CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207988Orig1s000

SUMMARY REVIEW

SUMMARY REVIEW OF REGULATORY ACTION

Date:	November 23, 2015
From:	Badrul A. Chowdhury, MD, PhD Director, Division of Pulmonary, Allergy, and Rheumatology Products, CDER, FDA
Subject:	Division Director Summary Review
NDA Number:	207988
Applicant Name:	Ardea Biosciences
Date of Submission:	December 29, 2014
PDUFA Goal Date:	December 29, 2015
Proprietary Name:	Zurampic
Established Name:	Lesinurad
Dosage form:	Tablet
Strength:	200 mg
Proposed Indications:	Treatment of hyperuricemia associated with gout in combination with xanthine oxidase inhibitor
Action:	Approval, pending finalized labeling, and outcome of CDER regulatory briefing scheduled for December 11, 2015

1. Introduction

Ardea Biosciences submitted this 505(b)(1) NDA to support approval of the use of lesinurad tablet at a dose of 200 mg once daily in combination with a xanthine oxidase inhibitor for the treatment of hyperuricemia associated with gout. This summary review provides an overview of the application with emphasis on the clinical section.

2. Background

Gout is an inflammatory arthritis associated with hyperuricemia and caused by the deposition of monosodium urate crystals in and around the tissues of joints and soft tissues, urate nephropathy, and nephrolithiasis. Symptomatic crystal deposition includes attacks of acute inflammatory arthritis, a chronic destructive arthropathy, and soft tissue accumulation of monosodium urate crystals (tophi). The prevalence of gout has been increasing over the past few decades, and has been recently estimated to affect approximately 3.9% of adults in the United States (8.3 million)[1]. The condition affects primarily middle-aged and older men and post-menopausal women. Obesity, hyperlipidemia, diabetes, hypertension, chronic renal insufficiency, metabolic syndrome, and cardiovascular disease are frequent comorbidities in patients with gout.

The course of gout is characterized by acute attacks of gouty arthritis alternating with attack-free periods of intercritical gout. A typical gouty arthritis attack (or gout flare) is

[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.

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. During initiation of uric acid lowering therapy for long-term management of gout (see paragraph below), patients are at increased risk of acute gouty attacks. It is common practice to use an agent to help reduce the frequency and severity of acute gout attacks during initiation of uric-acid lowering therapies. To this end, maintenance doses of either colchicine or an NSAID are continued; 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.

Chronic management of gout is founded upon control of hyperuricemia, as this approach targets the underlying pathology of the disease. The approaches to lower serum uric acid include the following:
(1) Lowering uric acid production, which is currently the most common approach of chronic management of gout. Drugs in this class include xanthine oxidase inhibitors, such as allopurinol, and febuxostat.
(2) Increasing urinary uric acid excretion (uricosurics) by inhibiting active renal reabsorption of uric acid through urate transporters in the proximal renal tubule epithelial cells (predominantly URAT1), resulting in increasing uric acid excretion. Drugs in this class include probenecid.
(3) Direct enzyme breakdown of uric acid by uricase into more soluble allantoin, which can be excreted in the urine. Human do not have endogenous uricase, therefore, animal derived proteins have been developed for human use. Drugs in this class include pegloticase and rasburicase.

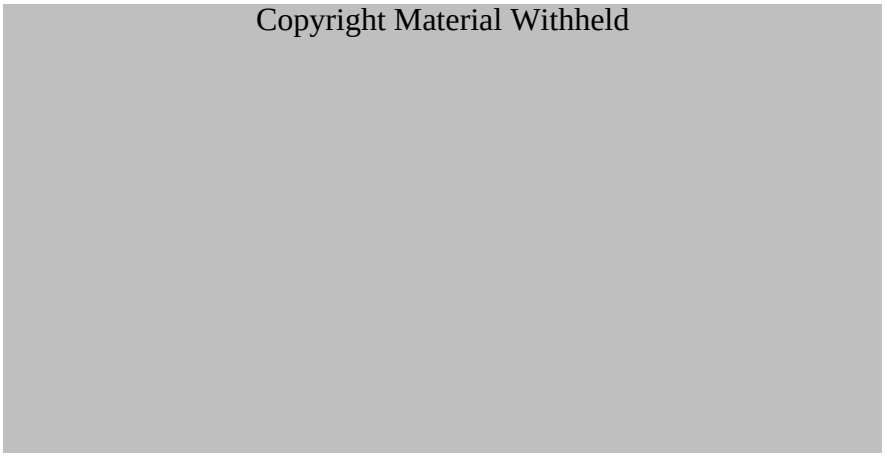

Figure 1. Schematic of lesinurad in current treatment options of gout (Source, Applicant submission)

Lesinurad, the subject of this NDA, is proposed to act by increasing uric acid excretion by inhibiting active renal reabsorption of uric acid primarily by inhibition of URAT1. The basic mechanism of lesinurad is similar to probenecid.

The current options for gout treatment are shown in Table 1. The approved doses of these agents, particularly allopurinol, and the major efficacy and safety considered of these products are relevant to place the lesinurad efficacy and safety data (discussed in section 7 and section 8 below) in context.

