CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207988Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

NDA	207988
Submission Date	12/29/2014
Brand Name	ZURAMPIC
Generic Name	Lesinurad
Clinical Pharmacology Reviewer	Jianmeng Chen, M.D., Ph.D.
Pharmacometrics Reviewer	Jianmeng Chen, M.D., Ph.D.
Pharmacogenomics Reviewer	Anuradha Ramamoorthy, Ph.D.
Pharmacometrics Team Leader	Yaning Wang, Ph.D.
Pharmacogenomics Team Leader	Christian Grimstein, Ph.D.
Clinical Pharmacology Team Leader (Acting)	Ping Ji, Ph.D.
OCP Division	Clinical Pharmacology Division II
OND Division	Division of Pulmonary, Allergy, and Rheumatology Products
Sponsor/Authorized Applicant	Ardea Biosciences, Inc.
Submission Type; Code	505(b)(1); standard review
Formulation; Strength(s)	Tablet 200 mg
Indication	Hyperuricemia associated with gout in combination with a xanthine oxidase inhibitor
Dosage Regimen	200 mg QD

Note – In this review, early development names RDEA594 is also used to refer to lesinurad

1. Executive Summary

Zurampic™ (lesinurad) a uricosuric drug that inhibits several transporters in kidney. Ardea Biosciences has submitted NDA207988 under 505(b)(1) pathway seeking the marketing approval for lesinurad for the indication of "for the treatment of hyperuricemia associated with gout in combination with a xanthine oxidase inhibitor". The proposed dosing regimen is 200 mg once daily in combination with a xanthine oxidase inhibitor, including allopurinol or febuxostat. The dosage form is tablet (200 mg).

1.1 Recommendations

The Office of Clinical Pharmacology (OCP) has reviewed the clinical pharmacology data submitted on 12/29/14 under NDA 207988. Lesinurad is not recommended in patients with creatinine clearance <45 mL/min due to the unfavorable benefit-to-risk ratio. An Advisory Committee meeting will be held on Oct 23, 2015 to discuss the review team's recommendations.

Labeling Recommendations:

Please see Section 3 for details.

1.2 Phase IV Commitments

None.

1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

1.3.1 Background

Zurampic™ (lesinurad) a uricosuric drug that inhibits several transporters in kidney. Lesinurad is proposed for the treatment of hyperuricemia associated with gout in combination with a xanthine oxidase inhibitor. It is supplied with 200 mg tablet formulation and the proposed dosing regimen is 200mg QD.

1.3.2 Biopharmaceutics

Over the course of the lesinurad clinical development program, a (b) (4) formulation, a capsule formulation, and a number of tablet formulations of lesinurad sodium salt and free acid have been used. The Phase 3 tablet formulation was shown to be completely absorbed, with an absolute bioavailability of approximately 100% in the fasted state, relative to an IV dose. The Phase 3 formulation was shown to have comparable exposure to the Phase 2 capsule and Phase 2 tablet formulations. Lesinurad tablet formulation to be used in the proposed commercial site (AstraZeneca AB) is bioequivalent to that used in the clinical development (b) (4)

1.3.3 Pharmacokinetics

Pharmacokinetics in Healthy Subjects

Absorption

The absolute bioavailability of lesinurad under fed conditions is about 100%. Systemic exposure ($AUC_{0-\infty}$) and peak plasma concentration (C_{max}) increased in proportion to the dose in the dose range of 5 to 1200 mg. T_{max} was reached by approximately 1-4 hours following oral administration under fed conditions. Coadministration with a high-fat meal decreases Cmax by up to 18% but does not alter AUC as compared with fasting state. The steady-state was reached after one dose with minimal accumulation.

Distribution

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

Metabolism and Excretion

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

Pharmacokinetics in Gout Patients

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

Pharmacokinetics in Specific Populations

Renal Impairment

The impact of renal impairment on the PK of lesinurad was evaluated in Studies 104 and 120. Study 104 evaluated a single dose of lesinurad 200 mg in adult volunteers with mild or moderate renal impairment. Study 120 evaluated a single dose of lesinurad 400 mg in adult volunteers with moderate or severe renal impairment. Lesinurad exposure (AUC) increased by 31%, 50-74% and 113%, respectively in subjects with mild, moderate and severe renal impairment compared with subjects with normal renal function.

Hepatic Impairment

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

Weight, Age, Race and Sex

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

Drug-Drug Interaction (DDI)

Effect of coadministered drugs on lesinurad

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

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

Effect of lesinurad on coadministered drugs

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

Based on *in vitro* studies, lesinurad is a substrate of OAT1 and OAT3 and a weak inhibitor of OATP1B1, OCT1, OAT1, and OAT3. However, *in vivo* drug interaction studies suggested that lesinurad does not decrease the renal clearance of furosemide (substrate of OAT1/3), or affect the exposure of metformin (substrate of OCT1). In

addition, consistent with the *in vitro* finding of being a URAT1 inhibitor, lesinurad reduces the exposure of oxypurinol, a URAT1 substrate, by 25%.

1.3.4 Exposure-Response Relationship

Exposure-Response Relationship for Efficacy
Dose(exposure)-response relationship for efficacy in gout patients was examined in the 3 Phase 3 studies (Studies 301, 302, 304). There is a dose response relationship for change from baseline in serum uric acid level (sUA), with a trend toward better efficacy with increasing dose or exposure.

Further, there appears to be a lower reduction in sUA levels with increasing degree of renal impairment in subjects with gout. The reduction in sUA was minimal in subjects with creatinine clearance< 45mL/min. This impact of renal impairment on lesinurad efficacy is consistent with its mechanism of action. Lesinurad acts as an inhibitor of several transporters in kidney and inhibits the reabsorption of uric acid. Its activity is dependent on the adequate glomerular filtration of uric acid.

Exposure-Response Relationship for Safety
The dose-safety relationship from the Phase 3 studies (Studies 301 and 302) showed that lesinurad decreased creatinine clearance (eCRCL) from baseline in a dose-dependent manner. This decrease in eCRCL was observed in all categories of renal impairment patients. On average, the decline in eCRCL appeared to stabilize after month 1. However, at individual level, the longer lesinurad treatment durations, the more number of patients with elevated serum creatinine levels.

1.3.5 Dose Selection
During clinical development of lesinurad, only once daily regimen was evaluated in the Phase 2 and 3 studies. The once daily dosing regimen was supported with the extended pharmacodynamics effect and safety concern. A direct relationship between concentration and serum uric acid (sUA) level and a dose-dependent sUA decrease was observed within the investigated lesinurad dose range of 100 and 600 mg. As lesinurad 400 mg qd was associated with acute uric acid nephropathy as evidenced by an increased incidence of sCr elevations and AEs of acute renal failure, lesinurad 200 mg QD is the proposed dosing regimen to seek approval.

The efficacy and safety of lesinurad were evaluated in studies that included gout patients with mild and moderate renal impairment. The efficacy and safety of lesinurad have not been evaluated in gout patients with severe renal impairment, with end stage renal disease (ESRD), or receiving dialysis. Given the lower response of lesinurad in eCRCL<45 mL/min group and the increased risk of decline in renal function (eCRCL) from baseline, we consider benefit-risk of lesinurad not favorable in eCRCL<45 mL/min group.

2. Question Based Review

2.1 List the *in vitro* and *in vivo* Clinical Pharmacology and Biopharmaceutics

studies and the clinical studies with PK and/or PD information submitted in the NDA or BLA

NDA 207988 consists of 31 in vitro studies with human materials (Table 1), 30 Phase 1 studies (Table 2), 1 Phase 2a (study 201), 3 Phase 2b (Studies 202, 203, and 204), and 4 Phase 3 studies (301, 302, and 304 for proposed indication, 303 for lesinurad monotherapy). Additionally, 3 meta-analysis and PopPK/PD reports were submitted to assess the effect of covariates, to understand the PK in special populations such as renal impairment patients, and to understand exposure-response relationship. Also, study SR13-015 evaluated data pooled from 5 clinical studies (Studies 109, 110, 111, 202, and 203) to assess the effect of genetic polymorphism of CYP2C9 on lesinurad PK.

Table 1. Lesinurad (RDEA594) and Its Major Metabolites M4 and M6 In Vitro Studies Using Human Biomaterials

ADME	Objective	Study/Report
Absorption	Caco-2 permeability assay for lesinurad	8ARDEP3R1
	Transport (Papp) studies of lesinurad	SR09-066
Distribution	Plasma protein binding	SR08-045, SR12-039
Metabolism	Metabolic profiling in microsomes and hepatocytes	SR08-056
	Possible Metabolic pathways	RDEA594-112-MET, RDEA594-105-MET-M4
	In vitro P450 reaction phenotyping, human recombinant CYPs	SR08-038
	In vitro P450 reaction phenotyping, human recombinant CYPs	SR11-031
	Glutathione conjugation to lesinurad	SR12-027
	UGT reaction phenotyping	SR10-002
	Evaluation of M4 formation	SR12-026
DDI potential	In vitro P450 inhibition	SR08-048, SR12-043
	In vitro UGT Inhibition	SR10-001
	In vitro CYP Induction in human hepatocytes	SR08-026, SR10-063
	Drug Interaction with mEH Inhibitors	SR12-044
Transporter	Evaluation as a substrate of hOATP1B1 and hOATP1B3 interaction in MDCK-II cells	SR11-044
	In vitro IC50 determination of lesinurad against hOATP1B1 and hOATP1B3 mediated transport of substrate	SR11-045
	In vitro IC50 determination of lesinurad against human BCRP mediated transport of substrate in Caco-2 cells expressing human BCRP	SR11-053
	In vitro IC50 determination of lesinurad against hOCT1 and hOCT2 mediated transport of substrate in MDCK-II cells	SR11-054, SR11-028
	In vitro assessment of Lesinurad as a substrate of hOCT1 and hOCT2 mediated transport in MDCK-II cells	SR11-055, SR11-029
	Interaction studies of lesinurad with human MRP2 (ABCC2) and human MRP4 (ABCC4) efflux transporters using indirect vesicular transport assays (substrate study)	SR11-099
	Evaluation of hOAT1 and hOAT3 interaction in oocytes	SR08-018
	Evaluation of URAT1, OAT1, and OAT3 interaction in oocytes	SR10-006
	Assessment of lesinurad-M4 as a an inhibitor of human OCT2, MATE1 and MATE2-K	SR14-007
	Interaction with MATE1 and MATE2K	SR11-020

