg (N=106)	LESU400 + FBX 80 mg (N=109)
Proportion with Best Response of CR by Month 12 [n, %]	23 (21%)	27 (26%)	33 (30%)
Diff. in Proportion vs PBO + FBX (95% CI)[1] P-value[2]		0.04 (-0.07, 0.16) 0.45	0.09 (-0.02, 0.21) 0.12

[1]Binomial confidence interval (CI) for difference in proportions
[2]Cochran-Mantel Haenszel test stratified by Day -7 renal function (eCrCl ≥60 ml/min versus <60 ml/min) and Day -7 sUA status (sUA ≥6.0 mg/dL), randomized values
Table courtesy Dr. Jade Wang

- Proportion of subjects with best tophus response (complete resolution [CR] or partial resolution [PR]) on at least 1 target tophus by Month 12: This was another unmet major secondary endpoint for this trial. Numerically higher proportions of subjects in the two lesinurad + FBX treatment groups experienced either CR or PR of a target tophus following 12-months of study treatment that were not significantly different as compared to the PBO + FBX group (**Table 50**).

Table 50 - Proportion of Subjects Who Experienced Complete or Partial Resolution of at least 1 Target Tophus by Month 12 in Study 304 (NRI; ITT Population)

	PBO + FBX80 mg (N=109)	LESU200 + FBX 80 mg (N=106)	LESU400 + FBX 80 mg (N=109)
Proportion with CR or PR by Month 12 [n, %]	55 (51%)	60 (57%)	64 (59%)
Diff. in Proportion vs PBO + FBX (95% CI)[1] P-value[2]		0.06 (-0.09, 0.21) 0.45	0.08 (-0.07, 0.23) 0.12

[1]Binomial confidence interval (CI) for difference in proportions
[2]Cochran-Mantel Haenszel test stratified by Day -7 renal function (eCrCl ≥60 ml/min versus <60 ml/min) and Day -7 sUA status (sUA ≥6.0 mg/dL), randomized values
Table courtesy Dr. Jade Wang

Gout Flare Requiring Treatment:
Treatment of gout patients with urate lowering therapies is associated with an increased risk of gout flare. Theoretically, the occurrence of gout flares should decrease once a subject's sUA level is < 6mg/dL. A total of 801 gout flares requiring treatment were reported by 180 subjects over the 12- month course of this study as follows: 244 gout flares in the PBO + FBX group, 311 flares in the LESU200 mg + FBX group and 246 flares in the LESU400 mg + FBX group. The majority (63%) of these gout flares occurred during the time period from baseline to the end of Month 6 with numerically higher rates of gout flares observed in the LESU400 mg + FBX (75%) and LESU200 mg

+ FBX (60%) groups as compared to PBO + FBX (54%). To prevent confounding of the gout flare assessments during Months 6 to 12, subjects were required to discontinue their gout flare prophylaxis regimens at the end of Month 5.

- Mean rate of subjects requiring treatment for a gout flare during the 6-month time period from Month 6 to Month 12: This was an ancillary secondary endpoint in this study (**Table 51**). Overall, the adjusted mean rates of gout flares requiring treatment were low during this time period. Comparable rates of gout flare were reported by subjects in the LESU200 mg + FBX and PBO + FBX treatment groups. A lower rate of gout flares was reported by subjects in the LESU400 mg + FBX group which was significantly different compared to the PBO + FBX group.

Table 51 - Mean Rate of Gout Flares requiring Treatment[1] per Subject from Month 6 to Month 12 in Study 304 (ITT Population)

	PBO + ALLO (N=206)	LESU200 mg + ALLO (N=204)	LESU400 mg + ALLO (N=200)
Adjusted Rate[2,3] of Gout Flare Requiring Treatment per Subject Months 6 to 12 (SD)	1.3 (0.25)	1.5 (0.31)	0.7 (0.15)
Incidence Rate Ratio (95% CI) vs PBO + ALLO		1.2 (0.7, 2.1)	0.5 (0.3, 1.0)
P-value		0.5493	0.0401

SD = Standard Deviation
[1]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 prior to the start or 3 days after the end of the gout flare.
[2]Estimates obtained from Negative Binomial Regression adjusted for Day -7 renal function (eCrCl ≥ 60 mL/min versus < 60 mL/min) and tophus status during Screening (presence versus absence), randomized values, and log follow-up time as the offset variable.
[3]Estimates of adjusted rate for each treatment group obtained from inputting empirical proportion of each stratification factor level under each study.
Adapted Sponsor's Table 14.2.4.1.a; p. Study 304 CSR

Patient Reported Outcomes (PROs):

The results from the five PRO assessments (e.g., HAQ-DI, HAQ VAS pain score, SF-36, PGA, TSQM and Sheehan Disability Scale) evaluated in this trial were as follows:

- Proportion of subjects achieving an improvement of ≥ 0.25 units in the HAQ-DI score at Month 12: This was the third unmet major secondary endpoint for this study. As noted previously, patients who participated in this study were minimally impaired as shown by their overall low mean HAQ-DI scores at baseline, which were lower for the LESU200 mg + FBX and LESU400 mg + FBX groups than the PBO + FBX group (0.671 and 0.586 versus 0.729, respectively). Smaller proportions of subjects in the two lesinurad + FBX treatment groups as compared to the PBO + FBX group achieved an improvement of ≥ 0.25 in their baseline HAQ-DI scores following 12 months of study treatment (**Table 52**).

Table 52 - Proportion of Subjects Achieving Health Assessment Questionnaire Disability Index (HAQ-DI) Improvement of ≥ 0.25 at Month 12 in Study 304 (Observed Cases; ITT Population)

	PBO + FBX80 mg (N=109)	LESU200 + FBX 80 mg (N=106)	LESU400 + FBX 80 mg (N=109)
Proportion of Subjects with Improvement of ≥0.25 from Baseline in HAQ-DI at Month 12 [n, %]	42 (53%)	34 (44%)	26 (33%)
Diff. in Proportion vs PBO + FBX (95% CI)[1] P-value[2]		-0.08 (-0.26, 0.09) 0.30	-0.19(-0.36,-0.02) 0.02

HAQ-DI assesses patient's level of functional ability with items scores ranging from 0-3 with 0 being the least disability.
[1]Binomial confidence interval (CI) for difference in proportions
[2]Cochran-Mantel Haenszel test stratified by Day -7 renal function (eCrCl ≥60 ml/min versus <60 ml/min) and Day -7 sUA status (sUA ≥6.0 mg/dL), randomized values
Table courtesy Dr. Jade Wang

The results from the HAQ VAS Pain Score, the SF-36 and the PGA which were ancillary secondary assessments in this study are listed in **Table 53.** Overall, limited improvements are noted on review of these results for the three treatment groups at both the Month 6 and Month 12 time points that were not significantly different.

Table 53 - Summary of Ancillary Secondary Patient Reported Assessments for Study 304 (Observed Cases – ITT Population)

Patient Reported Outcome Assessment	PBO + FBX80 mg (N=109)	LESU200 + FBX 80 mg (N=106)	LESU400 + FBX 80 mg (N=109)
Mean Δ (SD) in HAQ VAS Pain Score at:			
Month 6	-6.3 (32)	-1.3 (29)	-9.5 (27)
Adj. Diff. in Means vs PBO + ALLO (95% CI)		3.9 (-3.4, 11)	-3.0 (-10, 4.3)
p-value		0.2979	0.4183
Month 12	-9.5 (27)	-11 (26)	-14 (28)
Adj. Diff. in Means vs PBO + ALLO (95% CI)		-3.7 (-10, 2.7)	-5.6 (-12, 0.8)
p-value		0.2587	0.0877
Proportion of Subjects with Improvement ≥2.5 in SF-36 PCS at:			
Month 6	60%	44%	39%
Adj. Diff. in Means vs PBO + ALLO (95% CI)		-0.15(-0.30,-0.01)	-0.21(-0.36,-0.06)
p-value		0.0442	0.0062
Month 12	54%	51%	51%
Adj. Diff. in Means vs PBO + ALLO (95% CI)		-0.03 (-0.19, 0.13)	-0.03(-0.18, 0.13)
p-value		0.7049	0.7643
Mean Δ (SD) from Baseline PGA score at:			
Month 6	-13 (29)	-8.6 (25)	-17 (26)
Adj. Diff. in Means vs PBO + ALLO (95% CI)		-0.57(-6.54, 5.40)	-5.95(-11.9, 0.00)
p-value		0.8522	0.3761
Month 12	-15 (30)	-9.4 (26)	-18.4 (27)
Adj. Diff. in Means vs PBO + ALLO (95% CI)		0.18(-6.21, 6.56)	-6.91(-13.3,-0.56)
p-value		0.9560	0.03330

Adj.= Adjusted; Diff.= Difference; Δ = Change
HAQ VAS pain scores range from 0 (no pain) to 100 (worst pain) based on 100 mm visual analogue scale (VAS). SF-36
PGA scores range from 0-100 with lower scores indicating a higher patient global assessment
[1]Cochran-Mantel Haenszel test stratified by Day-7 renal function (eCrCl≥ 60 mL/min) and tophus status during screening (presence vs absence), randomization stratification values
[2]ANCOVA models with baseline value as a covariate and treatment group, Day -7 renal function (eCrCl ≥ 60 ml/min versus <60 ml/min), and tophus status during screening (presence versus absence) as factors, randomized values
Adapted Sponsor's Tables 14.2.4.2.a, 14.2.4.4.a, 14.2.4.8.a, and 14.2.4.11.a; p. 838, 922-927,1532 and 1820-1824 Study 302 CSR

- Total Treatment Satisfaction Question for Medication Score (TSQM): No apparent differences were noted the between the two lesinurad + FBX treatment groups and the PBO + FBX group regarding overall satisfaction (mean scores ranging 68 to 74), effectiveness satisfaction (mean scores ranging 68 to 72), and convenience satisfaction (mean scores ranging 80 to 81). The mean side effects scores were lower (meaning less satisfaction with side effects) for the LESU400 mg + FBX (52) and the LESU200 mg + FBX (58) groups as compared to the

mean score for this subscale reported by subjects in the PBO + FBX (70) treatment group.

- Mean change from baseline in the Sheehan Disability Scale (SDS): The mean baseline scores for each of these subscales (work/school, social life, family life/home, global function impairment, and days lost from work) comprising this assessment were all comparably low, indicating minimal impairment for all three treatment groups. Mean changes from baseline at the Month 6 and 12 time points for each of the subscales were similar for both LESU200 mg + FBX and PBO + FBX treatment groups. Comparable improvements were noted in the family life/home responsibilities subscale for both LESU400 mg + FBX and PBO + FBX groups but significantly greater improvements in the mean change from baseline in the work/school, social life and global function impairment subscales were observed in the LESU400 mg + FBX group as compared to the PBO + FBX group.

Efficacy Conclusions:
A significantly higher proportion of subjects treated with LESU400 mg + FBX achieved a sUA < 5mg/dL at Month 6 as compared to PBO + FBX which was sustained through the 12-month course of study treatment. The LESU200 mg + FBX group demonstrated a numerically higher response rate compared to the PBO + FBX group although the magnitude of response was smaller than observed for the LESU400 mg + FBX group and was not statistically significant. The findings from various sensitivity analyses and ancillary secondary sUA endpoints were generally supportive of the primary efficacy findings for the LESU400 mg + FBX group and suggestive of efficacy for the LESU200 mg + FBX group. Treatment with LESU400 mg + FBX and LESU200 mg + FBX resulted in greater proportions of subjects achieving higher threshold responses to sUA lowering (e.g., sUA <4 mg/dL and < 3 mg/dL) as compared to the placebo + FBX group. The majority of the results from the major and remaining ancillary secondary endpoints that assessed clinical benefits (e.g., tophi resolution, physical functioning and gout flares) related to lesinurad's ability to decrease sUA levels did not demonstrate a difference between the three treatment groups. A greater decrease in the frequency of gout flares during Months 6 through 12 and improvements in the work/school, social life and global function impairment subscales of the Sheehan Disability Scale following 12 months of treatment were observed in the LESU400 mg + FBX group as compared to the PBO + FBX group but no significant difference was observed for the LESU200 mg + FBX group compared to PBO + FBX.

Review of the common protocol utilized in Studies 306 and 307:
Title: A Long-Term Extension Study of Lesinurad in Combination with Allopurinol or Febuxostat for Subjects Completing an Efficacy and Safety Study of Lesinurad and Allopurinol (Study 306) or Lesinurad and Febuxostat (Study 307)

Dates Conducted:

1. Study 306 was started on February 18, 2013. The cut-off for the interim clinical study report was June 17, 2014.
2. Study 307 was started on March 20, 2013. The cut-off date for the interim clinical study report was June 10, 2014.

Objectives:

Primary Objective:

- Evaluate the long-term efficacy and safety of lesinurad when used in combination with either allopurinol (Study 306) or febuxostat (Study 307)

Secondary Objective:

- Assess the effect of lesinurad when used in combination with allopurinol (Study 306) or febuxostat (Study 307) on Health-Related Quality of Life and physical function

Study Design:
Studies 306 and 307 are ongoing phase 3 extension trials in gout subjects who had completed 12-months of double-blind treatment in core Studies 301 or 302 (allopurinol add-on studies) or core Study 304 (febuxostat add-on study). Patients who had been randomized to placebo in the preceding core studies were re-randomized in a double-blind manner via a 1:1 ratio to treatment with either lesinurad 200 mg or lesinurad 400 mg once daily with concomitant allopurinol or febuxostat while subjects who had been previously randomized to treatment with lesinurad 200 mg or 400 mg with either allopurinol or febuxostat in the core studies continued their blinded study treatment. Subjects transitioned to open-label treatment with lesinurad at the same dose level and continued on the same dose of allopurinol and/or febuxostat in these extensions trials following the locking of the associated core study's database and upon reaching at least Month 12 in the extension trial. Prophylactic gout flare therapy was also re-initiated by all subjects at the baseline visit in order to maintain blind while patients who had been formerly treated with placebo were starting study treatment with lesinurad. All gout prophylaxis regimens were to have been discontinued at Month 2 but could be continued for up to 6 months at the discretion of study investigators. Subjects who opted to participate in these extension studies are permitted to take lesinurad until they either withdraw from the study or for up to approximately 30 months (i.e., Canadian subjects) but no longer than approximately 6 months after lesinurad is marketed in that subject's study country. Patients who withdrew from treatment early were to return to the study site within 14-days for final safety assessment. The common protocol for these extension studies also mandated that subjects who withdrew prematurely from these studies for any reason who also had an elevated serum creatinine levels above their

baseline level from the core studies were to be followed for 3 months or until their serum creatinine level is ≤ 0.1 mg/dL of their core study baseline value.

Major Entry Criteria:
In order to be eligible for these trials, potential study subjects were to have:

- Completed the double-blind treatment period in Studies 301 and 302 or 304 and were actively receiving and tolerating study medication (lesinurad or placebo) with allopurinol or febuxostat at the Month 12 visit
- Agreed to use an effective non-hormonal method of birth control during the trial for at least 14 days after the last dose of study medication if were a female of childbearing potential

Treatment:
All subjects received lesinurad 200 mg or 400 mg tablets blinded to dose to be taken once daily with Applicant supplied allopurinol and/or febuxostat. The dose and dosing regimen of allopurinol and/or febuxostat were not to be changed during the course of these trials except when criteria for allowed dosing interruption and adjustment were met which were the same as described in the preceding core study reviews. Subjects who prematurely discontinued use of their xanthine oxidase inhibitor or lesinurad were to be removed from the study.

Removal of Patients from Treatment or Assessments
In addition to utilizing the same withdrawal criteria as the core studies, patients could be withdrawn from the extension studies if they develop a kidney stone or experience a serum creatinine level ≥ 3x subject's core baseline serum creatinine level or an absolute serum creatinine level ≥4.0 mg/dL or an estimated creatinine clearance (eCrCl) < 30 ml/minute.

Concomitant Medications:
The same medications that subjects were prohibited from taking concomitantly while participating in the core study protocols were also not permitted during the extension studies.

Efficacy and Safety Assessments
Table 54 and **Table 55** are flow charts of the scheduled study observations and procedures for Studies 306 and 307:

Table 54 – Schedule of Events and Procedures for Studies 306 and 307

Assessment/Procedure	Baseline (Day 1)[a]	Treatment Period[b]					Termination Visit[c]	Post-Termination Visits[c]
		Month 1	Month 2 - 5	Month 6	Month 7 - 11	Month 12 and Every 2 Months After Month 12		
Informed consent	√							
Confirm eligibility	√							
Concomitant medications	√	√	√	√	√	√	√	
Physical examination	√[d]						√	
Vital signs	√[d]	√	√	√	√	√	√	
Body weight and waist circumference[e]	√[d, e]			√		√[e]	√	
Hematology	√[d]	√	√	√	√	√	√	
Blood biochemistry (pregnancy test[f])	√[d]	√	√	√	√	√	√	√
Urinalysis	√[d]	√	√	√	√	√	√	
Assess AEs	√	√	√	√	√	√	√[g]	
Target tophus measurement[h]	√[d]		√	√	√	√	√	
Target tophus photograph[i]	√[d]		If resolved only	If resolved only	If resolved only	Month 12 only	√[i]	
Assess gout flares	√[d]		√	√	√	√	√	
PROs[j, k]	√[d]			√		√[k]		
Dispense gout flare prophylaxis[l]	√	√	√	√				
Dispense lesinurad	√	√	√	√	√	√		
Dispense Sponsor-supplied allopurinol	√	√	√	√	√	√		
Update patient eDiary	√							
Assess compliance with gout flare prophylaxis		√[m]	√[m]	√[m]				
Assess compliance with lesinurad and review dosing instructions[n]		√	√	√	√	√	√	

Adapted Sponsor's Table ; p. 29-31 Studies 30 and 307 Interim CSR

Table 55 - Schedule of Events and Procedures for Studies 306 and 307 (cont.)

Assessment/Procedure	Baseline (Day 1)[a]	Treatment Period[b]					Termination Visit[c]	Post-Termination Visits[c]
		Month 1	Month 2 - 5	Month 6	Month 7 - 11	Month 12 and Every 2 Months After Month 12		
Assess compliance with allopurinol		√	√	√	√	√	√	
Assess compliance with eDiary		√	√	√	√	√	√	

Abbreviations: AEs, adverse events; eDiary, Electronic Diary; PROs, patient reported outcomes.

[a] Baseline (Day 1) must be performed at the Month 12 visit of either Study RDEA594-301 or RDEA594-302. After the subject has signed the Informed Consent for participation in this extension study, assessments that were performed as part of the Month 12 visit of Study RDEA594-301 or RDEA594-302 do not need to be repeated for the Baseline Visit of this extension study. No study medication interruption between Study RDEA594-301 or RDEA594-302 and this extension study should occur.

[b] There is a ± 7 day window around the study visits for Months 1 through 12, and ± 14 day window around the study visits for the remaining study visits. A clinical month is considered to be 28 days. All scheduled visits should be referenced to Day 1.

[c] The Termination Visit should be performed for all subjects within approximately 14 days after their last dose of lesinurad.

[d] Results from Month 12 of Study RDEA594-301 or RDEA594-302 will be used.

[e] At Baseline, body weight from Month 12 of Study RDEA594-301 or RDEA594-302 will be used and only waist circumference will be measured. Body weight and waist circumference will be taken at Month 6 and then every 6 months thereafter.

[f] Serum pregnancy test is only required for female subjects of childbearing potential.

[g] At study termination, subjects with ongoing AEs/SAEs, including clinically relevant laboratory abnormalities, should be followed up by the Investigator for as long as medically indicated. The Sponsor retains the right to request additional information for any subject with ongoing AEs/SAEs at the end of the study, if judged necessary.

[h] For subjects with target tophi identified at Baseline in Study RDEA594-301 or RDEA594-302 will be measured using digital calipers at the specified time points.

[i] Photographs will be taken of target tophi at Month 6, Month 12, at resolution (if before Month 12), and at study termination (if before or at Month 12).

[j] PRO assessments include Short Form-36, Sheehan Disability Scale, Patient Global Assessment of Disease Activity, and Health Assessment Questionnaire - Disability Index.

[k] PROs will be performed at Month 6, Month 12, and then every 6 months thereafter.

[l] If applicable; gout flare prophylaxis is at the Investigator's discretion, but should only be initiated after the Investigator has confirmed eligibility. Gout flare prophylaxis should continue through at least Month 2; continuation after Month 2 is at the discretion of the Investigator, but should not exceed 6 months.

[m] If applicable.

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

[o] Serum creatinine values collected at the Termination Visit for subjects who withdraw from treatment before the study terminates at the Investigator site must be evaluated by the Investigator. Subjects who have a serum creatinine elevation at the Termination Visit, defined as a value > 0.1 mg/dL above their Baseline serum creatinine value (for the purpose of this assessment, Baseline serum creatinine is defined as a subject's Baseline serum creatinine value from RDEA594-301 or RDEA594-302), are required to return to the site monthly for blood biochemistry assessment. Upon receipt of those laboratory results, Investigators must schedule additional visits with the subject to continue to assess serum creatinine until the subject's serum creatinine value is ≤ 0.1mg/dL of their core Baseline value or until 3 monthly assessments after their Termination Visit have taken place, whichever comes first.

Adapted Sponsor's Table ; p. 29-31 Studies 30 and 307 Interim CSR

Outcome Measures:
Safety endpoints included the following:

- Incidence of treatment emergent adverse events
- Change from baseline in clinical lab safety tests (hematology, serum chemistry, urinalysis) and vital signs

Statistical Design, Definitions of Analyzed Populations and Analyses Plans:
Since Studies 306 and 307 are open-label continuations of Studies 301/302 and 304, respectively, no statistical sample size calculations were performed. These trials did not have prespecified analytical plans since all analyses were to be exploratory in nature using descriptive statistics and summarized accordingly. All analyses were to be performed on the safety populations which were defined for both studies as the population of subjects who received at least 1 dose of lesinurad under the extension protocols documented prior to the data cut-off dates for these interim study reports.

Study Conduct:
Two protocol amendments were made to the common protocol for Studies 306 and 307 prior to the unblinding of the dose of lesinurad:

1. Amendment 1 (implemented on June 17, 2013 for study 306 and on June 14, 2013 for study 307)
   Major changes to the protocol included additional safety measures as a result of the SAE reports of acute kidney failure and SAEs of kidney stones in the ongoing phase 3 studies. These changes were reviewed and agreed by the IDMC overseeing these studies.
   - Expanded guidance on subject hydration
   - Expanded the management algorithm if a subject experiences an elevated sCr or kidney stone
   - Expand guidance on the management of subjects who report symptoms that may indicate liver injury (study 307 only)
   - Added assessments of renal events of potential medical importance by an independent REAC
   - Inclusion of a review of dosing instructions in the schedule of events
   - Inclusion of a new appendix to provide guidance to sites in reviewing AEs and potential contributing factors in subjects who experience a sCr elevation $\geq$ 1.5 x baseline sCr value
2. Amendment 2 (implemented on December 24, 2013 for both studies 306 and 307)
   Major changes to the common protocol included additional safety measures as a result of the safety data from the phase 3 placebo controlled lesinurad monotherapy study 303 which showed a higher incidence of nephrotoxic AE in patients who received lesinurad 400 mg qd as compared to placebo. These changes were reviewed and agreed by the IDMC overseeing these studies.

- Addition of calculated creatinine clearance using the Cockcroft-Gault formula and IBW at all scheduled visits where sCr is assessed
- Required morning dose of concomitant xanthine oxidase inhibitor (XOI) be taken at the same time as lesinurad and subjects to interrupt their dose of lesinurad/placebo if their dose of XOI is interrupted
- Required subjects who permanently discontinue use of XOI to discontinue use of lesinurad/placebo immediately and will be removed from the study
- Any subject who experiences a kidney stone during the study must be withdrawn from treatment
- Increased frequency of subject monitoring
- Amendment of the management algorithm for subjects based on sCr and eCrCl, and to provide additional withdrawal from treatment guidelines
- Addition of continued follow-up of all subjects who completed the study and to not continue into an extension study, or who withdraw from treatment or from the study until sCr is $\leq$0.1 mg/dL of their baseline value or for 3 months

Disposition:
Of the 891 patients who completed the core studies 301 and 302, 718 enrolled and 714 were treated in the ongoing allopurinol add-on study 306 (**Table 56**). Over the two years that this trial has been ongoing, rates of discontinuation ranged from 12-19%. The most common reason for discontinuation was consent withdrawn followed by adverse event and noncompliance/protocol violation.

Table 56 – Subject Disposition for Study 306 (Safety Population)

	LESU200 mg + ALLO (Extension Therapy)			LESU400 mg + ALLO (Extension Therapy)		
	PBO + ALLO (N=121)	LESU200 + ALLO (N=240)	Total (N=361)	PBO + ALLO (N=122)	LESU400 + ALLO (N=231)	Total (N=353)
Completed Through Month 6 Visit on Lesinurad	62 (51%)	125 (52%)	187 (52%)	55 (45%)	120 (52%)	175 (50%)
Completed Through Month 12 Visit on Lesinurad	26 (22%)	42 (18%)	68 (19%)	19 (16%)	41 (18%)	60 (17%)
Completed Through Month 24 Visit on Lesinurad	2 (2%)	0	2 (1%)	0	0	0
Study Termination (Primary Reason):	11 (18%)	31 (13%)	53 (15%)	23 (19%)	28 (12%)	51 (14%)
Adverse Event	4 (3%)	9 (4%)	13 (4%)	4 (3%)	6 (3%)	10 (3%)
Gout Flare	0	0	0	2 (2%)	0	2 (1%)
Pregnancy	0	0	0	0	0	0
Required Treatment with Prohibited Medication	3 (3%)	3 (1%)	6 (2%)	3 (3%)	4 (2%)	7 (2%)
Noncompliance/Protocol Violation	6 (5%)	6 (3%)	12 (3%)	3 (3%)	6 (3%)	9 (3%)
Sponsor Terminated Study	1 (1%)	0	1 (<1%)	1 (1%)	0	1 (<1%)
Lost to Follow-Up	3 (3%)	4 (2%)	7 (2%)	1 (1%)	1 (<1%)	2 (1%)
Withdrew Consent	4 (3%)	9 (4%)	13 (4%)	8 (7%)	10 (4%)	18 (5%)
Death	1 (1%)	0	1 (<1%)	1 (1%)	1 (<1%)	2 (1%)
Ongoing	99 (82%)	209 (87%)	308 (85%)	99 (81%)	203 (88%)	302 (86%)

Adapted Sponsor's Table 4; p. 60 Study 306 CSR

Of the 235 patients who completed the core study 304, 196 enrolled and were treated in the ongoing febuxostat add-on study 307 (**Table 57**). Over the two years that this trial has been ongoing, rates of discontinuation ranged from 6-19%. The most common reason for discontinuation was noncompliance/protocol violation followed by withdrew consent and adverse event.

Table 57 - Subject Disposition for Study 307 (Safety Population)

	LESU200 mg + FBX (Extension Therapy)			LESU400 mg + FBX (Extension Therapy)		
	PBO + FBX80 (N=33)	LESU200 + FBX80 (N=64)	Total (N=97)	PBO + FBX80 (N=34)	LESU400 + FBX80 (N=65)	LESU400 + FBX (N=99)
Completed Through Month 6 Visit on Lesinurad	18(55%)	36(56%)	54 (56%)	19(56%)	35 (54%)	54(55%)
Completed Through Month 12 Visit on Lesinurad	7 (21%)	9 (14%)	16 (17%)	6 (18%)	9 (14%)	15 (15%)
Completed Through Month 24 Visit on Lesinurad	0	0	0	0	0	0
Study Termination (Primary Reason):	5 (15%)	12 (19%)	17 (18%)	6 (18%)	4 (6%)	10 (10%)
Adverse Event	0	2 (3%)	2 (2%)	3 (9%)	1 (2%)	4 (4%)
Gout Flare	0	0	0	0	1 (2%)	1 (1%)
Pregnancy	0	0	0	0	0	0
Required Treatment with Prohibited Medication	0	0	0	0	0	0
Noncompliance/Protocol Violation	3(9%)	4 (6%)	7(7%)	3(9%)	1 (2%)	4 (4%)
Sponsor Terminated Study	0	0	0	0	0	0
Lost to Follow-Up	0	1 (2%)	1 (1%)	0	0	0
Withdrew Consent	2 (6%)	4 (6%)	6 (6%)	0	1 (2%)	1 (1%)
Death	0	1 (2%)	1 (1%)	0	0	0
Ongoing	28(85%)	52 (81%)	80 (83%)	28(82%)	61 (94%)	89 (90%)

Adapted Sponsor's Table 4; p. 59 Study 307 CSR

Demographics

The demographic characteristics of the patient populations in these extension studies were similar to that observed in the overall populations in the concomitant allopurinol core studies 301 and 302 and the concomitant febuxostat core study 304. The subjects in the allopurinol add-on extension study 306 were predominantly male (97%), Caucasian (81%), with a mean age of 51 years. Similarly, patients in the febuxostat add-on extension study 307 were predominantly male (96%), Caucasian (79%), with a mean age of 53 years.

Results:

The results from the safety analyses for these extension studies will be discussed in Section 7.

6 Review of Efficacy

Efficacy Summary

The clinical data submitted in support of lesinurad as a treatment of hyperuricemia associated with gout in adults in combination with a xanthine oxidase inhibitor (XOI) was generated from three 12-month phase 3 trials, 301, 302 and 304. These were multiregional, randomized, double-blind, placebo-controlled, parallel group studies in 1,537 patients who failed to achieve serum uric acid (sUA) levels of <6 mg/dL (or <5 mg/dL in Study 304) despite treatment with a minimum of 8 weeks of allopurinol (at least 300 mg/day or 200 mg /day in subjects with eCrCl ≥45-60 mL/min) for Studies 301 and 302 or despite treatment with a "medically appropriate" dose of allopurinol or febuxostat for Study 304. These trials evaluated the urate lowering effect of 200 mg and 400 mg doses of lesinurad administered once daily with a concomitant XOI (allopurinol or febuxostat). In Studies 301 and 302, a greater proportion of patients achieved the primary endpoint (sUA <6 mg/dL at Month 6) in the lesinurad 200 mg + allopurinol treatment groups (Study 301: 54%; Study 302: 55%) and the lesinurad 400 mg + allopurinol treatment groups (Study 301:59%; Study 302: 67%) as compared to placebo + allopurinol (Study: 301 28%; Study 302: 23%). The differences between each of the lesinurad treatment groups and the placebo group were statistically significant for both trials (Study 301: p<0.0001; Study 302: p<0.001) but a dose-response effect between the two lesinurad groups + allopurinol was only demonstrated in Study 302. Over the 12-month courses of both studies, these differences in treatment responses between the lesinurad + allopurinol groups versus placebo + allopurinol were consistently maintained and support the durability of lesinurad's urate lowering effects. However, the magnitude of lesinurad's urate lowering effect was modest in both of these trials. For the lesinurad 200 mg + allopurinol treatment groups versus PBO + ALLO groups the adjusted difference in mean change over baseline ranged from 1.01-1.09 mg/dL at Month 6 to 0.89-0.93 mg/dL at Month 12 versus 1.23-1.36 mg/dL at Month 6 to 1.18-1.25 mg/dL at Month 12 for the lesinurad 400 mg + allopurinol treatment groups versus PBO + ALLO groups in these studies.

The results from the third trial, Study 304, were less robust. In this study, higher proportions of patients achieved the primary endpoint (sUA <5 mg/dL at Month 6) in a dose dependent manner in the lesinurad 200 mg + febuxostat (57%) and lesinurad 400 mg + febuxostat (76%) treatment groups as compared to the placebo + febuxostat group (47%). A statistically significant difference in response to study treatment was only noted for the lesinurad 400 mg + febuxostat group as compared to placebo (p<0.0001) in this trial. However, statistically significant differences in the proportions of patients treated with lesinurad 200 mg + febuxostat who achieved a sUA <5 mg/dL were observed at the Month 5, Month 8 and later time points as compared to the placebo + febuxostat group, which suggests that this dose does provide additional urate lowering effect. The differences in treatment responses between both lesinurad + febuxostat groups versus placebo + febuxostat were steadily maintained over the 12-months of

Study 304 and lend support to the durability of lesinurad's urate lowering effects. The magnitude of lesinurad's urate lowering effect was also modest in this trial. The adjusted difference in mean change from baseline in sUA for the lesinurad 200 mg + febuxostat group versus PBO + FBX group ranged from 0.79 mg/dL at Month 6 to 0.1.06 mg/dL at Month 12 which was similar to that observed with allopurinol in Studies 301 and 302. The adjusted difference in mean change from baseline in sUA for the lesinurad 400 mg + XOI group versus PBO + FBX ranged from 1.88 mg/dL at Month 6 to 1.66 mg/dL for Month 12 and was higher to that observed with allopurinol. Lesinurad's modest efficacy coupled with the lower threshold response of sUA <5 mg/dL, and the high proportion of patients already meeting the target sUA of <5 mg/dL in both the placebo and lesinurad groups at baseline (53% of placebo patients and 50% of lesinurad patients) were probable factors in the drug's failure to capture the Month 6 time point.

Since the primary endpoints for the pivotal studies were based on serum uric acid, additional support for a clinical benefit for treatment with lesinurad was to have been derived from a number of clinical major secondary endpoints that assessed gout flares and tophus resolution. No additional clinical benefit in terms of decreasing gout flares or the resolution or size of tophi was demonstrated with either the 200 mg or 400 mg lesinurad treatment groups in these three studies. There was also no improvement in the assessments for disability that were conducted in these studies, but this was probably due to the low level of disability at baseline for the patient populations in these trials.

The results from subpopulation analyses for age, race and region on pooled data for Studies 301 and 302 and separately for Study 304 showed that these factors did not impact on the efficacy results for these trials. A lack of treatment effect lesinurad was observed for female gender in these analyses for the pooled Studies 301 and 302. However, the small sample size for females precludes definitive conclusions about these findings. No statistically significant differences in treatment effect were observed for subgroups by baseline renal function (eCrCl: <45 mL/min, 45 to <60 mL/min, and $\geq$ 60 mL/min) for all three studies, baseline allopurinol dose (<300 mg/d, 300 mg/d, and >300 mg/d) for Studies 301 and 302, or baseline sUA level (< 5mg/dL and $\geq$ 5 mg/dL) for Study 304. Additional subgroup analyses showed that low dose ($\leq$ 325 mg/day) aspirin and thiazide and thiazide-like diuretics which are known to affect uric acid levels did not impact on the efficacy of lesinurad.

In the past, the administration of uricosuric agents like lesinurad was reserved for hyperuricemic patients who were classified as under-excretors of uric acid based on the results from a 24-hour urine collection. Due to the difficulties associated with obtaining adequate 24-urine collections and the ease of administering xanthine oxidase inhibitors, this practice has lost favor in clinical practice. The magnitude of lesinurad's urate lowering capabilities in the subpopulation of uric acid under-excretors is not known, since subjects who participated in the three pivotal studies were not required to undergo such assessments. If the Applicant had identified potential study subjects who were

under-excretors of uric acid and designed their pivotal trials around this subpopulation it is possible that the risk-benefit profile of lesinurad might have been more favorable. However, there does appear to be adequate statistical evidence to support the efficacy of both the 200 mg and 400 mg dose in the broader population of gout patients, and to support the proposed indication of treatment of hyperuricemia associated with gout in combination with a xanthine oxidase inhibitor.

6.1 Indication

The proposed indication for lesinurad is the treatment of hyperuricemia associated with gout in adults in combination with a xanthine oxidase inhibitor (XOI).

6.1.1 Methods

Efficacy data contained in the submission from the three, 12-month, multicenter, randomized, double-blind, placebo controlled parallel group trials 301, 302 and 304 conducted in patients with symptomatic hyperuricemia despite concomitant XOI therapy were reviewed to assess this application. Analyses of pertinent subgroups were also conducted. All primary and major secondary analyses were confirmed by the FDA's statistical reviewer. The design of the common protocol for studies 301 and 302 as well as the design of the protocol for 304 are discussed in Section 5.3.1.

6.1.2 Demographics

Demographic information, gout history, disease status and baseline disease activity, and concomitant medications used at baseline are presented in detail in the preceding Section 5.3.1 for the individual studies as follows: Study 301: Tables 10, 11, 13, and 14; Study 302: 24, 25, 27, and 28; and Study 304: 41, 42, 44 and 45.

6.1.3 Subject Disposition

Patient disposition is also described in detail in Section 5.3.1 as follows: Study 301: Table 8; Study 302: Tables 22; and Study 304: Table 39.

6.1.4 Analysis of Primary Endpoints

Studies 301 and 302:
The primary endpoint for Studies 301 and 302 was the proportion of patients with sUA less than 6 mg/dL by Month 6. In addition to being used as a surrogate endpoint in the regulatory setting to evaluate other urate lowering agents, sUA level $\leq$ 6 mg/dL is also the standard of care treatment target for individuals with symptomatic hyperuricemia and gout as per treatment guidelines published by the American College of

Rheumatology[4]. Long term urate lowering at this level is expected to result in fewer clinical manifestations of hyperuricemia such as recurrent gout attacks. As shown in **Table 58**, greater proportions of patients treated with both LESU400 + ALLO and LESU200 + ALLO achieved the target sUA as compared to patients treated with PBO + ALLO in both of these studies. The differences between each of the treatment groups and the placebo group were statistically significant for both studies. A dose response between the two lesinurad + ALLO groups was only demonstrated in Study 302 for this parameter.

Table 58 – Primary Endpoint: Proportion of Subjects with sUA Level <6.0 mg/dL by Month 6 for Studies 301 and 302 (ITT Population – Non-Responder Imputation)

Primary Endpoint	Study 301			Study 302		
	PBO + ALLO (N=201)	LESU200 mg + ALLO (N=201)	LESU400 mg + ALLO (N=201)	PBO + ALLO (N=206)	LESU200 mg + ALLO (N=204)	LESU400 mg + ALLO (N=200)
Proportion with sUA <6.0 mg/dL by Month 6	56 (28%)	109 (54%)	119 (59%)	48 (23%)	113 (55%)	133 (67%)
Diff. vs PBO + ALLO (95% CI)[1] P-Value[2]		0.26 (0.17, 0.36) <0.0001	0.31 (0.22, 0.41) <0.0001		0.32 (0.23, 0.41) <0.0001	0.43 (0.34, 0.52) <0.001

CI = Confidence interval
[1]Binomial confidence interval for difference in proportions
[2]Cochran-Mantel Haenszel test stratified by Day-7 renal function (eCrCl≥ 60 mL/min) and tophus status during screening (presence vs absence), randomization stratification values using nonresponder imputation for subjects missing Month 6 sUA.
Table courtesy Dr. Jade Wang

The Applicant provided the results from six sensitivity analyses for the primary efficacy endpoints for these studies that were prespecified in the SAP (e.g., last observation carried forward [LOCF] analysis; observed case analysis; reached target sUA <5 mg/dL at each Month 4, 5, and 6; reached target sUA <6 mg/dL logistic regression analysis, a CMH test stratified by Day -7 renal function and tophus status using actual values for these variables rather than stratification factor values; and the per protocol population analysis) which were generally supportive of the findings of the primary efficacy analysis. For Study 302, an additional sensitivity ITT analysis at Month that excluded subjects from Site 15006 in South Africa as a result of GCP issues at that site was also supportive of the primary results from that study. (Note: Reader is referred to the statistical review of this application by Dr. Jade Wang for further information regarding these sensitivity analyses and the results of additional sensitivity analyses that she conducted as part of her review of this application.)

[4] Khanna D, Fitzgerald JD, Khanna PP, et al. 2012 American College of Rheumatology guidelines for management of gout, part 1: systematic nonpharmacologic and pharmacologic therapeutic approaches to hyperuricemia. Arthritis Care Res. 2012; 64(10):1431-1446.

Study 304:

The primary endpoint for Study 304 was the proportion of patients with sUA less than 5 mg/dL by Month 6. Although a sUA level of ≤ 5 mg/dL has not been required as a primary endpoint in clinical trials with other urate lowering drugs, this lower threshold of sUA is the recommended clinical target for patients with refractory, chronic gout and/or high urate burden (tophaceous deposits)[1] which was the population studied in this trial. As shown in **Table 59**, higher proportions of patients treated with LESU200 mg + FBX and LESU400 mg + FBX achieved this level of response to study treatment in a dose dependent manner as compared to patients treated with PBO + FBX. The difference between the LESU400 mg + FBX group response versus the PBO + FBX group was statistically significant but the difference between the LESU200 mg + FBX and the PBO + FBX groups was not.

Table 59 – Month 6 Primary Endpoint Results for Study 304 (ITT Population – Non-Responder Population)

	PBO + FBX80 mg (N=109)	LESU200 + FBX 80 mg (N=106)	LESU400 + FBX 80 mg (N=109)
Proportion with sUA <5.0 mg/dL by Month 6	51 (47%)	60 (57%)	83 (76%)
Diff. in Proportions vs PBO + FBX (95% CI) P-Value[a]		0.10 (-0.03, 0.23) 0.1298	0.29 (0.17, 0.42) <0.0001

CI = Confidence interval
[1]Binomial confidence interval for difference in proportions
[2]Cochran-Mantel Haenszel test stratified by Day-7 renal function (eCrCl≥ 60 mL/min) and Day-7 sUA status (sUA≥ 6.0mg/dL vs <6.0 mg/dL), randomization stratification values using nonresponder imputation for subjects missing Month 6 sUA.
Table courtesy Dr. Jade Wang

The Applicant provided the results from seven sensitivity analyses for the primary efficacy endpoint (e.g., LOCF analysis; observed case analysis; reached target sUA <5 mg/dL at each Month 4, 5, and 6; per protocol population analysis; reached target sUA <5 mg/dL at Month 6 via logistic regression; and subject's personal median sUA reached target <5 mg/dL). The results of these sensitivity analyses for the LESU400 mg + FBX treatment group were generally supportive of the findings from the primary endpoint analysis. The results for the LESU200 mg + FBX treatment group were less robust. (Note: The reader is referred to the statistical review of this application by Dr. Jade Wang for further information regarding these sensitivity analyses and the results of additional sensitivity analyses that she conducted as part of her review of this application.)

6.1.5 Analysis of Secondary Endpoints

There were two major secondary endpoints for Studies 301 and 302 and three major secondary endpoints for Study 304 that were assessed in order to determine if a clinical benefit (e.g., gout flare, resolution of tophi and improvement in disability) was associated with the administration of lesinurad. These secondary assessments are presented below by corresponding assessment area. In order to control for multiplicity, the statistical analysis plans mandated the major secondary endpoints for Studies 301, 302 and 304 were to be analyzed via a sequential procedure in a prespecified descending order following testing of the primary endpoint. Due to the statistically non-significant finding for the major secondary endpoint analysis of gout flares for the LESU400 + ALLO treatment group, no further testing was to have been performed for Studies 301 and 302. Similarly, testing of the major secondary endpoints for Study 304 was to have stopped following the statistically non-significant finding for the primary endpoint of sUA <5 mg/dL for the LESU200 mg + FBX treatment group. For completeness, the results of the secondary endpoint analyses are being presented in this review. However, findings from the major secondary endpoints should not be considered statistically significant due to the hierarchical testing method used for multiple endpoints. Declaring statistical significance of the ancillary secondary endpoints using unadjusted p-values may be inappropriate due to multiplicity concerns.

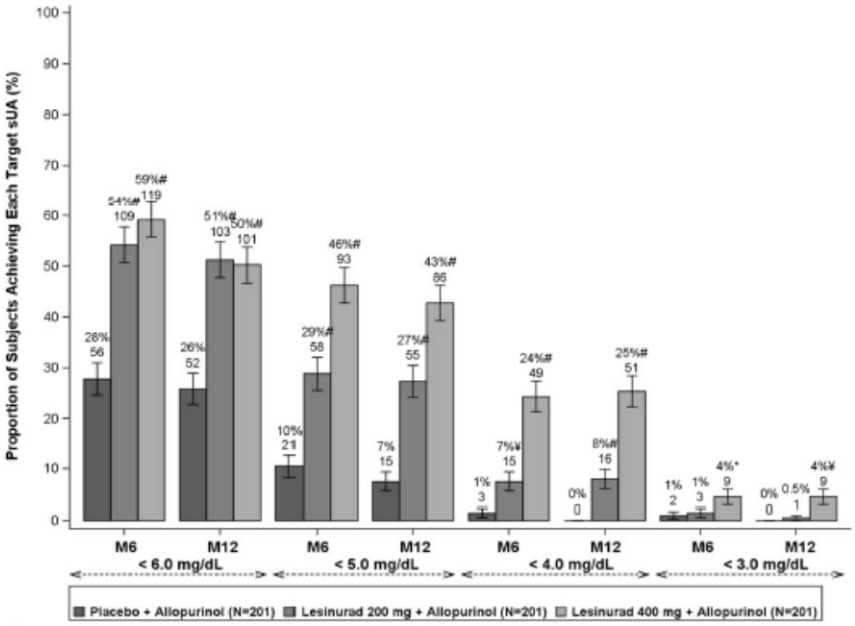
Serum Uric Acid Reduction

In support of lesinurad's urate lowering capability different threshold response levels than that explored by the primary endpoint such as <6.0 mg/dL, <5.0 mg/dL and <4.0 mg/dL were also assessed in the three pivotal trials.

Studies 301 and 302:

As shown in **Figure 10** and **Figure 11**, higher proportions of patients randomized to the two lesinurad + ALLO treatment groups achieved these pre-specified lower sUA threshold levels in a dose-dependent manner as compared to the PBO + ALLO group at the Months 6 and 12 time points in Studies 301 and 302. The differences between each of the treatment groups and the placebo group were statistically significant

Figure 10 – Subjects Achieving sUA <6.0 mg/dL, <5.0 mg/dL, <4.0 mg/dL, and <3.0 mg/dL at Months 6 and 12 in Study 301 (NRI) (ITT Population)

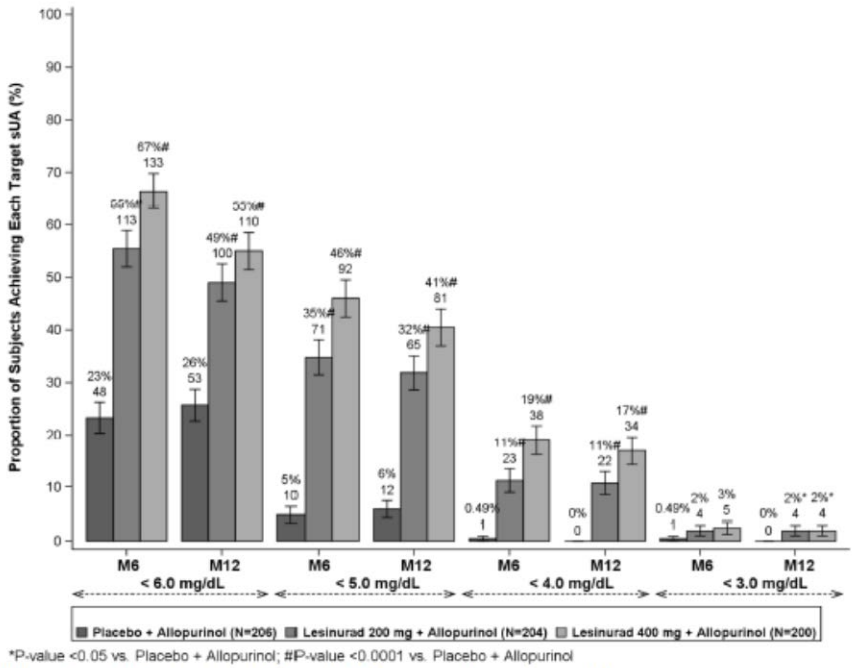


*P-value <0.05 vs. Placebo + Allopurinol; ¥P-value <0.01 vs. Placebo + Allopurinol
#P-value <0.0001 vs. Placebo + Allopurinol

Abbreviations: ITT, intent-to-treat; M, month; NRI, nonresponder imputation; sUA, serum urate.
Note: Numbers in the figure refer to % of subjects who achieved the target sUA at either Month 6 or Month 12 (M6 or M12) and the number of subjects in that group that achieved target. The targets are listed below the x-axis (< 6.0, < 5.0, < 4.0, and < 3.0 mg/dL). Proportions and standard errors are noted in the figure.
Source: Study 301 CSR Table 14.2.1.7, Table 14.2.1.8, Table 14.2.1.9, Table 14.2.1.10.

