

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

207988Orig1s000

OFFICE DIRECTOR MEMO

Office Deputy Director Decisional Memo

Date	December 22, 2015
From	Mary H. Parks
Subject	Office Deputy Director Decisional Memo
NDA/BLA #	207988
Supplement #	
Applicant Name	Ardea Biosciences, Inc.
Date of Submission	December 29, 2014
PDUFA Goal Date	December 29, 2015
Proprietary Name / Established (USAN) Name	Zurampic® (lesinurad)
Dosage Forms / Strength	Oral tablets/200 mg
Applicant Proposed Indication(s)/Populations	ZURAMPIC is a URAT1 inhibitor indicated in combination with a xanthine oxidase inhibitor for the treatment of hyperuricemia associated with gout in patients who have not achieved target serum uric acid levels with a xanthine oxidase inhibitor alone.
Action:	Approval

Overview

This new drug application is for Zurampic® (lesinurad), an inhibitor of the urate transport 1 (URAT 1) protein located on the proximal tubules in the kidney which mediates the reabsorption of uric acid thereby regulating blood uric acid concentrations. By inhibiting this transport protein, lesinurad reduces serum uric acid (sUA) in the bloodstream. The applicant is seeking an indication for the use of lesinurad in combination with xanthine oxidase inhibitors (XOI) for the treatment of hyperuricemia associated with gout.

The reader is referred to the Division Director's decisional memo and the Cross Discipline Team Leader (CDTL) memo for a thorough discussion of this application and its review by multiple FDA review disciplines. The Office level memo provides the high level summary of data supporting the final recommendation for approval.

There was not agreement between the clinical and biostatistical reviewers on final regulatory action. In addition, the Office of Clinical Pharmacology (OCP) is not recommending approval of lesinurad 200 mg once daily in patients with CrCl < 45 mL/min. My memo will address each of these discipline recommendations and how I considered their arguments in my final decision.

1. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

The benefit of lesinurad was assessed by a surrogate measure – serum uric acid level. Serum uric acid level is relied upon in clinical practice as part of the evaluation of a patient with gout; it is monitored during the treatment of gout; and targeted goals of sUA levels are recommended by U.S., British, and European treatment guidelines for the management of gout. FDA has accepted sUA level as the primary efficacy endpoint for approval of treatments for hyperuricemia associated with gout based on recommendations from an FDA meeting involving the Arthritis Advisory Committee held in June 2004. These recommendations are based on the following:

- Hyperuricemia, either through overproduction or underexcretion, is the underlying cause for gout
- There is an increased risk of monosodium urate crystal formation and deposition in the articular, periarticular, and subcutaneous tissues leading to clinical manifestations of gout such as acute attacks of gouty arthritis, chronic gouty arthropathy, and tophaceous gout with increasing levels of sUA; and
- Long-term cohort studies have demonstrated an improvement on clinical disease with the lowering of sUA levels in patients with gout

Although a surrogate endpoint is a substitute for a direct measure of clinical benefit, no therapies for the treatment of hyperuricemia associated with gout have been required to demonstrate a statistically significant effect on clinical outcomes because of the duration of trials necessary to evaluate such a treatment effect. With exception for pegloticase, which is reserved for patients who have failed conventional gout therapies given the risks of immunogenicity, anaphylaxis and serious infusion reactions, no approved therapies for hyperuricemia associated with gout have a labeled claim for reducing the number of acute gout attacks or resolution of tophi.

I am not aware of any recent data that call into question serum uric acid level as a surrogate for approval of ULTs to treat gout. Furthermore, the advisory committee panel for this application was asked whether “*the data provided 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 an XOP*”. The unanimous ‘yes’ (14 vs 0) vote would also suggest that nothing from this clinical development program has challenged the surrogacy of sUA.

However, as with any approval decision based on a surrogate, the absence of a direct measure of clinical benefit makes the benefit-risk calculus difficult when a safety issue arises. I believe this is at the crux of the recommendation made by Drs. Levin, Davi, and Permutt.

From this NDA, there is uncertainty in risk with lesinurad 200 mg which arose out of safety findings from Study 303 which compared lesinurad 400 mg to placebo in patients who are

intolerant of or have a contraindication to xanthine oxidase inhibitors. The safety concern in this trial was primarily renal, which carried over into the 400 mg treatment group in Studies 301, 302, and 304 – trials which evaluated the combined use of lesinurad with an XOI. Based on the mechanism of action of the drug and the notable imbalances between drug and placebo in Study 303, renal toxicity of lesinurad cannot be dismissed as spurious. The renal safety findings for the proposed marketed dosing regimen of lesinurad 200 mg once daily in the controlled portion of this program were predominantly laboratory abnormalities and none resulted in serious clinical sequelae. However, the program did not enroll a very large number of patients with renal impairment. For example, in the pivotal trials there were only 89 patients with baseline CrCL 30 to 45 ml/min; approximately 300 had CrCl < 60 ml/min. The applicant will be required to evaluate long-term renal safety as a condition of this approval and such a study will need to enroll more patients with baseline renal impairment.

There were also imbalances in CV events and death not favoring lesinurad. Like the renal events, there were very few events across the different treatment groups; however, unlike renal safety, a mechanistic plausibility was not identified for excess CV risk or mortality and the imbalance for these events may represent a spurious finding for a population with co-morbid risk factors for such events. Although I would not conclude absence of CV risk, I do not believe there is sufficient evidence to tip the benefit-risk scale based on the CV safety findings and would not require additional studies solely on those findings.

Several members from the advisory committee expressed concern on the lack of longer term studies including an excerpt from Dr. Beth Jonas:

“My primary concern is that we don’t have longer-term studies and that there is some concern primarily about renal insufficiency, and that gave me cause to worry about safety in that population.”

Dr. Levin also included excerpts from AC members in his memo that also captured similar sentiments as Dr. Jonas’s. I also note that while Dr. Levin’s first recommendation is to issue a Complete Response recommendation for this application, he is also willing to accept an approval with a PMR.

I concur that longer-term studies with lesinurad is desirable and necessary to better understand the benefits-risk of this drug in the gout patient population. However, I do not believe this study must be done pre-approval and that approval can be granted provided there is labeling that clearly communicates the risk of renal toxicity and minimizes use to the population that has a lower risk of renal toxicity. The PMR will be a 24-month trial of lesinurad 200 mg in a population of patients not yet achieving target sUA goal on an XOI. The study population will be patients with moderate renal impairment with CrCl of 30 to 60 ml/min. The primary objective will be to evaluate renal safety although other endpoints including CV safety and efficacy measures will be obtained. Details of the trial will require further discussion, including choice of comparators. Consideration will be given for a placebo and active control arm with probenecid.