	Assessment of lesinurad-M6 as a substrate or an inhibitor of human MRP2 and MRP4	SR13-006

(Source – reviewer summary)

Table 2: Clinical pharmacology studies

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Study	Objective	Population	Formulation
101	Dose proportionality, SAD, FIH	34 Healthy subjects	(b) (4)
102	Dose proportionality, MAD	64 Healthy subjects	(b) (4) IR capsule, (b) (4) capsule, (b) (4) tablet
103	Formulation finding (b) (4) vs IR	27 Healthy subjects	IR Capsule, (b) (4) tablets, (b) (4) tablets
104	Renal impairment	6 Healthy, 8 mild, 10 moderate	IR Capsule, 100mg
105	PK and PD interaction of febuxostat and lesinurad	36 Healthy Japanese subjects	IR Capsule, 100mg
106	Formulation finding (b) (4) vs IR	8 Healthy subjects	IR Capsule, 100mg, (b) (4) tablet 200 mg
107	Formulation finding, two IR formulation	8 Healthy subjects	IR Capsule 100mg, IR tablet 200mg (sodium salt)
108	DDI, effect on sildenafil	45 Healthy subjects	100 mg IR capsule
109	Formulation finding, crystalline free acid tablet vs IR capsule; food effect	23 Healthy subjects	100 mg IR capsule, 200 mg crystalline free acid tablet
110	PK and PD interaction of allopurinol and lesinurad	21 Hyper-uricemic subjects with symptomatic gout	100 mg IR capsule
111	PK and PD interaction of febuxostat and lesinurad	21 Hyper-uricemic subjects with symptomatic gout	100 mg IR capsule
112	Human radiolabelled ADME/mass balance	6 Healthy subjects	(b) (4)
113	DDI, effect on atorvastatin	28 Healthy subjects	200, 400 mg crystalline free acid tablet
114	DDI, effect on amlodipine	14 Healthy subjects	400 mg crystalline free acid tablet
115	DDI, effect on tolbutamide	14 Healthy subjects	400 mg crystalline free acid tablet
116	DDI, effect on repaglinide	13 Healthy subjects	400 mg crystalline free acid tablet
117	Thorough QT	89 Healthy subjects	400 mg crystalline free acid tablet
118	Hepatic impairment	8 Healthy, 8 mild, 8 moderate	400 mg crystalline free acid tablet
120	Renal impairment	6 Healthy, 6 moderate, 6 severe	400 mg crystalline free acid tablet
121	Pivotal food effect study	16 Healthy subjects	400 mg crystalline free acid tablet
122	DDI, fluconazole and rifampin effect on lesinurad	21 Healthy subjects	400 mg crystalline free acid tablet
123	DDI, effect on warfarin	18 Healthy subjects	400 mg crystalline free acid tablet
125	PK in Japanese subject	40 Healthy Japanese subjects	50, 100 and 200 mg crystalline free acid tablet
126	DDI, naproxen effect on lesinurad	21 Healthy subjects	400 mg crystalline free acid tablet
127	DDI, ranitidine effect on lesinurad	16 Healthy subjects	400 mg crystalline free acid tablet
128	DDI, effect on metformin, furosemide	23 Healthy subjects	400 mg crystalline free acid tablet
129	Relative bioavailability of two manufacture site	73 Healthy subjects	400 mg crystalline free acid tablet
130	DDI, calcium carbonate; magnesium hydroxide and aluminum hydroxide effect on lesinurad	73 Healthy subjects	400 mg crystalline free acid tablet
131	Absolute bioavailability	10 Healthy subjects	400 mg crystalline free acid tablet
132	Relative bioavailability of two manufacture site	54 Healthy subjects	400 mg crystalline free acid tablet

(Source: Reviewer summary)

2.1.1 What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology of this drug?

Zurampic™ (lesinurad) a uricosuric drug that inhibits several transporters in kidney. Lesinurad was also referred as RDEA594 during the development program and studied under IND102128 for the treatment of hyperuricemia associated with gout (IND opened in Oct 2009). There have been several interactions between Agency and Sponsor to discuss the clinical pharmacology program of the proposed product. The key Clinical Pharmacology agreements are summarized in Table 3. The NDA review is under standard review timelines.

Table 3. Summary of Regulatory history relevant to clinical pharmacology

PNDA (Sep 2014)	Dosing frequency discussion, FDA express concern "*QD dosing and the resultant intra-day sUA fluctuations may result in increased gout flares after flare prophylaxis is discontinued*" Agreed on general clinical pharm studies adequate to support NDA filing
Communication (Nov 2013)	Agree on the DDI plan, no need for DDI studies with CYP2B6 and CYP2C19
EOP2 (Aug 2011)	Agreed that sufficient information on characterization of elimination Recommend subgroup analysis in phase 3 studies to assess risk benefit in renal impairment patients

2.2 General Attributes of the Drug

2.2.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product?

Lesinurad is a small molecule drug. Its structure is shown in Figure 1 and its physicochemical properties are listed in Table 4.

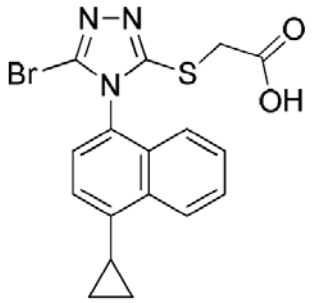


Figure 1. Molecular structure of lesinurad
(Source: Figure 1, section 3.2.S.1.2)

Table 4: Lesinurad physical chemical properties

Molecular Formula	$C_{17}H_{14}BrN_3O_2S$
Molecular Weight	404.28 g/mol
Physical State	Lesinurad is a white to off-white powder.
Polymorphism	(b) (4)

	(b) (4)
Dissociation Constants	Lesinurad is a weak carboxylic acid with one dissociation constant. The pKa was determined potentiometrically to be 3.2 (carboxylate).
Solubility	Lesinurad is a crystalline powder (b) (4) with low aqueous solubility at gastric pH but high solubility at intestinal pH (5.3 to 7.5) • <0.01 mg/mL up to pH 3.0 • ≥ 3.7 mg/mL at pH ≥ 6 • Solubility increases with increase in pH
Partition Coefficient	Moderately lipophilic, It has a log P (octanol/water) of 2.85 at 25 °C, which corresponds to a log D at pH 7.4 of -1.35.

(Source: Reviewer summary)

For the drug product, Zurampic is available as blue film-coated tablets for oral administration containing 200 mg lesinurad and the following inactive ingredients: lactose monohydrate, microcrystalline cellulose, hypromellose, crospovidone, and magnesium stearate. Zurampic tablets are coated with Opadry blue.

2.2.2 What are the proposed mechanism of action and therapeutic indications?

Lesinurad is proposed to act as a selective uric acid reabsorption inhibitor (SURI) that inhibits the URAT1 transporter. URAT1 is responsible for the majority of the reabsorption of filtered uric acid from the renal tubular lumen. By inhibiting URAT1, lesinurad increases uric acid excretion and thereby lowers serum uric acid (sUA). Lesinurad also inhibits OAT4, a uric acid transporter involved in diuretic-induced hyperuricemia.

The proposed indication is treatment of hyperuricemia associated with gout in combination with a xanthine oxidase inhibitor.

2.2.3 What are the proposed dosages and routes of administration?

The proposed dosing regimen is 200 mg once daily in combination with a xanthine oxidase inhibitor, including allopurinol or febuxostat . Lesinurad tablets should be taken orally in the morning with food and water.

2.2.4 What drugs (substances, products) indicated for the same indication are approved in the US?

The therapeutic goal in the management of gout is to lower sUA levels sufficiently to durably improve the signs and symptoms of gout, with a target sUA of < 6 mg/dL (360 µmol/L) at minimum. The drugs which are approved for treatment of gout in the US can be classified into the following classes:

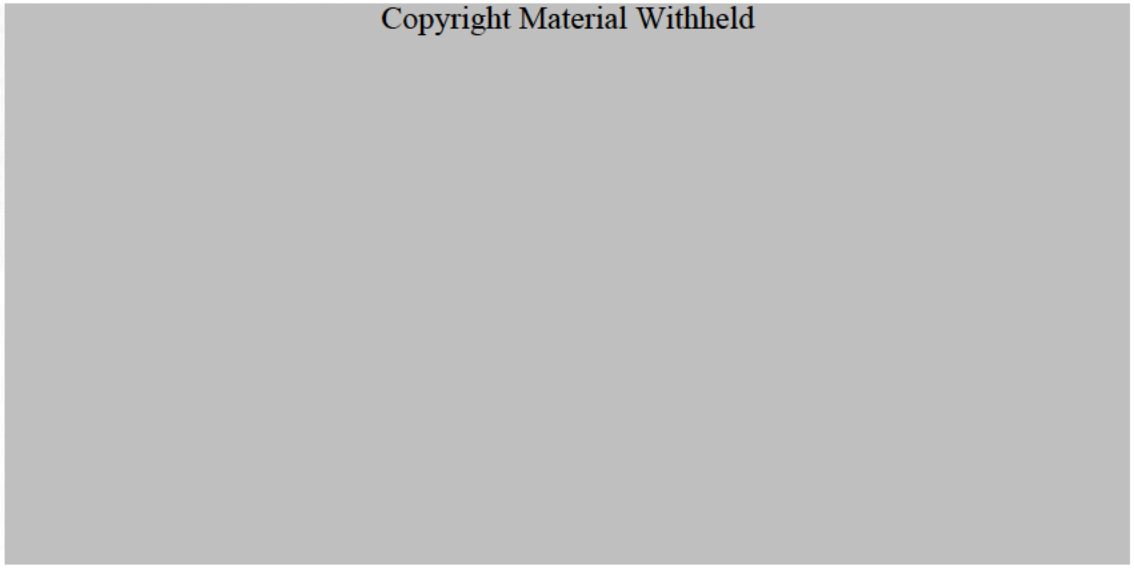
(a) Urate-lowering therapy (ULT, Figure 2)

- Oral xanthine oxidase (XO) inhibitors:
  - Allopurinol
  - Febuxostat (Uloric)
- Intravenous recombinant uricase:

- Pegloticase (Krystexxa)
- Uricosuric:
  - Probenecid

(b) Treatment/Prophylaxis against gout flare

- Colchicine
- NSAIDs
- Corticosteroid



Abbreviations: GI, gastrointestinal; XO, xanthine oxidase.
[a] Benzbromarone is approved in only a few markets.
Sources: Adapted from (Burns 2011) and the (Krystexxa [US package insert] Rev September 2012).