Adapted Sponsor's Fig. 11; p. 89 Summary of Clinical Efficacy

Figure 11 – Subjects Achieving sUA <6.0 mg/dL, <5.0 mg/dL, <4.0 mg/dL, and <3.0 mg/dL at Months 6 and 12 in Study 302 (NRI) (ITT Population)



*P-value <0.05 vs. Placebo + Allopurinol; #P-value <0.0001 vs. Placebo + Allopurinol

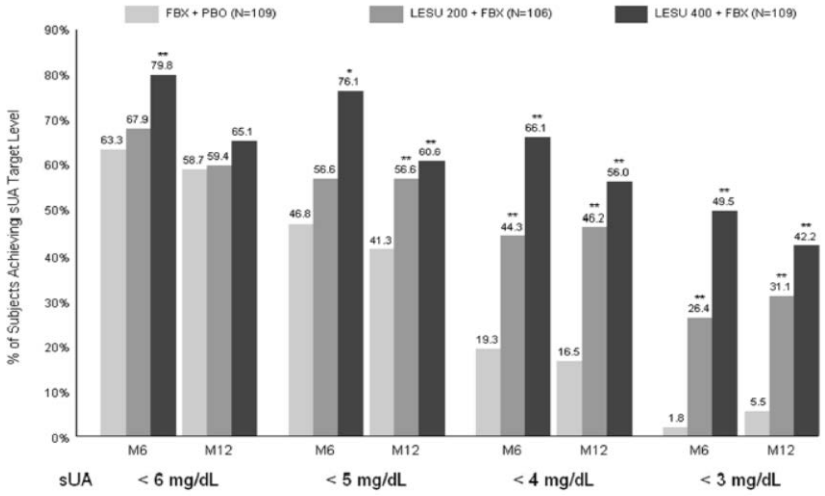
Abbreviations: ITT, intent-to-treat; M, month; NRI, nonresponder imputation; sUA, serum urate.
Note: Numbers in the figure refer to % of subjects who achieved the target sUA at either Month 6 or Month 12 (M6 or M12) and the number of subjects in that group that achieved target. The targets are listed below the x-axis (< 6.0, < 5.0, < 4.0, and < 3.0 mg/dL). Proportions and standard errors are noted in the figure.
Source: Study 302 CSR Table 14.2.1.7, Table 14.2.1.8, Table 14.2.1.9, Table 14.2.1.10.

Adapted Sponsor's Fig. 12; p. 90 Summary of Clinical Efficacy

Study 304:

As shown in **Figure 12**, higher proportions of patients randomized to the two lesinurad+ FBX treatment groups achieved sUA levels <6.0, <5.0, <4.0, and < 3.0 mg/dL in a dose dependent manner as compared to the PBO + FBX group at the Months 6 and 12 time points. Significant differences in the proportions of subjects who achieved <4.0 mg/dL and <3.0 mg/dL sUA levels at both the Month 6 and Month 12 time points and <5 mg/dL at Month 12 in the LESU200 mg + FBX group were shown on comparison with the PBO + FBX group. No differences were noted on the comparisons of the LESU200 + FBX group for sUA <6.0 mg/dL at Month 6 and Month 12 and for sUA <5.0 mg/dL at Month 6 as compared with the PBO + FBX group. Significant differences between the LESU400 mg + FBX group versus the PBO + FBX group were observed at both the Month 6 and Month 12 time points for each of these prespecified threshold sUA levels.

Figure 12 – Proportion of Subjects Achieving sUA < 6mg/dl, < 5 mg/dL, <4 mg/dL, and < 3.0 mg/dL at Months 6 and 12 in Study 304 ((NRI; ITT Population)



Abbreviations: FBX, febuxostat; ITT, Intent-to-treat; LESU, lesinurad; M, month; PBO, placebo; sUA, serum urate.
Note: Subjects missing an sUA result at each visit were treated as nonresponders.
* Indicates statistically significant $p < 0.025$ for LESU + FBX versus PBO + FBX using a 2-sided Cochran-Mantel Haenszel test stratified by Day-7 renal function and Day-7 sUA status (randomized values), adjusted for multiple comparisons.
** Indicates $p < 0.05$ for LESU + FBX versus PBO + FBX using a 2-sided Cochran-Mantel Haenszel test stratified by Day-7 renal function and Day-7 sUA status (randomized values), not adjusted for multiple comparisons.
Source: Table 14.2.1.1.a, Table 14.2.1.7, Table 14.2.1.8, Table 14.2.1.9, Table 14.2.1.10.

Adapted Sponsor's Fig. 13; p. 91 Summary of Clinical Efficacy

Gout Flares:

Initiation of urate lowering therapies in gout patients is known to be associated with an increased risk of gout flare. Theoretically, the occurrence of gout flares should decrease once a subject's sUA level is < 6 mg/dL. To prevent confounding of the gout flare assessments during Months 6 through 12, subjects were required to discontinue their gout flare prophylaxis regimens at the end of Month 5 in the three pivotal studies. Overall, a reduction in the occurrence of gout flares associated with the administration of lesinurad with a XOI was not consistently observed in these studies.

Studies 301 and 302:

The mean rate of subjects requiring treatment for a gout flare during the 6-month time period from Month 6 to Month 12 was an unmet major secondary endpoint for both lesinurad + ALLO treatment groups in Studies 301 and 302 (**Table 60**). Overall, the adjusted mean rates of gout flares requiring treatment were low during this prespecified time period and no differences between the three treatment groups were observed for this endpoint in Studies 301 and 302.

Table 60 - Mean Rate of Gout Flares requiring Treatment[1] per Subject for from Month 6 to Month 12 During Studies 301 and 302 (ITT Population)

Major Secondary Endpoint	Study 301			Study 302		
	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)
Adj. Rate[2,3] of Gout Flare Requiring Treatment per Subject Months 6 to 12 (SE)	0.62 (0.11)	0.62 (0.11)	0.55 (0.10)	0.89 (0.14)	0.78 (0.13)	0.83 (0.14)
Incidence Rate Ratio (95% CI) vs PBO + ALLO P-value		0.99 (0.61, 1.61) 0.98	0.88 (0.54, 1.43) 0.61		0.88 (0.57, 1.37) 0.57	0.93 (0.60, 1.45) 0.75

[1]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 prior to the start or 3 days after the end of the gout flare.
[2]Estimates obtained from Negative Binomial Regression adjusted for Day -7 renal function (eCrCl ≥ 60 mL/min versus < 60 mL/min) and tophus status during Screening (presence versus absence), randomized values, and log follow-up time as the offset variable.
[3]Estimates of adjusted rate for each treatment group obtained from inputting empirical proportion of each stratification factor level under each study.
Table Courtesy of Dr. Jade Wang

Study 304:

The mean rate of subjects requiring treatment for a gout flare during the 6-month time period from Month 6 to Month 12 was an ancillary secondary endpoint in this study (**Table 61**). Overall, the adjusted mean rates of gout flares requiring treatment were low during this time period. Comparable rates of gout flare were reported by subjects in the LESU200 mg + FBX and PBO + FBX treatment groups. A lower rate of gout flares was reported by subjects in the LESU400 mg + FBX group which was significantly different compared to the PBO + FBX group.

Table 61- Mean Rate of Gout Flares requiring Treatment[1] per Subject from Month 6 to Month 12 in Study 304 (ITT Population)

	PBO + ALLO (N=206)	LESU200 mg + ALLO (N=204)	LESU400 mg + ALLO (N=200)
Adjusted Rate[2,3] of Gout Flare Requiring Treatment per Subject Months 6 to 12 (SD)	1.3 (0.25)	1.5 (0.31)	0.7 (0.15)
Incidence Rate Ratio (95% CI) vs PBO + ALLO P-value		1.2 (0.7, 2.1) 0.5493	0.5 (0.3, 1.0) 0.0401

SD = Standard Deviation
[1]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 prior to the start or 3 days after the end of the gout flare.
[2]Estimates obtained from Negative Binomial Regression adjusted for Day -7 renal function (eCrCl ≥ 60 mL/min versus < 60 mL/min) and tophus status during Screening (presence versus absence), randomized values, and log follow-up time as the offset variable.
[3]Estimates of adjusted rate for each treatment group obtained from inputting empirical proportion of each stratification factor level under each study.
Adapted Sponsor's Table 14.2.4.1.a; p. Study 304 CSR

Studies 301 and 302:
These studies also looked at the proportion of subjects requiring treatment for gout flares at monthly intervals between Month 6 and Month 12 as a non-major secondary endpoint. Consistent with the other flare endpoint mentioned above, the proportion of subjects requiring treatment for gout flares for each monthly interval was low and comparable between the three treatment groups in both of these studies. (Data not shown.)

Study 304:
The proportion of subjects requiring treatment for gout flares at monthly intervals between Month 6 and Month 12 was not assessed in this trial.

Tophus Resolution:
Another clinical benefit associated with urate lowering therapy is the resolution of tophaceous deposits. At baseline, a total of 15% of the subjects in Study 301 and 24% of the subjects in Study 302 had tophi that qualified as a target tophus by prespecified study criteria. These subset populations were used in the analyses of the tophus response assessments in Studies 301 and 302. Since the protocol for Study 304 required patients to have one or more measurable tophus in order to participate in this trial, the entire study population was included in the tophus response evaluations. A dose-dependent trend in the reduction of tophaceous deposits in patients with high urate burden was observed in Study 304, but was not seen in Studies 301 and 302.

Studies 301 and 302:
The proportion of subjects with $\geq$ 1 target tophus at baseline who experienced complete resolution of at least 1 target tophus by Month 12 was the remaining major secondary endpoint for these trials that was also unmet. As shown in **Table 62**, the proportions of patients achieving a “complete” or “best” response at Month 12 were comparable for the three treatment groups. (Note: Although the p-value appears to be significant for the comparison between the LESU200 mg + ALLO and PBO + ALLO the difference favors the PBO + ALLO group.)

Table 62 - Proportion of Subjects with ≥1 Target Tophus at Baseline Who Experienced Complete Resolution of at least 1 Target Tophus by Month 12 During Study 301 and 302 (NRI; ITT Population with at Least 1 Target Tophus at Baseline)

Secondary Endpoint	Study 301			Study 302		
	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)
Subjects with at Least 1 Target Tophus at Baseline (ITT Population)	17	18	19	33	35	29
Proport. with Best Resp. of CR by Month 12 [n, %]	5 (29%)	0	4 (21%)	11 (33%)	11 (31%)	8 (28%)
Diff. in Proportion vs PBO + ALLO (95% CI)[1] P-value[2]		-0.29 (-0.51,-0.08) 0.02	-0.08 (-0.37, 0.20) 0.60		-0.02 (-0.24, 0.20) 0.85	-0.06 (-0.29, 0.17) 0.63

[1]Binomial confidence interval for difference in proportions
[2]Cochran-Mantel Haenszel test stratified by Day -7 renal function (eCrCl ≥ 60 mL/min versus < 60 mL/min), randomized values.
Table Courtesy Dr. Jade Wang

Study 304:

The proportion of subjects who experienced complete resolution of at least 1 target tophus by Month 12 was an unmet major secondary endpoint for this trial. Numeric increases in the proportions of subjects who experienced complete resolution (CR) in a target tophus following 12-months of treatment were observed for the two lesinurad + FBX groups in a dose-dependent manner, but were not significantly different as compared to the PBO + FBX group (**Table 63)**.

Table 63 - Proportion of Subjects Who Experienced Complete Resolution of at least 1 Target Tophus by Month 12 in Study 304 (NRI; ITT Population)

	PBO + FBX80 mg (N=109)	LESU200 + FBX 80 mg (N=106)	LESU400 + FBX 80 mg (N=109)
Proportion with Best Response of CR by Month 12 [n, %]	23 (21%)	27 (26%)	33 (30%)
Diff. in Proportion vs PBO + FBX (95% CI)[1] P-value[2]		0.04 (-0.07, 0.16) 0.45	0.09 (-0.02, 0.21) 0.12

[1]Binomial confidence interval (CI) for difference in proportions
[2]Cochran-Mantel Haenszel test stratified by Day -7 renal function (eCrCl ≥60 ml/min versus <60 ml/min) and Day -7 sUA status (sUA ≥6.0 mg/dL), randomized values
Table courtesy Dr. Jade Wang

Studies 301 and 302:

The mean percent change from baseline in the sum of the areas for all target tophi at each visit was a non-major secondary endpoint in these studies. As shown in **Table 64**, decreases in the mean sum area of all tophi were observed at both the Month 6 and Month 12 time points which were not significantly different on comparison between the three treatment groups.

Table 64 - Sum of the Areas of All Tophi at Month 6 and Month 12 in Subjects with at Least 1 Target Tophus at Baseline in Study 301 and 302 (Observed Cases; ITT Population – Subjects with at Least 1 Target Tophus at Baseline)

	Study 301			Study 302		
	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)
Subjects with at Least 1 Target Tophus at Baseline (ITT Pop.):						
Mean Area (mm^2) (SD)	17 322 (281)	18 335 (207)	19 254 (165)	33 373 (379)	35 347 (336)	29 560 (715)
% Change from Baseline to Month 6:						
n	16	13	13	31	30	24
Mean (SD)	-17 (47)	-5.5 (49)	-23 (47)	-21 (64)	-16 (64)	-27 (39)
Adj. Differ. in Means vs PBO + ALLO (95% CI)		4.3 (-33, 41)	-11 (-47, 26)		3.69(-126,33)	-3.68(-35, 28)
p-value[1]		0.8132	0.5639		0.8045	0.8176
Percent Change from Baseline to Month 12:						
n	16	13	13	28	27	26
Mean (SD)	33 (158)	12 (134)	-11 (116)	-39 (46)	-34 (92)	-31 (70)
Adj. Differ. in Means vs PBO + ALLO (95% CI)		-28(-136, 79)	-57(-164, 51)		3.90 (-34, 42)	7.91 (-30, 46)
p-value[1]		0.5985	0.2936		0.8382	0.6817

Diff. = Difference
Note: Only subjects with non-missing tophus measurements at a particular visit are included for that visit. End of study/early termination data are included in the appropriate visit month if no scheduled visit occurred during that visit month.
[1]p-values are from ANCOVA modes with baseline value as a covariate and treatment group and Day -7 renal function (eCrCl ≥60 ml/min vs <60 mL/min) as randomization factor values
Adapted Sponsor's Table 14.2.3.20; p779-784. Study 301 CSR

Study 304:

Instead of assessing the mean percent change from baseline in the sum of the areas for all target tophi at each visit, this trial evaluated the proportion of subjects with best tophus response (complete resolution [CR] or partial resolution [PR]) on at least 1 target tophus by Month 12. This was another unmet major secondary endpoint for Study 304. Numerically higher proportions of subjects in the two lesinurad + FBX treatment groups experienced either CR or PR of a target tophus following 12-months of study treatment that were not significantly different as compared to the PBO + FBX group (**Table 65**).

Table 65 - Proportion of Subjects Who Experienced Complete or Partial Resolution of at least 1 Target Tophus by Month 12 in Study 304 (NRI; ITT Population)

	PBO + FBX80 mg (N=109)	LESU200 + FBX 80 mg (N=106)	LESU400 + FBX 80 mg (N=109)
Proportion with CR or PR by Month 12 [n, %]	55 (51%)	60 (57%)	64 (59%)
Diff. in Proportion vs PBO + FBX (95% CI)[1]		0.06 (-0.09, 0.21)	0.08 (-0.07, 0.23)
P-value[2]		0.45	0.12

[1]Binomial confidence interval (CI) for difference in proportions
[2]Cochran-Mantel Haenszel test stratified by Day -7 renal function (eCrCl ≥60 ml/min versus <60 ml/min) and Day -7 sUA status (sUA ≥6.0 mg/dL), randomized values
Table courtesy Dr. Jade Wang

Patient Reported Outcomes:
The HAQ-DI assesses disease-related physical function. Scores for this instrument range from 0 to 3 with higher scores indicative of worse physical function. The minimum clinically important difference (MCID) for the HAQ-DI score is -0.22 in rheumatoid arthritis (RA). For their analyses in the gout trials, the Applicant used a HAQ-DI score of -0.25 as an individual threshold since it is the closest score above the MCID for RA; however the relevance of this MCID to gout populations is questionable, particularly for populations that do not have chronic active gout. In any case, overall, the results for these assessments did not demonstrate an improvement in disability for subjects administered lesinurad + XOI in the pivotal phase 3 studies. These are not unexpected findings, since the level of disability was not high at baseline for the subject populations in these trials.

Studies 301 and 302:
The proportion of subjects achieving a HAQ-DI improvement of ≥ 0.25 at Month 12 in Studies 301 and 302 was a non-major endpoint in these trials. Overall, minimal improvements are noted for this assessment for both trials that were generally similar for the three treatment groups **(Table 66**).

Table 66 – Proportion of Subjects Achieving Health Assessment Questionnaire Disability Index (HAQ-DI) Improvement of ≥ 0.25 at Month 12 in Studies 301 and 302 (Observed cases; ITT Population)

Secondary Endpoint	Study 301			Study 302		
	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)
Proportion of Subjects with Improvement ≥0.25 from Baseline in HAQ-DI at Month 12 [n, %]	51(35%)	42 (30%)	41 (29%)	59(39%)	46 (30%)	56 (38%)
Diff. in Proport. vs PBO + FBX (95% CI)[1]		-0.05 (-0.16, 0.06)	-0.06 (-0.17, 0.04)		-0.10 (-0.20, 0.01)	-0.01 (-0.12, 0.10)
P-value[2]		0.4120	0.2701		0.1025	0.8201

Diff.= Difference
HAQ-DI assesses patient's level of functional ability with items scores ranging from 0-3 with 0 being the least disability.
[1]Binomial confidence interval (CI) for difference in proportions
[2]Cochran-Mantel Haenszel test stratified by Day-7 renal function (eCrCl≥ 60 mL/min) and tophus status during screening (presence vs absence), randomization stratification values
Modified Sponsor's Table 14.2.4.2.a from Study CSR and Table 14.2.4.2.a from Study 302 CSR

Study 304:

The proportion of subjects achieving a HAQ-DI improvement of ≥ 0.25 at Month 12 was the third unmet major secondary endpoint for this study. As noted previously, patients who participated in this study were minimally impaired as shown by their overall low mean HAQ-DI scores at baseline, which were lower for the LESU200 mg + FBX and LESU400 mg + FBX groups than the PBO + FBX group (0.671 and 0.586 versus 0.729, respectively). Smaller proportions of subjects in the two lesinurad + FBX treatment groups as compared to the PBO + FBX group achieved an improvement of ≥ 0.25 in their baseline HAQ-DI scores following 12 months of study treatment (**Table 67**).

Table 67 - Proportion of Subjects Achieving Health Assessment Questionnaire Disability Index (HAQ-DI) Improvement of ≥ 0.25 at Month 12 in Study 304 (Observed Cases; ITT Population)

	PBO + FBX80 mg (N=109)	LESU200 + FBX 80 mg (N=106)	LESU400 + FBX 80 mg (N=109)
Proportion of Subjects with Improvement of ≥0.25 from Baseline in HAQ-DI at Month 12 [n, %]	42 (53%)	34 (44%)	26 (33%)
Diff. in Proportion vs PBO + FBX (95% CI)[1] P-value[2]		-0.08 (-0.26, 0.09) 0.30	-0.19(-0.36,-0.02) 0.02

HAQ-DI assesses patient's level of functional ability with items scores ranging from 0-3 with 0 being the least disability.
[1]Binomial confidence interval (CI) for difference in proportions
[2]Cochran-Mantel Haenszel test stratified by Day -7 renal function (eCrCl ≥60 ml/min versus <60 ml/min) and Day -7 sUA status (sUA ≥6.0 mg/dL), randomized values
Table courtesy Dr. Jade Wang

6.1.6 Other Endpoints

A number of patient reported outcomes (HAQ pain score, Short-Form-36 [SF-36], patient global assessment [PGA], the total treatment satisfaction question for medication score [TSQM], and the Sheehan Disability Scale [SDS]) were also evaluated as ancillary endpoints in the pivotal, phase 3 Studies 301, 302, and 304. The results from these assessments are shown in **Table 21**, **Table 35**, and **Table 53** and were generally not robust for either of the two lesinurad + XOI treatment groups as compared to PBO + XOI.

6.1.7 Subpopulations

Figure 13 through **Figure 16** contain forest plot analyses of the proportion of subjects achieving sUA <6.0 (or 5.0) mg/dL at Month 6 by lesinurad treatment group prepared by the FDA's statistician, Dr. Jade Wang. These analyses explore various demographic factors such as age (<65 and ≥ 65), sex (male and female), race (non-white and white), and region (non-US and US) that might have impacted on the efficacy results submitted in support of lesinurad. Other factors such as baseline renal function (eCrCl: <45 mL/min, 45 to <60 mL/min, and ≥ 60 mL/min), baseline allopurinol dose (<300 mg/d, 300 mg/d, and >300 mg/d) for Studies 301 and 302, and baseline sUA level (< 5mg/dL and ≥ 5 mg/dL) for Study 304 were also examined to determine if they had any influence on the results from the pivotal phase trials. Since Studies 301 and 302 shared a common protocol, the results from these trials were pooled in order to increase the sample size of the subgroups. Review of these data shows no statistically significant treatment effect by age group, race or region across the studies. However, a statistically significant treatment effect is observed for female gender for the pooled Studies 301 and 302. In view of the small sample size for females, no definitive conclusions can be drawn based on this subgroup analysis. In all three studies (301, 302 and 304), there

were no statistically significant treatment effect exerted by baseline renal function. Additionally, no statistically significant treatment effect by background allopurinol dose was observed for Studies 301 and 302 or by baseline sUA group for Study 304. (Note: The reader is referred to Dr. Jade Wang's review for additional information regarding these analyses.)

Figure 13 – Differences of Proportion for Subjects Treated with LESU200 mg + Allopurinol with Month 6 sUA Levels <6.0 mg/dL for the Pooled Studies 301 and 302 by Subgroup Factors (ITT Population; Non-Responder Imputation)

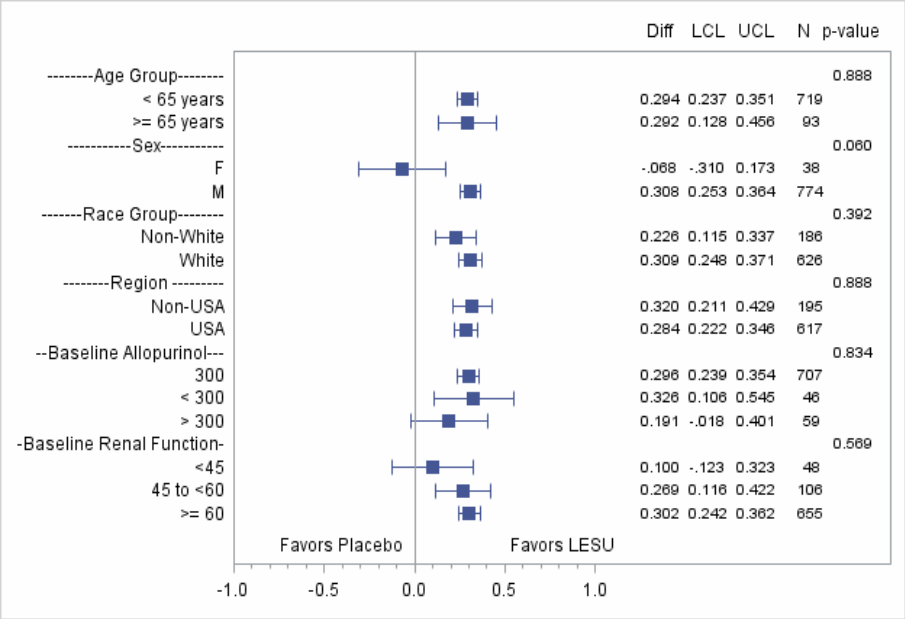


Table courtesy Dr. Jade Wang

Figure 14 – Differences of Proportion for Subjects Treated with LESU400 mg + Allopurinol with Month 6 sUA Levels <6.0 mg/dL for the Pooled Studies 301 and 302 by Subgroup Factors (ITT Population; Non-Responder Imputation)

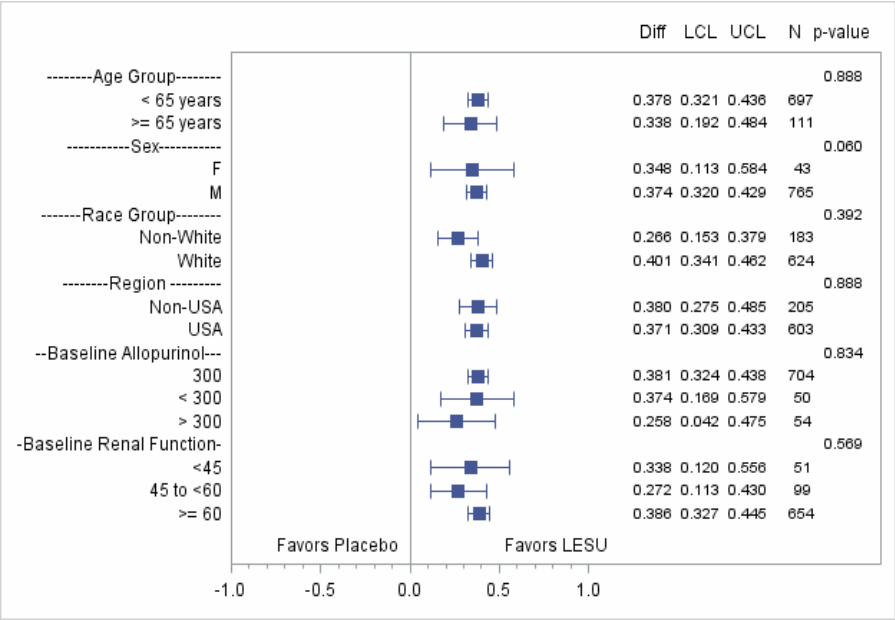


Table courtesy Dr. Jade Wang

Figure 15 – Differences of Proportion for Subjects treated with LESU200 mg + Febuxostat with Month 6 sUA Levels <5.0 mg/dL for Study 304 by Subgroup Factors (ITT Population; Non-Responder Imputation)

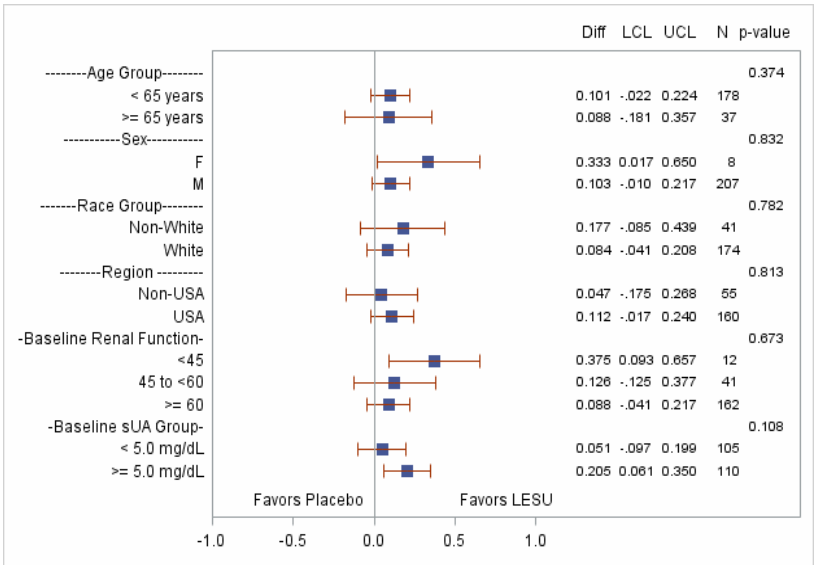


Table courtesy Dr. Jade Wang

Figure 16 – Differences of Proportion for Subjects Treated with LESU400 mg + Febuxostat with Month 6 sUA Levels <5.0 mg/dL for Study 304 by Subgroup Factors (ITT Population; Non-Responder Imputation)

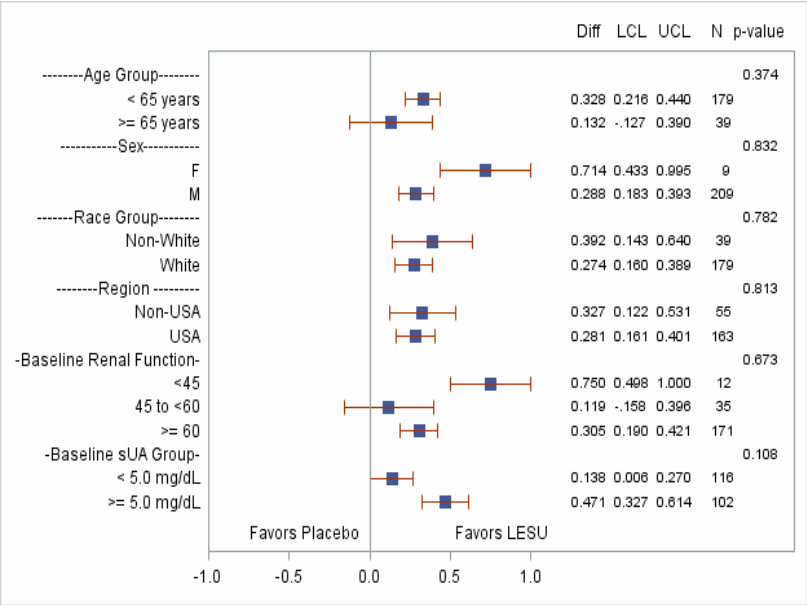


Table courtesy Dr. Jade Wang

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Low dose (≤ 325 mg/day) aspirin was used prophylactically for cardiovascular disease by 8% of subjects in the pooled, phase 3 Studies 301 and 302. Since aspirin is known to interact with the URAT1 transport of uric acid in a bimodal manner, the application contained subgroup analyses conducted on the pooled efficacy results for Studies 301 and 302 to determine if the use of low dose aspirin impacted on the efficacy results from these studies as well as the results from Study 304. Also included were analyses on subgroups of patients who were taking thiazide diuretics or thiazide-like diuretics which also have an effect on urate metabolism. Overall, the results of these analyses (**Table 68** and **Table 69**) show no effect by the concomitant use of these drugs with lesinurad with the exception of thiazide use at baseline for which the point estimate is not in favor of LESU200 mg + FBX patients in Study 304. However, the number of patients in this subgroup (n=18) is too small to draw a definitive conclusion.

Table 68 – Proportion of Subjects with sUA<6.0 mg/dL by Month 6 by Concomitant Use of Low-Dose Aspirin and Thiazide Diuretics for the Pooled Studies 301 and 302 (ITT Population; Non-Responder Imputation)

Subgroup Analyses	Pooled, 12-Month, Controlled Studies 301 and 302		
	PBO + ALLO (N= 407)	LESU200 mg + ALLO (N=405)	LESU400 mg + ALLO (N=401)
Low Dose (≤ 325 mg/d) Aspirin			
Proportion Subjects Taking ≤ 325 mg/d Aspirin at Baseline with sUA <6.0 mg/dL by Month 6	20/82 (24%)	38/63 (60%)	43/67 (64%)
Diff. Proportions vs PBO (95% CI)[1] p-value[2]		0.36 (0.21, 0.51) <0.0001	0.40 (0.25, 0.550 <0.0001
Proportion Subjects NOT Taking Low Dose Aspirin at Baseline with sUA <6.0 mg/dL by Month 6	84/325 (26%)	184/342 (54%)	209/334 (63%)
Diff. Proportions vs PBO (95% CI)[1] p-value[2]		0.28 (0.21, 0.35) <0.0001	0.37 (0.30, 0.440 <0.0001
Thiazide Diuretic Use			
Proportion Subjects Taking Thiazide Diuretic at Baseline with sUA <6.0 mg/dL by Month 6	17/55 (31%)	43/65 (65%)	45/64 (70%)
Diff. Proportions vs PBO (95% CI)[1] p-value[2]		0.34 (0.17, 0.51) 0.0002	0.39 (0.23, 0.56) <0.0001
Proportion Subjects NOT Taking Thiazide Diuretic at Baseline with sUA <6.0 mg/dL by Month 6	87/352 (25%)	179/339 (53%)	207/337 (61%)
Diff. Proportions vs PBO (95% CI)[1] p-value[2]		0.28 (0.21, 0.35) <0.0001	0.37 (0.30, 0.44) <0.0001
Thiazide-Like Diuretic Use			
Proportion Subjects Taking Thiazide-Like Diuretic at Baseline with sUA <6.0 mg/dL by Month 6	19/64 (30%)	48/79 (61%)	57/78 (73%)
Diff. Proportions vs PBO (95% CI)[1] p-value[2]		0.31 (0.16, 0.47) 0.0002	0.43 (0.28, 0.58) <0.0001
Proportion Subjects Taking NOT Thiazide-Like Diuretic at Baseline with sUA <6.0 mg/dL by Month 6	85/343 (25%)	174/326 (53%)	195/323 (60%)
Diff. Proportions vs PBO (95% CI)[1] p-value[2]		0.29 (0.22, 0.36) <0.0001	0.36 (0.29,0.43) <0.0001

CI= confidence interval
[1]Binomial confidence interval (CI) for difference in proportions
[2]Cochran-Mantel Haenszel test stratified by Day-7 renal function (eCrCl≥ 60 mL/min) and tophus status during screening (presence vs absence), randomization stratification values
Modified Sponsor's Tables 2.7.1.4, 2.7.1.2, and 2.7.1.3; ISE

Table 69 – Proportion of Subjects with sUA<5.0 mg/dL by Month 6 by Concomitant Use of Low-Dose Aspirin and Thiazide Diuretics for Study 304 (ITT Population; Non-Responder Imputation)

Subgroup Analyses	PBO + FBX	LESU200 mg + FBX	LESU400 mg + FBX
Low Dose (≤ 325 mg/d) Aspirin			
Proportion Subjects Taking ≤ 325 mg/d Aspirin at Baseline with sUA <5.0 mg/dL by Month 6	9/16 (56%)	13/18 (72%)	9/15 (60%)
Diff. Proportions vs PBO (95% CI)[1] p-value[2]		0.16 (-0.16, 0.48) 0.5987	0.04 (-0.31, 0.38) 0.9875
Proportion Subjects NOT Taking Low Dose Aspirin at Baseline with sUA <5.0 mg/dL by Month 6	42/93 (455)	47/88 (53%)	74/94 (79%)
Diff. Proportions vs PBO (95% CI)[1] p-value[2]		0.08 (-0.06, 0.23) 0.2536	0.34 (0.20, 0.47) <0.0001)
Thiazide Diuretic Use			
Proportion Subjects Taking Thiazide Diuretic at Baseline with sUA <5.0 mg/dL by Month 6	6/8 (75%)	7/10 (70%)	10/11 (91%)
Diff. Proportions vs PBO (95% CI)[1] p-value[2]		-0.05 (-0.46, 0.36) 0.4475	0.16 (-0.10, 0.50) 0.6429
Proportion Subjects NOT Taking Thiazide Diuretic at Baseline with sUA <5.0 mg/dL by Month 6	45/101 (45%)	53/96 (55%)	73/98 (75%)
Diff. Proportions vs PBO (95% CI)[1] p-value[2]		0.11 (-0.03,0.25) 0.0967	0.30 (0.17, 0.43) <0.001
Thiazide-Like Diuretic Use			
Proportion Subjects Taking Thiazide-Like Diuretic at Baseline with sUA <5.0 mg/dL by Month 6	6/9 (67%)	9/13 (69%)	9/17 (53%)
Diff. Proportions vs PBO (95% CI)[1] p-value[2]		0.03 (-0.37, 0.42) 0.4478	0.10 (-0.27, 0.47) 0.1990
Proportion Subjects Taking NOT Thiazide-Like Diuretic at Baseline with sUA <5.0 mg/dL by Month 6	45/100 (45%)	51/93 (55%)	79/92 (76%)
Diff. Proportions vs PBO (95% CI)[1] p-value[2]		0.10 (-0.04, 0.24) 0.1073	0.31 (0.18, 0.44) <0.0001

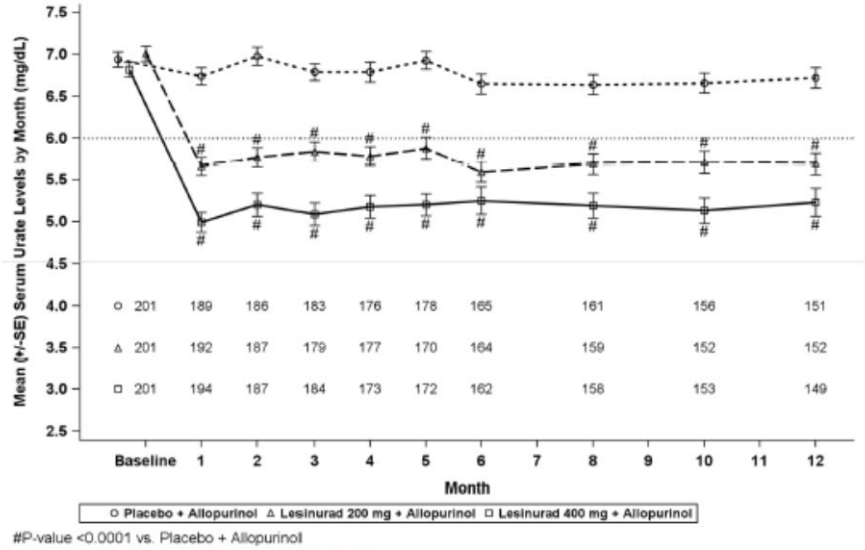
CI= confidence interval
[1]Binomial confidence interval (CI) for difference in proportions
[2]Cochran-Mantel Haenszel test stratified by Day-7 renal function (eCrCl≥ 60 mL/min) and tophus status during screening (presence vs absence), randomization stratification values
Modified Sponsor's Tables 3.5; ISE and Table 14.2.1.1p and 14.2.1.1q. p. 479-481; CSR 304

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

In support of lesinurad's persistence of efficacy, the Applicant submitted analyses that examined response to treatment with lesinurad + XOI at monthly intervals over a 12-

month treatment period for the three pivotal, phase 3 studies (301, 302, and 304). **Figure 17 and Figure 18** graphically depict the mean sUA level profiles for the three treatment groups for Studies 301 and 302. The maximum change related to lesinurad treatment appears to be in the first month of treatment; approximately 1-1.5 mg/dL decrease for the 200 mg dose and approximately 2 mg/dL for the 400 mg dose. The decrease appears to be consistent over time through Month 12. The baseline mean sUA for the PBO + XOI groups remains essentially unchanged over the course of these studies. At each visit, the mean changes in sUA levels over baseline for both lesinurad + ALLO groups were significantly different as compared to PBX + ALLO ($p<0.0001$) for each of these studies.

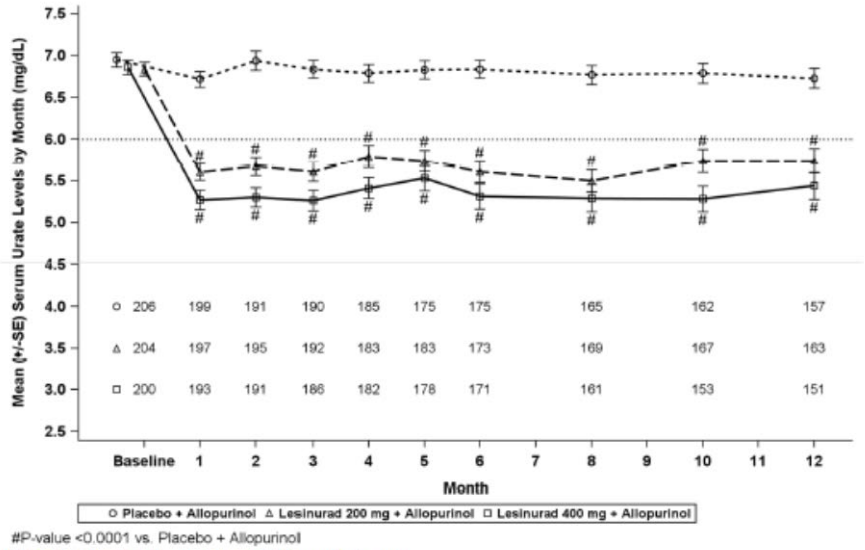
Figure 17 - Mean Serum Urate Levels by Visit in Study 301 (Observed Cases; ITT Population)



Abbreviations: ITT, intent-to-treat; SE, standard error.
Numbers indicate the number of subjects contributing data at each timepoint. Dotted line indicates target sUA (< 6.0 mg/dL). Statistical significance is based on the difference in least square mean percent change from Baseline.
Note: Months 7, 9, and 11 data are excluded because the timing of the last protocol amendment (Protocol Amendment 4), which added sUA assessments at these timepoints, resulted in minimal data collection at these timepoints for analysis.
Source: Study 301 CSR Table 14.2.1.22.

Adapted Sponsor's Fig. 14; p. 99 Summary of Clinical Efficacy

Figure 18 - Mean Serum Urate Levels by Visit in Study 302 (Observed Cases; ITT Population)

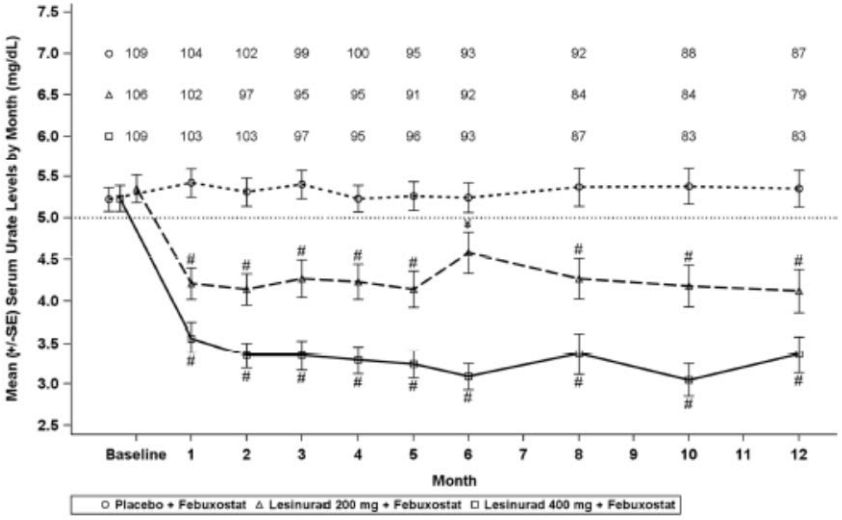


Abbreviations: ITT, intent-to-treat; SE, standard error.
Numbers indicate the number of subjects contributing data at each timepoint. Dotted line indicates target sUA (< 6.0 mg/dL). Statistical significance is based on the difference in least square mean percent change from Baseline.
Note: Months 7, 9, and 11 data are excluded because the timing of the last protocol amendment (Protocol Amendment 6), which added sUA assessments at these timepoints, resulted in minimal data collection at these timepoints for NRI analysis.
Source: Study 302 CSR Table 14.2.1.22.

Adapted Sponsor's Fig. 15; p. 100 Summary of Clinical Efficacy

Similar results were observed for Study 304. **Figure 19** graphically depicts the mean sUA level profiles for the three treatment groups by visit over the 12-month course of this trial. Within one month following initiation of study treatment, the two lesinurad + FBX groups separate out in a dose dependent manner from the PBO + FBX group, with a reduction in sUA of approximately 1 to 2 mg/dL. The decrease in mean sUA level remains constant for both lesinurad + FBX groups over the 12-months of study treatment. The baseline mean sUA level for the PBO + FBX group remains unchanged over the course of the study. As observed in Studies 301 and 302, the mean change in sUA from baseline at each visit for Study 304 was also significantly higher in both lesinurad + FBX treatment groups as compared with the PBO + FBX group.

Figure 19 - Mean sUA Levels by Visit in Study 304 (Observed Cases; ITT Population)



¥P-value <0.01 vs. Placebo + Febuxostat; #P-vallue <0.0001 vs. Placebo + Febuxostat

Abbreviations: ITT, intent-to-treat; SE, standard error.
Numbers indicate the number of subjects contributing data at each timepoint. Dotted line indicates target sUA (< 5.0 mg/dL). Statistical significance is based on the difference in least square mean percent change from Baseline.
Note: Months 7, 9, and 11 data were excluded because the timing of the last protocol amendment (Protocol Amendment 5), which added sUA assessments at these timepoints, resulted in minimal data at these timepoints for analysis.
Source: Study 304 CSR Table 14.2.1.22.

Adapted Sponsor's Fig. 16; p. 101 Summary of Clinical Efficacy

Due to concerns regarding the magnitude of treatment effect associated with the lesinurad groups displayed in Figures 6-9, the FDA's statistician, Dr. Jade Wang, also looked at the change from baseline in mean sUA levels at the Months 6 and 12 time points for each of the three, pivotal studies (301, 302 and 304) (**Table 70** through **Table 72**). In Studies 301 and 302, the magnitude of the treatment effect is modest for both lesinurad treatment groups. At the Month 6 time point for the LESU200 mg + ALLO treatment groups the adjusted differences in mean change from baseline in sUA versus PBO+ ALLO was 1.01 mg/dL and 1.09 mg/dL versus 1.23 mg/dL and 1.36 mg/dL for the LESU400 mg + ALLO treatment groups in Studies 301 and 302, respectively. At Month 12, the adjusted differences in mean change over baseline for the LESU200 mg + ALLO treatment groups versus PBO+ ALLO was 0.89 mg/dL and 0.93 mg/dL versus 1.18 mg/dL and 1.25 mg/dL for the LESU400 + ALLO treatment groups versus PBO + ALLO in Studies 301 and 302, respectively.