Table 1. Current treatment options for gout

Products	Approved Dosing	Efficacy and Safety
First Line Treatment: Xanthine Oxidase Inhibitors (XOI)		
Allopurinol	100-800 mg per day BID dosing for >300 mg/day	Efficacy: ~ 2- 3.5 mg/dL mean ↓sUA at 300 mg dose Safety: hypersensitivity reactions, cutaneous reactions, GI intolerance
Febuxostat	40-80 mg QD	Efficacy: ~ 4.5 mg/dL mean ↓sUA at 80 mg dose Safety: ↑LFT, skin rash, possible CV risk
Second Line Treatment: Uricosuric Agents		
Probenecid	500-1000 mg BID	Efficacy: ~ 2.9 mg/dL mean ↓sUA at 1.3 g/day dose Safety: nephrolithiasis
Third Line Treatment: Uricase		
Pegloticase	8 mg IV every 2 weeks	Efficacy: ~ 6.8 mg/dL mean ↓sUA Safety: anaphylaxis, infusion reaction, exacerbation of CHF
Source: Febuxostat NDA at Drugs@FDA (for allopurinol and febuxostat), Pegloticase NDA at Drugs@fda (for Pegloticase); Pui et al, J Rheum 2013 (for probenecid)		

Regulatory interaction between the Agency and Ardea Biosciences:

The Division and Ardea Biosciences had typical milestone meetings on lesinurad that included an End-of-Phase 2 meeting in July 2011, a general advice meeting (written feedback) in February 2014, and Pre-NDA meeting in September 2014. At the End-of-Phase 2 meeting and subsequent general advice meeting, there was an agreement on the primary endpoint of proportion of patients achieving a serum uric acid reduction to less than 6 mg/dL. The Agency raised concerns with renal adverse events and MACE related adverse events, particularly with lesinurad monotherapy and at high doses of lesinurad. The Agency raised questions about the justification of once-daily dosing regimen and whether a twice-daily dosing regimen would allow for a lower nominal dose. The Agency also expressed concern with using suboptimal dose of allopurinol in the studies. At the Pre-NDA meeting, the content and format of the NDA was discussed, and concerns raised about safety and dosing that were raised at earlier meetings were reiterated. The Agency noted that it was unclear whether Risk Evaluation and Mitigation Strategies (REMS) would be sufficient to address the identified safety concerns with high doses of lesinurad.

3. Chemistry, Manufacturing, and Controls

The proposed commercial drug product, Zurampic tablets, contains 200 mg of lesinurad and standard compendial excipients. The drug product will be packaged as bottles of 5, 30, or 90 tablets. The manufacturing processes for the drug substance and drug product are traditional and standard with no unique features. All manufacturing and testing facilities associated with this application have acceptable inspection status. The various DMFs associated with the manufacture of the product are adequate or do not require review due to adequate information in the NDA. An expiry of 36 months is proposed and supported by submitted data.

4. Nonclinical Pharmacology and Toxicology

The non-clinical development program for lesinurad consisted of toxicology studies in rats and monkeys, standard genotoxicity assays, carcinogenicity studies, and reproductive toxicology studies. The target organs of toxicity in rats and monkeys included the kidney and the GI tract. In rats, the dose of 600 mg/kg/day (119 x clinical exposure) was lethal due to kidney toxicity (tubular degeneration and single cell necrosis) and gastrointestinal toxicity (erosion, hemorrhage, congestion, single necrosis). At the dose of 300 mg/kg/day (36 x clinical exposure), kidney findings were limited to tubular dilatation and changes of clinical chemistry parameters. Low incidences of GI tract erosion were also observed. In 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.

Lesinurad was negative in standard genotoxicity assays. There was no evidence of tumorigenic potential in a 2-year carcinogenicity study in rats and in a 26-weeek carcinogenicity study in transgenic mice. In reproductive toxicology studies, fertility and reproductive performance were unaffected in rats, and there was no evidence of teratogenicity or other embryo-fetal developmental toxicity in rats or rabbits. There were decreases in pup viability and body weight as well as developmental delays in the pre-and post-natal development study in rats that may have been influenced by maternal toxicity.

Human subjects were found to form a didhydrodiol metabolite, termed M4, at 20.7% of total systemic drug exposure. The M4 metabolite was formed in humans by an epoxide intermediate termed M3c. Epoxide functional groups are known structural alerts for mutagenicity. Monkeys had evidence of forming the M3c metabolite; the epoxide metabolite was qualified for safety in the 12-month toxicology study in monkeys. Although the metabolite was not qualified for safety with respect to carcinogenicity, no additional nonclinical studies were required. Some concern with regard to the potential carcinogenic effects of M3c may be mitigated by its transient nature and the fact that, in humans, this molecule is detoxified to a didhydrodiol (M4).