Figure 2. Schematic of Lesinurad and Current Therapies for Gout
(Source: Figure 1, Clinical overview)

2.3 General Clinical Pharmacology

2.3.1 What are the design features of the clinical pharmacology and biopharmaceutics studies and the clinical studies used to support dosing or claims?

The clinical pharmacology and biopharmaceutics studies supporting this NDA and their design features are listed under section 2.1.

2.3.2 What is the basis for selecting the response endpoints and how are they measured in clinical pharmacology studies?

In the pivotal combination therapy studies (Studies 301, 302, and 304), the primary efficacy endpoint was the proportion of subjects reaching a target sUA level by Month 6. The target sUA level differed based on the study design and population. Studies 301 and 302 included subjects with gout who had an inadequate hypouricemic response to allopurinol and at least 2 gout flares in the 12 months prior. The target in these studies was to achieve an sUA < 6.0 mg/dL based on current treatment guidelines by ACR and the EULAR Standing Committee for International Clinical Studies Including

Therapeutics (ESCISIT) (Khanna 2012, Richette 2014). In Study 304, the target sUA was an sUA < 5.0 mg/dL as the subjects were required to have tophaceous gout and is consistent with international treatment guidelines for patients with greater disease severity and urate burden, such as those with tophi.

Key secondary endpoints include Mean rate of gout flares and tophus resolution. Other secondary endpoints include patient reported outcomes (HAQ-DI), absolute and percent change from baseline in sUA, Proportion of subjects whose sUA level was < 6.0 mg/dL, < 5.0 mg/dL, and < 4.0 mg/dL at each visit, etc.

sUA was measured in several clinical pharmacology studies. For assessment of the primary endpoint in pivotal studies, please see the medical and statistical reviews (Dr. Rosemarie Neuner and Dr. Yu Wang).

2.3.3 Are the active moieties in plasma and clinically relevant tissues appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Yes. In all relevant studies, lesinurad concentration was measured.

2.4 Exposure-Response

2.4.1 Is there a dose/exposure-response relationship for efficacy?

Yes, Phase 1 and 2 studies of lesinurad showed a direct relationship between lesinurad dose and sUA lowering, with doses of 100 mg qd and lower being relatively inactive and doses of 200 mg, 400 mg, and 600 mg qd showing dose-related effects on sUA and uUA. In the dose ranging study on background of allopurinol (Study 203), 3 doses of lesinurad (200 mg QD, 400 mg QD, and 600 mg QD) were compared with placebo over 28 days of treatment. The percent change from baseline in sUA following 4 weeks of treatment (primary efficacy endpoint) was statistically significant for lesinurad plus allopurinol compared with placebo plus allopurinol (Figure 3, -16.12%, -22.07%, and -30.35% in the 200 mg, 400 mg, and 600 mg dose groups, respectively, compared with +2.63% in the placebo group; $p < 0.0001$ for all comparisons).

In the non-responder imputation analysis, 63.0%, 73.8%, and 79.2% of subjects in the 200 mg, 400 mg, and 600 mg groups, respectively, and 25.0% in the placebo group had sUA < 6.0 mg/dL at Day 27 ($p < 0.0001$ for all comparisons), suggesting that the 200 and 400 mg doses are at the steep part of the dose response curve. Considering safety, two doses of lesinurad (200 mg QD, 400 mg QD) were included in the Phase 3 program.

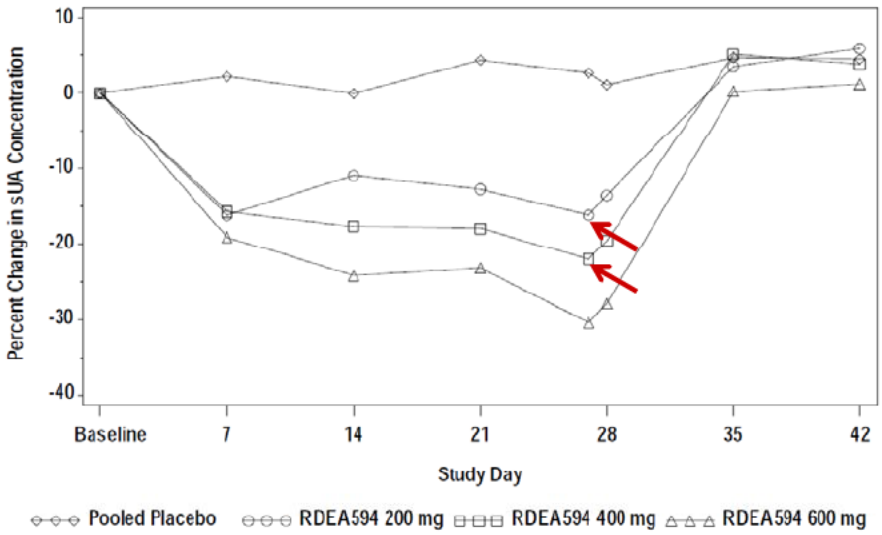


Figure 3. Mean Percent Change from Baseline in sUA Concentration by Study Visit
(Source: CSR rdea594-203, Fig 4)

Dose-response relationship for efficacy in gout patients was also examined in the 4 Phase 3 studies (Studies 301, 302, 303, 304). There is a dose response relationship for change from baseline in sUA, with a trend toward better efficacy with increasing dose (Figure 4A).

Consistent with the dose-response relationship, there is an exposure-response relationship for efficacy. With the efficacy endpoint of proportion of patients achieving target sUA, higher exposure is associated with higher response rate (Figure 4B). The highest exposure quartile corresponds to the average plasma concentrations that are likely to be achieved with the 400 mg QD dose.

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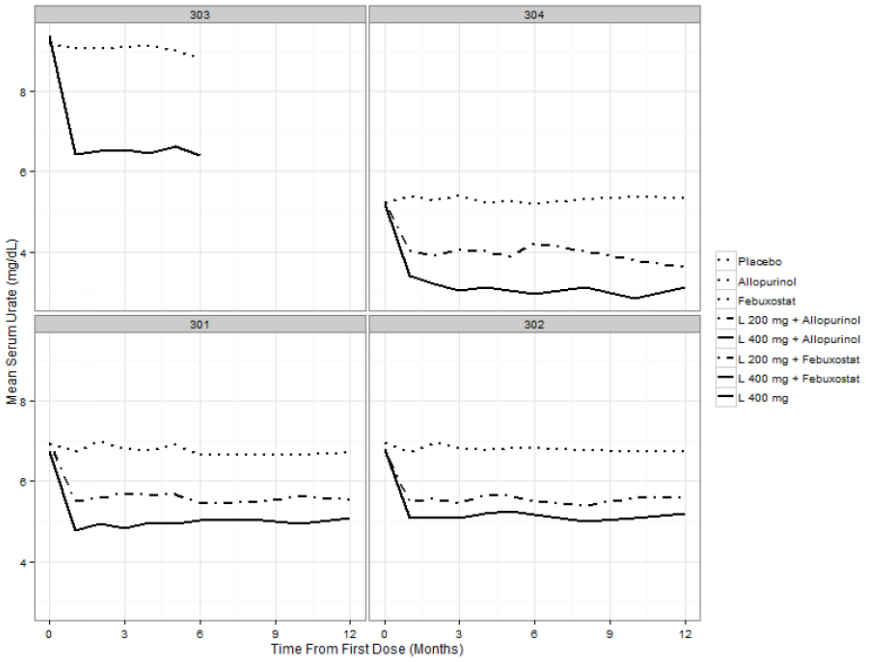
A. Change in serum uric acid



B. sUA responder analysis

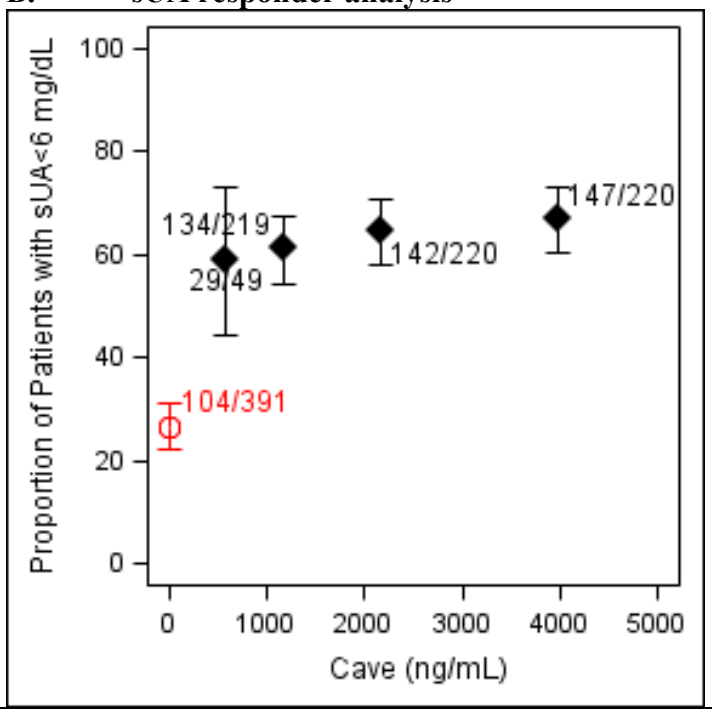


Figure 4: The Dose/exposure response for efficacy: A) Dose response for change in serum uric acid; B) serum uric acid responder analysis with steady state Cave (Study 301 and 302). The black symbols represent the mean and 95% CI in each exposure quartile. The red symbols represent the placebo group.

2.4.2 Is there an impact of renal impairment on the efficacy of lesinurad?

Yes, the severity of renal impairment appears to impact the efficacy of lesinurad.

The impact of renal function on lesinurad efficacy was evaluated in the Phase 3 studies (Studies 301 and 302). There appears to be a lower reduction in serum uric acid levels with increasing degree of renal impairment in subjects with gout. The reduction in sUA from baseline in subjects with creatinine clearance< 45mL/min was less than those in patients with normal renal function or with mild renal impairment (Table 5). Further, the responder analysis of pooled studies 301 and 302 also suggested that the efficacy in patients with creatinine clearance less than 45mL/min is minimal (Figure 5). This impact of renal impairment on lesinurad efficacy is consistent with its mechanism of action. Lesinurad acts as an inhibitor of several transporters in kidney and inhibits the reabsorption of uric acid. Its activity is dependent on the adequate glomerular filtration of uric acid.