Table 70 – Change From Baseline in Mean sUA Level at Month 6 and Month 12 Visits by Treatment Group for Study 301 (ITT Population; Observed Cases)

Study Visit	PBO + ALLO (N=201)	LESU 200 mg + ALLO (N=201)	LESU 400 mg + ALLO (N=201)
Baseline:			
n	201	201	201
Mean (SE)	6.99 (1.25)	7.01 (1.32)	6.83 (1.24)
Median (Min, Max)	6.70	6.80	6.70
	(3.8, 12.2)	(3.8, 13.3)	(3.6, 12.2)
Month 6:			
n	201	196	200
Mean (SE)	6.83 (1.24)	5.81 (1.71)	5.48 (2.17)
Median (Min, Max)	6.70 (3.6, 12.2)	5.50 (2.7, 13.2)	4.90 (1.7, 12.1)
Δ from Baseline to Month 6:			
n	195	196	200
Mean (SD)	-0.18 (1.65)	-1.21 (1.79)	-1.35 (2.08)
Median (Min, Max)	-0.30	-1.40 (-5.7, 7.8)	-1.70 (-6.6, 5.70
Adj. Diff. Means vs PBO+ALLO	(-6.7, 7.8)	**-1.01**	**-1.23**
(95%CI)		(-1.35, -0.66)	(-1.58, -0.89)
P-value		<0.001	<0.001
Month 12:			
n	195	196	200
Mean (SE)	6.86 (1.61)	5.97 (1.84)	5.54 (2.18)
Median (Min, Max)	6.60 (4.0, 12.4)	5.50 (2.7, 13.2)	4.90 (1.6, 12.1)
Δ from Baseline to Month 12:			
n	195	196	200
Mean (SD)	-0.10 (1.62)	-1.05 (1.86)	-1.29 (1.98)
Median (Min, Max)	-0.20 (-5.4, 7.8)	-1.20 (-5.4, 7.8)	-1.80 (-6.2, 5.5)
Adj. Diff. Means vs PBO+ALLO		**-0.93**	**-1.25**
(95%CI)		(-1.28, -0.58)	(-1.60, -0.90)
p-value		<0.001	<0.001

Table courtesy Dr. Jade Wang

Table 71 – Change From Baseline in Mean sUA Level at Month 6 and Month 12 Visits by Treatment Group for Study 302 (ITT Population; Observed Cases)

Study Visit	PBO + ALLO (N=206)	LESU 200 mg + ALLO (N=204)	LESU 400 mg + ALLO (N=200)
Baseline:			
n	206	204	200
Mean (SE)	6.99 (1.26)	6.84 (1.11)	6.86 (1.19)
Median (Min, Max)	6.80 (3.4, 11.3)	6.75 (4.0, 11.3)	6.80 (3.8, 11.0)
Month 6:			
n	200	199	197
Mean (SE)	6.97 (1.49)	5.80 (1.84)	5.54 (2.18)
Median (Min, Max)	6.80 (2.9, 12.1)	5.40 (1.9, 12.3)	5.00 (2.5, 15.8)
Δ from Baseline to Month 6:			
n	200	199	197
Mean (SD)	0.02 (1.30)	-1.03 (1.65)	-1.31 (2.06)
Median (Min, Max)	0.00 (-3.4, 5.0)	-1.10 (-6.8, 6.2)	-1.60 (-6.0, 6.7)
Adj. Diff. Means vs PBO+ALLO		**-1.09**	**-1.36**
(95%CI)		(-1.41, -0.76)	(-1.69, -1.03)
P-value		<0.001	<0.001
Month 12:			
n	200	199	197
Mean (SE)	6.99 (1.61)	6.02 (2.01)	5.74 (2.35)
Median (Min, Max)	6.75 (4.0, 12.1)	5.70 (2.5, 12.3)	5.00 (2.7, 15.8)
Δ from Baseline to Month 12:			
n	200	199	197
Mean (SD)	0.04 (1.48)	-0.81 (1.76)	-1.11 (2.25)
Median (Min, Max)	-0.10 (-4.0, 5.0)	-1.10 (-3.9, 6.2)	-1.60 (-6.1, 6.0)
Adj. Diff. Means vs PBO+ALLO		**-0.89**	**-1.18**
(95%CI)		(-1.25, -0.53)	(-1.54, -0.82)
p-value		<0.001	<0.001

Table courtesy Dr. Jade Wang

As shown in **Table 72**, the magnitude of treatment effect for lesinurad when administered with febuxostat was also modest in Study 304. The adjusted differences in mean change from baseline for the LESU400 mg + FBX treatment group versus PBO + FBX were 1.88 mg/dL at Month 6 and 1.66 mg/dL at Month 12 which were higher as compared to the urate lowering effect observed in Studies 301 and 302 when this dose was administered with allopurinol. However, the adjusted differences in mean change from baseline for the LESU200 mg + FBX treatment group were 0.79 mg/dL and 1.06 mg/dL at the Month 6 and Month 12 time points, respectively, which were similar to the urate lowering effect observed when the 200 mg dose of lesinurad was administered with allopurinol in Studies 301 and 302 (**Table 70** and **Table 71**).

Table 72 – Change From Baseline in Mean sUA Level at Month 6 and Month 12 Visits by Treatment Group for Study 304 (ITT Population; Observed Cases)

Study Visit	PBO + FBX80 mg (N=109)	LESU200 + FBX 80 mg (N=106)	LESU400 + FBX 80 mg (N=109)
Baseline:			
n	109	106	109
Mean (SE)	5.22 (1.53)	5.35 (1.72)	5.23 (1.64)
Median (Min, Max)	4.90	5.10	4.80
	(2.2, 9.6)	(2.0, 11.6)	(1.4, 10.0)
Month 6:			
n	106	103	106
Mean (SE)	5.41 (1.80)	4.68 (2.35)	3.49 (1.99)
Median (Min, Max)	4.90	4.00	2.80
	(2.9, 10.8)	(1.7, 11.0)	(1.0, 9.5)
Δ from Baseline to Month 6:			
n	106	103	106
Mean (SD)	0.18 (1.68)	-0.67 (1.99)	-1.69 (2.06)
Median (Min, Max)	0.00 (-3.6, 5.9)	-1.30 (-5.5, 5.6)	-2.00 (-7.0, 5.1)
Adj. Diff. Means vs PBO+ALLO		**-0.79**	**-1.88**
(95%CI)		(-1.28, -0.30)	(-2.36, -1.40)
P-value		0.002	<0.001
Month 12:			
n	106	103	106
Mean (SE)	5.59 (2.11)	4.60 (2.61)	3.90 (2.35)
Median (Min, Max)	5.05 (1.8, 13.0)	3.80 (1.4, 12.7)	3.25 (1.0, 9.5)
Δ from Baseline to Month 12:			
n	106	103	106
Mean (SD)	0.37 (2.21)	-0.75 (2.12)	-1.27 (2.42)
Median (Min, Max)	-0.10	-1.20 (-4.5, 5.6)	-1.70 (-7.0, 5.3)
Adj. Diff. Means vs PBO+ALLO	-4.3, 7.9	**-1.06**	**-1.66**
(95%CI)		(-1.65, -0.47)	(-2.25, -1.08)
p-value		<0.001	<0.001

Table courtesy Dr. Jade Wang

6.1.10 Additional Efficacy Issues/Analyses

None.

7 Review of Safety

Safety Summary

Review of the safety database for lesinurad +XOI identified concerns in four main areas: 1) a higher rate of deaths, 2) a higher rate of MACE events, 3) a higher rate of serious adverse events and 4) a higher rate of serious and non-serious renal-related adverse events. The dose-dependent higher incidences of serious and serious renal- related adverse events observed with LESU400 mg + XOI correlated with safety findings from the LESU400 mg monotherapy dose evaluated separately in a 6-month trial (Study 303).

There was a consistent overall numeric imbalance against lesinurad in deaths that occurred during the controlled portions of the pivotal, phase 3, lesinurad +XOI trials. Overall, the types of deaths were consistent with the risks related to the underlying and concomitant medical conditions (e.g., hypercholesterolemia, hypertension, diabetes mellitus, chronic kidney disease and cardiovascular disease) reported by these subjects. However, the exposure-adjusted incidence rates for death in the lesinurad groups were low overall, with highly overlapping confidence intervals, making it difficult to draw definitive conclusions.

There were four deaths in patients randomized to the two lesinurad + XOI treatment groups that were adjudicated by the cardiovascular endpoints adjudication committee as MACE events which occurred during the controlled portions of the pivotal phase 3 studies (301, 302, and 304). However, MACE events were seen in all study arms, including the PBO + XOI arm. The incidence rates for the number of subjects with MACE events and the overall number of MACE events for both the PBO + XOI and the LESU200 mg + XOI group were comparably low, but the risk for subjects with MACE events as well as the overall number of MACE events was nearly double for the LESU400 mg + XOI treatment group. This was also reflected in the numeric imbalances in the various types of MACE events, with higher rates of cardiovascular deaths and non-fatal MI particularly for the LESU400 mg +XOI group. When examined separately by XOI, the exposure-adjusted incidence in all treatment groups for MACE events was higher in the lesinurad + febuxostat Study 304 which was limited by the size of the study and the small numbers of adjudicated events. Once again, the overall small numbers of these types of events along with the highly overlapping confidence intervals make it difficult to draw definitive conclusions. Although some reassurance was provided by similarities observed in the MACE rate from a 6-month, open-label, prospective safety study of 1,732 patients with gout treated with allopurinol that was also adjudicated by the same CEAE and from the literature, it does not explain the dose-dependent increase in MACE events observed in the LESU400 mg + XOI treatment group or the apparent increase in MACE events when co-administered with febuxostat whose current USPI carries a cardiovascular warning.

A higher proportion of patients in the LESU400 mg +XOI group (9%) experienced serious adverse events during the three pivotal studies as compared to the PBO + XOI (6%) and LESU200 mg + XOI (5%) treatment groups. Similarly, a much higher proportion of serious adverse events was also reported by subjects in the LESU400 mg group (22%) as compared to placebo (9%) in the 6-month monotherapy study (303). Numerical imbalances in the number of serious adverse events were noted with higher incidences in the LESU400 mg + XOI treatment group versus PBO + XOI in the following system organ classes: Cardiac Disorders, Renal and Urinary disorders, and Metabolism and Nutrition Disorders. A numeric imbalance was also observed for the LESU200 mg + XOI group compared to PBO + XOI for Cardiovascular Disorders. In the 6-month monotherapy study, the imbalance in serious adverse events was primarily due to the number of serious adverse events listed under the Renal and Urinary Disorders system organ class for LESU400 mg treated subjects. The findings regarding serious Cardiac Disorders has already been discussed above as it pertains to MACE events. The higher rates of serious adverse events under the Metabolism and Nutritional Disorder system organ class were due to the number of cases of serious gout attacks experienced by subjects in the LESU400 mg + XOI group. This is not an unexpected finding due to the increase in risk for gout flares as a result of fluctuations in serum uric acid associated with urate lowering therapy.

The population in the lesinurad phase 3 studies had multiple risk factors for renal adverse events including chronic kidney disease (CKD), diabetic nephropathy, hypertension and congestive heart failure as well as the use of concomitant medications such as colchicine, NSAIDs, diuretics and ACE inhibitors. The risk for lesinurad-associated renal toxicity is best evidenced by safety data from the monotherapy Study 303. In this study, treatment with the drug is clearly associated with a marked increase in risk for renal adverse events (18%), including reversible and non-reversible creatinine elevations and serious renal-related adverse events (5%) including acute and chronic renal failure as there were no cases of renal adverse events observed in the placebo group. This risk appears to be dose-dependent, as a higher rate of renal adverse events was observed in subjects treated with LESU400 mg + XOI (12%) as compared to LESU200 mg +XOI (6%) and PBO + XOI (5%) in the three, pivotal lesinurad + XOI studies. A dose-dependent rate of renal adverse events was also seen when these data were examined by concomitant use of allopurinol (Studies 301 and 302). However, this phenomenon was not observed in Study 304 in which both lesinurad + febuxostat treatment groups (9-10%) had higher rates of renal adverse events than placebo (6%). All of the serious renal adverse events (acute and chronic renal failure) that occurred in the lesinurad + XOI treatment groups of Studies 301, 302 and 304 were experienced by patients treated with LESU400 mg + XOI. However, the two patients who developed acute renal failure that required hemodialysis in the safety database submitted in support of lesinurad were taking LESU200 mg +XOI in the extension studies. Unanswered questions remain regarding the true extent of the reversibility of drug's nephrotoxicity particularly since some patients continued to have serum elevations more

than 84 days after discontinuing lesinurad. The introduction of changes to the treatment algorithm for the management of serum creatinine elevations in the pivotal lesinurad + XOI studies occurred once the renal safety signal became apparent in the 6-month monotherapy study. Results of a cystatin C study in subjects who had post-dose dose changes in their serum creatinine levels in the lesinurad monotherapy study suggest that the changes in serum creatinine that occurred over the course of this study are likely to represent a change in GFR rather than a change related to some other factor such as proximal tubule secretion of creatinine. Unfortunately, the results of renal biopsies from patients who developed acute renal failure following exposure to lesinurad failed to provide clarification regarding the etiology of these patients' renal failure.
As a uricosuric agent, kidney stones would be an expected risk. A dose dependent risk for kidney stones was also seen as more subjects in the LESU400 mg + XOI group as compared to the LESU200 mg + XOI group developed kidney stones while participating in the pivotal phase 3 studies. A similar pattern was also observed for the occurrence of serious kidney stones in these trials.

As noted earlier in this review, the administration of uricosuric agents like lesinurad were previously reserved for hyperuricemic patients who were classified as under-excretors of uric acid based on the results from 24-hour urine collections. If the Applicant had identified potential study subjects who were under-excretors of uric acid and designed their pivotal trials around this subpopulation it is possible that the risk-benefit profile of lesinurad might have been more favorable. As such, lesinurad treatment is clearly associated with an increased risk of renal adverse events, including reversible and non-reversible creatinine elevations and serious renal-related adverse events. The risk appears to be dose-dependent, with the highest risk associated with use of lesinurad as monotherapy, without a concomitant xanthine oxidase inhibitor, which is why the Applicant is not pursuing a monotherapy indication for this drug. However, when evaluating the safety concerns specific to the proposed regimen of lesinurad 200 mg daily in combination with a xanthine oxidase inhibitor, the risk of adverse events does not consistently appear to be increased relative to the control group. Therefore, in contrast with higher doses or monotherapy use, the risk/benefit profile of the 200 mg daily dose in combination with XOI is adequately favorable, despite modest efficacy.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

In support of this NDA, the Applicant submitted safety data from a total of 41 clinical studies: 29 phase 1 trials (101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 120, 121, 122, 123, 125, 126, 127, 128, 129, 130, 131, and 132), four phase 2 trials (201, 202, 203, and 204), four phase 3 trials (301, 302,

303, and 304) and three phase 3 extension trials (305, 306 and 307). A tabular summary of these trials can be found in Table 2 in Section 5. Additional interim long term safety data from the ongoing phase 2b combination with allopurinol study 203 and from the ongoing extension studies 306 and 307 provided as of the cut-off date of November 4, 2014 and an update of events of special interest (renal SAEs and CV SAEs) as of the cut-off date of January 30, 2015 were submitted in the 120-day safety update on April 29, 2015 and are included in pertinent areas (deaths, SAEs, renal SAEs, and CV SAEs) of the following discussion.

Safety data from the 41 studies were summarized in the individual trial reports, the Integrated Summary of Safety and the electronic datasets for adverse events, lab data and vital signs. All safety analyses were performed on the double-blind safety population from the 12-month trials (301, 302 and 304) and the multiple-dose phase 2 studies and ongoing extension studies (306 and 307) in gout patients conducted by the Applicant as well as data contained in the 120-day safety update were examined by this safety officer. Monotherapy Study 303, which was a 6-month study, was evaluated separately.

7.1.2 Categorization of Adverse Events

Verbatim terms of AEs recorded in the case report forms (CRF) by investigators were coded by the Applicant using MedDRA dictionary Preferred Term (PT) and System Organ Class (SOC) versions 11.1 through 14.0. Version 14.0 was used for all Phase 3 studies and in the pooled analysis for the Phase 2b and Phase 3 studies that were included in the submission. A listing of all AEs coded in this manner including corresponding verbatim terms as well as differences between MedDRA versions 12.0 and 14.0 relevant to the phase 2b studies were included in the CRF for review. The MedDRA coding of the information generated from clinical trials conducted by the Applicant was generally acceptable. Additionally, the clinical lab and vital sign ranges for clinically significant abnormal results was reviewed and appeared to be appropriate.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

This application contained 12-months of double-blind safety data generated from the following three, phase 3 trials: 301, 302 and 304. These studies were of sufficiently similar design to allow for pooled analyses of the controlled safety data by lesinurad treatment group administered in combination with an XOI. The safety data from the phase 3 monotherapy Trial 303 was not pooled with the other phase 3 studies since the 200 mg dose of lesinurad was not evaluated in that trial and lesinurad was administered without a concomitant XOI (allopurinol or febuxostat). Analyses of safety data were performed on the safety population which was defined as all patients who received at least 1 dose of study medication.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

At the time of data cut-off for the ongoing trials 306 and 307 (November 4, 2014), the extent of exposure to lesinurad for the ten multiple dosing gout studies is shown in **Table 73** below. A total of 1800 patients with gout have been exposed to lesinurad in these trials out of which 949 patients have been treated with the to-be-marketed dose of 200 mg once a day. Approximately 1328 subjects have been exposed to any dose for approximately 6 months, 974 subjects have been exposed to any dose for approximately 48 weeks, and 297 subjects have been exposed to any dose for approximately 96 weeks (2 years). These numbers exceeded minimum safety database recommendations for chronic use products as outlined in the ICH E1A guidance document.

Table 73 – Duration of Lesinurad Exposure in Gout Clinical Trials (201, 202, 203, 301, 302, 303, 304, 305, 306 and 307)

Dose	Number of Subjects	Person-Time (Years)
200 mg	949	855.8
400 mg	1070	953.2
600 Mg	133	129.7
Total:	1800	1939.2

Duration of Exposure:	Number of Subjects
Any Dose	1800
≥4 weeks	1698
≥12 Weeks	1498
≥24 Weeks	1328
≥48 Weeks	974
≥72 Weeks	626
≥96 Weeks	297
≥120 Weeks	123
≥144 Weeks	54
Total:	1800

Total Exposure: 1800 subjects exposed (any dose) for approximately 1939.2-years

Adapted Sponsor's Tables 1.3.2 and 1.2.2; 120-Day Safety Update – Integrated Summary of Safety (ISS)

7.2.2 Explorations for Dose Response

As part of their development program for lesinurad, the Applicant evaluated doses of the drug ranging from 5 mg to 600 mg once daily in healthy volunteers, patients with gout, and special populations with renal insufficiency and hepatic impairment. Pharmacodynamic (PD) data from phase 1 and 2 trials revealed that doses of ≤100 mg once daily of lesinurad were relatively inactive in lowering sUA. However, a dose-

dependent reduction in sUA was observed with doses of 200 mg, 400 mg and 600 mg of lesinurad administered once daily after 7 to 21 days of continuous dosing. In the lesinurad monotherapy study 202, higher proportions of subjects achieved a sUA < 6.0 mg/dL in the 400 mg once daily (28%) and 600 mg once daily (45%) treatment groups as compared to the 200 mg once daily group (7%). However, a marginal difference in sUA lowering efficacy was observed for the 400 mg and 600 mg once daily doses of lesinurad when administered as combination therapy with allopurinol (Study 110). In the dose-ranging, placebo-controlled, phase 2b Study 203 which evaluated doses of 200 mg, 400 mg and 600 mg of lesinurad administered once daily in combination with allopurinol in gout patients with elevated sUA levels, 63% of subjects in the 200 mg lesinurad group, 74% of subjects in the 400 mg lesinurad group, and 79% of subjects in the 600 mg lesinurad group achieved a sUA < 6 mg/dL as compared to 25% of subjects in the placebo group after 4 weeks of treatment. Based on these results, there appeared to be limited additional clinical benefit associated with the 600 mg dose as compared to the 400 mg dose of lesinurad when administered once daily in combination with allopurinol.

The doses of lesinurad to be evaluated in combination with febuxostat were identified via pharmacokinetic/pharmacodynamic (PK/PD) modeling. Based on data from a phase 1 drug-drug interaction trial (Study 105) that evaluated 200 mg of lesinurad when administered with 40 mg of febuxostat in healthy volunteers, the Applicant's PK/PD model estimated that a 200 mg dose of lesinurad in combination with febuxostat 80 mg would result in an intraday average sUA reduction of up to approximately 60% compared to approximately 50% for an 80 mg monotherapy dose of febuxostat after 1 week of treatment. Additional dose explorations with the 400 mg and 600 mg doses of lesinurad when administered in combination with 40 mg and 80 mg doses of febuxostat were conducted during phase 1 PK/PD testing in gout patients which showed approximately a 3% to 5% difference in sUA lowering capability for the 400 mg and 600 mg doses of lesinurad when administered in combination with 80 mg of febuxostat once daily.

In view of lesinurad's short serum half-life of approximately 5 hours, questions regarding the adequacy of the Applicant's dose explorations to support clinical evaluation of the 200 mg once daily and 400 mg once daily doses of lesinurad in the phase 3 studies were raised by the Agency at the EOP2 meeting and again following the identification of the renal toxicity signal in the phase 3 trials. The Applicant's rationale for once-daily dosing in the morning is to avoid nocturnal high concentrations of uric acid when urine pH and volume are low resulting in markedly reduced uric acid solubility and therefore reducing the risk of urinary urate precipitation and stone formation. Because lower nominal doses given more than once daily were not evaluated, it is not clear whether this rationale for using higher doses once daily is justified.

7.2.3 Special Animal and/or In Vitro Testing

The Applicant did not conduct any special animal and/or in vitro testing with lesinurad to support its safety profile.

7.2.4 Routine Clinical Testing

The following clinical and lab testing were conducted at screening and baseline and during study visits at Week 2, Months 1, 2, 3, 4, 5,6, 7, 8, 9, 10 , 11, 12/termination visit and the safety follow-up visit for subjects who did not enter the extension studies except where noted in trials 301, 302, 303 (only through Month 6/termination visit and safety follow-up), 304, 305 (terminated early), 306, 307 submitted in support of lesinurad's safety profile:

- Physical exam and weight (screening and termination visits)
- Vital signs: Pulse, sitting blood pressure, respiratory rate, and temperature
- Complete cell count (CBC) with differential and platelet count, hemoglobulin and hematocrit; PT/PTT
- Serum chemistries; albumin, alkaline phosphatase, ALT, AST, BUN, calcium, bicarbonate, chloride, creatinine, glucose, lactic dehydrogenase, phosphorus, potassium, sodium, direct bilirubin, total bilirubin, total protein, creatine kinase and uric acid
- Urinalysis: including pH, specific gravity, protein, glucose, ketones, nitrite, occult blood, bilirubin, and urobilinogen
- 12-lead ECG: (screening, baseline, Month 6, and Month 12/termination visit)
- Serum pregnancy test (females of childbearing potential only)

Additionally, patients participating in the extension Studies 306 and 307 will have the above clinical and lab testing performed every 2 months following the Month 12 visit until these trials are completed. Overall, the types of clinical lab testing and physical assessments as well as the timing of these assessments were appropriate for the population studied in these trials.

7.2.5 Metabolic, Clearance, and Interaction Workup

In support of this NDA, the Applicant submitted 30 phase 1 and two phase 2 studies conducted in healthy volunteers, Japanese subjects and gout patients that evaluated the pharmacokinetics (PK), pharmacodynamics (PD), and population PK in subjects with renal and hepatic impairment as well as potential drug-drug interactions with lesinurad involving major cytochrome (CYP) P450 enzymes and liver and renal transporters. These biopharmaceutical evaluations showed that lesinurad is predominantly metabolized via the CYP2C9 pathway and is a weak inducer of the CYP3A isoenzyme. Co-administration with CYP2C9 inducers results in an

approximately 50% increase in exposure to lesinurad while co-administration of drugs that are CYP3A substrates may result in a decrease in the efficacy of these agents. Plasma exposures to lesinurad were shown to be approximately 50-70% higher in patients with moderate renal impairment (estimated creatinine clearance of 30-59 mL/min) than in patients with normal renal function (estimated creatinine clearance >60 mL/min). Additional information regarding the results of these studies is presented and discussed in the preceding section 4.4.3 of this review.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

A major concern with the use of uricosuric agents is renal-related toxicity due to crystalluria and an increased risk for development of renal colic (stones) and urate nephropathy. This risk is particularly elevated in patients who are over-excretors of uric acid or who have a history of renal stones. Mitigation efforts to address this concern include maintaining adequate hydration and considering urine alkalinization. These measures were listed as clinical recommendations to study investigators in the lesinurad protocols at baseline, but did not become mandatory until cases of acute renal failure and kidney stones became apparent in the ongoing phase 3 studies raised renal toxicity concerns (protocol amendments 3 and 4 for Studies 301 and 302, amendments 4 and 5 for Study 304, and amendment 4 for Study 303).

7.3 Major Safety Results

All safety analyses were performed on the population who received at least 1 dose of study medication. **Table 74** summarizes adverse events (AEs) that were reported in the lesinurad + XOI pooled safety database for the controlled studies (301, 302, and 304) as well as the 6- month, controlled, lesinurad monotherapy study (303) by treatment group. The majority of the patients in these studies experienced at least 1 AE over the course of the trial. The proportions of subjects experiencing a treatment emergent adverse event (TEAE) were higher in the lesinurad 200 mg + XOI and 400 mg + XOI treatment groups as compared to the PBO + XOI for the pooled, 12-month, controlled studies. The proportions of patients in the 12-month controlled studies who experienced a severe TEAE, a serious AE, or a TEAE leading to study medication discontinuation in the LESU200 mg + XOI treatment group were similar to that of the PBO group. However, higher rates for these TEAEs are observed for the LESU400 mg + XOI treatment group for the 12-month, controlled studies. A similar pattern of higher incidence rates for these TEAEs was also observed for LESU400 mg treatment group as compared to PBO in the 6-month monotherapy study. Numerically more subjects in the LESU400 mg + XOI group in the 12-month controlled studies and in the LESU400 mg group in the 6-month monotherapy study experienced a serious renal adverse event as compared to the placebo groups in these studies. All of the deaths reported during the 12-month controlled studies and the 6-month monotherapy study occurred in

patients randomized to the lesinurad treatment groups with numerically more deaths occurring in patients treated with LESU400 mg +XOI. These deaths will be discussed further below.

Table 74 – Summary of Subjects by Treatment Group Who Experienced Treatment Emergent Adverse Events and Deaths During the 12-Month Placebo Controlled Lesinurad Combination XOI Studies 301, 302 and 304 and the 6-Month Placebo Controlled Lesinurad Monotherapy Study 303 (Safety Population)

	Combined 12-M, Studies 301, 302 and 304				6-M, Monotherapy Study 303	
	PBO + XOI (N=516)	LESU200 + XOI (N=511)	LESU400 + XOI (N=510)	Total LESU +XOI (N=1021)	PBO (N=107)	LESU400 (N=107)
Any Treatment Emergent Adverse Event (TEAE)	363 (70%)	386 (76%)	407 (80%)	793 (78%)	70 (65%)	83 (78%)
Any Severe TEAE	41 (8%)	47 (9%)	59 (12%)	106 (10%)	4 (4%)	16 (15%)
Any Serious TEAE	29 (6%)	24 (5%)	44 (9%)	68 (7%)	4 (4%)	9 (8%)
Any Serious Renal TEAE	4 (1%)	0	8 (2%)	8 (1%)	0	6 (15%)
Any TEAE Leading to Study Medication Discontinuation	28 (5%)	32 (6%)	48 (9%)	80 (8%)	6 (6%)	20 (19%)
Deaths	0	2 (<1%)	3 (1%)	5 (<1%)	0	1 (1%)

Modified Sponsor's Tables 4.1.1.1, 4.8.1.1, 4.9.1.1 and 4.4.1.1 from the Integrated Safety Summary (ISS); Tables 14.3.1.1.a and 14.3.1.5a from Study 303 CSR

7.3.1 Deaths

As of the cut-off date for the 120-day safety follow-up there were a total of 17 deaths reported in the lesinurad clinical development program as follows: 6 deaths reported in the phase 3 placebo-controlled studies (301, 302, 303 and 304), 9 deaths during the phase 3 uncontrolled extension studies (305, 306, and 307), and 2 deaths in phase 1/2 studies (118 and 203). **Table 75** lists these 17 deaths and the 3 deaths that occurred after the screening period and prior to the receipt of the randomized/assigned study medication in the phase 2b and 3 clinical studies 203 and 302 by treatment group. (Note: The 3 deaths that occurred after the screening period and prior to the receipt of the randomized/assigned study medication are included for completeness and will not be discussed further in this review.)

Table 75 – Summary of Subjects Who Died While Participating in Lesinurad Studies

Subject Number	Age/Race /Sex	Cause of Death	Onset	Pertinent History
Double-Blind, Controlled Studies: Lesinurad 200 mg qd + XOI				
304-05064-406	78 yo White Male	Pulseless Electrical Activity (PEA) (Adjudicated MACE)	Day 122	H/O Hyperlipidemia, pulmonary embolism, thrombophlebitis, first degree atrioventricular block, DM, HTN, and stroke. Concomitant Meds: Febuxostat 80 mg qd, colchicine 0.6 mg qd. indomethacin, naproxen sodium, acetylsalicylic acid, and nebivolol hydrochloride. Pt. collapsed after C/O of not feeling well with difficulty breathing after sustaining head trauma post fall. He was pronounced dead due to pulseless electrical activity (PEA) following documentation of no cardiac activity on ultrasound despite cardiopulmonary resuscitation efforts by EMT and ER staff.
301-05376-103	48 yo Black Male	Cardiac Arrest (Adjudicated MACE)	Day 233	H/O CHF, CAHD, LVH, left atrial dilatation, HTN, hypercholesterolemia, DM, chronic renal failure, kidney stones, ↑serum creatinine and obesity. Concomitant Meds: Allopurinol 300 mg qd, isosorbide dinitrate, atorvastatin, furosemide, hydralazine, losartan, glibenclamide, insulin lispro and insulin glargine. Pt. had a witnessed cardiopulmonary arrest and was pronounced dead on arrival at local hospital despite cardiac resuscitation efforts by witness and EMT. No autopsy conducted.
Double-Blind, Controlled Studies: Lesinurad 400 mg qd + XOI				
304-05056-401	71 yo White Male	Congestive Cardiac Failure (Adjudicated MACE)	Day 68 (78)	H/O MI, severe LVH, hypercholesterolemia, chronic atrial fibrillation, obesity, HTN, insomnia, GERD, CKD, peripheral edema, renal embolism, kidney stones, osteoarthritis, unilateral blindness, corneal transplant, S/P multiple fractures and lower back surgery. Concomitant Meds: Febuxostat 80 mg qd, colchicine 0.6 mg qd, carvedilol, potassium chloride, ASA, digoxin, furosemide, metolazone, rimexolone, simvastatin, dabigatran , and mometasone furoate. Pt. was hospitalized on Day 61 for acute cardiac failure and angina pectoris with ↑sCr after ↓furosemide due to leg cramps. He was diuresed and D/C'd when stable on furosemide 80 mg BID. On Day 68 the pt. was re-hospitalized due to exacerbation of CHF with mental status changes, acute prerenal failure and liver injury. Study meds were D/C'd. He was transferred to ICU for treatment that included central line placement, pressor therapy, digoxin, diuretics, intubation and mechanical ventilation. Ejection fraction was 10% C/W severe cardiomyopathy on echocardiogram. CXR was suggestive of LLL pneumonia. Abd. and pelvic CT showed ascites, gaseous distension of large bowel with hepatic parenchymal disease. Blood cultures were positive for alpha hemolytic streptococcus, diphtheroids and coagulase negative staphylococcus. WBC 15 x 10^9/L, sCr 1.29 mg/dL and BUN 72 mg/dL. The case was turned over to the palliative care team. On Day 78 the pt. was extubated and placed on morphine drip and died. No autopsy was performed. Death was attributed acute cardiac failure, arteriosclerotic heart disease, ARF and respiratory failure.

Table 75 – Summary of Subjects Who Died While Participating in Lesinurad Studies (cont.)

Subject Number	Age/Race /Sex	Cause of Death	Onset	Pertinent History
Double-Blind, Controlled Studies: Lesinurad 400 mg qd + XOI (cont.)				
303-05230-308	50 yo Puerto Rican Male	Cause of Death Unknown (Adjudicated MACE)	Day 199	H/O Hypothyroidism, anxiety, depression, hypercholesterolemia, hypertriglyceridemia, intolerance to allopurinol, intervertebral disc protrusion, and tobacco use. Concomitant Meds: colchicine 0.6 mg qd, levothyroxine, alprazolam, bupropion, atorvastatin, Vitamin D and Oxycocet. Pt.'s last study visit was on Day 99 (Month 3 visit). He subsequently missed visits and informed study site he did not want to continue in the trial due to personal reasons. Multiple attempts to contact pt. to return for early termination visit were unsuccessful. Study site learned of his death (Day 199) through emergency contact number. Requests for autopsy report and death certificate were unsuccessful.
302-17006-207	51 yo Maori Male	Gastric Cancer	Day 360	H/O Alpha thalassemia, active chronic gastritis, hypercholesterolemia, hypertriglyceridemia, LVH, current tobacco use and FH of gastric cancer. Concomitant Meds: Allopurinol 300 mg qd, cilazapril, domperidone, omeprazole, hyoscine and metoclopramide. Pt. hospitalized on Day 314 for cachexia and a 25 kg weigh loss over last 10 months. Abdominal CT was suspicious for gastric malignancy (linitis plastica) but gastric and duodenal biopsies were negative for malignancy on gastroscopy. He declined nasogastric feeding and was discharged home and from study on Day 331. Cause of death attributed to gastric carcinoma on Day 360.
302-15003-210	58 yo Asian Male	Pulmonary Edema (Adjudicated MACE)	Day 242	H/O CAD, angina pectoris, S/P CABG, HTN, prior tobacco use. Concomitant Meds; Allopurinol 300 mg qd, colchicine 0.5 mg qd, ASA, atenolol, isosorbide mononitrate and dinitrate, nifedipine, carvedilol, furosemide, ciprofloxacin, prednisone, clopidogrel bisulfate. (**Baseline sCr 1.11 mg/dL**.)Pt. hospitalized on Day 155 for chest pain due to triple vessel CAD and underwent an unsuccessful coronary angioplasty since he was not a candidate for bypass surgery. He was re-hospitalized on Day 191 with a life-threatening MI due to severe triple vessel disease on angiogram. He was treated again medically until stable and discharged on study meds only to be re-hospitalized on Day 211 for evaluation of **↑sCr 3.51 mg/dL and ↑BUN 64 mg/dL**. Denied taking NSAIDs. Renal ultrasound revealed two small renal cysts. No peripheral edema. Nephrology consultant attributed renal impairment due to right-sided renal artery stenosis, HTN, ischemic heart disease, and LV dysfunction and failure as well as possibly study meds. Study med was D/C'd but colchicine and allopurinol continued. **Day 225 sCr 3.57 mg/dL.** On Day 242 he returned to ER C/O CXP and difficult breathing and died as a result of cardiorespiratory failure due to pulmonary edema, HTN and CAHD. No autopsy performed.

Table 75 – Summary of Subjects Who Died While Participating in Lesinurad Studies (cont.)

Subject Number	Age/Race /Sex	Cause of Death	Onset	Pertinent History
Extension Studies 306 and 307: Lesinurad 200 mg qd				
307-05192-411	53 yo Black Male	Subarachnoid hemorrhage (Adjudicated MACE)	Day 373	H/O HTN, moderate renal insufficiency, BPH, TIA, peripheral edema and obesity. Concomitant Meds: Febuxostat 80 mg qd and colchicine 0.6 mg qd, amlodipine, furosemide, lisinopril, metoprolol, terazosin. Pt. completed 12-months of treatment with lesinurad 200 mg qd + Febuxostat in study 304 and enrolled in extension study 307 where he continued the same study medications. On day 41 of study 307 he was hospitalized after suffering a small occipital infarct that progressed to a massive subarachnoid hemorrhage thought to be secondary to ruptured left posterior communicating artery aneurysm. The pt. was declared brain dead and died on Day 41 after being removed from life support. No autopsy was performed.
306-05395-210	62 yo White Male	Ischemic Cardio-myopathy	Day 386 (Day 49 of lesinurad treat-ment)	H/O HTN, DM, myocardial infarction, GERD, obesity, hypercholesterolemia, hypertriglyceridemia, and prior tobacco use. Concomitant Meds: ASA, amitriptyline, furosemide, insulin, Lisinopril, metformin, metoprolol, pravastatin, saxagliptin hydrochloride, zolpidem tartrate, and naproxen. Pt. had completed 12-months of treatment with PBO + allopurinol in study and initiated treatment with lesinurad 200 mg qd + allopurinol when he enrolled in extension study 306. On Day 8 of study 306, he was hospitalized for treatment of methicillin-sensitive staph aureus sepsis secondary to diabetic foot ulcer and wrist cellulitis. His hospital course was complicated by acute renal failure, worsening of type II DM, metabolic encephalopathy, hypothyroidism, hypersensitivity vasculitis, pulmonary edema and respiratory failure as a result of congestive heart failure secondary to acute myocardial infarction. Treatment included antibiotics, diuresis, haloperidol, levothyroxine, skin biopsy, surgical debridement of foot ulcer, and electrocardioversion for SVT. On Day 49 he was transferred to a rehab facility where he was found cyanotic, unresponsive and pulseless in bed. CPR was initiated but discontinued due to DNR order. No autopsy was performed.
306-05185-117	65 yo White Male	Coronary Artery Disease (CAD)	Day 519	H/O Hypercholesterolemia, HTN, heart failure, heart murmur, and S/P two myocardial infarctions (1994 and 2008). Concomitant Meds: Allopurinol 300 mg qd, furosemide, carvedilol, and rosuvastatin. Pt. completed 12-months of treatment with lesinurad 200 mg qd + allopurinol in study 301, and continued same study treatment when he enrolled in extension study 306. Pt. died at home. Cause of death attributed to coronary artery disease on death certificate. No autopsy was performed.

Table 75 – Summary of Subjects Who Died While Participating in Lesinurad Studies (cont.)

Subject Number	Age/Race /Sex	Cause of Death	Onset	Pertinent History
Extension Studies 306 and 307: Lesinurad 200 mg qd (cont.)				
306-05285-104	51 yo White Male	Subarachnoid hemorrhage (Adjudicated MACE)	Day 636	H/O Cholecystitis, pancreatitis, osteoarthritis, bursitis and current tobacco use. Concomitant Meds: Allopurinol 300 mg qd, fenofibrate, lisinopril, celecoxib, prednisone, orthoxicol, cortisone and indomethacin. Pt. had completed 12-months of treatment with PBO + allopurinol in study 301 and initiated treatment with lesinurad 200 mg qd + allopurinol when he enrolled in extension study 306. On Day 636, he was hospitalized after suffering a subarachnoid hemorrhage documented on head CT. On Day 649, the pt. died as the result of a total occlusion of the left internal carotid artery due to thrombosis.
Extension Studies 305, 306, and 307: Lesinurad 400 mg qd				
306-05097-115	37 yo White Male	Pulmonary Embolism (Adjudicated MACE)	Day 373 (Day 39 of LESU400 mg qd)	H/o Obesity. Concomitant Meds: Allopurinol 300 mg qd, colchicine 0.6 mg qd and Vitamin B12 supplement. Pt. had completed 12 months of treatment PBO + allopurinol in Study 301 and initiated treatment with lesinurad 400 mg qd + allopurinol when he enrolled in extension study 306. On Day 30 of Study 306, he developed fever and chills with cough productive of yellow sputum. Over the next 7 days, he developed severe shortness of breath and suffered a cardiopulmonary arrest while being transported to ER where he died despite resuscitation efforts. On autopsy, the pt. was found to have pulmonary thromboembolism that was attributed to his morbid obesity.
305-05264-302	62 yo White Male	Cause of Death Unknown (Adjudicated MACE)	Day 380 (?)	H/O HTN, third degree atrioventricular block, hypercholesterolemia, hyperglycemia, S/P hip replacement with prior tobacco use. Concomitant Meds: ASA, atorvastatin, Lisinopril, amlodipine, diphenhydramine, and metformin. After completing 6 months of PBO treatment in Study 303, the pt. was found to have asymptomatic supraventricular bradycardia on EKG at baseline visit for extension Study 305 when he initiated treatment with lesinurad 400 mg qd. On Day 47 he was hospitalized for evaluation of HTN and asymptomatic third degree heat block. W/U included abnormal stress test with PVCs and ischemia, and TTE and CT angiography which showed LVH, mitral annular calcification and valve thickening, trivial stenosis and mild/moderate triple vessel CAD. Pt. had a pacemaker inserted based on the study EKG conducted on Day 169. In [redacted] (b) (6) study site was informed that the pt. had been found dead at home on an unknown date earlier that month. Multiple attempts to obtain information regarding his death were unsuccessful.

Table 75 – Summary of Subjects Who Died While Participating in Lesinurad Studies (cont.)

Subject Number	Age/Race /Sex	Cause of Death	Onset	Pertinent History
Extension Studies 305, 306, and 307: Lesinurad 400 mg qd (cont.)				
306-03006-203	60 yo White Male	Ischemic Stroke (Adjudicated MACE)	Day 460 or 463	H/O Ischemic heart disease, HTN, DM, Gilbert's syndrome, hypercholesterolemia, obesity, varicose veins and S/P laryngeal cancer. Concomitant Meds: Allopurinol 300 mg qd, ASA, atorvastatin, carvedilol, indapamide, ketoprofen, metformin, ramipril, spironolactone, valsartan and amlodipine. Pt. completed 12-months of treatment with lesinurad 400 mg qd + allopurinol in study 302 and entered extension study 306 where he continued his study medications. On Day 119 of Study 306, pt. was hospitalized for left sided hemiparesis due to a nonhemorrhagic stroke on head CT. An extensive ischemic stroke occurred following administration of thrombolytic therapy documented on second head CT. Pt. died on Day 122 of extension study as a result of cardiopulmonary arrest secondary to ischemic stroke.
306-05110-113	53yo White Male	Suicide	Day 553 (Day 223 of LESU400 mg qd)	H/O Cardiac murmur, obesity, astigmatism, metabolic syndrome, S/P hip fracture with arthroplasty, and S/P road traffic accident. Concomitant Meds: Allopurinol 300 mg qd and unspecified herbal supplement. Pt. had completed 12-months of treatment with PBO + allopurinol in study 301 and initiated treatment with lesinurad 400 mg qd + allopurinol when he enrolled in study 306. On Day 223 of study 306, he committed suicide by self-inflicted gunshot wound. Toxicology test results included blood ethanol level of 0.06 g/dL and negative urine drug screen. According to coroner's investigation the pt. was reportedly being blackmailed and had a remote suicide attempt.
306-10005-216	76 yo White Male	Cerebral infarct (Adjudicated MACE)	Day 652	H/O HTN, myocardial infarction, angina pectoris, S/P prostatectomy, and S/P chemical burns to the eye. Concomitant Meds: allopurinol 300mg qd, lisinopril, pentoxifylline and naftidrofuryl. Pt. completed 12-months of treatment in study 302 with lesinurad 400 mg qd + allopurinol that was continued when he enrolled in study 306. Pt. died on Day 655 following hospitalization for cerebrovascular accident. Autopsy revealed death was due to cerebral infarct as a result of thrombosis of pre-cerebral arteries.

Table 75 – Summary of Subjects Who Died While Participating in Lesinurad Studies (cont.)

Subject Number	Age/Race /Sex	Cause of Death	Onset	Pertinent History
Phase 1 and 2 Studies (Lesinurad 200-600 mg)				
118-001-009	57 yo Male	Suicide	Day 45	H/O Hepatitis C, insomnia, and deafness. No information regarding concomitant meds. Following the administration of a single dose of 400 mg of lesinurad in study 118, the pt. experienced chills, diffuse arthralgias, and nausea on Day1. He committed suicide 45 days later.
203-0309-005	41 yo White Male	Cerebral Embolism	Day 169	H/O HTN, hyperlipidemia, obesity, avascular necrosis of bilat. hips, and S/P total hip replacement. Concomitant Meds: Allopurinol 200 mg qd and colchicine 0.5 mg qd. Pt. completed the core study 203 treatment with lesinurad 200 mg qd and entered the double-blind extension. He underwent dose titration every 4 weeks until a dose of 600 mg qd of lesinurad was reached. On Day 169, the pt. was found dead at home. Autopsy was performed and cause of death was attributed to cerebral embolism.
Deaths Reported Prior to Receipt of Randomized Study Medications				
203-0401-111*	64 yo White Male	Myocardial Infarction*	--	H/O Hyperlipidemia, DM, HTN, and obesity. Concomitant Meds: Allopurinol and colchicine. Pt. suffered a fatal myocardial infarction after having been randomized to Cohort 2 but prior to receiving study medications.
302-05001-206	54 yo White Male	Cause of Death Unknown (Adjudicated MACE)	--	H/O CHF, cardiomyopathy, CAD, atrial fibrillation, shortness of breath, angina pectoris, HTN, obesity, sleep apnea, bilat. LE edema, depression, left pulmonary vein stenosis and hepatic steatosis. Concomitant Meds: Allopurinol 300 mg qd, lisinopril, metoprolol, sildenafil, and prednisone. Study site learned of his death through obituary notice. Pt. reportedly died in his sleep. No autopsy performed.
302-15019-203	57 yo White Male	Post-Surgical Complications Following Hernia Repair (Adjudicated non-MACE)	--	H/O HTN, peptic ulcer disease, hiatal hernia and prior tobacco use. Concomitant Meds: HCTZ, nifedipine and omeprazole. Pt. was considered a screening failure since he refused to adhere to study protocol visit schedule. He was withdrawn from the trial before receiving study medications. He died approximately 30 days post-study withdrawal due to post-surgical complications (leaking bowels) following hernia repair surgery.

H/O = History of; C/O = Complained of; Pt.= Patient; DM= Diabetes mellitus; HTN=Hypertension; ER= Emergency room; CHF= Congestive heart failure; CAHD = Coronary arterial heart disease; LVH = Left ventricular hypertrophy; EMT= Emergency medical technicians; MI= Myocardial infarction; GERD= Gastroesophageal reflux disease; ASA= Aspirin, sCr= serum creatinine; D/C'd Discontinued; CAD= Coronary artery disease; S/P = Status post; CABG= Coronary arterial bypass; CXP =Chest pain; BPH Benign prostatic hypertrophy; TIA = Transient ischemic attack; SVT= Supraventricular tachycardia; DNR = Don not resuscitate TTE= Transesophageal echocardiogram; PVC= Premature ventricular contractions; LE= Lower extremity; HCTZ= Hydrochlorothiazide
*Subject 203-0309-005 died of a myocardial infarction prior to being randomized into Study 203. No information was included in the Cardiovascular Endpoints Committee Adjudication (CEAC) report if this case had been adjudicated.

Overall, the types of deaths listed in the preceding table are consistent with the risks related to the underlying and concomitant medical conditions reported by these subjects. Fourteen out of the 17 deaths that occurred in lesinurad safety database were

adjudicated as MACE events that will be discussed later in this review. Of the 3 remaining deaths, 1 was due to gastric cancer in a patient (Subject 302-17006-207) with a family history of this disease and 2 (Subjects 118-001-009 and 306-05110-113) were due to suicides. Subject 118-001-009 committed suicide 42 days after having completed a single dose phase 1 study of lesinurad while Subject 306-05110-113 reportedly had mitigating social circumstances including a remote suicide attempt as per the coroner's report. It is doubtful that exposure to lesinurad played a role in the deaths of these three subjects.