Probenecid is the only available uricosuric and current treatment guidelines for its use are comparable to the proposed indication for lesinurad. Despite its low costs and familiar risk

profile, its utilization is quite low for reasons that are unclear. In my review of this application, which included a literature search of available therapies for gout, I am struck by the limited number of RCTs of available therapies for such a highly prevalent condition whose clinical description has been well-described as fall back as ancient times. Indeed, the treatment guidelines are based more on clinical experience than well-controlled experiments. A study comparing the long-term safety (and efficacy) of lesinurad to probenecid will not only better inform us on the safety of this drug but may also inform the scientific community on future treatment guidelines for gout.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Gout is a disease of excess uric acid production or under excretion. When blood uric acid levels exceed urate solubility (~6.8 mg/dL), there is an increased risk for monosodium urate crystals formation and deposition into joints and tissues resulting in severely painful joint attacks. Prolonged disease can result in joint deformities and formation of tophi in soft tissues that can be physical deforming.	Disease is well-recognized and described in medical textbooks/literature. Several treatment guidelines (US, British, and European) have similar recommendations on management which is to target serum uric acid level to below 6 mg/dL and lower if there is higher burden of disease (e.g. tophaceous gout)
Current Treatment Options	Urate-lowering therapies (ULTs) approved for the treatment of hyperuricemia associated with gout include: Xanthine oxidase inhibitors – allopurinol and febuxostat Uricosurics – probenecid Uricases – pegloticase	Xanthine oxidase inhibitors considered 1 st line but may not be able to lower serum uric acid level to recommended target goal for patient. In that scenario, uricosuric is recommended as add-on. Pegloticase is a third-line agent given risk of anaphylaxis.
Benefit	Lowers serum uric acid level when added onto allopurinol or febuxostat. This is an accepted surrogate for drug approval. No long-term RCTs have established a reduction in clinical outcomes associated with ULTs although cohort studies have shown reduced rate of tophi and acute gout attacks with lower serum uric acid level.	Given episodic and inconsistent pattern of presentation for gout attacks and tophi deposition, requiring clinical outcomes may be impracticable. No prior approved gout therapies have been required to

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p>2004 FDA advisory committee of Arthritis Drugs Committee confirmed the appropriateness of reliance on this surrogate for drug approval.</p>	<p>demonstrate an effect on clinical outcomes.</p> <p>AC panel for lesinurad voted 14 to 0 that clinically meaningful benefit was established based on serum uric acid level reduction.</p>
Risk	<p>Renal toxicity, particularly in patients with elevated baseline serum uric acid level and who received lesinurad 400 mg alone. Other risk factors for renal toxicity may include baseline renal impairment. Based on mechanism of drug's action, nonclinical and clinical findings, renal toxicity is a valid concern. Limited number of patients with moderate renal impairment (CrCl <60) were studied.</p> <p>Imbalance in cardiovascular events at lesinurad 400 mg once daily dose. Too few events with imbalance in single digits between treatment groups. Signal may be spurious finding.</p>	<p>No serious renal AE observed at the dose to be marketed (200 mg). Predominant AE was increased in serum creatinine.</p>
Risk Management	<p>Labeling to include Boxed warning on renal toxicity</p> <p>Restrict indication to only those patients who have failed to reach target serum uric acid level with a xanthine oxidase inhibitor</p> <p>Restrict indication to only those with CrCl 45 ml/min and recommend baseline and routine renal function monitoring.</p> <p>Require a 24-month active-controlled renal safety trial as a PMR</p>	<p>Uncertainty in risk at lesinurad 200 mg can be mitigated with labeling and restriction of use to limited population. Additional renal study required will better inform long-term safety of product and will also capture events related to efficacy.</p>

2. Further discussion to support regulatory action

Background

Gout is an inflammatory arthritis associated with hyperuricemia which may be due to overproduction of uric acid from purine metabolism and/or its under-excretion by the kidneys. Although not all patients with hyperuricemia develop gout, population studies have shown an increased incidence of gout with increasing serum uric acid (sUA) level as it exceeds the limit of urate solubility (~6.8 mg/dL) at physiologic temperature and pH.¹ Beyond this level there is an increased risk of monosodium urate crystal formation and deposition in the articular, periarticular, and subcutaneous tissues leading to clinical manifestations of gout such as acute attacks of gouty arthritis, chronic gouty arthropathy, and tophaceous gout.

Based on the understanding of the pathogenesis of disease, treatment guidelines for the management of gout put forward by the American College of Rheumatology (ACR), European League Against Rheumatism (EULAR), and the British Society for Rheumatology (BSR) have all recommended that urate-lowering therapy (ULT) target a sUA goal of < 6 mg/dL.^{2,3,4} In those with greater disease severity (e.g., tophi or chronic tophaceous gout arthropathy), practice guidelines recommend targeting a lower sUA level. The principle behind these specific recommendations is to lower sUA levels to below the threshold of saturation of uric acid in body fluids and to mobilize urate deposits.

Admittedly, there is a paucity of data from adequate and well-controlled trials showing that ULTs reduce the clinical burden of disease (i.e, prevention of acute gout attacks and dissolution of tophi). However, data from long-term cohort studies have shown an association between lowering sUA with ULTs and these clinical outcomes.^{5,6} Despite the lack of conclusive evidence from randomized controlled trials (RCTs) establishing the clinical benefits of ULTs in the treatment of gout, serum uric acid (sUA) level was identified as an acceptable surrogate marker for demonstration of efficacy for gout therapies during the June 2004 public FDA meeting involving the Arthritis Advisory Committee.⁷ At this meeting some experts on the panel also noted that the duration of follow-up on treatment

¹ Campion EW et al. Asymptomatic hyperuricemia. Risks and consequences in the normative aging study. *Am J Med.* 82(3):421-426.

² 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 and Research* 64(10), October 2012, pp 1431-1446.

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* 2007; 1 of 17.

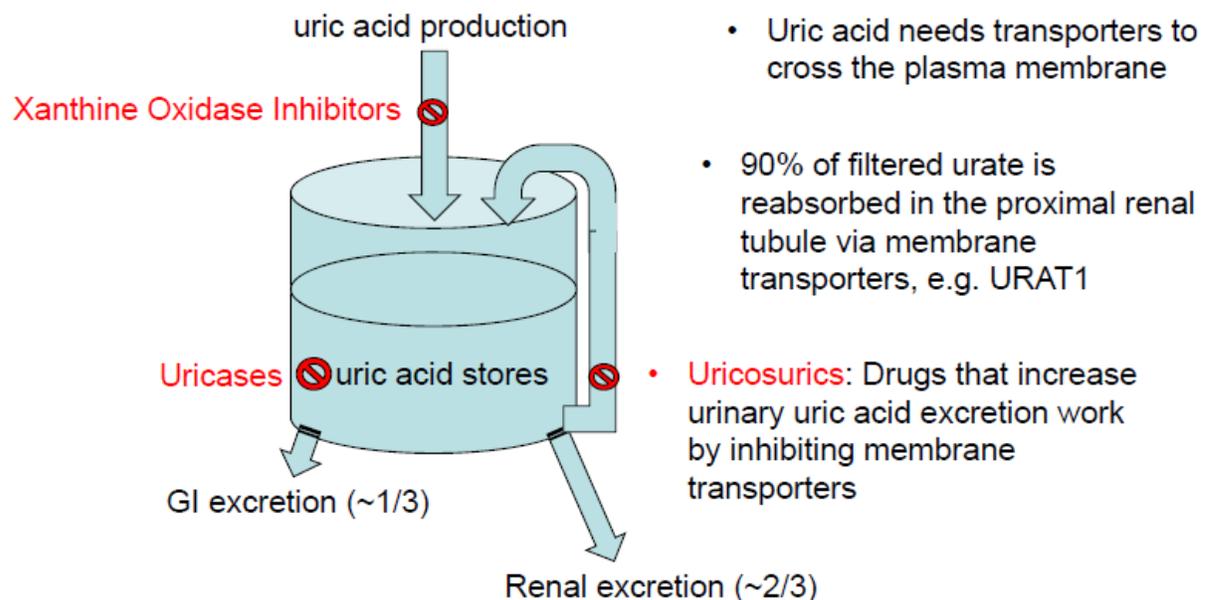
⁵ Perez-Ruiz F et al. Effect of urate lowering therapy on the velocity of size reduction of tophi in chronic gout. *Arthritis Care and Research* 2002, 47(4):356-360.

