Testimony before the FDA's Arthritis Advisory Committee Regarding Lesinurad for Hyperuricemia Associated With Gout: No Unique Benefits, But Serious Risks

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(I have no financial conflicts of interest)

Major Comments

Public Citizen strongly opposes approval of lesinurad for treatment of hyperuricemia associated with gout in combination with a xanthine oxidase inhibitor because:

- **The drug offers meager clinically meaningful benefits relative to placebo for gout patients with hyperuricemia;**
- **The drug has serious risks, including definite significant renal toxicity and possible cardiovascular toxicity; and**
- **As a result, the risks of the drug far outweigh its benefits.**

Efficacy Assessment

The FDA reviewers emphasized that the magnitude of lesinurad's urate-lowering effect was only modest for all three pivotal trials (301, 302, and 304).

Efficacy Assessment

More importantly, the FDA reviewers noted that the changes in the surrogate endpoint were not associated with any statistically significant differences favoring the 200 mg lesinurad-treated subjects on clinically meaningful secondary endpoints in any of the three pivotal clinical trials.

Table 1: Study 301, Key Secondary Endpoint Results

	Placebo + ALLO (N=201)	Lesinurad 200mg + ALLO (N=201)	Lesinurad 400mg + ALLO (N=201)
Mean adjusted rate of gout flares requiring treatment per subject in months 6-12 (standard error)	0.58 (0.10)	0.57 (0.10)	0.51 (0.09)
Incidence rate ratio vs. placebo + ALLO (95% CI) p-value		0.99 (0.61, 1.61) p = 0.98	0.88 (0.54, 1.43) p = 0.61
Of patients with ≥1 tophus at baseline, proportion with target tophus resolution at 12 months	5/17 (29%)	0/18 (0%)	4/19 (21%)
Difference vs. placebo + ALLO (95% CI), p-value		-0.29 (-0.51, -0.08) p = 0.02	-0.08 (-0.37, 0.20) p = 0.60

Abbreviations: ALLO, allopurinol; CI, confidence interval

Table 2: Study 302, Key Secondary Endpoint Results

	Placebo + ALLO (N=206)	Lesinurad 200mg + ALLO (N=204)	Lesinurad 400mg + ALLO (N=200)
Mean adjusted rate of gout flares requiring treatment per subject in months 6-12 (standard error)	0.83 (0.13)	0.73 (0.12)	0.77 (0.13)
Incidence rate ratio vs. placebo + ALLO (95% CI) p-value		0.88 (0.57, 1.37) p = 0.57	0.93 (0.60, 1.45) p = 0.75
Of patients with ≥1 tophus at baseline, proportion with target tophus resolution at 12 months	11/33 (33%)	11/35 (31%)	8/29 (28%)
Difference vs. placebo + ALLO (95% CI), p-value		-0.02 (-0.24, 0.20) p = 0.85	-0.06 (-0.29, 0.17) p = 0.63

Abbreviations: ALLO, allopurinol; CI, confidence interval

Table 3: Study 304, Select Key and Other Secondary Endpoint Results

	Placebo + FBX (N=109)	Lesinurad 200mg + FBX (N=106)	Lesinurad 400mg + FBX (N=109)
Mean adjusted rate of gout flares requiring treatment per subject in months 6-12 (standard error)	1.3 (0.25)	1.5 (0.31)	0.7 (0.15)
Incidence rate ratio vs. placebo + FBX (95% CI), p-value		1.2 (0.7, 2.1) p = 0.55	0.5 (0.3, 1.0) p = 0.04
Proportion with a CR or PR of at least one target tophus by month 12	55 (51%)	60 (57%)	64 (59%)
Difference vs. placebo + FBX (95% CI), p-value		0.06 (-0.09, 0.21) p = 0.45	0.08 (-0.07, 0.23) p = 0.12

Abbreviations: FBX, febuxostat; CI, confidence interval; CR, complete resolution; PR, partial resolution

Major Safety Concerns

- Renal adverse events
- Major cardiovascular adverse events (MACE)
- Serious adverse events
- Deaths

Renal Toxicity: Preclinical Data

Chronic toxicology studies showed evidence of kidney toxicity in rats…. 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 …. 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. … [These findings] suggest lesinurad has the potential for kidney and GI tract toxicity.

