ARTHRITIS
ADVISORY COMMITTEE MEETING

October 23, 2015

NDA 207988: Lesinurad for the proposed indication of treatment of hyperuricemia associated with gout in combination with a xanthine oxidase inhibitor

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FDA Briefing Package

Division Memorandum

Date: September 28, 2015

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To: Members, Arthritis Advisory Committee

Subject: Overview of the FDA background materials for new drug application (NDA) 207988—Lesinurad for the proposed indication of treatment of hyperuricemia associated with gout, in combination with a xanthine oxidase inhibitor

Introduction

Thank you for your participation in the Arthritis Advisory Committee (AAC) meeting to be held on October 23, 2015. As members of the AAC, you provide important expert scientific advice and recommendations to the US Food and Drug Administration (the Agency) on the regulatory decision-making process related to the approval of a drug or biologic product for marketing in the United States. The upcoming meeting is to discuss new drug application (NDA) 207988 for lesinurad, a uricosuric drug for the proposed indication of treatment of hyperuricemia associated with gout in combination with a xanthine oxidase inhibitor.

The content of this document and the materials prepared by the Agency reflect the preliminary findings and opinions based on reviews of the information submitted by the applicant, Ardea Biosciences, Inc. These materials do not represent the final position of the Agency. The opinions and insights provided by you at this AAC meeting will be an important factor in our decision on this application.

The clinical and statistical issues related to the lesinurad clinical trial results are the primary focus of this AAC meeting. In determining approvability of additional indications for a product, there may be factors, other than clinical data, that the Agency may take into consideration in the regulatory decision-making process. These additional factors will not be the focus of this AAC meeting.

Attached are the background materials for this meeting. In addition to this memorandum, the FDA background materials include the clinical and statistical briefing documents.

Background

Gout is a metabolic disorder characterized by reduced clearance or overproduction of uric acid leading to hyperuricemia, which in turn can result in monosodium urate (MSU) crystal formation around the joints and soft tissues, urate nephropathy, and nephrolithiasis. The prevalence of gout has been increasing over the past few decades, and has been recently estimated to affect approximately 3.9% of adults in the United States (8.3 million)[1]. The condition affects primarily middle-aged and older men and post-menopausal women. Obesity, hyperlipidemia, diabetes, hypertension, chronic renal insufficiency, metabolic syndrome, and cardiovascular disease are frequent comorbidities in patients with gout.

The course of gout is characterized by acute attacks of gouty arthritis alternating with attack-free periods of intercritical gout. A typical course of gouty arthritis attack (or gout flare) is characterized by acute inflammation of the affected joint and surrounding tissues associated with often excruciating pain, tenderness, erythema, and swelling. If left untreated, the acute inflammatory episode is self-limited, typically peaking within 24-48 hours and eventually subsiding within 7-10 days. Treatment of acute attacks utilizes anti-inflammatory treatment of various mechanisms, such as colchicine, nonsteroidal anti-inflammatory drugs (NSAIDS), or corticosteroids. It is common practice to use an agent to help reduce the frequency and severity of acute gout attacks, for which a patient is at increased risk during initiation of uric-acid lowering therapies. To this end, maintenance doses of either colchicine or an NSAID are continued as prophylaxis against gout flares; typically until the serum uric acid level has been maintained within the target range and there have been no acute attacks for 3 to 6 months.

The chronic management of gout is founded upon control of hyperuricemia, as only this approach treats the underlying pathology of the disorder. The mechanistic approaches to lowering serum uric acid (sUA) include:

- Lowering uric acid production. This is currently the most common approach to treatment, via xanthine oxidase inhibitors, i.e., allopurinol and febuxostat.
- Increasing urinary uric acid excretion (uricosurics). Uricosurics such as probenecid inhibit active renal reabsorption of uric acid through urate transporters in proximal tubule epithelial cells (predominantly URAT1), resulting in increased urinary uric acid excretion.
- Direct enzymatic breakdown of uric acid. Because humans do not possess an endogenous uricase, drugs such as pegloticase and rasburicase are derived from foreign proteins, and their use is limited by immunogenicity. Uricase breaks down uric acid into the much more soluble allantoin, which can then be excreted in the urine.

Relevant Regulatory History

[1] Zhu Y, Pandya BJ, Choi HK, "Prevalence of gout and hyperuricemia in the US general population: the National Health and Nutrition Examination Survey 2007-2008." Arthritis Rheum 2011; 63:3136-3141.

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 $\geq$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 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 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.

Product Information

Lesinurad inhibits the function of multiple carrier proteins that transport uric acid in the renal proximal tubule epithelium, including Uric Acid Transporter 1 (URAT1) and Organic Anion Transporters (OAT) 1, 3 and 4. Currently, URAT1 is considered to be the major luminal pathway for uric acid reabsorption in humans; however it is likely that the glucose transporter GLUT9 also contributes to uric acid excretion, via the basolateral aspect of the proximal tubule cell.[2] The contribution of the OAT transporters to the overall renal transport of uric acid in humans is not as clear, although OAT4 is thought to be the mechanism by which hydrochlorothiazide cause uric acid elevation.[3]

Lesinurad is a 200 mg tablet with a proposed dosing regimen of 200 mg orally once daily. The absolute bioavailability of lesinurad following oral administration under fed conditions is approximately 100% and time to maximum concentration (Tmax) is approximately 1 to 4 hours. The terminal half-life of lesinurad is approximately 5 hours. Systemic exposure and peak plasma concentration increases in proportion to the dose in the dose range of 5 to 1200 mg. Lesinurad undergoes oxidative metabolism mainly via cytochrome P450 CYP2C9. Approximately 63% of the administered dose is excreted in urine and 32% is eliminated in feces. Lesinurad exposure (area-under-the-curve [AUC]) increased by 31%, 50-74%, and 113%, respectively, in subjects with mild (eCrCl[4] $\geq$60 ml/min), moderate (eCrCl 45 to <60 ml/min), and severe (eCrCl <45 ml/min) renal impairment.

Chronic toxicology studies showed evidence of kidney toxicity in rats and GI tract toxicity in both rats and monkeys. In rats, the dose of 600 mg/kg/day (119 x clinical exposure) was lethal due to kidney toxicity (tubular degeneration and single cell necrosis) and gastrointestinal toxicity (erosion, hemorrhage, congestion, single necrosis). At the dose of 300 mg/kg/day (36 x clinical exposure), kidney findings were limited to tubular dilatation and changes of clinical chemistry parameters. Low incidences of GI tract erosion were observed. For monkeys, the dose of 600 mg/kg/day (11 x clinical exposure) was lethal due to GI tract toxicity (erosions and hemorrhage in colon and rectum and severe diarrhea and emesis). There was no GI tract toxicity at lower doses; however, bile duct hyperplasia was observed at 200 mg/kg/day. NOAELs of 100 mg/kg/day in both rats and monkeys provide exposure margins of 15- and 3-fold relative to the clinical exposure. While these findings would not preclude approval of the proposed clinical dose, they suggest lesinurad has the potential for kidney and GI tract toxicity. The kidney toxicity observed in the rat would not be likely to be due to uric acid crystalluria or nephrolithiasis, as rats, like most mammals, possess functional uricase, and have low serum uric acid levels (in the range of 1 to 2 mg/dL)[5].

[2] Bobulescu I.A. and O.W. Moe, "Renal transport of uric acid: evolving concepts and uncertainties." Adv Chronic Kidney Dis. 2012 November; 19(6):358-371.
[3] Bach M.H. and P.A. Simkin, "Uricosuric drugs: the once and future therapy for hyperuricemia?" Curr Opin Rheumatol 2014, 26:169-175.
[4] eCrCl = estimated Creatinine Clearance
[5] Johnson RJ et al., "The Planetary Biology of Ascorbate and Uric Acid and their Relationship with the Epidemic of Obesity and Cardiovascular Disease." Med Hypotheses 2008; 71(1):22-31.

Clinical and Statistical

Overview of the clinical program

The phase 3 clinical development program for lesinurad consisted of four studies:

- Studies 301 (n=603) and 302 (n=610), which were replicate studies in patients who had been taking at least 300 mg/day allopurinol (200 mg/day in patients with estimated creatinine clearance of less than 60 ml/min at baseline) for at least 8 weeks and still had a serum uric acid level of 6.5 mg/dL or greater at the screening visit (and $\geq$6.0 mg/dL at the Day -7 visit) and also had at least 2 gout flares in the preceding 12 months. Patients were randomized to receive placebo, lesinurad 200 mg, or lesinurad 400 mg daily in addition to their background allopurinol for 12 months. Patients also received gout flare prophylaxis with colchicine (or nonsteroidal anti-inflammatory drugs [NSAIDs] if not able to take colchicine) starting Day -14 through Month 5.
- Study 304 (n=324) was also a 12-month study of placebo, lesinurad 200 mg, or lesinurad 400 mg daily, but added on to a background of febuxostat. All patients began or were switched to febuxostat 80 mg for a 21-day run-in period prior to beginning study treatment. In patients not taking urate lowering therapy (ULT), sUA had to be at least 8 mg/dL, but in patients who were on ULT previously, sUA had to be at least 6 mg/dL. Patients also had to have at least 1 measurable tophus on the hands/wrists and/or feet/ankles at least 5 mm in width and up to 20 mm in length. Patients received gout prophylaxis with colchicine (or NSAIDs if not able to take colchicine) from Day -21 through Month 5.
- Study 303 (n=214) was a 6-month study of lesinurad 400 mg monotherapy compared to placebo in subjects with gout who had intolerance or contraindication to treatment with a xanthine oxidase inhibitor. Patients had to have a sUA level of >6.5 mg/dL at the screening and Day -7 visit. Patients received gout prophylaxis with colchicine (or NSAIDs if not able to take colchicine) starting Day -14 through Month 5. Patients with a documented history or suspicion of kidney stones were excluded.

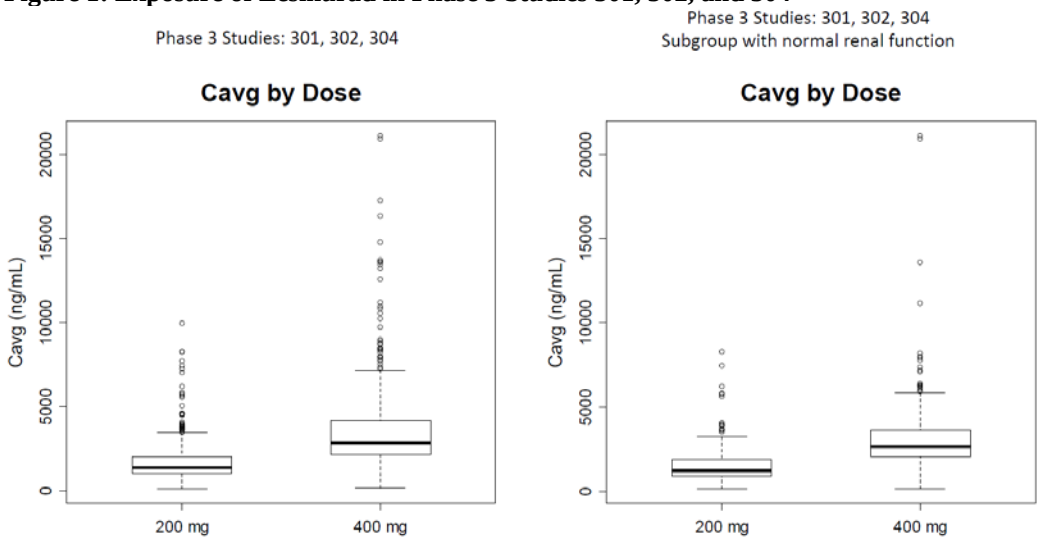
Dose/Dosing Frequency Selection

Only once daily dose regimens were explored in the lesinurad clinical development program. Two 4-week dose-ranging studies were conducted during phase 2—Study 202 and Study 203; both evaluated doses of 200, 400, or 600 mg daily of lesinurad. Study 202 evaluated lesinurad alone (except for colchicine 0.6 mg daily given as prophylaxis for gout flares) and Study 203 evaluated lesinurad in combination with allopurinol compared to allopurinol alone (also on a background of colchicine prophylaxis). Both studies showed a dose-dependent reduction in sUA. In Study 203, the percent change from baseline in sUA following 4 weeks of treatment was 16% for the 200 mg dose, 22% for the 400 mg dose, and 30% for the 600 mg dose. The applicant decided that the additional effect of 600 mg over 400 mg was only marginally greater when used in combination with allopurinol, so 400 mg was selected as the higher dose in the phase 3 studies. The 100 mg dose (evaluated in phase 1) did not appear to result in sustained

sUA reductions over 24 hours, and thus was not explored in phase 2. As shown in Figure 1 below, although the average concentration was higher in the 400 mg dose group compared to the 200 mg dose group in Studies 301, 302, and 304, the exposure for these two doses was largely overlapping.

The applicant's rationale for only exploring a once daily (specifically morning) dose regimen is that despite lesinurad's short half-life, the majority of the reduction in sUA is still maintained at 24 hours. Additionally, the applicant wanted to avoid high urinary uric acid concentrations during nighttime, when urine pH and volume are the lowest, in order to reduce the risk of uric acid precipitation. Although this rationale is not unreasonable, in light of apparent dose-dependent toxicity in the controlled phase 3 studies, this raises the question of whether a lower nominal dose given twice daily may have provided similar efficacy with a better safety profile.

