CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207988Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	(electronic stamp)
From	Sarah Yim, M.D. Supervisory Associate Director Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Subject	Cross-Discipline Team Leader Review
NDA/BLA # **Supplement#**	NDA 207988 Original
Applicant	Ardea Biosciences, Inc.
Date of Submission	December 29, 2014
PDUFA Goal Date	December 29, 2015
Proprietary Name / Established (USAN) names	Zurampic® / Lesinurad
Dosage forms / Strength	Oral Tablets / 200 mg
Proposed Indication(s)	1. Treatment of hyperuricemia associated with gout in combination with a xanthine oxidase inhibitor
Recommended:	*Approval*

1. Introduction

This new drug application (NDA), submitted by Ardea Biosciences, is for lesinurad, a new molecular entity proposed as a 200 mg tablet taken orally once daily for the treatment of hyperuricemia associated with gout, in combination with a xanthine oxidase inhibitor. Lesinurad is a uricosuric, and like the approved uricosuric probenecid, works by inhibiting the main urate transporter, URAT1. Like probenecid, lesinurad also has a short half-life (approximately 5 hours). However, only once daily dosing was studied in the entire clinical development program. Doses below 200 mg were not evaluated in phase 2 or phase 3 studies because they did not result in sustained serum uric acid (sUA) reduction over 24 hours. The phase 3 clinical development program for lesinurad consisted of four studies: Study 301 and Study 302, which were replicate 12-month studies of lesinurad 200 mg or lesinurad 400 mg vs. placebo on background allopurinol; Study 304, a 12-month study of lesinurad 200 mg or lesinurad 400 mg vs. placebo on background febuxostat 80 mg; and Study 303, a 6-month study of lesinurad 400 mg monotherapy compared to placebo in patients with gout who had intolerance or contraindication to treatment with a xanthine oxidase inhibitor.

As will be discussed later in this review, the monotherapy study demonstrated a marked imbalance in renal adverse events with lesinurad 400 mg compared to placebo, and this renal safety signal was also observed with lesinurad 400 mg in the background xanthine oxidase inhibitor studies, albeit to a lesser degree. For this reason, the applicant is only seeking approval for the 200 mg dose of lesinurad. However, the renal safety signal is

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not entirely absent with the 200 mg dose, and the urate-lowering effect is also smaller. Therefore the benefit-risk profile of the 200 mg dose may also be questioned, although I believe it is sufficiently favorable to support approval, as will be discussed further below.

2. 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 for the average patient is characterized by acute attacks of gouty arthritis alternating with attack-free periods of intercritical gout, during which time the patient is asymptomatic. 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. A subset of patients has chronic tophaceous gouty arthropathy, which is a chronically active form, although the extent and severity of inflammatory and deforming features may be variable.

The chronic management of gout is founded upon control of hyperuricemia, as only this approach treats the underlying pathology of the disorder. The therapeutic goal of urate-lowering therapy is to promote crystal dissolution and prevent crystal formation by maintaining serum uric acid levels below the saturation point for monosodium urate, which is approximately 6.8 mg/dL[2]. In addition to the physiological basis for this target, cohort studies have shown that maintaining uric acid levels below this target is associated

[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.
[2] Perez-Ruiz F and F Liote, "Lowering Serum Uric Acid Levels: What is the Optimal Target for Improving Clinical Outcomes in Gout?" Arthritis Rheum (Arthritis Care & Research) October 2007; 57(7):1324-1328

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with a reduction in tophi[3], depletion of knee synovial fluid urate crystals[2], and a reduced frequency of gout attacks[4]. However, a lower sUA target (e.g., ≤5 mg/dL) may be needed to achieve improvement in gout signs and symptoms in some patients, such as patients with a higher disease burden (e.g., palpable tophi, more frequent or severe attacks, or chronic active gout).[5]

The mechanistic approaches to lowering 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.

Table 1: Currently Available FDA-Approved Urate-Lowering Therapies

Product	Approved Dosing	Efficacy and Safety
Xanthine Oxidase Inhibitors (XOI)		
Allopurinol	100-800 mg/d; Doses >300 mg/d divide into BID administration	300 mg dose, ~2 to 3.5 mg/dL mean ↓ in serum uric acid (sUA); Hypersensitivity reactions, cutaneous reactions, GI intol.
Febuxostat	40-80 mg QD	80 mg dose, ~4.5 mg/dL mean ↓ sUA; LFT ↑, rash, possible CV risk
Uricosurics		
Probenecid	500-1000 mg BID ($T_{1/2}$ 3-8 hours)	Mean 1.3 g/d dose, ~2.9 mg/dL mean ↓ sUA; Nephrolithiasis, Drug-Drug interact.
Uricase Enzymes		
Pegloticase	8 mg IV q2wks	Mean ↓sUA ~6.6 to 6.8 mg/dL; Immunogenicity with anaphylaxis/infusion reactions/loss of efficacy; CHF

Sources: Febuxostat (includes allopurinol data) and pegloticase reviews at Drugs@FDA. For probenecid: Pui K et al., J Rheumatol 2013; 40:872-876

[3] Zhang W et al., "EULAR evidence-based recommendations for gout. Part II: Management. Report of a task force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT)." Ann Rheum Dis. 2006; 65:1312-1324.
[4] Jordan KM et al., "British Society for Rheumatology and British Health Professionals in Rheumatology Guideline for the Management of Gout." Rheumatology (Oxford) 2007
[5] Khanna D et al., "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.

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Relevant Regulatory History

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.

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3. CMC/Device

Drug Substance: Joseph Leginus, Ph.D./Donna Christner, Ph.D.; Drug Product: Arthur B. Shaw, Ph.D.; Process and Microbiology: Huai Ted Chang/Zhigang Sun; Facility: Robert Wittorf, PharmD/Mahesh Ramanadham; Biopharmaceutics: Kimberly Raines, Ph.D./Sandra Suarez, Ph.D.; Application Technical Lead: Craig Bertha; Project Manager: Steven Kinsley

- **General product quality considerations**

Lesinurad is a new molecular entity with a chemical name of 2((5-bromo-4-(4-cyclopropylnaphthalen-1-yl)-4*H*-1,2,4-triazol-3-yl)thio)acetic acid, a molecular formula of $C_{17}H_{14}BrN_3O_2S$, and molecular weight of 404.28 g/mol. The drug substance (DS) is a white to off-white crystalline powder that is non-hygroscopic and has a melting point of 169-171ºC. Manufacturing process controls were considered adequate. Impurity and degradant specifications have been adequately supported and qualified from a nonclinical perspective. The applicant provided sufficient stability data to support a proposed retest period of (b) (4) months for the drug substance (b) (4) .

The drug product (DP) is a 200 mg blue film-coated immediate release tablet with excipients including hypromellose 2910, microcrystalline cellulose, lactose monohydrate, crospovidone, magnesium stearate, and Opadry Blue (b) (4). The DP manufacturing process is a (b) (4). The product is then bottled in high density polyethylene (HDPE) with a desiccant. The applicant provided sufficient data to support a 36 month expiry at controlled room temperature.

- **Facilities review/inspection**

All DS manufacturers were recently inspected (earliest (b) (4)) and were classified "no action indicated (NAI)". (b) (4) is responsible for the quality control testing of the lesinurad drug substance, which does not require any unique testing. The firm was last inspected in (b) (4) and was classified "voluntary action indicated (VAI)". The firm's responses to the inspectional findings were reviewed and found to be adequate. Based on these previous inspections and pre-inspection risk analysis, Office of Pharmaceutical Quality (OPQ) agreed to waive inspections for all facilities pertaining to the DS and concluded that the DS facilities are acceptable with respect to NDA 207988.