Table 5. Effects of baseline renal function on sUA decline compared to placebo (study 301and 302, dose of 200 mg QD, posthoc analysis)

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

(Source: Reviewer analysis, see statistical review by Dr. Yu Wang)

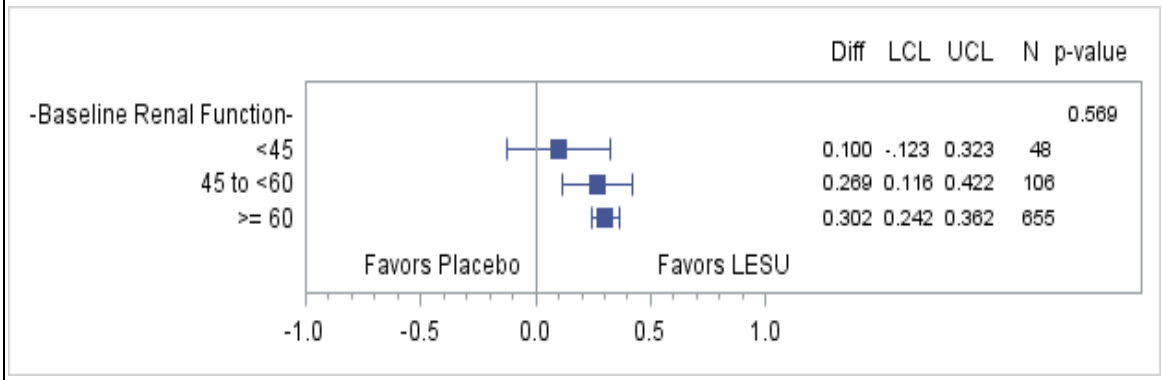


Figure 5. Pooled studies301 and 302 subgroup analysis of lesinurad 200 over placebo estimated sUA responder rate difference and 95% confidence interval. None responder imputation-ITT
(Source: Reviewer analysis by Dr. Yu Wang, study 301 and 302)

A pharmacokinetic-pharmacodynamic model was built with an Emax model. Renal function was identified as the only covariate that impacts the lesinurad efficacy. The final Emax model suggested that for a patient with CRCL of 30ml/min, 55% of the efficacy will be preserved at similar lesinurad exposure; For a patient with CRCL of 60ml/min, 80% of the efficacy will be preserved at similar lesinurad exposure. This is consistent

with the observed efficacy data in phase 3 studies.

2.4.3 Is there a dose/exposure-response relationship for safety?

Yes, there is a dose-response relationship for renal toxicity.

The dose-response relationship for safety was assessed in the Phase 3 studies (Studies 301 and 302). Lesinurad decreased eCRCL from baseline in a dose-dependent manner. This decrease in eCRCL was observed in all categories of renal impairment patients (Figure 6). On average, the decline in eCRCL appeared to stabilize after month 1. However, at individual level, more patients have serum creatinine elevations with longer lesinurad treatment durations (Figure 7).

While the eCRCL decline was observed in patients with all categories of baseline renal function, the decline of eCRCL led to more severe consequence in patients with worse baseline renal function. In 5% (5/101) of patients with moderate renal impairment at baseline, the eCRCL declined to <30mL after 6 to 12 months treatment of lesinurad 200mg+XOI, compared to 1% (1/101)in the placebo+XOI group(Table 6). Some of these patients end up requiring dialysis as the renal function declined in the Phase 3 studies.

See Dr. Rosemarie Neuner's clinical review for detailed information on safety analysis.

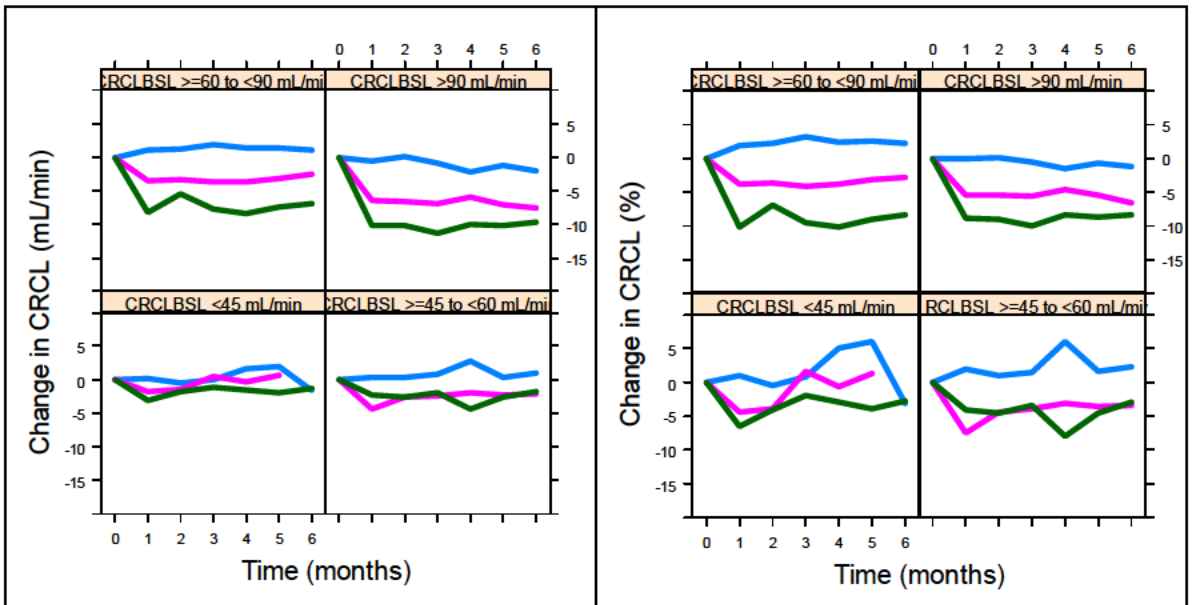


Figure 6. Mean change in eCRCL (mL/min) and relative change in Ecrcl(%)from baseline over time in patients with different baseline CRCLs. Blue: Placebo+Allo, Pink: Lesinurad 200mg+Allo, Green: Lesinurad 400mg+Allo

(Source: Reviewer analysis, Studies 301 and 302)

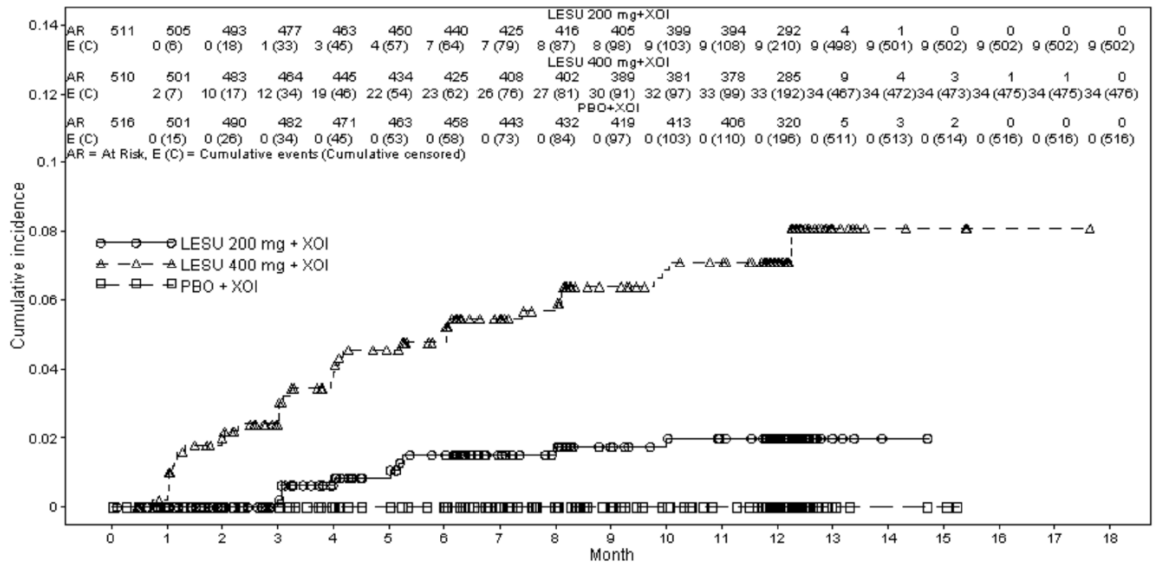


Figure 7: Cumulative Incidence of Serum Creatinine Elevations≥2.0 x Baseline in the Pivotal Phase 3 Studies (12-Month Studies 301, 302, and 304)
(Source: Figure 5, lesinurad renal safety report)

Table 6. Shift From Baseline to Last Post-Baseline Estimated Creatinine Clearance Category During Core Study (Studies 301, 302, and 304)

Placebo (n=516)

	Last eCrCl (mL/min)					
Baseline eCrCl (mL/min)	>=90 n (%)	>=60-<90 n (%)	>=30-<60 n (%)	<30 n (%)	Missing n (%)	Total n (%)
>=90	154 (30.0)	19 (3.7)	1 (0.2)	0	6 (1.2)	180 (35.0)
>=60-<90	45 (8.8)	171 (33.3)	8 (1.6)	0	5 (1.0)	229 (44.6)
>=30-<60	0	29 (5.6)	68 (13.2)	1 (0.2)	3 (0.6)	101 (19.6)
<30	0	0	4 (0.8)	0	0	4 (0.8)
Total	199 (38.7)	219 (42.6)	81 (15.8)	1 (0.2)	14 (2.7)	514 (100)

Lesinurad 200mg+XOI (n=511)

	Last eCrCl (mL/min)					
Baseline eCrCl (mL/min)	>=90 n (%)	>=60-<90 n (%)	>=30-<60 n (%)	<30 n (%)	Missing n (%)	Total n (%)
>=90	167 (32.7)	29 (5.7)	0	0	4 (0.8)	200 (39.2)
>=60-<90	31 (6.1)	153 (30.0)	15 (2.9)	0	9 (1.8)	208 (40.8)
>=30-<60	0	21 (4.1)	75 (14.7)	5 (1.0)	0	101 (19.8)
<30	0	0	0	1 (0.2)	0	1 (0.2)
Total	198 (38.8)	203 (39.8)	90 (17.6)	6 (1.2)	13 (2.5)	510 (100)

Lesinurad 400mg+XOI (n=510)

	Last eCrCl (mL/min)					
Baseline eCrCl (mL/min)	>=90 n (%)	>=60-<90 n (%)	>=30-<60 n (%)	<30 n (%)	Missing n (%)	Total n (%)
>=90	152 (29.9)	45 (8.9)	1 (0.2)	0	5 (1.0)	203 (40.0)
>=60-<90	24 (4.7)	162 (31.9)	24 (4.7)	2 (0.4)	1 (0.2)	213 (41.9)
>=30-<60	1 (0.2)	17 (3.3)	70 (13.8)	3 (0.6)	1 (0.2)	92 (18.1)
<30	0	0	0	0	0	0
Total	177 (34.8)	224 (44.1)	95 (18.7)	5 (1.0)	7 (1.4)	508 (100)

(Source: Table 9.5.4.1, ias-16)

2.4.4 Does the dose-response relationship for effectiveness and safety support the proposed doses of 200 mg QD in gout patients?