The nonclinical team is the lead discipline in the determination of the Established Pharmacologic Class (EPC) of a product. Lesinurad decreases the reabsorption of uric acid from the renal proximal tubule by inhibiting the function of the transporters URAT1 and OAT4, located on the apical surface of renal tubular epithelial cells. Like probenecid, lesinurad also inhibits the in vitro function of OAT1 and OAT3 (transporters responsible for uric acid secretion). The nonclinical team agrees with the Sponsor's proposal to use URAT1 inhibitor as the EPC given that URAT1 is the principal transporter responsible for uric acid reabsorption in humans.

5. Clinical Pharmacology and Biopharmaceutics

Ardea Biosciences submitted results from a comprehensive clinical pharmacology program that included studies to assess the pharmacokinetics and metabolism of the drug product.

The absolute bioavailability of lesinurad is approximately 100% after oral dosing with no significant food effect with Cmax occurring within 1 to 4 hours. Lesinurad is extensively bound to plasma proteins (greater than 98%), mainly to albumin. Lesinurad undergoes oxidative metabolism mainly via CYP2C9. Elimination of lesinurad is through urine (over 60%) and feces (approximately 30%). Patients with renal impairment have increased lesinurad exposure, approximately 31%, 50-73%, and 113%, with mild, moderate, and severe renal impairment, respectively. Hepatic impairment has about 7% and 33% increased exposure with mild and moderate impairment, respectively. In various drug interaction studies, the findings of note were increased lesinurad exposure with inhibitors of CYP2C9, and reduced plasma concentration of CYP3A4 substrates with lesinurad.

Dose dependent decrease in serum uric acid was seen with lesinurad doses studied that ranged from 100 mg to 600 mg once daily. Ardea Biosciences proposed 200 mg once daily as the proposed dose primarily because of renal adverse effects with 400 mg once daily dose. Although pharmacokinetic data is suggestive of more frequent dosing, such as twice daily, Ardea Biosciences proposed once daily dosing primarily to avoid uric acid urolithiasis that may be associated with evening dosing. Exposure data with 200 mg and 400 mg once daily dosing from phase 3 studies showed that mean exposure was higher with higher lesinurad dose, but there was substantial overlap of exposure between the two dose groups. This raises the question of whether a lower nominal dose given twice daily may have provided similar efficacy with a better safety profile.

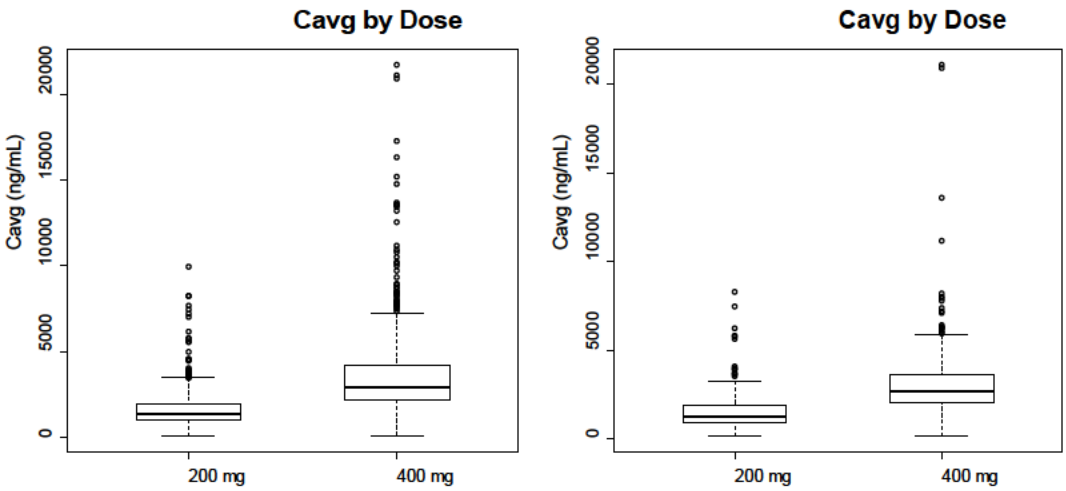

Figure 2. Exposure to lesinurad in phase 3 studies shown as box and whisker plots. Left panel shows exposure data from all patients for all studies (studies 301, 302, 303, and 304). Right panel shows exposure data from patients with normal renal function in studies on background xanthine oxidase inhibitors (studies 301, 302, and 304).

6. Clinical Microbiology

Not applicable.

7. Clinical and Statistical – Efficacy

a. Overview of the clinical program

Some characteristics of the relevant clinical studies that form the basis of the review and regulatory decision for this application are shown in Table 2. The design and conduct of these studies are briefly described below, followed by efficacy findings and conclusions. Safety findings are discussed in the following section.