A pre-inspection risk analysis was also performed for the DP manufacturer, tester, and packaging. AstraZeneca Sterile Operations (FEI# 3003342394) manufactures lesinurad tablets (immediate release) using (b) (4) . A review of AstraZeneca's manufacturing capabilities has been conducted and the firm manufactures a variety of dosage forms, including immediate and extended release tablets. The firm's most recent inspection was in (b) (4). The inspection was classified VAI with concerns

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around maintenance of HVAC, CIP and equipment qualifications. The firm's corrective actions and responses were reviewed and considered adequate. The other two sites, AstraZeneca Pharmaceuticals LP (FEI# 2517100), and AstraZeneca (FEI# 3002806411) were reviewed for tablet packaging and testing operations, respectively. AstraZeneca Pharmaceuticals, LP was most recently inspected in (b) (4) and classified VAI. The firm is acceptable for packaging operations. AstraZeneca was inspected in (b) (4) and was classified NAI. AstraZeneca is acceptable for laboratory operations. Based on the previous inspections and risk analysis, OPQ agreed with the proposal to waive inspections based on the risk analysis review and consider all drug product manufacturing firms acceptable with respect to NDA 207988.

- **Other notable issues**

There were no outstanding issues. Office of Pharmaceutical Quality reviewers recommended approval without any phase 4 requirements, commitments, or agreements.

4. Nonclinical Pharmacology/Toxicology

Primary reviewer: Matthew Whittaker, Ph.D.; Secondary Reviewer: Timothy Robison, Ph.D.

- **General nonclinical pharmacology/toxicology considerations**

Lesinurad (also known as RDEA594) decreases the reabsorption of uric acid from the renal proximal tubule by inhibiting the function of carrier proteins that transport uric acid. Inhibition of URAT1 and OAT4, located on the apical surface of renal tubular epithelial cells, is likely to be principal mechanism of action. Inhibition of the function of OAT1 and OAT3, located on the basolateral membrane of tubular epithelial cells, is not expected to play a major role in the pharmacodynamic effect of lesinurad. Lesinurad inhibits transporter function with potency in the 3 – 7 μM range. The pharmacological actions and binding affinities of lesinurad are relatively similar to probenecid.

Rats and monkeys were used in the in vivo nonclinical development program. Lesinurad is absorbed rapidly after oral administration in rats and monkeys. Oral bioavailability is greater in rats (73%) than in monkeys (41%). Lesinurad is primarily eliminated via feces in nonclinical species while humans eliminate lesinurad primarily in urine. All metabolites observed in humans are also synthesized in at least one nonclinical species.

Chronic toxicology studies with RDEA594 were conducted in rats (26 weeks) and monkeys (12 months). In both studies, animals were dosed by oral gavage at up to 600 mg/kg/day. Common target organs of toxicity in the rat and monkey include the kidney and GI tract. Premature deaths related to toxicities in these organs were observed in HD animals (600 mg/kg/d) 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

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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. The monkey is the more sensitive species, with an $AUC_{0\text{-}24h}$ of 82.6 μg*hr/ml. This NOAEL supports the maximum clinical RDEA594 exposure at the proposed dose of 200 mg/day.

- **Carcinogenicity**

Lesinurad was negative in a standard battery of genotoxicity assays. There was no evidence of tumorigenic potential in a 2 year carcinogenicity study conducted in rats or in a 26 week carcinogenicity study in TgRasH2 mice.

- **Reproductive toxicology**

Female rats that were treated with lesinurad (oral) at 300 mg/kg/day exhibited prolonged estrous cycles and a slight increase in mean number of days to mate compared to controls. In addition, slightly decreased mean numbers of corpora lutea and implantation sites were observed in this dose group. All of these findings were observed in the presence of overt toxicity. There was no evidence of teratogenicity or any other embryo-fetal developmental toxicity in rats and rabbits that received oral lesinurad doses up to 300 and 75 mg/kg/day, respectively, during the period of organogenesis. Lesinurad was found to distribute to the milk of lactating rats at exposure levels comparable to plasma. Mean time to vaginal patency was significantly delayed in F1 females offspring of rats treated with ≥ 200 mg/kg/day in a pre- and postnatal development study.

- **Other notable issues**

Ardea has submitted a complete nonclinical pharmacology and toxicology program for lesinurad. From the nonclinical perspective, the application is recommended for approval. There are no outstanding nonclinical issues and no additional nonclinical studies are required.

5. Clinical Pharmacology/Biopharmaceutics

Primary clinical pharmacology/pharmacometrics reviewer: Jianmeng Chen, M.D., Ph.D.; Secondary clinical pharmacology reviewer: Ping Ji, Ph.D.; Secondary pharmacometrics reviewer: Yaning Wang, Ph.D.; Primary pharmacogenomics reviewer:

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Anuradha Ramamoorthy, Ph.D.; Secondary pharmacogenomics reviewer: Christian Grimstein, Ph.D.

- **General clinical pharmacology/biopharmaceutics considerations**

Absorption: The absolute bioavailability of lesinurad under fed conditions is about 100%. Systemic exposure ($AUC_{0-\infty}$) and peak plasma concentration (C_{max}) increased in proportion to the dose in the dose range of 5 to 1200 mg. T_{max} was reached by approximately 1-4 hours following oral administration under fed conditions. Coadministration with a high-fat meal decreases C_{max} 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 Zurampic. 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.

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).

- **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 (≤325 mg) or thiazide diuretics did not affect the efficacy of lesinurad.

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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%.

- **Intrinsic factors potentially affecting elimination: age, gender, hepatic insufficiency and renal impairment**

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. The impact of renal impairment on the efficacy and safety of lesinurad is discussed later in this section.

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 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.

- **Thorough QT study or other QT assessment**

A thorough QT study (Study 117) was conducted in healthy subjects given 400 and 1600 mg of lesinurad. Lesinurad did not impact the QT/QTc interval.

- **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.

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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.

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).

Response (mean sUA) by dose in each of the phase 3 studies and response (proportion achieving sUA $\leq$6 mg/dL) by exposure in Studies 301 and 302 are shown in Figure 1 and Figure 2 below. Figure 1 shows a separation between the 200 and 400 mg dose of lesinurad, although the magnitude of the difference appears to be similar to the difference observed in phase 2 dose-ranging studies. For the proposed dose of 200 mg, the mean sUA lowering is approximately 1 mg/dL. With respect to the proportion of patients achieving an sUA $\leq$6 mg/dL (Figure 2), there is only a small difference in the proportion of responders between the lowest and highest exposure quartiles, but this may be related to the binary nature of the endpoint.