Dosing frequency

During clinical development of lesinurad, only QD regimen was evaluated in all Phase 2 and 3 studies. While FDA has expressed concerns about the daily variation of sUA with once daily dosing regimen (Table 3), the sponsor suggested that the once daily dosing regimen was supported by the extended pharmacodynamics effect of lesinurad and theoretical safety concern of evening dosing.

The PK half-life of lesinurad is 5 hours. The normal urate half-life (in absence of URAT1 inhibitor) ranges from approximately 20 hours to 56 hours. Maximal lowering of serum uric acid (sUA) during steady state occurs at approximately 8 hours post-dose with less urate lowering effect remains after 24 hours postdose (Figure 8). Sponsor suggested that urine volume is substantially reduced at night, so twice daily dosing would result in the highest concentrations of urinary uric acid, which would increase the potential for crystallization.

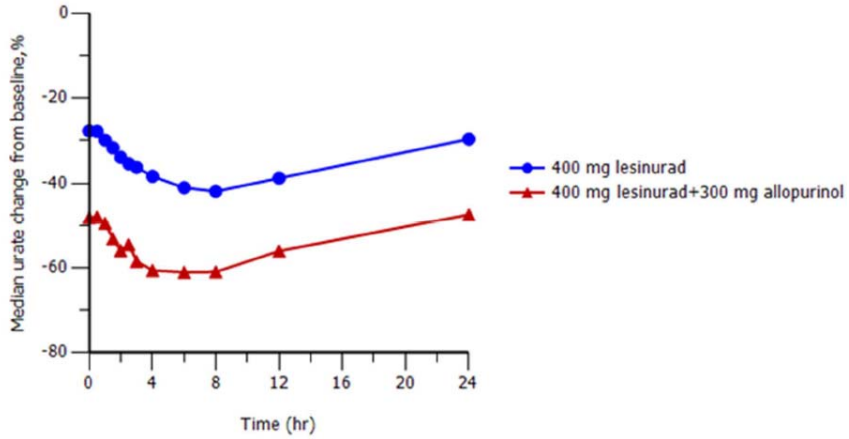


Figure 8. Median Plasma Uric Acid Change from Baseline Following Multiple QD Dosing of 400 mg Lesinurad , gout patients, on Steady State Day 7 (Study 110)
(Source: section 2.7.3, summary of clinical pharmacology, Figure 17)

Dose selection

Dose response was observed for both efficacy and safety (section 2.4.1 and section 2.4.3). Phase 3 studies indicated that lesinurad 400 mg qd was associated with acute uric acid nephropathy as evidenced by an increased incidence of sCr elevations and AEs of acute renal failure. Thus, it is concluded that lesinurad 200 mg is the appropriate dose for which to seek approval.

Recommendation for patients with different baseline renal functions

OCP recommends the following regulatory and labeling actions. An Advisory Committee meeting will be held on Oct 23, 2015 to discuss the review team's recommendations.

I Dosing in gout patients with normal renal function (eCRCL ≥ 90mL/min) and mild renal impairment (eCRCL = 60-<90 mL/min):

The sponsor proposes lesinurad 200 mg be administered with food and water. OCP

review team recommends approval in this population.

II Dosing in moderate renal impaired patients with an estimated creatinine clearance of 30-<60 mL/min:

Lesinurad acts as an inhibitor of several transporters in kidney, and inhibits the reabsorption of uric acid. Activity of lesinurad is dependent on the renal function of patients. There appears to be an attenuated uric acid lowering activity in patients with eCRCL less than 45mL/min based on the integrated PK/PD analysis, which is supported by the subgroup analysis (see section 2.4.2 and PM review).

The renal safety evaluation also suggested that the decline of renal function led to more severe consequence in patients with worse baseline renal function (see section 2.4.3).

Given the lower response of lesinurad in eCRCL<45 mL/min group and the increased risk of decline in renal function (eCRCL) from baseline, we consider benefit-risk of lesinurad not favorable in eCRCL<45 mL/min group. As another uricosuric drug probenecid was not recommended in patients with eCRCL<50mL/min by ACR guideline, and the data were sparse for patients with eCRCL between 45-50 mL/min in the lesinurad program, our analysis also supports similar recommendations for treatment with lesinurad. This risk benefit analysis has been communicated to clinical team.

Overall, we recommends:

In patients with eCRCL ≥45 mL/min

- Recommend for approval.
- Labeling explicitly cautioning language for adverse events, and renal function monitoring.

In patients with eCRCL<45 mL/min

- Do not use lesinurad because of unfavorable benefit-to-risk ratio.

2.4.5 Does this drug prolong QT/QTc Interval?

No, lesinurad does not prolong QT/QTc interval.

A thorough QT study (Study 117) was conducted in healthy subjects given super-therapeutic dose of 400 and 1600 mg. The supratherapeutic doses of 400 mg and 1600 mg did not impact the QT/QTc interval in healthy subjects. The largest upper bounds of the 2-sided 90% CI for the mean difference between lesinurad and placebo were below 10 ms (Table 7), the threshold for regulatory concern as described in ICH E14 guidelines. Please see QT-IRT review (by Dr. Janice Brodsky, DARRT date 10/23/2012, IND102128) for details.

Table 7. The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for Lesinurad and the Largest Lower Bound for Moxifloxacin (FDA Analysis)

Treatment	Time (h)	ΔΔQTcI (ms)	90% CI (ms)
Lesinurad 400 mg	2	2.9	(1.0, 4.8)
Lesinurad 1600 mg	6	3.5	(1.4, 5.7)
Moxifloxacin 400 mg	3	9.8	(7.9, 11.6)

* Multiple endpoint adjustment was not applied. The largest lower bound after Bonferroni adjustment for 4 timepoints is 7.9 ms.

(Source: Review by Dr. Janice Brodsky)

2.5 What are the PK characteristics of the drug?

2.5.1 What are the single and multiple dose PK parameters of parent drug and relevant metabolites in healthy adults?

Single dose PK in healthy adults

In a study in healthy adults, lesinurad was assessed following single dosing of lesinurad (b) (4) at 5 to 600 mg. The mean plasma concentration-time profile is shown in Figure 9. Following oral administration, lesinurad was readily absorbed with a median Tmax ranging between 0.5 to 0.75 hours in the fasted state (5 mg to 200 mg) and 0.25 to 1.5 hours in the fed state (100 mg to 600 mg). Lesinurad appears to follow bi-exponential disposition kinetics in healthy male volunteers (Figure 9). The terminal half-life after single dose was 2.73 to 34.6 hours across the different dose groups (Table 8). However, the large majority of lesinurad was eliminated within the first 24 hours postdose. The mean residence time of lesinurad in plasma after oral dosing was approximately 2.91 to 5.94 hours. PK parameters after single dose of lesinurad under fasting and fed conditions are summarized in Table 8.

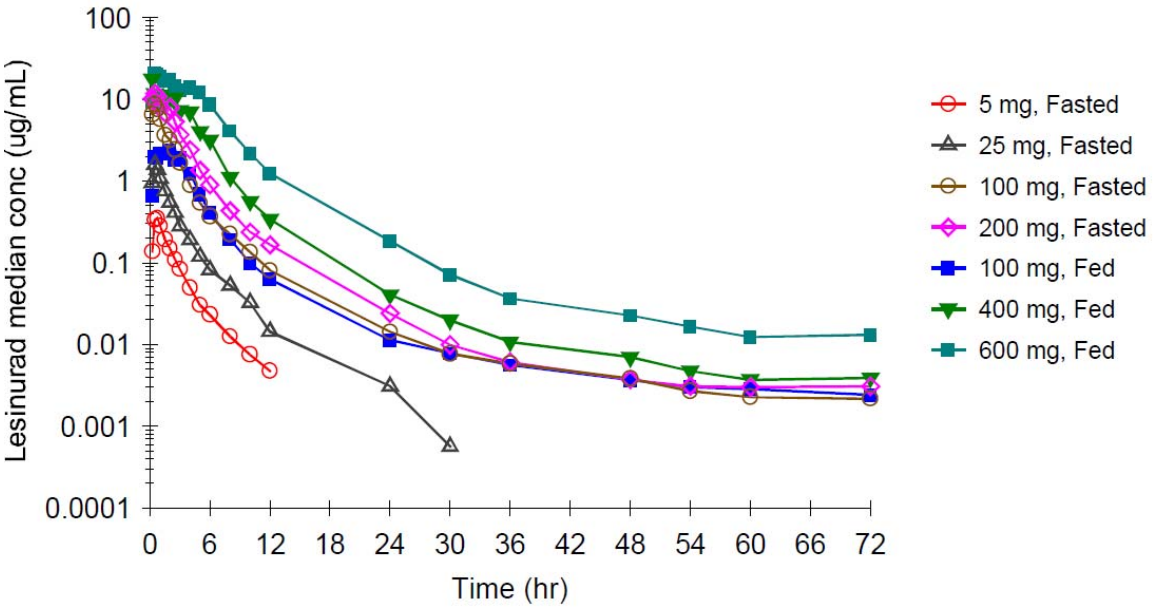


Figure 9: Median Plasma Concentration Profiles of Lesinurad Following Single Oral Doses of Lesinurad (b) (4) Under Fasted and Fed Conditions
(Source – Figure 1, summary of clin pharm)