Figure 1: Exposure of Lesinurad in Phase 3 Studies 301, 302, and 304



Source: FDA clinical pharmacology reviewer, Dr. Jianmeng Chen

Study Population

Table 1 below includes selected demographic and disease characteristics from the phase 3 studies. Overall, the demographic and disease characteristics were generally similar across the studies. There were intentional differences related to the specific gout subpopulation targeted, such as the requirement to have at least 1 gouty tophus in Study 304, and the requirement to have had intolerance or a contraindication to treatment with a xanthine oxidase inhibitor in Study 303. Study 304 enrolled a relatively well-controlled population of tophaceous gout patients, as illustrated by the baseline mean serum urate of 5.27 mg/dL and the high proportion of patients (50%) who were already meeting the primary endpoint target urate level of <5.0 mg/dL at baseline. By contrast, due to intolerance or contraindication, patients in Study 303 were often not taking a xanthine oxidase inhibitor, and had a correspondingly higher baseline serum urate of 9.33 mg/dL. Overall, patients had a longstanding diagnosis of gout in these studies: an average of 12

years in Study 301 and 302, 15 years in Study 304, and 11 years in Study 303. A minority of patients (up to 20%) in these studies had at least moderate (<60 ml/min) renal impairment.

Table 1: Selected Demographic and Disease Characteristics of the Phase 3 Studies

Demo. or Dis. Characteristic	Study 301 (N=603)	Study 302 (N=610)	Study 304 (N=324)	Study 303 (N=214)
Age (years), Mean (SD)	52 (11)	51 (11)	54 (11)	54 (12)
Gender				
Male	567 (94%)	587 (96%)	309 (95%)	195 (91%)
Female	36 (6%)	23 (4%)	15 (5%)	19 (9%)
Race (two most prevalent):				
White	460 (76%)	482 (79%)	259 (80%)	175 (82%)
Black	90 (15%)	58 (10%)	35 (11%)	20 (9%)
No. Gout Flares in Past 12 Mos				
Mean (SD)	5 (4)	6 (6)	7 (8)	6 (7)
Median	4	4	4	4
Proportion of Pts with Tophi	87 (14%)	144 (24%)	323 (99.7%)	54 (25%)
Baseline sUA (mg/dL)				
Mean (SD)	6.94 (1.27)	6.90 (1.19)	5.27 (1.63)	9.33 (1.51)
Proportion Already at Target ***(<6.0 for Studies 301, 302, 303 or <5.0 for Study 304)***	112 (19%)	116 (19%)	163 (50%)	1 (<1%)
Baseline dose of XOI (mg/d)				N/A
Allopurinol, Mean (SD)	307 (60)	312 (75)		
Febuxostat			80*	
Gout Flare Prophylaxis				
Colchicine	504 (84%)	507 (83%)	276 (85%)	179 (84%)
NSAID	95 (16%)	110 (18%)	56 (17%)	35 (16%)
Baseline Renal Function (ml/min)				
eCrCl <90, n (%)	364 (60%)	371 (61%)	214 (66%)	126 (59%)
eCrCl <60, n (%)	128 (21%)	98 (16%)	75 (23%)	38 (18%)
eCrCl <45, n (%)	47 (8%)	22 (4%)	20 (6%)	20 (9%)

*All patients had at least 21 days of exposure to febuxostat 80 mg in the run-in period.
Source: Clinical Study Reports for Studies 301, 302, 304 (Table 7&8), and 303.

Efficacy findings

Results for lesinurad vs. placebo on background allopurinol: Studies 301 and 302

As shown in Table 2 below, in Studies 301 and 302, which were comprised of gout patients receiving background allopurinol, a significantly higher proportion of patients in both lesinurad treatment groups achieved the primary endpoint target of sUA <6.0 mg/dL by Month 6 compared to placebo-treated patients. For the proposed dose of 200 mg, approximately 30% more patients reached the target sUA in both studies compared to placebo. To illustrate the treatment effect from a different perspective, Table 2 includes change from baseline in serum urate levels. Change from baseline to Month 1 is shown in Table 2 because the change in sUA appeared to plateau by Month 1, and more patients remained in the studies at this timepoint than in later visits. For the 200 mg dose, sUA decreased by 1.2 to 1.3 mg/dL on average; the treatment effect was somewhat larger for

the 400 mg dose (1.6 to 1.8 mg/dL) and in analyses of observed data (i.e., limited to patients who were remaining in the study) at each visit. Regarding key secondary endpoints, there was not a significant difference between treatment groups in terms of the rate of gout flares per subject between Month 6 and Month 12. Although there was a significant difference in target tophus resolution between placebo and the 200 mg group in Study 301, the results favored placebo and were not consistent with other efficacy results. Given the small sample size of patients with tophi, definitive conclusions regarding this endpoint cannot be drawn.

Table 2: Summary Efficacy Results for Studies 301 and 302 (ITT Population)

	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)
sUA: Change from Baseline to Month 1 Observed Cases, n Mean (SD)	189 -0.22 (1.27)	192 -1.33 (1.32)	194 -1.84 (1.53)	199 -0.23 (1.22)	197 -1.23 (1.19)	193 -1.58 (1.59)
Primary Endpoint						
Proportion with sUA <6.0 mg/dL by Mo. 6 Nonresponder Imputation	56 (28%)	109 (54%)	119 (59%)	48 (23%)	113 (55%)	133 (67%)
Diff. vs PBO + ALLO (95% CI) p-value		0.26 (0.17, 0.36) <0.001	0.31 (0.22, 0.41) <0.001		0.32 (0.23, 0.41) <0.001	0.43 (0.34, 0.52) <0.001
Key Secondary EPs						
Adj. Rate of Gout Flare Requiring Treatment per Subject Mo. 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 vs PBO+ALLO (95%CI) 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
Of patients with at least one tophus at baseline, proportion with target tophus resolution by Mo. 12	5/17 (29%)	0/18 (0%)	4/19 (21%)	11/33 (33%)	11/35 (31%)	8/29 (28%)
Diff. vs PBO+ALLO (95% CI) p-value		-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

Sources: Table 14.2.1.22 of Study 301 Clinical Study Report (CSR) and Table 14.2.1.22 of Study 302 CSR; FDA statistical review of key endpoints

Results for lesinurad vs. placebo on background febuxostat: Study 304

Selected efficacy results for Study 304, which was comprised of gout patients who had at least one tophus and who received concomitant febuxostat (FBX), are shown in Table 3 below. Although a higher proportion of patients in both lesinurad treatment groups achieved the primary endpoint target of sUA <5.0 mg/dL by Month 6 compared to placebo-treated patients, the difference in proportions for the proposed dose of 200 mg

was 10%, and was not statistically significant. However, as noted in Table 1, 50% of patients were already meeting the primary endpoint target at baseline. In terms of change from baseline in serum urate levels, the treatment effect size appears to be similar to Studies 301 and 302, with a decrease of 1.15 mg/dL for the 200 mg dose and 1.62 mg/dL for the 400 mg dose. For the key secondary endpoint of the proportion of patients achieving a complete resolution of their target tophus by Month 12, there was not a significant difference between treatment groups. Other key secondary endpoints not listed in Table 3 include the proportion of patients who experienced complete or partial resolution of at least one target tophus by Month 12 (there were no significant differences between treatment groups), and the proportion of patients achieving a Health Assessment Questionnaire-Disability Index (HAQ-DI) improvement of at least 0.25 units at Month 12 (there was no significant difference between placebo and LESU200 mg, but significantly more placebo patients achieved this level of improvement compared to LESU400 mg). For consistency with Studies 301 and 302, Table 3 includes the adjusted rate of gout flare requiring treatment per subject in Months 6 to 12. Although there was a significant decrease in the rate of gout flares per subject between Month 6 and Month 12 for the 400 mg dose, there was no difference for the 200 mg dose.

Table 3: Summary Efficacy Results for Study 304 (ITT Population)

	PBO + FBX 80 mg (N=109)	LESU200 + FBX 80 mg (N=106)	LESU400 + FBX 80 mg (N=109)
sUA: Change from Baseline to Month 1 **Observed Cases, n** **Mean (SD)**	104 0.23 (1.26)	102 -1.15 (1.75)	103 -1.62 (1.72)
Primary Endpoint			
Proportion with sUA <5.0 mg/dL by Month 6 Nonresponder Imputation	51 (47%)	60 (57%)	83 (76%)
Diff. in Proportions vs PBO + FBX **(95% CI)** **p-value**		0.10 (-0.03, 0.23) 0.13	0.29 (0.17, 0.42) <0.001
Selected Secondary Endpoints			
Proportion with a best response of complete resolution of a target tophus by Month 12	23 (21%)	27 (25%)	33 (30%)
Diff. in Proportions vs PBO+FBX (95% CI) **p-value**		0.04 (-0.07, 0.16) 0.45	0.09 (-0.02, 0.21) 0.12
Adjusted Rate 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 vs PBO + ALLO (95% CI) **p-value**		1.2 (0.7, 2.1) 0.5493	0.5 (0.3, 1.0) 0.0401

Sources: Table 14.2.1.22 and Table 21 of the Study 304 CSR, FDA statistical review of key endpoints

Results for lesinurad 400 mg monotherapy vs. placebo monotherapy: Study 303

As the 400 mg dose and monotherapy use are not being proposed for marketing due to renal safety concerns (see safety section below), efficacy results for Study 303 will not be addressed in detail here, but Study 303 met its primary endpoint, and efficacy results are consistent with efficacy results from the other phase 3 studies.

Safety findings

Safety Overview

As shown in Table 4 below, lesinurad 400 mg was associated with an increased incidence of adverse events (AE), serious adverse events (SAE), serious renal AE, major cardiovascular adverse events (MACE), and death, compared to placebo. Lesinurad 200 mg was not associated with an increased incidence of SAE, renal SAE, or MACE, compared to placebo, and was associated with a smaller increased risk of adverse events compared to lesinurad 400 mg, suggesting toxicity with lesinurad is dose-dependent.

Table 4: Safety Overview—Phase 3 Trial Controlled Periods

	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)
Subjects with Any Treatment Emergent Adverse Event (TEAE), n (%)[a]	363 (70%)	386 (76%)	407 (80%)	793 (78%)	70 (65%)	83 (78%)
Exp-Adj Incidence of TEAEs Events/100 patient-years[a]	88.5	96.9	103.5	100.2	154.2	201.0
Any Serious TEAE[b], n (%)	29 (6%)	24 (5%)	44 (9%)	68 (7%)	4 (4%)	9 (8%)
Exp-Adj Incidence of Serious TEAE (Events/100py)[b]	7.1	6.0	11.2	8.6	8.8	21.8
Any Serious Renal TEAE[c], n(%)	2 (<1%)	0	5 (1%)	5 (<1%)	0	5 (5%)
Exp-Adj Incidence of Serious Renal TEAE (Events/100py)[c]	0.5	0	1.3	0.6	0	12.1
Subj. with MACE event[d], n (%)	3 (1%)	4 (1%)	8 (2%)	12 (1%)	0	1 (1%)
No. of MACE events[d]	4	4	9	13	0	1
Exp-Adj Incidence of MACE[d] (Events/100py)	0.95	0.96	2.18	1.57	0	2.42
Deaths[e], n (%)	0	2 (0.4%)	3 (0.6%)	5 (0.5%)	0	1 (1%)
Exp-Adj Incidence of Death[e] (Events/100py)	0	0.50	0.76	0.63	0	2.42

[a]Sources: Table 4.2.2.1 Integrated Summary of Safety; Exp-adj incidence for Study 303 not reported, but was calculated using patient-year exposure is 45.4 for placebo and 41.3 for LESU400 mg, from Table 32 Summary of Clinical Safety

[b]Sources: Table 4.8.2.1 Integrated Summary of Safety, Table 32 Summary of Clinical Safety

[c]Sources: Renal Safety Report, Table 7 and Table 5; Exp-adj incidence calculated: see footnote a and e

[d]MACE=Major Adverse Cardiovascular Event = cardiovascular death, nonfatal MI, or nonfatal stroke; Sources: Table 19 and Section 4.3.8.4.1. in the Cardiovascular Safety Report; for Study 303, see footnote a

[e]Sources: Exposure from Table 4.2.2.1 Integrated Summary of Safety: 398.2 pt-yrs for LESU200 mg, 393.2 for LESU400 mg, 791.4 pt-yrs for Total Lesu, and 410 pt-yrs for placebo; for Study 303, see footnote a

Although the gout population has multiple comorbidities that increase the risk of cardiovascular and renal disease, this underlying predisposition would be expected in all treatment groups in the lesinurad studies. As placebo-group exposure was similar or slightly higher than the exposure in the individual lesinurad arms, a lower incidence in the placebo groups is not attributable to differences in exposure. Therefore, the increased incidence seen in the individual lesinurad arms (in addition to the dose-dependent nature of the incidence) suggests a contribution of lesinurad over and above what might be expected in the underlying population.