Table 2. Relevant clinical studies

ID Year *	**Study Characteristics †** - **Patient age, mean (range)** - **Patient characteristics** - **Study duration**	**Treatment groups ‡**	**N**	**Primary efficacy variables**	**Countries**
Pivotal Efficacy and Safety Studies – lesinurad with background allopurinol 300 mg QD or lower					
301 [02/12 - 07/14]	- 52 (22-81) yr - sUA ≥6.5 mg/dL despite being on at least 300 mg QD allopurinol for ≥8 weeks, and ≥ 2 gout flares in prior year - 12 month	Les 200 mg QD+Allo Les 400 mg QD+Allo Placebo + Allo	201 201 201	Proportion of patients achieving serum uric acid <6.0 mg/dL at month 6	US (100%)
302 [12/11 - 07/14]	- 51 (21-82) yr - sUA ≥6.5 mg/dL despite being on at least 300 mg QD allopurinol for ≥8 weeks, and ≥ 2 gout flares in prior year - 12 month	Les 200 mg QD+Allo Les 400 mg QD+Allo Placebo + Allo	204 200 206	Proportion of patients achieving serum uric acid <6.0 mg/dL at month 6	US (51%), Canada, Europe, Australia, New Zealand, South Africa
Pivotal Efficacy and Safety Studies – lesinurad monotherapy					

ID Year *	Study Characteristics † - Patient age, mean (range) - Patient characteristics - Study duration	Treatment groups ‡	N	Primary efficacy variables	Countries
303 [02/12 - 10/13]	- 54 (25-82) yr - sUA ≥6.5 mg/dL, intolerance or contraindication to treatment with XOI - 12 month	Les 400 mg QD Placebo	107 107	Proportion of patients achieving serum uric acid <6.0 mg/dL at month 6	US (73%), Canada, Europe, Australia, New Zealand, South Africa
Pivotal Efficacy and Safety Studies – lesinurad with background febuxostat 80 mg QD					
304 [02/12 - 04/14]	- 54 (22-82) yr - sUA ≥8 mg/dL for those on no ULT or ≥6 mg/dL for those on ULT, and ≥1 tophus - 12 month	Les 200 mg QD+Fbx Les 400 mg QD+Fbx Placebo + Fbx	106 109 109	Proportion of patients achieving serum uric acid <5.0 mg/dL at month 6	US (75%), Canada, Europe, Australia, New Zealand
Safety Studies					
305	- Open OLE of study 303; terminated based on renal safety	Les 400 mg QD	143	Safety (Les monotherapy)	
306	- Ongoing OLE up to 30 month of study 301 and study 302	Les 200 mg QD+Allo Les 400 mg QD+Allo	361 353	Safety (Les with allopurinol)	
307	- Ongoing OLE up to 30 month of study 304	Les 200 mg QD+Fbx Les 400 mg QD+Fbx	97 99	Safety (Les with febuxostat)	

* [Month/year study started-completed]
† sUA = Serum uric acid, XOI = xanthine oxidase inhibitor, ULT = urate lowering therapy, OLE = open label extension
Les = Lesinurad; Allo = Allopurinol. Fbx: febuxostat
§ Number randomized

b. Design and conduct of the studies

The pivotal Studies 301, 302, 303, and 304 assessed efficacy and safety of lesinurad in patients with differing disease characteristics and differing background treatments as shown in Tables 2 and 3. Patients in Studies 301 and 302 were on background allopurinol at least 300 mg/day (200 mg/day in patients with estimated renal clearance of less than 60 ml/min), and patients in Study 304 were on background febuxostat 80 mg/day. Patients in Study 303 had intolerance or contraindication to treatment with a xanthine oxidase inhibitor, and lesinurad was used as monotherapy (the lesinurad monotherapy treatment option was later dropped by Ardea Biosciences because of renal safety concerns). The study design and conduct are shown in Table 2 and Figure 3. In all studies patients received gout flare prophylaxis with colchicine or NSAIDs. Patients were instructed to take lesinurad at the same time as the morning dose of xanthine oxidase inhibitor (Studies 301, 302, and 304) with at least 8 oz or 240 mL of water. In a later protocol amendment patients were instructed to stay well hydrated (68 oz or 2 L of liquid per day) as a precautionary measure for renal safety. The primary efficacy variable in all studies were the proportion of patients with sUA (serum uric acid) <6 mg/dL (Studies 301, 302, and 303) or <5 mg/dL (Study 304) by month 6. Secondary efficacy variables protected for multiplicity were gout flares requiring treatment from end of month 6 to end of month 12 (Studies 301 and 302), complete resolution of ≥1 target tophus by month 12 (Studies 301, 302, and 304), complete or partial (≥50%) resolution of ≥1 target tophus by month 12 (Study 304), and improvemnt from baseline in HAQ-DI of least 0.25 at month 12 (Study 304).