As noted in the preceding **Table 74**, there is a consistent overall numeric imbalance against lesinurad in deaths that occurred during the controlled portions of the phase 3 trials. However, as shown in **Table 76** the exposure-adjusted incidence rates for death in the lesinurad groups were low overall, with highly overlapping confidence intervals, making it difficult to draw definitive conclusions.

Table 76- Exposure-Adjusted Incidence of Death in Studies 301, 302, 303, and 304

	Combined 12-M, Studies 301, 302 and 304				6-M, Monotherapy Study 303	
	PBO+ XOI	LESU200 mg + XOI	LESU400 mg + XOI	Total Lesinurad + XOI	PBO	LESU400 mg
Number of Subjects	516	511	510	1021	107	107
Subject-Year	421.3	414.6	413	827.5	47.0	44.9
Number of deaths	0	2	3	5	0	1
Death Rate/100 Subject-Years	0	0.48	0.73	0.60	0	2.23
95% Confidence Intervals	(0.00, 0.88)	(0.06,1.74)	(0.15, 2.12)	(0.20, 1.41)	(0.00, 7.85)	(0.06,12.42)

Modified Sponsor's Table 2; submitted on August 19, 2015.; Updated in information response dated Aug. 26, 2015

Analyses that incorporate the uncontrolled-long term extension data are difficult to interpret, given that there may be a bias related to the non-random nature of patients remaining in the study, as they may be in the best condition or those whom are tolerating treatment the best. Furthermore, no new safety signals were identified in the long-term extension data. Therefore analyses from the long-term extension are not presented here.

7.3.2 Nonfatal Serious Adverse Events

Table 77 is an abridged summary of the serious adverse events (SAEs) observed during the controlled lesinurad studies by MedDRA system organ class and preferred term. Overall, the proportions of patients who had a SAE were similar for the placebo and LESU200 mg + XOI treatment groups but higher in the LESU400 mg + XOI

treatment group in the pooled safety database for the 12-month, controlled, combination studies. Similarly, a much higher proportion of SAEs was also reported by subjects in the LESU400 mg treatment group as compared to placebo in the 6-month, lesinurad monotherapy study. Numeric imbalances in the number of SAEs were noted with higher incidences in the LESU400 mg + XOI treatment group versus placebo in the following system organ classes (SOC): Cardiac Disorders, Renal and Urinary Disorders, and Metabolism and Nutrition Disorders. A numeric imbalance is also observed for the LESU200 mg + XOI group compared to placebo in the Cardiac Disorders SOC. In the 6-month monotherapy study, the imbalance in SAEs is primarily due to the number of SAEs listed under the Renal and Urinary Disorders SOC observed in LESU400 mg treated subjects. Serious cardiac and renal events will be discussed separately in other sections of this review.

The higher rate of SAEs under the Metabolism and Nutritional Disorder SOC are due to the number of cases of serious gout attacks experienced by subjects in the LESU400 mg +XOI group. This is not an unexpected finding due to the increase in risk for gout flares as a result of fluctuations in serum uric acid associated with urate lowering therapy.

Table 77 – Serious Adverse Events (SAEs) by MedDRA System Organ Class/Preferred Term in Pooled Population from 12-Month Phase 3 Studies 301, 302 and 303 and the 6-Month Phase 3 Monotherapy Study 303 by Treatment Group (Safety Population)

System Organ Class/ Preferred Term	Combined 12-M, Studies 301, 302 and 304				6-M, Monotherapy Study 303	
	PBO + XOI (N=516)	LESU200 +XOI (N=511)	LESU400 + XOI (N=510)	Total LESU +XOI (N=1021)	PBO (N=107)	LESU400 (N=107)
Any Serious Adverse Event	**29 (6%)**	**24 (5%)**	**44 (9%)**	**68 (7%)**	**4 (4%)**	**9 (8%)**
Infections and Infestations	**6 (1%)**	**4 (1%)**	**6 (1%)**	**10 (1%)**	**2 (2%)**	**0**
Pneumonia	2 (<1%)	2 (<1%)	1 (<1%)	3 (<1%)	0	0
Bronchopneumonia	0	0	1 (<1%)	1 (<1%)	0	0
Cellulitis	1 (<1%)	0	1 (<1%)	1 (<1%)	0	0
Empyema	0	1 (<1%)	0	1 (<1%)	0	0
Escherichia Infection	0	0	1 (<1%)	1 (<1%)	0	0
Influenza	0	1 (<1%)	0	1 (<1%)	00	0
Pyelonephritis Chronic	0	0	1 (<1%)	1 (<1%)	0	0
Sinobronchitis	0	1 (<1%)	0	1 (<1%)	0	0
Vulval Abscess	0	0	1 (<1%)	1 (<1%)	0	0
Vulval Cellulitis	0	0	1 (<1%)	1 (<1%)	0	0
Abscess Limb	2 (<1%)	0	0	0	0	0
Appendicitis	1 (<1%)	0	0	0	0	0
Diverticulitis	1 (<1%)	0	0	0	1 (1%)	0
Gastroenteritis	0	0	0	0	1 (1%)	0
Neoplasms Benign, Malignant and Unspecified	**3 (1%)**	**2 (<1%)**	**5 (1%)**	**7 (1%)**	**0**	**1 (1%)**
Basal Cell Carcinoma	0	0	2 (<1%)	2 (<1%)	0	0
Gastric Cancer	0	0	1 (<1%)	1 (<1%)	0	0
Metastatic Neoplasm	0	0	1 (<1%)	1 (<1%)	0	0
Ovarian Adenoma	0	1 (<1%)	0	1 (<1)	0	1 (1%)
Ovarian Epithelial Cancer	0	0	0	0	0	0
Parathyroid Tumor Benign	0	1(<1%)	0	1 (<1)	0	0
Prostate Cancer	1 (<1%)	0	1(<1%)	1 (<1)	0	0
Lung Neoplasm Malignant	1 (<1%)	0	0	0	0	0
Pancreat. Neuroend. Tumor	1 (<1%)	0	0	0	0	0
Metabolism and Nutrit. Dis.	**0**	**1 (1%)**	**5 (1%)**	**7 (1%)**	**1 (1%)**	**1 (1%)**
Gout	0	0	4 (1%)	4 (<1%)	1 (1%)	1 (1%)
Dehydration	0	1 (<1%)	1 (<1%)	2 (<1%)	0	0
Type 2 Diabetes Mellitus	0	1 (<1%)	0	1 (<1%)	0	0
Psychiatric Disorders	**1 (<1%)**	**1 (<1%)**	**1 (<1%)**	**2 (<1%)**	**0**	**0**
Depression	0	1 (<1%)	0	1 (<1%)	0	0
Dissociative Disorder	0	0	1 (<1%)	1 (<1%)	0	0
Suicide Attempt	1 (<1%)	0	0	0	0	0
Nervous System Disorders	**6 (1%)**	**0**	**0**	**0**	**0**	**1 (1%)**
Ear and Labyrinth Dis.	**1 (<1%)**	**0**	**1 (<1%)**	**1 (<1%)**	**0**	**0**

Modified Sponsor's Tables 4.8.1.1 from the Integrated Summary of Safety (ISS) and Table 14.3.1.1.15.a. from the CSR for Study 303

Table 77 – Serious Adverse Events (SAEs) by MedDRA System Organ Class/Preferred Term in Pooled Population from 12-Month Phase 3 Studies 301, 302 and 303 and the 6-Month Phase 3 Monotherapy Study 303 by Treatment Group (Safety Population) (cont.)

System Organ Class/ Preferred Term	Combined 12-M, Studies 301, 302 and 304				6-M, Monotherapy Study 303	
	PBO + XOI (N=516)	LESU200 +XOI (N=511)	LESU400 + XOI (N=510)	Total LESU +XOI (N=1021)	PBO (N=107)	LESU400 (N=107)
Cardiac Disorders	**2 (1%)**	**10 (2%)**	**14 (3%)**	**24 (2%)**	**2 (2%)**	**0**
Acute Myocardial Infarction	0	1 (<1%)	4 (1%)	5 (1%)	0	0
Coronary Artery Disease	0	3 (1%)	2 (<1%)	5 (1%)	1 (1%)	0
Cardiac Failure Congestive	0	1 (<1%)	3 (1%)	4 (<1%)	0	0
Myocardial Infarction	1 (<1%)	0	3 (1%)	3 (<1%)	0	0
Angina Pectoris	0	1(<1%)	1 (<1%)	2 (<1%)	0	0
Atrial Fibrillation	0	2 (<1%)	0	2 (<1%)	0	0
Atrial Flutter	0	0	1 (<1%)	1 (<1%)	0	0
Cardiac Arrest	0	1(<1%)	0	1 (<1%)	0	0
Cardiac Failure Acute	0	0	1 (<1%)	1 (<1%)	0	0
Intracardiac Thrombus	0	0	1 (<1%)	1 (<1%)	0	0
Myocardial Ischemia	0	1(<1%)	0	1 (<1%)	0	0
Pericardial Effusion	0	0	0	0	1 (1%)	0
Pulseless Electrical Activity	0	1 (<1%)	0	1 (<1%)	0	0
Arrhythmia	1 (<1%)	0	0	0	0	0
Vascular Disorders	**0**	**0**	**1 (<1%)**	**1 (<1%)**	**0**	**0**
Respiratory, Thoracic and Mediatinal Disorders	**1 (<1%)**	**0**	**1 (<1%)**	**1 (<1%)**	**0**	**0**
Gastrointestinal Disorders	**2 (<1%)**	**2 (<1%)**	**2 (<1%)**	**4 (<1%)**	**0**	**0**
Hepatobiliary Disorders	**0**	**2 (<1%)**	**1 (<1%)**	**3 (<1%)**	**0**	**0**
Cholecystitis Acute	0	1 (<1%)	1 (<1%)	2 (<1%)	0	0
Bile Duct Stone	0	1 (<1%)	0	1 (<1%)	0	0
Musculoskeletal and Connective Tissue Dis.	**2 (<1%)**	**3 (1%)**	**4 (1%)**	**7 (1%)**	**0**	**0**
Osteoarthritis	2 (<1%)	0	2 (<1%)	2 (<1%)	0	0
Arthralgia	0	1 (<1%)	0	1 (<1%)	0	0
Back Pain	0	1 (<1%)	0	1 (<1%)	0	0
Flank Pain	0	1 (<1%)	0	1 (<1%)	0	0
Intervert.Disc Degeneration	0	0	1 (<1%)	1 (<1%)	0	0
Spinal Column Stenosis	0	0	1 (<1%)	1 (<1%)	0	0
Joint Contracture	1 (<1%)	0	0	0	0	0
Renal and Urinary Disorders	**4 (1%)**	**0**	**8 (2%)**	**8 (1%)**	**0**	**6 (6%)**
Nephrolithiasis	1 (<1%)	0	2 (<1%)	2 (<1%)	0	0
Renal Failure Acute	2 (<1%)	0	2 (<1%)	2 (<1%)	0	2 (2%)
Calculus Ureteric	0	0	1 (<1%)	1 (<1%)	0	1 (1%)
Renal Failure	0	0	1 (<1%)	1 (<1%)	0	2 (2%)
Renal Failure Chronic	0	0	1 (<1%)	1 (<1%)	0	0
Renal Impairment	0	0	1 (<1%)	1 (<1%)	0	1 (1%)
Stag Horn Calculus	0	0	1 (<1%)	1 (<1%)	0	0
Urinary Retention	1 (<1%)	0	0	0	0	0
Gen. Dis. and Adm. Site Cond.	**2 (<1%)**	**2 (<1%)**	**1 (<1%)**	**3 (<1%)**	**0**	**1 (1%)**
Injury, Poisoning and Procedural Complications	**3 (1%)**	**3 (1%)**	**1 (<1%)**	**4 (<1%)**	**0**	**0**

Modified Sponsor's Tables 4.8.1.1 from ISS and Table 14.3.1.1.15.a. from the CSR for Study 303

In the pooled 12-month, controlled studies, the exposure-adjusted incidence rate for SAEs for the LESU400 mg + XOI group was approximately 1.5-2 times higher as for the LESU200 mg +XOI subjects and placebo subjects (LESU400 mg +XOI: 11.2 SAEs/100 subject-years; LESU200 mg + XOI group: 6.0 SAEs/100 subject-years; and placebo group: 7.1 SAEs/100 subject-years). Similarly, in the 6-monotherapy study, the exposure-adjusted incidence rate for SAEs for the LESU400 mg group was nearly 2.5 times higher as for placebo treated subjects (LESU400 mg: 21.8 SAEs/ 100 subject-years; placebo: 8.8 SAEs/100 subject-years). This apparent increased risk for serious adverse events with the 400 mg dose of lesinurad with or without concomitant XOI is concerning particularly in light of the marginal efficacy observed. No other safety signals were identified on review of these data separately by XOI inhibitor (allopurinol or febuxostat), or the data collected from the ongoing long term extension studies (including the 120-day safety follow-up) or phase 1 and 2 studies.

7.3.3 Dropouts and/or Discontinuations

Table 78 summarizes adverse events (AEs) by system organ class and preferred term that resulted in patients discontinuing from the controlled lesinurad studies. Overall, the proportions of patients who discontinued due to an AE were similar for the placebo and LESU200 mg + XOI treatment groups as compared to the LESU400 mg + XOI treatment group in the pooled safety database for the 12-month, controlled, studies (301, 302 and 304). A much higher proportion of subjects withdrew due to an AE in the LESU400 mg treatment group as compared to placebo in the 6-month, monotherapy study (303). Examination of the data displayed in this table reveals Renal and Urinary Disorders, Musculoskeletal and Connective Tissue Disorders, and Investigations, General Disorders and Administration Site Conditions and Gastrointestinal Disorders were the most common types of AEs resulting in patients withdrawing from the 12-month, controlled studies (301, 302 and 304). In the 6-month monotherapy study 303, a similar pattern was observed with the most common types of AEs resulting in subjects withdrawing in the Renal and Urinary Disorders, Musculoskeletal and Connective Tissue Disorders, Gastrointestinal Disorders, and General Disorders and Administration Site Conditions.

The higher rate of discontinuations in the Renal and Urinary Disorders SOC were due to cases of renal failure and renal impairment in the LESU400 mg with/without XOI treatment groups as compared to placebo in these studies. More subjects in the 400 mg lesinurad treatment groups also withdrew due to myalgias, back pain, and pain in the extremity than in the placebo groups. The higher withdrawal rate for the Investigations SOC in the pooled safety database for the 12-month, controlled studies was primarily due to increased blood creatinine levels in the LESU400 mg + XOI treatment group versus placebo. This is not an unexpected finding since the protocols for studies 301, 302, and 304 were amended to withdraw patients whose serum creatinine levels became elevated following the observation of nephrotoxicity in the monotherapy study

303. Numerically more subjects treated with higher doses of lesinurad withdrew due to Gastrointestinal Disorders as a result of nausea and upper abdominal pain in the LESU400 mg + XOI treatment group in the 12-month, controlled studies and diarrhea in the 400 mg lesinurad treatment group in the 6-month monotherapy study. However, no discernable pattern is observed for the LESU200 mg + XOI treatment group for this SOC. Numerically more lesinurad treated patients withdrew from the controlled studies due to General Disorders and Administration Site Conditions. Additional review of the AEs listed under this SOC does not reveal any discernable pattern. Review of these data separately by XOI (allopurinol and febuxostat) and collected from the ongoing long term extension studies and the phase 1 and 2 studies did not identify any other safety concerns.

Table 78 – Treatment Emergent Adverse Events (TEAE) Leading to Discontinuation of Randomized Study Medication by MedDRA System Organ Class/Preferred Term in Pooled Population from 12-Month Phase 3 Studies 301, 302 and 303 and the 6-Month Phase 3 Monotherapy Study 303 by Treatment Group (Safety Population)

System Organ Class/ Preferred Term	Combined 12-M, Studies 301, 302 and 304				6-M, Monotherapy Study 303	
	PBO + XOI (N=516)	LESU200 + XOI (N=511)	LESU400 + XOI (N=510)	Total LESU + XOI (N=1021)	PBO (N=107)	LESU400 (N=107)
Any TEAE Leading to Discont. of Randomized Study Meds	**28 (5%)**	**32 (6%)**	**48 (9%)**	**80 (8%)**	**6 (6%)**	**20 (19%)**
Infections and Infestations	**0**	**1 (<1%)**	**0**	**1 (<1%)**	**0**	**0**
Pneumonia	0	1 (<1%)	0	1 (<1%)	0	0
Neoplasms Benign, Malignant and Unspecified	**1 (<1%)**	**0**	**2 (<1%)**	**2 (<1%)**	**0**	**1 (1%)**
Basal Cell Carcinoma	0	0	1 (<1%)	1 (<1%)	0	0
Gastric Cancer	0	0	1 (<1%)	1 (<1%)	0	0
Lung Neoplasm Malignant	1 (<1%)	0	0	0	0	0
Ovarian Epithelial Cancer	0	0	0	0	0	1 (1%)
Blood and Lymph. Syst. Dis.	**1 (<1%)**	**1 (<1%)**	**0**	**1 (<1%)**	**0**	**0**
Metabolism and Nutrition Dis.	**0**	**1 (<1%)**	**3 (1%)**	**4 (<1%)**	**0**	**0**
Diabetes Mellitus Inadeq. Cont.	0	0	1 (<1%)	1 (<1%)	0	0
Gout	0	0	1 (<1%)	1 (<1%)	0	0
Hypertriglyceridemia	0	0	1 (<1%)	1 (<1%)	0	0
Type 2 Diabetes Mellitus	0	1 (<1%)	0	1 (<1%)	0	0
Psychiatric Disorders	**0**	**0**	**1 (<1%)**	**1 (<1%)**	**0**	**0**
Confusional State	0	0	1 (<1%)	1 (<1%)	0	0
Nervous System Disorders	**4 (1%)**	**3 (1%)**	**5 (1%)**	**8 (1%)**	**2 (2%)**	**1 (1%)**
Headache	1 (<1%)	1 (<1%)	2 (<1%)	3 (<1%)	2 (2%)	0
Dizziness	1 (<1%)	0	2 (<1%)	2 (<1%)	0	1 (1%)
Paresthesia	0	0	1 (<1%)	1 (<1%)	0	0
Sciatica	0	1 (<1%)	0	1 (<1%)	0	0
Syncope	0	1 (<1%)	0	1 (<1%)	0	0
Cerebrovascular Accident	1 (<1%)	0	0	0	0	0
Subarachnoid Hemorrhage	1 (<1%)	0	0	0	0	0
Eye Disorders	**1 (<1%)**	**0**	**1 (<1%)**	**1 (<1%)**	**1 (1%)**	**0**
Ear and Labyrinth Disorders	**1 (<1%)**	**0**	**1 (<1%)**	**1 (<1%)**	**0**	**0**
Cardiac Disorders	**2 (<1%)**	**3 (1%)**	**3 (1%)**	**6 (1%)**	**1 (1%)**	**0**
Acute Myocardial Infarction	0	0	1 (<1%)	1 (<1%)	0	0
Cardiac Arrest	0	1 (<1%)	0	1 (<1%)	0	0
Cardiac Failure Congestive	0	0	1 (<1%)	1 (<1%)	0	0
Coronary Artery Disease	0	1 (<1%)	0	1 (<1%)	0	0
Myocardial Infarction	1 (<1%)	0	1 (<1%)	1 (<1%)	0	0
Pulseless Electrical Activity	0	1 (<1%)	0	1 (<1%)	0	0
Atrial Fibrillation	1 (<1%)	0	0	0	0	0
Angina Pectoris	0	0	0	0	1 (1%)	0
Vascular Disorders	**0**	**0**	**1 (<1%)**	**1 (<1%)**	**0**	**0**
Flushing	0	0	1 (<1%)	1 (<1%)	0	0
Respiratory, Thoracic and Mediastinal Disorders	**2 (<1%)**	**0**	**1 (<1%)**	**1 (<1%)**	**1 (1%)**	**0**

Modified Sponsor's Tables 4.9.1.1. and14.3.1.14.b from the ISS and Study 303 CSR

Table 78 – Treatment Emergent Adverse Events (TEAE) Leading to Discontinuation of Randomized Study Medication by MedDRA System Organ Class/Preferred Term in Pooled Population from 12-Month Phase 3 Studies 301, 302 and 303 and the 6-Month Phase 3 Monotherapy Study 303 by Treatment Group (Safety Population) (cont.)

System Organ Class/ Preferred Term	Combined 12-M, Studies 301, 302 and 304				6-M, Monotherapy Study 303	
	PBO + XOI (N=516)	LESU200 + XOI (N=511)	LESU400 + XOI (N=510)	Total LESU + XOI (N=1021)	PBO (N=107)	LESU400 (N=107)
Any TEAE Leading to Discont. of Randomized Study Meds	**28 (5%)**	**32 (6%)**	**48 (9%)**	**80 (8%)**	**6 (6%)**	**20 (19%)**
Gastrointestinal Disorders	**2 (<1%)**	**4 (1%)**	**4 (1%)**	**8 (1%)**	**2 (2%)**	**4 (4%)**
Nausea	0	1 (<1%)	2 (<1%)	3 (<1%)	0	1 (1%)
Abdominal Pain Upper	1 (<1%)	0	2 (<1%)	2 (<1%)	0	0
Abdominal Pain	0	1 (<1%)	0	1 (<1%)	0	1 (1%)
Diarrhea	1 (<1%)	1 (<1%)	0	1 (<1%)	0	2 (2%)
Gastroesophageal Reflux Dis.	0	1 (<1%)	0	1 (<1%)	1 (1%)	0
Abdominal Discomfort	0	0	0	0	1 (1%)	1 (1%)
Dry Mouth	0	0	0	0	1 (1%)	0
Hepatobiliary Disorders	**0**	**1 (<1%)**	**1 (<1%)**	**2 (<1%)**	**0**	**0**
Cholecystitis Acute	0	1 (<1%)	0	1 (<1%)	0	0
Liver Injury	0	0	1 (<1%)	1 (<1%)	0	0
Skin and Subcut. Tiss. Dis.	**1 (<1%)**	**3 (1%)**	**1 (<1%)**	**4 (<1%)**	**0**	**1 (1%)**
Pruritus	0	2 (<1%)	0	2 (<1%)	0	0
Rash	0	1 (<1%)	1 (<1%)	2 (<1%)	0	0
Dermatitis	0	1 (<1%)	0	1 (<1%)	0	0
Hemorrhagic Subcutaneous	1 (<1%)	0	0	0	0	0
Psoriasis	0	0	0	0	0	1 (1%)
Musculoskeletal and Connective Tiss. Disorders	**2 (<1%)**	**3 (1%)**	**9 (2%)**	**12 (1%)**	**3 (3%)**	**3 (3%)**
Myalgia	0	1 (<1%)	3 (1%)	4 (<1%)	0	1 (1%)
Back Pain	1 (<1%)	1 (<1%)	2 (<1%)	3 (<1%)	1 (1%)	0
Flank Pain	0	1 (<1%)	1 (<1%)	2 (<1%)	0	1 (1%)
Pain in Extremity	0	0	2 (<1%)	2 (<1%)	0	0
Osteonecrosis	0	0	1 (<1%)	1 (<1%)	0	0
Tendonitis	0	0	1 (<1%)	1 (<1%)	0	0
Arthralgia	1 (<1%)	0	0	0	2 (2%)	0
Joint Stiffness	1 (<1%)	0	0	0	0	0
Muscle Spasms	1 (<1%)	0	0	0	1 (1%)	0
Muscle Weakness	0	0	0	0	0	1 (1%)
Renal and Urinary Disorders	**5 (1%)**	**3 (1%)**	**9 (2%)**	**12 (1%)**	**1 (1%)**	**9 (8%)**
Renal Failure	0	2 (<1%)	3 (1%)	5 (1%)	0	3 (3%)
Nephrolithiasis	3 (1%)	1 (<1%)	1 (<1%)	2 (<1%)	0	0
Renal Failure Acute	0	0	2 (<1%)	2 (<1%)	0	2 (2%)
Renal Impairment	0	0	2 (<1%)	2 (<1%)	0	4 (4%)
Acute Prerenal Failure	0	0	1 (<1%)	1 (<1%)	0	0
Renal Failure Chronic	1 (<1%)	0	1 (<1%)	1 (<1%)	0	0
Nephrosclerosis	1 (<1%)	0	0	0	0	0
Dysuria	0	0	0	0	1 (1%)	0
Calculus Ureteric	0	0	0	0	0	1 (1%)

Modified Sponsor's Tables 4.9.1.1. and14.3.1.14.b from the ISS and Study 303 CSR

Table 78 – Treatment Emergent Adverse Events (TEAE) Leading to Discontinuation of Randomized Study Medication by MedDRA System Organ Class/Preferred Term in Pooled Population from 12-Month Phase 3 Studies 301, 302 and 303 and the 6-Month Phase 3 Monotherapy Study 303 by Treatment Group (Safety Population) (cont.)

System Organ Class/ Preferred Term	Combined 12-M, Studies 301, 302 and 304				6-M, Monotherapy Study 303	
	PBO + XOI (N=516)	LESU200 + XOI (N=511)	LESU400 + XOI (N=510)	Total LESU + XOI (N=1021)	PBO (N=107)	LESU400 (N=107)
Any TEAE Leading to Discont. of Randomized Study Meds	**28 (5%)**	**32 (6%)**	**48 (9%)**	**80 (8%)**	**6 (6%)**	**20 (19%)**
Reprod. Syst. and Breast Dis.	**0**	**1 (<1%)**	**0**	**1 (<1%)**	**0**	**0**
Erectile Dysfunction	0	1 (<1%)	0	1 (<1%)	0	0
General Disorders and Administration Site Conditions	**1 (<1%)**	**3 (1%)**	**4 (1%)**	**7 (1%)**	**0**	**3 (3%)**
Non-Cardiac Chest Pain	0	1 (<1%)	2 (<1%)	3 (<1%)	0	0
Fatigue	0	0	2 (<1%)	2 (<1%)	0	1 (1%)
Edema Peripheral	0	2 (<1%)	0	2 (<1%)	0	0
Asthenia	0	0	1 (<1%)	1 (<1%)	0	0
Pain	1 (<1%)	0	1 (<1%)	1 (<1%)	0	1 (1%)
Feeling Jittery	0	0	0	0	0	1 (1%)
Investigations	**9 (2%)**	**7 (1%)**	**11 (2%)**	**18 (2%)**	**1 (1%)**	**2 (2%)**
Blood Creatinine Increased	4 (1%)	4 (1%)	9 (2%)	13 (1%)	0	2 (2%)
Liver Function Test Abnormal	1 (<1%)	2 (<1%)	1 (<1%)	3 (<1%)	0	0
Blood CPK Increased	2 (<1%)	1 (<1%)	1 (<1%)	2 (<1%)	0	0
Blood Amylase Increased	0	0	1 (<1%)	1 (<1%)	0	0
WBC Count Decreased	0	1 (<1%)	0	1 (<1%)	0	0
Alanine Aminotransferase Inc	2 (<1%)	0	0	0	0	0
Aspart. Aminotransferase Inc.	2 (<1%)	0	0	0	0	0
Blood Bilirubin Increased	1 (<1%)	0	0	0	0	0
Gamma-Glutamyltransferase ↑	1 (<1%)	0	0	0	0	1 (1%)
Hemoglobin Increased	1 (<1%)	0	0	0	0	0
Blood Glucose Inc.	0	0	0	0	1 (1%)	0
Blood Bicarbonate Decreased	0	0	0	0	0	1 (1%)
Blood Phosphorus Increased	0	0	0	0	0	1 (1%)
Blood Urea Increased	0	0	0	0	0	1 (1%)
Injury, Poisoning and Procedural Complications	**2 (<1%)**	**0**	**0**	**0**	**0**	**0**

Modified Sponsor's Tables 4.9.1.1. and14.3.1.14.b from the ISS and Study 303 CSR

7.3.4 Significant Adverse Events

Table 79 is an abridged summary of AEs by system organ class observed during the controlled studies by treatment arm that were rated as severe in nature by study investigators. Severity of adverse events observed in the lesinurad phase 3 trials was classified using the Rheumatology Common Toxicity Criteria (RCTC) v.2.0[5]. A higher

[5] Woodworth T, Furst DE, Alten R, et al. Standardizing Assessment and Reproting of Adverse Effects in Rheumatology Clinical Trials II: the Rheumatology Common Toxicity Criteria v2.0. J Rheumatol 2007;34:1401-14.

proportion of patients experienced severe AEs in the LESU400 mg + XOI treatment group than in the placebo or LESU200 mg +XOI groups in the pooled safety database from the 12-month, controlled studies (301, 302 and 304). Similarly, a higher proportion of subjects in the LESU400 mg treatment group also experienced severe treatment emergent AEs than placebo in the 6-month, lesinurad monotherapy study. The most commonly reported severe treatment emergent AEs in the pooled safety database for the 12-month, controlled studies were: Infections and Infestations, Musculoskeletal and Connective Tissue Disorders, Investigations, Cardiac Disorders, and Metabolism and Nutrition Disorders. In the 6-month, lesinurad monotherapy study the most commonly reported severe treatment emergent AEs occurred in the Renal and Urinary Disorders, Investigations and Musculoskeletal and Connective Tissue Disorders SOCs. Further review of the data displayed in **Table 79**, reveals small numerical imbalances mainly not in favor of the LESU400 mg + XOI treatment group and LESU400 mg monotherapy treatment group for these SOCs. With the exception of the Infections and Infestations, the pattern of severe treatment emergent AEs mirrors that observed for the SAEs and premature discontinuations from study treatment discussed previously in this review. Additional explorations of the severity data for severe Infections and Infestations did not reveal any discernable pattern for the lesinurad treatment groups and appeared to the be related to the risks of underlying and concomitant medical conditions of the patients who participated in these studies and/or seasonal patterns of infectious illnesses (e.g., influenza, bronchitis sinusitis, upper respiratory tract infection and pneumonia).

No other safety signals were identified on severity data reviewed separately by XOI inhibitor (allopurinol or febuxostat), or collected from the ongoing long term extension studies or phase 1 and 2 studies.

Table 79 - Summary of Severe Adverse Events by MedDRA System Organ Class in Pooled Population from 12-Month Phase 3 Studies 301, 302 and 304 and the 6-Month Phase 3 Monotherapy Study 303 by Treatment Group (Safety Population)

System Organ Class	Pooled 12-M, Studies 301, 302 and 304				6-M, Monotherapy Study 303	
	PBO + XOI (N=516)	LESU200 + XOI (N=511)	LESU400 + XOI (N=510)	Tot. LESU + XOI (N=1021)	PBO (N=107)	LESU400 (N=107)
All Severe TEAEs:	**41 (9%)**	**47 (9%)**	**59 (12%)**	**106 (10%)**	**4 (4%)**	**16 (15%)**
Infections and Infestations	5 (1%)	11 (2%)	9 (2%)	20 (2%)	1 (1%)	1 (1%)
Neoplasms Benign, Malignant and Unspecified	3 (1%)	0	2 (<1%)	2 (<1%)	0	1 (1%)
Immune Syst. Disorders	1 (<1%)	0	0	0	0	0
Metabolism and Nutrit. Dis.	2 (<1%)	4 (1%)	6 (1%)	10 (1%)	0	1 (1%)
Psychiatric Disorders	0	2 (<1%)	2 (<1%)	4 (<1%)	0	0
Nervous System Disorders	4 (1%)	4 (1%)	3 (1%)	7 (1%)	0	1 (1%)
Eye Disorders	1 (<1%)	0	0	0	1 (1%)	0
Ear and Labyrinth Disorders	1 (<1%)	0	0	0	0	0
Cardiac Disorders	1 (<1%)	6 (1%)	5 (1%)	11 (1%)	1 (1%)	0
Vascular Disorders	2 (<1%)	5 (1%)	3 (1%)	8 (1%)	0	0
Respiratory, Thoracic and Mediastinal Disorders	1 (<1%)	0	2 (<1%)	2 (<1%)	0	0
Gastrointestinal Disorders	5 (1%)	3 (1%)	5 (1%)	8 (1%)	0	1 (1%)
Hepatobiliary Disorders	1 (<1%)	2 (<1%)	1 (<1%)	3 (<1%)	0	0
Skin and Subcutaneous Dis.	3 (1%)	3 (1%)	1 (<1%)	4 (<1%)	0	0
Musculoskeletal and Connective Tissue Dis.	5 (1%)	10 (2%)	8 (2%)	18 (2%)	1 (1%)	3 (3%)
Renal and Urinary Disorders	3 (1%)	1 (<1%)	9 (2%)	10 (1%)	0	7 (7%)
Reprod. Syst. and Breast Dis.	0	1 (<1%)	1 (<1%)	2 (<1%)	0	0
Gen. Disorders and Administ. Site Conditions	1 (<1%)	1 (<1%)	5 (1%)	6 (1%)	1 (1%)	1 (1%)
Investigations	11 (2%)	6 (1%)	8 (2%)	14 (1%)	0	5 (5%)
Injury, Poisoning and Procedural Complications	5 (1%)	2 (<1%)	4 (1%)	6 (1%)	0	1 (1%)

Note: AEs coded using MedDRA v14.0. For each SCO and PT, Subjects are included only once even if they experience multiple events in that SCO or PT, at the maximum toxicity for that AE.
Modified Sponsor's Table 4.4.1.1 and Table 14.3.1.5.a from the ISS and Study 303 CSR, respectively.

7.3.5 Submission Specific Primary Safety Concerns

7.3.5.1 Cardiovascular Events

In view of the high rate of co-morbidity factors for cardiovascular disease in patients with gout coupled with past regulatory experience with other urate lowering therapies reviewed for marketing approval as well as the cardiovascular events Warning contained in the current label for Uloric® (febuxostat), it was recommended that the Applicant have an independent, blinded, cardiovascular endpoints adjudication

committee (CEAC) to review possible cardiovascular events from the controlled phase 3 as well as the ongoing, long-term extension phase 2 and 3 studies for lesinurad. In their analysis of these data, the CEAC used the following definitions from the FDA Guidance for Industry on Diabetes Mellitus –Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes (December 2008) and the draft revision to the EMA Guideline on Clinical Medicinal Products in the Treatment of Diabetes Mellitus (September 2011):

Major Adverse Cardiovascular Events (MACE)

- Cardiovascular (CV) deaths
- Non-fatal myocardial infarction (MI)
- Non-fatal stroke

Non-Major Adverse Cardiovascular Events (Non-MACE)

- Unstable angina with urgent coronary revascularization
- Urgent cerebral revascularization (non-elective)
- Congestive heart failure with hospitalization
- Arrhythmia not associated with ischemia
- Venous and peripheral arterial thromboembolic event
- Transient ischemic attack (TIA)
- Other cardiovascular event

Table 80 summarizes the results of the CEAE's analysis as it pertains to data from the three, 12-month, controlled lesinurad +XOI studies (301, 202, and 304) and from the 6-month, monotherapy study (303). There were a total of 17 MACE events that occurred in 15 (1%) out of the 1537 subjects who participated in the three, 12-month controlled studies. Thirteen out of these 15 patients with MACE events had multiple risk factors for CV disease (smoking, hypertension, diabetes and hypercholesterolemia) and pre-existing cardiovascular conditions such as a previous MI, stroke, heart failure, angina pectoris, transient ischemic attack, peripheral vascular disease, and carotid or coronary intervention (angioplasty, bypass surgery or endarterectomy). Nine out of these 15 subjects also had underlying chronic kidney disease with baseline CrCl <60 ml/min which is another risk factor for cardiovascular events. Only one of the two remaining patients who had adjudicated MACE events (non-fatal MIs) had no co-morbid risk factors or underlying cardiac conditions (Subject 302-05137-209 a 53 year old male) while the other patient (Subject 301-05019-111 45 year old male) had a history of hypercholesterolemia. Both of these patients had been randomized to receive treatment with LESU400 mg +XOI.

Overall, the rates for MACE events were comparable for the LESU200 + XOI and PBO treatment groups in the pooled, 12-Month, phase 3 studies (301, 302 and 304) (**Table 80**). A numerical imbalance not in favor of the LESU400 mg + XOI treatment group is observed that is primarily driven by the seven subjects randomized to this treatment group who had a non-fatal MI. More patients in the PBO + XOI group had non-fatal

strokes than in the two lesinurad +XOI treatment groups. As noted previously, the 4 MACE deaths that occurred during these three controlled, phase 3 studies were in patients randomized to the two lesinurad + XOI treatment groups.

In the 6-month, monotherapy study, one event was adjudicated by the CEAE as a MACE event that occurred in patient randomized to treatment with LESU400 mg. This was the sudden death of Subject 303-05230-308 who died of unknown causes 199 days post his last dose of lesinurad. Reported cardiovascular comorbidities at baseline for this subject included hypercholesterolemia and hypertriglyceridemia. Based on the data shown in **Table 80,** no major imbalance in MACE events is observed for the two treatment groups in the 6-month, monotherapy study. Given the comparable background rates of reported cardiovascular comorbidities it is unclear to this medical reviewer why an imbalance in MACE events is observed in the LESU400 mg + XOI group from the pooled, 12-month, lesinurad + XOI studies (301, 302 and 304) that is not observed in the LESU400 mg group from the 6-month, monotherapy study (303); however the smaller sample size and shorter duration of the controlled period in Study 303 may be contributory. Irrespective of the reason(s), the lack of signal in Study 303 is not sufficient on its own to alleviate the concern raised by the imbalance in Studies 301, 302, and 304.

Table 80 – Incidence of Adjudicated Treatment-Emergent Cardiovascular Adverse Events by Category in the Pooled population from the 12-Month Phase 3 Studies 301, 302, and 304 and the 6-Month Phase 3 Monotherapy Study 303 by Treatment Group (Safety Population)

	Pooled 12-Month, Studies 301, 302 and 304				6- Month, Monotherapy Study 303	
	PBO + XOI (N=516) n (%) [# Events]	LESU200 + XOI (N=511) n (%) [# Events]	LESU400 + XOI (N=510) n (%) [# Events]	Tot. LESU + XOI (N=1021) n (%) [# Events]	PBO (N=107) n (%) [# Events]	LESU400 mg (N=107) n (%) [# Events]
Pts. With Events Sent for Adjudication	28 (5%) [38]	32 (6%) [44]	28 (6%) [47]	60 (6%) [91]	4 (4%) [5]	5 (5%) [6]
# of Pts. With Adjud. Events Classified as CV Event:	15 (3%) [17]	18 (4%) [21]	15 (3%) [24]	33 (3%) [45]	1 (1%) [1]	1 (1%) [1]
Non-Mace Events:						
Unstable Angina w/Urgent Coronary Revascul.	0	0	0	0	0	0
Urgent Cerebral Revascul.	0	0	0	0	0	0
CHF with Hospitalization	1 (<1%) [1]	1 (<1%) [1]	3 (1%) [4]	4 (<1%) [5]	0	0
Arrhyth. W/O Ischemia	7 (1%) [7]	4 (1%) [5]	1 (<1%) [1]	5 (1%) [6]	0	0
Venous and Periph. Art. Thromboembolic Event	1 (<1%) [1]	2 (<1%) [2]	0	2 (<1%) [2]	0	0
TIA	1 (<1%) [2]	0	0	0	0	0
Other CV Event	2 (<1%) [2]	8 (2%) [9]	6 (1%) [10]	14 (1%) [19]	1 (1%) [1]	0
MACE Events:						
Cardiovascular Death	0	2 (<1%)	2 (<1%)[b]	4 (<1%)[b]	0	1 (1%)
Non-Fatal MI	1 (<1%) [1][a]	2 (<1%) [2]	7 (1%) [7][b]	9 (1%) [9][b]	0	0
Non-Fatal Stroke	3 (1%) [3][a]	0	0	0	0	0
Number of Subjects with MACE Events:	3 (1%) [4]	4 (1%) [4]	8 (2%) [9]	12 (1%) [13]	0	1 (1%) [1]

Pts.= patients; Adjud. = adjudicated; Revascul.= Revascularization; Arrhyth.= Arrhythmia; Periph.= Peripheral
MACE events are defined as CV death, non-fatal MI, and non-fatal stroke
Subjects with multiple CEAC–adjudicated events can be counted in more than one category
[a, b]Two subjects experienced more than 1 MACE event: Subject 301-05345-105 who had a non-fatal MI and a non-fatal stroke in the PBO +XOI group and Subject 302-15003-210 who had a non-fatal MI and subsequent CV death in the LESU400 mg + XOI group.
Adapted Sponsor's Table 4.14.1.1. from ISS and Sponsor's table 16.3.1.3 and 14.3.2.2. from CSR for Study 303

The exposure-adjusted incidence rates of MACE events for the pooled, 12-month, controlled lesinurad + XOI studies are presented in **Table 81**. The incidence rates for the number of subjects with MACE events and the overall number of MACE events for both the PBO + XOI and the LESU200 mg + XOI group were comparably low, however the risk for subjects with MACE events as well as the overall number of MACE events is nearly double for the LESU400 mg + XOI treatment group. This is also reflected in the numeric imbalances in the various types of MACE events, with higher rates of CV deaths and non-fatal MI particularly for the LESU400 mg +XOI group. However, the small numbers of these types of events along with the highly overlapping confidence intervals make it difficult to draw definitive conclusions.

Table 81 – Exposure-Adjusted Incidence Rate of MACE Events in the Pooled, 12-Month, Controlled Lesinurad + XOI Studies (301, 302, and 304)

	PBO + XOI (N=516)[1] (421 PY)[2]	LESU200 + XOI (N=511)[1] (415 PY)[2]	LESU400 + XOI (N=510)[1] (413 PY)[2]	Total LESU + XOI (N=1021)[1] (828 PY)[2]
Number of Subjects with MACE events	3	4	8	12
Incidence Rate[3] (95% CI)[4]	0.71 (0.23, 2.21)	0.96 (0.36, 2.57)	1.94 (0.97, 3.87)	1.45 (0.82, 2.56)
Number of MACE Events	4	4	9	13
Incidence Rate[5] (95% CI)[4]	0.95 (0.36, 2.53)	0.96 (0.36, 2.57)	2.18 (1.13, 4.19)	1.57 (0.91, 2.71)
Number of Subjects with CV Death	0	2	2	4
Incidence Rate (95% CI)		0.48 (0.12, 1.93)	0.48 (0.12,1.94)	0.48 (0.18, 1.29)
Number of Subjects with Non-Fatal MI	1	2	7	9
Incidence Rate (95% CI)	0.24 (0.03, 1.69)	0.48 (0.12, 1.93)	1.70 (0.81, 3.56)	1.09 (0.57, 2.09)
Number of Subjects with Non-Fatal Stroke	3	0	0	0
Incidence Rate (95% CI)	0.71 (0.23, 2.21)			

PY= Patient years; CI = Confidence interval
Treatment-emergent AEs are those that started on or after the first randomized study medication dose date, or those that started prior to the first randomized study medication dose date but worsened during the double-blind treatment period of the study. Subjects with multiple events can be counted in more than one category. MACE events include CV death, non-fatal MI, and non-fatal stroke.
[1]Unique number of subjects in safety population
[2]Person-year = (date of completion/discontinuation - date of first dose of study drug +1)/365.25.
[3]Incidence rate= number of subjects with MACE events per 100 person-years.
[4]The 95% confidence intervals are based on Poisson regression.
[5]Incidence rate = number of MACE events per 100 person-year.
Adapted Sponsor's Table 16.2.1 Ad Hoc IAS

In order to provide context for these findings, the Applicant also included MACE data adjudicated by the same CEAE from a 6-month, open-label, prospective safety study of 1,732 patients with gout who were treated with allopurinol by Becker et al[6]. In this study,

[6] Becker MA, Fitz-Patrick D, Choi H, Dalbeth N, et al. An open-label, 6-month study of allopurinol safety in gout: The LASSO study. In press. Seminars in Arthritis & Rheumatism, 2015.

which utilized the same entry criteria as the three, 12-month, phase 3, controlled lesinurad + XOI trials (301, 302 and 304), the MACE rate was 1.42 events/100 patient-years (95% CI:0.68, 2.62) which is similar to that observed for the combined LESU200 mg + XOI and LESU400 + XOI groups, as shown in **Table 81**.

Due to the lack of CV deaths adjudicated to the PBO +XOI treatment group, the Applicant turned to the published literature to find a reference cardiac mortality rate. The MACE CV mortality rates for the lesinurad treatment groups shown in **Table 81** are lower than the unadjusted CV mortality rate of 2.31 CV deaths/100 patient years for subjects with gout reported in the National Health and Nutrition Examination Survey (NHANES) study in subjects with gout (Stack, et al[7]). The gout population evaluated in the NHANES study had demographic and disease characteristics that were similar to the population evaluated in the lesinurad phase 3 studies suggesting that this is a relevant comparison.

Since the current USPI for febuxostat carries a cardiovascular events warning, the Applicant also supplied analyses of MACE events by concomitant XOI (allopurinol versus febuxostat) (**Table 82**). The exposure adjusted incidence rates for patients who received lesinurad with allopurinol in the pooled Studies 301 and 302 are similar to those for the combined XOI pooled safety population shown in **Table 81** above. By contrast, the pattern of events observed in Study 304 does not suggest a dose-dependent increase with lesinurad; but the exposure-adjusted incidence in all the treatment groups, including the PBO + febuxostat group, is higher. Due to the limited size of Study 304 and the small numbers of adjudicated MACE events, it is difficult to draw definitive conclusions.

[7] Stack AG, Hanley A, Casserly LF, Cronin CJ, et al. Independent and conjoint associations of gout and hyperuricemia with total and cardiovascular mortality. Q J Med 2013; 106:647-658.