Renal Safety

Table 5: Incidence of Renal-Related AE and Serum Creatinine Elevations in the Phase 3 Studies

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 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%)
Any Renal-Related AE	**23 (5%)**	**29 (6%)**	**60 (12%)**	**89 (8%)**	**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
sCr Elevation Category						
≥1.5 x Baseline	12 (2%)	29 (6%)	73 (14%)	102 (10%)	0	26 (24%)
≥2.0 x Baseline	0	9 (2%)	34 (7%)	43 (4%)	0	9 (8%)
≥3.0 x Baseline	0	4 (1%)	12 (2%)	16 (2%)	0	4 (4%)
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. Serum creatinine (sCR) elevation categories are cumulative: subjects can be counted in more than one category, so perentages can sum to greater than 100%. Baseline is defined as the highest sCr value recorded within 14 days prior to the first dose of randomized study medication.
Sources: Integrated Summary of Safety (ISS): Tables 4.17.8.1 and 14.17.8.3; Tables 4.17.5.1 and 14.17.5.3; Tables 9.1.1.1 and 9.1.1.3, Tables 4.17.5.12 and 4.17.5.13

As shown in Table 5 above, lesinurad 400 mg was associated with an increased incidence of renal AE, serious renal AE, serum creatinine elevations, and kidney stone AE, compared to placebo. Lesinurad 200 mg was not associated with an increased incidence of serious renal AE or kidney stone AE, but was associated with a smaller increase in the incidence of overall renal AE and serum creatinine elevations.

The only patient with a serious renal AE requiring hemodialysis or biopsy during the controlled period of the trials was on lesinurad 400 mg monotherapy in Study 303. The patient was 25 years old and had normal renal function at baseline but was hospitalized on Day 5 of treatment with abdominal pain radiating to the back, nausea, vomiting, and an sUA of almost 9 mg/dL and BUN 45 mg/dL. The patient was also taking naproxen 375 mg for gout prophylaxis along with esomeprazole 20 mg qd for GI protection. The patient's biopsy showed focal acute tubular necrosis and minimal tubulointerstitial fibrosis. The patient's acute renal failure resolved by Day 26. Two patients on lesinurad 200 mg and allopurinol in the long-term extension studies developed acute-on-chronic renal failure requiring dialysis (at Day 381 and Day 567). An additional patient on lesinurad 400 mg and allopurinol developed acute renal failure at Day 413 in the long term extension and received a renal biopsy which showed acute tubular cell injury. All patients had comorbidities and/or concomitant medications that would increase their underlying risk for renal complications. However, it is likely that lesinurad treatment was an additional risk factor that contributed to the occurrence of at least two of these renal events.

Cardiovascular Safety

The applicant conducted a comprehensive cardiovascular (CV) safety assessment of the lesinurad clinical development program that included an independent Cardiovascular Endpoints Adjudication Committee (CEAC) who prospectively reviewed and adjudicated adverse events according to a CEAC charter in the phase 3 studies. All deaths and potential CV events identified by study investigators or the CEAC chair were adjudicated, and if considered to be CV in nature, were classified into Major Cardiovascular Event (MACE) and non-MACE CV categories. The MACE categories were CV death, nonfatal myocardial infarction (MI), and nonfatal stroke.

Table 6 below summarizes the results of the adjudicated cardiovascular events. Generally, there was no clear or consistent imbalance in non-MACE rates between the treatment groups. However, there was an imbalance in MACE incidence and exposure-adjusted incidence in the lesinurad 400 mg groups of the phase 3 studies compared to lesinurad 200 mg or placebo. There were a small number of events and the confidence intervals are overlapping; however, the pattern of increase in risk with the 400 mg dose is consistent with other adverse events, such as serious adverse events and renal-related events.

Table 6: Adjudicated Cardiovascular Adverse Events in the Phase 3 Studies

	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:						
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:						
Cardiovascular Death	0	2 (<1%)	2 (<1%)[b]	4 (<1%)	0	1 (1%) [1]
Non-Fatal MI	1 (<1%) [1][a]	2 (<1%) [2]	6 (1%) [7][b]	8 (1%) [9]	0	0
Non-Fatal Stroke	2 (1%) [3][a]	0	0	0	0	0
Total No. of Subjects with MACE:	3 (1%) [4]	4 (1%) [4]	8 (2%) [9]	12 (1%) [13]	0	1 (1%) [1]
Total No. of MACE	4	4	9	13	0	1
Exp-Adj Incidence of MACE (Events/100py)(95% CI)	0.95 (0.36, 2.53)	0.96 (0.36, 2.57)	2.18 (1.13, 4.19)	1.57 (0.91, 2.71)	0	2.42

Pts.= patients; Adjud. = adjudicated; Revascul.= Revascularization; Arrhyth.= Arrhythmia; Periph.= Peripheral
MACE 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]One subject experienced a non-fatal MI and a non-fatal stroke
[b]One subject experienced a non-fatal MI and subsequent CV death
Sources: Table 4.14.1.1. from ISS and Table 42, 16.3.1.3, 14.3.2.2. from CSR for Study 303; Table 19 and Section 4.3.8.4.1. in the Cardiovascular Safety Report

Benefit-risk assessment

Based on the information provided, the Advisory Committee will be asked to consider whether the benefit-risk profile of lesinurad is adequate for the proposed indication of treatment of hyperuricemia associated with gout in combination with a xanthine oxidase inhibitor. There are a number of points to consider:

- While lesinurad treatment did increase the proportion of patients achieving their target serum urate levels in the phase 3 studies, the average treatment effect for the proposed dose of lesinurad 200 mg was a decrease in sUA of approximately 1.1 to 1.3 mg/dL.
- Lesinurad 400 mg was associated with an increased incidence of adverse events, serious adverse events, serious and non-serious renal AE, major cardiovascular adverse events (MACE), and death, compared to placebo.
- Lesinurad 200 mg was associated with a smaller increased risk of adverse events, overall renal AE, and serum creatinine elevations compared to lesinurad 400 mg, suggesting toxicity with lesinurad is dose-dependent. The exposure of the 200 mg and 400 mg dose is largely overlapping, raising questions about whether the safety profile of the 200 mg dose will be consistent if used in a larger population with more variability, if approved.

Summary

The purpose of this AAC meeting is to discuss the adequacy of the data submitted by Ardea Biosciences to support approval of lesinurad for the proposed indication of treatment of hyperuricemia associated with gout in combination with a xanthine oxidase inhibitor. The Committee's input will be invaluable in this determination. In this regard, we ask the Committee to keep in mind the following discussion topics.

Draft Topics for Discussion

1. Discuss the efficacy data for lesinurad.
   a) Discuss the efficacy of the proposed dose of 200 mg and whether the decrease in sUA observed would be considered clinically meaningful.
2. Discuss the safety data for lesinurad.
   a) Discuss the safety of the proposed dose of 200 mg, with specific focus on renal and cardiovascular safety
   b) Discuss the dose dependent toxicity of lesinurad in light of the safety profile of the 400 mg dose
      a. Comment on whether the overlapping exposure of the 200 mg and 400 mg doses raises concerns about the potential toxicity of 200 mg if exposed to a broader population of gout patients post-marketing.
      b. Comment on whether the justification for once-daily dosing is adequate, given that it remains a question whether a lower nominal dose given more frequently might have provided similar efficacy with a better safety profile.

3. Overall, do the data provide substantial evidence that lesinurad provides a clinically meaningful beneficial effect in the treatment of hyperuricemia associated with gout, in combination with a xanthine oxidase inhibitor?

4. Is the safety profile of lesinurad adequate to support approval of lesinurad for the treatment of hyperuricemia associated with gout, in combination with a xanthine oxidase inhibitor?

5. Does the Committee recommend approval of lesinurad for the proposed indication of treatment of hyperuricemia associated with gout, in combination with a xanthine oxidase inhibitor?

FDA Joint Clinical-Statistical Briefing Document for the ARTHRITIS ADVISORY COMMITTEE MEETING

October 23, 2015

NDA 207988: Lesinurad for the proposed indication of treatment of hyperuricemia associated with gout in combination with a xanthine oxidase inhibitor

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1 Executive Summary

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 >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 the clinic, and was also not a requirement in the lesinurad clinical development program. While this is not unreasonable, this may have had an impact on the risk-benefit profile of lesinurad, with some patients experiencing less efficacy or more toxicity because urinary under-excretion was not the cause of their hyperuricemia. This Advisory Committee panel will be asked to discuss the available efficacy and safety data, and whether the risk/benefit profile for the use of lesinurad in a more general gout population, such as the one studied, is adequately favorable.

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, and is also the mechanism by which probenecid exerts its uricosuric effect. 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 Available Treatments for Proposed Indication

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

Lesinurad is a new molecular entity and is not currently commercially available.

2.4 Important Safety Issues With Consideration to Related Drugs

Benzbromarone, sulfinpyrazone and probenecid comprise the uricosuric class of drugs which can be used in patients who are underexcretors of urate. Probenecid is the only uricosuric currently available in the U.S. Like lesinurad, probenecid also interferes with

renal absorption of uric acid by inhibiting URAT1. Probenecid also inhibits OAT1 and OAT3, as well as GLUT9.[1] Based in part on concerns regarding urolithiasis and decreased efficacy in patients with creatinine clearance below 50 ml/min, American College of Rheumatology treatment guidelines[2] include caveats such as not using uricosurics in patients with urolithiasis or in patients with a creatinine clearance below 50 ml/min, or in patients with elevated urine uric acid. The guidelines also recommend monitoring of urinary uric acid during therapy, and considering urine alkalinization and increasing fluid intake.

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 $\geq$6.5 at 6 to 8 hours post lesinurad dosing with mandatory

[1] Bach MH and PA Simkin, "Uricosuric drugs: the once and future therapy for hyperuricemia?" Curr Opin Rheumatol 2014, 26:169-175.
[2] 2012 American College of Rheumatology Guidelines for Management of Gout. Part 1: Systematic Nonpharmacologic and Pharmacologic Therapeutic Approaches to Hyperuricemia. Arthritis Care & Research, October 2012, 64(10):1431-1446.

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.

3 Other Relevant Discipline-Specific Information

3.1 Clinical Pharmacology

3.1.1 Pharmacokinetics in Healthy Subjects

Absorption
The absolute bioavailability of lesinurad under fed conditions is about 100%. Systemic exposure (AUC0-∞) and peak plasma concentration (Cmax) increased in proportion to the dose in the dose range of 5 to 1200 mg. Tmax was reached by approximately 1-4 hours following oral administration under fed conditions. Coadministration with a high-fat meal decreases Cmax by up to 18% but does not alter AUC as compared with fasting state. The steady-state was reached after one dose with minimal accumulation.

Distribution
Plasma protein binding for lesinurad is high, primarily to albumin, with bound fraction of 98%.The volume of distribution at steady-state (Vss) is approximately 20.3 liters.

Metabolism and Excretion
Lesinurad undergoes oxidative metabolism mainly via cytochrome P450 CYP2C9. Plasma exposure of metabolites is minimal (<10% of unchanged lesinurad). Metabolites are not known to contribute to the uric acid lowering effects of lesinurad. A transient oxide metabolite is rapidly eliminated by microsomal epoxide hydrolase in the liver and not detected in plasma. Approximately 63% of administered dose is excreted in urine and 32% is eliminated in feces. The terminal half-life of lesinurad is approximately 5 hours.

3.1.2 Pharmacokinetics in Gout Patients

The PK of lesinurad in subjects with gout was assessed in 2 drug-drug interaction studies and 4 phase 2 studies. In addition, sparse PK samples were also collected in the phase 3 studies and analyzed using population PK methods. Overall, the PK of lesinurad was similar in healthy subjects and patients with gout. The population PK analysis showed that typical CL/F value in subjects in gout patients (phase 3 studies) was approximately 18% lower than that observed in healthy subjects in (Phase 1 studies).

3.1.3 Pharmacokinetics in Specific Populations

Renal Impairment
The impact of renal impairment on the PK of lesinurad was evaluated in Studies 104 and 120. Study 104 evaluated a single dose of lesinurad 200 mg in adult volunteers with mild or moderate renal impairment. Study 120 evaluated a single dose of lesinurad 400 mg in adult volunteers with moderate or severe renal impairment. Lesinurad exposure (AUC) increased by 31%, 50-74% and 113%, respectively in subjects with mild, moderate and severe renal impairment compared with subjects with normal renal function. As shown in **Table 2** below, decreasing renal function was associated with increased average exposure and higher variability in exposure; however the numbers of patients also generally decreased with decreasing renal function and is also likely contributing to the variability observed.

Table 2: Effect of Baseline Renal Function on Avg. Conc. of Lesinurad Under Steady-State in Phase 3 Subjects, Studies 301, 302, and 304, 200 mg QD Dose

	Cave (ng/mL), mean (SD) in patients with various baseline renal function (CrCl)									
Study	**≥90mL/min**	**N**	**60 - < 90 mL/min**	**N**	**45 - < 60 mL/min**	**N**	**30 - < 45 mL/min**	**N**	**< 30 mL/min**	**N**
301	1666(1222)	87	1806(1403)	56	2371(1809)	26	2655(2460)	8	1518	1
302	1536(1240)	85	1450(837)	77	1910(1121)	17	2652(2953)	4	2068	1
304	1401(590)	37	1742 (858)	36	1970 (745)	16	2327 (625)	5	-	0
Total	1566(1144)	209	1630(1069)	169	2130(1396)	59	2558(2099)	17	1793(389)	2

Source: FDA clinical pharmacology/pharmacometrics reviewer Dr. Jianmeng Chen

Hepatic Impairment
The effect of hepatic impairment on the metabolism of lesinurad was studied in mild and moderate hepatic impairment subjects and compared with healthy volunteers following a 400 mg dose of lesinurad (Study 118). Mild or moderate hepatic impairment (Child-Pugh Classes A and B) had no significant effect on lesinurad PK. No dose adjustment of lesinurad is necessary in mild and moderate hepatic impaired patients. Lesinurad is not recommended in patients with severe hepatic impairment.

Weight, Age, Race and Sex

Race, ethnicity, age and sex did not significantly impact the PK of lesinurad. No dose adjustments are recommended based on weight, age, race and sex.