Renal Toxicity: Clinical Trials

The safety data from the phase 3 randomized clinical trials for lesinurad provide overwhelming evidence that the drug causes acute kidney injury in humans. The mechanisms for this lesinurad-induced renal injury likely include uric-acid-induced nephropathy, as well as direct toxicity to renal tubular cells.

Renal Toxicity: Clinical Trials (cont.)

Table 38: Renal-Related TEAE in the Controlled Phase 3 Studies

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

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

Renal Toxicity: Clinical Trials (cont.)

Table 44: SCr by Elevation Category in the Controlled Phase 3 Studies

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

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

Modified Sponsor's Tables 9.1.1.1 and 9.1.1.3; ISS

Renal Toxicity: Clinical Trials (cont.)

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

Variable	Pooled 12-M, Studies 301, 302 and 304				6-M, Monotherapy Study 303	
	PBO + XOI (N=516)	LESU200 + XOI (N=511)	LESU400 + XOI (N=510)	Tot. LESU + XOI (N=1021)	PBO (N=107)	LESU400 (N=107)
sCr ↑≥ 2.0 x Baseline						
Number of Pts. With:						
No Elevation	516(100%)	502 (98%)	476 (93%)	978 (96%)	107(100%)	98 (92%)
At Least 1 Elevation	0	9 (2%)	34 (7%)	43 (4%)	0	9 (8%)
1 Elevation	0	9 (2%)	28 (6%)	37 94%)	0	7 (7%)
2 Elevations	0	0	6 (1%)	6 (1%)	0	2 (2%)
>2 Elevations	0	0	0	0	0	0
Total Number of Elevations	**0**	**9**	**40**	**49**	**0**	**11**
Total # of Resolutions	0	8 (89%)	32 (80%)	40 (82%)	0	6 (55%)
# Resolut. S/P Interruption of Study Meds	0	2 (22%)	9 (23%)	11 (22%)	0	1 (9%)
# Resolut. W/O Interrupt. of Study Meds	0	6 (67%)	23 (58%)	29 (59%)	0	5 (46%)
Time to Resolution:	(n=0)	(n=9)	(n=40)	(n=49)	(n=0)	(n=11)
1-14 days	0	5 (56%)	7 (18%)	12 (25%)	0	1 (9%)
>14-28 days	0	0	10 (25%)	10 (20%)	0	0
>28-56 days	0	1(11%)	8 (20%)	9 (18%)	0	4 (36%)
>56-84 days	0	0	5 (13%)	5 (10%)	0	1 (9%)
>84 days	0	2 (22%)	2 (5%)	4 (8%)	0	1
Unresolved at Last Assessment	0	1 (11%)	8 (20%)	9 (18%)	0	5 (46%)

Renal Toxicity: Clinical Trials (cont.)

Two subjects who had normal baseline renal function and developed acute kidney failure while taking lesinurad underwent kidney biopsies, both of which revealed acute tubular necrosis (ATN). In both cases, lesinurad cannot be ruled out as the cause for the ATN.

Renal Toxicity: Clinical Trials (cont.)

Importantly, after the protocols for the ongoing phase 3 trials (studies 301, 302, and 304) were amended in June 2013, based on emerging renal safety data, to instruct all subjects to drink two liters of fluid per day, no change was seen in exposure-adjusted incidence rates for renal-related adverse events pre- and post-amendment: 8.4 renal-related adverse events/100 patient-years versus 9.5 renal-related adverse events/100 patient-years, respectively, for the 200 mg lesinurad groups; and 17.0 renal-related adverse events/100 patient-years versus 15.5 renal-related adverse events/100 patient-years, respectively, for the 400 mg lesinurad groups.

Renal Toxicity: Clinical Trials (cont.)

In addition, real-world use of lesinurad — outside the context of a carefully monitored clinical trial and inevitably for off-label uses —undoubtedly will lead to rates of renal adverse events that exceed those seen in the phase 3 clinical trials. It is thus not unlikely that, if approved, lesinurad will trigger an epidemic of drug-induced acute kidney injury.