Table 82- Exposure-Adjusted Incidence Rate of MACE Events in the Pooled, 12-Month, Controlled Lesinurad + Allopurinol Studies 301 and 302) and the 12-Month, Controlled Lesinurad + Febuxostat Study 304)

	12-Month Controlled Studies 301 and 302			12-Month Controlled Study 304		
	PBO + ALLO (N=407)[1] (332 PY)[2]	LESU200 + ALLO (N=405)[1] (330 PY)[2]	LESU400 + ALLO (N=401)[1] (325 PY)[2]	PBO + FBX80 mg (N=109)[1] (89 PY)[2]	LESU200 + FBX 80 mg (N=106)[1] (85 PY)[2]	LESU400 + FBX 80 mg (N=109)[1] (88 PY)[2]
Number of Subjects with MACE Events	2	2	6	1	2	2
Incidence Rate[3] (95% CI)[4]	0.60 (0.15, 2.41)	0.61 (0.15, 2.43)	1.85 (0.83, 4.11)	1.13 (0.16, 7.99)	2.35 (0.59, 9.41)	2.28 (0.57, 9.11)
Number of MACE Events	3	2	7	1	2	2
Incidence Rate[5] (95% CI)[4]	0.90 (0.29, 2.80)	0.61 (0.15, 2.43)	2.15 (1.03, 4.52)	1.13 (0.16, 7.99)	2.35 (0.59, 9.41)	2.28 (0.57, 9.11)
Number of Subjects with CV Death	0	1	1	0	1	1
Incidence Rate (95% CI)		0.30 (0.04, 2.15)	0.31 (0.04, 2.15)		1.18 (0.17, 8.35)	1.14 (0.16, 8.09)
Number of Subjects with Non-Fatal MI	1	1	6	0	1	1
Incidence Rate (95% CI)	0.30 (0.04, 2.14)	0.30 (0.04, 2.15)	1.85 (0.83, 4.11)		1.18 (0.17, 8.35)	1.14 (0.16, 8.09)
Number of Subjects with Non-Fatal Stroke	2	0	0	1	0	0
Incidence Rate (95% CI)	0.60 (0.15, 2.41)			1.13 (0.16, 7.99)		

PY= person years; CI = Confidence interval
Treatment-emergent AEs are those that started on or after the first randomized study medication dose date, or those that started prior to the first randomized study medication dose date but worsened during the double-blind treatment period of the study. Subjects with multiple events can be counted in more than one category. MACE events include CV death, non-fatal MI, and non-fatal stroke.
[1]Unique number of subjects in safety population
[2]Person-year = (date of completion/discontinuation - date of first dose of study drug +1)/365.25.
[3]Incidence rate= number of subjects with MACE events per 100 person-years.
[4]The 95% confidence intervals are based on Poisson regression.
[5]Incidence rate = number of MACE events per 100 person-year.
Modified Sponsor's Ad Hoc Tables 16.2.1 and 16.2.2

Due to concerns regarding the potential for additive CV risk from concomitant NSAID use, the Applicant also submitted the results of an analysis of the incidence of CEAC adjudicated MACE events by type of prophylaxis in the 12-month controlled, lesinurad + XOI studies (301, 302, and 304). Fewer patients randomized to the lesinurad + XOI treatment groups used NSAIDs (n=150) for prophylactic therapy as compared to colchicine (n=875) in these studies. No apparent increase in the risk for overall MACE events in patients who took concomitant NSAIDs with lesinurad +XOI was noted on review of this subanalysis (data not shown).

Identification of the emerging renal safety signal resulted in amendments to all ongoing protocols regarding maintaining adequate hydration with 2 liters of fluid a day. As a result of safety concerns related to the high incidence of pre-existing cardiac disease and chronic kidney disease in the patient population who participated in the pivotal phase 3 lesinurad + XOI studies, the Applicant performed a post-hoc analysis of the overall exposure-adjusted incidence rates of CV events and MACE events between the three treatment groups on the safety database from the pooled, 12-month, controlled lesinurad + XOI studies pre and post-hydration amendments. For completeness, they also looked at SMQs for heart failure and hypertension, cardiovascular-related AEs such as CHF, pulmonary edema, left ventricular failure, cardiac arrhythmia, and volume overload as well as clinically relevant changes in systolic and diastolic blood pressure pre- and post- amendment. Review of the results from these analyses did not identify any increase in the risk for CV or MACE events or for the other terms associated with volume overload status due to increased hydration; however, whether patients complied with the amendment and how much fluid they may have actually ingested daily is not available, making it difficult to ascertain whether there are any safety concerns related to the amendment. No additional safety signals were identified on review of safety data from the long term extension studies contained in the 120-day safety update.

7.3.5.2 Renal Adverse Events

Because of possible renal toxicity related to lesinurad's mechanism of action as a uricosuric, both the Applicant and FDA closely evaluated renal abnormalities in the lesinurad safety database. As previously mentioned, imbalances in the number of serious renal adverse events (**Table 77**) were observed in the four, phase 3, controlled studies. This subsection will focus on renal adverse events including selected renal lab parameters followed by a review of kidney stones. As shown in **Table 83**, a marked imbalance in the rates of renal adverse events was observed with LESU400 mg in the phase 3, 6-month, controlled monotherapy study (303). No renal adverse events were reported in the placebo arm of the study. The adverse events with LESU400 mg spanned the clinical spectrum from increases in blood creatinine and urea levels to acute and chronic failure. In the phase 3, 12-month, controlled lesinurad + XOI studies (301, 302 and 304), the proportion of subjects with any renal-related adverse event was

similar for the LESU200 mg + XOI and PBO + XOI treatment groups but higher in the LESU400 mg + XOI group, suggestive of a dose-dependent pattern of nephrotoxicity. The most common renal-related adverse event in all the phase 3 studies was increased blood creatinine, and this appeared to be the predominant renal-related AE causing the imbalance between treatment groups. The rates for the other renal-adverse events listed in **Table 83** were comparable across treatment groups in the pooled, controlled lesinurad + XOI studies, but the increased risk of other renal AEs with lesinurad treatment is clearly seen in the monotherapy Study 303, which is also a shorter duration study.

Table 83- Incidence of Renal-Related Treatment-Emergent Adverse Events (TEAEs) in the Pooled, 12-Month, Phase 3, Lesinurad + XOI Controlled Studies 301, 302, and 304 and the 6-Month, Controlled Monotherapy Study 303

Preferred Term (PT)	Pooled 12-M, Studies 301, 302 and 304				6-M, Monotherapy Study 303	
	PBO + XOI (N=516)	LESU200 + XOI (N=511)	LESU400 + XOI (N=510)	Tot. LESU + XOI (N=1021)	PBO (N=107)	LESU400 (N=107)
Any Renal-Related AE	**23 (5%)**	**29 (6%)**	**60 (12%)**	**89 (9%)**	**0**	**19 (18%)**
Blood Creatinine Increased	12 (2%)	22 (4%)	40 (8%)	62 (6%)	0	9 (8%)
Blood Urea Increased	3 (1%)	7 (1%)	7 (1%)	14 (1%)	0	2 (2%)
Renal Failure	6 (1%)	4 (1%)	6 (1%)	10 (1%)	0	3 (3%)
Renal Impairment	0	1 (<1%)	5 (1%)	6 (1%)	0	4 (4%)
Acute Renal Failure	2 (<1%)	0	4 (1%)	4 (<1%)	0	3 (3%)
Chronic Renal Failure	3 (1%)	1 (<1%)	2 (<1%)	3 (<1%)	0	1 (1%)
Urine Output Decreased	0	0	3 (1%)	3 (<1%)	0	0
Acute Prerenal Failure	0	0	2 (<1%)	2 (<1%)	0	0
Creatinine Renal Clearance Decreased	0	0	2 (<1%)	2 (<1%)	0	0

For each PT, subjects are included only once, even if they experienced multiple events with that PT.
Modified Sponsor's Tables 4.17.5.1 and 14.17.5.3; ISS

These data were also examined by separate xanthine oxidase inhibitor (allopurinol or febuxostat) (**Table 84**). LESU400 mg + ALLO was associated with the highest rate of renal adverse events in Studies 301 and 302, with the rate of renal AEs being similar in the LESU200 mg + ALLO and PBO + ALLO groups. By contrast, in Study 304, a similar rate of renal AEs was observed in the LESU200 mg + FBX and LESU400 mg + FBX groups. Given the differences in study size, population and concomitant XOI, it is difficult to draw conclusions about the apparent lack of dose-dependent effect in Study 304. However Study 304 is consistent with the Studies 301 and 302 in demonstrating a generally higher rate of renal adverse events associated with lesinurad treatment when compared to the placebo control group.

Table 84 - Incidence of Renal-Related Treatment-Emergent Adverse Events (TEAEs) in the 12-Month, Phase 3, Controlled Studies by Combination XOI

Preferred Term (PT)	12- Month Allopurinol Studies 301 and 302				12-Month Febuxostat Study 304			
	PBO + ALLO (N=407)	LESU200 + ALLO (N=405)	LESU400 + ALLO (N=401)	Tot. LESU + ALLO (N+806)	PBO + FBX 80 (N=109)	LESU200 + FBX 80 (N=106)	LESU400 + FBX 80 (N=109)	Tot. LESU + FBX 80 (N=215)
Any Renal AE	17 (4%)	20 (5%)	49 (12%)	69 (9%)	6 (6%)	9 (9%)	11 (10%)	20 (9%)
Blood Creat. ↑	9 (2%)	15 (4%)	32 (8%)	47 (6%)	3 (3%)	7 (7%)	8 (7%)	15 (7%)
Blood Urea ↑	2 (1%)	6 (2%)	6 (2%)	12 (2%)	1 (1%)	1 (1%)	1 (1%)	2 (1%)
Renal Failure	4 (1%)	3 (1%)	6 (2%)	9 (1%)	2 (2%)	1(1%)	0	1 (1%)
Renal Impair.	0	0	4 (1%)	4 (1%)	0	1 (1%)	1 (1%)	2(1%)
Acute Renal Failure	1 (<1%)	0	3 (1%)	3 (<1%)	1 (1%)	0	1 (1%)	1 (1%)
Urine Output ↓	0	0	3 (1%)	3 (<1%)	0	0	0	0
Creat. Renal Clearance ↓	0	0	2 (1%)	2 (<1%)	0	0	0	0
Renal Fail. Chr	2 (1%)	1 (<1%)	1 (<1%)	2 (<1%)	1 (1%)	0	1 (1%)	1 (1%)
Acute Prerenal Fail.	0	0	1 (<1%)	1 (<1%)	0	0	1 (1%)	1 (1%)

For each PT, subjects are included only once, even if they experienced multiple events with that PT.
Modified Sponsor's Tables 4.17.5.2; ISS

As a result of the emerging renal safety issue, a major protocol amendment to the ongoing phase 3 studies was introduced in June 2013 instructing all patients to drink 2 liters of fluid per day to maintain adequate hydration. No change in the exposure-adjusted incidence rates for renal-related adverse events pre and post-amendment were noted as follows: 8.4 renal-related adverse events/100 patient-years versus 9.5 renal-related adverse events/100 patient-years, respectively, for the LESU200 mg + XOI group; and 17.0 renal-related adverse events/100 patient-years versus 15.5 renal-related adverse events/100 patient-years, respectively, for the LESU400 mg + XOI group. However, as fluid intake was not documented, compliance with the safety amendment instruction is not known.

As shown in **Table 85**, all of the serious renal-related adverse events occurred in the LESU400 mg arm of the 6-month, controlled monotherapy study resulting in an imbalance compared to PBO in that trial. There were no serious renal-related adverse events observed in the LESU200 mg + XOI arm of the pooled, 12-month, controlled combination studies but a numeric imbalance in the number of serious renal-related adverse events not in favor of the LESU400 mg + XOI arm of those trials is observed as compared to PBO + XOI.

Table 85 – Incidence of Renal-Related Serious Treatment Emergent Adverse Events in the Pooled, 12-Month, Phase 3, Lesinurad + XOI Controlled Studies 301, 302, and 304 and the 6-Month, Controlled Monotherapy Study 303

Preferred Term	Pooled 12-M, Studies 301, 302 and 304				6-M, Monotherapy Study 303	
	PBO + XOI (N=516)	LESU200 + XOI (N=511)	LESU400 + XOI (N=510)	Tot. LESU + XOI (N=1021)	PBO (N=107)	LESU400 (N=107)
Any Serious Renal AE	2 (<1%)	0	5 (1%)	5 (1%)	0	5 (5%)
Renal Failure Acute	2 (<1%)	0	2 (<1%)	2 (<1%)	0	2 (2%)
Renal Failure	0	0	1 (<1%)	1 (<1%)	0	2 (2%)
Renal Failure Chronic	0	0	1 (<1%)	1 (<1%)	0	0
Renal Impairment	0	0	1 (<1%)	1 (<1%)	0	1 (1%)

For each PT, subjects are included only once, even if they experienced multiple events with that PT.
Modified Sponsor's Tables 4.17.8.1 and 14.17.8.3; ISS

The case reports for the 7 subjects who developed serious renal adverse events from the pooled, 12-month, phase 3, controlled lesinurad + XOI studies as well as the case reports from the 5 subjects in the 6-month, monotherapy study were reviewed by this medical reviewer and summarized in **Table 86**.

Table 86 – Summary of Subjects Who Developed Serious Renal-Related Adverse Events While Participating in the Phase 3 Lesinurad Studies 301, 302, 303 and 304

Subject	Age/Sex	Study Drug	Onset	Concomitant Meds	Event
Pooled, 12-Month, Phase 3, Lesinurad + XOI Studies (301, 302, and 303)					
302-05349-204	70 yo/BM	PBO + ALLO	Day 16	Colchicine, lovastatin, ASA, carvedilol, fosinopril sodium, furosemide, potassium choloride, ranitidine and tramadol	H/O chronic renal failure with **baseline sCr 1.46 mg/dL with GFR 61 ml/min**, OA, irregular heart rate, S/P CABG, hypokalemia, and peripheral edema. C/O 2-3 days constant left upper quadrant abd. and flank pain with nausea. ↑**sCr 2.89 mg/dL and GFR 32 ml/min** with unremarkable UA. CT abd/pelvis →midline umbilical hernia without obstruction/strangulation. Repeat sCr 2.52 mg/dL and BUN 29 mg/dL. RX included APAP, hydrocodone, cyclobenzaprine, and IVF. Diruretic, KCL and study meds D/C'd. ARF resolved on Day 19. Pt. withdrawn from study due to noncompliance/protocol deviation on Day 66 with **sCr 2.23 mg/dL** and **BUN 26 mg/dL**. F/U Day 92 **sCr 2.39 mg/dL with GFR 33 ml/min**, **BUN 28 mg/dL** and CK 473 U/L. Pt. referred for nephrology evaluation. Repeat sCr 2.0 mg/dL on Day 97.

Table 86 – Summary of Subjects Who Developed Serious Renal-Related Adverse Events While Participating in the Phase 3 Lesinurad Studies 301, 302, 303 and 304 (cont.)

Subject	Age/Sex	Study Drug	Onset	Concomitant Meds	Event
Pooled, 12-Month, Phase 3, Lesinurad + XOI Studies (301, 302, and 303) (cont.)					
304-05164-405	54yo/WM	PBO + FBX	Day 128	Colchicine, ibuprofen, tramadol, HCTZ, and levothyroxine	H/O Chronic renal insufficiency with **baseline sCr 1.33 mg/dL and GFR 66 ml/min,** and HTN. On Day 84 ↑sCr 1.96 mg/dL with GFR 45 ml/min; Day 112 sCr 1.61. mg/dL with GFR 54 ml/min. On Day 128 hospitalized due to ARF with dehydration, and orthostatic HTN S/P diarrhea x 10 days with **sCr 2.61 mg/dL**, **GFR 26 ml/min**, BP 135/69 mm Hg. RX'd with IVF, potassium and amlodipine with D/C HCTZ, and colchicine, and lisinipril. UA reportedly unremarkable. On Day 130 **sCr 1.30 mg/dL** with **GFR 58 ml/min. On Day 351 F/U sCr 1.38 mg/dL and GFR 63 ml/min.**
301-05115-108	47yo/WM	LESU 400mg + ALLO	Day 9	Colchicine, lisinopril, celecoxib, and valproate semisodium	H/O Accidental lithium overdose, renal failure secondary to lithium with **baseline sCr 0.98 mg/dL**, and **GFR 99 ml/min**, bipolar disorder, HTN, hypercholesterolemia, BPH with H/O urinary retention. Pt. started a prohibited med (valproate semisodium) for his bipolar disorder on Day 7. Hospitalized on Day 9 for acute renal failure with hypovolemia and **sCr 13.78 mg/dL**, **BUN 92 mg/dL**, **GFR 4 ml/min**, CK 266 U/L, BP 106/54 mm Hg. UA remarkable for pH 5.5 with small amount of bacteria and mucus. Renal sonogram: Bilat. normal kidneys in size and echogenicity. Abd./Pelvic CT: Mildly distended ureters with markedly thickened bladder wall. RX'd with IVF and foley catheter. Urology consult concluded pt. had long-standing bladder outlet obstruction with urinary retention. Levofloxacin started on Day 16 for UTI [E.coli]. Hematuria secondary to accidental removal of foley catheter. sCr ↓ to 2.5 mg/dL on Day 18. Pt. withdrawn from study on Day 21; F/U **sCr 1.3 mg/dL** with **GFR 91 ml/min** on Day 50.

Table 86 – Summary of Subjects Who Developed Serious Renal-Related Adverse Events While Participating in the Phase 3 Lesinurad Studies 301, 302, 303 and 304 (cont.)

Subject	Age/Sex	Study Drug	Onset	Concomitant Meds	Event
Pooled, 12-Month, Phase 3, Lesinurad + XOI Studies (301, 302, and 303) (cont.)					
302-1510-216	43yo/WM	LESU 400 mg + ALLO	Day 203	Colchicine, diclofenac, etoricoxib, thomapyrin, mersyndol, Ultracet, and APAP	H/O Hypercholesterolemia with **baseline sCr 1.0 mg/dL and GFR 113 ml/min**. Pt. had been taking various NSAIDs for soft tissue injury (Day-11 to Day 20) and bursitis ((Day 123-Day 147).Hospitalized on Day 203 for bloating, loin pain, and sharp bilat. lumbar pain x 1 day. BP 152/97 mm Hg, **sCr 3.27 mg/dL, BUN 32 mg/dL**, UA reportedly WNL. Results of ASLO titer, antiDNase B, aldolase, and ANA all neg. UAs remarkable for trace to 2+ protein with occasional WBCs/RBCs. Abd. sonogram: WNL. RX'd with IVF, APAP, colchicine and esomeprazole for ARF with gout flare. Day 204 labs: **sCr 3.01 mg/dL, BUN 31 mg/dL, GFR 23 ml/min.** Nephrology consultant noted pt. had been taking "more than 4-6 tablets of diclofenac daily". On Day 206 ARF had resolved with sCr 1.39 mg/dL GFR 55 ml/min, BUN 16 mg/dL and GFR 55 mL/min and pt. was D/C'd from hospital. He was withdrawn from study on Day 208. F/U labs on Day 225: **sCr 0.90 mg/mL** and **eGFR 86 ml/min.**
302-15003-210	58yo/ Asian M	LESU 400 mg + ALLO	Day 242	Colchicine, ASA, atenolol, isosorbide mononitrate and dinitrate, nifedipine, carvedilol, furosemide, ciprofloxacin, prednisone, and clopidogrel bisulfate	H/O CAD, angina pectoris, S/P CABG, HTN, and prior tobacco use with **baseline sCr 1.11 mg/dL and GFR 68 ml/min**. Pt. hospitalized on Day 155 for chest pain due to triple vessel CAD and underwent an unsuccessful coronary angioplasty since he was not a candidate for bypass surgery. He was re-hospitalized on Day 191 with a life-threatening MI due to severe triple vessel disease on angiogram. He was treated again medically until stable and discharged on study meds only to be re-hospitalized on Day 211 for evaluation of **↑sCr 3.51 mg/dL and ↑BUN 64 mg/dL**. Denied taking NSAIDs. Renal ultrasound revealed two small renal cysts. No peripheral edema. Nephrology consultant attributed renal impairment due to right-sided renal artery stenosis, HTN, ischemic heart disease, and LV dysfunction and failure as well as possibly study meds. Study med was D/C'd but colchicine and allopurinol continued. **Day 225 sCr 3.57 mg/dL with GFR 21 ml/min.** On Day 242 he returned to ER C/O CXP and difficult breathing and died as a result of cardiorespiratory failure due to pulmonary edema, HTN and CAHD. No autopsy performed. Death adjudicated as MACE event.

Table 86 – Summary of Subjects Who Developed Serious Renal-Related Adverse Events While Participating in the Phase 3 Lesinurad Studies 301, 302, 303 and 304 (cont.)

Subject	Age/Sex	Study Drug	Onset	Concomitant Meds	Event
Pooled, 12-Month, Phase 3, Lesinurad + XOI Studies (301, 302, and 303) (cont.)					
304-05151-401	44yo/WM	LESU 400 mg + FBX	Day 255	Colchcine, lansoprazole, lisinopril, ASA, pitavastatin calcium, metoprolol, nitroglycerin, nifedipine, and ibuprofen	H/O Ischemic cardiomyopathy, MI, S/P cardiac stent, S/P CABG, HTN, esophageal stenosis, muscle spasms, DVT, Factor V Leiden mutation, GERD, hyperlipidemia, hypercholesterolemia, and anxiety with **baseline sCr 0.93 mg/dL with GFR 107 ml/min**. On Day 164, pt. was hospitalized for angina pectoris due to running out of lisinopril and metoprolol. He was D/C'd home on Day 165. On Day 255 pt. was re-hospitalized for angina pectoris, dehydration and ARF with generalized weakness, leg cramps after heavy ETOH ingestion. Labs: ↑sCr 1.7 mg/dL ↑CK 632 U/L, CK MB 11.0 ng/ml with ST wave inversions, sinus bradycardia and ↑QT wave on ECG. Review of sCr prior to hospitalization showed **sCr ranged from 2.67 mg/dL on Day 169 to 1.43 mg/dL on Day 223 with GFRs 37-70 ml/min**. UAs were remarkable for trace protein with occasional WBCs. He was treated with IVF, nitroglycerin and ibuprofen with resolution of ARF, angina pectoris and dehydration on Day 257. **Pt. had ↑sCr 1.76 mg/dL on Day 279. Retested on Day 283 showed sCr 3.35 mg/dL with GFR 30 ml/min.** Study meds were D/C'd. On **Day 342 F/U sCr 1.11 mg/dL with GFR 90 ml/min**.
304-03016-406	70yo/WM	LESU 400 mg + FBX	Day 65	Colchicine, indapamide, telmisartan, nitrendipine, dimeticone, and ketoprofen	H/O HTN, right inguinal hernia, and renal cyst x 30 yrs with **baseline sCr 1.83 mg/dL, BUN 38 mg/dL, and GFR 34 ml/min**. On Day 65 pt.hospitalized for diagnostic testing of chronic renal failure with **sCr 2.1 mg/dL, BUN 45 mg/dL, GFR 33 mL/min. and 0.5 g proteinuria on 24-hr. collection.** (Renal impairment determined to be chronic after identified at screening and persisted for the 3 months that he was in study.) Abd. sonogram normal renal parenchyma with no signs of stasis and multiple thick walled renal cysts bilat. ranging from 13-40 mm in diameter. UAs remarkable for changes in protein (1-2+), with occasional WBCs/RBCs during study. Pt. was D/C'd from hospital with diagnosis of Stage 3 CKD and continued in study. On Day 172 sCr 1.8 mg/dL, BUN 38 mg/dL, and GFR 34.1 mL/min. On **Day 203 sCr 2.31 mg/dL, BUN 17.2 mmol/L and GFR 26.6 ml/min**. Treatment with lesinurad interrupted on Day 214. On Day 232 sCr 1.79 mg/dL and BUN 12.8 mmol/L. Lesinurad restarted on Day 216 but permanently D/C'd on Day 235 due to CKD. On Day 336, **F/U sCr 1.66 mg/dL, BUN 41 mg/mL, and GFR 37.0 ml/min.**

Table 86 – Summary of Subjects Who Developed Serious Renal-Related Adverse Events While Participating in the Phase 3 Lesinurad Studies 301, 302, 303 and 304 (cont.)

Subject	Age/Sex	Study Drug	Onset	Concomitant Meds	Event
6-Month, Monotherapy Study 303					
303-05042-307	25yo/WM	LESU 400 mg	Day 2	Naproxen and esomeprazole	H/O Intermittent back pain with **baseline sCr 0.94 mg/dL and GFR 140 ml/min**. Pt. had generalized edema at Day -4 prior to randomization after starting naproxen prophylaxis for gout flares. He was hospitalized **Day 5** due to abd. pain radiating to back, N/V and ARF with **sCr 8.86 mg/dL** and **BUN 45 mg/dL**. Urinalysis reportedly unremarkable. Abd. CT: No hydronephrosis or obstructive uropathy; + hepatic steatosis. W/U neg. for ANA, anti-dsDNA, Sm/RNP and Sjogren's Ab and glomerular basement membrane IgG. Bx: Focal acute tubular necrosis and minimal tubulo-interstitial fibrosis. EM: mild glomerular BM thickening suggesting early dysmetabolic syndrome type injury. Treated with IVF, promethazine, ondansetron and morphine with resolution of ARF on **Day 11 with sCr 2.75 mg/dL**. On Day 27 sCr 0.95 mg/dL and remained below baseline through final visit on **Day 182 at sCr 0.79 mg/dL with GFR 166 ml/min.**
303-05359-301	47yo/WM	LESU 400 mg	Day 57	Colchcine, diclofenac, morphine, ondansetron, hydromorphone, solucortef, metoprolol, tramadol, APAP, and hydrocodone	H/O Intolerance to allopurinol, hypersensitivity to naproxen and hypercholesterolemia **with baseline sCr 0.87 mg/dL and GFR 97 ml/min.**. On Day 57 pt. was reported as having **renal impairment with sCr 1.66 mg/dL (≥ 1.5 x baseline) and GFR 51 ml/min**. On Day 83, he experienced a gout flare and began taking diclofenac. On **Day 85 his sCr 3.36 mg/dL (≥ 3x baseline**) and **GFR 25 ml/min**. Study medication, colchicine and diclofenac were D/C'd. He was instructed to increase his hydration but was hospitalized due to a gout flare on **Day 88 with sCr 2.64 mg/dL** and **GFR 26 ml/min** which came down to sCr 1.61 mg/dL three days later at discharge on Day 92. Renal sonogram: showed 1 cm left renal anechoic cyst. UAs unremarkable. On **Day 116 sCr 1.0 mg/dL (1.2 x baseline) with GFR 83 ml/min.** At F/U visit on **Day 186 sCr. 0.74 mg/dL with GFR 113 ml/min**.

Table 86 – Summary of Subjects Who Developed Serious Renal-Related Adverse Events While Participating in the Phase 3 Lesinurad Studies 301, 302, 303 and 304 (cont.)

Subject	Age/Sex	Study Drug	Onset	Concomitant Meds	Event
6-Month, Monotherapy Study 303 (cont.)					
303-05095-304	43yo/WM	LESU 400 mg	Day 99	Colchicine, tadalafil, and ASA	H/O Hypertriglyceridemia with **baseline sCr 1.22 mg/dL** and **GFR 75 ml/min.** Pt. had multiple interruptions of lesinurad during the first 90 days of study treatment due to GERD, jittery feeling, paraesthesia, and syncope. Lesinurad was resumed on Day 92 and later that day the pt. C/O dizziness, muscular weakness, jitteriness with diarrhea and nausea that resulted in lesinurad permanently D/C'd on Day 92. On Day 99 pt. was found to have **ARF with a BUN 70 mg/dL and phosphorus 7.0 mg/dL – sCr was not assessed.** On **Day 102 sCr 3.1 mg/dL (≥2 x baseline), BUN 42 mg/dL, phosphorus 4.9 mg/dL, GFR 22 ml/min, and potassium 5.7 mEq/L**. He was immediately hospitalized for ARF with sCr 2.8 mg/dL and BUN 39 mg/dL and reported taking 1300 mg ASA tid for past 14 days with colchicine 0.6 mg bid x 1 month. He was RX'd with IVF and ↓**sCr 1.8 mg/dL, BUN 24 mg/dL, and GFR 41 mL/min after 3 days** of treatment. UA reportedly unremarkable. Pt. was D/C'd and seen in F/U by nephrologist on **Day 116 at which time his sCr 1.3 mg/dL, BUN 14 mg/dL, GFR 60 ml/min** phosphorus 3.2 mg/dL, and potassium 4.4 mEq/L. On F/U Day 183 **sCr 1.0 mg/dL and GFR 90 ml/min.**
303-15001-304	59yo/WM	LESU 400 mg	Day 111	Colchicine, ASA, spironolactone, torasemide, carvedilol, irbesartan, simvastatin, and levothyroxine	H/O Hyperlipidemia, HTN, heart failure, and obesity with **baseline sCr 1.35 mg/dL and GFR 57 ml/min**. Pt. reportedly had elevated **sCr 1.41 mg/dL starting on Day -28**. Following initiation of lesinurad, his **sCr ↑ to 1.79 mg/dL on Day 30** and to **1.97 mg/dL with GFR 41 ml/min on Day 106** at which time he was found to have ↑CK 1351 U/L. On Day 111, the pt. was hospitalized for renal failure with ↑ **sCr 3.3 mg/dL (≥ 2 x baseline) on Day 115** leading to permanent D/C of lesinurad. UAs showed occasional WBC. ARF resolved on Day 119. Repeat **sCr 1.52 mg/dL (≤1.2 x baseline) with GFR 53 ml/min on Day 127.**

Table 86 – Summary of Subjects Who Developed Serious Renal-Related Adverse Events While Participating in the Phase 3 Lesinurad Studies 301, 302, 303 and 304 (cont.)

Subject	Age/Sex	Study Drug	Onset	Concomitant Meds	Event
6-Month, Monotherapy Study 303 (cont.)					
303-17002-303	51yo/WM	LESU 400 mg	Day 30	Colchicine and etoricoxib	H/O Past tobacco use with **baseline sCr 1.01 mg/dL with GFR 95 ml/min**. On Day 30 pt. C/O feeling unwell, thirsty, nauseated with metallic taste in his mouth and **sCr 2.04 mg/dL (≥ 2 x baseline)** with **GFR 47 ml/min** after taking etoricoxib for 5 days for a gout flare. Lesinurad was temporarily stopped due to renal impairment. Gout flare prophylaxis with colchicine was D/C'd and pt. was switched to etoricoxib 90 mg qd. On **Day 40 sCr 1.14 mg/dL** and lesinurad was re-stated on Day 63. After taking 1 tablet of lesinurad, the pt. C/O feeling unwell, thirsty, flushed, nauseated with metallic taste in his mouth. Both lesinurad and etoricoxib were permanently D/C'd. On **Day 65 repeat sCr 2.56 mg/dL (≥ 2 x baseline)** with **GRF 38 ml/min** and ↑BP 171/114 mm Hg attributed to renal impairment. On Day 66 sCr 2.29 mg/dL and continued to ↓1.14 mg/dL on Day 98. Urinalysis was remarkable for occasional WBCs. His **sCr was 1.05 mg/dL on Day 118** and has remained close (within 0.1 mg/dL) to baseline on F/U through Day 228.

H/O = history of; sCr= serum creatinine; GFR= glomerular filtration rate; OA = osteoarthritis, ARF= acute renal failure; S/P= status post; CABG = coronary arterial bypass graft; HTN = hypertension; NSAIDs= nonsteroidal anti-inflammatory drugs; APAP= acetaminophen; IVF = intravenous fluids; UA= urinalysis; WBC= white blood cells; RBC = red blood cells; RX= treatment; D/C= discontinued; F/U= follow-up; HCTZ= hydrochlorothiazide; ASLO= antisteptolysin O titer; LV= left ventricle; DVT= deep vein thrombosis; CK= creatine kinase; BX= biopsy

Of the two subjects randomized to treatment with placebo + XOI who developed acute renal failure while participating in the 12-month, lesinurad + XOI studies, one patient (Subject 302-05349-204) had underlying chronic kidney disease while the other patient (Subject 304-0564-405) became dehydrated following an episode of diarrhea. Additionally, both of these subjects were taking concomitant medications known to impact on renal function (colchicine, diuretics and angiotensin converting [ACE] inhibitors) including allopurinol (Subject 302-05349-204) and febuxostat (Subject 304-05164-405). The time to onset to acute renal failure also varied in both of these cases (Day 16 versus Day 128).

Of the five cases of serious renal adverse event cases observed in patients treated with LESU400 mg + XOI (Subjects 301-05115-108, 302-15010-216, 302-15003-210, 304-03016-406, and 304-05151-401), one patient (Subject 304-03016-406) had underlying chronic kidney disease with a baseline sCr 1.83 mg/dL and GFR 34 mg/dL as a result of renal parenchymal disease (renal cysts), while the remaining four patients had normal renal function with baseline serum creatinines (sCr) ranging from 0.93-1.22 mg/dL and glomerular filtration rates (GFRs) ranging 68 - 113 ml/min. One patient (Subject 301-

05115-108) initiated treatment with a prohibited medication (valproate semisodium) for his underlying bipolar disorder on Day 7 without informing the study investigator which resulted in his hospitalization for acute renal failure (ARF) on Day 9. The consulting urologist also thought that this patient's underlying benign prostatic hypertrophy (BPH) and past history of urinary retention may have played a role in this event. Of the remaining three cases, two patients (Subject 302-15003-210 and Subject 304-05151-401) had cardiac events that may have played a role in the development of acute renal failure. The remaining case (Subject 302-1510-216) reported taking various NSAIDs for a variety of soft tissue aliments including a gout flare and exceeded the recommended dose for one of these agents which are known to cause renal failure. Additional review of these five cases, reveals all of them were taking various medications that can negatively impact on renal function including colchicine, NSAIDs, aspirin, diuretics, ACE inhibitors and ARBs as well as their underlying allopurinol (3 cases) and febuxostat (2 cases). Time to onset was also variable ranging from Day 9 through Day 255 with onset in the three later cases occurring after a triggering event such as a cardiovascular event (2 cases) or gout flare associated with increased intake of concomitant NSAID (1 case). Of note, Subject 302-15003-210 also received two doses of radiographic contrast dye while undergoing coronary angiograms after presenting with worsening coronary artery disease and an acute myocardial infarction during his study participation. Although there were multiple confounding factors involved in all five renal failure cases, it is difficult to exclude lesinurad as another contributing factor since these patients' renal function appeared to be fairly stable until they entered these trials.

Similar findings were noted on review of the five cases of serious renal adverse events for the 6-month, monotherapy Study 303 with four out of the five patients (Subjects 303-05042-307, 303-05359-301, 303-05095-304, and 303-17002-303) using NSAIDs as either prophylactic or acute treatment for gout along with colchicine when they developed acute renal failure. The remaining patient (Subject 303-15001-304) who had underlying congestive heart failure, hypertension and chronic kidney disease with a baseline sCr 1.35 and GFR 57 ml/min was taking concomitant colchicine with a diuretic and angiotensin receptor blocker when he developed acute renal failure. Time to onset varied as well from Day 2 to Day 111 in these cases. However, elevations in sCr were noted within the first 30-60 days of initiating treatment with lesinurad in Subjects 303-05042-307, 303-05359-301, 303-15001-3034 and 303-17002-303 suggesting that the drug affects renal function.

In the long-term extension studies 305, 306, and 307, there were ten patients who developed serious renal adverse events (2 cases were coded as "renal impairment" and 8 cases were coded as "acute renal failure"):

- Extension Study 305 (2 cases): Subjects 305-15014-304 and 305-16019-301. Both patients had received placebo in Study 303 and initiated treatment with LESU400 mg monotherapy upon enrollment into the extension Study 305.
- Extension Study 306 (6 cases): Subjects 306-05185-108, 306-05097-106, 306-05074-219, 306-05306-110, 306-08001-204 and 306-05095-109. Three out of

these 6 patients (Subjects 306-05074-219, 306-08001-204 and 306-05095-109) had been taking LESU200 mg + ALLO, 2 patients (Subjects 306-05185-108 and 306-05097-106) had been taking LESU 400 mg + ALLO while participating in the preceding controlled studies 301 and 302 which they continued taking upon enrollment in the extension study. The remaining patient (Subject 306-05306-110) who had been taking PBO + ALLO while participating in Study 302 initiated treatment with LESU400 mg + ALLO when he enrolled in the extension study.

- Extension Study 307 (2 cases): Subject 307-05287-413 and 307-17002-408. Subject 307-05287-413 was taking PBO + FBX in Study 304 and was started on LESU400 mg + FBX when he entered the extension study while Subject 307-05287-413 continued to take the same dose of study medication (LESU200 mg + FBX) as he did in the controlled study.

These cases were similar to the cases from the controlled studies in that these patients had underlying medical conditions affecting the kidney (hypertension, diabetes mellitus, heart failure, chronic kidney disease, renal cysts, urinary tract infections, and dehydration) compounded by concomitant use of medications that can affect kidney function (colchicine, NSAIDs, diuretics, and ACE inhibitors).Time to onset for serious renal adverse events (acute on chronic versus acute renal failure versus renal impairment) for the six patients who continued taking the same doses of lesinurad as they did in the controlled studies ranged from 381 to 579 days. Renal work-ups for these cases were unremarkable.

The four subjects who were taking placebo in the preceding controlled studies but initiated treatment with lesinurad 400 mg as monotherapy (305-15014-304 and 305-16019-301), or with concomitant allopurinol 300 mg (Subject 306-05306-110) or with concomitant febuxostat 80 mg (Subject 307-05287-413) upon enrollment in the extension studies had time to onset for acute renal failure ranging from 35 to 213 days. In addition to taking concomitant medications affecting the kidney (colchicine, NSAIDS, ACE inhibitors, and diuretics) two of these cases (Subjects 305-15015-304 and 306-05306-110) became dehydrated due to proctitis/bowel prep for colonoscopy and a severe gout attack, respectively, prior to developing acute renal failure. Another case (Subject 305-16019-301) developed acute renal failure following a bout of probable renal stones after taking LESU400 mg as monotherapy for 212 days. The remaining case (Subject 307-05287-413) who had a history of hypertension and prior acute kidney injury (baseline sCr 1.03 mg/dL and GFR 105 ml/min) was found to have 2+ proteinuria with 12 RBCs and 14 WBCs on urinalysis and an elevated serum creatinine 2.60 mg/dL and GFR 42 ml/min on routine study visit on Day 33 at which time he also reported having a concurrent gout attack. All of these patients' renal function improved with intravenous hydration, pain medications and stopping lesinurad and colchicine. Renal work-ups were again unremarkable.

No patients died as a result of renal-related toxicity in the lesinurad clinical development program. (Note: The death of Subject 302-15003-210's was adjudicated by the CEAC

as a MACE event.) Review of the safety database submitted in support of lesinurad revealed two patients (Subjects 306-08001-204 and 306-05095-109) went on to require hemodialysis and two patients (Subjects 303-05042 and 306-05097-106) had renal biopsies as a result of developing acute or worsening renal failure while participating in phase 3 studies of the drug (**Table 87**). All four of these cases were confounded by concomitant use of medications (NSAIDs, colchicine, ACE inhibitors) that affect renal function while two out of the four also had underlying CKD and other medical conditions (hypertension, congestive heart failure, diabetes nephropathy, cocaine abuse and cardiopulmonary arrest) that increased their risk for renal failure. Both patients who underwent renal biopsy presented with symptoms suggestive of acute flank pain syndrome[8]. However, the renal histopathology results from these cases did not clarify the etiology of their acute renal failure.

[8] Harter JG: Acute flank pain and hematuria: lessons from adverse drug reaction reporting. J Clin Pharmacol 1988:;28:560-565.

Table 87 – Serious Renal AEs Resulting in Renal Dialysis and/or Biopsy

Subject	Age/Sex	Study Drug	Onset	Event	Renal Bx/Dialysis
303-05042-307	25yo/WM	LESU400	Day 2	Was taking naproxen 375 mg/esomeprazole 20 mg qd for gout prophylaxis at baseline. Had generalized edema at Day -4 prior to randomization. **Baseline sCr 0.94 mg/dL and GFR 140 ml/min**. Hospitalized Day 5 due to abd. pain radiating to back, N/V and sCr 8.86 mg/dL and BUN 45 mg/dL. Urinalysis remarkable for occasional WBC. Acute renal failure resolved on Day 26 with sCr 1.11 mg/dL. Repeat **sCr 0.79 mg/dL and GFR 166 ml/min on Day 182.**	Abd. CT: No hydronephrosis or obstructive uropathy; + hepatic steatosis. W/U neg. for ANA, anti-dsDNA, Sm/RNP and Sjogren's Ab and glomerular basement membrane IgG. Bx: Focal acute tubular necrosis and minimal tubulointerstitial fibrosis. EM: mild glomerular BM thickening suggesting early dysmetabolic syndrome type injury
306-08001-204	62yo/WM	LESU200 + ALLO 300 mg	Day 381	H/O Crohn's disease, S/P ilectomy, ileocolostomy, TIA, stroke, monoparesis, pancreatitis, HTN, proteinuria, chronic renal failure with **baseline sCr 2.75 mg/dL and GFR 32 ml/min**, renal cyst, urethral stenosis, and urethrotomy. Concomitant Meds: colchicine, naproxen, valsartan, metoprolol, co-diovan, amlodipine, ASA, torasemide, spironolactone, amiodarone, quinine sulfate. Hospitalized for CXP with angina due to CHF and myocarditis. Developed pneumonia, Vfib and was resuscitated/intubated S/P cardiopulmonary arrest. Had ICD implanted**. Developed acute on chronic renal failure with ↑sCr 4.8 mg/dL.**	Underwent hemodialysis from Day 54 to Day 72. (sCr ranged from 3.5 to 4.5 mg/dL with GFR 14-20 ml/min). Discharged to rehab on Day 90. Day 113 sCr 3.09 mg/dL with GFR 15 ml/min off-dialysis.

Bx = biopsy; H/O = history of; adb.= abdominal; N/V = nausea/vomiting; W/U = work-up; c/w= consistent with; ANA= antinuclear antibody; Ab= antibody, EM= electronmicroscopy; BM = basement membrane; DM = diabetes mellitus; CXP = chest pain; CKD= chronic kidney disease; LE= lower extremity; RX'd= treated; ASA = aspirin; Vfib= ventricular fibrillation; EF= ejection fraction; S/P = status post; ICD= implanted cardiac defibrillator; CHF = congestive heart failure; UPEP= urinary protein electrophoresis

Table 87 – Serious Renal AEs Resulting in Renal Dialysis and/or Biopsy (cont.)

Subject	Age/Sex	Study Drug	Onset	Event	Renal Bx/Dialysis
306-05097-106	40yo/WM	LESU400 + ALLO 300 mg	Day 413	H/o Drug hypersensitivity and back pain. **Baseline sCr 1.07 mg/dL with GFR 90 ml/min.** Concomitant Meds; Colchicine and naproxen. C/O bilat. flank pain with **sCr 3.3 mg/dL, GFR 29 ml/min** and urinalysis positive for trace blood and protein 30 mg/dL. Abd. CT: no stones or obstructive uropathy but bilat. peri-nephric stranding without hydronephrosis. **Acute renal failure resolved Day 448 with sCr 1.15 mg/dL and GFR 84 ml/min.**	Bx: Acute tubular cell injury w/o primary glomerulopathy. EM: diffuse BM sclerosis w/with thickening and diffuse epithelial foot process effacement. Epithelial tubular profile showed patchy diffuse acute tubular cell injury with areas of sloughing and denudation of the lining epithelium but no tubulitis. No IC deposition. Suggestive of primary focal segmental glomerulosclerosis Additional W/U neg.
306-05095-109	46yo/ Hawaiian M	LESU200 + ALLO 300 mg	Day 567	H/O occasional methamphetamines and cocaine abuse, DM, diabetic nephropathy, proteinuria, obesity, hypercholesterolemia, Class III or IV CHF with EF 20%, idiopathic cardiomyopathy, implanted cardioverter-defibrillator with **baseline sCr 1.5 mg/dL and GFR 54 ml/min.** Concomitant Meds; colchicine, furosemide, simvastatin, insulin and carvedilol. Developed cellulitis of LE with ↑**sCr 2.93 mg/dL and GFR 23 ml/min** and CHF. RX'd with vancomycin with worsening renal function. Renal sonogram: ↑echogenicity c/w renal disease but no hydronephrosis. +ANA, and SSA Ab with low C3. UPEP: proteinuria with predominance of albumin and gamma fractions but no monoclonal band.	Refused B x. Hemodialysis initiated with **sCr 7.96 mg/dL**. CRF attributed to underlying CKD, diabetic nephropathy with nephrotic proteinuria and concomitant meds.

Bx = biopsy; H/O = history of; adb.= abdominal; N/V = nausea/vomiting; W/U = work-up; c/w= consistent with; ANA= antinuclear antibody; Ab= antibody, EM= electronmicroscopy; BM = basement membrane; DM = diabetes mellitus; CXP = chest pain; CKD= chronic kidney disease; LE= lower extremity; RX'd= treated; ASA = aspirin; Vfib= ventricular fibrillation; EF= ejection fraction; S/P = status post; ICD= implanted cardiac defibrillator; CHF = congestive heart failure; UPEP= urinary protein electrophoresis

Table 88 shows that a higher proportion of subjects in the LESU400 mg arm of the 6-month, monotherapy Study 303 discontinued treatment with study medication due to renal adverse events than placebo treated subjects. Numerically more patients also discontinued treatment with study medications as a result of developing a renal-related adverse event in the LESU400 mg + XOI treatment group as compared to the LESU200mg + XOI and PBO + XOI groups in the 12-month, phase 3, controlled lesinurad + XOI studies (301, 302 and 304). This numerical imbalance is primarily due

to a higher number of patients who experienced increases in blood creatinine levels in the LESU400 mg + XOI group. The interpretation of these results is complicated by the last protocol amendment introduced to the ongoing three, 12-month, phase 3, controlled lesinurad + XOI studies which changed the withdrawal criteria for elevations in serum creatinine (mandatory withdrawal if sCr>3 x baseline level).

Table 88- Incidence of Renal-Related Treatment-Emergent Adverse Events (TEAEs) Leading to Discontinuation of Randomized Medications in the Pooled, 12-Month, Phase 3, Lesinurad + XOI Controlled Studies 301, 302, and 304 and the 6-Month, Controlled Monotherapy Study 303

Preferred Term	Pooled 12-M, Studies 301, 302 and 304				6-M, Monotherapy Study 303	
	PBO + XOI (N=516)	LESU200 + XOI (N=511)	LESU400 + XOI (N=510)	Tot. LESU + XOI (N=1021)	PBO (N=107)	LESU400 (N=107)
Any Renal PT AE	5 (1%)	6 (1%)	17 (3%)	23 (2%)	0	10 (9%)
Blood Creat. Increased	4 (1%)	4 (1%)	9 (2%)	13 (1%)	0	2 (2%)
Renal Failure	0	2 (<1%)	3 (1%)	5 (1%)	0	3 (3%)
Renal Failure Acute	0	0	2 (<1%)	2 (<1%)	0	2 (2%)
Renal Impairment	0	0	2 (<1%)	2 (<1%)	0	4 (4%)
Acute Prerenal Failure	0	0	1 (<1%)	1 (<1%)	0	0
Renal Failure Chronic	1 (<1%)	0	1 (<1%)	1 (<1%)	0	0
Blood Urea Increased	0	0	0	0	0	1 (1%)

For each PT, subjects are included only once, even if they experienced multiple events with that PT.
Modified Sponsor's Tables 4.17.11.1 and 14.17.11.3; ISS

In order to better understand lesinurad's effects on the kidney, serum creatinine levels over the course of the four, phase 3 studies were also examined. As shown in **Table 89**, all of the elevations in sCr in the 6-month, monotherapy Study 303 occurred in patients receiving treatment with LESU400 mg once daily. Dose-dependent proportions of subjects with elevations in sCr by $\geq$ 1.5, $\geq$ 2.0, $\geq$ 3.0 x baseline were observed in the two lesinurad + XOI treatment groups in the pooled, 12-month, phase 3, controlled studies (301, 302 and 304).