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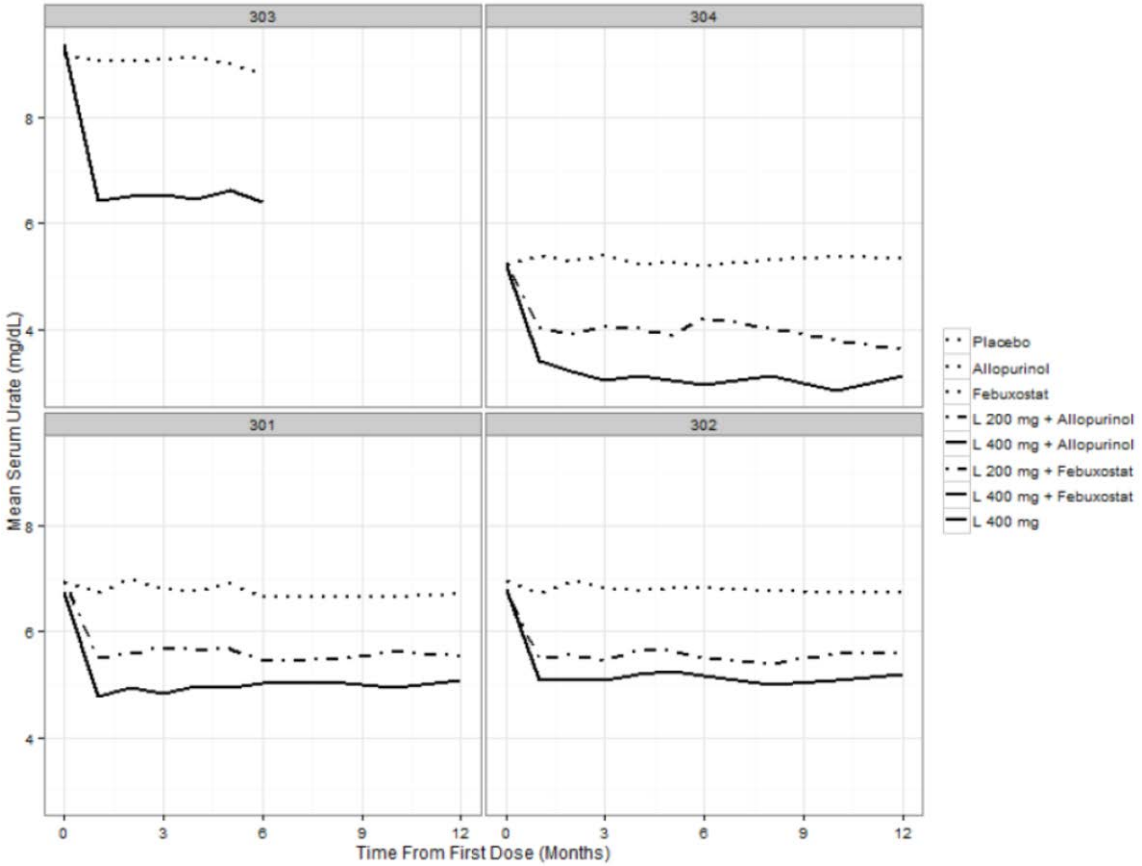
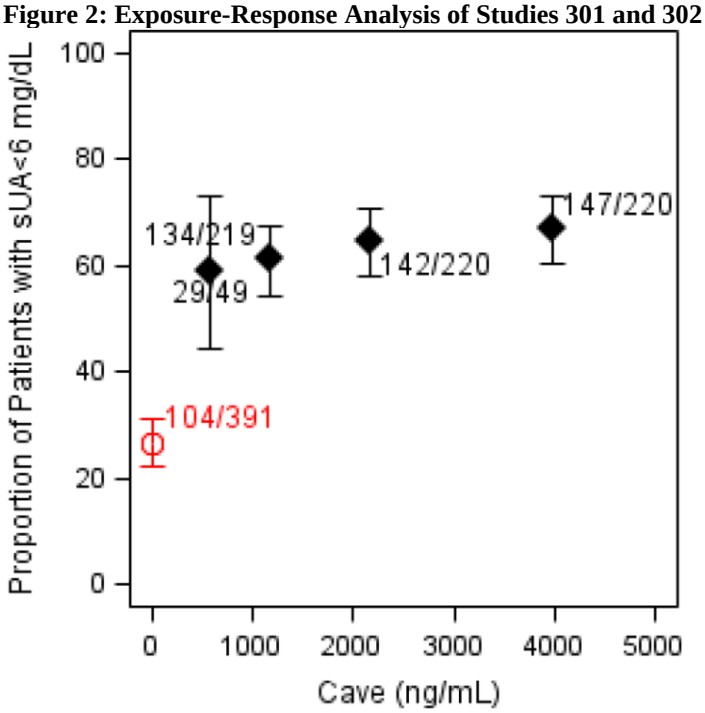
Figure 1: Dose-Response Relationship in Each of the Phase 3 Studies



Source: Figure 4, Clinical pharmacology review by Dr. Jianmeng Chen

Figure 2: Exposure-Response Analysis of Studies 301 and 302



Source: Figure 4, Clin Pharm Review. Symbol=mean, Bars=95% Confidence Interval

Exposure-Response for Safety

As will be discussed in more detail in the safety section (Section 8) below, there also appears to be a dose-response relationship for safety. This includes dose-dependent increases in renal adverse events and serum creatinine elevations, serious adverse events/serious renal adverse events (with the 400 mg dose) and major adverse cardiovascular events (with the 400 mg dose), and deaths.

Impact of Renal Impairment on Efficacy and Safety

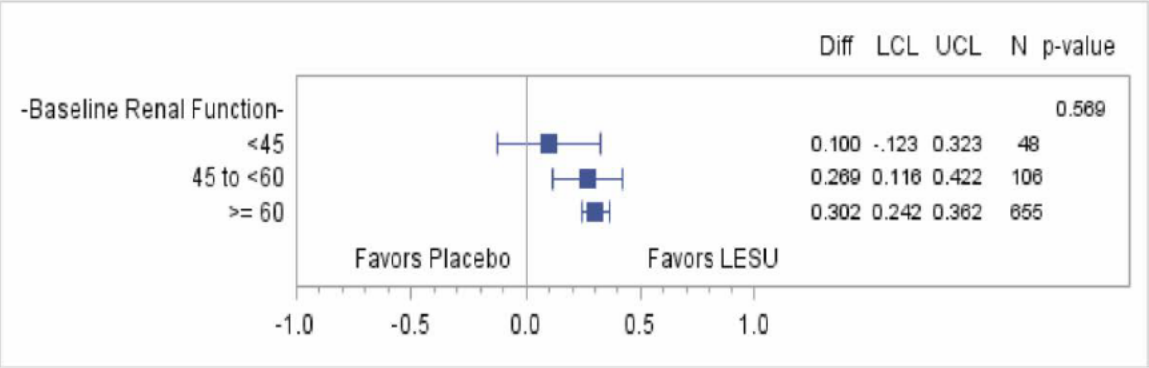
Urinary uric acid excretion would be expected to decrease with decreasing glomerular filtration and cause decreased efficacy, which is the case with the currently approved URAT1 inhibitor, probenecid. This also appears to be the case with lesinurad. FDA clinical pharmacology and statistical reviewers evaluated the data from Studies 301 and 302. Despite higher exposures in patients with the greatest renal impairment (estimated glomerular filtration rate [eGFR] <45 ml/min), the reduction in sUA compared to placebo appears to be much smaller in this group, as shown in Table 2 and Figure 3, below.

Table 2: Effect of Baseline Renal Function on Treatment-Related Decline in sUA

	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

Figure 3: Efficacy Subgroup Analysis of Lesinurad 200 mg Over Placebo in the Proportion of Responders (Meeting Target sUA) in Pooled Studies 301 and 302, by Renal Function Category



Source: FDA statistical reviewer analysis by Dr. Yu Wang

The number of patients with moderate or severe renal impairment in these studies was small, so definitive conclusions cannot be drawn; however Emax modeling generated by FDA pharmacometrics reviewers also identified renal function as the only covariate that impacts the efficacy of lesinurad. The Emax model predicted that for a patient with an

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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.

With respect to safety, there did not appear to be an obvious difference in risks between renal function subgroup categories. However, given the higher exposure in patients with eCrCl (or eGFR)[6] <60 ml/min and the dose-dependent safety concerns, there remains uncertainty regarding the conclusion that there is not a difference in the safety profile of lesinurad in this subgroup. Additionally, there appears to be decreased efficacy in this subgroup, worse with worsening levels of renal dysfunction. Because of the small numbers and small amount of urate-lowering in the <45 ml/min subgroup, the favorability of the benefit-risk of lesinurad is most uncertain in this population.