⁶ Shoji A et al. A retrospective study of the relationship between serum urate level and recurrent attacks of gouty arthritis: evidence for reduction of recurrent gouty arthritis with antihyperuricemic therapy. *Arthritis Care & Research.* 2004;51(3):321-325.

⁷ <http://www.fda.gov/ohrms/dockets/ac/04/transcripts/2004-4044T1.htm>

necessary to observe an effect on clinical outcomes may be so long as to make it impracticable to require clinical outcomes as a primary endpoint. One member also added that unlike rheumatoid arthritis where clinical disease presents more along a continuum, the clinical flares of gout are episodic and unpredictable, further contributing to the difficulty of designing a trial that will capture sufficient number of events to evaluate effect of lowering sUA levels on clinical outcomes.

Since 2004, FDA has approved two products (febuxostat and pegloticase) for chronic use in patients with gout based on their ability to effectively lower sUA levels. Table 1 from Dr. Neuner's review summarizes all the FDA-approved and available therapies for the treatment of hyperuricemia which are categorized into three classes: xanthine oxidase inhibitors (XOI), uricosurics, and uricases. The following figure presented by Dr. Yim at the October 23, 2015 advisory committee meeting for lesinurad shows where in the pathway of purine metabolism and uric acid production these different classes of ULTs affect.



The uricase, pegloticase, is indicated for the treatment of chronic gout in adult patients refractory to conventional therapy. It is administered as an intravenous infusion every two weeks in a healthcare setting by healthcare providers due to the increased risk for anaphylaxis and infusion reactions. Given the unique clinical circumstances for which pegloticase is indicated and administered, its availability did not weigh in considerably in the benefit-risk assessment of lesinurad.

Xanthine oxidase inhibitors

Xanthine oxidase is the enzyme responsible for the conversion of hypoxanthine to xanthine and xanthine to uric acid, the end product of purine metabolism. The two available XOIs in the U.S. are the purine analog *allopurinol*, and *febuxostat*, a nonpurine inhibitor of XO.

Allopurinol was first marketed in 1966 and is available in 100 or 300 mg strength tablets with generics availability. The starting dose should be no greater than 100 mg daily with gradual upward titration to maximal tolerated dose. Although the maximal recommended dosage is 800 mg daily in patients without renal impairment or with only mild renal impairment, few patients are prescribed more than 300 mg/day. In a 6-month, open-label study designed to evaluate the safety of allopurinol in over 1700 patients, investigators were encouraged but not required to titrate allopurinol doses to achieve target sUA < 6mg/dL. The majority of patients received the 300 mg dose (65.4%) and 20.2% were titrated to > 300 mg.⁸ Drug utilization data also suggest that 300 mg once daily is the more commonly prescribed dosing regimen (see Dr. Pham's review from Division of Epidemiology II). Skin rash, including severe reactions such as Stevens-Johnson syndrome, is a serious safety concern associated with allopurinol use. An increased risk of severe skin toxicity has been observed in patients with HLA-B*5801 such that recommendations for pharmacogenomics testing has been recommended in certain Asian subpopulations such patients of Han Chinese or Thai extraction where there is an increased allele prevalence.^{9,10} Other safety concerns include hepatotoxicity and generalized vasculitis.

Febuxostat was approved in 2009 in dosage strengths of 40 and 80 mg with the recommended starting dose of 40 mg once daily and titration to 80 mg once daily if after 2 weeks sUA level has not fallen below 6 mg/dL. There is no recommendation for dose reduction in patients with moderate renal impairment. An imbalance in cardiovascular thromboembolic events was observed in RCTs reviewed in the NDA although there were too few events to establish conclusively a causal role associated with febuxostat. This NDA was discussed at an advisory committee and received an overall recommendation for approval but several members encouraged a prospectively designed trial to evaluate CV risk. The applicant was required to conduct a cardiovascular outcomes trial for febuxostat under FDAAA and that is currently ongoing.

As noted earlier, there is a dearth of data from long-term randomized controlled trial with ULTs; however, the development program for febuxostat did include three active- and placebo-controlled trials of 6 to 12 month's duration providing some comparative efficacy and safety data between febuxostat and allopurinol. Febuxostat 80 mg resulted in a greater proportion of patients achieving sUA < 6 mg/dL compared to allopurinol 300 mg daily and comparable efficacy was observed between febuxostat 40 mg and allopurinol 300 mg daily dosing. In patients with renal impairment, both febuxostat 80 and 40 mg once daily provided greater efficacy than allopurinol 200 mg daily. There was no significant treatment effect of either drug on gout flares or tophi reduction for either ULT compared to placebo. Febuxostat's approval did not require a demonstration of efficacy on gout flares or tophi reduction to better weigh against the CV safety concerns.

Uricosurics

⁸ Becker MA et al. An open-label, 6-month study of allopurinol safety in gout: The LASSO study. *Seminars in Arthritis and Rheumatism*. 2015;45:174-183.

⁹ Hung SI et al. HLA-B*5801 allele as a genetic marker for severe cutaneous adverse reactions caused by allopurinol. *Proc Natl Acad Sci* 2005;102:4134-4139.

¹⁰ Tassaneeyakul W et al. Strong association between HLA-B*5801 and allopurinol-induced Stevens-Johnson syndrome and toxic epidermal necrolysis in a Thai population. *Pharmacogenet Genomics* 2009;19:704-709.

In general, treatment guidelines recommend XOIs as first-line treatment for hyperuricemia associated with gout although there is not a recommendation of any one over the other unless clinical circumstances dictate (e.g., serious skin reaction to allopurinol). A uricosuric may be prescribed as an alternative first-line agent when XOIs are inappropriate or contraindicated. When XOIs are insufficient at achieving targeted sUA levels, a uricosuric may be added, particularly if urinary under-excretion of UA has been documented. A uricosuric may not be appropriate in patients with a history of kidney or bladder stones and patients may require increased daily water intake and urine alkalinization to reduce the risk of urolithiasis.

Probenecid is the only available uricosuric indicated for the treatment of gout in the U.S. It was approved in 1951 and there is limited efficacy and safety data from RCTs although in one small study comparing probenecid monotherapy to allopurinol monotherapy, probenecid lowered sUA from a mean of 8.5 mg/dL to 5.2 mg/dL but a greater average reduction was observed with allopurinol.¹¹ Safety concerns include blood dyscrasias, development of uric acid kidney stones and reduced clearance of certain co-administered drugs (e.g., beta-lactam antibiotics). In a recent analysis of pharmacy claims data from 2009 to 2012, the prevalence of probenecid use for the treatment of gout was low throughout each year evaluated comprising between 1.2% to 2.4% prescriptions filled in a cohort of 955,356 patient members.¹² Hence, while there is an available uricosuric agent for the treatment of gout, its placement in the treatment algorithm by society guidelines and its utilization pattern do not show widespread use.

The development program for lesinurad included studies to evaluate its efficacy and safety as both a monotherapy and in combination with an XOI. Due to safety concerns, predominantly renal, in the monotherapy trial, the applicant is only seeking an indication for lesinurad's use in combination with an XOI.

Clinical Pharmacology

Please see review authored by Dr. Jianmeng Chen.