Table 89 – Incidence of Serum Creatinine (mg/dL) Elevations by Category in the Pooled, 12-Month, Phase 3, Lesinurad + XOI Controlled Studies 301, 302, and 304 and the 6-Month, Controlled Monotherapy Study 303

Variable	Pooled 12-M, Studies 301, 302 and 304				6-M, Monotherapy Study 303	
	PBO + XOI (N=516)	LESU200 + XOI (N=511)	LESU400 + XOI (N=510)	Tot. LESU + XOI (N=1021)	PBO (N=107)	LESU400 (N=107)
sCr Elevation Category:						
sCr ≥ 1.5 x Baseline	12 (2%)	29 (6%)	73 (14%)	102 (10%)	0	26 (24%)
sCr ≥ 2.0 x Baseline	0	9 (2%)	34 (7%)	43 (4%)	0	9 (8%)
sCr ≥ 3.0 x Baseline	0	4 (1%)	12 (2%)	16 (2%)	0	4 (4%)

sCr=serum creatinine. Elevation categories are cumulative: subjects can be counted in more than one category, so percentages can sum to >100%. Baseline is defined as the highest sCr value recorded ≤14 days prior to the first dose of randomized study medication.
Modified Sponsor's Tables 9.1.1.1 and 9.1.1.3; ISS

Table 90 shows the occurrence of sCr elevations ≥ 1.5 x and ≥ 2.0 baseline by treatment group and their time to resolution in the four phase 3 studies. In the 6-month, monotherapy Study 303, 26 patients experienced at least one elevation in their serum creatinine levels ≥ 1.5 x baseline in the LESU400 mg treatment group. An additional 9 subjects in this treatment group had at least one elevation in sCr level ≥ 2.0 x baseline. Dose dependent patterns of at least one elevation in sCr ≥ 1.5 x and ≥ 2.0 baseline were observed in subjects treated with LESU200 mg + XOI and LESU400 mg +XOI versus PBO +XOI in the pooled, 12-month, phase 3, controlled studies (301, 302 and 304). A similar pattern of elevations was observed for these data when examined by individual xanthine oxidase inhibitors (data not shown). More patients in the LESU400 mg + XOI treatment group had two or more elevations in sCr ≥ 1.5 x and ≥ 2.0 x baseline than in the LESU200 mg + XOI group which mainly occurred in subjects taking concomitant allopurinol.

Table 90 – Serum Creatinine (mg/dL) Elevations ≥ 1.5 x and ≥ 2.0 x Baseline and Resolution in the Pooled, 12-Month, Phase 3, Lesinurad + XOI Controlled Studies 301, 302, and 304 and the 6-Month, Controlled Monotherapy Study 303

Variable	Pooled 12-M, Studies 301, 302 and 304				6-M, Monotherapy Study 303	
	PBO + XOI (N=516)	LESU200 + XOI (N=511)	LESU400 + XOI (N=510)	Tot. LESU + XOI (N=1021)	PBO (N=107)	LESU400 (N=107)
sCr ↑≥ 1.5 x Baseline						
Number of Pts. With:						
No Elevation	504 (98%)	482 (94%)	437 (86%)	919 (90%)	107(100%)	81 (76%)
At Least 1 Elevation	12 (2%)	29 (6%)	73 (14%)	102 (10%)	0	26 (24%)
1 Elevation	12 (2%)	28 (6%)	52 (10%)	80 (8%)	0	22 (21%)
2 Elevations	0	1 (<1%)	18 (4%)	19 (2%)	0	3 (3%)
>2 Elevations	0	0	3 (1%)	3 (<1%)	0	1 (1%)
Total Number of Elevations	**12**	**30**	**97**	**127**	**0**	**31**
Total # of Resolutions	9 (75%)	27 (90%)	80 (83%)	107 (84%)	0	16 (52%)
# Resolut. S/P Interruption of Study Meds	0	7 (23%)	16 (17%)	23 (18%)	0	1 (3%)
# Resolut. W/O Interrupt. of Study Meds	9 (75%)	20 (67%)	64 (66%)	84 (66%)	0	15 (48%)
Time to Resolution:	**(n=12)**	**(n=30)**	**(n=97)**	**(n=127)**	**(n=0)**	**(n=31)**
1-14 days	1 (8%)	9 (30%)	13 (13%)	22 (17%)	0	1 (3%)
>14-28 days	1 (8%)	3 (10%)	21 (22%)	24 (19%)	0	3 (10%)
>28-56 days	3 (25%)	10 (33%)	25 (25%)	35 (28%)	0	6 (19%)
>56-84 days	2 (17%)	2 (7%)	10 (10%)	12 (9%)	0	3 (10%)
>84 days	2 (17%)	3 (10%)	11 (11%)	14 (11%)	0	3 (10%)
Unresolved at Last Assessment	**3 (25%)**	**3 (10%)**	**17 (18%)**	**20 (16%)**	0	**15 (48%)**

sCr=serum creatinine
Baseline is defined as the highest sCr value recorded ≤14 days prior to the first dose of randomized study medication. A resolution is defined as a sCr value of ≤ 1.2 x baseline following an elevation. A subject remains elevated until a resolution is observed. Denominators are the total number of elevations in each group.
Modified Sponsor's Tables 9.1.5.1.1 and 9.1.5.1.3; ISS

Table 90 – Serum Creatinine (mg/dL) Elevations ≥ 1.5 x and ≥ 2.0 x Baseline and Resolution in the Pooled, 12-Month, Phase 3, Lesinurad + XOI Controlled Studies 301, 302, and 304 and the 6-Month, Controlled Monotherapy Study 303 (cont.)

Variable	Pooled 12-M, Studies 301, 302 and 304				6-M, Monotherapy Study 303	
	PBO + XOI (N=516)	LESU200 + XOI (N=511)	LESU400 + XOI (N=510)	Tot. LESU + XOI (N=1021)	PBO (N=107)	LESU400 (N=107)
sCr ↑≥ 2.0 x Baseline						
Number of Pts. With:						
No Elevation	516(100%)	502 (98%)	476 (93%)	978 (96%)	107(100%)	98 (92%)
At Least 1 Elevation	0	9 (2%)	34 (7%)	43 (4%)	0	9 (8%)
1 Elevation	0	9 (2%)	28 (6%)	37 94%)	0	7 (7%)
2 Elevations	0	0	6 (1%)	6 (1%)	0	2 (2%)
>2 Elevations	0	0	0	0	0	0
Total Number of Elevations	**0**	**9**	**40**	**49**	**0**	**11**
Total # of Resolutions	0	8 (89%)	32 (80%)	40 (82%)	0	6 (55%)
# Resolut. S/P Interruption of Study Meds	0	2 (22%)	9 (23%)	11 (22%)	0	1 (9%)
# Resolut. W/O Interrupt. of Study Meds	0	6 (67%)	23 (58%)	29 (59%)	0	5 (46%)
Time to Resolution:	**(n=0)**	**(n=9)**	**(n=40)**	**(n=49)**	**(n=0)**	**(n=11)**
1-14 days	0	5 (56%)	7 (18%)	12 (25%)	0	1 (9%)
>14-28 days	0	0	10 (25%)	10 (20%)	0	0
>28-56 days	0	1(11%)	8 (20%)	9 (18%)	0	4 (36%)
>56-84 days	0	0	5 (13%)	5 (10%)	0	1 (9%)
>84 days	0	2 (22%)	2 (5%)	4 (8%)	0	1
Unresolved at Last Assessment	**0**	**1 (11%)**	**8 (20%)**	**9 (18%)**	0	**5 (46%)**

sCr=serum creatinine
Baseline is defined as the highest sCr value recorded ≤14 days prior to the first dose of randomized study medication. A resolution is defined as a sCr value of ≤ 1.2 x baseline following an elevation. A subject remains elevated until a resolution is observed. Denominators are the total number of elevations in each group.
Modified Sponsor's Tables 9.1.5.1.1 and 9.1.5.1.3; ISS

In the 6-month, controlled monotherapy Study 303, ≥ 52% of patients who experienced an elevation in sCr ≥ 1.5 x and ≥ 2.0 x baseline had resolution of these events within 90 days, with ≥ 46% of the cases resolving without interruption of study medications (**Table 90**). Overall, higher rates of resolution in elevations in sCr ≥ 1.5 x and ≥ 2.0 x baseline occurred in the two lesinurad + XOI treatment groups that comprised the pooled, 12-month, phase 3, controlled studies than in the monotherapy study. Additionally, ≥ 58% of patients in the LESU400 mg + XOI group and > 67% of patients in the LESU200 mg +XOI group had resolution of these elevations in sCr without interruption of their study medications. However, the proportions of patients in the LESU200 mg + XOI group who had unresolved elevations in sCr ≥ 1.5 x and ≥ 2.0 x baseline after 90 days was lower than in the two lesinurad 400 mg treatment groups with (> 18%) and without XOI (> 46%). The interpretation of the results of the time to resolution analysis presented in **Table 90** is complicated by the last two major protocol amendments to the then ongoing

phase 3, controlled lesinurad studies which introduced changes to the treatment algorithm (e.g., maintaining adequate hydration with 2 liters of fluid a day, optional urinary alkalinization for subjects with urinary pH <6.5, stopping concomitant medications that negatively affect the kidney and mandatory withdrawal for subjects whose sCr > 3x baseline value) that was used by study investigators in managing subjects who had elevations in sCr during these studies. No additional information was provided in the Application regarding the success of these interventions or medical treatment such as intravenous hydration that were given to patients with marked elevations in serum creatinine.

The Applicant also conducted subgroup analyses to assess the impact of NSAIDs/colchicine and presence/absence of tophi had on sCr elevations. The results of these subgroup analyses did not demonstrate a relationship between these factors and elevations in sCr in patients who participated in the pooled, 12-month, phase 3, controlled Studies 301, 302 and 304 (data not shown).

Table 91 shows the point estimates and 95% confidence intervals for the incidence rates for sCr elevations by category for the pooled, 12-month, phase 3, controlled lesinurad + XOI studies (301, 302 and 304). The risk for developing elevations in sCr $\geq$ 1.5, $\geq$ 2.0, and $\geq$ 3.0 x baseline with the LESU400 mg +XOI is nearly triple that of the risk observed in the corresponding LESU200 mg + XOI groups with non-overlapping confidence intervals.

Table 91 – Incidence Rate and 95% Confidence Intervals for Serum Creatinine Elevations by Category in Pooled, 12-Month, Phase 3, Controlled Lesinurad + XOI Studies (301, 302, and 304)

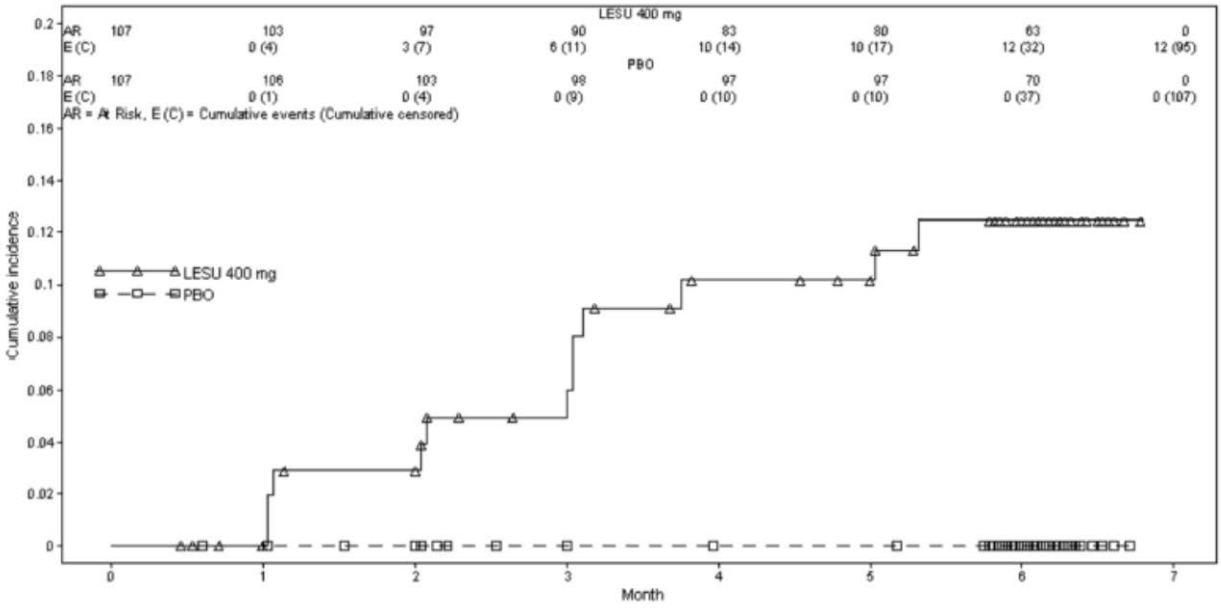
	Pooled 12-M, Studies 301, 302 and 304			
	PBO + XOI (N=516)	LESU200 + XOI (N=511)	LESU400 + XOI (N=510)	Tot. LESU + XOI (N=1021)
Pts. with sCr≥ 1.5 x BSL Incid. Rate (95% CI)	12 2.3 (1.2,4.0)	29 5.7 (3.8,8.0)	73 14.3 (11.4,17.7)	102 10.0 (8.2, 12.0)
Pts. with sCr≥ 2.0 x BSL Incid. Rate (95% CI)	0	9 1.8 (0.8, 3.3.)	34 6.7 (4.7, 9.2)	43 4.2 (3.1, 5.6)
Pts. with sCr≥ 3.0 x BSL Incid. Rate (95% CI)	0	4 0.8 (0.2, 2.0)	12 2.4 (1.2, 4.1)	16 1.6 (0.9, 2.5)

Modified Sponsor's Table 15.12.4

Cystatin C is an endogenous 120 amino-acid protein produced by all nucleated cells and has known functions as an inhibitor of lysosomal proteinases and cysteine proteases. Similar to creatinine, cystatin C has been used as a marker of glomerular filtration rate (GFR), but it appears to be less influenced by age, gender, race, and muscle mass than creatinine. In order to obtain a better understanding of the elevations in sCr observed in patients treated with lesinurad, the Applicant evaluated the correlation of plasma creatinine and cystatin C in a subset of subjects who had post-dose changes in their sCr level ≥ 1.5 x baseline while participating in the 6-month, monotherapy study (303). A strong correlation was seen between cystatin C and changes from baseline in the plasma creatinine of subjects in the elevated creatinine group. This suggests that the changes in sCr that occurred over the course of this study are likely to represent a change in GFR rather than a change related to some other factor such as proximal tubule secretion of creatinine.

To evaluate the impact of duration of lesinurad exposure to the incidence renal toxicity, the Applicant included Kaplan Meier plots of cumulative incidence of sCr elevations ≥ 2.0 x baseline for subjects in the 6-month, controlled monotherapy Study 303 and the pooled, 12-month, phase 3, controlled lesinurad + XOI studies (301, 302 and 304) (**Figure 20** and **Figure 21**, respectively). These figures show a steady accumulation of serum creatinine elevations over time in the LESU400 mg group, compared to a general plateau in incidence by 6 months for LESU200 mg group. By comparison, the incidence in the placebo groups did not increase over the duration of the studies. Additionally, a dose-dependent increase in the cumulative incidence for elevations in sCr ≥ 2.0 x baseline is evident, as shown in **Figure 21**.

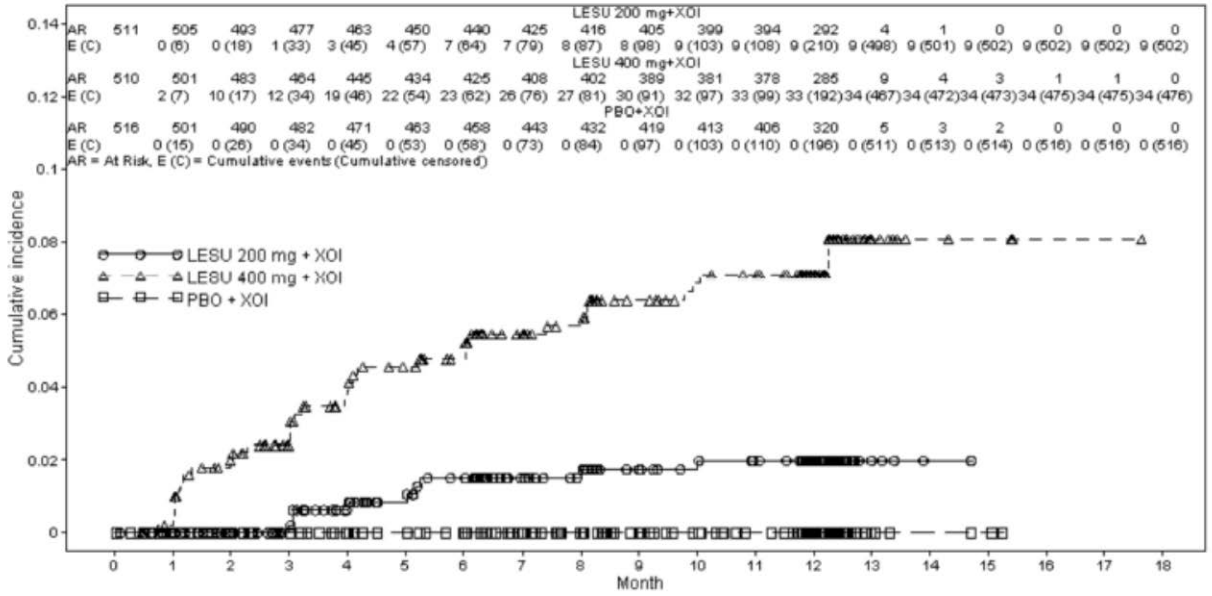
Figure 20 – Cumulative Incidence of Serum Creatinine (mg/dL) Elevations ≥2.0 x Baseline in the 6-Month, Phase 3, Monotherapy Study 303



Abbreviations: LESU, lesinurad; PBO, placebo.
Note: Baseline is defined as the highest serum creatinine value recorded ≤ 14 days prior to the first dose of randomized study medication.
Dataset: ADTTELB2.

Adapted Sponsor's Fig.7; p. 92 Renal Safety Report

Figure 21 – Cumulative Incidence of Serum Creatinine (mg/dL) Elevations ≥2.0 x Baseline in the Pooled, 12-Month, Phase 3, Controlled Lesinurad +XOI Studies (301, 302, and 303)



Abbreviations: LESU, lesinurad; PBO, placebo; XOI, xanthine oxidase inhibitor (allopurinol/febuxostat).
Note: Baseline is defined as the highest serum creatinine value recorded ≤ 14 days prior to the first dose of randomized study medication. Data points after 12 months represent follow-up data in a small number of subjects.
Dataset: ADTTELB2.

Adapted Sponsor's Fig.5; p. 86 Renal Safety Report

Table 92 shows the results of a shift analysis for renal function based on eCrCl for patients in the pooled, 12-month, phase 3 controlled studies. A shift from moderate renal impairment (eCrCL ≤ 30-60 mL/min) to severe renal impairment (eCrCL <30 mL/min) is observed in 3% (3/92) of patients in the LESU400 mg + XOI group and 5% (5/101) of patients in the LESU200 mg + XOI group as compared to 1% (1/101) patients in the PBO + XOI group in these studies.

Table 92 – Shift From Baseline in Renal Function Category for Subjects by Treatment Group in the Pooled, 12-Month, Phase 3, Controlled Lesinurad + XOI Studies (301, 302, and 304)

Placebo (n=516)

	Last eCrCl (mL/min)					
Baseline eCrCl (mL/min)	>=90 n (%)	>=60-<90 n (%)	>=30-<60 n (%)	<30 n (%)	Missing n (%)	Total n (%)
>=90	154 (30.0)	19 (3.7)	1 (0.2)	0	6 (1.2)	180 (35.0)
>=60-<90	45 (8.8)	171 (33.3)	8 (1.6)	0	5 (1.0)	229 (44.6)
>=30-<60	0	29 (5.6)	68 (13.2)	1 (0.2)	3 (0.6)	101 (19.6)
<30	0	0	4 (0.8)	0	0	4 (0.8)
Total	199 (38.7)	219 (42.6)	81 (15.8)	1 (0.2)	14 (2.7)	514 (100)

Lesinurad 200mg+XOI (n=511)

	Last eCrCl (mL/min)					
Baseline eCrCl (mL/min)	>=90 n (%)	>=60-<90 n (%)	>=30-<60 n (%)	<30 n (%)	Missing n (%)	Total n (%)
>=90	167 (32.7)	29 (5.7)	0	0	4 (0.8)	200 (39.2)
>=60-<90	31 (6.1)	153 (30.0)	15 (2.9)	0	9 (1.8)	208 (40.8)
>=30-<60	0	21 (4.1)	75 (14.7)	5 (1.0)	0	101 (19.8)
<30	0	0	0	1 (0.2)	0	1 (0.2)
Total	198 (38.8)	203 (39.8)	90 (17.6)	6 (1.2)	13 (2.5)	510 (100)

Lesinurad 400mg+XOI (n=510)

	Last eCrCl (mL/min)					
Baseline eCrCl (mL/min)	>=90 n (%)	>=60-<90 n (%)	>=30-<60 n (%)	<30 n (%)	Missing n (%)	Total n (%)
>=90	152 (29.9)	45 (8.9)	1 (0.2)	0	5 (1.0)	203 (40.0)
>=60-<90	24 (4.7)	162 (31.9)	24 (4.7)	2 (0.4)	1 (0.2)	213 (41.9)
>=30-<60	1 (0.2)	17 (3.3)	70 (13.8)	3 (0.6)	1 (0.2)	92 (18.1)
<30	0	0	0	0	0	0
Total	177 (34.8)	224 (44.1)	95 (18.7)	5 (1.0)	7 (1.4)	508 (100)

Mild impairment: eCrCL $\leq$ 45-60 mL/min; Moderate impairment: eCrCL $\leq$ 30-45 mL/min; Severe Impairment: eCrCl <30 mL/min.
Table courtesy of Dr. Jianmeng Chen, Clinical Pharmacology Reviewer (Source: Sponsor's Table 9.5.4.1 IAS-6).

Due to concerns for potential additive risk for renal toxicity with higher doses of allopurinol, the Applicant also conducted various subgroup analyses involving the 86 subjects who were taking >300 mg qd of allopurinol in the pooled, 12-month, phase 3, controlled Studies 301 and 302 (**Table 93**). No obvious safety signal is identified on review of the data presented in **Table 93**, however, the small number of subjects taking >300 mg qd of allopurinol in these studies precludes definitive conclusions.

Table 93 – Incidence of Selected Renal Adverse Events by Allopurinol Dose Subgroups in the Pooled, 12-Month, Phase 3 Controlled Studies 301 and 302

System Organ Class	Subject Population	PBO +ALLO n (%)	LESU 200 mg + ALLO n (%)	LESU 400 mg + ALLO n (%)	Total LESU + ALLO n (%)
Sample size	Overall ALLO Population	407	405	401	806
	Baseline ALLO >300 mg/day	28	31	27	58
	High Renal Function Adjusted ALLO dose[a]	73	81	78	159
Any renal-related TEAE	Overall ALLO Population	17 (4.2)	20 (4.9)	49 (12.2)	69 (8.6)
	Baseline ALLO >300 mg/day	2 (7.1)	0	3 (11.1)	3 (5.2)
	High Renal Function Adjusted ALLO dose[a]	NA	NA	NA	NA
Blood creatinine increased	Overall ALLO Population	9 (2.2)	15 (3.7)	32 (8.0)	47 (5.8)
	Baseline ALLO >300 mg/day	1 (3.6)	0	2 (7.4)	2 (3.4)
	High Renal Function Adjusted ALLO dose[a]	4 (5.5)	4 (4.9)	10 (12.8)	14 (8.8)
Blood urea increased	Overall ALLO Population	2 (0.5)	6 (1.5)	6 (1.5)	12 (1.5)
	Baseline ALLO >300 mg/day	0	0	0	0
	High Renal Function Adjusted ALLO dose[a]	0	2 (2.5)	2 (2.6)	4 (2.5)
Any TEAE in the Renal and Urinary Disorders SOC	Overall ALLO Population	20 (4.9)	16 (4.0)	33 (8.2)	49 (6.1)
	Baseline ALLO >300 mg/day	3 (10.7)	1 (3.2)	3 (11.1)	4 (6.9)
	High Renal Function Adjusted ALLO dose[a]	6 (8.2)	5 (6.2)	7 (9.0)	12 (7.5)
sCr elevation ≥ 1.5 x Baseline	Overall ALLO Population	9 (2.2)	24 (5.9)	62 (15.5)	86 (10.7)
	Baseline ALLO >300 mg/day	2 (7.1)	1 (3.2)	4 (14.8)	5 (8.6)
	High Renal Function Adjusted ALLO dose[a]	NA	NA	NA	NA

Abbreviations: ALLO, allopurinol; LESU, lesinurad; PBO, placebo; MedDRA, Medical Dictionary for Regulatory Activities; NA, not available; SOC, System Organ Class; sCr, serum creatinine; TEAE, treatment-emergent adverse event.
Note: Adverse events are treatment-emergent and coded using the MedDRA version 14.0. For the SOC and renal-related TEAEs, within each subgroup population, subjects are included only once, even if they experienced multiple events in that category.
[a] Subjects with high renal function adjusted Baseline allopurinol dose are defined as subjects with Baseline allopurinol dose > 300 mg for Day -7 eCrCl ≥ 60 mL/min or Baseline allopurinol dose > 200 mg for Day -7 eCrCl < 60 mL/min.
Source: IAS Table 4.2.1.2, Table 4.17.5.2, Table 9.1.1.2, Ad Hoc Table 15.4.1, Ad Hoc Table 15.4.2, Ad Hoc Table 15.9.5, and Ad Hoc Table 15.12.3.

Modified Sponsor's Table 33; Lesinurad Renal Safety Report

An independent blinded Renal Events Adjudication Committee (REAC) comprised of three nephrologists was convened by the Applicant when the renal safety signal became apparent from the emerging phase 3 data with Amendment 3 for Studies 301 and 302 and Amendment 4 for Study 304 which were introduced on June 14, 2013. The REAC conducted a post hoc review of all AEs within the MedDRA Acute Renal Failure Standardized MedDRA Query [SMQ] that were serious or lead to discontinuation of randomized study medication as well as all increases in serum creatinine (sCr) ≥1.5 times the baseline visit value contained in the safety database from the controlled, phase 3 studies and in the ongoing, long-term extension phase 2 and 3 studies for lesinurad. The REAC also adjudicated all SAEs in the Acute Renal Failure SMQ in the phase 1 and 2 studies. This committee additionally provided an assessment of the relative potential contribution to the renal event by the subject's medical history, concomitant medications, and AEs/procedures. In their review included in the application, the REAC examined a total of 132 cases as follows: 18 renal-related adverse events in the PBO + XOI group; 36 renal-related adverse events in the LESU200 mg + XOI group; and 96 renal-related adverse events in the LESU400 mg + XOI group. Based on their examination of these cases, they determined that 97% of the adjudicated renal-related adverse events were associated with one or more potential

confounder as follows: chronic renal disease (CKD) and dehydration in the PBO + XOI group; CKD, gout flare and infection in the LESU200m g+ XOI group and CKD, NSAID use and infection in the LESU400mg + XOI group.

In summary, as expected, the population in the lesinurad phase 3 studies had multiple risk factors for renal toxicity. However, as best evidenced in monotherapy Study 303, lesinurad treatment is clearly associated with an increased risk of renal adverse events, including reversible and non-reversible creatinine elevation and serious renal-related adverse events. The risk appears to be dose-dependent, with the highest risk being with use of lesinurad as monotherapy, without a concomitant xanthine oxidase inhibitor.

7.3.5.3 Nephrolithiasis (Kidney Stones)

In view of its mechanism of action, the use of lesinurad would be anticipated to increase the risk for developing nephrolithiasis or kidney stones particularly in patients who are under-excretors of uric acid. Subjects with a history of kidney stones were prohibited from participating in the 6-month monotherapy Study 303 but were permitted to enroll in the three, phase 3 lesinurad +XOI combination studies (301, 302 and 304). Approximately 10-16% of the patients who participated in the phase 3, lesinurad + XOI combination studies reported a history of kidney stones. However, randomization to the treatment groups in these trials was not stratified for this confounding risk factor. In order to better assess the risk for developing renal stones due to treatment with lesinurad, the Applicant included safety evaluations based on an extensive customized list of 11 preferred terms for kidney stones AEs (e.g., nephrolithiasis, calculus bladder, calculus ureteric, staghorn calculus, renal stone removal, etc.) as well as 32 broader-based, urogenital tract preferred terms associated with renal stones (e.g., costovertebral angle tenderness, flank pain, ureteric obstruction, urinary tract obstruction, etc.) separately or in combination (e.g., flank pain and hematuria, costovertebral angle tenderness and hematuria) from the Renal and Urinary Disorders SOC, Investigations SOC, and the Surgical and Medical Procedures SOC in order to maximize the capture of potential cases.

Table 94 lists the cases of kidney stones identified in the safety database from the pooled, phase 3, 12-month, controlled lesinurad + XOI studies (301, 302 and 304) and the 6-month, controlled lesinurad monotherapy Study 303, using the customized preferred terms for kidney stones. Overall, the proportions of subjects with these types of AEs was comparably low in all of the treatment groups but slight numeric imbalances not in favor of the LESU400 mg + XOI and LESU400 mg monotherapy groups are noted on comparison to the respective placebo groups in these studies. Of note, numerically more cases of nephrolithiasis were observed in the PBO + XOI and LESU400 mg + XOI groups as compared to the LESU200 + XOI group in the pooled, phase 3, controlled lesinurad +XOI studies. There were no cases of renal stones in subjects treated with placebo in the 6-month, lesinurad monotherapy study. Additionally there was one case of staghorn calculus which occurred in the LESU400 mg treatment group. Since

patients with history of renal stones are at an increased risk for renal stones when treated with uricosuric agents, the demographic history of the subjects who reported experiencing kidney stones was reviewed. Of the patients who developed a kidney stone adverse event (**Table 94**) while participating in the three, phase 3, 12-month controlled lesinurad +XOI studies, 8 subjects in the PBO +XOI group had a prior history of renal stones versus 2 subjects in the LESU200 mg +XOI group and 3 subjects in the LESU400 mg +XOI group.

Table 94 – Incidence of Kidney Stone Adverse Events in the Pooled, 12-Month, Phase 3, Controlled Studies 301, 302 and 304 and the 6-Month, Controlled Monotherapy Study 303

Preferred Term (PT)	12-M, Studies 301, 302 and 304				6-M, Monotherapy Study 303	
	PBO + XOI (N=516)	LESU200 + XOI (N=511)	LESU400 + XOI (N=510)	Tot. LESU + XOI (N=1021)	PBO (N=107)	LESU400 (N=107)
Any Kidney Stone PT	**9 (2%)**	**3 (1%)**	**13 (3%)**	**16 (2%)**	**0**	**1(1%)**
Nephrolithiasis	9 (2%)	3 (1%)	11 (2%)	14 (1%)	0	1 (1%)
Calculus Ureteric	0	0	3 (1%)	3 (<1%)	0	1 (1%)
Calculus Urinary	0	0	1 (<1%)	1 (<1%)	0	1 (1%)
Staghorn Calculus	0	0	1 (<1%)	1 (<1%)	0	0

For each PT, subjects are included only once, even if they experienced multiple events with that PT.
Modified Sponsor's Tables 4.17.5.12 and 14.17.5.13; ISS

Review of these data separately by xanthine oxidase inhibitor (allopurinol or febuxostat) revealed a persistent numeric imbalance of cases of nephrolithiasis in the LESU400 mg + ALLO group (9 cases; 2%) as compared to the PBO + ALLO (5 cases; 1%) and LESU200 mg +XOI groups (2 cases; 1%). A similar pattern was also seen with the lesinurad + febuxostat treatment groups (LESU400 mg + FBX: (2 cases; 2%); PBO + FBX: (4 cases; 4%) and LESU200 mg + FBX: (1 case; 1%). This suggestion of a dose-dependent risk for renal stones is not unexpected in view of lesinurad's mechanism of action as a uricosuric.

Use of the 32 broader urogenital tract-related terms for kidney stones resulted in identification of more potential cases of renal stones across all treatment groups except the PBO group in the 6-month, lesinurad monotherapy study (**Table 95**). The increases in the overall rates for the LESU200 mg + XOI and PBO +XOI treatment groups is primarily due to numerically more cases of flank pain that occurred in these treatment groups as compared to the LESU400 mg +XOI group. The small, numeric imbalances noted in the previous analysis persist for the nephrolithiasis cases observed for the LESU400 mg + XOI treatment group versus the LESU200 mg +XOI group in the pooled, phase 3, 12-month, controlled, lesinurad +XOI studies (301, 302 and 304) and on comparison of the LESU400 mg group to PBO in the 6-month, monotherapy study (303).

Table 95 – Incidence of Urogenital Tract Related Terms for Kidney Stones in the Pooled, 12-Month, Phase 3, Controlled Studies 301, 302 and 304 and the 6-Month, Controlled Monotherapy Study 303

Preferred Term (PT)	12-M, Studies 301, 302 and 304				6-M, Monotherapy Study 303	
	PBO + XOI (N=516)	LESU200 + XOI (N=511)	LESU400 + XOI (N=510)	Tot. LESU + XOI (N=1021)	PBO (N=107)	LESU400 (N=107)
Urogenital Tract Related Terms:	**17 (3%)**	**13 (3%)**	**17 (3%)**	**30 (3%)**	**0**	**2 (2%)**
Nephrolithiasis	9 (2%)	3 (1%)	11 (2%)	14 (1%)	0	1 (1%)
Flank Pain	6 (1%)	7 (1%)	4 (1%)	11 (1%)	0	0
Calculus Ureteric	0	0	3 (1%)	3 (<1%)	0	1 (1%)
Renal Colic	1 (<1%)	2 (<1%)	1 (<1%)	3 (<1%)	0	0
Calculus Urinary	0	0	1 (<1%)	1 (<1%)	0	1 (1%)
Flank Pain AND Hematuria	0	1 (<1%)	1 (<1%)	1 (<1%)	0	1 (1%)
Renal Pain	0	1 (<1%)	0	1 (<1%)	0	0
Staghorn Calculus	0	0	1 (<1%)	1 (<1%)	0	0
Costovertebral Angle Tenderness	1 (<1%)	0	0	0	0	0

For each PT, subjects are included only once, even if they experienced multiple events with that PT.
Modified Sponsor's Tables 4.17.5.12 and 14.17.5.13; ISS

Table 96 shows that there is a numeric imbalance in the cases of serious kidney stone AEs which is highest in the LESU400 mg treatment group, although there was a small number of cases overall. No additional serious cases of kidney stones were identified using the broader urogenital tract-related terms for this AE. Review of these data separately by xanthine oxidase inhibitor (allopurinol or febuxostat) revealed all the cases of serious kidney stones associated with lesinurad therapy occurred in patients who received treatment with LESU400 mg + allopurinol. Review of the case reports for subjects who developed serious kidney stones while participating in these phase 3 lesinurad studies revealed two patients (Subject 301-05075- 106 and Subject 302-05061-205) had histories of staghorn calculus with urinary tract infection and renal calculi, respectively, while the PBO +XOI treated patient (Subject 304-03008-401) had a history of renal calculi. The results of the analysis using the broader urogenital tract-related terms for kidney stones were similar with identification of one case of serious flank pain. Review of the case report for this patient (Subject 302-05061-205) who was treated with LESU200 mg + ALLO revealed he had flank pain associated with community-acquired pneumonia with a pleural effusion.

Table 96 – Incidence of Serious Kidney Stone Adverse Events in the Pooled, 12-Month, Phase 3, Controlled Studies 301, 302 and 304 and the 6-Month, Controlled Monotherapy Study 303

Preferred Term (PT)	12-M, Studies 301, 302 and 304				6-M, Monotherapy Study 303	
	PBO + XOI (N=516)	LESU200 + XOI (N=511)	LESU400 + XOI (N=510)	Tot. LESU + XOI (N=1021)	PBO (N=107)	LESU400 (N=107)
Any Kidney Stone PT	1 (<1%)	0	3 (1%)	3 (<1%)	0	1 (1%)
Nephrolithiasis	1 (<1%)	0	2 (<1%)	2 (<1%)	0	0
Calculus Ureteric	0	0	1 (<1%)	1 (<1%)	0	1 (1%)
Staghorn Calculus	0	0	1 (<1%)	1 (<1%)	0	0

For each PT, subjects are included only once, even if they experienced multiple events with that PT.
Modified Sponsor's Tables 4.17.8.11 and 14.17.8.13; ISS

Table 97 shows that the numbers of patients who discontinued randomized study medications due to kidney stone adverse eventss was low in these phase 3 studies. Review of the case reports for discontinuations from randomized study medications identified one patient (Subject 302-15017-216) treated with LESU400 mg +XOI who had developed nephrolithiasis early in the trial (Day 58). Treatment with study medication was interrupted until the renal stone AE had resolved and was restarted. However, he had an episode of back pain on Day 167 that resulted in permanent discontinuation of study medications.

Table 97- Incidence of Serious Kidney Stone Adverse Events Leading to Discontinuation of Randomized Study Medications in the Pooled, 12-Month, Phase 3, Controlled Studies 301, 302 and 304 and the 6-Month, Controlled Monotherapy Study 303

Preferred Term (PT)	12-M, Studies 301, 302 and 304				6-M, Monotherapy Study 303	
	PBO + XOI (N=516)	LESU200 + XOI (N=511)	LESU400 + XOI (N=510)	Tot. LESU + XOI (N=1021)	PBO (N=107)	LESU400 (N=107)
Any Kidney Stone PT	3 (1%)	1 (<1%)	1 (<1%)	2 (<1%)	0	1 (1%)
Nephrolithiasis	3 (1%)	1 (<1%)	1 (<1%)	2 (<1%)	0	1 (1%)

For each PT, subjects are included only once, even if they experienced multiple events with that PT.
Modified Sponsor's Tables 4.17.11.11 and 14.17.11.13; ISS

The Applicant also submitted analyses of kidney stone AE incidence and prevalence rates by time interval (0-3, 0-6, 6-12, 12-18 and >18 months) in support of lesinurad's safety profile. However, these analyses are difficult to interpret in light of the addition of renal stone prophylaxis measures in the midst of the studies (amendment 3 June 2013) and amendment 4 (January 2014) which mandated that subjects who develop kidney stones were to be removed from the ongoing clinical studies.

7.3.5.4 Hepatotoxicity

Due to safety concerns regarding the potential for additive risk of hepatotoxicity, the safety database for lesinurad was also reviewed for cases of elevated liver function tests (LFTs) and liver toxicity since the use of the xanthine oxidase inhibitors has been associated with elevated transaminase levels and has resulted in a label WARNING for fatal hepatotoxic events with febuxostat (Uloric®). No clinically meaningful differences were noted on examination of mean changes from baseline or shift table analyses for the LFT parameters AST (SGOT), ALT (SGPT), and total or direct bilirubin for subjects who participated in the three, 12-month, phase 3 controlled lesinurad + XOI studies (301, 302 and 304). (Data not shown.) For completeness, the Applicant also conducted an outlier analysis to identify potential cases of drug induced hepatotoxicity as defined by Hy's law (e.g., AST >3 x ULN or ALT > 3 x ULN AND Alkaline Phosphatase < 2 x ULN AND Total Bilirubin > 2 x ULN). No cases meeting this definition were identified, as shown in Table 98.

Table 98 – Incidence of Potential Hepatotoxic Adverse Events in the 12-Month, Phase 3 Controlled Lesinurad + XOI Studies 301, 302 and 304

Toxicity Criterion	Timepoint	PBO + XOI (N=516)	LESU200 + XOI (N=511)	LESU400 + XOI (N=510)	Tot. LESU + XOI (N=1021)
AST> 3 X ULN	**Baseline**	0	0	1 (<1%)	1 (<1%)
	Overall	10 (2%)	10 (2%)	6 (1%)	16 (2%)
ALT > 3 X ULN	**Baseline**	0	0	1 (<1%)	1
	Overall	6 (1%)	5 (1%)	6 (<1%)	11 (2%)
AST >3 x ULN and ALT >3 x ULN	**Baseline**	0	0	0	0
	Overall	2 (<1%)	4 (1%)	3 (1%)	7 (1%)
AST >3 x ULN or ALT > 3 x ULN AND Alkaline Phosphatase < 2 x ULN AND Tot. Bilirubin > 2 x ULN	**Baseline**	0	0	0	0
	Overall	0	0	0	0

AST = aspartate aminotransferase; ALT = alanine aminotransferase; ULN = Upper limit of normal
Modified Sponsor's Table 10.1.1; ISS.

The Applicant also submitted the results of hepatic disorders identified by using standardized MedDRA query search terms in the pooled safety databases for the three, 12-month, controlled, phase 3 lesinurad + XOI studies (301, 302 and 304) and the phase 3, 6-month, monotherapy study (303) (**Table 99**). The overall incidences are comparable across the treatment groups and no discernable patterns of liver toxicity are noted.

Table 99 – Incidence of Hepatic Disorders Identified Via Standardized MedDRA Query (SMQ) Search Terms in the Pooled, 12-Month, Phase 3, Controlled Studies 301, 302 and 304 and the 6-Month, Controlled Monotherapy Study 303

Sub-SMQ/Preferred Term	12-M, Studies 301, 302 and 304				6-M, Monotherapy Study 303	
	PBO + XOI (N=516)	LESU200 + XOI (N=511)	LESU400 + XOI (N=510)	Tot. LESU + XOI (N=1021)	PBO (N=107)	LESU400 (N=107)
Any Hepatic-Relat. Disord.	29 (6%)	24 (5%)	19 (4%)	43 (4%)	4 (4%)	4 (4%)
Hepatic Cholestasis and Jaundice AEs:	2 (<1%)	0	0	0	0	0
Hyperbilirubinemia	1 (<1%)	0	0	0	0	0
Ocular Icterus	1 (<1%)	0	0	0	0	0
Severe Hepatic AEs:	2 (<1%)	5 (1%)	3 (1%)	8 (1%)	0	1 (1%)
Hepatic Steatosis	2 (<1%)	5 (1%)	1 (<1%)	6 (1%)	0	1 (1%)
Hepatic Cyst	0	0	1 (<1%)	1 (<1%)	0	0
Hepatitis Toxic	0	0	1 (<1%)	1 (<1%)	0	0
Liver Injury	0	0	1 (<1%)	1 (<1%)	0	0
Liver-related Investigations:	27 (5%)	20 (4%)	16 (3%)	36 (4%)	4 (4%)	3 (3%)
γ-glutamyltransferase Inc.	10 (2%)	7 (1%)	6 (1%)	13 (1%)	1 (1%)	1 (1%)
Transaminase Inc.	0	0	0	0	0	1 (1%)
ALT Inc.	8 (2%)	7 (1%)	4 (1%)	11 (1%)	2 (2%)	0
AST Inc.	8 (2%)	7 (1%)	1 (<1%)	8 (1%)	0	0
Hepatic Enzyme Inc.	1 (<1%)	1 (<1%)	3 (1%)	4 (<1%)	1(1%)	0
Liver Function Test Abn.	6 (1%)	2 (<1%)	2 (<1%)	4 (<1%)	0	0
Hepatic Function Test Abn.	0	1 (<1%)	2 (<1%)	3 (<1%)	0	0
Blood AP ↑	0	0	2 (<1%)	2 (<1%)	0	0
Transaminase Inc.	0	1 (<1%)	0	1 (<1%)	0	0
Blood Bilirubin Inc.	1 (<1%)	0	0	0	0	0
Hepatomegaly	1 (<1%)	0	0	0	0	0
Hyperbilirubinemia	1 (<1%)	0	0	0	0	0
Hepatic Mass	0	0	0	0	0	1 (<1%)

Modified Sponsor's Table 4.18.1.1 and Table 4.18.1.3 from ISS

Since there is some uncertainty about different potential for hepatotoxicity between allopurinol and febuxostat, this hepatotoxicity analysis was also performed by individual xanthine oxidase inhibitor (**Table 100**). Higher overall rates are observed in the lesinurad + febuxostat treatment groups as well as the PBO + FBX group in Study 304 as compared to the corresponding treatment groups in the pooled analysis for the lesinurad + allopurinol Studies 301 and 302. These imbalances were primarily driven by abnormalities in various liver-related Investigations (e.g., LFTs), consistent with what is described in the current febuxostat (Uloric®) label.

The safety database for the phase 3 lesinurad studies also contained 7 case reports of elevated liver function tests that resulted in patients discontinuing study medications.

Two out of these seven cases occurred in patients who participated in Study 302: 1 patient treated with PBO + ALLO 300 mg qd (Subject 302-05066-205) and 1 patient treated with LESU200 mg + ALLO 300 mg qd (Subject 302-05216-209). The latter patient was also taking 200 mg ibuprofen twice daily, which can cause elevated LFTs. Both of these patients discontinued treatment with study medication as a result of Rheumatology Common Toxicity Criteria (RCTC) Grade 2 elevations in their LFTs which resolved after their study medications were discontinued. The remaining 5 cases occurred in patients who participated in Study 304: 1 patient treated with LESU200 mg + FBX 80 mg qd (Subject 304-05194-404); 2 patients treated with LESU400 mg + FBX 80 mg qd (Subjects 304-05056-401 and 304-17002-413); and 2 patients treated with PBO + FBX 80 mg qd (Subjects 304-05232-402 and 304-04001-408). Four out of these 5 patients who received lesinurad with febuxostat had RCTC Grade 3-4 elevations which resulted in discontinuation of their study medications and resolved over time. Of note, Subject 304-04001-408 who was treated with PBO + FBX 80 mg qd had a diagnosis of Gilbert's disease and Subject 304-05056-401 was coded as having "liver injury" that occurred during a protracted hospitalization for exacerbation of his underlying congestive heart failure that resulted in his death.(For more information the reader is referred to **Table 75**.) Review of the safety database for the extension studies, as well as the phase 2 studies and data contained in the 120-day safety follow-up did not reveal any subjects who met the criteria for hepatotoxicity.