- **Other notable issues**

From a clinical pharmacology perspective, there are no issues precluding approval. The clinical pharmacology team recommends that labeling include a precaution against use of lesinurad in patients with eCrCl or eGFR <45 ml/min.

6. Clinical Microbiology

The drug product is not a sterile product and the drug substance is non hygroscopic. Materials (excipients and (b) (4)), manufacturing, and packaging controls are in place to ensure microbiological control during the manufacture of lesinurad tablets. As per the CMC microbiology review team, this is acceptable.

7. Clinical/Statistical- Efficacy

Primary clinical reviewer: Rosemarie Neuner, MD MPH; Primary statistical reviewer: Yu (Jade) Wang, Ph.D.; Secondary reviewers: Ruthanna Davi, Ph.D., Gregory Levin, Ph.D.

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 eCrCl <60 ml/min at baseline) for at least 8 weeks and still had a serum uric acid

[6] Both estimated creatinine clearance (eCrCl) and estimated glomerular filtration rate (eGFR) are calculated using serum creatinine level, using various estimating equations. Refer to the National Kidney Foundation's FAQ on GFR estimates at: https://www kidney.org/sites/default/files/docs/12-10-4004_abe_faqs_aboutgfrrev1b_singleb.pdf. Although there may be minor differences between these, for purposes of rough approximation for drug exposure and renal function category subgroup analyses, both terms are considered interchangeably in this review.

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level of 6.5 mg/dL or greater at the screening visit (and ≥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.

Study Population

Table 3 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.

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Table 3: 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 4 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 4 also includes change from baseline in serum urate levels. Change from baseline to Month 1 is shown in Table 4 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.

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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 (patients in all groups were on background allopurinol) 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 4: 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 EP						
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 5 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 3, 50% of

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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 5 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 5 also 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 5: 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

Study 303 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. Although this use and population is not being proposed for marketing,

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this study was useful to demonstrate the isolated effect of lesinurad alone. As shown in Table 6 below, 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. Table 6 includes the change from baseline to Month 1 in serum urate levels, which was a decrease of 2.78 mg/dL for the 400 mg dose. This is about 1 mg/dL more than the effect of 400 mg in the xanthine oxidase inhibitor studies, and may be due to the higher baseline uric acid in the population. Regarding key secondary endpoints, there was not a significant difference between treatment groups in terms of the proportion of patients requiring treatment for a gout flare during Month 6, or in the proportion of patients achieving a ≥0.25 unit improvement in the Health Assessment Questionnaire Disability Index (HAQ-DI). The selection of 0.25 units of improvement is based on the minimum clinically important difference (MCID) in Rheumatoid Arthritis patients, but is of unclear relevance to patients with gout.

Table 6: Summary Efficacy Results for Study 303 (ITT Population)

	PBO (N=107)	LESU400 (N=107)
sUA: Change from Baseline to Month 1 **Observed Cases, n** **Mean (SD)**	103 -0.10 (0.95)	96 -2.78 (1.82)
Primary Endpoint		
Proportion with sUA <6.0 mg/dL by Month 6 Nonresponder Imputation	2 (1.9%)	32 (29.9%)
Diff. in Proportions vs PBO **(95% CI)** **p-value**		0.28 (0.19, 0.37) <0.0001
Key Secondary Endpoints		
Proportion requiring treatment for a gout flare during Month 6	14/96 (14.6%)	10/85 (11.8%)
Diff. in Proportions vs PBO (95% CI) **p-value**		-0.03 (-0.13, 0.07) 0.6829
Proportion achieving HAQ-DI improvement of ≥0.25 units at Month 6	29/107 (27.1%)	26/107 (24.3%)
Diff. in Proportions vs PBO (95% CI) **p-value**		0.01 (-0.13, 0.14) 0.9738

Sources: Table 14.2.1.19, Table 16, and Table 14.2.3.1.a of the Study 303 CSR

- **Includes discussion of both the statistical reviewer review and the clinical efficacy review with explanation for CDTL's conclusions and ways that any disagreements were addressed.**

Both the primary statistical reviewer, Dr. Wang, the secondary statistical reviewer, Dr. Levin, and the clinical team agree that there is convincing statistical evidence that lesinurad lowers serum uric acid levels in patients with gout and increased the proportion of patients achieving target serum uric acid levels in the phase 3 controlled studies. However, there was no statistical evidence of benefit for secondary endpoints which would be considered direct measures of patient benefit as a result of uric acid reduction, such as rate of gout flares and tophi resolution. In addition, there were trends toward worse outcomes with lesinurad treatment for patient-reported outcomes such as HAQ-DI,

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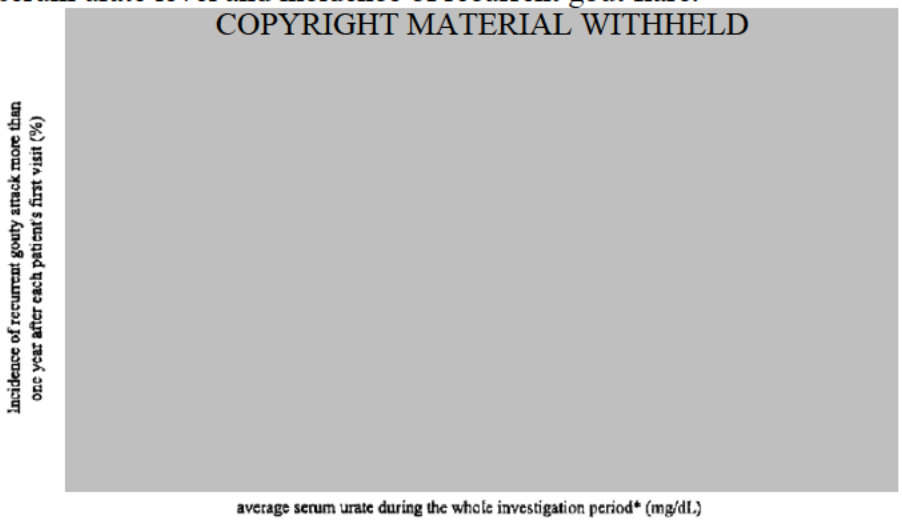
patient pain score, SF-36 PCS and patient global assessment of disease activity. The lack of support from outcomes assessing direct clinical benefit may cause uncertainty regarding the clinical relevance of the primary endpoint of target serum uric acid level ≤6 mg/dL (or ≤5 mg/dL in Study 304), and the interpretability of the treatment effect observed. Therefore, I will review the support for this endpoint in the following paragraphs.

A target serum uric acid level ≤6 mg/dL is the recommended goal of urate-lowering therapy in widely accepted gout treatment guidelines issued by the American College of Rheumatology (ACR)[7], the European League Against Rheumatism (EULAR)[8] and other professional societies. The support for this target and its relationship to clinical benefits includes the following:

- Based on in vitro studies, the physiological saturation level of monosodium urate in serum or plasma at body temperature (37ºC) is approximately 6.8 mg/dL. Above this level precipitation of crystals occurs, and below this level monosodium urate goes into solution.[9] As gout is a problem of uric acid precipitation, there is a physiological basis for the treatment goal of maintaining serum urate levels below the saturation point.
- Relationship of gout flares and sUA levels:
    1. A retrospective study that evaluated the relationship between average serum uric acid level and incidence of recurrent gout attacks in 267 patients over a 3-year period showed a direct correlation between average serum urate level and incidence of recurrent gout flare.