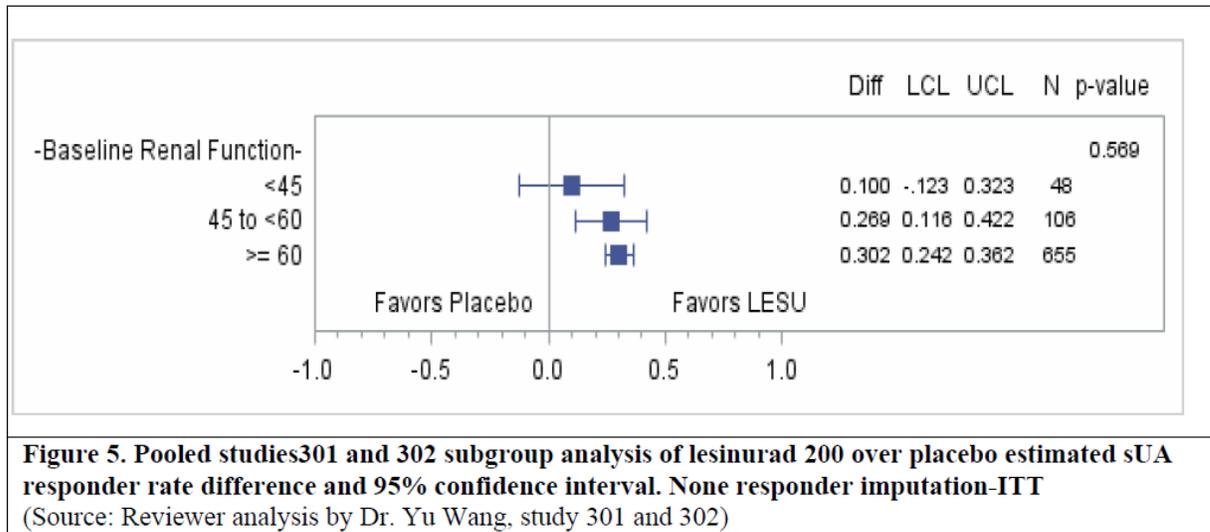
Renal Impairment

Two studies were conducted to evaluate the impact of renal impairment on lesinurad PK. Lesinurad exposure increased by 31%, 50-74%, and 113%, respectively in subjects with mild, moderate and severe renal impairment compared with subjects with normal renal function.

Efficacy appears diminished with increasing degree of renal impairment. The following forest plot created by FDA statistical reviewer, Dr. Wang, shows the reduced efficacy with reduce baseline CrCL. This was a post-hoc analysis and the number of patients in the CrCL < 45 ml/min subgroup is small. However, as noted by Dr. Chen, the reduced efficacy of lesinurad with worsening renal function may be an expected finding as there is less uric acid delivered to the proximal tubule due to a lower glomerular filtration rate.

¹¹ Scott JL. Comparison of allopurinol and probenecid. *Ann Rheum Disease*. 1966;25:623-627.

¹² Meyer Lauren et al. Trends in medication utilization and the cost of treatment for gout. *Amer J of Pharmacy Benefits*. May/June 2013. Online publication - https://ajmc.s3.amazonaws.com/_media/_pdf/AJPB_13mayjun_DrugTrends_123to128.pdf



Given the higher drug exposure and reduced efficacy in patients with impaired renal function, the Office of Clinical Pharmacology does not recommend use of lesinurad 200 mg in patients with CrCl \leq 45 ml/min. Clinical review staff concur with this recommendation.

Drug-Drug Interactions

Lesinurad is a substrate of CYP2C9 and when co-administered with fluconazole, a CYP2C9 inhibitor, exposures were increased by 56%. Conversely, co-administration with a CYP29 inducer may decrease exposure and therapeutic effect of lesinurad.

Subgroup analysis of two Phase 3 trials did not show an effect of low dose aspirin (\leq 325 mg) or thiazide diuretics on lesinurad efficacy.

Lesinurad is a weak CYP3A4 inducer and may reduce plasma concentration of sensitive CYP3A4 substrates.

Clinical/Statistical – Efficacy

Please see reviews from Drs. Yim, Neuner, and Wang.

The applicant submitted the results from 3 pivotal trials to support efficacy for the use of lesinurad added on to an XOI. All three were 12-month, randomized, double-blind, placebo-controlled trials. Two of the studies were replicate studies in which lesinurad 200 or 400 mg, added on to allopurinol, were compared to placebo added on to allopurinol (Studies 301 and 302). These two trials did not require the presence of tophi for study inclusion. One study compared lesinurad 200 or 400 mg added on to febuxostat 80 mg to placebo added on to febuxostat 80 mg (Study 304). This trial required that patients have tophaceous gout for study inclusion. The following table from Dr. Wang’s review compares and contrasts the three studies.

Table 1: List of Key Phase 3 Studies in the Clinical Development Program (From Dr. Wang’s review)

	Treatment Period	# of Randomized Subjects per Arm	Study Population
301 (CLEAR 1)	12 month	PBO/LESU200 /LESU400 =203/202/202 with ALLO as background therapy	Inadequate responders to ALLO: -Had a history of at least 2 gout flares in the prior year -Already on a stable medically appropriate dose of ALLO for at least 8 weeks at screening
302 (CLEAR 2)	12 month	PBO/LESU200 /LESU400 =206/204/201 with ALLO as background therapy	-Had sUA levels repeatedly greater than the recommended treatment goal
304 (CRYSTAL)	12 month	PBO/LESU200 /LESU400=109/106/109 with FBX as background therapy	Subjects with: -Tophaceous gout -Elevated sUA

Source: Reviewer

Abbreviations: ALLO, Allopurinol; FBX, Febuxostat.

The primary efficacy endpoint in all three trials was the proportion of patients by Month 6 whose sUA level was below a pre-specified threshold. For Studies 301 and 302, this cutpoint was < 6 mg/dL and for Study 304, the cutpoint was < 5 mg/dL. This lower target threshold was selected because Study 304 enrolled patients with a higher burden of disease (i.e., all patients had tophaceous gout). There were key secondary endpoints which were to capture the clinical impact of reducing sUA. These endpoints included rate of gout flares and proportion of patients with resolution of tophi. Patient reported outcomes assessments were also evaluated as secondary endpoints. All efficacy assessments were evaluated under a pre-specified hierarchical analysis plan as described in Dr. Wang’s review under Section 3.2.3.

Table 2 adapted from Dr. Yim’s and Neuner’s reviews summarizes selected demographics in the three pivotal trials.

Table 2: Selected Demographic and Disease Characteristics of the 3 Pivotal Trials

Demo. or Dis. Characteristic	Study 301 (N=603)	Study 302 (N=610)	Study 304 (N=324)
Age (years), Mean (SD)	52 (11)	51 (11)	54 (11)
Gender			
Male	567 (94%)	587 (96%)	309 (95%)
Female	36 (6%)	23 (4%)	15 (5%)
Race (two most prevalent):			
White	460 (76%)	482 (79%)	259 (80%)
Black	90 (15%)	58 (10%)	35 (11%)
No. Gout Flares in Past 12 Mos			
Mean (SD)	5 (4)	6 (6)	7 (8)
Median	4	4	4
Proportion of Pts with Tophi	87 (14%)	144 (24%)	323 (99.7%)
Baseline sUA (mg/dL)			
Mean (SD)	6.94 (1.27)	6.90 (1.19)	5.27 (1.63)
Proportion Already at Target (<i><6.0 for Studies 301 and 302 or <5.0 for Study 304</i>)	112 (19%)	116 (19%)	163 (50%)
Baseline dose of XOI (mg/d)			
Allopurinol, Mean (SD)	307 (60)	312 (75)	
Febuxostat			80*
Gout Flare Prophylaxis			
Colchicine	504 (84%)	507 (83%)	276 (85%)
NSAID	95 (16%)	110 (18%)	56 (17%)
Baseline Renal Function (ml/min)			
eCrCL \geq90, n (%)	236 (39%)	237 (39%)	110 (34%)
eCrCl <90, n (%)	364 (60%)	371 (61%)	214 (66%)
eCrCL \geq 60, n(%)	474 (79%)	510 (84%)	249 (77%)
eCrCl <60, n (%)	128 (21%)	98 (16%)	75 (23%)
eCrCL \geq 45, n(%)	553 (92%)	586 (96%)	304 (94%)
eCrCl <45, n (%)	47 (8%)	22 (4%)	20 (6%)

*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.