Table 100 – Incidence of Hepatic Disorders Identified Via Standardized MedDRA Query Search Terms in the Pooled, 12-Month, Controlled Lesinurad + Allopurinol Studies 301 and 302 and 12-Month, Controlled Lesinurad + Febuxostat Study 304

Sub-SMQ/ Preferred Term	12-Month Controlled Studies 301 and 302				12-Month Controlled Study 304			
	PBO + ALLO (N=407)	LESU200 + ALLO (N=405)	LESU400 + ALLO (N=401)	Tot. LESU + ALLO (N=806)	PBO + FBX 80 mg (N=109)	LESU200 + FBX 80 mg (N=106)	LESU400 + FBX 80 mg (N=109)	Tot. LESU + FBX (N=215)
Any Hepatic-Relat. Dis.	20 (5%)	13 (3%)	13 (3%)	26 (5%)	9 (8%)	11 (10%)	6 (6%)	17 (8%)
Hepatic Cholestasis and Jaundice AEs:	2 (1%)	0	0	0	0	0	0	0
Hyperbilirubinemia	1 (<1%)	0	0	0	0	0	0	0
Ocular Icterus	1 (<1%)	0	0	0	0	0	0	0
Severe Hepatic AEs:	2 (1%)	3 (1%)	2 (1%)	5 (1%)	0	2 (2%)	1 (1%)	3 (1%)
Hepatic Steatosis	2 (1%)	3 (1%)	1 (<1%)	4 (1%)	0	2 (2%)	0	2 (1%)
Hepatic Cyst	0	0	1 (<1%)	1 (<1%)	0	0	0	0
Hepatitis Toxic	0	0	1 (<1%)	1 (<1%)	0	0	0	0
Liver Injury	0	0	0	0	0	0	1 (1%)	1 (1%)
Liver-Relat. Investigat.:	18 (4%)	11 (3%)	11 (3%)	22 (3%)	9 (8%)	11 (3%)	5 (5%)	14 (7%)
γ-glutamyltransferase ↑	7 (2%)	5 (1%)	5 (2%)	10 (1%)	3 (3%)	5 (1%)	1 (1%)	3 (1%)
ALT Inc.	4 (1%)	3 (1%)	2 (1%)	5 (1%)	4 (4%)	3 (1%)	2 (2%)	6 (3%)
AST Inc.	3 (1%)	4 (1%)	3 (1%)	5 (1%)	5 (5%)	4 (1%)	0	3 (1%)
Hepatic Enzyme Inc.	1 (<1%)	0	2 (1%)	3 (<1%)	0	0	0	1 (1%)
Blood AP ↑	0	0	2 (1%)	2 (<1%)	0	0	0	0
Hepat. Funct. Test Abn.	0	0	0	2 (<1%)	0	0	0	1(1%)
Liver Funct. Test Abn.	4 (1%)	1 (<1%)	0	1 (<1%)	2 (2%)	1 (<1%)	2 (2%)	3 (1%)
Transaminase Inc.	0	1 (<1%)	0	1 (<1%)	0	1 (<1%)	0	0
Blood Bilirubin Inc.	1 (<1%)	0	0	0	0	0	0	0
Hepatomegaly	0	0	0	0	1 (1%)	0	0	0
Hyperbilirubinemia	1 (<1%)	0	0	0	0	0	0	0

Modified Sponsor's Table 4.18.1.2 from ISS

7.3.5.5 Increased Creatinine Phosphokinase (CK)

Since colchicine was used as prophylactic gout therapy by many patients through Month 5 of the phase 3 lesinurad studies and is known to cause rhabdomyolysis and myopathy, the Applicant submitted analyses of creatinine phosphokinase (CK) levels collected over the course of these trials. Examination of the mean changes from baseline to the Month 5 visit for CK levels revealed a 21% mean percent change for the LESU200 mg +XOI group versus 2% for the LESU400 mg + XOI and 4% for the PBO +XOI groups for the pooled, 12-month, phase 3 controlled lesinurad + XOI studies. No clinically relevant changes were noted for this parameter at the Month 6 visit for the three treatment groups following discontinuation of colchicine. When examined by separate xanthine oxidase inhibitor (allopurinol or febuxostat), marked increases in the mean percent change over baseline were noted for the LESU200 + FBX 80 mg group (88%) and the LESU400 mg + FBX 80 mg group (27%) versus PBO + FBX 80 mg group (14%) in Study 304 which resolved by the Month 6 visit. No clinically relevant changes were noted on examination of the three treatment groups in the pooled lesinurad + XOI Studies 301 and 302 at these time points. Data for CK levels from the Month 5 and Month 6 visits for the LESU400 mg and PBO treatment groups in the 6-month, monotherapy study were unremarkable for this parameter. As expected, review of the corresponding median CK values for the Months 5 and 6 visits for all treatment groups showed less variability.

Examination of shift table analyses for CK showed similar proportions of subjects in the LESU200 + XOI (10%), LESU400 mg + XOI (9%) and PBO + XOI (8%) treatment groups who had shifts from normal values at baseline to high at Month 5 that were still present at the last visit assessment for this parameter in the 12-month, phase 3 controlled lesinurad +XOI studies. Similar findings were observed when the shift analysis data for CK was examined by separate xanthine oxidase inhibitor as well as for the two treatment groups in the 6-month, monotherapy Study 303. To better understand this, the sponsor also submitted the results from an outlier analysis for CK elevations that exceed 5-times and 10-times the upper limit of normal (ULN) for the 12-month, phase 3 controlled lesinurad + XOI studies (301, 302 and 303) (**Table 101**). The results from the outlier analyses for each separate xanthine oxidase inhibitor (allopurinol or febuxostat) were comparable to those shown in **Table 101**. The sponsor also submitted the results from muscle toxicity assessments for subjects with a CK >5 x ULN by visit. Review of the results from these assessments showed that the majority of patients had external causes for their CK elevations such as a strenuous workout, sustained falls and/or body injury, received an intramuscular injection or admitted to increased alcohol intake within the 7 days prior to study assessment of CK.

Table 101 – Incidence of Markedly Elevated Creatinine Phosphokinase (CK) Adverse Events in the 12-Month, Phase 3 Controlled Lesinurad + XOI Studies 301, 302 and 304

Toxicity Criterion	Timepoint	PBO + XOI (N=516)	LESU200 + XOI (N=511)	LESU400 + XOI (N=510)	Tot. LESU + XOI (N=1021)
CK > 5 X ULN	**Baseline**	0	1 (<1%)	0	0
	Overall	21 (4%)	17 (3%)	16 (3%)	33 (3%)
CK > 10 X ULN	**Baseline**	0	0	3 (1%)	3 (<1%)
	Overall	9 (2%)	6 (1%)	8 (2%)	14 (1%)

Modified Sponsor's table 11.1.1 ISS

The safety database submitted in support of lesinurad also contained four case reports of subjects who discontinued study medications due to increased CK values: 1 patient was treated with LESU200 mg + FBX 80 mg qd (Subject 304-05194-404), 1 patient was treated with LESU400 mg + ALLO 300 mg qd (Subject 301-05408-103), and 2 patients were treated with PBO + ALLO 300 mg qd. All five subjects were taking concomitant colchicine at the time their creatinine phosphokinases became elevated. Three of these subjects were also taking concomitant HMG-CoA reductase inhibitors which carry a drug class Warning for myopathy and rhabdomyolysis. No additional cases of elevated CK were reported in the 120-day safety follow-up in the ongoing extension studies nor were identified on review of the safety data generated from the phase 1 and 2 studies conducted with lesinurad.

Based on the data reviewed, there does not appear to be a risk for myopathy and rhabdomyolysis associated with lesinurad.

7.3.5.5 Hypersensitivity Adverse Events

Both allopurinol and febuxostat are known to cause hypersensitivity reactions that can present as a variety of skin manifestations. A query of the lesinurad safety database for these types of adverse events identified 1 case (0.9%) of hypersensitivity reaction reported for the LESU400 mg group during the phase 3, 6-month, controlled monotherapy Study 303 that was not classified as serious. No cases of skin adverse events that could potentially be due to hypersensitivity manifestations to lesinurad were reported in this trial. Three (0.8%) additional cases of non-serious drug hypersensitivity that occurred in the LESU400 mg +XOI group were identified on review of the data from the pooled, phase 3, 12-month, controlled lesinurad + XOI studies (301, 302 and 304). No additional information was included in the application regarding these four cases of "hypersensitivity." There were 7 cases of urticaria reported in the pooled safety database for the controlled lesinurad + XOI studies as follows: 3 cases (0.6%) in the LESU200 mg + XOI treatment group, 2 cases (0.4%) in the LESU400 mg + XOI treatment group, and 2 cases (0.4%) in the PBO + XOI group. Further review revealed that they all occurred in patients taking allopurinol. There were also 6 cases of allergic

dermatitis reported in these trials: 1 case (0.2%) in the LESU200 mg + XOI treatment group, 3 cases (0.6%) in the LESU400 mg + XOI group, and 1 case (0.2%) in the PBO + XOI group. The rate of patients who reported experiencing rashes was approximately 2% in all three treatment groups in the phase 3, controlled lesinurad + XOI studies. Additionally, cases of pruritus were observed in patients treated with LESU200 mg + XOI (7 cases; 1.4%) and LESU400 mg + XOI (3 cases; 0.6%) but not in the PBO + XOI group for these studies. Of note, there were a total of 2 cases of photosensitivity reaction reported that occurred in the lesinurad + XOI treatment groups (1 case in each group). Review of the safety databases from the phase 2 studies identified two additional cases of urticaria that occurred in patients taking lesinurad with allopurinol and 1 case of allergic dermatitis also in a patient taking lesinurad with allopurinol. No definitive conclusions regarding lesinurad's ability to cause drug hypersensitivity reactions can be drawn given that the majority of the cases observed in the safety database were confounded by the concomitant use of allopurinol which is known to cause these types of events.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Most patients (>65%) experienced an adverse event while participating in the controlled portions of the phase 3 studies for lesinurad. Table 102 lists the frequency of the adverse events observed in these studies by system organ class (SOC) and treatment group. Higher overall rates of AEs were observed in the lesinurad treatment groups as compared to their respective placebo groups in these studies. Infections and Infestations, Musculoskeletal and Connective Tissue Disorders, Investigations, Injury, Poisoning and Procedural Complications and Gastrointestinal Disorders were the most common types of adverse events observed for the three, 12-month, controlled lesinurad +XOI studies. As noted earlier, the higher rate of Infections and Infestations observed in the lesinurad + XOI treatment groups versus the PBO + XOI group in the 12-month, controlled studies was due to seasonal illnesses (upper respiratory tract infection, nasopharyngitis and influenza) and is the primary reason for the higher overall rates observed in the lesinurad + XOI groups. The rates for the other system organ classes for the pooled safety database for these three trials are generally similar across the treatment groups. More imbalances are noted not in favor of the LESU400 mg group in the 6-month, monotherapy study as compared to PBO in the following SOCs: Metabolic and Nutritional Disorders, Renal and Urinary Disorders Gastrointestinal Disorders, General Disorders and Administration Site Conditions and Investigations.

Table 102 – Summary of Common Adverse Events by System Organ Class (SOC) by Randomized Treatment Group Medications in the Pooled, 12-Month, Phase 3, Controlled Studies 301, 302 and 304 and the 6-Month, Controlled Monotherapy Study 303

System Organ Class/ Preferred Term	Combined 12-M, Studies 301, 302 and 304				6-M, Monotherapy Study 303	
	PBO + XOI (N=516)	LESU200 + XOI (N=511)	LESU400 + XOI (N=510)	Total LESU + XOI (N=1021)	PBO (N=107)	LESU400 (N=107)
Any AEs:	363 (70%)	386 (76%)	407 (80%)	793 (78%)	70 (65%)	83 (78%)
Infections and Infestations	175 (34%)	203 (40%)	207 (41%)	410 (40%)	29 (27%)	31 (29%)
Neoplasms Benign, Malignant and Unspecified	12 (2%)	9 (2%)	14 (3%)	23 (2%)	0	1 (1%)
Blood and Lymph. Syst. Dis.	9 (2%)	8 (2%)	8 (2%)	16 (2%)	0	3 (3%)
Immune Syst. Disorders	9 (2%)	2 (<1%)	9 (2%)	11 (1%)	0	0
Endocrine Disorders	5 (1%)	5 (1%)	6 (1%)	11 (1%)	0	2 (2%)
Metabolism and Nutrit. Dis.	36 (7%)	45 (9%)	50 (10%)	95 (9%)	3 (3%)	10 (9%)
Psychiatric Disorders	21 (4%)	23 (5%)	19 (4%)	42 (4%)	2 (2%)	3 (3%)
Nervous System Disorders	56 (11%)	72 (14%)	61 (12%)	133 (13%)	10 (9%)	9 (8%)
Eye Disorders	19 (4%)	19 (4%)	10 (2%)	29 (3%)	4 (4%)	1 (1%)
Ear and Labyrinth Disorders	9 (2%)	7 (1%)	6 (1%)	13 (1%)	2 (2%)	1 (1%)
Cardiac Disorders	20 (4%)	17 (3%)	22 (4%)	39 (4%)	3 (3%)	2 (2%)
Vascular Disorders	33 (6%)	41 (8%)	45 (9%)	86 (8%)	9 (8%)	7 (7%)
Respiratory, Thoracic and Mediastinal Disorders	42 (8%)	53 (10%)	54 (11%)	107 (11%)	5 (5%)	13 (12%)
Gastrointestinal Disorders	89 (17%)	92 (18%)	103 (20%)	195 (19%)	16 (15%)	32 (30%)
Hepatobiliary Disorders	5 (1%)	9 (2%)	6 (1%)	15 (2%)	0	2 (2%)
Skin and Subcutaneous Dis.	33 (6%)	44 (9%)	38 (8%)	82 (8%)	7 (7%)	7 (7%)
Musculoskeletal and Connective Tissue Dis.	136 (26%)	149 (29%)	145 (28%)	294 (29%)	21 (20%)	25 (23%)
Renal and Urinary Disorders	34 (7%)	24 (5%)	39 (8%)	63 (6%)	4 (4%)	16 (15%)
Reprod. Syst. and Breast Dis.	10 (2%)	11 (2%)	16 (3%)	27 (3%)	1 (1%)	2 (2%)
Congenital, Familial and Genetic Disorders	0	0	1 (<1%)	1 (<1%)	0	0
Gen. Disorders and Administ. Site Conditions	58 (11%)	56 (11%)	51 (10%)	107 (11%)	3 (3%)	16 (15%)
Investigations	92 (18%)	85 (17%)	119 (23%)	204 (20%)	8 (8%)	18 (17%)
Injury, Poisoning and Procedural Complications	100 (19%)	95 (19%)	105 (21%)	200 (20%)	19 (18%)	9 (8%)
Social Circumstances	1 (<1%)	0	0	0	0	0

Modified Sponsor's Table 4.2.1.1 from the ISS; and Table 14.3.1.2.a from CSR 303, p. 756-769.

Table 103 is a truncated list of the most commonly reported adverse events reported by 2% or more patients in the lesinurad + XOI treatment groups during the 12-month, controlled studies (301, 302 and 304). The adverse events by preferred MedDRA term most commonly reported by lesinurad + XOI treated subjects were upper respiratory tract infection, nasopharyngitis, arthralgia, back pain, and hypertension. Overall, the rates for individual adverse events were similar across the treatment groups. No dose dependent phenomena are apparent on the basis of these data. No other safety issues

were identified on review of adverse event data generated from the other lesinurad studies included in the application's safety database.

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Table 103 – Summary of Common Adverse Events by Preferred Term Occurring in ≥2% of Subjects Treated with Lesinurad by Randomized treatment Group During the 12-Month, Controlled, Lesinurad + XOI Studies 301, 302, and 304

Preferred Term	PBO + XOI (N=516)	LESU200 + XOI (N=511)	LESU400 + XOI (N=510)	Total LESU + XOI (N=1021)
Upper Respiratory Tract Infection	44 (8.5%)	46 (9.0%)	57(11.2%)	103 (10.1%)
Nasopharyngitis	43 (8.3%)	45 (8.8%)	47 (9.2%)	92 (9.0%)
Arthralgia	41 (7.9%)	42 (8.2%)	32 (6.3%)	74 (7.2%)
Back Pain	39 (7.6%)	41 (8.0%)	29 (5.7%)	70 (6.9%)
Hypertension	25 (4.8%)	31 (6.1%)	35 (6.9%)	66 (6.5%)
Blood Creatinine Incr.	12 (2.3%)	22 (4.3%)	40 (7.8%)	62 (6.1%)
Headache	21 (4.1%)	27 (5.3%)	30 (5.9%)	57 (5.6%)
Blood Creatine Phosphokinase Inc.	25 (4.8%)	23 (4.5%)	30 (5.9%)	53 (5.2%)
Diarrhea	23 (4.5%)	23 (4.5%)	27 (5.3%)	50 (4.9%)
Influenza	14 (2.7%)	26 (5.1%)	16 (3.1%)	42 (4.1%)
Sinusitis	13 (2.5%)	17 (3.3%)	20 (3.9%)	37 (3.6%)
Pain in Extremity	17 (3.3%)	20 (3.9%)	16 (3.1%)	36 (3.5%)
Muscle Strain	17 (3.3%)	14 (2.7%)	21 (4.1%)	35 (3.4%)
Nausea	22 (4.3%)	13 (2.5%)	19 (3.7%)	32 (3.1%)
Cough	15 (2.9%)	14 (2.7%)	17 (3.3%)	31 (3.0%)
Bronchitis	13 (2.5%)	14 (2.7%)	16 (3.1%)	30 (2.9%)
Myalgia	11(2.1%)	13 (2.5%)	17 (3.3%)	30 (2.9%)
Urinary Tract Infection	14 (2.7%)	11 (2.2%)	18 (3.5%)	29 (2.8%)
Contusion	18 (3.5%)	12 (2.3%)	16 (3.1%)	28 (2.7%)
Fatigue	8 (1.6%)	13 (2.5%)	12 (2.4%)	25 (2.4%)
Joint Sprain	9 (1.7%)	14 (2.7%)	11 (2.2%)	25 (2.4%)
Pyrexia	16 (3.1%)	9 (1.8%)	15 (2.9)	24 (2.4%)
Dizziness	7 (1.4%)	8 (1.6%)	14 (2.7%)	22 (2.2%)
Edema Peripheral	11 (2.1%)	11 (2.2%)	11 (2.2%)	22 (2.2%)
Vomiting	10 (1.9%)	12 (2.3%)	10 (2.0%)	22 (2.2%)
Constipation	9 (1.7%)	11 (2.2%)	10 (2.0%)	21 (2.1%)
Fall	15 (2.9%)	12 (2.3%)	9 (1.8%)	21 (2.1%)
Gastroenteritis	13 (2.5%)	12 (2.3%)	9 (1.8%)	21 (2.1%)
Gastroesophageal Reflux Disease	4 (0.8%)	14 (2.7%)	7 (1.4%)	21 (2.1%)
Muscle Spasms	11 (2.1%)	12 (2.3%)	9 (1.8%)	21 (2.1%)
Rash	10 (1.9%)	10 (2.0%)	11 (2.2%)	21 (2.1%)
Laceration	8 (1.6%)	6 (1.2%)	13 (2.5%)	19 (1.9%)
Blood Glucose Inc.	6 (1.2%)	9 (1.8%)	9 (1.8%)	18 (1.8%)
Osteoarthritis	10 (1.9%)	8 (1.6%)	10 (2.0%)	18 (1.8%)
Type 2 Diabetes Mellitus	3 (0.6%)	10 (2.0%)	8 (1.6%)	18 (1.8%)
Blood Triglycerides Inc.	15 (2.9%)	5 (1.0%)	12 (2.4%)	17 (1.7%)
Hypertriglyceridemia	6 (1.2%)	10 (2.0%)	7 (1.4%)	17 (1.7%)
Insomnia	9 (1.7%)	10 (2.0%)	6 (1.2%)	16 (1.6%)
Tendonitis	10 (1.9%)	10 (2.0%)	6 (1.2%)	16 (1.6%)
Non-Cardiac Chest Pain	7 (1.4%)	10 (2.0%)	5 (1.0%)	15 (1.5%)
Nephrolithiasis	9 (1.7%)	3 (0.6%)	11(2.2%)	14 (1.4%)

Modified Sponsor's table 4.12.1.1; ISS

7.4.2 Laboratory Findings

Laboratory data from the three phase 3, 12-month controlled lesinurad + XOI studies (301, 302 and 304) was presented as follows: change from baseline by parameter and the proportion of markedly abnormal values relative to baseline. The Applicant provided normal range of values for each lab parameter assessed. They were reviewed and the clinically acceptable range for normal appeared appropriate.

7.4.3 Hematology Parameters

Due to concerns for additive bone marrow toxicity associated with the need for co-administration of colchicine and xanthine oxidase inhibitors with lesinurad, the safety database was reviewed for cases of cytopenias particularly in the three, 12-month, phase 3, controlled studies (301, 302 and 304). The majority of patients in all treatment groups of these trials had hematology values that were within the normal range at baseline and at the last visit. No clinically meaningful changes from baseline were noted for the various hematology parameters across treatment groups for these phase 3 controlled studies. Review of shift changes from normal to the low range did not reveal any clinically meaningful trends for WBC and differential counts. Shifts from normal to the low range in platelet count data were comparable across treatment arms. More patients in the LESU400 mg +XOI group (6%) experienced shifts to below the normal range in hemoglobin then in the LESU200 mg + XOI (2%) and PBO + XOI (3%) groups. In each of the two lesinurad +XOI treatment arms 5% of subjects had shifts from the normal to low range for hematocrit as compared to 2% in the PBO +XOI group. The pattern of hematology parameters for the 6-month, monotherapy study was similar to those in pooled, 12-month, controlled lesinurad + XOI studies. There was one case report each of decreased white count and thrombocytopenia in the four, phase 3 studies. Subject 301-05183-105 was a 54 year old white male randomized to LESU200 mg + XOI (allopurinol 300 mg qd) who developed a RCTC Grade 3 decreased WBC count that resolved with discontinuation of lesinurad. This patient was also taking concomitant colchicine as prophylactic therapy for gout flares at the time he developed leukopenia. Subject 301-05314-113 was a 77 year old white male who developed RCTC Grade 1 thrombocytopenia while taking LESU200 mg + XOI (allopurinol 300 mg qd) which resolved with discontinuation of both lesinurad and allopurinol. This patient was also taking a number of other medications that can also cause thrombocytopenia (naproxen and lisinopril). Overall, no new safety issues related to hematologic lab assessments associated with the use of lesinurad were identified on review of these data.

7.4.4 Serum Chemistries and Electrolytes

Since gout can also affect the kidney by the formation of urate stones or causing gouty nephropathy (parenchymal disease) test results of renal function related parameters (albumin, BUN, calcium, carbon dioxide, creatinine, phosphate, and potassium) collected over the course of the pooled, 12-month, controlled lesinurad + XOI studies (301, 302 and 304) were reviewed for potential safety signals. No meaningful trends were noted on examination of changes from baseline or shift table analyses for the following parameters: albumin, calcium, and phosphate.

Review of shift table analyses in serum creatinine from normal at baseline to RCTC Grade 3 or 4 post-baseline value at any time during over the course of the pooled, phase 3 controlled studies showed 10% of subjects in the LESU400 mg + XOI group experienced such shifts as compared to 3% in the LESU200 mg + XOI group and 1% in the PBO + XOI group. These changes are the result of lesinurad's effects on the kidney. (Reader is referred to the preceding renal adverse events section for more information.) Small increases were noted on review of the mean changes and percent mean changes from baseline in BUN for the three treatment groups, but are not clinically significant. However, more patients in the LESU200 mg + XOI (25%) and LESU400 mg + XOI (24%) groups had shift changes from normal at baseline to a high at any time post-baseline during these studies as compared to PBO+ XOI (15%). This is not unexpected since BUN values should reflect the lesinurad-induced elevations in serum creatinine observed over the course of these trials. Similar mean changes from baseline in bicarbonate were noted for the two lesinurad treatment groups which were less than that observed in the PBO + XOI group but were not clinically significant. Shifts from normal at baseline to low post-baseline values in bicarbonate occurred in 23% of PBO + XOI subjects versus 20% and 21% of subjects in the LESU200 mg +XOI and LESU400 mg + XOI groups, respectively, and reflect the changes in renal function associated with the administration of lesinurad.

No clinically meaningful trends in changes from baseline or shift table analysis for potassium were noted. However, due to concerns of hyperkalemia associated with worsening renal function, review of case reports identified two patients (Subjects 301-05185-108 and 301-05278-112) who had elevated serum potassium levels of 5.6 mmol/L noted at Months 12 and 10, respectively, that were associated with elevated sCr $\geq$ 1.5 x baseline at these visits. Review of the remaining electrolytes and chemistry parameters was remarkable for mean values at baseline at or above the upper limit of the reference range of 5.6 mmol/L for glucose in all treatment groups most likely due to the number of subjects with metabolic syndrome or diabetes mellitus who participated in these studies. No meaningful changes from baseline in glucose were noted. Shifts from baseline normal to high at last value in glucose were comparable across the three treatment groups.

Overall, similar findings were noted on examination of these parameters for the 6-month, monotherapy study (303). Other than the safety signals of elevations in serum

creatinine and eCrCl discussed earlier in this review and the corresponding changes in BUN, no additional safety signals were identified on review of the serum electrolytes and chemistries for lesinurad.

7.4.5. Liver function Tests

See the preceding hepatotoxicity section.

7.4.6 Urinalysis

Review of the urinalysis mean changes and shift from baseline did not reveal any clinically meaningful trends overall for glucose, ketones, or occult blood. As to be expected, higher mean changes over baseline for the presence of uric acid and uric acid crystals were observed in both lesinurad + XOI treatment groups (20-26%) as compared to the PBO + XOI group (3%) for the pooled, 12-month, phase 3 controlled studies (301, 302, and 304). The proportion of subjects of subjects with samples positive for uric acid crystals was higher for patients treated with concomitant allopurinol than febuxostat. The Applicant notes the presence of uric acid crystals in the urine samples collected over the course of these trials is consistent with lesinurad's mechanism of action but post-collection handling (up to 72 hours at room temperature prior to testing) may have contributed to ex vivo crystal precipitation. The occurrence of proteinuria was also assessed in these studies by spot urine protein-creatinine ratios. In the pivotal phase 3 lesinurad studies, urine creatinine was tested in real time by ambient method at baseline, Months 3, 6, and 12, and retrospectively by frozen sample testing at all other time points for samples less than 6 months old. As a result, urine protein-creatinine data were not available for all subjects/visits. Using a value of $\geq$ 0.2 mg/mg as the definition of clinically meaningful proteinuria, no significant differences in the mean change from baseline urine protein-creatinine ratio over the course of the three, phase 3, controlled lesinurad + XOI studies was noted: LESU200 mg + XOI: 0.03; LESU400 mg + XOI: 0.03 and PBX +XOI: 0.03. For completeness, the Applicant also submitted the results from a mean change over baseline analysis of subgroups of patients who had elevations in sCr $\geq$ 1.5 or $\geq$ 2.0 x baseline which were also unremarkable for any clinically significant trends. Shift from baseline to maximum urine protein- creatinine ratio defined by ratio values of <0.2, $\geq$ 2.0 to <1.0, and $\geq$1.0 mg/mg analyses for subjects with or without sCr elevations $\geq$ 1.5 x baseline and subjects with or without sCr elevations $\geq$ 2.0 x baseline during these studies revealed no clinically meaningful trends in subjects shifting from urine protein-creatinine ratio category at baseline of <2.0 mg/mg to a maximum post-baseline value $\geq$0.2 mg/mg.

Overall, similar findings were noted on examination of the urinalysis parameters for the 6-month, monotherapy study (303). No additional safety signals were identified on review of the urinalysis results for lesinurad.

7.4.3 Vital Signs

According to the protocols for the four phase 3 studies, patients' vital signs (systolic and diastolic blood pressure, respiratory rate, pulse rate and temperature) were assessed at the screening visit, Day-14, Day -7, baseline, Week 2 and every monthly visit through the final study visit. Review of the mean changes from baseline and shift of minimum and maximum post-baseline results for the vital sign parameters for the safety population from each of the four phase 3 studies submitted in support of lesinurad failed to identify any safety issues.

7.4.4 Electrocardiograms (ECGs)

The results from a thorough QT (TQT) study (Study 117) conducted with moxifloxacin as a positive control was submitted by the Applicant in support of lesinurad's safety profile. No significant QTc prolongation effects of supratherapeutic doses (400 mg and 1600 mg) of lesinurad were detected in this TQT study according to Dr. Janice Brodsky of the agency's interdisciplinary review team for QT studies who examined the data from this trial. (Refer to review dated October 23, 2012 under IND 102128).

Serial 12-lead ECGs were performed on all patients participating in the three, 12-month, phase 3, controlled studies (301, 302, 303 and 304) at Day -7, baseline and at the Month 6 (studies 301, 302 and 304) and Month12 or final visit which were read by central readers and reviewed by the CEAE. No notable changes from baseline or differences between treatment groups in mean and median values for ventricular rate, RR duration, PR duration, QRS duration, QT duration, and QcF were observed in the serial ECGs from these studies. Overall, the number and incidence of any ECG-associated adverse events was low and similar across the treatment groups: PBO + XOI: 2 (0.4%) cases of ECG-related adverse events; LESU200 mg + XOI: 1(0.2%) case ECG-related adverse events; and LESU400 mg + XOI: 3 (0.6%) cases ECG-related adverse events. Four out of these five ECG-related adverse events occurred in patients treated with concomitant allopurinol; the remaining case occurred in a patient treated with concomitant febuxostat. The number and incidence of new-onset atrial fibrillation was also low and similar on comparison between the three treatment groups: PBO + XOI: 2 (0.4%) cases of new onset atrial fibrillation; LESU200 mg + XOI: 1(0.2%) case of new onset atrial fibrillation; and LESU400 mg + XOI: 1 (0.2%) case of new onset atrial fibrillation. There was one case of new-onset atrial flutter that occurred in a patient in the LESU400 mg +XOI group. No ECG-associated adverse events, and no findings of new onset-atrial fibrillation or atrial flutter were reported in the 6-month, monotherapy study (303). No new or unexpected safety signals were identified on review of the ECG results for lesinurad.

7.4.5 Special Safety Studies/Clinical Trials

The Applicant did not conduct any special safety studies or clinical trials in support of lesinurad's safety profile.

7.4.6 Immunogenicity

Not applicable for this application since lesinurad is a small molecular entity that does not contain proteins or protein derivatives that would elicit an immunogenic response.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

As summarized in the preceding **Table 77** and discussed over the course of this safety review, examination of the safety data collected from the three, phase 3, 12-month, controlled, lesinurad + XOI studies (301, 302, and 304) revealed a dose-dependent relationship exists for the occurrence of renal-related adverse events as well as serious adverse events with the 400 mg dose of lesinurad when administered once a day with a concomitant xanthine oxidase inhibitor (XOI). Additional support for renal-related dose-dependent adverse events came from the 6-month, controlled, Study 303 which evaluated the 400 mg once a day dose of lesinurad as monotherapy. In this study a higher rate of renal-related adverse events was observed than in the pooled safety database for the three, phase 3, controlled lesinurad + XOI studies (301, 302 and 304). (Reader is referred to the preceding renal adverse events section for additional information.)

7.5.2 Time Dependency for Adverse Events

Overall, review of the cumulative long term exposure data generated from the ongoing studies 306 and 307 did not reveal any additional safety signals associated with prolonged exposure to lesinurad when concomitantly administered with an XOI. Study 305, which was the long term extension study for patients who completed the controlled, monotherapy Study 303, was terminated early due to the high rate (17%) of renal-related adverse events observed in subjects. The rate of renal related adverse events observed in Study 305 was higher in subjects who had been previously-treated with PBO in the preceding controlled monotherapy study (19%) than subjects who continued receiving monotherapy with LESU400 mg once daily (14%). Overall, 4% of the participating patients in this extension trial discontinued treatment with study medication due to renal-related adverse events. The rate of discontinuation of study medications

due to renal-related adverse events was also slightly higher in previously treated PBO subjects (5%) versus subjects (3%) who continued treatment with the same dose of lesinurad. The rate of elevations in sCr≥ 1.5 x baseline value was 31% and was again higher in formerly PBO-treated patients who were initiating lesinurad monotherapy (35% versus 26%). The two subjects who had serious renal-related adverse events (1 case of acute renal failure and 1 case of renal impairment) had been treated with PBO while participating in the preceding monotherapy study (303).

7.5.3 Drug-Demographic Interactions

Overall, review of the cumulative long term exposure data generated from the ongoing studies 306 and 307 did not reveal any additional safety signals associated with prolonged exposure to lesinurad when concomitantly administered with an XOI. Study 305, which was the long term extension study for patients who completed the controlled, monotherapy Study 303, was terminated early due to the high rate (17%) of renal-related adverse events observed in subjects. The rate of renal related adverse events observed in Study 305 was higher in subjects who had been previously-treated with PBO in the preceding controlled monotherapy study (19%) than subjects who continued receiving monotherapy with LESU400 mg once daily (14%). Overall, 4% of the participating patients in this extension trial discontinued treatment with study medication due to renal-related adverse events. The rate of discontinuation of study medications due to renal-related adverse events was also slightly higher in previously treated PBO subjects (5%) versus subjects (3%) who continued treatment with the same dose of lesinurad. The rate of elevations in sCr≥ 1.5 x baseline value was 31% and was again higher in formerly PBO-treated patients who were initiating lesinurad monotherapy (35% versus 26%). The two subjects who had serious renal-related adverse events (1 case of acute renal failure and 1 case of renal impairment) had been treated with PBO while participating in the preceding monotherapy study (303).

7.5.4 Drug-Disease Interactions

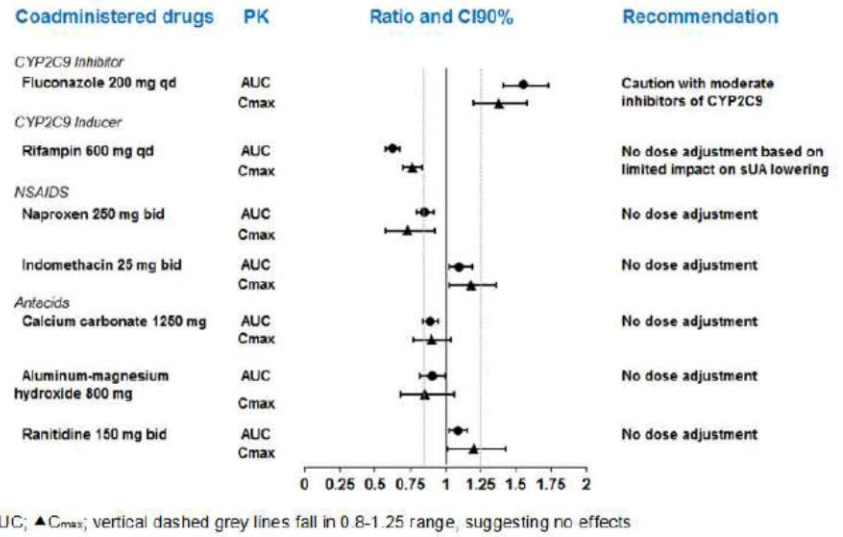
Since patients with hepatic impairment were excluded from lesinurad's phase 2/3 clinical development program, the Applicant conducted a phase 1, single dose study (Study 118) in subjects with mild to moderate hepatic impairment. Mild to moderate hepatic impairment (Child-Pugh Classes A and B) had no significant effect on lesinurad's PK profile based on data from this study examined by the clinical pharmacology reviewer. In view of these findings, adjustment in the dose of lesinurad in patients with mild to moderate hepatic impairment is not required. Since lesinurad was not studied in subjects with moderate to severe hepatic impairment, use of the drug in this population is not recommended.

The effect of renal impairment on the PK profile of lesinurad was evaluated in the two phase 1 studies (104 and 120). Studies 104 and 120 assessed single doses of 200 mg and 400 mg of lesinurad in adult volunteers with mild-to-moderate or moderate-to-severe renal impairment, respectively. Lesinurad exposure (AUC) increased by 31%, 50-74% and 113%, respectively, in subjects with mild-to-moderate and severe impairment as compared to subjects with normal renal function. The efficacy and safety of lesinurad was also evaluated in phase 2 and 3 studies that included gout patients with mild-moderate renal impairment (eCrCL $\geq$ 45 mL/min). Gout subjects with moderate renal impairment had less overall efficacy and had a higher occurrence of renal-related adverse events compared to patients with mild renal impairment or normal renal function. Lesinurad's efficacy and safety was not evaluated in gout patients with severe renal impairment, with end stage renal disease (ESRD), or receiving dialysis. In view of its mechanism of action, the drug is not expected to be effective in these populations. (Note: The reader is referred to the agency's clinical pharmacology review for additional information regarding these studies.)

7.5.5 Drug-Drug Interactions

Lesinurad is a substrate of CYP2C9 and is a weak CYP3A4 inducer. Included in the application were the results from seven phase 1 studies that assessed the effects of lesinurad on co-administered drugs used to treat gout such as febuxostat, allopurinol colchicine, and NSAIDs (naproxen and indomethacin) as well as the results from eight drug-drug interaction (DDI) studies which are listed in Table 2. The findings from these studies are summarized in **Figure 22** and **Figure 23**:

Figure 22 – Effect of Co-Administered Drugs on Pharmacokinetics of Lesinurad

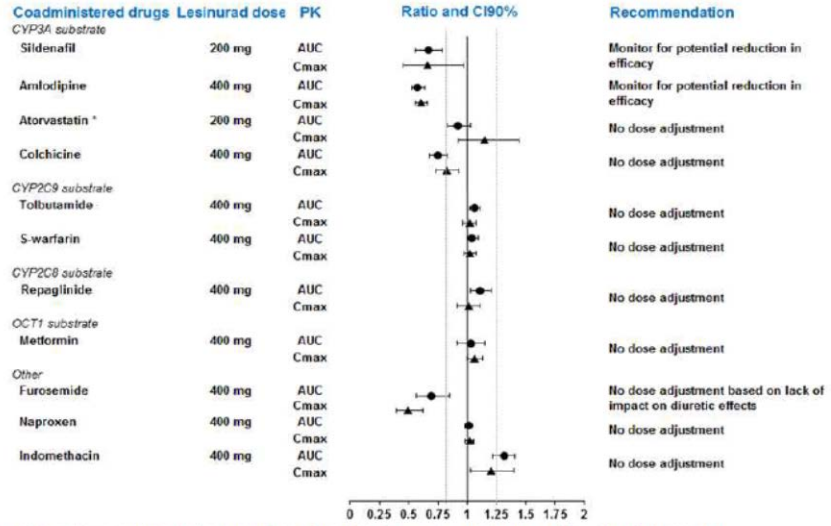


● AUC; ▲C_{max}; vertical dashed grey lines fall in 0.8-1.25 range, suggesting no effects

Note: Geometric mean ratio and 90% confidence interval (CI90%) are presented.
Source: Study 122 CSR, Study 126 CSR, Study 130 CSR, and Study 127 CSR.

Modified Sponsor's Fig. 3; p. 24 Clinical Overview

Figure 23 – Effect of Lesinurad on the Pharmacokinetics of Co-Administered 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.
Source: Study 108 CSR, Study 110 CSR, Study 113 CSR, Study 114 CSR, Study 115 CSR, Study 116 CSR, Study 123 CSR, Study 126 CSR, and Study 128 CSR.

Modified Sponsor's Fig. 4; p. 26 Clinical Overview

Since lesinurad exposure is increased when it is co-administered with inhibitors of CYP2C9 it should be used with caution in patients taking moderate inhibitors of

CYP2C9 such as fluconazole and amiodarone. Exposure to lesinurad is decreased when it is co-administered with inducers of CYP2C9 (e.g., rifampin) which could potentially result in a decrease in the therapeutic efficacy of lesinurad. Since lesinurad is a weak CYP3A4 inducer, concomitant use of lesinurad with CYP3A4 substrates such as sildenafil and amlodipine could potentially result in reduced efficacy of these drugs. No dose adjustments for lesinurad are required when it is co-administered with the other drugs tested shown in **Figure 22** and **Figure 23**. Subgroup analyses of subjects in Studies 301 and 302 taking concomitant low dose aspirin (≤325 mg/day) or thiazide diuretics showed that these drugs did not impact on the efficacy of lesinurad. (Note: The reader is referred to the agency's clinical pharmacology review for additional information regarding these studies.)

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Review of the safety databases for the four phase 3 studies (301, 302, 303 and 304) identified seven cases of malignancy. Six of out of these eight cases occurred in patients taking LESU400 mg +XOI: 2 cases of prostate cancer (304-17004-40 and 302-05015-202), 1 case of gastric carcinoma (Subject 302-17006-207), 1 case of metastatic sarcomatoid carcinoma (Subject 301-05239-103), 1 case of oral basal cell carcinoma (Subject 301-05075-107), and 1 case of basal carcinoma of the skin involving multiple sites (302-16019-208). The remaining two cases of malignancy occurred in patients randomized to placebo: 1 case of pancreatic neuroendocrine tumor (well differentiated neoplasm on histopathology) (Subject 302-05318-205) and 1 case of malignant lung neoplasm (Subject 301-05098-109). In view of the lack of a discernable pattern of neoplasms and the presence of confounding factors (e.g., positive family history and history of tobacco use/smoking) identified on review of five out the six malignancy case reports for subjects treated with lesinurad, there does not appear to be an increase in risk for carcinogenicity associated with lesinurad. Additional support for the lack of carcinogenicity comes from the genotoxicity and animal carcinogenicity studies contained in the application which showed lesinurad was not mutagenic nor clastogenic and was not associated with an increase in risk for neoplasms in animals. (The reader is referred to the pharmacology/toxicology review of this application for additional information.)

7.6.2 Human Reproduction and Pregnancy Data

The study protocols for the four phase 3 trials that generated the safety data in support of this new drug application prohibited pregnant and breast feeding women from participating in these studies. Additionally, the studies' entry criteria required women of

reproductive potential to practice effective methods of contraception for the duration of the trials and to have negative urine pregnancy testing at screening. Thus, no female subjects were reported to have become pregnant during these trials.

7.6.3 Pediatrics and Assessment of Effects on Growth

Not applicable.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Based on the safety profile of single doses of up to 1600 mg and multiple daily doses of up to 600 mg evaluated in the phase 1 and phase 2 trials conducted as part of lesinurad's clinical development program, the Applicant defined an overdose of the drug to be a single daily dose >1200 mg. According to the Applicant, there were no reported cases of overdose involving >1200 mg of lesinurad as a single dose in the drug's safety database. However, there were two cases coded as "overdose" that occurred in phase 3 studies in which the amount of lesinurad ingested by the subjects did not exceed that prespecified definition of an overdose. Subject 303-05150-301 was a 56 year-old, white male with a history of attention deficit/ hyperactivity disorder and hypertension who accidently ingested 800 mg qd of lesinurad (400 mg twice a day) for two weeks (Day 33 to Day 51) as a result of confused state induced by his hypertension medication (lisinopril). This patient reported experiencing disorientation, anorexia, dry mouth and peripheral edema that were evaluated as RCTC Grade I in intensity during the higher lesinurad dosing period. Lesinurad dosing was temporarily withheld starting on Day 56 and resumed on Day 64. This patient was subsequently lost to follow-up on Day 148. The second case involved a 46 year-old white male (Subject 302-17004-204) who was hospitalized after he intentionally overdosed on 7 bottles of beer, brake fluid, tramadol, paracetamol, venlafaxine, quetiapine, clonazepam, dothiepin hydrochloride and allopurinol due to worsening suicidal depression secondary to chronic back pain. Following stabilization of his psychiatric condition, he continued on blinded therapy post-discharge from the hospital. It is unlikely that lesinurad will be abused since its pharmacologic action does not affect the central nervous system and the drug can cause nephrotoxicity including kidney stones. No formal studies on the withdrawal or rebound effects of lesinurad were conducted in support of its safety.

7.7 Additional Submissions / Safety Issues

Additional safety information that was contained in the Applicant's 120-day safety update submitted on April 30, 2015 has been incorporated into the appropriate subsections of this review.

8 Postmarket Experience

Lesinurad is a new molecular entity (NME) that has not been approved for marketing in any country.

APPEARS THIS WAY ON ORIGINAL

9 Appendices

9.1 Literature Review/References

The Applicant did not submit the results from a search of the worldwide literature in support of lesinurad's safety profile. A literature search was conducted by this medical officer on August 25, 2015 using the search engine PubMed. A total of 9 citations in English were identified. Examination of these citations which included articles describing the results from phase 1 and 2 studies submitted in support of lesinurad's safety and efficacy as well as discussions of new therapeutic treatments under clinical development for gout did not reveal any new potential safety signals associated with the use of lesinurad.

References:

1. Khanna D, Fitzgerald JD, Khanna PP, et al. 2012 American College of Rheumatology guidelines for management of gout, part 1: systematic nonpharmacologic and pharmacologic therapeutic approaches to hyperuricemia. Arthritis Care Res. 2012;64(10):1431-1446.
2. Dalbeth N, McQueen FM, Singh JA, et al. Tophus measurement as an outcome measure for clinical trials of chronic gout: progress and research priorities. J Rheum 2011;38(7):1458-1461.
3. Singh JA, Taylor WJ, Simon LS, Khanna PP, et al. Patient-Reported Outcomes in Chronic Gout: A Report from OMERACT 10. J Rheum. 2011; 38(7):1452-1457.
4. Woodworth T, Furst DE, Alten R, et al. Standardizing Assessment and Reproting of Adverse Effects in Rheumatology Clinical Trials II: the Rheumatology Common Toxicity Criteria v2.0. J Rheumatol 2007;34:1401-14.
5. Becker MA, Fitz-Patrick D, Choi H, Dalbeth N, et al. An open-label, 6-month study of allopurinol safety in gout: The LASSO study. In press. Seminars in Arthritis & Rheumatism, 2015.
6. Stack AG, Hanley A, Casserly LF, Cronin CJ, et al. Independent and conjoint associations of gout and hyperuricemia with total and cardiovascular mortality. Q J Med 2013; 106:647-658. [1]
7. Harter JG: Acute flank pain and hematuria: lessons from adverse drug reaction reporting. J Clin Pharmacol 1988:;28:560-565.

9.2 Labeling Recommendations

Based on review of the data submitted in support of this application, the following are recommendations that should be included in the drug's label:

1. The indication should note that lesinurad is indicated for the treatment of hyperuricemia associated with gout in combination with a xanthine oxidase inhibitor. The primary justification for this is that the safety of lesinurad as monotherapy is not acceptable.
2. A warning regarding the risk for serious renal adverse events to occur particularly in patients with lower than normal renal reserve (e.g., subjects with eCrCL $\leq$60 mL/min). This warning should also include information regarding the dose-

dependent increase in risk for serious renal adverse events and MACE events to occur particularly in patients with underlying CKD.

3. Additional consideration as to when to discontinue treatment with lesinurad based on serum creatinine elevations particularly in patients with underlying CKD in view of the patients who required dialysis in the safety database.
4. Although Study 304 failed to capture its primary endpoint, information describing the trial's results should be included under Section 14 of the label to enable healthcare providers to determine if the benefits of prescribing lesinurad outweigh the risks for their patients.
5. Under Section 14, the descriptions of the phase 3 studies should also include the mean change in sUA observed with the to-be-marketed dosing regimen of lesinurad with XOI.

9.3 Advisory Committee Meeting

An Arthritis Advisory Committee (AAC) meeting is scheduled for October 23, 2015 to discuss the risks and benefits associated with the use of lesinurad based on the efficacy and safety issues identified during the agency's review of the data submitted in support of this application.

10 Financial Disclosure

Clinical Investigator Financial Disclosure
Review Template

Application Number: NDA 207,988

Submission Date: December 29, 2015

Applicant: Ardea Biosciences, Inc.

Product: Lesinurad (Zurampic®)

Reviewer: Rosemarie Neuner, MD, MPH

Date of Review: September 2, 2015

Covered Clinical Study (Name and/or Number): Study RDEA594-301 CLEAR 1; Study RDEA-594-302 CLEAR 2; and Study RDEA-594-304 CRYSTAL

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 505		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 2		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: 2 Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from applicant)

Number of investigators with certification of due diligence (Form FDA 3454, box 3) 9		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from applicant)

Discuss whether the applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry *Financial Disclosure by Clinical Investigators*.[9] Also discuss whether these interests/arrangements, investigators who are sponsor employees, or lack of disclosure despite due diligence raise questions about the integrity of the data:

- If not, why not (e.g., study design (randomized, blinded, objective endpoints), clinical investigator provided minimal contribution to study data)
- If yes, what steps were taken to address the financial interests/arrangements (e.g., statistical analysis excluding data from clinical investigators with such interests/arrangements)

Briefly summarize whether the disclosed financial interests/arrangements, the inclusion of investigators who are sponsor employees, or lack of disclosure despite due diligence affect the approvability of the application.