Source: Shoji et al. Arthritis Care & Research 2004; 51(3):321-5

[7] Khanna D et al., "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.
[8] Zhang W et al., "EULAR evidence-based recommendations for gout. Part II: Management. Report of a task force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT)." Ann Rheum Dis. 2006; 65:1312-1324.
[9] Loeb JN, "The influence of temperature on the solubility of monosodium urate." Arthritis Rheum 1972; 15:189-92.

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2. In an actively controlled trial of allopurinol or benzbromarone in 36 patients with gout and renal insufficiency, in the 28 patients who achieved sUA levels <6 mg/dL, the mean number of gout attacks fell from 3.4 in the 12 months before starting urate-lowering therapy to 0.71 in the first 6 months of treatment, 0.21 during months 6 to 12, 0.06 in months 12 to 18, and 0 during months 18 to 24.[10]
3. In a cohort study at a Veteran's Affairs (VA) medical center, 57 male patients with crystal-proven gout who were begun on allopurinol were followed at intervals for 2 to 10 years. At end of study, patients who had sUA >6 mg/dl (38/57, 67%) had a mean of 6 gout attacks in that past year. Patients who had an sUA ≤6 mg/dL (19/57, 33%) had a mean of 1 attack in the past year.[11]
4. The Febuxostat/allopurinol Comparative Extension Long-Term Study (EXCEL) evaluated the clinical course of patients achieving sUA <6 mg/dL with urate-lowering therapy for up to 40 months. In this subgroup of patients, the proportion of patients experiencing a flare requiring treatment progressively decreased over time.[12]

- Relationship of tophi reduction/resolution and sUA
  1. Sixty patients at one center were prospectively evaluated with clinical, biochemical, and radiographic assessments to explore the critical factors associated with development of tophaceous gout. Patients with tophaceous gout had a mean serum urate level of 9.2 mg/dL compared to patients without tophi (average 7.2 to 7.6 mg/dL).[13]
  2. In one observational, prospective study of 63 patients at one clinic with tophaceous gout treated with allopurinol, benzbromarone, or both, the velocity of tophi reduction was linearly related to the mean serum urate level during therapy, with lower serum urate levels being associated with a faster velocity of tophi reduction. The mean time from onset of urate-lowering therapy to disappearance of the target tophus for the entire group was approximately 21 months. When broken down by serum urate levels, average reduction was as follows:[14]
     - sUA 6.1 to 7.0 mg/dL: average reduction of 0.53 mm/month
     - sUA 5.1 to 6.0 mg/dL: average reduction of 0.77 mm/month
     - sUA 4.1 to 5.0 mg/dL: average reduction of 0.99 mm/month
     - sUA ≤4.0 mg/dL: average reduction of 1.52 mm/month

[10] Perez-Ruiz et al., "Treatment of chronic gout in patients with renal function impairment: an open, randomized, actively controlled study." J Clin Rheumatol 1999; 5:49-55
[11] Li-Yu J et al., "Treatment of chronic gout. Can we determine when urate stores are depleted enough to prevent attacks of gout? J Rheumatol 2001; 28:577-80.
[12] Becker MA et al., "Clinical efficacy and safety of successful longterm urate-lowering with febuxostat or allopurinol in subjects with gout." J Rheumatol 2009; 36:1273-82.
[13] Nakayama DA et al., "Tophaceous gout: a clinical and radiographic assessment." Arthritis Rheum 1984; 27(4):468-471.
[14] Perez-Ruiz et al., "Effect of urate-lowering therapy on the velocity of size reduction of tophi in chronic gout." Arthritis Rheum (Arthritis Care & Research), 2002; 47(4):356-360.

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3. In the EXCEL study described above, patients maintaining sUA <6 mg/dL experienced a 45 to 65% reduction in primary tophus size over the 40 month period, a 45 to 60% reduction in the mean number of tophi, and 35 to 45% had complete resolution of their primary tophi.[11]

The question of the utility of serum uric acid as a surrogate endpoint for clinical trials of urate-lowering therapies was discussed at the June 2, 2004 Arthritis Advisory Committee meeting. Panelists noted that the available clinical data were limited, but were consistent in supporting a clinical benefit in gout patients from maintaining serum uric acid below the solubility level (e.g., sUA ≤6 mg/dL). However, panelists also recommended that gout flare endpoints be included in drug development trials. There was no consensus about inclusion of tophi reduction endpoints as some panelists believed measurement to be difficult and variable. In discussion of optimal trial duration, panelists generally believed that longer durations (greater than 6 months) would be needed for flare, tophi, or health-related quality of life, but did not come to consensus on a specific duration.

FDA has precedent for accepting the proportion of patients achieving a target serum uric acid ≤6 mg/dL (or ≤5 mg/dL) as the primary endpoint to support approval of Uloric® (febuxostat), approved in February 2009. Similar to lesinurad, febuxostat also increased the proportion of patients achieving serum uric acid level ≤6 mg/dL, but did not show a difference in flares or tophi resolution during the controlled period of the phase 3 studies, which ranged from 6 to 12 months. Krystexxa® (pegloticase), approved in September 2010 for the subpopulation of gout patients who are refractory to conventional therapy, utilized a variation on the target sUA endpoint: the proportion of patients maintaining a plasma uric acid <6 mg/dL for at least 80% of the time during months 3 and 6, in two trials which were 6 months in duration. Pegloticase increased the proportion of patients meeting this endpoint, but also showed an increase in the proportion of patients with resolution of a target tophus and had a numeric trend toward flare improvement in months 3 through 6. However, pegloticase has a unique mechanism of action as a uricase, which causes direct enzymatic breakdown of uric acid and can result quickly in very low sUA levels (as low as 1 mg/dL), which in turn expedites the depletion of excess urate stores.

At the Arthritis Advisory Committee meeting for this application, on October 23, 2015, the Committee was asked to discuss and vote on whether the efficacy of lesinurad 200 mg was clinically meaningful. The Committee voted 14 to 0 in favor of this conclusion. Panelists also commented that a group mean decrease of 1 mg/dL was a clinically meaningful difference, particularly in the context of an increased proportion of patients reaching the target serum urate levels of ≤6 mg/dL. Panelists noted that the lack of difference on gout flares or tophi resolution would not be surprising in a 1-year trial and were reassured by the uncontrolled extension data showing continued declines in flare rates and an increase in patients achieving tophi resolution.

In summary, the endpoint of proportion of patients achieving a target serum uric acid level of <6 mg/dL is consistent with the widely accepted and recommended therapeutic goal of urate-lowering therapy in gout. Although clinical data to support this target are

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limited, studies are consistent. This target has a physiological basis and directly addresses the underlying pathophysiology of gout, in keeping serum uric acid levels below the physiological saturation point. Endpoints reflecting clinical outcomes in gout have not been consistently demonstrable in typical clinical development trials of 1 year or less, but this is not surprising, as potentially long durations with serum urate below the saturation point may be needed to deplete excess body stores of urate and improve clinical outcomes.

- **Summary of notable efficacy issues**

The clinical and statistical review teams are in agreement that lesinurad convincingly demonstrated an increase in the proportion of patients meeting target serum uric acid <6 mg/dL in the phase 3 studies. However the statistical team has expressed concern about uncertainty regarding the clinical benefit of the urate-lowering effect demonstrated, since clinical benefit was not demonstrated during the controlled period of the lesinurad studies. The clinical team agrees with the academic community and the Arthritis Advisory Committee viewpoint that clinical benefit is expected with longer-term treatment and that substantial evidence of the efficacy of lesinurad has been adequately demonstrated.