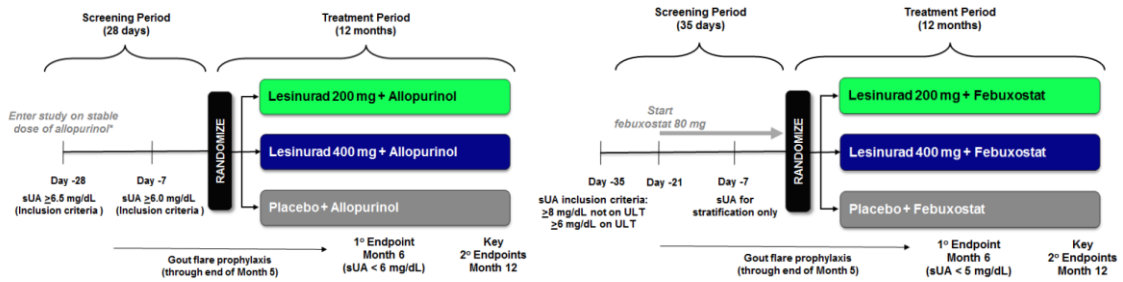

Figure 3. Study design for Studies 301 and 302 (add-on to allopurinol) in left panel, and for Study 304 (combination with febuxostat) in right panel [Source: Ardea Biosciences Advisory Committee briefing document]

c. Efficacy findings and conclusions

The submitted data from the clinical program support efficacy of lesinurad at a dose of 200 mg once daily dosed in the morning in combination with a xanthine oxidase inhibitor for the treatment of hyperuricemia associated with gout.

Dose and dosing schedule:

In the early development program, a range of doses was explored. Doses of 25 mg or less had essentially no sUA lowering effect, and the efficacy of the100 mg dose was not sustained over 24 hours. Doses of 200, 400, and 600 mg resulted in sustained sUA reduction over 24 hours. In lesinurad monotherapy studies, 400 and 600 mg seemed to be effective, but the 200 mg dose had minimum effect. In the lesinurad combination studies with xanthine oxidase inhibitors, all three doses were effective, but there was no incremental benefit with the 600 mg dose over the 400 mg dose. Based on these findings, Ardea Biosciences carried forward the 200 mg and 400 mg doses into the pivotal studies (Table 2), which is reasonable. In the phase 3 studies (described below), lesinurad 400 mg monotherapy was associated with higher rates of renal adverse events, which is the reason Ardea Biosciences is not pursuing the 400 mg dose or monotherapy with lesinurad any further.

The once daily dosing frequency is based on the observation from earlier studies that lesinurad increased maximum urinary uric acid excretion within 6 hours following dosing. The once daily morning dosing was the only dose studied in the pivotal studies with the justification to avoid high urinary acid concentration during nighttime when urine pH and urine volume is low, thereby reducing the risk of urinary uric acid precipitation and risk of stone formulation. This justification seems reasonable.

Efficacy findings:

Patients enrolled in the studies were typical of gout program with longstanding symptomatic gout with elevated sUA levels (Table 3).

In patients with gout receiving background allopurinol (Studies 301 and 302), a significantly higher proportion of patients in both lesinurad treatment groups achieved the primary target sUA by month 6 compared to placebo (Table 4). For the proposed dose of

200 mg, approximately 30% more patients reached the target sUA in both studies. In patients with gout receiving background febuxostat (Study 304), although a higher proportion of patients in both lesinurad treatment groups achieved the primary target sUA by month 6 compared to placebo, the difference for the proposed dose of 200 mg was 10% and not statistically significant. However, in this study, approximately 50% of patients had already reached the target sUA with a three week run-in period of febuxostat before adding lesinurad, and thus had less room for further benefit. Secondary efficacy variables were generally not supportive of a beneficial response of lesinurad and some of the responses seemed to benefit placebo over lesinurad (Table 4). The secondary efficacy measures, some of which, particularly gout flares, are direct measures of clinical benefit, were not considered pivotal for demonstration of efficacy partly because studies lasting up to 12 months are not considered to be sufficient in duration to assess such benefits. Data estimating the magnitude of long-term benefit in these direct measures that should be expected based on specific changes in serum uric acid are not available. A target serum uric acid level of 6 mg/dL or lower is the recommended goal of urate lowering therapy in widely accepted gout treatment guidelines issued by the professional societies such as the American College of Rheumatology (ACR),[2] and the European League Against Rheumatism (EULAR).[3]

Although both the 200 mg and 400 mg doses of lesinurad achieved the primary target level of sUA more frequently than placebo and the 400 mg dose was numerically superior to the 200 mg dose, Ardea Biosciences is proposing the 200 mg dose in combination with xanthine oxidase inhibitor because of renal safety concerns with the 400 mg dose (discussed further in section 8). For the same renal safety concerns, monotherapy with lesinurad is also not proposed. The dose of allopurinol used in these studies was 300 mg per day, which is less than the labeled highest dose of allopurinol. Ardea Bioscience's reasoning for using this lower dose of allopurinol was that because of safety concerns allopurinol is generally not used in clinical practice at doses higher than 300 mg per day.

Table 3. Summary of key baseline characteristics for the pivotal studies

	Study 301 Add-on allopurinol			**Study 302** Add-on allopurinol			**Study 303** Monotherapy		**Study 304** Add on febuxostat		
	Les 200	Les 400	Pbo	Les 200	Les 400	Pbo	Les 400	Pbo	Les 200	Les 400	Pbo
Duration since gout diagnosis (years)											
	13	11	12	12	11	11	11	11	16	13	15
Number of gout flares in past 12 months (mean)											
	4.8	4.9	4.8	6.7	6.1	5.8	6.2	6.2	6.9	7.0	6.1
Tophi at baseline (mean number of target tophi)											
	1.8	2.1	1.8	2.0	2.5	2.2			1.8	1.8	1.9
Renal function (% of patients)											
Cr Cl <90	58	62	61	61	57	65	59	59	65	62	72
Cr Cl <60	22	20	20	14	15	19	16	20	26	20	23

[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 & Research, October 2012; 64(10):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.