Table 8: Summary of the Pharmacokinetic Parameters for RDEA594 Following Single Oral Doses

	Dose of RDEA594						
Parameter	5 mg (fasted) (N=4)	25 mg (fasted) (N=4)	100 mg (fasted) (N=4)	200 mg (fasted) (N=4)	100 mg (fed) (N=4)	400 mg (fed) (N=4)	600 mg (fed) (N=4)
$AUC_{(0\text{-}24\ h)}$ (µg·h/mL)	0.787 0.407, 1.52	3.12 2.45, 3.98	17.5 10.7, 28.8	31.9 21.0, 48.5	10.9 8.33, 14.2	56.4 34.9, 91.2	106 53.8, 209
$AUC_{(0\text{-}\infty)}$ (µg.h/mL)	0.779 0.396, 1.53	3.15 2.46, 4.03	17.9 10.8, 29.6	32.2 21.2, 49.1	11.2 8.65, 14.5	56.9 35.2, 92.1	108 54.1, 216
C_{max} (µg/mL)	0.303 0.134, 0.685	1.54 1.17, 2.04	7.68 4.46, 13.2	11.8 9.16, 15.2	3.21 1.62, 6.33	17.7 13.5, 23.2	22.0 16.1, 30.1
T_{max}[a] (h)	0.75 0.50-1.00	0.50 0.50-0.50	0.50 0.50-1.00	0.50 0.25-0.50	1.50 0.25-2.50	0.25 0.25-1.00	0.875 0.50-5.00
$AUC_{(0\text{-}\infty)}$ (norm)	10.2 6.44, 16.2	10.6 8.22, 13.6	12.4 6.07, 25.5	12.5 8.39, 18.5	8.89 6.47, 12.2	11.7 7.94, 17.2	15.7 7.67, 32.3
C_{max} (norm)	3.97 2.26, 6.97	5.18 4.59, 5.85	5.34 2.39, 11.9	4.56 2.89, 7.18	2.54 1.52, 4.26	3.64 2.92, 4.54	3.21 2.04, 5.06
$t_{½}$ (h)	2.73 1.46, 5.09	3.99 3.40, 4.68	12.7 4.64, 34.6	5.97 4.63, 7.70	34.6 17.3, 69.3	5.19 5.03, 5.35	8.04 2.61, 24.8
MRT (h)	2.93 2.33, 3.70	2.91 2.21, 3.82	3.76 2.51, 5.64	3.09 2.40, 3.99	5.74 4.86, 6.78	3.70 2.96, 4.63	4.82 3.08, 7.56
CL/F (mL/min)	107 54.4, 210	132 103, 169	93.1 56.3, 154	103 67.9, 157	149 115, 193	117 72.4, 190	92.5 46.3, 185
V_z/F (L)	25.3 20.1, 31.8	45.7 31.6, 66.1	102 24.4, 427	53.4 27.7, 103	445 232, 854	52.6 33.4, 82.8	64.4 17.2, 242

(Source – 11-1, Study 101 report)

Single dose PD in healthy adults

A dose-dependent decrease in sUA concentrations resulted from the oral administration of lesinurad over the 100 mg (fed/fasted) to 600 mg (fed) dose range, with maximum suppression of sUA occurring at the first sampling timepoint of 6 hours postdose (Figure 10). The duration of the suppression of sUA concentrations in serum increased with increasing lesinurad dose, from approximately 12 hours at 100 mg (fed/fasted) to beyond 24 hours postdose at the highest dose level (600 mg [fed]).

Excretion of uUA appeared to increase with increasing dose with the majority of statistically significant differences to placebo found across the 0 to 6 hour interval for the amount of uric acid recovered in urine (Aeur, 600 mg), renal clearance of uric acid (CLur; 100 mg, 400 mg, and 600 mg [fed]) and fractional excretion of uric acid (FEUA, 100 mg [fasted] and 100 mg to 600 mg [fed]).

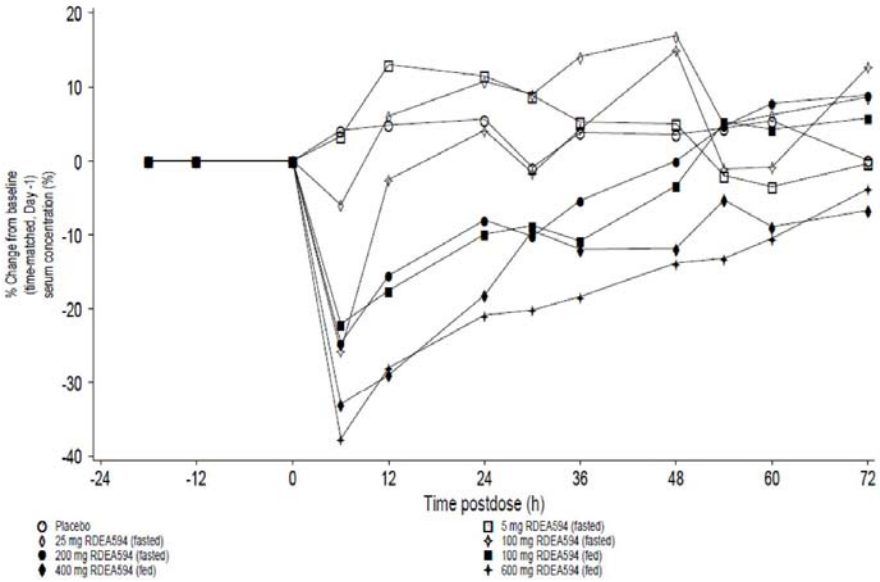


Figure 10. Median Percent Time-Matched Changes from Baseline (Day -1) in Serum Urate Concentrations Following Single Ascending Oral Doses of Lesinurad in Healthy Volunteers (Study 101)

(Source: Figure 11, summary of clin pharm)

Multiple-dose PK in healthy adults

Multiple-dose PK of lesinurad was characterized in study 102 with several formulations. Lesinurad PK after multiple doses was consistent with the single dose PK. The median T_{max} was about 0.75-5 hr and mean apparent terminal $t_{1/2}$ ranged from 3.77-10.6 hrs. Accumulation after multiple doses was minimal. Mean accumulation ratio for all doses ranged from 0.85 to 1.27, which was as expected based on short half-life and QD dosing regimen. The steady state was reached after one dose. Mean plasma PK profiles are shown in Figure 11 and summary PK parameters are listed in Table 9. From other studies, measurement of trough concentrations indicated that steady-state was achieved within 24-48 hrs after initiating repeat dosing.

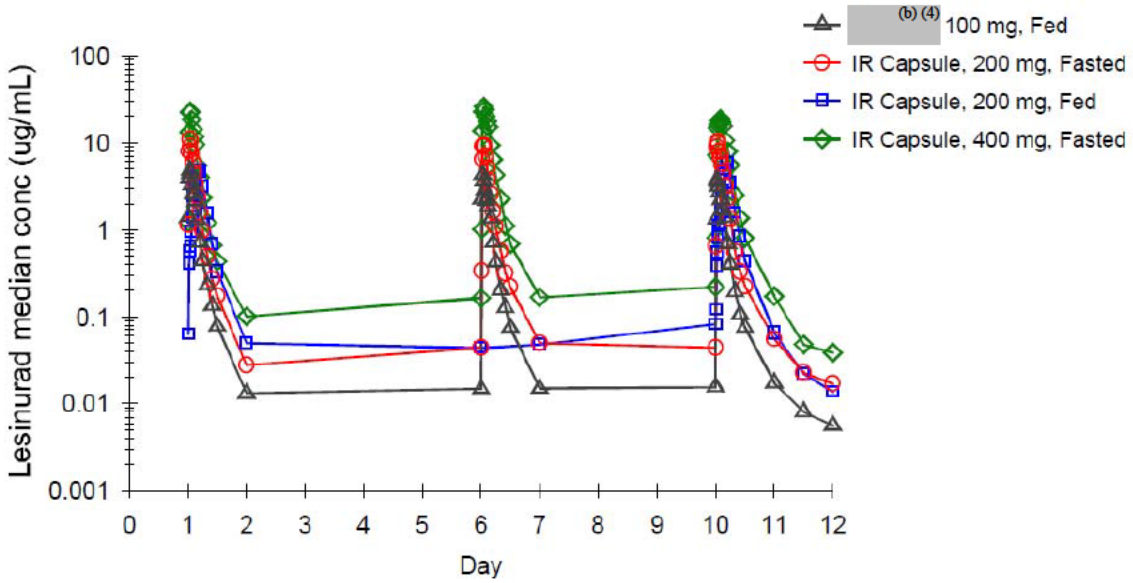


Figure 11: Median Plasma Concentration Profiles of Lesinurad Following Once Daily Multiple Oral Doses of Lesinurad (b) (4) or Immediate-Release Capsules
(Source – Figure 7, Summary of clin pharm)

Table 9: Summary of the Pharmacokinetic Parameters for RDEA594 Following Multiple Oral Doses (Segment I)