Notable observations of these selected baseline characteristics include:

- Half of the patients in Study 304 had baseline sUA levels below the targeted threshold for assessment of efficacy (<5 mg/dL)
- The majority of patients had baseline renal function \geq 60 ml/min; fewer than a quarter of study subjects had moderate renal impairment at baseline with eCrCL of 30-60 ml/min (patients excluded from trials if eCrCL <30 ml/min at screening)

The following table is from Dr. Yim’s review where she summarized the primary and secondary efficacy results for the two studies evaluating efficacy of lesinurad in combination with allopurinol.

Table 3. Summary Efficacy Results for Studies 301 and 302 (ITT Population) – courtesy of Dr. Yim

	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

*Subjects with missing data at Month 6 were treated as non-responders

In both Studies 301 and 302, treatment with lesinurad 200 or 400 mg in combination with allopurinol resulted in statistically more patients achieving a targeted sUA level of < 6 mg/dL as compared to allopurinol alone. A higher proportion achieved this goal in the lesinurad 400 mg treatment group than lesinurad 200 mg group but the difference was not statistically significant. Table 3 also presented the treatment effect on sUA as change from baseline at Month 1 in observed cases. The mean change from baseline in the lesinurad 200 treatment groups was -1.33 and -1.23 mg/dL in Studies 301 and 302, respectively. The mean reduction was slightly higher in the lesinurad 400 mg dose groups: -1.84 and -1.58 in Studies 301 and 302, respectively. Figure 4 in Dr. Neuner’s review displays the mean change from baseline in observed cases throughout the 12-month treatment period which shows a sustained effect of treatment.

There was no difference across treatment groups in both studies in the rate of gout flares and based on the statistical analysis plan no further testing was to be performed beyond this point. However, for descriptive purposes the findings were summarized in FDA reviews. In the subset of patients with tophi at baseline, a higher proportion of patients in placebo had complete resolution at Month 12 compared to both lesinurad dose groups.

Dr. Yim created a similar table summarizing efficacy in Study 304 which I have copied below.

Table 4: Summary Efficacy Results for Study 304 (ITT Population) – courtesy of Dr. Yim

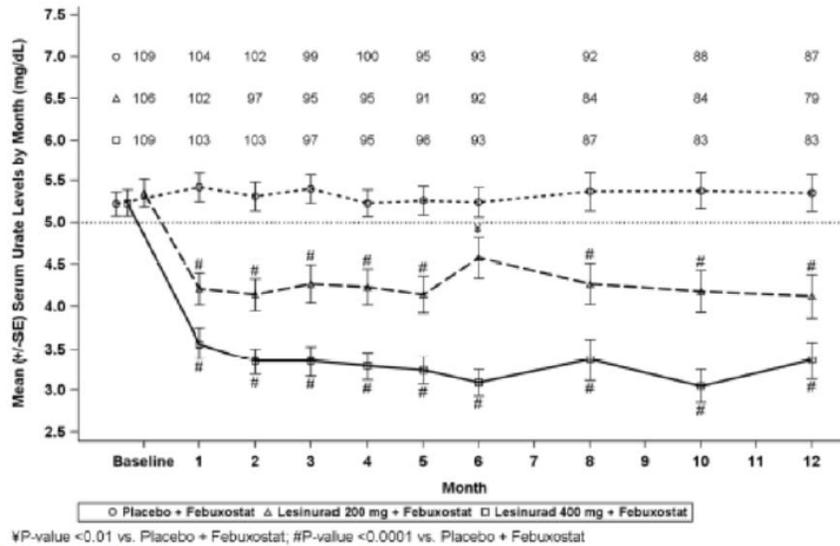
	PBO + FBX 80 mg (N=109)	LESU200 + FBX 80 mg (N=106)	LESU400 + FBX 80 mg (N=109)
sUA: Change from Baseline to Month 1 Observed Cases, n Mean (SD)	104 0.23 (1.26)	102 -1.15 (1.75)	103 -1.62 (1.72)
Primary Endpoint*			
Proportion with sUA <5.0 mg/dL by Month 6 Nonresponder Imputation	51 (47%)	60 (57%)	83 (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

*Subjects with missing data at Month 6 were treated as non-responders

Although both lesinurad doses resulted in a greater proportion of patients achieving a target sUA of < 5 mg/dL by Month 6, a statistically significant difference from placebo was only observed with lesinurad 400 mg dose group. The mean change from baseline in these two doses were comparable to what was observed in Studies 301 and 302. The clinical reviews pointed to the high percentage of patients already at target sUA at baseline as possibly contributing to the difficulty in demonstrating a difference between placebo and lesinurad 200 mg.

Dr. Neuner presented the mean sUA levels over the 12-month treatment course for observed cases and also the proportion of patients achieving different cutpoints of sUA at Months 6 and 12 in Study 304. I have copied these two figures below.

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

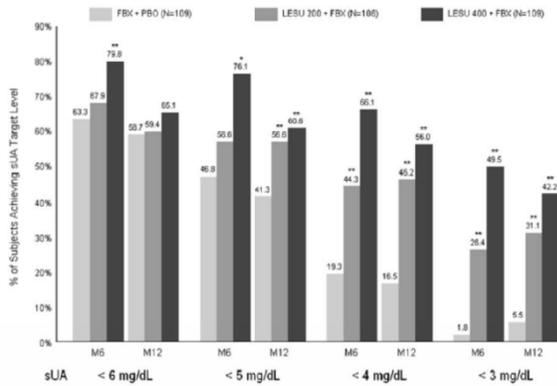


VP-value <0.01 vs. Placebo + Febuxostat, #P-value <0.0001 vs. Placebo + Febuxostat
 Abbreviations: ITT, intent-to-treat; SE, standard error.
 Numbers indicate the number of subjects contributing data at each timepoint. Dotted line indicates target sUA (< 5.0 mg/dL). Statistical significance is based on the difference in least square mean percent change from Baseline.
 Note: Months 7, 9, and 11 data were excluded because the timing of the last protocol amendment (Protocol Amendment 5), which added sUA assessments at these timepoints, resulted in minimal data at these timepoints for analysis.
 Source: Study 304 CSR Table 14.2.1.22.

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

At each time point, there was a significant difference between both doses of lesinurad compared to placebo for mean change from baseline in sUA levels.

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



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

A significant effect on the proportion of patients achieving selected cutpoints in sUA levels was significant across all comparisons to placebo for the lesinurad 400 mg dose group except

Month 12 for the < 6 mg/dL threshold. Although a significant effect was sporadically observed for the lesinurad 200 mg dose group, in all comparisons there was a numerically higher proportion of patients treated with lesinurad 200 mg versus placebo who achieved a sUA level below a specified threshold.