3.1.4 Drug-Drug Interactions

Effect of Coadministered Drugs on Lesinurad
Lesinurad is a substrate of CYP2C9. Lesinurad exposure is increased by 56% when lesinurad is co-administered with fluconazole, an inhibitor of CYP2C9. Lesinurad should be used with caution in patients taking moderate inhibitors of CYP2C9 (e.g., fluconazole, amiodarone). Lesinurad exposure is decreased when lesinurad is co-administered with inducers of CYP2C9 (e.g., rifampin), which may decrease the therapeutic effect of lesinurad.

Aspirin may affect lesinurad's URAT1 inhibiting activity, and decrease the uric acid lowering activity of lesinurad. Thiazide may increase sUA, and antagonize the activity of lesinurad. Subgroup analysis in study 301 and 302 suggested that low dose aspirin (≤325mg) or thiazide diuretics did not affect the efficacy of lesinurad.

Effect of lesinurad on coadministered drugs
Lesinurad is a weak CYP3A4 inducer. Concomitant use with lesinurad reduced the plasma concentration of sensitive CYP3A4 substrates (e.g., sildenafil, amlodipine), and possibly reduce the efficacy of sensitive CYP3A4 substrates. Patients should not rely on hormonal contraception alone when taking lesinurad.

Based on in vitro studies, lesinurad is a substrate of OAT1 and OAT3 and a weak inhibitor of OATP1B1, OCT1, OAT1, and OAT3. However, in vivo drug interaction studies suggested that lesinurad does not decrease the renal clearance of furosemide (substrate of OAT1/3), or affect the exposure of metformin (substrate of OCT1). In addition, consistent with the in vitro finding of being a URAT1 inhibitor, lesinurad reduces the exposure of oxypurinol, a URAT1 substrate, by 25%.

3.1.5 Exposure-Response/Dose Selection

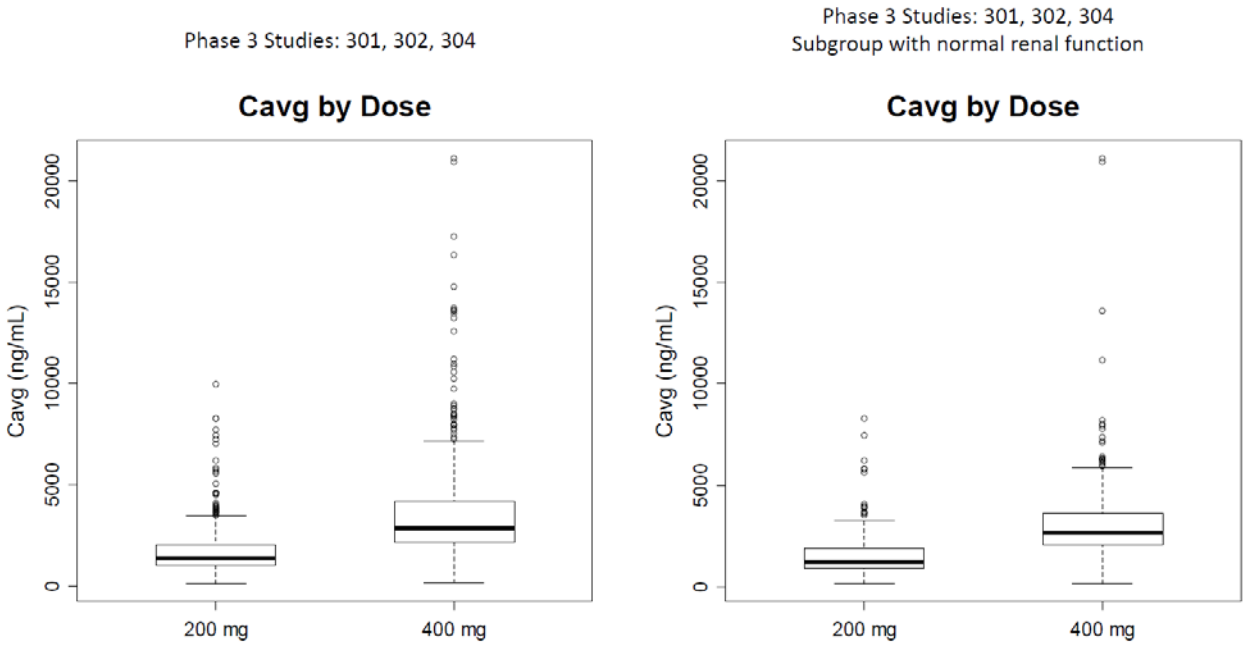
During the clinical development of lesinurad, only a once-daily regimen was evaluated. The rationale for the once-daily regimen was that a decrease in sUA was still observed at 24 hours with this regimen, and that this regimen would avoid high urinary uric acid (uUA) concentrations at night, when urine pH and volume are the lowest, in order to reduce the risk of uric acid precipitation.

Two 4-week dose-ranging studies were conducted during phase 2—Study 202 and Study 203; both evaluated doses of 200, 400, or 600 mg daily of lesinurad. Study 202 evaluated lesinurad alone (except for colchicine 0.6 mg daily given as prophylaxis for gout flares) and Study 203 evaluated lesinurad in combination with allopurinol compared to allopurinol alone (also on a background of colchicine prophylaxis). Both studies showed a dose-dependent reduction in sUA. In Study 203, the percent change

from baseline in sUA following 4 weeks of treatment was 16% for the 200 mg dose, 22% for the 400 mg dose, and 30% for the 600 mg dose. The applicant decided that the additional effect of 600 mg over 400 mg was only marginally greater when used in combination with allopurinol, so 400 mg was selected as the higher dose in the phase 3 studies. The 100 mg dose (evaluated in phase 1) did not appear to result in sustained sUA reductions over 24 hours, and thus was not explored in phase 2.

As shown in Figure 1 below, although the average concentration was higher in the 400 dose group compared to the 200 mg dose group in Studies 301, 302, and 304, the exposure for these two doses was overlapping.

Figure 1: Exposure of Lesinurad in Phase 3 XOI Studies 301, 302, and 304



Source: FDA clinical pharmacology reviewer, Dr. Jianmeng Chen

Exposure-Response for Efficacy

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 (-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).

A caveat with the aforementioned exposure-response is that lesinurad appears to be less effective with increasing degree of renal impairment. FDA clinical pharmacology and statistical reviewers evaluated the data from Studies 301 and 302. Despite higher exposures in patients with the greatest renal impairment (<45 ml/min), the reduction in sUA compared to placebo appears to be minimal in this group. The number of patients with moderate or severe renal impairment in these studies was small, so definitive conclusions cannot be drawn; however, FDA pharmacometrics reviewers built a pharmacokinetic-pharmacodynamic Emax model and renal function was identified as the only covariate that impacts the efficacy of lesinurad. The Emax model predicted that for a patient with an estimated creatinine clearance (eCrCl) of 30 ml/min, 55% of the efficacy would be preserved at a given exposure. For a patient with an eCrCl of 60 ml/min, 80% of the efficacy would be preserved at a given exposure. These predictions were consistent with the observed efficacy data in the phase 3 studies.

Table 3: Effect of Baseline Renal Function on sUA Decline

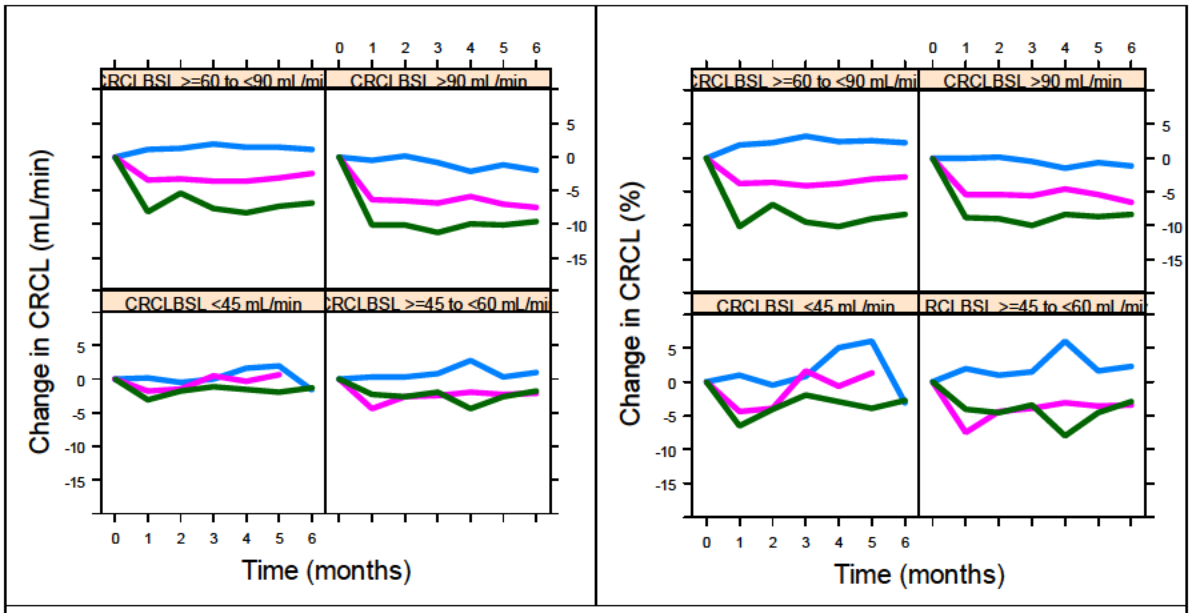
	Difference of Least Square Mean, sUA (mg/dL), Study 301+302			
Baseline Renal Function	LESU200 + ALLO v. PBO+ALLO	LL	UL	N
<45	-0.288	-1.37	0.795	46
45 to <60	-0.807	-1.32	-.294	105
>= 60	-1.13	-1.40	-.861	637

Source: FDA statistical reviewer analysis, by Dr. Yu Wang

Exposure-Response for Safety

As will be discussed in more detail in the safety section below, there also appears to be a dose-response relationship for safety, and in particular, renal toxicity. Data from the Studies 301 and 302 showed that lesinurad decreased eCrCl from baseline in a dose-dependent manner. As shown in Figure 2 below, this decrease in eCrCl was observed in all categories of renal impairment.

Figure 2: Change from Baseline in eCrCl by Renal Category, Studies 301&302



Mean change in eCrCl (mL/min) and relative change in eCrCl(%)from baseline over time in patients with different baseline CrCls. Blue: Placebo+Allo, Pink: Lesinurad 200mg+Allo, Green: Lesinurad 400mg+Allo

Source: FDA statistical/clinical pharmacology reviewer analyses

3.2 Preclinical Pharmacology/Toxicology

Chronic toxicology studies showed evidence of kidney toxicity in rats and GI tract toxicity in both rats and monkeys. In rats, the dose of 600 mg/kg/day (119 x clinical exposure) was lethal due to kidney toxicity (tubular degeneration and single cell necrosis) and gastrointestinal toxicity (erosion, hemorrhage, congestion, single necrosis). At the dose of 300 mg/kg/day (36 x clinical exposure), kidney findings were limited to tubular dilatation and changes of clinical chemistry parameters. Low incidences of GI tract erosion were observed. For monkeys, the dose of 600 mg/kg/day (11 x clinical exposure) was lethal due to GI tract toxicity (erosions and hemorrhage in colon and rectum and severe diarrhea and emesis). There was no GI tract toxicity at lower doses; however, bile duct hyperplasia was observed at 200 mg/kg/day. NOAELs of 100 mg/kg/day in both rats and monkeys provide exposure margins of 15- and 3-fold relative to the clinical exposure. While these findings would not preclude approval of the proposed clinical dose, they suggest lesinurad has the potential for kidney and GI tract toxicity. The kidney toxicity observed in the rat would not be likely to be due to uric acid crystalluria or nephrolithiasis, as rats, like most mammals, possess functional uricase, and have low serum uric acid levels (in the range of 1 to 2 mg/dL)[3].

[3] Johnson RJ et al., "The Planetary Biology of Ascorbate and Uric Acid and their Relationship with the Epidemic of Obesity and Cardiovascular Disease." Med Hypotheses 2008; 71(1):22-31.

4 Sources of Clinical Data

4.1 Tables of Studies/Clinical Trials

The clinical development program for lesinurad includes 29 phase 1 studies, 6 phase 2 studies, and 7 phase 3 studies. The phase 2 and phase 3 studies are summarized in **Table 4** and **Table 5** below.

Table 4: Design Features of the Lesinurad Phase 2 Trials

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
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.	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	N=126	Males and Females with Gout and an inadequate hypo-uricemic response to	Safety and Efficacy

Assess safety and tolerability of lesinurad in combination with allopurinol in pts with gout		--Multiple doses of 0.6 mg qd colchicine in fed state		standard of care allopurinol	
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 5: Design Features of the Lesinurad Phase 3 Trials

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

Table 5: Design Features of the Lesinurad Phase 3 Trials (continued)

Study /Objectives	Study Design/ Duration/ No. Sites	Dosage Regimen/ Route of Adm.	No. of Subjects	Diagnosis/ Entry Criteria	End-points
Phase 3 Studies (cont.):					
RDEA594-303; 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
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)

4.2 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[4]. 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 reproducible methodology by the Outcomes Measures in Rheumatology (OMERACT) 10[5].

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)[6] 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

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.
5 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.
6 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.

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.