8. Safety

- **Adequacy of the database/safety overview**

The number of patients treated with lesinurad in the gout clinical development program, and the duration of treatment, are summarized in Table 7 below. For the proposed dose of 200 mg, 949 patients were treated for approximately 856 person-years. The majority of patients exposed to any dose of lesinurad received at least 24 weeks of treatment, with 974 patients being treated for at least 48 weeks. The amount of exposure to lesinurad in the gout clinical development program exceeds the recommendations of the International Conference on Harmonization (ICH) E1 Guideline[15] and is considered adequate to assess the safety profile of lesinurad.

[15] ICH E1: "The extent of population exposure to assess clinical safety for drugs intended for long-term treatment of non-life threatening conditions," http://www.ich.org

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Table 7: 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)

Safety Overview

As shown in Table 8 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.

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.

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Table 8: 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

- **General discussion of deaths, SAEs, discontinuations due to AEs, general AEs, and results of laboratory tests.**

Deaths

As of the cut-off date for the 120-day safety update, there were a total of 17 deaths reported in the lesinurad clinical development program: 6 deaths occurred during the placebo-controlled study periods of phase 3 studies 301, 302, 303 and 304, 9 deaths occurred during the phase 3 uncontrolled extension studies (305, 306, and 307), and 2 deaths occurred in earlier phase studies (118 and 203).

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During the controlled period of studies 301, 302, 303, and 304, there were no deaths in the placebo group, 2 deaths (both adjudicated as major adverse cardiovascular events [MACE]) in the group of patients taking lesinurad 200 mg, and 4 deaths (3 related to MACE and 1 related to gastric cancer) in the group of patients receiving lesinurad 400 mg. The patient-year exposure to placebo was the same or slightly higher than the exposure to lesinurad 200 mg or lesinurad 400 mg, so the imbalance in deaths would not be attributable to a difference in exposure periods and could suggest an increased risk with lesinurad. However, the numbers in the controlled period are small, and gout patients have a baseline increased risk of cardiovascular morbidity and mortality, so definitive conclusions cannot be drawn.

Serious Adverse Events

As noted in Table 8 above, there was an increased incidence of serious adverse events (SAE) with lesinurad 400 mg in the controlled phase 3 studies (8-9% with lesinurad 400 mg vs. 4-6% with placebo). The incidence of SAE with lesinurad 200 mg did not appear to be elevated compared to placebo. The most common SAE were in the cardiac and renal disorder categories, and will be addressed below in the specific discussion of renal safety and cardiovascular safety.

Discontinuations due to Adverse Events

More patients discontinued from lesinurad treatment in a dose-dependent manner. In the studies with background xanthine oxidase inhibitors, 9% of patients taking lesinurad 400 mg, 6% of patients taking lesinurad 200 mg, and 5% of patients taking placebo discontinued due to adverse events. In the monotherapy Study 303, 19% of patients taking lesinurad 400 mg discontinued vs. 6% of placebo-treated patients. The most common reasons for discontinuation included renal and gastrointestinal disorders.

Common Adverse Events

The incidence of common adverse events also increased in a dose-dependent manner with lesinurad treatment. In the background xanthine oxidase inhibitor studies, 80% of patients on lesinurad 400 mg experienced an adverse event compared to 76% of patients on lesinurad 200 mg and 70% of patients on placebo. With lesinurad 400 mg monotherapy in Study 303, 78% of patients experienced an adverse event compared to 65% of placebo-treated patients. The most commonly reported preferred terms in the combined lesinurad groups included upper respiratory tract infection (10%), nasopharyngitis (9%), arthralgia (7%), back pain (7%), hypertension (6.5%), and creatinine increased (6%).

Laboratory Tests

Hematology: No clinically meaningful changes from baseline were noted for the various hematology parameters across treatment groups for the phase 3 controlled studies.

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Serum Chemistries and Electrolytes: No clinically meaningful changes from baseline were noted in the phase 3 studies with respect to electrolytes, bicarbonate, glucose, albumin, calcium, and phosphate. Small increases in blood urea nitrogen (BUN) were observed, consistent with increases in serum creatinine noted. Changes in serum creatinine will be discussed in more detail below in the renal safety section.

Liver Enzymes: No clinically meaningful differences in changes from baseline were observed in the phase 3 studies. Outlier analyses also did not demonstrate any consistent trends of increased occurrence with lesinurad treatment. No cases meeting Hy's law criteria were identified.[16]

Creatine Phosphokinase (CPK or CK): No consistent trends of increased CK were observed with lesinurad treatment in the phase 3 studies.

Urinalysis: No consistent trends were noted for urinary glucose, ketones, protein, or occult blood. Higher proportions of urinary samples from lesinurad-treated patients were positive for uric acid crystals, but samples may have been evaluated up to 72 hours at room temperature prior to testing, and this would likely increase the likelihood of uric acid precipitation. In any case, this finding would be consistent with the mechanism of action of lesinurad as a uricosuric.

- **Immunogenicity**

As lesinurad is a small molecule, non-protein product, an assessment of immunogenicity was not required or provided.

- **Special safety concerns**

Renal Safety

As lesinurad is a uricosuric and has a similar mechanism of action as probenecid, a predisposition to renal toxicity via increased urinary uric acid and precipitation of urate would be expected. However, as noted in Section 4 above, nonclinical studies in rats and monkeys also identified the kidney as a target organ of toxicity of lesinurad (at supratherapeutic exposures), and the mechanism of that toxicity is unclear.

As shown in Table 9 below, lesinurad 400 mg was associated with an increased incidence of renal AE, serious renal AE, serum creatinine elevations, and with monotherapy use, kidney stone AE, compared to placebo. Lesinurad 200 mg was not associated with an

[16] Hy's Law criteria: AST or ALT >3 times upper limit of normal (ULN), alkaline phosphatase <2 x ULN, and an increase in bilirubin ≥2 x ULN, without other reason to explain findings. For more information, refer to the FDA Guidance for Industry, Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009. Website: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf, accessed 11/21/15

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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.

Table 9: 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

Ten of 12 of the serious renal adverse events that occurred during the controlled period of the phase 3 studies occurred with lesinurad 400 mg treatment, with the remaining two events occurring with placebo treatment in the background xanthine oxidase inhibitor studies. No serious renal adverse events occurred with lesinurad 200 mg in the controlled period. In the long-term extension studies 305, 306, and 307, there were 10 patients who developed serious renal adverse events. Four out of 10 were in placebo patients who had initiated treatment with lesinurad 400 mg in the extension study, four patients were continuing on lesinurad 200 mg from the controlled period, and two patients were

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continuing on lesinurad 400 mg from the controlled period. All patients had confounding risk factors; however it is likely that lesinurad was a contributing factor in some cases.

Table 10 below includes additional details on the characteristics of episodes of serum creatinine (sCr) elevations ≥2 x baseline. Similar trends were noted with lower levels of sCr elevation (i.e., ≥1.5 x baseline). For the proposed dose of 200 mg, only 9 patients (2%) experienced sCr elevation ≥2 x baseline. Of those 9 patients, 8 had resolved abnormalities by the time of their last assessment. Six patients resolved their creatinine elevations without interruption of study medication, and 5 patients had resolved their abnormalities within 14 days.

Table 10: Serum Creatinine (sCr) Elevation ≥2.0 x Baseline and Time to Resolution

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%)**

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

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

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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 11 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. The pattern of increase in risk with the 400 mg dose is consistent with other adverse events, such as serious adverse events. The incidence of MACE and non-MACE with the proposed 200 mg dose of lesinurad appears to be generally similar to the placebo group. However, it should be noted that the number of events is small, and the confidence intervals are highly overlapping, so definitive conclusion cannot be drawn on the basis of these data.