Again, based on hierarchical testing plan, no further tests were to be performed beyond primary efficacy analysis in Study 304. For completeness, Table 4 summarizes these findings which overall showed no difference across the treatment groups on these clinical endpoints.

Conclusions on Efficacy

For the proposed marketed dose of lesinurad 200 mg, two pivotal trials demonstrated a significantly greater proportion of patients achieving targeted sUA levels when lesinurad 200 mg is added-on to allopurinol compared to placebo added-on to allopurinol. In one trial of patients with tophaceous gout, lesinurad 200 mg added on to febuxostat 80 mg resulted in more patients achieving a targeted sUA of < 5 mg/dL compared to placebo but the treatment difference was not statistically significant at Month 6. However, additional efficacy analyses of mean sUA levels measured over the course of the 12-month treatment period showed statistically significantly lower sUA levels achieved with lesinurad 200 mg over placebo when added to febuxostat 80 mg. An effect on reducing the rate of gout flares or resolution of tophi was not demonstrated in any of the pivotal trials.

Safety

Please see Dr. Neuner’s clinical review for a detailed discussion of safety findings in this program. My memo will focus primarily on renal and CV safety. Although the applicant is not seeking a monotherapy indication or proposing to market the lesinurad 400 mg dose, I summarize the safety findings from Study 303 below as it was in this trial that the renal safety concerns were pronounced and led to modifications in safety monitoring for lesinurad (b) (4).

Renal Safety

The most notable difference in adverse events reported between lesinurad and placebo came from the monotherapy Study 303 comparing lesinurad 400 mg once daily to placebo in patients with gout who were intolerant of, or had a contraindication to an XOI. In this trial there were 6 SAEs in the *Renal and Urinary Disorders* SOC/PTs reported in lesinurad treatment versus none in placebo. More patients in the lesinurad group discontinued treatment as a result of an AE in this same SOC/PT compared to placebo. Table 5 summarizes these findings and is adapted from Tables 77 and 78 from Dr. Neuner’s review.

Table 5. SAEs and TEAEs leading to discontinuation in the Renal and Urinary Disorders SOC/PT from Study 303

System Organ Class/Preferred Term	Placebo N = 107	Lesinurad 400 mg QD N = 107
SAEs in Renal and Urinary Disorders	0 (0%)	6 (6%)
-renal failure acute	0	2 (2%)
-calculus ureteric	0	1 (1%)

-renal failure	0	2 (2%)
-renal impairment	0	1 (1%)
Treatment-emergent AEs in Renal and Urinary Disorder	1 (1%)	9 (8%)
-renal failure	0	3 (3%)
-renal failure acute	0	2 (2%)
-renal impairment	0	4 (4%)
-dysuria	1 (1%)	0
-calculus ureteric	0	1 (1%)

The mean baseline sUA in Study 303 was 9.33 mg/dL, substantially higher than the mean baseline value in the combination with XOI studies. The higher UA levels may have contributed to a greater risk of urinary UA load and precipitation exacerbated by the uricosuric effect of lesinurad. As a result of the renal safety findings from Study 303, protocol amendments were put into place for ongoing Phase 3 trials in June 2013.

Dr. Neuner provides a detailed breakdown of different analyses of renal-related adverse events in Section 7.3.5.2 of her review. In the pooled 12-month controlled portion of Studies 301, 302, and 304, which compared the combined use of lesinurad 200 or 400 mg with an XOI to placebo added on to the XOI, the incidence of any renal-related treatment-emergent AE was higher in the lesinurad 400 + XOI treatment group (12%) compared to placebo or lesinurad 200 mg + XOI (5% and 6%, respectively) with blood creatinine increase comprising the majority of these renal-related AEs. Increased blood creatinine AEs were reported between 2 and 8% across the treatment groups whereas other renal-related AEs were reported in no more than 2% of patients. Dr. Neuner delved further on these findings by use of XOI (allopurinol or febuxostat) as summarized in her Table 84 pasted below.

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

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

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

Laboratory abnormalities contributed to the majority of the reported renal AEs. Increased blood creatinine level was reported in more patients treated with lesinurad than placebo in both

databases of XOI combination trials. A dose-related increase was observed in the combined Studies 301 and 302 of lesinurad 200 mg or 400 mg added on to allopurinol but not in the febuxostat combination Study 304. All other events occurred in $\leq 2\%$ of patients and there was little difference in rates across the treatment groups.

Any serious renal AEs by PTs were reported in only the lesinurad 400 mg and placebo treatment groups. See Table 85 from Dr. Neuner’s review and copied below. In the Monotherapy Study 303, the imbalance was marked with 5 vs 0 serious AEs, not favoring lesinurad 400 mg. In the 12-month controlled pooled database of Studies 301, 302, and 304, the incidence of serious renal AEs was numerically higher in the lesinurad 400 mg group (n=5; 0.98%) versus placebo (n=2; 0.39%), but there were very few events to allow any meaningful comparative analysis. No serious renal AEs were reported with the lesinurad 200 mg + XOI treatment.

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

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

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

Dr. Neuner reviewed the CRFs of the serious renal AEs in the placebo and lesinurad 400 mg groups and summarized them in Table 86 of her review. Reflective of the patient population, all the patients had underlying co-morbid medical conditions and/or were on concomitant medication which could have contributed to the serious event. Some patients had a preceding event which might have resulted in the deterioration in renal function. All but one of the 5 patients in lesinurad 400 mg + XOI treatment group who had a serious renal AE had baseline eGFR > 60 ml/min. One of the 5 patients expired with cause of death reported as MACE. The drug was discontinued in the remaining patients and renal function returned to normal in all cases. Dr. Neuner noted similar confounding variables in the patients with serious renal AEs in Study 303 which again occurred in only the lesinurad 400 mg treated patients. Unlike the serious events which occurred in the XOI combination studies, the onset of the event appeared sooner after initiation of therapy suggesting a more pronounced and acute effect when lesinurad was administered as monotherapy in patients with higher baseline sUA levels. For the lesinurad 400 mg + XOI cases, the range of days to onset of serious event was 9 to 255 with an average day to onset of 155 whereas in the lesinurad 400 mg monotherapy cases the range of days to onset was 2 to 111 with the average day to onset of 60.

A more sensitive assessment of renal effects focused on increases in serum creatinine levels. In Table 89, Dr. Neuner summarized the incidence of serum creatinine level increase by >

1.5x, 2.0x, and 3.0x baseline values. In the Monotherapy 303 trial, no placebo-treated patients had an increase in serum creatinine > 1.5x baseline. In contrast 24% of patients in the lesinurad 400 mg group had an increase > 1.5x baseline. In the add-on to XO1 trials, there was a dose-dependent increase in incidence of increased serum creatinine from baseline with 2%, 6%, and 14% of patients reporting an increase > 1.5x in the placebo, lesinurad 200 mg, and lesinurad 400 mg groups, respectively.