4.2.1 Common protocol for 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

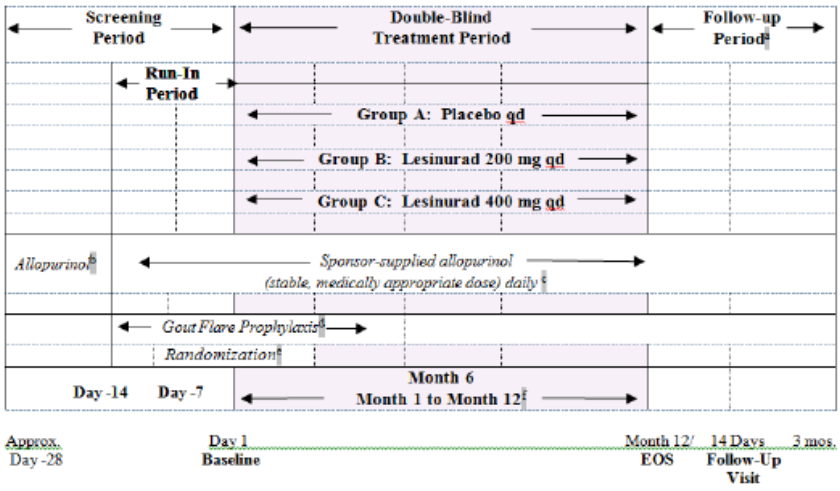
Secondary Objectives:

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

Figure 3: Study Design Schema 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 6 below summarizes the major inclusion and exclusion criteria for Studies 301 and 302.

Table 6: 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 $\geq$ 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:

Table 7: Selected Procedures/Evaluations for Studies 301 and 302

	Screening Period			Baseline Day 1	Double-Blind Treatment Period				Follow-up
	Screening Day -28	Run-In Period			Week 2	Months 1-6	Months 7-11	Month 12 / Early Termination	
		Day -14	Day -7						
History	X								
Physical		X						X	
Vital signs	X	X	X	X	X	X	X	X	X
Initiate gout flare prophylaxis		X							
Randomization				X					
Compliance checks			X	X	X	X	X	X	
Urinalysis	X			X		X	X	X	X
Hematology	X			X		X	X	X	X
Blood Biochemistry (incl sUA)	X		X	X		X	X	X	X
Tophus assessment				X		3, 6	9	X	

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.

4.2.2 Protocol for 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:

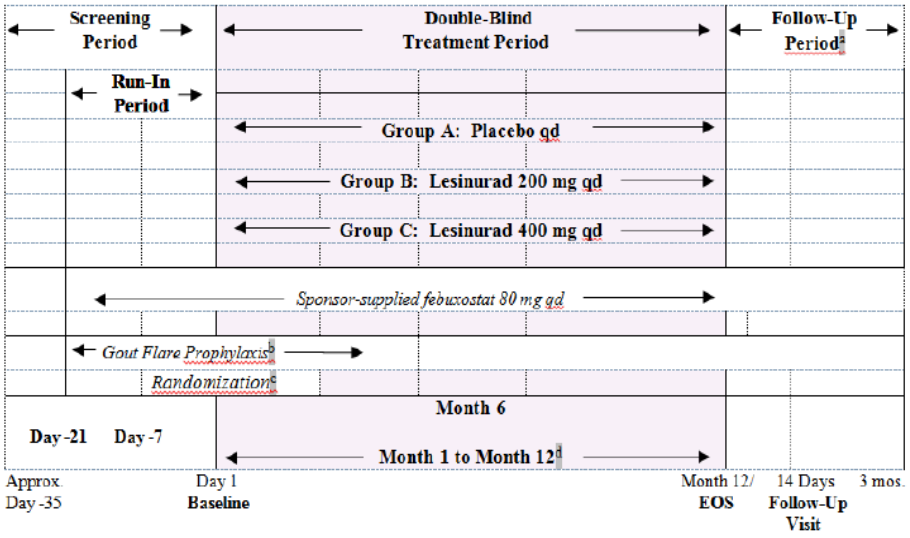
- Assess the efficacy of lesinurad by Month 6 when used in combination with febuxostat as compared to febuxostat monotherapy

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 4: Study Design Schema 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 6**, 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 7 days 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.

Table 8 Selected Procedures/Evaluations for Study 304

	Screening Period			Baseline Day 1	Double-Blind Treatment Period				Follow-up
	Screening Day -35	Run-In Period			Week 2	Months 1-6	Months 7-11	Month 12 / Early Termination	
		Day -21	Day -7						
History	X								
Physical	X							X	
Vital signs	X	X	X	X	X	X	X	X	X
Initiate gout flare prophylaxis		X							
Randomization				X					
Compliance checks			X	X	X	X	X	X	
Urinalysis	X			X		X	X	X	X
Hematology	X			X		X	X	X	X
Blood Biochemistry (incl sUA)	X		X	X		X	X	X	X
Tophus assessment				X		3, 6	9	X	

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.

4.2.3 Protocol for Study 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.

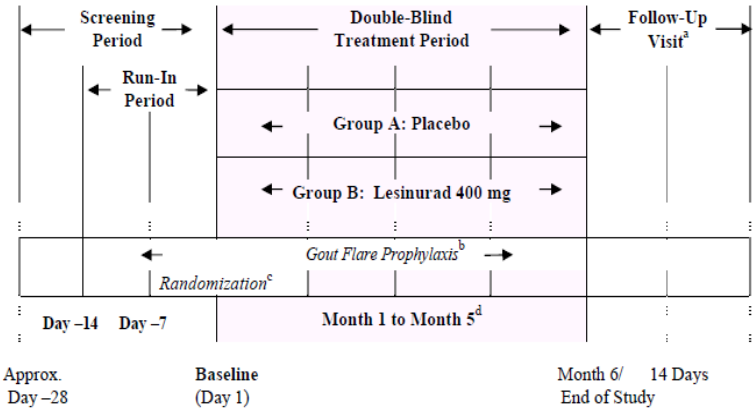
Objectives:
Primary objectives:
- Assess the efficacy of lesinurad monotherapy compared to placebo by Month 6

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.

Figure 5: Study Design Schema 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).

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 5** 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.

Table 9: Selected Procedures/Evaluations for Study 303

	Screening Period			Baseline Day 1	Double-Blind Treatment Period			Follow-up
		Run-In Period						
	Screening Day -28	Day -14	Day -7		Week 2	Months 1-5	Month 6 / Early Termination	
History	X							
Physical		X					X	
Vital signs	X	X	X	X	X	X	X	X
Initiate gout flare prophylaxis		X						
Randomization				X				
Compliance checks			X	X	X	X	X	
Urinalysis	X			X		X	X	X
Hematology	X			X		X	X	X
Blood Biochemistry (incl sUA)	X		X	X		X	X	X

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.

5 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 ≥ 5 mg/dL) for Study 304. Additional subgroup analyses showed that low dose (≤ 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.

5.1 Indication

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

5.1.1 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.

5.1.2 Demographics and Baseline Disease Characteristics

5.1.2.1 Study 301

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.

Table 11 Baseline Gout Characteristics for Subjects Enrolled in Study 301

	PBO + ALLO (N=201)	LESU200 mg + ALLO (N=201)	LESU400 mg + ALLO (N=201)	Total (N=603)
Meeting ARA Diagnostic Criteria, n (%)	**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 diameter)*				
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)**
Proportion <6.0, n (%)	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%)
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

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** above). 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.

5.1.2.2 Study 302

As summarized by the following tables (**Table 12 and Table 13**), 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 12**). 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%).

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 13**). 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 13**). 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 12: Baseline Demographic Characteristics of Subj. 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

Table 13: Baseline Gout Characteristics for Subjects Enrolled in Study 302

	PBO + ALLO (N=206)	LESU200 mg + ALLO (N=204)	LESU400 mg + ALLO (N=200)	Total (N=610)
Meeting ARA Diagnostic Criteria, n (%)	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)**
Proportion <6.0, n (%)	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%)
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

5.1.2.3 Study 304

As summarized by the following tables (**Table 14 and Table 15**), 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 14**). 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 major imbalances in these demographic factors across treatment groups were noted.

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 15**). 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 15**). 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 14: Baseline Demographic Characteristics for Subj. 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

Table 15: Baseline Gout Characteristics of Subjects Enrolled in Study 304

	PBO + FBX80 mg (N=109)	LESU200 + FBX 80 mg (N=106)	LESU400 + FBX 80 mg (N=109)	Total (N=324)
Meeting ARA Diagnostic Criteria, n (%)	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)**
Proportion <5.0, n (%)	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

5.1.3 Subject Disposition

5.1.3.1 Study 301

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 16**). (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.)

Table 16: Subject Disposition in 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%)

Source: FDA statistical review by Dr. Yu (Jade) Wang

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.

5.1.3.2 Study 302

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 17**, 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 17: Subject Disposition in 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

5.1.3.3 Study 304

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.

Table 18: Subject Disposition in 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%)

Source: FDA statistical review by Dr. Yu (Jade) Wang

As shown in **Table 18** above, 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.

5.1.4 Analysis of Primary Endpoint(s)

5.1.4.1 Study 301

The primary efficacy endpoint for both Study 301 and Study 302 was the proportion of patients with sUA less than 6 mg/dL by Month 6. As shown in **Table 19**, a higher proportion of patients treated with lesinurad at both the 200 mg and 400 mg doses met this sUA target and the differences between each of the lesinurad groups and the placebo group were statistically significant. Although the proportion of responders was higher with lesinurad 400 mg compared to 200 mg, the magnitude of the difference between the groups was not consistent between studies.

Table 19: Primary Efficacy Analysis for Study 301 and Study 302 (ITT Population)

	Study 301			Study 302		
	PBO + ALLO	LESU 200 mg + ALLO	LESU 400 mg + ALLO	PBO + ALLO	LESU 200 mg + ALLO	LESU 400 mg + ALLO
ITT Population	N = 201	N = 201	N = 201	N = 206	N = 204	N = 200
Proportion with sUA < 6.0 mg/dL by Month 6, [n (%)]	56 (27.86)	109 (54.23)	119 (59.20)	48 (23.30)	113 (55.39)	133 (66.50)
Difference in proportions vs. PBO + ALLO (95% CI)[2]		0.26 (0.17, 0.36)	0.31 (0.22, 0.41)		0.32 (0.23, 0.41)	0.43 (0.34, 0.52)
p-value for comparison to PBO[34]		< 0.001	< 0.001		< 0.001	< 0.001

1. Subjects missing the Month 6 sUA result are treated as non-responders
2. Binomial confidence interval for difference in proportions
3. Cochran-Mantel Haenszel test stratified by Day -7 renal function and tophus status during Screening (randomized values)
4. p-value should be compared to α=0.025 to determine statistical significance according to the pre-specified Bonferonni correction to control type I error

Source: FDA statistical review by Dr. Yu (Jade) Wang

5.1.4.2 Study 302

See **Table 19**, above.

5.1.4.3 Study 304

The primary efficacy endpoint for Study 304 was the proportion of patients with sUA less than 5 mg/dL by Month 6. As shown in **Table 20** below, higher proportions of patients treated with 200 mg or 400 mg of lesinurad achieved the target sUA by Month 6. While the difference in proportions between lesinurad and placebo was statistically significant for the lesinurad 400 mg group, the difference was smaller (10%) for the

proposed 200 mg dose, and was not statistically significant. However, as noted in **Table 15** above, approximately 50% of patients were already meeting the target sUA level of <5.0 mg/dL at baseline in this study, which reduced the likelihood of being able to demonstrate a statistically significant difference between treatment groups.

Table 20: Primary Efficacy Analysis for Study 304 (ITT Population)

	Study 304		
	PBO + FBX 80 mg	**LESU 200 mg + FBX 80 mg**	**LESU 400 mg + FBX 80 mg**
ITT Population	N = 109	N = 106	N = 109
Proportion with sUA < 5.0 mg/dL by Month 6, [n (%)]	51 (46.79)	60 (56.60)	83 (76.15)
Difference in proportions vs. PBO + FBX 80 mg (95% CI)[2]		0.10 (-0.03, 0.23)	0.29 (0.17, 0.42)
p-value for comparison to PBO[3,4]		0.13	< 0.001

1. Subjects missing the Month 6 sUA result are treated as non-responders
2. Binomial confidence interval for difference in proportions
3. Cochran-Mantel Haenszel test stratified by Day -7 renal function and sUA level at Day -7.
4. p-value should be compared to α=0.025 to determine statistical significance according to the pre-specified Bonferroni correction to control type I error

Source: FDA statistical review by Dr. Yu (Jade) Wang

5.1.5 Analysis of Secondary Endpoints(s)

5.1.5.1 Study 301

In Study 301, 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 LESU200mg+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%).

In Study 302, 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 in both studies were required to discontinue their gout flare prophylaxis regimens at the end of Month 5. The mean rate of gout flares requiring treatment during

the 6-month time period from Month 6 to Month 12 was a key secondary endpoint in these studies. 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 21** below).

Table 21: Key Secondary Endpoint (Study 301 and Study 302): Mean Rate of Gout Flares Requiring Treatment (ITT Population)

	Study 301			Study 302		
	PBO + ALLO	LESU 200 mg + ALLO	LESU 400 mg + ALLO	PBO + ALLO	LESU 200 mg + ALLO	LESU 400 mg + ALLO
ITT Population	N = 201	N = 201	N = 201	N = 206	N = 204	N = 200
Adjusted rate[2, 3] of gout flare requiring treatment per subject in Months 6 to 12 (Standard Error)[2]	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[2] (95% CI) vs. PBO + ALLO		0.99 (0.61, 1.61)	0.88 (0.54, 1.43)		0.88 (0.57, 1.37)	0.93(0.60, 1.45)
p-value[2]		0.98	0.61		0.57	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.