	Study 301 Add-on allopurinol			Study 302 Add-on allopurinol			Study 303 Monotherapy		Study 304 Add on febuxostat		
Cr Cl <45	6	8	10	3	3	5	7	12	8	7	4
sUA level mean (mg/dL) at baseline											
	7.0	6.8	7.0	6.8	6.9	7.0	9.5	9.2	5.4	5.2	5.2

Table 4. Summary efficacy results for the pivotal studies

	Study 301 Add-on allopurinol			Study 302 Add-on allopurinol			Study 303 Monotherapy		Study 304 Add on febuxostat		
	Les 200	Les 400	Pbo	Les 200	Les 400	Pbo	Les 400	Pbo	Les 200	Les 400	Pbo
Primary efficacy variable											
Proportion of patients with sUA <6 mg/dL (Studies 301, 302, 303) and <5 mg/dL (Study 304) at month 6											
% patients	54	59	28	55	67	23	30	2	57	76	47
Δ vs pbo	0.26	0.31		0.32	0.43		0.28		0.10	0.29	
95% CI	0.17, 0.36	0.22, 0.41		0.23, 0.41	0.34, 0.52		0.19, 0.37		-0.03, 0.23	0.17, 0.42	
P vs pbo	<0.001	<0.001		<0.001	<0.001		<0.001		0.13	<0.001	
Serum uric acid reduction from baseline to month 6, Adjusted differences											
Mean	-1.00	-1.23		-1.08	-1.36		-1.58		-0.79	-1.88	
95% CI	-1.35, -0.66	-1.58, -0.89		-1.41, -0.75	-1.69, -1.03		-2.03, -1.13		-1.28, -0.30	-2.36, -1.40	
P vs pbo	<0.001	<0.001		<0.001	<0.001		<0.001		0.002	<0.001	
Secondary efficacy variables											
Gout flares requiring treatment during months 6, Adjusted rate (Studies 301, 302, and 304) or proportions (Study 303)											
Rate or Prop.	0.57	0.51	0.58	0.73	0.77	0.83	12%	15%	1.5	0.7	1.3
Rate ratio	0.99	0.88		0.88	0.93		3%	-	1.2	0.5	-
P vs pbo	0.98	0.61		0.57	0.75		0.68	-	0.55	0.04	-
Complete resolution of ≥1 target tophus by month 12, Difference in proportions											
Proportion	00	21%	29%	31%	28%	33%	NA	NA	26%	30%	21%
Δ vs pbo	-29%	-8%		-2%	-6%		NA	NA	4%	9%	-
P vs pbo	0.02	0.60		0.85	0.63		NA	NA	0.45	0.12	-
HAQ-DI improvement of ≥0.25, month 12 (Studies 301, 302, and 304), month 6 (Study 303), Difference in proportions											
Proportion	30%	29%	35%	30%	38%	39%	33%	32%	44%	33%	53%
Δ vs pbo	-5%	-6%		-10%	-1%		1%	-	-8%	-19%	-
P vs pbo	0.41	0.27		0.10	0.82		0.92	-	0.30	0.02	-

A caveat in the efficacy finding is that lesinurad may be less effective with increasing degree of renal impairment. FDA review of Studies 301 and 302 appears to show that despite higher exposure in patients with greatest renal impairment, the reduction in sUA compared to placebo appears to be smaller in this group. The number of patients with moderate or severe renal impairment in these studies was small, therefore, limiting the strength of this conclusion and the numerical trends varied with dose. Nevertheless, it would be reasonable to limit the use of lesinurad to patients with normal or near normal renal function. The Agency and Ardea Biosciences are conducing further analysis of the data to determine the renal function cut off that would be used in the labeling. This analysis has not been completed at the time this review was finalized.

8. Safety

a. Safety database

The safety assessment of lesinurad was primarily based on the studies shown in Table 1. The safety database was large and adequate.

b. Safety findings and conclusion

The submitted data support the safety of lesinurad at a dose of 200 mg once daily dosed in the morning in combination with a xanthine oxidase inhibitor (allopurinol or febuxostat) for the treatment of hyperuricemia associated with gout.

Ardea Biosciences conducted a comprehensive safety analysis of the available data. Safety assessment in the clinical studies included evaluation of deaths, serious adverse events (SAEs[4]), common adverse events (AEs), vital signs, physical examination, clinical laboratory and hematology measures, and ECGs. Given the mechanism of action of lesinurad and the target patient population, safety events of interest were renal, and cardiovascular safety and major cardiovascular events (MACE).

Deaths, SAEs, dropouts and discontinuations:

Death was an infrequently reported event in the lesinurad clinical development program. Deaths occurring after active treatment included 6 during pivotal placebo-controlled studies, and 9 during open label extension studies. None of the deaths were considered by the investigator or Ardea Biosciences to be related to treatment with lesinurad.