Table 89 – Incidence of Serum Creatinine (mg/dL) Elevations by Category in the Pooled, 12-Month, Phase 3, Lesinurad + XO1 Controlled Studies 301, 302, and 304 and the 6-Month, Controlled Monotherapy Study 303

Variable	Pooled 12-M, Studies 301, 302 and 304				6-M, Monotherapy Study 303	
	PBO + XO1 (N=516)	LESU200 + XO1 (N=511)	LESU400 + XO1 (N=510)	Tot. LESU + XO1 (N=1021)	PBO (N=107)	LESU400 (N=107)
sCr Elevation Category:						
sCr ≥ 1.5 x Baseline	12 (2%)	29 (6%)	73 (14%)	102 (10%)	0	26 (24%)
sCr ≥ 2.0 x Baseline	0	9 (2%)	34 (7%)	43 (4%)	0	9 (8%)
sCr ≥ 3.0 x Baseline	0	4 (1%)	12 (2%)	16 (2%)	0	4 (4%)

sCr=serum creatinine. Elevation categories are cumulative: subjects can be counted in more than one category, so percentages can sum to >100%. Baseline is defined as the highest sCr value recorded ≤14 days prior to the first dose of randomized study medication.

Modified Sponsor's Tables 9.1.1.1 and 9.1.1.3; ISS

From Table 6 below, the majority of these patients had resolution of their laboratory abnormalities without study drug interruption (see yellow highlighted numbers in table).

Table 6. Outcome of Increase Serum Creatinine Levels > 1.5x Baseline in Pooled 12-month Studies 301, 302, and 304 (adapted from Table 90 in Dr. Neuner's review)

	Pbo + XO1	Lesinurad 200 + XO1	Lesinurad 400 + XO1
Total # of Serum Cr Elevations >1.5x	12	30	97
-# resolved after study drug discontinuation	0	7/30 (23%)	16/97 (17%)
-# resolved <u>without</u> study drug discontinuation	9/12 (75%)	20/30 (67%)	64/97 (66%)
Time to Resolution:			
1-14 days	1 (8%)	9 (30%)	13 (13%)
>14-28 days	1 (8%)	3 (10%)	21 (22%)
>28-56 days	3 (25%)	10 (33%)	25 (25%)
>56-84 days	2 (17%)	2 (7%)	10 (10%)
>84 days	2 (17%)	3 (10%)	11 (11%)
Unresolved at Last Assessment	3 (25%)	3 (10%)	17 (18%)

There were no placebo-treated patients with serum creatinine elevations > 2x baseline. There were 9 and 40 patients in the lesinurad 200 and 400 mg groups, respectively, with elevations > 2x baseline. The majority of these patients (8 and 32, respectively) had resolution of

laboratory abnormalities, most without interruption of study medications (see yellow highlighted numbers in Table 7). Only 1 patient in the lesinurad 200 mg dose group and 8 in the lesinurad 400 mg dose group had unresolved lab abnormality at last assessment. Recall that no serious renal-related AEs were associated with lesinurad serum creatinine increases, including this one patient with unresolved serum creatinine increase.

Table 7. Outcome of Increase Serum Creatinine Levels > 2x Baseline in Pooled 12-month Studies 301, 302, and 304 (adapted from Table 90 in Dr. Neuner’s review)

	Pbo + XOI	Lesinurad 200 + XOI	Lesinurad 400 + XOI
Total # of Serum Cr Elevations > 2x	0	9	40
-# resolved after study drug discontinuation	NA	2/9 (22.2%)	9/40 (22.5%)
-# resolved <u>without</u> study drug discontinuation	NA	6/9 (66.7%)	23/40 (57.5%)
Time to Resolution:			
1-14 days	NA	5 (56%)	7 (18%)
>14-28 days		0	10 (25%)
>28-56 days		1(11%)	8 (20%)
>56-84 days		0	5 (13%)
>84 days		2 (22%)	2 (5%)
Unresolved at Last Assessment	NA	1 (11%)	8 (20%)

There were two patients receiving lesinurad 200 mg who experienced serious renal AEs during the open-label extension treatment periods. Table 87 from Dr. Neuner’s review summarizes the events and additional workup. Both patients had other confounding variables and risk factors that could contribute to renal failure requiring dialysis.

Conclusions on renal safety

There were findings of renal toxicity associated with lesinurad in this NDA review. In particular, the 400 mg dose administered as monotherapy in patients with a contraindication or intolerant to XOIs was associated with a higher risk of renal AEs, including cases of renal failure. For this reason, the applicant is only pursuing marketing of lesinurad 200 mg and only as add-on therapy to an XOI. The following language is being proposed in a boxed warning:

WARNING: INCREASED RISK OF ACUTE RENAL FAILURE, MORE COMMON WHEN USED WITHOUT A XANTHINE OXIDASE INHIBITOR

See full prescribing information for complete boxed warning.

- Acute renal failure has occurred with ZURAMPIC and was more common when ZURAMPIC was given alone.
- ZURAMPIC should be used in combination with a xanthine oxidase inhibitor. (1.1, 5.1, 6.1)

The absence of any serious renal AE and the low incidence of serum creatinine increase during the controlled periods for lesinurad 200 mg + XOI are reassuring. However, there were only 89 patients with baseline CrCl below 45 ml/min and 301 patients with baseline CrCl below 60 ml/min. These patients may be at greater risk for renal toxicity related to lesinurad or, at a minimum, are more vulnerable to drug-related toxicities. Additional studies in patients with renal impairment will be necessary to better characterize the safety of lesinurad and will be required under FDAAA. For now, with adequate labeling for baseline and on-treatment renal monitoring and restrictions on use in patients with renal impairment, I believe this dose and indication can be approved.

CV safety

An independent adjudication committee was established to adjudicate CV events in a blinded fashion from the controlled Phase 3 trials and ongoing, long-term extension periods of Phase 2 and 3 studies. The table below is excerpted from Drs. Neuner's and Yim's review. There was a higher number of MACE (n=8) experienced by subjects in lesinurad 400 mg dose group compared to placebo (n=3). I do not believe there is a large enough difference between lesinurad 200 mg and placebo (4 vs 3) to conclude an excess risk with this proposed dose for marketing.

Concerns raised about the CV safety of this drug appear to focus on the higher incidence rate in the 400 mg dose group and the overall low event rate does not afford us sufficient data to conclude that the 200 mg dose group is absent any CV risk. However, I do not believe the CV safety findings are sufficient to require a CVOT as a pre-marketing or post-marketing trial. Unlike the renal safety concern, there was no other signal from non-clinical or negative effect of lesinurad on CV biomarkers such as lipids or blood pressure to support an argument that the imbalances in CV events of single digits can be attributed to drug. In fact, if we are to require such a trial based on these events, I would have to wonder whether we should ignore the finding of 3 nonfatal strokes occurring in the placebo group, as there was a signal not favoring placebo on these events.

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

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

PY= Patient years; CI = Confidence interval

Treatment-emergent AEs are those that started on or after the first randomized study medication dose date, or those that started prior to the first randomized study medication dose date but worsened during the double-blind treatment period of the study. Subjects with multiple events can be counted in more than one category. MACE events include CV death, non-fatal MI, and non-fatal stroke.

¹Unique number of subjects in safety population

²Person-year = (date of completion/discontinuation - date of first dose of study drug +1)/365.25.

³Incidence rate= number of subjects with MACE events per 100 person-years.

⁴The 95% confidence intervals are based on Poisson regression.

⁵Incidence rate = number of MACE events per 100 person-year.

Adapted Sponsor's Table 16.2.1 Ad Hoc IAS

Conclusions on CV safety

In conclusion, there were too few MACE to make a definitive conclusion on CV safety; however, the signal based on imbalances of some single digit CV events and the absence of signals from other data sources do not support a CVOT requirement. I do acknowledge the desire of several AC members and FDA reviewers for more data on CV safety and would require that CV events be adjudicated as additional safety assessment in the required renal safety trial.

Advisory Committee Meeting

Please see Section 9 of Dr. Yim's review for the voting results and summary discussion at the October 23, 2015 advisory committee meeting. I would like to highlight the following regarding the discussion points/voting results.