Source: FDA statistical review by Dr. Yu (Jade) Wang

As shown in **Table 11** and **Table 13** above, approximately 9% and 16% of patients in Studies 301 and 302 respectively had at least 1 tophus meeting the protocol specified criterion of being between 5 mm and 20 mm in diameter. As shown in **Table 22** below, lesinurad treatment was associated with the same or fewer responders, defined as patients who had at least one target tophus with complete resolution by Month 12. In Study 301, the difference between lesinurad 200 mg and placebo was statistically significant, in favor of placebo. However, these results should be interpreted with caution in light of the small sample size of patients with at least one target tophus at baseline.

Table 22: Key Secondary Endpoint (Study 301 and Study 302): Of Subjects with ≥1 Target Tophus at Baseline, the Proportion who Experience ≥1 Complete Resolution by Month 12

	Study 301			Study 302		
	PBO + ALLO	LESU 200 mg + ALLO	LESU 400 mg + ALLO	PBO + ALLO	LESU 200 mg + ALLO	LESU 400 mg + ALLO
Subjects with at least one target tophus at baseline - ITT Population	N = 17	N = 18	N = 19	N = 33	N = 35	N = 29
Proportion with a best response of CR by Month 12 [n (%)]	5 (29.4)	0	4 (21.1)	11 (33.3)	11 (31.4)	8 (27.6)
Difference in proportions vs. PBO + ALLO (95% CI)[1]		-0.29 (-0.51 -0.08)	- 0.08 (-0.37, 0.20)		-0.02 (-0.24, 0.20)	-0.06 (-0.29, 0.17)
p-value[2]		0.02	0.60		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.

Source: FDA statistical review by Dr. Yu (Jade) Wang

5.1.5.2 Study 302

See **Tables 21** and **22** above.

5.1.5.3 Study 304

Subjects in Study 304 were required to have at least one target tophus at baseline, and complete resolution of at least one target tophus by Month 12 was a key secondary endpoint. As shown in **Table 23** below, there were numeric increases in the proportion of subjects experiencing at least one complete resolution in the lesinurad treatment groups compared to placebo, in a dose-dependent manner. However, the differences between the treatment groups were not statistically significant. As shown in **Table 24** below, similar results were observed for the key secondary endpoint of proportion of subjects experiencing at least one complete or partial resolution of a target tophus by Month 12.

Table 23: Key Secondary Endpoint (Study 304): Proportion of Subjects with Complete Resolution of at Least One Target Tophus by Month 12 (ITT Pop.)

	Study 304		
	PBO + FBX 80 mg	LESU 200 mg + FBX 80 mg	LESU 400 mg + FBX 80 mg
ITT Population	N = 109	N = 106	N = 109
Proportion with a best response of CR by Month 12 [n (%)]	23 (21.1)	27 (25.5)	33 (30.3)
Difference in proportions vs. PBO + FBX 80 mg (95% CI)[1]		0.04 (-0.07 0.16)	0.09 (-0.02, 0.21)
p-value[2]		0.45	0.12

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), and and Day -7 sUA status (sUA ≥ 6.0 mg/dL versus < 6.0 mg/dL), randomized values.

Source: FDA statistical review by Dr. Yu (Jade) Wang

Table 24: Key Secondary Endpoint (Study 304): Proportion of Subjects with Complete or Partial Resolution of at Least One Target Tophus by Month 12 (ITT)

	Study 304		
	PBO + FBX 80 mg	LESU 200 mg + FBX 80 mg	LESU 400 mg + FBX 80 mg
ITT Population	N = 109	N = 106	N = 109
Proportion with a CR or PR by Month 12 [n (%)]	55 (50.51)	60 (56.6)	64 (58.7)
Difference in proportions vs. PBO + FBX 80 mg (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 for difference in proportions
2. Cochran-Mantel Haenszel test stratified by Day -7 renal function (eCrCl ≥ 60 mL/min versus < 60 mL/min), and and Day -7 sUA status (sUA ≥ 6.0 mg/dL versus < 6.0 mg/dL), randomized values.

Source: FDA statistical review by Dr. Yu (Jade) Wang

Study 304 included some patients who had more baseline flares and disease activity, and included a key secondary endpoint of the proportion of subjects achieving an improvement of at least 0.25 units in the Health Assessment Questionnaire Disability Index (HAQ-DI). The applicant chose 0.25 units because it represents the value identified as the minimum clinically important difference (MCID) in rheumatoid arthritis patients, and its generalizability to the gout population in this study is not clear. Additionally, patients in Study 304 had relatively low HAQ-DI scores at baseline (mean of 0.671 in the lesinurad 200 mg group, 0.586 in the lesinurad 400 mg group, and 0.729 in the placebo group). Nonetheless, as shown in **Table 25** below, a lower proportion of patients achieved the target HAQ-DI improvement at Month 12 in the lesinurad groups compared to the placebo group. The proportion decreased in a dose-dependent manner, and the difference between the lesinurad 400 mg group and the placebo group was statistically significant.

Table 25: Key Secondary Endpoint (Study 304): Proportion of Subjects Achieving a HAQ-DI Improvement of at least 0.25 units at Month 12 (Observed Cases)

	Study 304		
	PBO + FBX 80 mg	LESU 200 mg + FBX 80 mg	LESU 400 mg + FBX 80 mg
ITT Population	N = 109	N = 106	N = 109
Observed Cases	N_a= 80	N_a= 77	N_a= 78
Proportion with a HAQ-DI improvement of >= 0.25 at Month 12 [n (%)]	42 (52.5)	34 (44.2)	26 (33.3)
Difference in proportions vs. PBO + FBX 80 mg (95% CI)[1]		-0.08 (-0.26 0.09)	-0.19 (-0.36, -0.02)
p-value[2]		0.30	0.02

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), and and Day -7 sUA status (sUA ≥ 6.0 mg/dL versus < 6.0 mg/dL), randomized values.

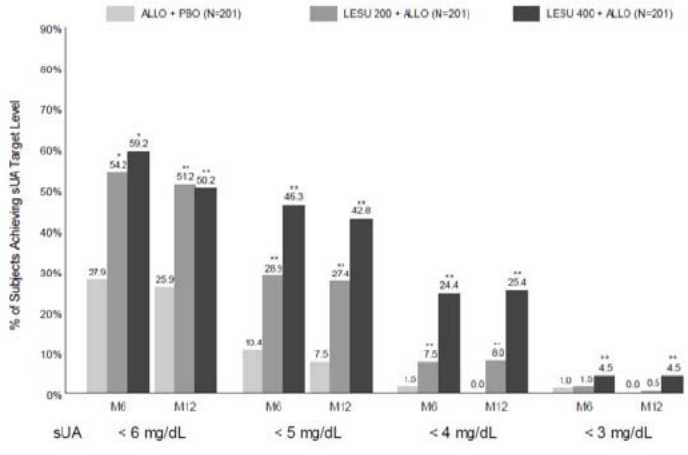
Source: FDA statistical review by Dr. Yu (Jade) Wang

5.1.6 Other Endpoints

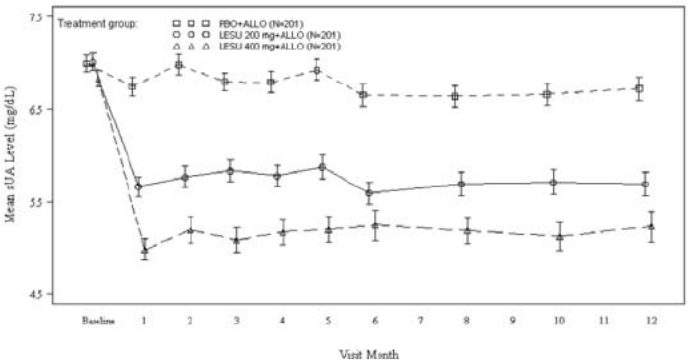
5.1.6.1 Other sUA Level Targets and Mean Change in sUA by Visit

As shown in Figures 6, 7, and 8 below, lesinurad treatment was associated with a dose-dependent decrease in sUA, with a decrease of ~1.2 to 1.3 mg/dL for the 200 mg dose, and ~1.6 to 1.8 mg/dL for the 400 mg dose. There was a corresponding increase in the proportion of subjects achieving sUA levels <6, <5, <4, and <3 mg/dL.

Figure 6: Study 301 sUA Level Responders and Mean sUA Level by Visit

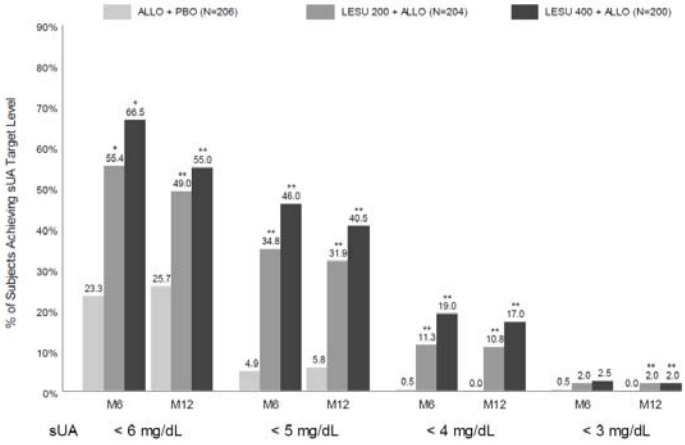


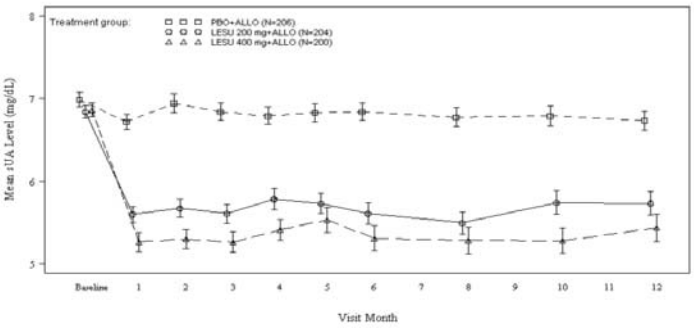
Abbreviations: ALLO, allopurinol; ITT, intent-to-treat; LESU, lesinurad; M, month; PBO, placebo; sUA, serum urate.
* $p < 0.025$ for LESU + ALLO versus PBO + ALLO.
** $p < 0.05$ for LESU + ALLO versus PBO + ALLO.
Note: Subjects missing an sUA result were treated as nonresponders. All comparisons used a 2-sided Cochran-Mantel Haenszel test stratified by Day-7 renal function and Day-7 sUA status (randomized stratification factor values), with nonresponder imputation and no adjustment for multiple comparisons.
Source: Tables 14.2.1.7, 14.2.1.8, 14.2.1.9, 14.2.1.10.



Source: Fig 6, Study 301 CSR

Figure 7: Study 302 sUA Level Responders and Mean sUA Level by Visit

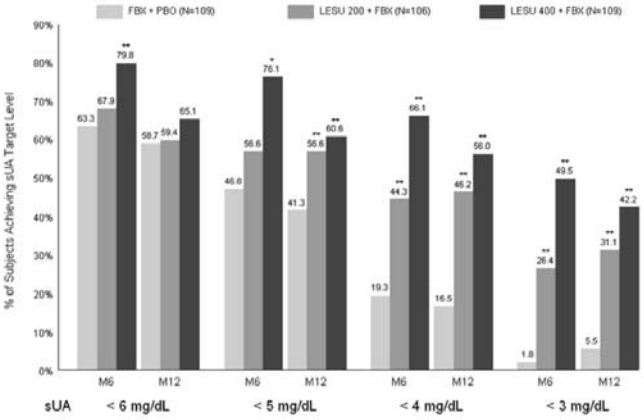


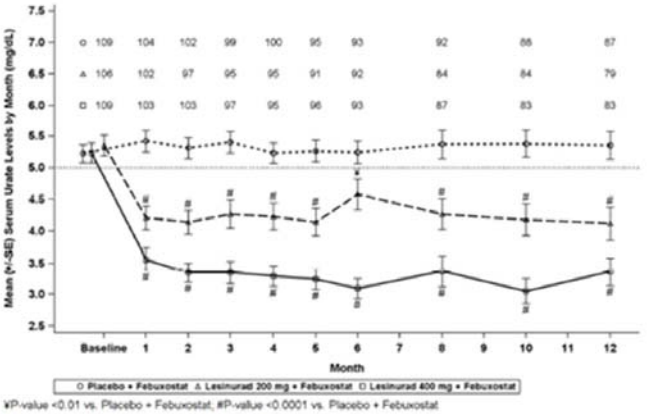


Abbreviations: ALLO, allopurinol; ITT, Intent-to-treat; LESU, lesinurad; M, month; PBO, placebo; sUA, serum urate.
* $p < 0.025$ for LESU + ALLO versus PBO + ALLO.
** $p < 0.05$ for LESU + ALLO versus PBO + ALLO.
Note: Subjects missing sUA result were treated as nonresponders. All comparisons used a 2-sided Cochran-Mantel Haenszel test stratified by Day-7 renal function and Day-7 sUA status (randomized stratification factor values), with nonresponder imputation and no adjustment for multiple comparisons.
Source: Table 14.2.1.7, Table 14.2.1.8, Table 14.2.1.9, Table 14.2.1.10.

Source: Fig 6, Study 302 CSR

Figure 8: Study 304 sUA Level Responders and Mean Change in sUA by Visit





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

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.