Parameter	Dose of RDEA594							
	100 mg (IR (b) (4) fed) (N=6)		200 mg (IR capsules, fasted) (N=6)		400 mg (IR capsules, fasted) (N=6)		200 mg (IR capsules, fed) (N=6)	
	Day 1	Day 10	Day 1	Day 10	Day 1	Day 10	Day 1	Day 10
AUC_τ (µg.h/mL)	14.2 (12.4, 16.2)	12.1 (10.6, 13.7)	28.7 (24.1, 34.1)	33.1 (28.1, 39.1)	70.5 (52.0, 95.8)	89.8 (67.1, 120)	29.8 (20.7, 43.0)	30.3 (23.3, 39.2)
AUC_∞ (µg.h/mL)	14.2 (12.5, 16.2)	NA	28.9 (24.2, 34.5)	NA	71.2 (52.4, 96.8)	NA	30.2 (20.8, 43.9)	NA
C_{max} (µg/mL)	4.74 (3.41, 6.59)	4.02 (2.86, 5.67)	10.8 (9.26, 12.5)	11.7 (9.27, 14.9)	23.1 (16.9, 31.6)	21.9 (18.3, 26.2)	5.54 (4.44, 6.91)	6.51 (5.46, 7.76)
T_{max}[a] (h)	0.750 (0.25-2.50)	0.625 (0.50-2.50)	0.750 (0.75-1.50)	0.750 (0.50-2.00)	1.00 (0.75-1.50)	2.00 (1.00-4.00)	5.00 (4.00-6.00)	4.50 (3.00-5.00)
AUC_τ (norm)	10.1 (8.90, 11.4)	8.56 (7.33, 9.99)	11.4 (8.23, 15.7)	13.1 (9.88, 17.5)	14.2 (10.7, 18.8)	18.1 (13.6, 24.0)	11.7 (7.76, 17.5)	11.8 (8.75, 16.0)
AUC_∞ (norm)	10.1 (8.95, 11.4)	NA	11.5 (8.27, 15.9)	NA	14.3 (10.8, 19.0)	NA	11.8 (7.80, 17.9)	NA
C_{max} (norm)	3.36 (2.48, 4.56)	2.86 (2.03, 4.01)	4.27 (3.69, 4.94)	4.66 (3.35, 6.49)	4.65 (3.65, 5.92)	4.41 (3.57, 5.44)	2.16 (1.59, 2.95)	2.55 (2.16, 3.00)
$t_{½}$ (h)	4.23 (3.74, 4.78)	10.6 (7.43, 15.1)	4.72 (4.03, 5.53)	8.91 (7.59, 10.5)	5.03 (4.33, 5.85)	7.48 (6.22, 8.99)	3.77 (3.38, 4.20)	8.20 (5.85, 11.5)
MRT (h)	3.19 (2.68, 3.80)	3.92 (3.34, 4.60)	3.35 (2.81, 4.00)	4.26 (3.90, 4.65)	3.60 (2.97, 4.37)	4.67 (3.80, 5.75)	6.45 (5.08, 8.19)	7.20 (6.44, 8.06)
CL/F or CL_{ss}/F (L/h)	7.02 (6.16, 8.00)	8.29 (7.27, 9.46)	6.92 (5.80, 8.25)	6.04 (5.11, 7.13)	5.61 (4.13, 7.63)	4.46 (3.33, 5.97)	6.62 (4.55, 9.62)	6.61 (5.10, 8.57)
V_{ss}/F (L)	22.4 (17.8, 28.2)	32.5 (25.4, 41.6)	23.2 (21.3, 25.3)	25.7 (21.6, 30.6)	20.2 (15.1, 27.1)	20.8 (17.5, 24.7)	42.7 (34.0, 53.5)	47.6 (39.7, 57.0)
R_{AUC_τ}	NA	0.851 (0.729, 0.992)	NA	1.09 (0.765, 1.56)	NA	0.949 (0.628, 1.43)	NA	1.18 (0.819, 1.69)
$R_{C_{max}}$	NA	0.849 (0.633, 1.14)	NA	1.16 (0.968, 1.38)	NA	1.27 (1.01, 1.61)	NA	1.01 (0.850, 1.21)

	Dose of RDEA594							
	200 mg (b) (4) capsules, fed) (N=6)		400 mg (b) (4) capsules, fed) (N=6)		600 mg (b) (4) capsules, fed) (N=6)		200 mg (b) (4) tablets, fed) (N=6)	
Parameter	Day 1	Day 7	Day 1	Day 7	Day 1	Day 7	Day 1	Day 7
AUC_τ (µg.h/mL)	26.1 (20.4, 33.3)	25.1 (21.2, 29.7)	51.8 (40.8, 65.7)	53.9 (44.6, 65.1)	73.0 (61.3, 87.0)	84.9 (73.5, 98.1)	20.9 (17.3, 25.3)	21.2 (18.7, 24.1)
AUC_∞ (µg.h/mL)	26.3 (20.6, 33.7)	NA	52.3 (41.3, 66.3)	NA	73.7 (61.9, 87.7)	NA	21.1 (17.4, 25.5)	NA
C_{max} (µg/mL)	8.18 (5.49, 12.2)	7.71 (5.91, 10.0)	13.8 (11.5, 16.7)	15.7 (13.9, 17.7)	20.1 (17.3, 23.3)	20.8 (16.4, 26.4)	6.16 (4.60, 8.25)	5.57 (4.24, 7.31)
T_{max}[a] (h)	3.00 (1.00, 3.00)	3.50 (2.00-5.00)	3.00 (1.50, 3.00)	2.50 (1.50-4.00)	2.50 (1.50, 5.00)	3.50 (1.00-5.00)	1.75 (1.00, 5.00)	4.50 (2.00-6.00)
AUC_τ (nom)	10.4 (7.93, 13.6)	9.98 (7.99, 12.5)	11.0 (7.94, 15.2)	11.4 (8.77, 14.9)	9.62 (8.08, 11.5)	11.2 (10.0, 12.5)	8.79 (8.05, 9.61)	8.92 (7.58, 10.5)
AUC_∞ (nom)	10.5 (8.00, 13.7)	NA	11.1 (8.03, 15.4)	NA	9.72 (8.17, 11.6)	NA	8.87 (8.10, 9.71)	NA
C_{max} (nom)	3.25 (2.12, 4.98)	3.07 (2.35, 4.01)	2.94 (2.31, 3.75)	3.33 (2.71, 4.10)	2.65 (2.18, 3.20)	2.74 (2.22, 3.39)	2.59 (1.96, 3.43)	2.34 (1.66, 3.30)
$t_{½}$ (h)	4.56 (4.24, 4.90)	6.98 (6.04, 8.06)	4.01 (2.94, 5.47)	8.40 (6.80, 10.4)	4.14 (2.78, 6.17)	7.89 (5.22, 11.9)	4.11 (3.83, 4.41)	5.65 (5.28, 6.05)
MRT (h)	4.67 (4.09, 5.33)	5.90 (5.21, 6.69)	4.94 (4.33, 5.64)	5.50 (4.80, 6.29)	4.71 (3.85, 5.77)	5.95 (5.12, 6.90)	4.71 (3.48, 6.37)	6.67 (5.50, 8.07)
CL/F or CL_{ss}/F (L/h)	7.59 (5.94, 9.70)	7.97 (6.74, 9.43)	7.65 (6.03, 9.69)	7.43 (6.15, 8.97)	8.14 (6.84, 9.69)	7.06 (6.12, 8.16)	9.50 (7.85, 11.5)	9.44 (8.31, 10.7)
V_{ss}/F (L)	35.5 (26.0, 48.3)	47.1 (36.9, 60.0)	37.8 (28.1, 50.9)	40.8 (37.0, 45.1)	38.4 (31.2, 47.2)	42.0 (38.9, 45.4)	44.7 (30.4, 65.8)	62.9 (52.0, 76.1)
$R_{AUC\tau}$	NA	0.961 (0.855, 1.08)	NA	1.04 (0.861, 1.26)	NA	1.16 (1.07, 1.26)	NA	1.01 (0.815, 1.26)
R_{Cmax}	NA	0.943 (0.633, 1.41)	NA	1.13 (0.964, 1.33)	NA	1.04 (0.877, 1.22)	NA	0.904 (0.670, 1.22)

(Source – Table 11-1, 11-2, study report 102)

Multiple-dose PD in healthy adults

A statistically significant treatment-dependent decrease in sUA concentrations was found, compared with placebo, following multiple qd oral administration of lesinurad as IR formulations (100 mg to 400 mg over 10 days, Figure 12) and (b) (4) formulations (200 mg to 600 mg over 7 days). Similarly, excretion of uUA increased with increasing doses of lesinurad. Maximum suppression of sUA occurred at the first sampling timepoint of 12 hours postdose, which corresponded with maximal uUA excretion at the earliest time interval of 0 to 12 hours postdose. The effects of sUA reduction were observed through 24 hours postdose at 100 mg to 600 mg dosing.

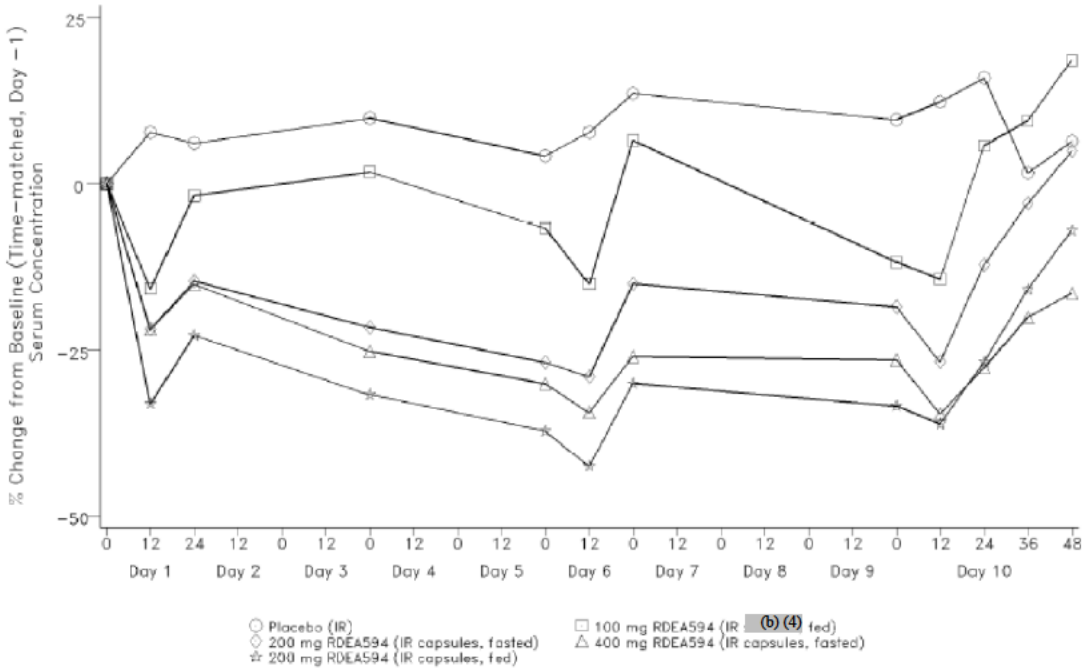


Figure 12. Median Percent Changes from Baseline (Time-Matched, Day -1) in Serum Urate Concentrations Following Multiple Oral Immediate-Release Doses of Lesinurad (Day 1 to Day 10) in Healthy Volunteers (Study 102)
(source: Figure 12, summary of clin pharm)

2.5.2 How does the PK of the drug and its relevant metabolites in healthy adults compare to that in patients with the target disease?