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Table 11: 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

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- **Discussion of primary reviewer's comments and conclusions**

Dr. Neuner notes that lesinurad treatment is clearly associated with an increased risk of renal adverse events, serum creatinine elevation that is not always reversible, and serious adverse events including MACE. The risk appears to be dose-dependent, with the highest risk associated with the use of lesinurad as monotherapy. However when evaluating the safety of lesinurad 200 mg specifically, the risk of adverse events is not consistently increased relative to the control group. Therefore, Dr. Neuner believes the benefit-risk profile of lesinurad 200 mg in combination with a xanthine oxidase inhibitor is adequately favorable.

- **Highlight differences between CDTL and review team with explanation for CDTL's conclusion and ways that the disagreements were addressed**

I agree with Dr. Neuner that the benefit-risk profile of lesinurad 200 mg in combination with a xanthine oxidase inhibitor is adequately favorable to support approval. The safety of lesinurad 200 mg is generally similar to the control group, with the exception of a small increased risk of serum creatinine elevations.

- **Discussion of notable safety issues (resolved or outstanding).**

1) Renal safety: Renal safety concerns were predominantly with lesinurad 400 mg, particularly with monotherapy use. Although there was a higher incidence of serum creatinine elevations with lesinurad, the imbalances were small (e.g., for sCr elevation >2 x baseline, the incidence was 2% for lesinurad 200 mg and 0% for placebo). No serious renal AEs were reported with lesinurad 200 mg during the controlled period of the phase 3 studies. While it is true that there is overlapping exposure between the 200 and 400 mg doses, there was also a clear distinction between the two dose groups in the pattern and incidence of renal AE and sCr elevations. I believe there is sufficient experience with the 200 mg dose to reassure that the risk with 200 mg is sufficiently low to support approval.
2) Cardiovascular safety: There were few MACE events and overlapping confidence intervals. The background risk of cardiovascular events is higher in gout patients, e.g, a hazard ratio of 1.26 for any myocardial infarction.[17] While there was an imbalance in the 400 mg group, there was not an imbalance in the 200 mg group (lesinurad 400 mg 2%, lesinurad 200 mg 1%, and placebo 1%). Acknowledging that there remains considerable uncertainty, urate-lowering therapy is not intended or purported to reduce cardiovascular outcomes, and the small number of events would not suggest a major safety concern. In my opinion, a cardiovascular outcomes study (pre- or post-marketing) is not warranted based on the available information, and the observed imbalance in MACE should be addressed via a Warning in the prescribing information.

[17] Abeles AM, "Hyperuricemia, Gout, and Cardiovascular Disease: An Update." Curr Rheumatol Rep 2015; 17:13

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9. Advisory Committee Meeting

An Arthritis Advisory Committee meeting was convened on October 23, 2015 to discuss this application. The Committee was asked to discuss and vote on the efficacy and safety of the proposed dose of 200 mg once daily of lesinurad, keeping in mind the dose-dependent toxicity exhibited by the 400 mg dose of lesinurad. The questions, discussions, and voting are summarized below. The reader is also referred to the full transcript which will be posted on the FDA Arthritis Advisory Committee website.

1. **DISCUSSION:** Discuss the efficacy of the proposed dose of lesinurad 200 mg and whether the decrease in sUA observed would be considered clinically meaningful.

   Committee Discussion: *The majority of the committee agreed that the trials demonstrated efficacy of the proposed dose of lesinurad 200 mg and that the decrease in serum uric acid (sUA) was clinically meaningful. Some members of the committee did not agree that there was enough data collected to demonstrate the efficacy given that the trials were limited to 12 months, and added that longer controlled studies were needed to evaluate clinical outcomes such as reduction in tophi or gout flares. However, it was noted that the lesinurad trials, including duration, met the FDA standards for trial design. Members of the committee stated that the small observed average decrease of 1mg/dL sUA would be expected to translate to clinically meaningful benefits in the broader population, especially when lesinurad would be prescribed for a longer period of time than studied.*

2. **DISCUSSION:** Discuss the safety of the proposed dose of lesinurad 200 mg, with specific focus on renal and cardiovascular safety.

   Committee Discussion: *The committee stated that there were too few events to make conclusions on the cardiovascular safety profile of lesinurad. The majority of the committee expressed concerns about the safety of lesinurad in patients with moderate to severe renal dysfunction however it was difficult to draw conclusions in light of different analyses shown by the sponsor and FDA that appeared to support conflicting conclusions. Specifically, it was not clear how reversible the changes in renal function were in the studies. Members of the committee agreed that more specific guidelines regarding the frequency of renal function (serum creatinine and CrCl) monitoring need to be communicated to health providers in the product labeling. One member of the committee stated concerns about the narrow therapeutic index of lesinurad given that the minimum effective dose of 200 mg was very close the maximum safe dose of 400 mg.*

3. **DISCUSSION:** Discuss the dose dependent toxicity of lesinurad in light of the safety profile of the 400 mg dose, and in your discussion, comment on the following:

   a. Comment on whether the overlapping exposure of the 200 mg and 400 mg doses raises concerns about the potential toxicity of the 200 mg if exposed to a broader population of gout patients post-marketing.

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Committee Discussion*: The committee did not have any concerns about the potential toxicity of the 200 mg dose of lesinurad if used in a broader population of gout patients in a post-marketing setting, given the overlapping exposure of the 200 mg and 400 mg doses.*

b. Comment on whether the justification for once-daily dosing is adequate given that it remains an open question whether a lower nominal dose given more frequently might have provided similar efficacy with a better safety profile.

Committee Discussion*: The majority of the committee stated that there was adequate justification for once-daily dosing of lesinurad 200 mg despite not knowing whether a lower nominal dose given more frequently might have provided similar efficacy with a better safety profile. The committee noted that previous experience with other uricosurics (i.e. probenecid) have demonstrated that there is a concern for increased risk of nephrolithiasis (kidney stones) with nocturnal dosing, and given their similar pharmacology, once daily dosing of lesinurad is more preferable over more frequent dosing (i.e. twice daily dosing). Another member of the committee added that compliance would likely be less if lesinurad was approved for twice daily dosing.*

4. **VOTE:** Overall, do the data provide substantial evidence that lesinurad 200 mg once daily provides a clinically meaningful beneficial effect in the treatment of hyperuricemia associated with gout, in combination with a xanthine oxidase inhibitor?

Yes= 14 **No= 0** **Abstain= 0**

a. **DISCUSSION:** Please explain the rationale for your vote.

Committee Discussion: *The committee unanimously agreed (14 members) that the data demonstrated substantial evidence that lesinurad 200 mg once daily provides a clinically meaningful beneficial effect in the treatment of hyperuricemia associated with gout, in combination with a xanthine oxidase inhibitor. Members of the committee stated that although the average observed decrease of 1mg/dl in serum uric acid was small, this would translate to clinically meaningful benefits with long term treatment.*

5. **VOTE:** Is the safety profile of lesinurad 200 mg once daily adequate to support approval of lesinurad for the treatment of hyperuricemia associated with gout in combination with a xanthine oxidase inhibitor?

Yes= 7 **No= 6** **Abstain= 1**

a. **DISCUSSION:** Please explain the rationale for your vote.

Committee Discussion: *A slight majority of the committee (7 members) agreed that the safety profile of lesinurad 200 mg once daily was adequate to support its approval for the treatment of hyperuricemia associated with gout in combination with a xanthine oxidase inhibitor, with the caveat that more stringent guidelines for renal function monitoring be*

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specified in the product labeling. The six members who voted "No" and the member who abstained agreed that additional safety data was needed in order to draw conclusions about the cardiovascular and renal safety of this product, particularly in patients with renal insufficiency.