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.

5.1.6.2 Mean Rate of Gout Flares Requiring Treatment in Study 304

As was shown in **Table 21** above, there was no significant difference between treatment groups in Study 301 and 302 for the endpoint of mean rate of gout flares requiring treatment. Although this outcome was not a key secondary endpoint in Study 304, it was assessed, and results are summarized in **Table 26** below. 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.

As shown in **Table 26** below, there was no significant difference between lesinurad 200 mg and placebo. Although there was a statistically significant decrease in the mean rate of gout flare in the lesinurad 400 mg group of this study, results in Study 301 and 302 were not consistent with this result.

Table 26: Mean Rate of Gout Flares Requiring Treatment per Subject from Month 6 to Month 12 (ITT Population)

	PBO + FBX 80mg (N=109)	LESU200 mg + FBX 80mg (N=106)	LESU400 mg + FBX 80mg (N=109)
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

5.1.6.3 Proportion of Subjects Achieving a HAQ-DI Improvement of at least 0.25 Units at Month 12 in Studies 301 and 302

As shown in **Table 25** above, lesinurad treatment was associated with a lower proportion of patients experiencing a HAQ-DI improvement of at least 0.25 units, in a dose-dependent manner. As shown in **Table 27** below, results for this endpoint in

Studies 301 and 302 were consistent, with a lower proportion of patients in the lesinurad treatment groups achieving this level of improvement. However, the differences between the lesinurad groups and the placebo group are not statistically significant.

Table 27: Proportion of Subjects with HAQ-DI Improvement of at least 0.25 Units at Month 12

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

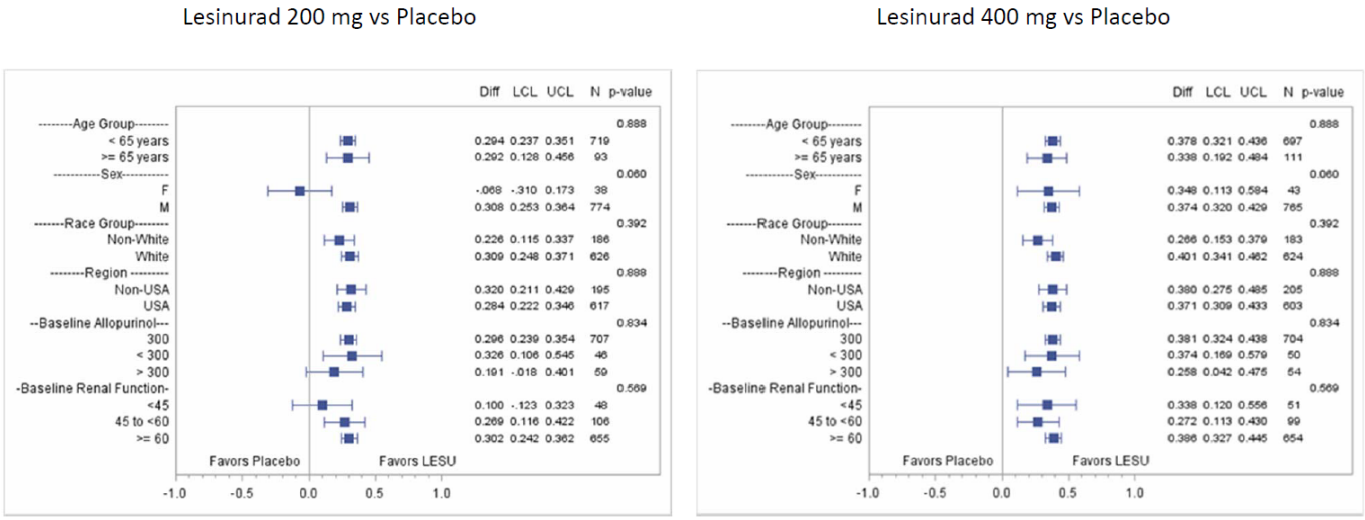
5.1.6.4 Other Patient Reported Outcomes

Other patient reported outcomes such as the HAQ Visual Analogue Scale (VAS) Pain score, Short Form-36 (SF-36), patient global assessment (PGA), total treatment satisfaction question for medication (TSQM) score, and the Sheehan Disability Scale (SDS) were also evaluated as ancillary endpoints in Studies 301, 302, and 304. No consistent improvement over placebo was observed for these endpoints with lesinurad treatment.

5.1.7 Subpopulations

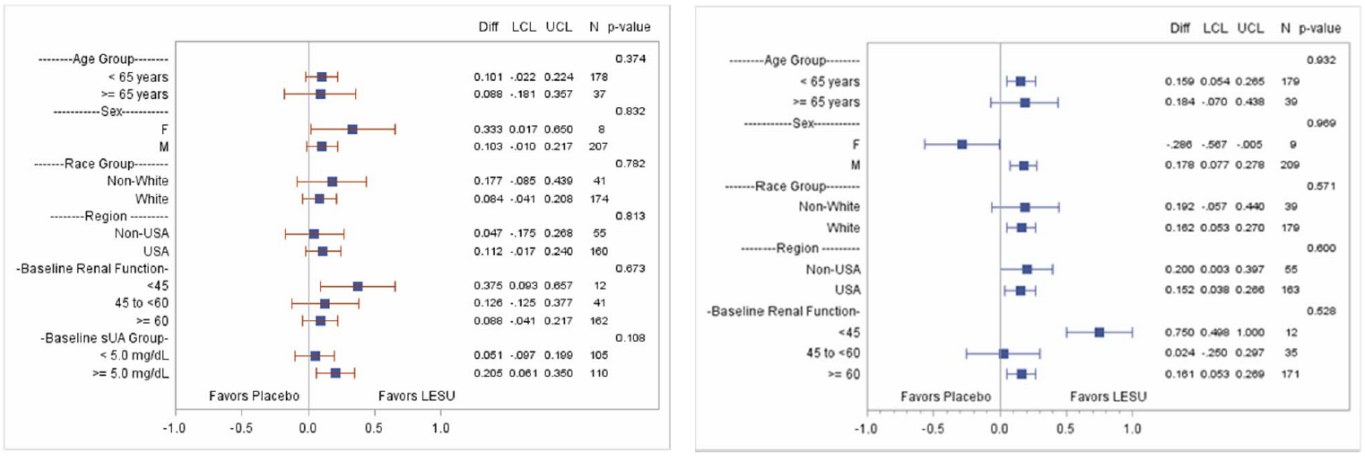
As shown in Figures 9 and 10 below, results for the subgroups in the studies were generally consistent with the overall results supporting the efficacy of lesinurad. The female subgroup in these analyses was small and no consistent trend was observed between doses and studies.

Figure 9: Pooled Studies 301 and 302, Differences in Proportion of Subjects with Month 6 sUA Levels <6.0 mg/dL, Lesinurad vs Placebo, by Selected Subgroups (ITT Population, Non-responder Imputation)



Source: FDA statistical review by Dr. Yu (Jade) Wang

Figure 10: Study 304, Differences in Proportion of Subjects with Month 6 sUA Levels <5.0 mg/dL, LESU200 mg + FBX vs. PBO + FBX, by Selected Subgroups (ITT Population, Non-responder Imputation)



Source: FDA statistical review by Dr. Yu (Jade) Wang

6 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.

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 the clinic, and was also not a requirement in the lesinurad clinical development program. While this is not unreasonable, this may have had an impact on the risk-benefit profile of lesinurad, with some patients experiencing less efficacy or more toxicity because urinary under-excretion was not the cause of their hyperuricemia. This Advisory Committee panel will be asked to discuss the available efficacy and safety data, and whether the risk/benefit profile for the use of lesinurad in a more general gout population, such as the one studied, is adequately favorable.

6.1 Methods

6.1.1 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). 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.

6.1.2 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.

6.1.3 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.

6.2 Adequacy of Safety Assessments

6.2.1 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 28** 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 28: 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)

6.2.2 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.

6.2.3 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.

6.2.4 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).

6.2.5 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).

6.3 Major Safety Results

All safety analyses were performed on the population who received at least 1 dose of study medication. **Table 29** below 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 29: Safety Overview: Phase 3 Studies

	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

6.3.1 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 30** below 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 30: Narratives of Deaths Occurring During the 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 30: Narratives of Deaths Occurring in the Phase 3 Studies (continued)

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 30: Narratives of Deaths Occurring in the Phase 3 Studies (continued)

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 30: Narratives of Deaths Occurring in the Phase 3 Studies (continued)

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 30: Narratives of Deaths Occurring in the Phase 3 Studies (continued)

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 30: Narratives of Deaths Occurring in the Phase 3 Studies (continued)

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 29**, 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 31** below, 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 31: Exposure-Adjusted Incidence of Death in Controlled Phase 3 Studies

	Combined 12-M, Studies 301, 302 and 304				6-M, Monotherapy Study 303	
	PBO+ XOI	LESU200 mg + XOI	LESU400 mg + XOI	Total LESU + 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.

6.3.2 Nonfatal Serious Adverse Events

Table 32 below 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.

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.

Table 32: Serious Adverse Events (SAE) in the Controlled Phase 3 Studies

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%)	0	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 32: SAEs in the Controlled Phase 3 Studies (continued)

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 Mediastinal 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

6.3.3 Dropouts and/or Discontinuations

Table 33 below 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 33: Treatment Emergent Adverse Events (TEAE) Leading to Discontinuation of Randomized Study Medication in the Controlled Phase 3 Studies

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 33: TEAE Leading to Discontinuation of Randomized Study Medication in the Controlled Phase 3 Studies (continued)

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 33: TEAE Leading to Discontinuation of Randomized Study Medication in the Controlled Phase 3 Studies (continued)

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 CK 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

6.3.4 Significant Adverse Events

Table 34 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[7]. A higher 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

7 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.

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 34**, 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 34: Severe Adverse Events in the Controlled Phase 3 Studies

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 SOC and PT, Subjects are included only once even if they experience multiple events in that SOC 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.

6.3.5 Submission Specific Primary Safety Concerns

6.3.5.1 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 35 below 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.

Table 35: Adjudicated Cardiovascular Treatment-Emergent Adverse Events in the Controlled Phase 3 Studies

	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

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 35**, above). 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 35** above, 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.

The exposure-adjusted incidence rates of MACE events for the pooled, 12-month, controlled lesinurad + XOI studies are presented in **Table 36** below. 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.

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[8]. In this study, 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-

[8] 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.

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 36**.

Table 36: Exposure-Adjusted Incidence Rate of MACE in Studies 301, 302, & 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	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	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

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 36** 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[9]). 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 37**, below). The exposure adjusted incidence rates for

[9] 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.

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 36** 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.

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.

Table 37: Exposure-Adjusted Incidence of MACE, by Xanthine Oxidase Inhibitor, Studies 301, 302, & 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

6.3.5.2 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 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 38** below, 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 38** 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 38: Renal-Related TEAE in the Controlled Phase 3 Studies

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 39** below). 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 39: Renal-Related TEAEs by XOI, Studies 301, 301 & 304

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 40** below, 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 40: Serious Renal-Related AE in the Controlled Phase 3 Studies

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 41** below.

Table 41: Narratives of Serious Renal-Related AEs in the Phase 3 Studies

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 41: Narratives of Serious Renal-Related AEs (continued)

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 lisinopril. 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 41: Narratives of Serious Renal-Related AEs (continued)

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 41: Narratives of Serious Renal-Related AEs (continued)

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 41: Narratives of Serious Renal-Related AEs (continued)

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 41: Narratives of Serious Renal-Related AEs (continued)

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 41: Narratives of Serious Renal-Related AEs (continued)

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. All five cases 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 42** below). 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[10]. However, the renal histopathology results from these cases did not clarify the etiology of their acute renal failure.

Table 42: Narratives of Serious Renal AEs Resulting in Dialysis 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. Con.Meds: colchicine, naproxen, valsartan, metoprolol, co-diovan, amlodipine, ASA, torasemide, spironolactone, amiodarone, quinine sulfate. Hospitalized for CXP with angina due to CHF and myocarditis. Dev. pneumonia, Vfib and was resuscitated S/P cardiopulmonary arrest. Had ICD implanted. **Dev. 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.

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

Table 42: Narratives of Serious Renal-Related AEs Resulting in Dialysis or Biopsy

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 43 below 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 43: Renal-Related AEs Leading to Discontinuation of Randomized Study Medication in the Controlled Phase 3 Studies

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

As shown in **Table 44** below, 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 ≥ 1.5, ≥ 2.0, ≥ 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 44: SCr by Elevation Category in the Controlled Phase 3 Studies

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 45 below 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 45: SCr Elevation ≥1.5 x Baseline, Number and Reversibility of Changes

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 46: SCr Elevation ≥2 x Baseline, Number and Reversibility of Changes

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 45** and **46**). 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 **Tables 45** and **46** 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 47 below 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 ≥ 1.5, ≥ 2.0, and ≥ 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.