The committee was asked if 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. To this voting question there was a unanimous vote 'yes' (14 vs 0). I believe this vote and the discussions that followed support the continued reliance on sUA levels as a surrogate for approval of ULTs.

The committee was then asked to vote on whether the safety profile of lesinurad 200 mg once daily was adequate to support approval of lesinurad for the treatment of hyperuricemia

associated with gout in combination with a xanthine oxidase inhibitor. To this question there was a near split vote with 7 voting ‘yes’, 6 voting ‘no’, and 1 abstention.

The final voting question was whether the committee would 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. To this question there was a majority 10 votes ‘yes’. Four voted ‘no’ and there were no absentions.

Unlike the voting results on benefit, I believe that the voting results AND discussions surrounding these last two questions reflect the uncertainty in risks identified in this program. Interpretation of these voting results and discussion points are also open to interpretation depending on which side of the equation of approval/non-approval one takes. As I am recommending approval, I did review statements made by panel members at the AC meeting who recommended against approval or had expressed reservations despite their recommendation for approval. Interestingly, none of these statements requested a cardiovascular outcomes trial. I have taken into consideration the concerns raised in these excerpts in my final recommendation for approval and the type of PMR to be conducted.

Pediatrics

A full waiver was granted for pediatric study requirements as the indication is limited to the adult population.

Benefit-Risk Assessment

The benefit of lesinurad was assessed by a surrogate measure – serum uric acid level. Serum uric acid level is relied upon in clinical practice as part of the evaluation of a patient with gout; it is monitored during the treatment of gout; and targeted goals of sUA levels are recommended by U.S., British, and European treatment guidelines for the management of gout. FDA has accepted sUA level as the primary efficacy endpoint for approval of treatments for hyperuricemia associated with gout based on recommendations from an FDA meeting involving the Arthritis Advisory Committee held in June 2004. These recommendations are based on the following:

- Hyperuricemia, either through overproduction or underexcretion, is the underlying cause for gout
- There is an increased risk of monosodium urate crystal formation and deposition in the articular, periarticular, and subcutaneous tissues leading to clinical manifestations of gout such as acute attacks of gouty arthritis, chronic gouty arthropathy, and tophaceous gout with increasing levels of sUA; and
- Long-term cohort studies have demonstrated an improvement on clinical disease with the lowering of sUA levels in patients with gout

Although a surrogate endpoint is a substitute for a direct measure of clinical benefit, no therapies for the treatment of hyperuricemia associated with gout have been required to demonstrate a statistically significant effect on clinical outcomes because of the duration of

trials necessary to evaluate such a treatment effect. With exception for pegloticase, which is reserved for patients who have failed conventional gout therapies given the risks of immunogenicity, anaphylaxis and serious infusion reactions, no approved therapies for hyperuricemia associated with gout have a labeled claim for reducing the number of acute gout attacks or resolution of tophi.

I am not aware of any recent data that call into question serum uric acid level as a surrogate for approval of ULTs to treat gout. Furthermore, the advisory committee panel for this application was asked whether “*the data provided 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 an XOI*”. The unanimous ‘yes’ (14 vs 0) vote would also suggest that nothing from this clinical development program has challenged the surrogacy of sUA.

However, as with any approval decision based on a surrogate, the absence of a direct measure of clinical benefit makes the benefit-risk calculus difficult when a safety issue arises. I believe this is at the crux of the recommendation made by Drs. Levin, Davi, and Permutt.

From this NDA, there is uncertainty in risk with lesinurad 200 mg which arose out of safety findings from Study 303 which compared lesinurad 400 mg to placebo in patients who are intolerant of or have a contraindication to xanthine oxidase inhibitors. The safety concern in this trial was primarily renal, which carried over into the 400 mg treatment group in Studies 301, 302, and 304 – trials which evaluated the combined use of lesinurad with an XOI. Based on the mechanism of action of the drug and the notable imbalances between drug and placebo in Study 303, renal toxicity of lesinurad cannot be dismissed as spurious. The renal safety findings for the proposed marketed dosing regimen of lesinurad 200 mg once daily in the controlled portion of this program were predominantly laboratory abnormalities and none resulted in serious clinical sequelae. However, the program did not enroll a very large number of patients with renal impairment. For example, in the pivotal trials there were only 89 patients with baseline CrCL 30 to 45 ml/min; approximately 300 had CrCl < 60 ml/min. The applicant will be required to evaluate long-term renal safety as a condition of this approval and such a study will need to enroll more patients with baseline renal impairment.

There were also imbalances in CV events and death not favoring lesinurad. Like the renal events, there were very few events across the different treatment groups; however, unlike renal safety, a mechanistic plausibility was not identified for excess CV risk or mortality and the imbalance for these events may represent a spurious finding for a population with co-morbid risk factors for such events. Although I would not conclude absence of CV risk, I do not believe there is sufficient evidence to tip the benefit-risk scale based on the CV safety findings and would not require additional studies solely on those findings.

Several members from the advisory committee expressed concern on the lack of longer term studies including an excerpt from Dr. Beth Jonas:

“My primary concern is that we don’t have longer-term studies and that there is some concern primarily about renal insufficiency, and that gave me cause to worry about safety in that population.”

Dr. Levin also included excerpts from AC members in his memo that also captured similar sentiments as those of Dr. Jonas's. I also note that while Dr. Levin's first recommendation is to issue a Complete Response recommendation for this application, he is also willing to accept an approval with a PMR.

I concur that longer-term studies with lesinurad is desirable and necessary to better understand the benefits-risk of this drug in the gout patient population. However, I do not believe this study must be done pre-approval and that approval can be granted provided there is labeling that clearly communicates the risk of renal toxicity and minimizes use to the population that has a lower risk of renal toxicity. The PMR will be a 24-month trial of lesinurad 200 mg in a population of patients not yet achieving target sUA goal on an XOI. The study population will be patients with moderate renal impairment with CrCl of 30 to 60 ml/min. The primary objective will be to evaluate renal safety although other endpoints including CV safety and efficacy measures will be obtained. Details of the trial will require further discussion, including choice of comparators. Consideration will be given for a placebo and active control arm with probenecid.

Probenecid is the only available uricosuric and current treatment guidelines for its use are comparable to the proposed indication for lesinurad. Despite its low costs and familiar risk profile, its utilization is quite low for reasons that are unclear. In my review of this application, which included a literature search of available therapies for gout, I am struck by the limited number of RCTs of available therapies for such a highly prevalent condition whose clinical description has been well-described as fall back as ancient times. Indeed, the treatment guidelines are based more on clinical experience than well-controlled experiments. A study comparing the long-term safety (and efficacy) of lesinurad to probenecid will not only better inform us on the safety of this drug but may also inform the scientific community on future treatment guidelines for gout.

Labeling

Please see approved label attached with action letter.

The Indications and Usage is for patients who have failed to achieve target sUA levels despite maximally tolerated XOIs. The population will also be limited to only those with CrCl \geq 45 ml/min. All patients will need to have baseline renal function tests and while on treatment with emphasis on closer monitoring in patients with CrCl $<$ 60 ml/min. There will also be a Boxed Warning regarding the renal safety, noting that the increased risks were highest in patients who received lesinurad as monotherapy.

Risk Evaluation and Mitigation Strategies

None

Postmarketing Requirements and Commitments

A 24-month renal safety trial will be required under FDAAA.

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/s/

MARY H PARKS
12/22/2015