Serious adverse events (SAEs) occurred with 8.6%, 4.7%, and 5.6% frequency for the lesinurad 400 mg, lesinurad 200 mg, and placebo group, respectively. Events most frequently reported as SAE were related to renal and urinary disorders, cardiac disorders, and infections.

Adverse events leading to discontinuations occurred with 9.4%, 6.3%, and 5.4% frequency for the lesinurad 400 mg, lesinurad 200 mg, and placebo group, respectively. Increased blood creatinine was the most common adverse event leading to discontinuation with 1.8%, 0.8%, and 0.8% frequency for the lesinurad 400 mg, lesinurad 200 mg, and placebo group, respectively.

Common adverse events:

Common adverse events that were seen with at least 2% or higher frequency, and with 1% or higher frequency in the lesinurad treatment groups compared to placebo included

[4] Serious Adverse Drug Experience is defined in 21 CFR 312.32 as any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience (defined in the same regulation as any adverse drug experience that places the patient or subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred), inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect.

hypertension, headache, influenza, increased blood creatinine, and gastroesophageal reflex disease.

Laboratory findings and ECGs:

No clinically meaningful effects on hematologic or chemistry or ECG parameters were noted in the clinical program except for renal function tests, which are described below.

Renal safety:

Adverse events related to kidneys occurred in a dose-depended fashion with lesinurad (Table 5). Frequencies of these adverse events were higher for the 400 mg dose compared to placebo, and were more comparable for the 200 mg dose and placebo. Dose related renal adverse events are not surprising given the increased uric acid excretion with lesinurad and the underlying risk of patients with gout for renal injury.

During the controlled studies, one patient developed a SAE of acute renal failure. This patient was on lesinurad 400 mg monotherapy (Study 303). He was 25 years old and had normal renal function at baseline. On Day 5 of treatment the patient was hospitalized with abdominal pain and renal function abnormality (serum creatinine of 8.86 mg/dL and BUN 46 mg/dL). The patient was on concomitant naproxen and omeprazole. Renal biopsy showed acute tubular necrosis and minimal tubulointerstitial fibrosis. The patient's acute renal failure resolved by Day 26 without hemodialysis. However, two other patients in an open label long-term extension study on lesinurad 200 mg developed acute-on-chronic renal failure requiring dialysis (at day 381 and day 567). An additional patient with normal renal function at baseline in an open label long-term extension study on lesinurad 400 mg developed acute renal failure at Day 413 and underwent renal biopsy that showed acute tubular cell injury. His acute renal failure resolved on Day 448 without hemodialysis. All these patients had comorbidities or concomitant medications that could increase risk for renal complications, however, it is likely that lesinurad was an additional risk factor that contributed to these renal adverse events.

Based on this finding, along with the MACE findings (described below), Ardea Biosciences is no longer pursuing the 400 mg dose.

Table 5. Incidence of renal-related adverse events in pivotal studies 301, 302, and 304

	Lesinurad 400 mg + XOA (n = 510)	Lesinurad 200 mg + XOI (n= 511)	Placebo + XOI (n= 516)
Blood creatinine increased	11.8 %	5.7 %	4.5 %
Blood urea increased	7.8 %	4.3 %	2.3 %
Renal failure	1.2 %	0.8 %	1.2 %
Renal failure, acute	0.8 %	0.0 %	0.4 %
Nephrolithiasis	2.2 %	0.6 %	1.7 %

Cardiovascular adverse events, and MACE events:

Adverse events related to cardiovascular safety occurred in a dose dependent fashion with lesinurad. This is a finding of concern because of underlying cardiovascular co-morbidity with gout. Blood pressure, blood lipid levels, and ECGs findings were not effected by lesinurad. There was a numerical trend in blood pressure increase, with 6.9%, 6.1%, and 4.8% frequency for the lesinurad 400 mg, lesinurad 200 mg, and placebo group, respectively. The number of MACE events was generally low in the clinical program, but there was a numerical imbalance, particularly with the 400 mg dose. Ardea Biosciences is no longer pursuing the 400 mg dose because of these findings and the renal safety findings described above.

Table 6. Incidence of adjudicated MACE events (Studies 301, 302, and 304)

	Lesinurad 400 mg + XOA (n = 510)	Lesinurad 200 mg + XOI (n= 511)	Placebo + XOI (n= 516)
Number of patients with adjudicated CV events	15	18	17
MACE	8	4	3
CV death	2	2	0
Nonfatal MI	7	2	1
Nonfatal stroke	0	0	3

c. REMS/RiskMAP

Ardea Biosciences submitted a risk management plan that included a medication guide and communication plan, in addition to routine surveillance. No REMS will be required for this product. Although there are safety issues with lesinurad as noted in Section 8 above, it was thought a REMS or RiskMAP would not be useful to mitigate these.