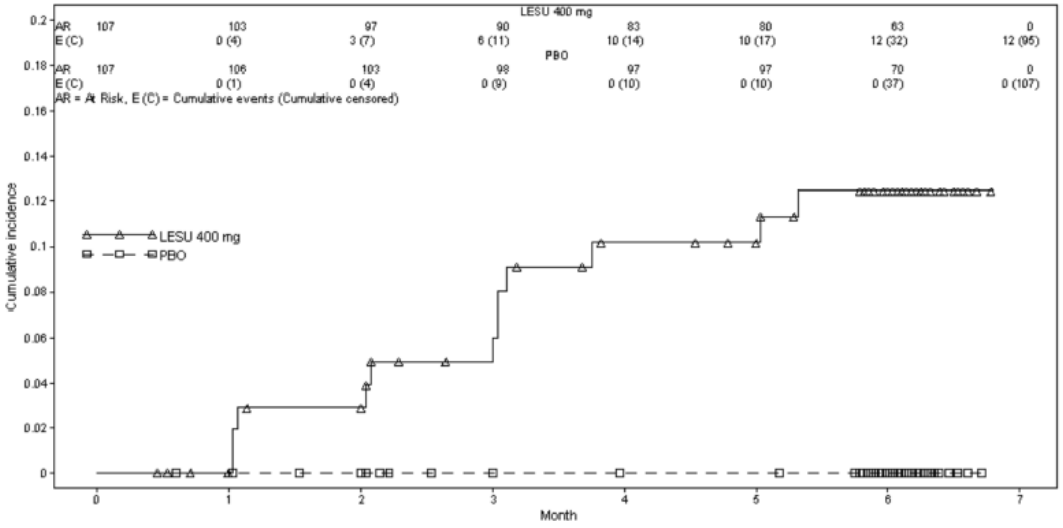
Table 47: SCr Elevations by Category, with 95% Confidence Intervals

	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.

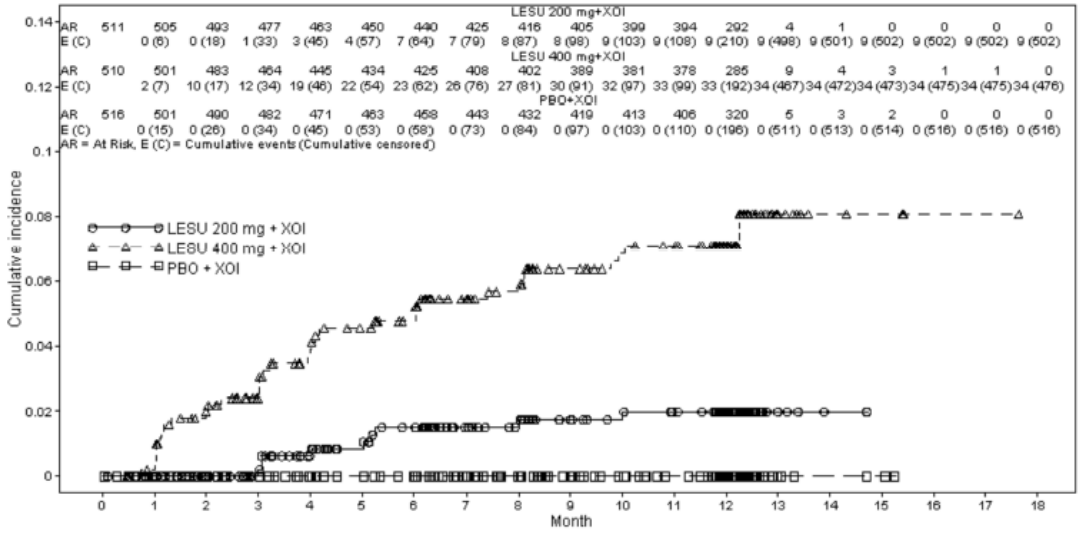
Figure 11 – Cumulative Incidence of SCr Elevations ≥2.0 x Baseline in Study 303



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 12 – Cumulative Incidence of SCr Elevations ≥2.0 x Baseline in Studies 301, 302, 304



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

To evaluate the impact of duration of lesinurad exposure to the incidence of renal toxicity, the Applicant included Kaplan-Meier plots of cumulative incidence of sCr

elevations ≥2.0 x baseline for subjects in monotherapy Study 303 and Studies 301, 302, and 304, which included concomitant xanthine oxidase inhibitors (Figures 11 and 12 above). 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 the 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 12 above.

Table 48 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 48 – Shift From Baseline in Renal Function Category for Subjects by Treatment Group in 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 ≤ 45-60 mL/min; Moderate impairment: eCrCL ≤ 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 49**). No obvious safety signal is identified on

review of the data presented in **Table 49**, however, the small number of subjects taking >300 mg qd of allopurinol in these studies precludes definitive conclusions.

Table 49 – Incidence of Selected Renal AEs by Allopurinol Dose Subgroups in 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 LESU200mg + 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.

6.3.5.3 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 50 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 50**) 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 50 – Incidence of Kidney Stone AEs in the Controlled Phase 3 Studies

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 51**). 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 51 – Incidence of Urogenital Tract Related Terms for Kidney Stones in the Controlled Phase 3 Studies

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 52 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 52 – Serious Kidney Stone AEs in the Controlled Phase 3 Studies

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 53 shows that the numbers of patients who discontinued randomized study medications due to kidney stone adverse events 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 53- Incidence of Serious Kidney Stone AEs Leading to Discontinuation of Randomized Study Medication in the Phase 3, Controlled Studies

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.

6.3.5.4 Hepatotoxicity

Due to safety concerns regarding the potential for additive risk of hepatotoxicity with xanthine oxidase inhibitors, the safety database for lesinurad was also reviewed for

cases of elevated liver enzyme abnormalities and hepatotoxicity. 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.) The Applicant also conducted an analysis of patients with significant liver enzyme elevations (defined as > 3 x upper limit of normal [ULN]) and patients meeting Hy's law criteria. Hy's law has been utilized by FDA to identify drugs likely to be capable of causing severe liver injury. Hy's law is based on the observation by the eponymous Dr. Hy Zimmerman that drug-induced jaundice caused by hepatocellular injury, and without an obstructive component, has a high rate of bad outcomes; approximately 10-50% mortality, in the era before liver transplant.

The components of Hy's law are a combination of transaminases elevation to greater than 3 x ULN and total bilirubin greater than 2 x ULN, and no evidence of bilirubin obstruction, such as elevated alkaline phosphatase, or Gilbert's syndrome. Based on original estimates of mortality, severe drug-induced liver injury can be estimated to occur at a rate of at least 1/10th the rate of Hy's law cases. The Applicant used a modified version of the criteria to screen for cases (i.e. AST or ALT > 3 x ULN, total bilirubin >2 x ULN and no significant alkaline phosphatase elevation, defined as <2 x ULN). No cases meeting the modified definition were identified, as shown in **Table 54**.

Table 54 – Incidence of Significant Liver Enzyme Elevations and modified Hy's Law Criteria in Studies 301, 302 & 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 or ALT >3 x ULN, Total Bili >2 x ULN and Alkaline Phosphatase < 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 (SMQ) 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 55**). The overall incidences

are comparable across the treatment groups and no discernable patterns of liver toxicity are noted.

Table 55 – Results of Hepatic SMQ Search of the Controlled Phase 3 Studies

Standardized MedDRA Query (SMQ) SOC/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 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 ↑	10 (2%)	7 (1%)	6 (1%)	13 (1%)	1 (1%)	1 (1%)
ALT ↑	8 (2%)	7 (1%)	4 (1%)	1 (1%)	2 (2%)	0
AST ↑	8 (2%)	7 (1%)	1 (<1%)	8 (1%)	0	0
Hepatic Enzyme ↑	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 ↑	0	1 (<1%)	0	1 (<1%)	0	1 (1%)
Blood Bilirubin ↑	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 56**). 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. 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 56 – Results of Hepatic SMQ Search, by Xanthine Oxidase Inhibitor

Standardized MedDRA Query (SMQ) SOC/PT	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 ↑	4 (1%)	3 (1%)	2 (1%)	5 (1%)	4 (4%)	3 (1%)	2 (2%)	6 (3%)
AST ↑	3 (1%)	4 (1%)	3 (1%)	5 (1%)	5 (5%)	4 (1%)	0	3 (1%)
Hepatic Enzyme ↑	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 ↑	0	1 (<1%)	0	1 (<1%)	0	1 (<1%)	0	0
Blood Bilirubin ↑	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

6.3.5.5 Creatine Kinase (CK) Elevation

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 creatine kinase (CK) [also known as creatine 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 57**). The results from the outlier analyses for each separate xanthine oxidase inhibitor (allopurinol or febuxostat) were comparable to those shown in **Table 57**. 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 57 – Incidence of Markedly Elevated Creatine Kinase (CK) in 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.

6.3.5.6 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.

6.4 Supportive Safety Results

6.4.1 Common Adverse Events

Most patients (>65%) experienced an adverse event while participating in the controlled portions of the phase 3 studies for lesinurad. **Table 58** 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 58 – Common Adverse Events in the Phase 3 Studies

System Organ Class (SOC)	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 59 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 most commonly reported AE in the lesinurad groups 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.

Table 59 – Common Adverse Events by Preferred Term Occurring in ≥2% of Subjects Treated with Lesinurad During 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 Increase	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 Increase	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 Increase	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

6.4.2 Laboratory Findings

6.4.2.1 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 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 than 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.

6.4.2.2 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. Two patients were identified (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 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.

6.4.2.3 Liver Enzymes

See Hepatotoxicity section 6.3.5.4 above.

6.4.2.4 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.

6.4.3 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 did not identify any safety issues.

6.4.4 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 FDA's interdisciplinary review team for QT studies, who examined the data from this trial.

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.

6.4.5 Special Safety Studies/Clinical Trials

Not applicable.

6.4.6 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.

6.5 Other Safety Explorations

6.5.1 Dose Dependency for Adverse Events

As discussed in the preceding safety sections, 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.)

6.5.2 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$\geq$ 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).

6.5.3 Drug-Demographic Interactions

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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$\geq$ 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).

6.5.4 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.

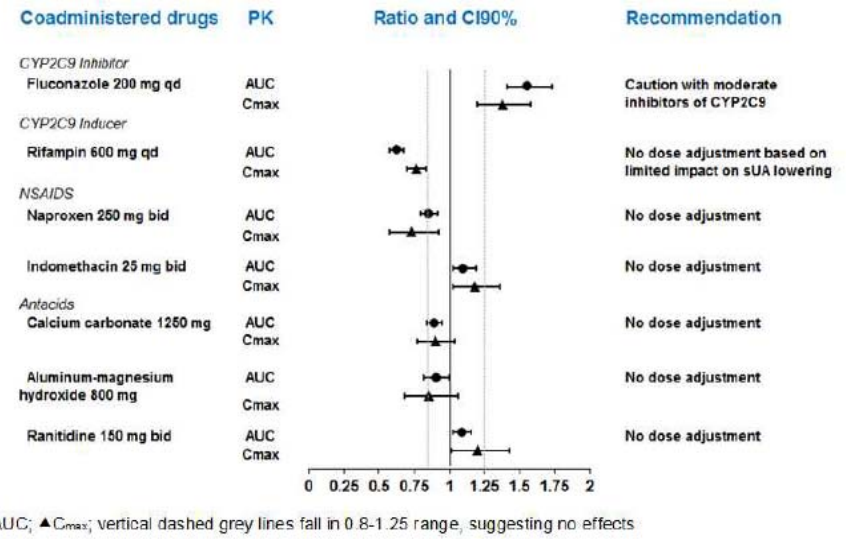
The effect of renal impairment on the PK profile of lesinurad was evaluated in the two phase 1 studies (104 and 120). Studies 104 and 120 assessed single doses of 200 mg and 400 mg of lesinurad in adult volunteers with mild-to-moderate or moderate-to-severe renal impairment, respectively. Lesinurad exposure (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.

6.5.5 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. The findings from these studies are summarized in **Figure 13** and **Figure 14** below.

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 13** and **Figure 14**. Subgroup analyses of subjects in Studies 301 and 302 taking concomitant low dose aspirin ($\leq$325 mg/day) or thiazide diuretics showed that these drugs did not impact on the efficacy of lesinurad.

Figure 13 – Effect of Co-Administered Drugs on Pharmacokinetics of Lesinurad

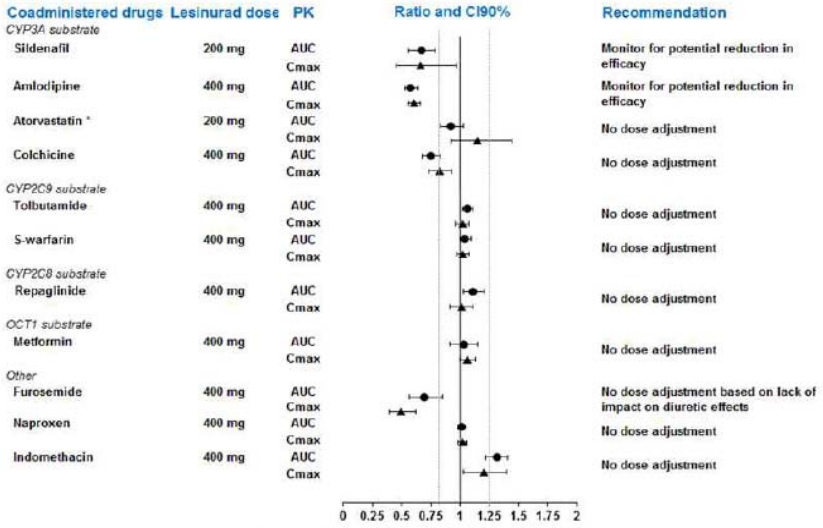


● AUC; ▲C_{max}; vertical dashed grey lines fall in 0.8-1.25 range, suggesting no effects

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 14 – 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

6.6 Additional Safety Evaluations

6.6.1 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.

6.6.2 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.

6.6.3 Pediatrics and Assessment of Effects on Growth

Lesinurad has not been studied in pediatric patients.

6.6.4 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.