The financial disclosure Form 3454 signed by the Applicant certified that only two Clinical Investigators who participated in Studies (b) (6) had financial arrangements as a paid consultants as defined in 21 CFR 54.2 (a). According to the submitted Form 3455, these individuals had a consulting agreement with the Applicant for which they were paid honoraria. To minimize the potential bias of clinical study results by any of the disclosed arrangements or interests, the phase 3 safety and efficacy studies were randomized, placebo-controlled, double-blind trials and the Clinical Investigators were not given access to study results until after the database lock for each study. In addition, the enrollment contribution for these two Clinical Investigators was low and should further prevent any bias that could affect the outcome of the studies.

Additionally, none of the principal investigators or sub investigators reportedly had a proprietary interest in this product or a significant equity in Ardea Biosciences Inc., which is commercially developing lesinurad for marketing in this country as described in 21 CFR 54.2(b).

[9] See [web address].

10.1 Additional Study Reports

Protocol RDEA594-303

Title: A Phase 3 Randomized Double-Blind, Multicenter, Placebo-Controlled, Study to Assess the Efficacy and Safety of Lesinurad Monotherapy Compared to Placebo in Subjects with Gout and an Intolerance or Contraindication to a Xanthine Oxidase Inhibitor (LIGHT).

Dates Conducted: This trial was started on February 3, 2012 and completed on October 23, 2013.

Study Sites: A total of 103 study sites screened subjects in 7 countries: United States (US), Canada, Belgium, Germany, Australia, New Zealand, and South Africa.

Objectives:
Primary objectives:

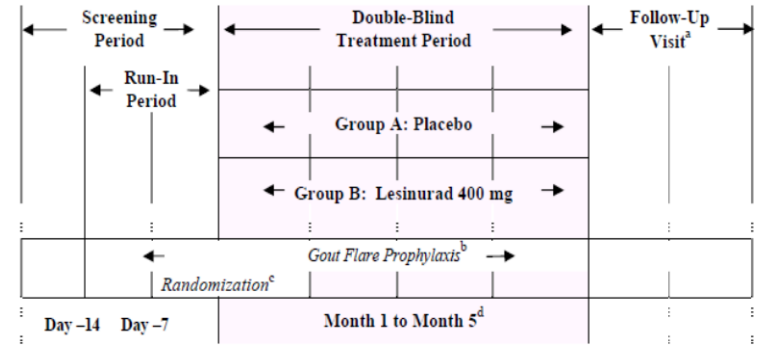
- Assess the efficacy of lesinurad monotherapy compared to placebo by Month 6

Secondary objectives:

- Evaluate the safety of lesinurad monotherapy
- Evaluate via population analysis the influence of intrinsic factors (age, sex, race, body weight, renal function, concomitant medication use) on oral clearance of lesinurad
- Assess the effect of lesinurad monotherapy on Health-Related Quality of Life and physical function

Overall Design:
This was to have been a multicenter, randomized, double-blind, placebo-controlled, parallel group trial in gout patients who were unable to tolerate or for whom xanthine oxidase inhibitors were medically contraindicated. The study was comprised of three parts: an initial 28-day screening period (which included a run-in period of approximately 14 days) followed by a 6-month, double-blind treatment period and a 14-day follow-up period. The following **Figure 24** is a schema of the trial:

Figure 24 – Design Scheme for Study 303



[a] Subjects 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.
[b] Prophylactic treatment for gout flare consisted of colchicine 0.5 to 0.6 mg once daily or nonsteroidal anti-inflammatory drug ± proton pump inhibitor through Month 5.
[c] Subjects whose serum urate was ≥ 6.5 mg/dL at the Screening Visit and the Day -7 Visit could have been randomized at Day 1.
[d] Study visits at Week 2 and monthly beginning at Months 1 through Month 6 (or early termination).

Modified Sponsor's Fig. 1; p. 34 CSR Study 303

During the run-in period of the screening phase, study candidates were to have initiated prophylactic gout therapy. Subjects who have successfully completed the study's screening process were to have been randomized via a 1:1 ratio stratified by Day -7 renal function (estimated creatinine clearance ≥ 60 ml/min versus < 60 ml/min calculated by the Cockcroft-Gault formula using ideal body weight) and tophus status during screening (presence of at least 1 tophi versus absence of tophi) to one of following 2 treatment groups:

- Dosing Regimen A: Placebo
- Dosing Regimen B: lesinurad 400 mg QD

All gout flare prophylaxis regimens were to have been discontinued at Month 5. Patients who completed this study were to have the option of continuing to receive active treatment with lesinurad by enrolling in a 12-month, open-label extension trial (Study 305). Subjects who did not enter the OLE study were to have been seen for safety within 14 days of completing the double-blind portion of these trials. Patients who discontinued study treatment were to have continued with protocol-specific procedures until they complete the trial.

Study Entry Criteria: This study utilized the same major inclusion and exclusion criteria as the common protocol for Studies 301 and 302 which are listed in the preceding **Table 3** with the following exceptions:

- Must have a history (either by medical record or patient interview) of intolerance or a contraindication to either allopurinol or febuxostat

- Individuals with a documented history or suspicion of kidney stones were not permitted to participate in this trial

Treatment: Study medication was to have been supplied as 400 mg tablets of lesinurad or matching placebo. All doses of lesinurad/placebo were to have been taken in the morning with food and 1 cup of water. Subjects were instructed to drink 2 liters of liquid a day and to remain well hydrated throughout the day. Compliance was to have been assessed by the number of study medication tablets returned. The protocol permitted the temporary stopping of study medication and gout prophylaxis due to suspected drug toxicity or clinically meaningful increases in serum creatinine. Resumption of the same dose of study medications (e.g., lesinurad or matching placebo) was to have occurred when medically appropriate or when the patient's serum creatinine had returned to within 0.2 mg/dL of its level prior to elevation. Additionally, subjects who had temporally discontinued study medication due to an increase in serum creatinine were to have been instructed to increase their daily fluid intake to at least 2 liters/day and start a urine alkalinization regimen (e.g., sodium bicarbonate at 650 mg once or twice daily or potassium citrate 30-40 mEq/day) in order to increase the solubility of urinary uric acid.

Concomitant Medications: The same restrictions or prohibitions of certain medications as listed in the common protocol for Studies 301 and 302 applied to this protocol.

Gout Flare Treatment:
Patients who experienced an acute gout flare during the study were to have been treated with an individualized anti-inflammatory regimen that included colchicine (acute flare regimen), a NSAID with a PPI, or corticosteroids administered via the intra-articular or oral route.

Study Procedures: The following **Table 104** and **Table 105** are tabular flow charts of the scheduled study visits and protocol specified procedures and evaluations that were to have been completed.

Table 104 – Schedule of Procedures and Evaluations for Study 303

Assessment/Procedure	Screening Period			Baseline (Day 1)	Double-Blind Treatment Period**			Follow-Up***
	Screening Visit -Day -28*	Run-In Period						
		Day -14	Day -7		Week 2	Months 1 -5	Month 6/Early Termination Visit	Follow-Up
Informed Consent	√							
Review Eligibility Criteria	√							
Confirm Eligibility		√	√	√				
Demographics	√							
Review Baseline Characteristics of Gout, Including Flares	√							
Medical and Surgical History (including comorbidities)	√							
Record ULTs	√							
Concomitant Medications	√	√	√	√	√	√	√	√
Patient Reported Outcomes*				√		Month 3	√	
Assess AEs		√	√	√	√	√	√	√
Assess Compliance With Gout Flare Prophylaxis			√	√	√	√		
Assess Gout Flares			√	√	√	√	√	√
Provide eDiary and Training				√				
Assess Compliance With eDiary					√	√	√	
Physical Examination		√					√[b]	
Vital Signs	√	√	√	√	√	√	√	√

Modified Sponsor's Table 1; p. 35 CSR 303

Table 105 – Schedule of Procedures and Evaluations for Study 303 (cont.)

Assessment/Procedure	Screening Period			Baseline (Day 1)	Double-Blind Treatment Period**			Follow-Up***
	Screening Visit –Day -28*	Run-In Period						
		Day -14	Day -7		Week 2	Months 1-5	Month 6/Early Termination Visit	Follow-Up
12-Lead ECG (triplicate)			√	√		Month 1	√	
Urinalysis	√			√		√	√	√
Urine Biomarkers				√		√	√	
Spot Urine				√		Month 3	√	
Hematology	√			√		√	√	√
Blood Biochemistry (including sUA, pregnancy test[c], and CK)[d]	√		√	√		√	√	√
Record Patient Responses to Muscle Assessment Questions				√		√	√	√
Plasma Sample for PK and Biomarkers				√		√	√	
Genetic Testing (OPTIONAL single sample collection)				√				
Initiate Gout Flare Prophylaxis[e]		√						
Randomization				√				
Dispense Lesinurad/Placebo				√	√	√		
Assess Compliance With Lesinurad/Placebo and Review Dosing Instructions[f]					√	√	√	

Abbreviations: AEs, adverse events; CK, creatine kinase; ECG, electrocardiogram; eDiary, electronic diary; PK, pharmacokinetics; sUA, serum urate; ULT, urate-lowering therapy.

* Screening started approximately 28 days (Day -28) prior to Baseline (Day 1) and was performed no more than 2 weeks prior to initiation of gout flare prophylaxis by Day -14. There was a ± 1 day window around the Run-in Period Visits (Day -14 and Day -7).

** There was a ± 7 day window around the Double-blind Treatment Period Visits, except Week 2 which was ± 4 days. A clinical month was considered to be 28 days. All scheduled visits were referenced to Day 1.

*** Subjects who did not enter an extension study completed a safety Follow-up Visit within approximately 14 days of completing the Double-blind Treatment Period.

[a] Patient-Reported Outcome assessments included Health Assessment Questionnaire - Disability Index, Short Form-36, Sheehan Disability Scale, and Patient Global Assessment.

[b] Excluding height and waist circumference.

[c] Serum pregnancy test was conducted only on female subjects of childbearing potential.

[d] HCV and HBV were only evaluated during Screening and at Baseline (Day 1) to confirm study eligibility.

[e] Investigator confirmed eligibility prior to prescribing prophylaxis.

[f] All doses of lesinurad/placebo were taken in the morning with food and 1 cup (8 oz; 240 mL) of water. With Protocol Amendment 4, subjects were instructed to drink 2 liters (68 oz) of liquid a day. For example, another 3 cups (24 oz; 720 mL) of liquid during the 3 to 4 hours after taking the study medication was encouraged, and then the subject was to remain well hydrated (an additional 4 cups [32 oz; 960 mL] of liquid) throughout the day.

Modified Sponsor's Table 2; p. 356 CSR 303

Outcome Measures:

Primary efficacy endpoint:

- Proportion of patients with sUA <6 mg/dL by Month 6

Secondary efficacy endpoints:

This study had a number of secondary endpoints as follows:

- Proportion of subjects whose sUA level is <6.0 mg/dL, <5.0 mg/dL and <4.0 mg/dL at each visit
- Absolute and percent change from baseline in sUA levels at each visit
- Proportion of subjects requiring treatment for a gout flare at monthly intervals between Month 6 and Month 12

- Proportion of subjects with an improvement from baseline in the Health Assessment Questionnaire – Disability Index (HAQ-DI) of at least 0.25 at Month 12
- Mean change from baseline to Month 12 in the physical component scale of the Short Form-36 (SF-36)
- Mean change from baseline in the Sheehan Disability Scale (SDS)
- Mean change from baseline in Patient Global Assessment (PGA) of Disease Activity

Statistical Analysis: The primary and secondary efficacy analyses as well as the safety analyses were to have done on the intent-to-treat (ITT) population which was defined as all randomized patients who have received at least 1 dose of study drug. The Cochran-Mantel-Haenszel (CMH) test stratified for Day -7 renal function and tophus status during screening was to have been used to calculate a pairwise comparison of the primary endpoint which was the proportion of patients who achieve a sUA <6.0 mg/dL by Month 6 between for the lesinurad and placebo arms. Subjects with missing values at Month 6 for any reason were to have been considered non-responders for all efficacy endpoint analyses. Since patients with a sUA <6 mg/dL at baseline had already reached target sUA prior to randomization, data for these subjects was to have been set to missing in both the numerator and denominator for the primary analysis. Last observation carried forward and a completers analysis was to have been used as sensitivity analyses. sUA response rates were to have also been analyzed via a logistic regression model testing for an association between the response rate and treatment arm while controlling for Day -7 renal function and tophus status at screening.

Analysis of the continuous secondary efficacy endpoints were to have been conducted via ANCOVA while all categorical response endpoints were to have been via a CMH model. These analyses were to have been adjusted for Day -7 renal function and tophus status at screening.

Study Conduct: This protocol was amended four times: nonsubstantial Amendments 1 and 2 on March 2, 2012 and March 8, 2012; Amendment 3 on July 6, 2012 addressed FDA comments to the protocol and clarified procedures and processes; and Amendment 4 on June 17, 2013 whose primary purpose was to put into place additional safety measures following reports of serious adverse events of acute renal failure and kidney stones in the phase 3 studies for which a relationship to lesinurad could not be excluded. This amendment made the same changes to the protocol for Study 303 as Amendment 3 made to the common protocol for Studies 301 and 302 and Amendment 4 to the protocol for Study 304. (Note: Reader is referred to Study Conduct Section of review for the common protocol for Studies 301 and 302 and the review of the protocol for Study 304 for additional information.)

Disposition: A total of 214 subjects were randomized: 107 patients in the LESU400 mg group and 107 in the PBO group. One hundred seventy eight subjects (178; 83%)

completed the study (with or without completing randomized study medication, out of which 162 subjects completed 6 months of treatment with randomized study medications. A higher proportion of patients in the LESU400 mg group (33%) discontinued study treatment than in the placebo group (16%). The most common reasons for discontinuing randomized study medication in the LESU400 mg and placebo groups were treatment emergent adverse events (19% versus 6%) and consent withdrawn (9% versus 6%). The proportion of subjects who completed the study (with or without completing randomized study medication) was also lower in the LESU400 mg group (79%) as compared to the placebo group (88%). The same pattern for study withdrawal prematurely as noted previously for discontinuation of study medications was observed: TEAEs (7% for LESU400 mg vs 3% for placebo) and consent withdrawn (10% LESU400 mg versus 7% for placebo).

Overall, the treatment groups were well balanced with regard to baseline demographics and disease characteristics. The patients in this trial were predominantly male (91%), White (82%) with a mean age of 54 years and mean duration of gout of approximately 11 years. There were more subjects ≥ 65 years old in the placebo group (25%) than in the LESU400 mg group (19%). Twenty-five percent (25%) of subjects had tophi at screening. The mean number of gout flares in the 12 months prior to study entry was approximately 6 flares/subject. The majority of subjects (70%) had at least 1 predefined comorbidity at baseline but a higher proportion of patients in the LESU400 mg group had ≥ 3 comorbidities (25%) compared to the placebo group (16%). The most frequently reported comorbidities for subjects in this trial were: hypertension, hypercholesterolemia, diabetes mellitus, and hypertriglyceridemia. Overall, 18% of subjects had moderate renal impairment (eCrCl: 30 to <60 ml/min) but no patients with severe impairment (eCrCl: <30 mg/min) were enrolled in this trial. The majority of subjects were taking colchicine (84%) as gout flare prophylaxis while the remaining 16% used NSAIDs. Overall, compliance with study medication was high and comparable across study arms (>94%).

Efficacy: A higher proportion of subjects in the LESU400 mg group (30%) achieved the primary endpoint of a sUA < 6.0 mg/dL at Month 6 versus the placebo group (2%). The difference between the two study groups was statistically significant ($p<0.0001$). The results from various sensitivity analyses of the primary endpoint (e.g., LOCF analysis, observed case analysis, reached target sUA < 6 mg/dL at each Month 4, 5, and 6; and reached target sUA < 6mg/dL at Month 6 via logistic regression) were generally supportive of the findings from the primary endpoint analysis.

No multiplicity correction was planned in the protocol or implemented for the secondary endpoints. Due to multiplicity concerns, declaring statistical significance of these secondary endpoints using unadjusted p-values may be inappropriate.

- Proportion of subjects whose sUA level is <6.0 mg/dL, <5.0 mg/dL and <4.0 mg/dL at each visit: Higher proportions of subjects in the LESU400 mg group achieved sUA <6.0 mg/dL, < 5 mg/dL, and < 4mg/dL compared to placebo. The

difference was statistically significantly different between treatment groups for the proportions of subjects who achieved sUA < 6.0 mg/dL and < 5 mg/dL at each post-baseline monthly visit through Month 6 as compared to placebo ($p \leq 0.0002$) but only at Months 1 and 6 for the proportion of subjects who achieved a sUA <4.0 mg/dL ($p \leq 0.0422$).

- Absolute and percent change from baseline in sUA levels at each visit: A greater reduction (mean and percent change) was observed for subjects treated with LESU400 mg versus placebo over the 6 –month course of Study 303. Treatment with LESU400 mg resulted in significantly greater reductions in mean percent change in sUA from baseline as compared to placebo at Month 6 (-25% versus -2%; respectively; $p<0.0001$).
- Proportion of subjects requiring treatment for a gout flare at monthly intervals between Month 6 and Month 12: The protocol required patients to discontinue all gout flare prophylaxis treatments at the end of Month 5 to prevent confounding of the results for this assessment. The proportion of subjects requiring treatment for a gout flare during month 6 was lower in the LESU 400 mg group compared to placebo (12% versus 15%, respectively), but the difference between the treatment groups was not statistically significant.

A number of patient reported outcomes (PRO) (e.g., HAQ-DI, Short-Form-36 [SF-36], patient global assessment [PGA], and the Sheehan Disability Scale [SDS]) were also evaluated as ancillary endpoints in this study. The results from these assessments were not statistically significantly different for the LESU400 mg treatment group as compared to the placebo group. This is not unexpected since subjects had minimal impairment at baseline as assessed by these PROs.

Safety: There was one death in the LESU400 mg group reported in this study, Subject 303-05230-308, who died of unknown causes 199 days after his last dose of study medication. As a result of the limited information available concerning this death it was adjudicated as a MACE event by the CEAE. No major imbalance across treatment arms was observed for cardiovascular events in this trial. (Note: Reader is referred to **Table 75** for more information regarding this death and **Table 80** for MACE events.) The safety data from Study 303 is discussed in detail with the safety data from the three other phase 3 studies in the preceding Section 7: Summary of Safety Section 7.3; Deaths Section 7.3.1; Serious Adverse events section 7.3.2; Dropouts and Discontinuations Section 7.3.3; Significant Adverse Events Section 7.3.4.; Submission Specific Primary Safety Concerns Section 7.3.5 (Sections 7.3.5.1 through 7.3.5.5.) and Common Adverse Events Section 7.4.1. Overall, a clear renal safety signal was observed in the LESU400 mg group as compared to placebo.

Conclusions: A significantly greater proportion of subjects treated with LESU400 mg achieved a sUA < 6 mg/dL at Month 6 as compared to placebo which was sustained through the 6-month course of study treatment and supported by multiple sensitivity analyses. Results that assessed clinical benefit (e.g., gout flares and disability)

associated with this decrease in sUA were not robust for the LESU400 mg treatment group. In this study, treatment with lesinurad was clearly associated with a marked increase in risk for renal adverse events (18%), including reversible and non-reversible creatinine elevations and serious renal-related adverse events (5%) including acute and chronic renal failure as well as kidney stones as there were no cases of renal adverse events observed in the placebo group. Although treatment with LESU400 mg in combination with XOI was also associated with an increased risk of adverse events of interest, the magnitude of the risk appears to be greater when LESU400 mg was used as monotherapy. Therefore, the Applicant is not pursuing the 400 mg dose or a monotherapy indication for the drug.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ROSEMARIE NEUNER
09/17/2015

SARAH K YIM
09/17/2015

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA Number: 207,988 **Applicant: Ardea Biosciences/Astra Zeneca** **Stamp Date: December 29, 2014**

Drug Name: Lesinurad (Zurampic®) **NDA Type: Original**

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2).	X			505(b)(1)
505(b)(2) Applications					
13.	If appropriate, what is the reference drug?			X	
14.	Did the applicant provide a scientific bridge demonstrating the relationship between the proposed product and the referenced product(s)/published literature?			X	
15.	Describe the scientific bridge (e.g., BA/BE studies)			X	
DOSE					
16.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? **Study Number:** RDEA594-202 **Study Title:** Randomized, Double-Blind, Multicenter, Placebo-Controlled, Safety, and Efficacy Study of RDEA594 Versus Placebo in the Treatment of Hyperuricemia in Patients with Gout	X			

	Content Parameter	Yes	No	NA	Comment
	Sample Size: N=123 **Arms:** 4 **Location in submission:** Section 5.3.5.4 **Study Number:** RDEA594-203 **Study Title:** Randomized, Double-Blind, Multicenter, Placebo-Controlled, Combination Study to Evaluate the Safety, Efficacy, and Potential Pharmacokinetic Interaction of RDEA594 and Allopurinol in Gout Patients with an Inadequate Hypouricemic Response with Standard Doses of Allpurinol **Sample Size:** N=208 **Arms:** 5 **Location in submission:** Section 5.3.5.1				
EFFICACY					
17.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? **Pivotal Study #1:** RDEA594-301 – A Phase 3 Randomized, Double-Blind, Multicenter, Placebo-Controlled, Combination Study to Evaluate the efficacy and Safety of Lesinurad and Allopurinol Compared to Allopurinol Alone in Subjects with Gout Who Have Had an Inadequate Hypouricemic Response to Standard of Care Allopurinol **Indication:** Treatment of Hyperuricemia Associated with Gout in combination with an Xanthine Oxidase Inhibitor (XOI) **Pivotal Study #2:** RDEA594-302 – A Phase 3 Randomized, Double-Blind, Multicenter, Placebo-Controlled, Combination Study to Evaluate the efficacy and Safety of Lesinurad and Allopurinol Compared to Allopurinol Alone in Subjects with Gout Who Have Had an Inadequate Hypouricemic Response to Standard of Care Allopurinol **Indication:** Treatment of Hyperuricemia Associated with Gout in combination with an XOI **Pivotal Study #3:** RDEA594-304 - A Phase 3 Randomized, Double-Blind, Multicenter, Placebo-Controlled, Combination Study to Evaluate the efficacy and Safety of Lesinurad and Febuxostat Compared to Febuxostat Alone at Lowering Serum Uric Acid and Resolving Tophi in Subjects with Tophaceous Gout **Indication:** Treatment of Hyperuricemia Associated with Gout in combination with an XOI	X			
18.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
19.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
20.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	
SAFETY					
21.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
22.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?	X			
23.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
24.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?	X			
25.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
26.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	X			
27.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
28.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
OTHER STUDIES					
29.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			
30.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
31.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			
ABUSE LIABILITY					
32.	If relevant, has the applicant submitted information to assess the abuse liability of the product?	X			
FOREIGN STUDIES					
33.	Has the applicant submitted a rationale for assuming the			X	Pivotal Studies 301, 302

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	applicability of foreign data in the submission to the U.S. population?				and 304 contained subjects from foreign sites. These trials were conducted as per agreements reached with FDA, CHMP, MHRA (UK), and MPA (Sweden).
DATASETS					
34.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
35.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
36.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
37.	Are all datasets to support the critical safety analyses available and complete?	X			
38.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
39.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
40.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	
FINANCIAL DISCLOSURE					
41.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
42.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? ____Yes____

Refer to the appended slides from the February 13, 2014 filing meeting for additional information regarding this application.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

1. We refer you to the EOP2 meeting minutes dated July 21, 2011, our written responses to you dated February 28, 2014 and May 8, 2014 as well as the pre-NDA filing minutes dated October 24, 2014 in which we have raised concerns regarding both the safety and efficacy of lesinurad. These specific concerns include:
    a. Adequacy of dose ranging/dosing interval selection, in light of apparent dose-related safety concerns
    b. Renal and cardiovascular safety profile of lesinurad
    c. The interpretability of the safety data in light of the timing of the safety-related protocol amendments implemented in the then ongoing confirmatory phase 3 studies.
    d. Adequacy of the overall risk-benefit profile, especially in light of the primary efficacy results for your third pivotal study, RDEA594-304, as well as the lack of

secondary outcome support in that study and in your two, replicate pivotal studies, RDEA594-301 and-302. Final determination of the drug's overall risk/benefit will be a review issue.

2. According to the labeling included in your submission, you are proposing that lesinurad be indicated for the treatment of hyperuricemia associated with gout in combination with a xanthine oxidase inhibitor. As noted in the pre-NDA filing meeting minutes, you do not appear to have the data necessary to support this expanded indication in view of the equivocal results from study RDEA594-304, which assessed the safety and efficacy of 200 mg/day of lesinurad when co-administered with 80 mg/day of febuxostat. Additionally, determination of a second line therapy indication with allopurinol in gout patients with hyperuricemia will depend upon the robustness of results from safety and efficacy subanalyses of subjects who participated in the pivotal phase 3 studies, RDEA594-301 and-302, while taking > 300 mg/day of allopurinol.

Rosemarie Neuner, MD, MPH
Clinical Reviewer, CDER/ODEII/DPARP

Sarah Yim, MD
Supervisory Associate Director, CDER/ODEII/DPARP

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NDA 207,988 Lesinurad (Zurampic)

Indication: Treatment of hyperuricemia associated with gout in combination with a xanthine oxidase inhibitor

Sponsor: Ardea Biosciences/Astra Zeneca
Filing Meeting: February 13, 2014

1

U.S. Food and Drug Administration
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NDA 207988 Lesinurad (Zurampic)

- Selective URAT1 inhibitor
- Proposed indication:
- Treatment of hyperuricemia associated with gout in combination with xanthine oxidase inhibitor (XOI)

Figure 1: Schematic of Lesinurad and Current Therapies for Gout

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- XO inhibitors
  - Allpurinol: → approved up to 800 mg/d
    - Toxicities renal (dose adjustment), liver, bone marrow and skin (hypersens tivity)
  - Febuxostat: → approved at 40 and 80 mg/d
    - No dose adjustment for m ld-moderate renal impairment
    - CV and hepatic warnings
    - PMR study assessing MACE in US (b) (4)

2

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NDA 207988 Lesinurad – Regulatory History

- EOP2
  - Agreement reached on 1º and 2º EPs (latter to support former which is a surrogate), definition of "inadequate responders" to allopurinol, doses carried forward to P3, adequacy of dose ranging in P2, and use CV adjudication committee to review MACE
- Dec. 2013
  - Sponsor amended ongoing study protocols to minimize risk of nephrotoxicity (ARF, ↑sCr) observed in RCT monotherapy Study 303
  - Added post hoc renal adjudication committee to review renal AEs
- Feb. 2014
  - IRB stopped OLE monotherapy Study 305 due to renal toxicity in Study 303
  - Agency agreed to proposed safety modifications but informed sponsor that labeling indication and instructions for use should reflect what was done in clinical trials, and renal AE analysis parameters
- Sept. 2014 preNDA filing meeting
  - Agency concerns persisted in view of dose-related renal and CV AEs
  - Interpretability of lesinurad's safety data was questionable due to timing of safety-related protocol amendments in the then ongoing confirmatory studies
  - Risk/benefit assessment was uncertain given the questionable primary EP results from febuxostat add on Study 303 and the lack of secondary outcome support in all 3 pivotal Phase 3 studies
  - Since febuxostat add-on Study 304 was an equivocal study, they did not have the necessary data to support the proposed expanded indication of RX of hyperuricemia associated with gout in combination with XOI
  - Determination of second line therapy indication w th allopurinol would depend on robustness of safety and efficacy analyses of subjects taking >300 mg/d allopurinol

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Phase 3 Clinical Development

Phase 3 Core Pivotal Studies in Combination with XO Inhibitor	
Efficacy and safety in combination with ALLO in inadequate responders to ALLO	2 studies (Studies 301 and 302): 12-month DB core Study RDEA594-301: LESU 200 mg + ALLO (N=201), LESU 400 mg + ALLO (N=201), or PBO + ALLO (N=201). LESU doses were qd. ALLO doses were from 200 mg to 800 mg daily. 12-month DB core Study RDEA594-302: LESU 200 mg + ALLO (N=204), LESU 400 mg + ALLO (N=206), or PBO + ALLO (N=206). LESU doses were qd. ALLO doses were from 200 mg to 800 mg daily.
Efficacy and safety in combination with FBX in subjects with tophaceous gout	1 study (RDEA594-304): 12-month DB core Study RDEA594-304: LESU 200 mg + FBX 80 mg (N=106), LESU 400 mg + FBX (N=109), or PBO + FBX (N=<=109). LESU and FBX doses were qd.
Phase 3 Core Study Monotherapy	
Efficacy and safety as monotherapy in subjects with an intolerance or contraindication to XO inhibitors	1 study (Study 303): 6-month DB core Study RDEA594-303: LESU 400 mg (N=107) or PBO (N=107)
Phase 3 Extension Studies	
Interim safety in combination with ALLO in inadequate responders to XO inhibitors	1 study (Study 306): Ongoing up to 30-month OL extension Study RDEA594-306: LESU 200 mg + ALLO (N=362) or LESU 400 mg + ALLO (N=359)
Interim safety in combination with FBX in subjects with tophaceous gout	1 study (Study 307): Ongoing up to 30-month OL extension Study RDEA594-307: LESU 200 mg + FBX 80 mg (N=97) or LESU 400 mg + FBX (N=99)
Safety as monotherapy in subjects with an intolerance or contraindication to XO inhibitors	1 study (Study 305): OL extension Study RDEA594-305: LESU 400 mg (N=143). Terminated early.

High rate of Grade 3/4 renal toxicity (16% for 400 mg lesinurad vs 3% for PLO) in monotherapy trial (Study 303) resulted in premature termination of OLE.

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Primary EP Results for Allopurinol Add-On Studies 301 and 302

	PBO + ALLO (N=291) n (%)	LESU 200 mg + ALLO (N=201) n (%)	LESU 400 mg + ALLO (N=201) n (%)
Study 301			
Proportion with sUA < 6.0 mg/dL at Month 6	56 (27.9)	109 (54.2)	119 (59.2)
Difference in proportions vs. PBO + ALLO (95% CI)		0.26 (0.17, 0.36)	0.31 (0.22, 0.41)
p-value*		<0.0001	<0.0001
	(N=206)	(N=204)	(N=200)
Study 302	n (%)	n (%)	n (%)
Proportion with sUA < 6.0 mg/dL at Month 6	48 (23.3)	113 (55.4)	133 (66.5)
Difference in proportions vs. PBO + ALLO (95% CI)		0.32 (0.23, 0.41)	0.43 (0.34, 0.52)
p-value*		<0.0001	<0.0001

Abbreviations: ALLO,allopurinol; LESU, lesinurad; PBO, placebo sUA, serum urate.
Note: Subjects missing the Month 6 sUA result are treated as non-responders.
* Cochran-Mantel Haenszel test stratified by Day -7 renal function (eCrCl ≥ 60 mL/min versus < 60 mL/min) and tophus status during Screening (presence versus absence), randomized values.

Both studies failed to capture the 2 key secondary EP: rate of gout flares and tophi resolution

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Overall Summary of TEAEs for Allopurinol Add-On Studies 301 and 302

	PBO + ALLO (N=201) n (%)	LESU 200 mg +ALLO (N=201) n (%)	LESU 400 mg +ALLO (N=201) n (%)
Study 301			
Adverse Event Category			
Any treatment-emergent adverse event (TEAE)	138 (68.7)	147 (73.1)	156 (77.6)
Any TEAE with RCTC toxicity Grade 3 or 4	12 (6.0)	22 (10.9)	29 (14.4)
Any serious TEAE	11 (5.5)	9 (4.5)	16 (8.0)
Any fatal TEAE	0	1 (0.5)	0
Any TEAE leading to randomized study medication discontinuation	8 (4.0)	16 (8.0)	14 (7.0)
	(N=206)	(N=204)	(N=200)
Study 302	n (%)	n (%)	n (%)
Adverse Event Category			
Any treatment-emergent adverse event (TEAE)	146 (70.9)	152 (74.5)	161 (80.5)
Any TEAE with RCTC toxicity Grade 3 or 4	23 (11.2)	19 (9.3)	27 (13.5)
Any serious TEAE	8 (3.9)	9 (4.4)	19 (9.5)
Any fatal TEAE	0	0	2 (1.0)
Any TEAE leading to randomized study medication discontinuation	11 (5.3)	7 (3.4)	19 (9.5)

Abbreviations: ALLO, allopurinol; LESU, lesinurad; PBO, placebo; RCTC, rheumatology common toxicity criteria; TEAE, treatment-emergent adverse events.
Note: Treatment-emergent adverse events are those that started on or after the first randomized study medication dose date, or those that started prior to the first randomized study medication dose date but worsened during the double-blind treatment period of the study. Gout flares were captured via an electronic diary and recorded as an adverse event only if each met the definition of a serious adverse event. For each category, subjects are included only once, even if they experienced multiple events in that category.

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Renal AE Analyses for Allopurinol Add-On Studies 301 and 302

Preferred Term	PBO + ALLO (N=407) n (%)	LESU 200 mg + ALLO (N=405) n (%)	LESU 400 mg + ALLO (N=401) n (%)
Any treatment-emergent renal-related adverse event	17 (4.2)	20 (4.9)	50 (12.5)
Blood creatinine increased	9 (2.2)	15 (3.7)	33 (8.2)
Blood urea increased	2 (0.5)	6 (1.5)	6 (1.5)
Renal failure	4 (1.0)	3 (0.7)	6 (1.5)
Renal impairment	0	0	4 (1.0)
Renal failure acute	1 (0.2)	0	3 (0.7)
Urine output decreased	0	0	3 (0.7)
Creatinine renal clearance decreased	0	0	2 (0.5)
Renal failure chronic	2 (0.5)	1 (0.2)	1 (0.2)
Acute prerenal failure	0	0	1 (0.2)

Abbreviations: ALLO, allopurinol; LESU, lesinurad; PBO, placebo.
Note: Treatment-emergent adverse events are those that started on or after the first randomized study medication dose date, or those that started prior to the first randomized study medication dose date but worsened during the double-blind treatment period of the study. Adverse events are coded using MedDRA version 14.0. For each preferred term (PT), subjects are included only once, even if they experienced multiple events in that PT.

Table 20: Subjects With Serum Creatinine (mg/dL) Elevations by Category (Safety Population), Studies RDEA594-301 and RDEA594-302

	PBO + ALLO	LESU 200 mg + ALLO	LESU 400 mg + ALLO
Study 301	(N=201)	(N=201)	(N=201)
Serum Creatinine Elevation Category			
sCr ≥ 1.5 x Baseline	2 (1.0)	12 (6.0)	32 (15.9)
sCr ≥ 2.0 x Baseline	0	2 (1.0)	12 (6.0)
sCr ≥ 3.0 x Baseline	0	0	3 (1.5)
Study 302	(N=206)	(N=204)	(N=200)
Serum Creatinine Elevation Category			
sCr ≥ 1.5 x Baseline	7 (3.4)	12 (5.9)	30 (15.0)
sCr ≥ 2.0 x Baseline	0	4 (2.0)	16 (8.0)
sCr ≥ 3.0 x Baseline	0	3 (1.5)	6 (3.0)

Abbreviations: ALLO, allopurinol; LESU, lesinurad; PBO, placebo; sCr, serum creatinine.
Note: Categories are cumulative; subjects can be counted in more than one category, so percentages can sum to > 100%. Baseline is defined as the highest serum creatinine value recorded ≤ 14 days prior to the first dose of randomized study medication.

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Subjects with CEAC Adjudicated TE MACE Events in Allopurinol Add-On Studies 301 and 302

	PBO + ALLO (N=407)[a] (361.2 PY)[b]	LESU 200 mg + ALLO (N=405)[a] (358.3 PY)[b]	LESU 400 mg + ALLO (N=401)[a] (353.5 PY)[b]
Number of subjects with MACE[c] events	2	2	6
Incidence Rate[d] (95% CI)[e]	0.55 (0.14, 2.21)	0.56 (0.14, 2.23)	1.70 (0.76, 3.78)
Number of MACE[c] events	3	2	7
Incidence Rate[d] (95% CI)[e]	0.83 (0.27, 2.58)	0.56 (0.14, 2.23)	1.98 (0.94, 4.15)
CV death	0	1, 0.28 (0.04, 1.98)	1, 0.28 (0.04, 2.01)
Non-fatal myocardial infarction	1, 0.28 (0.04, 1.97)	1, 0.28 (0.04, 1.98)	6, 1.70 (0.76, 3.78)
Non-fatal stroke	2, 0.55 (0.14, 2.21)	0	0

Abbreviations: ALLO, allopurinol; CEAC, Cardiovascular Endpoints Adjudication Committee; CV, cardiovascular; LESU, lesinurad; MACE, Major Adverse Cardiovascular Event; PBO, placebo.
Note: Treatment-emergent adverse events are those that started on or after the first randomized study medication dose date, or those that started prior to the first randomized study medication dose date but worsened during the double-blind treatment period of the study. Subjects with multiple CEAC-adjudicated events can be counted in more than one category.
[a] Unique number of subjects in safety population.
[b] Person-year.
[c] MACE events are defined as cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke.
[d] Incidence rate = number of subjects with MACE events per 100 person-year.
[e] The 95% confidence intervals are based on Poisson regression.
[f] Incidence rate = number of MACE events per 100 person-year.

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Primary Efficacy Results for Febuxostat Add-On Study 304

	PBO + FBX 80 mg (N=109) n (%)	LESU 200 mg + FBX 80 mg (N=106) n (%)	LESU 400 mg + FBX 80 mg (N=109) n (%)
NRI			
Proportion with sUA < 5.0 mg/dL at Month 6	51 (46.8)	80 (56.6)	83 (76.1)
Difference in proportions vs. PBO + FBX 80 mg (95% CI)		0.10 (-0.03, 0.23)	0.29 (0.17, 0.42)
p-value[a]		0.1298	<0.0001
LOCF Imputation[b]			
Proportion with sUA < 5.0 mg/dL at Month 6	54 (50.9)	66 (64.1)	88 (83.0)
Difference in proportions vs. PBO + FBX 80 mg (95% CI)		0.13 (-0.00, 0.26)	0.32 (0.20, 0.44)
p-value[a]		0.0377	<0.0001
Observed Cases[c]			
Proportion with sUA < 5.0 mg/dL at Month 6	51 (54.8)	60 (65.2)	83 (89.2)
Difference in proportions vs. PBO + FBX 80 mg (95% CI)		0.10 (-0.04, 0.24)	0.34 (0.22, 0.46)
p-value[a]		0.0560	<0.0001

Abbreviations: CI, confidence interval; FBX, febuxostat; ITT, future-to-treat; LOCF, last observation carried forward; LESU, lesinurad; NRI, non-responder imputation; PBO, placebo; sUA, serum urate.
Note: Subjects missing the Month 6 sUA result are treated as non-responders.
[a] Cochran-Mantel Haenszel test stratified by Day -7 renal function (eCrCl ≥ 60 mL/min versus < 60 mL/min) and Day -7 sUA status (sUA ≥ 6.0 mL/min versus < 6.0 mL/min); randomized values.
[b] The last post-Baseline sUA result prior to Month 6 is carried forward for subjects who are missing the Month 6 sUA result.
[c] Only subjects with a non-missing sUA result at Month 6 are included in the Observed Cases analysis.

Failed to capture all 3 key secondary EPs: complete tophi resolution, partial tophi resolution, and improvement in HAQ-DI of at least 0.25 at Month 12

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Summary of TEAEs in Febuxostat Add-On Study 304

Adverse Event Category	PBO + FBX 80 mg (N=109) n (%)	LESU 200 mg + FBX 80 mg (N=106) n (%)	LESU 400 mg + FBX 80 mg (N=109) n (%)
Any treatment-emergent adverse event (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 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)

Abbreviations: FBX, febuxostat; LESU, lesinurad; PBO, placebo; RCTC, rheumatology common toxicity criteria; TEAE, treatment-emergent adverse events.
Note: Treatment-emergent adverse events are those that started on or after the first randomized study medication dose date, or those that started prior to the first randomized study medication dose date but worsened during the double-blind treatment period of the study. Gout flares were captured via an electronic diary and recorded as an adverse event only if each met the definition of a serious adverse event. For each category, subjects are included only once, even if they experienced multiple events in that category.

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Renal AE Analyses for Febuxostat Add-On Study 304

Preferred Term	PBO + FBX 80 mg (N=109) n (%)	LESU 200 mg + FBX 80 mg (N=106) n (%)	LESU 400 mg + FBX 80 mg (N=109) n (%)	POOLED LESU + FBX 80 mg (N=215) n (%)
Any treatment-emergent renal-related adverse event	6 (5.5)	9 (8.5)	11 (10.1)	20 (9.3)
Blood creatinine increased	3 (2.8)	7 (6.6)	8 (7.3)	15 (7.0)
Blood urea increased	1 (0.9)	1 (0.9)	1 (0.9)	2 (0.9)
Renal impairment	0	1 (0.9)	1 (0.9)	2 (0.9)
Acute prerenal failure	0	0	1 (0.9)	1 (0.5)
Renal failure	2 (1.8)	1 (0.9)	0	1 (0.5)
Renal failure acute	1 (0.9)	0	1 (0.9)	1 (0.5)
Renal failure chronic	1 (0.9)	0	1 (0.9)	1 (0.5)

Abbreviations: FBX, febuxostat; LESU, lesinurad; PBO, placebo.
Note: Treatment-emergent adverse events are those that started on or after the first randomized study medication dose date, or those that started prior to the first randomized study medication dose date but worsened during the double-blind treatment period of the study. Adverse events are coded using MedDRA version 14.0. For each preferred term (PT), subjects are included only once, even if they experienced multiple events in that PT.

Table 29: Incidence of Serum Creatinine (mg/dL) Elevations by Category (Safety Population), Study RDEA594-304

Serum Creatinine Elevation Category	PBO + FBX 80 mg (N=109) n (%)	LESU 200 mg + FBX 80 mg (N=106) n (%)	LESU 400 mg + FBX 80 mg (N=109) n (%)
sCr ≥ 1.5 x Baseline	3 (2.8)	5 (4.7)	11 (10.1)
sCr ≥ 2.0 x Baseline	0	3 (2.8)	6 (5.5)
sCr ≥ 3.0 x Baseline	0	1 (0.9)	3 (2.8)

Abbreviations: FBX, febuxostat; LESU, lesinurad; PBO, placebo; sCr, serum creatinine.
Note: Categories are cumulative; subjects can be counted in more than 1 category, so percentages can sum to > 100%. Baseline is defined as the highest serum creatinine value recorded ≤ 14 days prior to the first dose of randomized study medication.

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Subjects with CEAC Adjudicated TE MACE Events in Febuxostat Add-On Study 304

	PBO + FBX 80 mg (N=109)[a] (96.6 PY)[b]	LESU 200 mg + FBX 80 mg (N=106)[a] (92.4 PY)[b]	LESU 400 mg + FBX 80 mg (N=109)[a] (95.4 PY)[b]
Number of subjects with MACE[c] events	1	2	2
Incidence Rate[d] (95% CI)[e]	1.04 (0.15, 7.35)	2.16 (0.54, 8.66)	2.10 (0.52, 8.38)
CV death	0	1, 1.08 (0.15, 7.68)	1, 1.05 (0.15, 7.44)
Non-fatal myocardial infarction	0	1, 1.08 (0.15, 7.68)	1, 1.05 (0.15, 7.44)
Non-fatal stroke	1, 1.04 (0.15, 7.35)	0	0

Abbreviations: FBX, febuxostat; LESU, lesinurad; PBO, placebo.
Note: CEAC, Cardiovascular Endpoints Adjudication Committee; CV, cardiovascular. Treatment-emergent adverse events are those that started on or after the first randomized study medication dose date, or those that started prior to the first randomized study medication dose date but worsened during the double-blind treatment period of the study. Subjects with multiple CEAC-adjudicated events can be counted in more than one category.
a Unique number of subjects in safety population.
b Person-year.
c MACE events are defined as cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke.
d Incidence rate = number of subjects with MACE events per 100 person-year.
e The 95% confidence intervals are based on Poisson regression.

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Proposed Labeling and REMS

- Label
  - Using (b) (4) to describe results of febuxostat add-on Study 303 in Sect. 14 Clinical Studies
  - Very creative language is used in describing results of (b) (4)
- REMS
  - Communication plan consists of a website and letters to professional organizations and HCP likely to prescribe lesinurad to inform them of risks of acute renal injury and need to co-administrate with XOI due to increase risk in renal toxicity when given as monotherapy
  - (b) (4)

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Midcycle Deliverables

- Efficacy
  - Primary analysis for the 3 pivotal studies
  - Subgroup and sensitivity analysis of the primary efficacy endpoint of each study
  - Key secondary endpoints
  - Subgroup analyses for patients >300 mg allopurinol
- Integrated Safety Summary
  - Deaths, SAEs including renal and MACE
  - Common AEs
  - Marked lab abnormalities

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Consult List

- Consults to the following
  - DMETS/OSE: proprietary name review
  - DSI: site audits
  - DDMAC et al: labeling and MG review
  - DRISK: REMS
  - PeRC
    - iPSP submitted to IND 102,128 requesting full waiver for neonates, infants, children and adolescents between ages birth to <18 years due to rarity of disease
    - Need to submit iPSP for concurrence for NDA

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NDA 207,988 Lesinurad (Zurampic) - Filing Meeting

Back Up Slides

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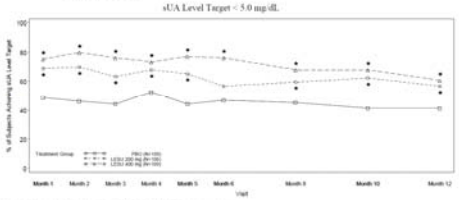
Longitudinal Plot of sUA Response by Month for Febuxostat Add-On Study 304

Figure 8: Proportion of Subjects Achieving Serum Urate Level Targets by Visit Line Plot Using Non-Responder Imputation (ITT Population), Study RDEA594-304



Abbreviations: LESU, lesinurad; PBO, placebo; sUA, serum urate.
* Indicates statistical significance of treatment group vs. placebo at the 0.05 level 2-sided using Cochran-Mantel Haenszel test stratified by Day-7 renal function and Day-7 sUA status (randomized values).

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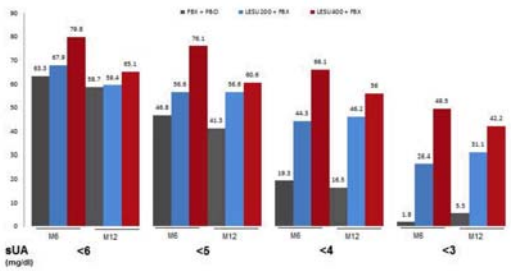
Proportion of Subjects Achieving sUA Targets at Months 6 and 12 (NRI ITT) in Febuxostat Add-On Study 304



Abbreviations: FBX, febuxostat; LESU, lesinurad; M, month; PBO, placebo; sUA, serum urate.

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/s/

ROSEMARIE NEUNER
02/26/2015

SARAH K YIM
02/26/2015