9. Advisory Committee Meeting

A meeting of the Arthritis Advisory Committee (AAC) was held on October 23, 2015, to discuss this application. Issues for discussion were the proposed dose of lesinurad 200 mg and the proposed dosing frequency of once daily, the clinical meaningfulness of the magnitude of the sUA reduction observed, the safety of the proposed dose with specific focus on renal and cardiovascular safety, and the dose dependency of safety findings with lesinurad in light of the unacceptable safety profile of the lesinurad 400 mg once daily dose. Voting questions were on efficacy, safety and approvability. The committee was of the opinion that the submitted studies demonstrated that lesinurad at the proposed dose of 200 mg once daily decreased sUA of a magnitude that was clinically meaningful. The committee expressed concerns about the safety of lesinurad in patients with moderate to severe renal insufficiency; however, the Committee found it difficult to draw a specific conclusion because of seemingly conflicting conclusions presented by Ardea Biosciences and the FDA. The Committee noted the narrow therapeutic index of the drug for renal

adverse reactions. The committee was not overly concerned about the cardiovascular safety given the small number of events. The Committee generally noted that the product could be safely used with appropriate labeling to communicate the safety findings and having some renal function monitoring in place. The voting, as shown in Table 7, reflects the discussion that occurred at the meeting.

Table 7. AC voting on efficacy, safety, and approvability

	Yes	No	Abstain
Efficacy	14	0	0
Safety	7	6	1
Approval	10	4	0

10. Pediatric

Ardea Biosciences submitted a request for waiver of pediatric studies because gout is an adult disease and rarely occurs in children; therefore, specific pediatric studies are not feasible. In children, gout occurs almost exclusively in the setting of hypoxanthine-guanine phosphoribosyltransferase (HGPRT) deficiency (also known as Lesch-Nyhan syndrome and Kelley-Seegmiller syndrome), which are rare diseases. This application was discussed at the Center's Pediatric Review Committee (PeRC) meeting on July 8, 2015, and PeRC agreed with the requested waiver.

11. Other Relevant Regulatory Issues

a. DSI Audits

DSI audited two clinic representative sites from the pivotal studies. The clinical and statistical review teams recommended the sites because these sites enrolled larger number of patients compared to other sites. No irregularities were identified that would impact data integrity. During review of the submission, no irregularities were found that would raise concerns regarding data integrity. No ethical issues were present. All studies were performed in accordance with the acceptable ethical standards.

b. Financial Disclosure

The applicant submitted acceptable financial disclosure statements. No potentially conflicting financial interests were identified.

c. Others

There are no outstanding issues with consults received so far from other groups in CDER. Some of the consults are pending, particularly because the labeling review is ongoing and not finalized at the time of finalizing this review.

12. Labeling

a. Proprietary Name

The proprietary name Zurampic was reviewed by DMEPA and found to be acceptable.

b. Physician Labeling

The labeling review is still ongoing at the time of finalizing this review. The major issues for labeling, which need to be finalized with Ardea Biosciences, are appropriate communication of the safety findings in the label, specifically renal safety findings, the apparent lesser efficacy seen in patients with renal insufficiency, and the target gout patients for lesinurad. The target patients will likely be limited to exclude patients with renal insufficiency, the exact magnitude of which has not yet been finalized.

c. Carton and Immediate Container Labels

There are no outstanding issues noted so far from other groups in CDER. Final review decision on these are still pending.

d. Patient Labeling and Medication Guide

Lesinurad will have a Medication Guide.

13. Action and Risk Benefit Assessment

a. Regulatory Action

Ardea Biosciences has submitted adequate data to support approval of the use of lesinurad tablet at a dose of 200 mg once daily in combination with a xanthine oxidase inhibitor for the treatment of hyperuricemia associated with gout. The proposed regulatory action is approval, pending finalized labeling, and outcome of CDER regulatory briefing scheduled for December 11, 2015.

b. Risk Benefit Assessment

The overall risk benefit assessment supports approval of the use of lesinurad tablet at a dose of 200 mg once daily in combination with a xanthine oxidase inhibitor for the treatment of hyperuricemia associated with gout. The major risk identified is the adverse events related to kidneys occurred in a dose-depended fashion with lesinurad, which was not acceptable for the 400 mg dose, but seemed to occur at a lower frequency with the proposed dose of 200 mg dose that was more comparable to the placebo group than the 400 mg group. Appropriate labeling to restrict use of lesinurad based on renal function and periodic monitoring of renal function would be adequate to assure safe use of the product. The submitted efficacy data showed that in patients with gout receiving background allopurinol, a significantly higher proportion of patients achieved the primary target by month 6 compared to placebo with the proposed dose of 200 mg once daily. A target serum uric acid level 6 mg/dL or lower is the recommended goal of urate lowering therapy in widely accepted gout treatment guidelines issued by the professional societies such as the American College of Rheumatology (ACR), and the European League Against Rheumatism (EULAR), which was achieved by lesinurad at the proposed dose of 200 mg once daily added to xanthine oxidase inhibitor allopurinol.

c. Post-marketing Risk Management Activities

No other post-marketing risk management activities are required.

d. Post-marketing Study Commitments

None.

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/s/

BADRUL A CHOWDHURY
11/23/2015