Cardiovascular Risk: Clinical Trials

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

System Organ Class/ Preferred Term	Combined 12-M, Studies 301, 302 and 304				6-M, Monotherapy Study 303	
	PBO + XOI (N=516)	LESU200 +XOI (N=511)	LESU400 + XOI (N=510)	Total LESU +XOI (N=1021)	PBO (N=107)	LESU400 (N=107)
Cardiac Disorders	**2 (1%)**	**10 (2%)**	**14 (3%)**	**24 (2%)**	**2 (2%)**	**0**
Acute Myocardial Infarction	0	1 (<1%)	4 (1%)	5 (1%)	0	0
Coronary Artery Disease	0	3 (1%)	2 (<1%)	5 (1%)	1 (1%)	0
Cardiac Failure Congestive	0	1 (<1%)	3 (1%)	4 (<1%)	0	0
Myocardial Infarction	1 (<1%)	0	3 (1%)	3 (<1%)	0	0
Angina Pectoris	0	1(<1%)	1 (<1%)	2 (<1%)	0	0
Atrial Fibrillation	0	2 (<1%)	0	2 (<1%)	0	0
Atrial Flutter	0	0	1 (<1%)	1 (<1%)	0	0
Cardiac Arrest	0	1(<1%)	0	1 (<1%)	0	0
Cardiac Failure Acute	0	0	1 (<1%)	1 (<1%)	0	0
Intracardiac Thrombus	0	0	1 (<1%)	1 (<1%)	0	0
Myocardial Ischemia	0	1(<1%)	0	1 (<1%)	0	0
Pericardial Effusion	0	0	0	0	1 (1%)	0
Pulseless Electrical Activity	0	1 (<1%)	0	1 (<1%)	0	0
Arrhythmia	1 (<1%)	0	0	0	0	0

Cardiovascular Risk: Clinical Trials (cont.)

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

	Pooled 12-Month, Studies 301, 302 and 304				6- Month, Monotherapy Study 303	
	PBO + XOI	LESU200 + XOI	LESU400 + XOI	Tot. LESU + XOI	PBO	LESU400 mg
MACE Events:						
Cardiovascular Death	0	2 (<1%)	2 (<1%)[b]	4 (<1%)[b]	0	1 (1%)
Non-Fatal MI	1 (<1%) [1][a]	2 (<1%) [2]	7 (1%) [7][b]	9 (1%) [9][b]	0	0
Non-Fatal Stroke	3 (1%) [3][a]	0	0	0	0	0
Number of Subjects with MACE Events:	3 (1%) [4]	4 (1%) [4]	8 (2%) [9]	12 (1%) [13]	0	1 (1%) [1]

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

Cardiovascular Risk: Clinical Trials (cont.)

Table 36: Exposure-Adjusted Incidence Rate of MACE in Studies 301, 302, & 304

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

PY= Patient years; CI = Confidence interval

Cardiovascular Risk: Clinical Trials (cont.)

Although the number of MACE events was small, the cardiovascular safety signal should be assumed to be real, particularly for a drug that offers meager benefits and is not a breakthrough treatment for a life-threatening disease.

Other Notable Safety Data

Table 29: Safety Overview: Phase 3 Studies

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

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

Risk-Benefit Assessment

Gout is not a life-threatening disease, and, importantly, there are multiple FDA-approved drugs already on the market. Lesinurad does not offer any major unique or breakthrough benefits compared to these approved therapies, and, in fact, the data for studies 301, 302, and 304 show at best meager clinically meaningful benefits.

Risk-Benefit Assessment (cont.)

In contrast to the limited benefits, the clinical trials have documented very serious safety concerns, the most significant being compelling evidence of nephrotoxicity and a troubling cardiovascular safety signal. The currently available data thus demonstrate that the risks of the drug far exceed its benefits.

Risk-Benefit Assessment (cont.)

There is no evidence that instructing patients to drink at least two liters of fluid per day and always combining lesinurad with a xanthine oxidase inhibitor will prevent the type of renal injury seen during the clinical trials of lesinurad. Indeed, adverse renal events occurred despite such measures during the phase 3 clinical trials. Moreover, such proposed renal-risk mitigation steps presume that the renal toxicity seen in the clinical trials is due only or primarily to uric acid nephropathy. However, given the preclinical animal data and clinical trial data, that assumption is likely false.

Risk-Benefit Assessment (cont.)

In addition, as previously stated, real-world use of lesinurad undoubtedly will lead to rates of renal and other adverse events that exceed those seen in the phase 3 clinical trials.

Conclusions

The only reasonable course of action for the FDA, given the available data, is to reject approval of the NDA for lesinurad. FDA approval, with reliance on warnings in the product labeling, a risk evaluation and mitigation strategy, and postmarket safety studies, would be a reckless approach and would not be in the interests of public health because it would cause much more harm than benefit.

Therefore, we urge the committee to recommend that the FDA not approve lesinurad.