6. **VOTE:** Do you recommend approval of lesinurad 200 mg once daily for the proposed indication of treatment of hyperuricemia associated with gout in combination with a xanthine oxidase inhibitor?

   Yes= 10 No= 4 Abstain= 0

   a. **DISCUSSION:** If you voted yes, are there any additional studies recommended post-approval?

      Committee Discussion: *The majority of the committee (10 members) recommended the approval of lesinurad 200mg once daily for the proposed indication of treatment of hyperuricemia associated with gout in combination with a xanthine oxidase inhibitor. These members reiterated that there is a significant need for effective medications for gout patients and that this drug has proven to be effective in clinical trials. They stated that long term studies (greater than 24 months) examining alternative split dosing at 7am and 2pm, decrease in gouty flares, and long term side effect profiles (including renal and cardiovascular safety) should be carried out post-approval in the broader population of gout patients.*

   b. **DISCUSSION:** If you voted no, what additional studies are recommended prior to approval?

      Committee Discussion: *Four members of the committee did not recommend the approval of lesinurad 200 mg once daily for the proposed indication of treatment of hyperuricemia associated with gout in combination with a xanthine oxidase inhibitor based on the available safety data. These members reiterated the need for long term safety trials. One member of the committee stated that the number needed to treat was not balanced by the number needed to harm, and was concerned that the current safety data was not clear on whether patients with renal insufficiency would benefit or be harmed by this drug.*

10. Pediatrics

The applicant requested a full waiver from the requirements of the Pediatric Research Equity Act (PREA) on the basis that gout does not occur in pediatric patients and therefore necessary studies would be impossible or highly impracticable. The Agency's Pediatric Review Committee (PeRC) discussed this application on July 8, 2015 and agreed with the requested waiver.

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11. Other Relevant Regulatory Issues

- **Application Integrity Policy (AIP)**—Not applicable.
- **Exclusivity or patent issues of concern**—No issues.
- **Financial disclosures**—No issues.
- **Other GCP issues**—No issues
- **Office of Scientific Investigation audits**

Clinical site inspections were performed for two sites in Study 301 and a single site in Study 302. These sites were selected on the basis of relatively larger enrollment and response rates. The Office of Scientific Investigation (OSI) recommended the clinical data as adequate to support review.

- **Other discipline consults**—Not applicable.
- **Any other outstanding regulatory issues**—No issues

12. Labeling

- **Proprietary name**—Proposed and accepted as Zurampic.
- **Important issues raised by brief discussion of OSE, OPDP, and OMPP comments**—pending at this time.
- **Physician labeling**—final labeling is still under negotiation at this time.
    - The applicant has agreed to include a Boxed Warning regarding renal adverse events.
    - The applicant has agreed to include a Warning about cardiovascular adverse events.
    - Use in patients with impaired renal function: the applicant proposed a contraindication for use in patients with eGFR <30 ml/min. At a labeling teleconference on November 17, 2015, the review team and the applicant discussed the efficacy and safety of lesinurad in renal function category subgroups. The review team discussed the rationale for not recommending use of lesinurad in patients with eGFR <45 ml/min. The applicant's counterproposal label is pending at this time.
- **Carton and immediate container labels**—No issues.
- **Patient labeling/Medication guide**—The applicant has proposed a medication guide, which is reasonable. Negotiation on final wording is pending at this time.

13. Recommendations/Risk Benefit Assessment

- **Recommended Regulatory Action**

I recommend approval of the 200 mg once daily dose of lesinurad for the treatment of hyperuricemia associated with gout in combination with a xanthine oxidase inhibitor.

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- **Risk Benefit Assessment**

1) Benefit of lesinurad 200 mg once daily in combination with a xanthine oxidase inhibitor
   a. The statistical and clinical review teams were in agreement that lesinurad 200 mg treatment increased the proportion of patients meeting target serum urate levels. In Studies 301 and 302, with background allopurinol, lesinurad 200 mg resulted in approximately 26 to 32% more patients reaching sUA <6 mg/dL compared to placebo. In Study 304, on a background febuxostat 80 mg, lesinurad 200 mg resulted in approximately 10% more patients reaching sUA <5 mg/dL compared to placebo.

   As discussed in Section 7 above, there is a physiological basis for the selection of target sUA of <6 mg/dl as being below the saturation point of uric acid in the body. Depending on a patient's excess urate burden and the degree of urate-lowering below the saturation point, improvement in clinical outcomes may not be observed for a long time (longer than 6 months to 1 year), but available data in the literature support the conclusion that it would be expected. The lack of improvement in clinical outcomes during the 1-year controlled period of the lesinurad trials is consistent with other trials of urate-lowering therapy (e.g., febuxostat) and does not indicate inadequate evidence of efficacy.

2) Risks of lesinurad 200 mg once daily in combination with a xanthine oxidase inhibitor
   a. Renal safety: Renal safety concerns were predominantly with lesinurad 400 mg, particularly with monotherapy use. Although there was a higher incidence of serum creatinine elevations with lesinurad, the imbalances were small (e.g., for sCr elevation >2 x baseline, the incidence was 2% for lesinurad 200 mg and 0% for placebo). No serious renal AEs were reported with lesinurad 200 mg during the controlled period of the phase 3 studies. While it is true that there is overlapping exposure between the 200 and 400 mg doses, there was also a clear distinction between the two dose groups in the pattern and incidence of renal AE and sCr elevations. I believe there is sufficient experience with the 200 mg dose to reassure that the risk with 200 mg is sufficiently low to support approval.
   b. Cardiovascular safety: There were few MACE events during the controlled period of the phase 3 studies. While there was an imbalance in the 400 mg group, there was not an imbalance in the 200 mg group (lesinurad 400 mg 2%, lesinurad 200 mg 1%, and placebo 1%). Acknowledging that there remains considerable uncertainty, urate-lowering therapy is not intended or purported to reduce cardiovascular outcomes, and the small number of events would not suggest a major safety concern. In my opinion, a cardiovascular outcomes study (pre- or post-marketing) is not warranted based on the available information, and the observed imbalance in MACE should be addressed via a Warning in the prescribing information.

In summary, although the average urate-lowering effect of lesinurad 200 mg is small (approximately 1 mg/dL), for those patients who have not yet achieved target sUA <6 mg/dL, this additional urate-lowering effect would be important and clinically meaningful. The risks of lesinurad 200 mg are correspondingly small, and mainly involve serum creatinine elevation, which can be monitored. In my opinion, the benefit-risk balance of lesinurad 200 mg is adequately favorable to support approval.

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- **Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies (REMS)**

I do not recommend a Risk Evaluation and Mitigation Strategy (REMS). Risks with the proposed dose of 200 mg may be adequately addressed via labeling and a Medication Guide.

- **Recommendation for other Postmarketing Requirements and Commitments**

No postmarketing requirements or commitments are recommended.

- The available clinical data with lesinurad 200 mg is adequate to characterize the renal safety concerns and an additional post-marketing study is not likely to reveal new concerns.
- As noted in Section 8 above, a cardiovascular outcomes study does not appear warranted given the low number of events in the trials and the lack of an imbalance with the lesinurad 200 mg once daily dose regimen.
- While a longer-term controlled efficacy study to assess clinical outcomes would be of academic interest, there is sufficient support for the use of target sUA $\leq$6 mg/dL as an efficacy endpoint in clinical development programs of urate-lowering therapies for gout, and the treatment effect of lesinurad for this endpoint is clear.

- **Recommended Comments to Applicant**

None.

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/s/

SARAH K YIM
11/22/2015