Lesinurad PK was assessed in subjects with gout in 2 DDI studies (Studies 110 and 111) and 4 Phase 2 studies (Studies 202, 203, 201, and 204).

Plasma exposures in subjects with hyperuricemia were generally similar or slightly lower than those observed in healthy subjects. The key PK variables of lesinurad in subjects with hyperuricemia compared with normal healthy subjects are presented in Table 10.

Table 10: Summary (Geometric Mean, 95% CI) of Lesinurad Pharmacokinetic Parameters Following Once Daily Multiple Oral Doses of Lesinurad Immediate-Release Capsules in Subjects With Hyperuricemia or Normal Healthy Subjects

Population	Study (Phase)	Dose (mg)	N	Geometric Mean (95% CI)			
				T_{max}[a] (hr)	C_{max} (µg/mL)	AUC_{0-24} (µg·hr/mL)	$t_{1/2}$ (hr)
Hyperuricemic	110 (Phase 1b)	400	10	3.00 (1.50-6.00)	8.40 (6.48-10.9)	43.7 (33.0-57.9)	3.90 (3.49-4.35)
		600	10	4.00 (2.50-4.00)	18.0 (14.0-23.1)	90.2 (71.4-114)	4.49 (4.00-5.05)
	203 (Phase 2b)	200	4	4.00 (2.50-6.00)	4.10 (1.73-9.70)	24.2 (13.8-42.2)	3.75 (3.11-4.53)
		400	17[b]	2.50 (0.00-4.00)	3.94 (1.60-9.69)	23.3 (9.62-56.3)	5.18 (3.64-7.37)
		400	13[c]	2.50 (1.50-4.00)	10.0 (8.54-11.7)	57.2 (51.0-64.1)	3.65 (3.36-3.97)
Normal Healthy	105 (Phase 1)	200	12	3.00 (2.00-4.00)	6.85 (6.24-7.52)	27.4 (24.0-31.4)	4.49 (4.12-4.89)
		400	12	2.00 (1.50-5.00)	15.0 (13.0-17.2)	59.7 (50.6-70.5)	4.88 (4.39-5.43)

Abbreviations: AUC_{0-24}, area under the concentration-time curve from time 0 to 24 hours postdose; CI, confidence interval; C_{max}, maximum observed concentration; $t_{1/2}$, apparent terminal half-life; T_{max}, time of occurrence of maximum observed concentration.

[a] Presented as median (range).

[b] The 400 mg dose group included 4 subjects who showed unusually low C_{max} (below 0.3 µg/mL) and AUC (below 3 µg·hr/mL).

[c] An additional calculation was performed for the 400 mg dose group to exclude 4 subjects who showed unusually low C_{max} (below 0.3 µg/mL) and AUC (below 3 µg·hr/mL).

(source: Table 5, summary of clin pharm)

In population PK analysis, the clearance of lesinurad (posthoc CL/F median of 6.48L/h) was lower in gout patients than in healthy subjects (posthoc CL/F median of 8.31L/h), possibly due to an elderly age group for gout patients and inter-study variability (Figure 13). Inter-individual variability of PK parameters was generally higher in patients than in healthy volunteers (Eg. IIV for CL/F is 29.8% in healthy subjects, and 63.4% in all patients), likely due to the more heterogeneous population, e.g. in terms of covariate distribution, co-medication, and potential disease dependent changes in physiology.

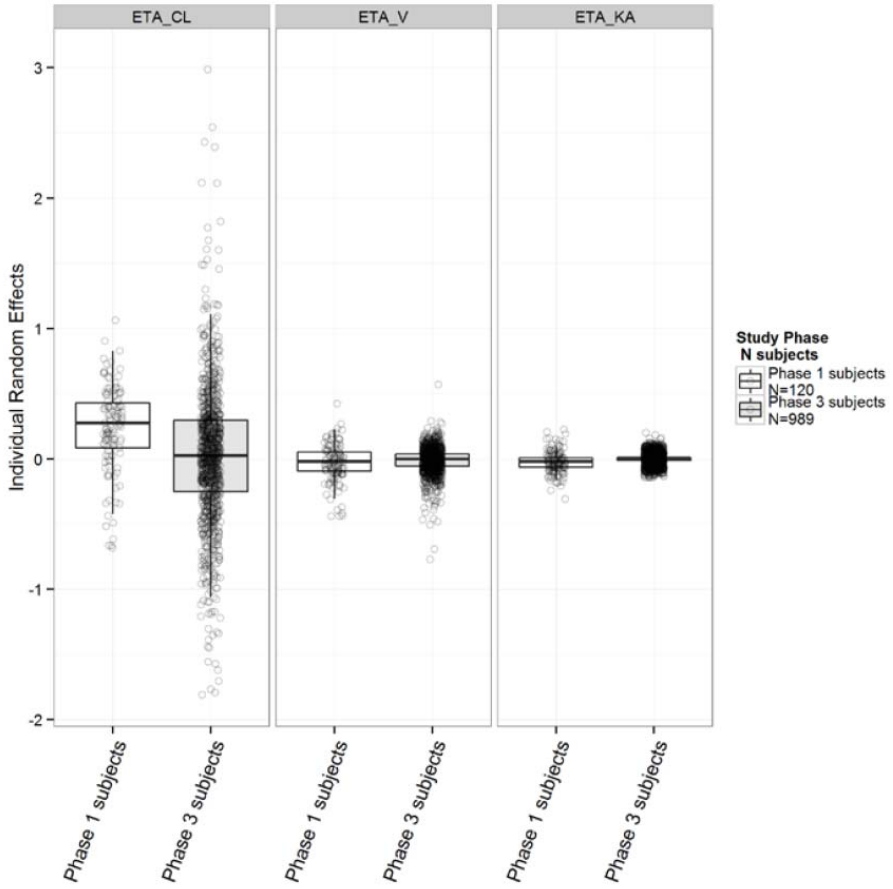


Figure 13. Relationship between Post-Hoc ETA_CL, ETA_V and ETA_KA of Lesinurad and Study Phase – Structural Population PK model Based on Phase 1 and 3 Data in healthy and gout populations
(Source: Figure 5.4-1, popPK-lesinurad-analysis)

2.5.3 What is the inter- and intra-subject variability of the PK parameters in healthy volunteers and patients with the target disease?

Based on population PK analysis of lesinurad in gout patients, the IIV for CL/F expressed as coefficient of variation was 63.4%, IIV in Vc/F was 12.2%, IIV in V2/F was 20.5%, IIV in KA was 121.7%, and IOV for Vc/F was 13.6%. See pharmacometrics review in appendix 4.1 for details.

2.5.4 What are the characteristics of drug absorption?

Lesinurad has an absolute bioavailability of approximately 100%, indicating complete absorption and a lack of gut wall and hepatic first pass metabolism. In-vitro studies demonstrated that lesinurad is not a P-gp substrate, and is a minor substrate of BCRP (see sections 2.7.3 and 2.7.4). Lesinurad was readily absorbed following a single dose of free acid (FA) tablets with a median Tmax of 1-4 hours under fed conditions. Administration with a high-fat meal decreases lesinurad Cmax by up to 18% but does not alter AUC as compared with fasted state. In clinical trials, ZURAMPIC was administered with food.

2.5.5 What are the characteristics of drug distribution?

Following a single IV dose of 100 µg [14C]lesinurad, the volume of distribution at steady state was 20.3 L (Study 131). Following oral administration of 400 mg [14C] lesinurad, mean plasma-to-blood ratios of lesinurad AUC and Cmax ranged between 1.80 and 1.84, indicating that radioactivity was largely contained in the plasma space and did not penetrate or partition extensively into red blood cells.

In vitro studies determined high plasma protein binding for lesinurad with the bound fraction (f_B) in humans to be greater than 97.7% at concentrations from 1 to 50 µM and was primarily bound to albumin.

2.5.6 Does the mass balance study suggest renal or hepatic as the major route of elimination?

According to data from mass balance study, both renal and hepatic routes contribute to the elimination of lesinurad, with most of the lesinurad dose excreted in urine. In the human AME study (Study 112), a mean of 63.4% of the lesinurad dose was recovered in urine and 32.3% was recovered in feces through the last collection interval. Urinary recovery was essentially complete by 24 hours postdose (mean of 61.1% of the dose recovered).

Overall, ~64.2% of lesinurad dose was eliminated as metabolites in both urine and feces, and ~31% of lesinurad was excreted in urine as unchanged drug (Table 11). Lesinurad and 2 oxidation metabolites, M3 and M4, were major components in human urine, accounting for 31.3%, 12.0%, and 15.7% of the dose, respectively. In human feces, the dominant component was debrominated metabolites, M2, M5, and M5b, indicating the involvement of intestinal microflora in lesinurad metabolism.

Table 11: Metabolic Balance of Urine and Faeces Samples Following a Single Dose of 600 mg [14C]lesinurad

Matrix	Time (hr)	Dose %										
		M1	M2	M3	M3b	M4	M5	M5b	M16	Others	Lesinurad	Total
Urine	0-144	1.5	0.3	12.0	1.0	15.7	ND	ND	0.5	1.2	31.3	63.4
Faeces	0-144	ND	4.8	0.3	1.9	5.0	3.6	7.8	1.1	7.5	1.5	33.5

(Source: Table 11-8, CSR 112)

2.5.7 What is the percentage of total radioactivity in plasma identified as parent drug and metabolites?

In plasma, the major component was unchanged lesinurad. Mean plasma lesinurad to plasma radioactivity ratios of AUC0-24 and AUC∞ were 0.618 and 0.463, respectively, indicating that the majority of circulating radioactivity in plasma in the first 24 hours postdose was attributed to lesinurad but after 24 hours was mainly due to metabolites.

Lesinurad contributesto approximately 93% of radioactivity in plasma at 3 hours postdose(**Table 12**). The predominant metabolites detected in humans were M3 and M4, with no human metabolite measuring >5% of unchanged lesinurad in plasma for both

Cmax and AUC. The results were consistent with other studies following long term qd administration of lesinurad up to 44 weeks in gout patients (study 202).

Table 12: Metabolic Profiles of Pooled Human Plasma, Urine, and Faeces Samples Following a Single Dose of 600 mg [14C]lesinurad

Matrix	Time (hr)	Radioactivity %										
		M1	M2	M3	M3b	M4	M5	M5b	M16	Others	Lesinurad	Total
Plasma	3	ND	ND	2.2	ND	2.0	ND	ND	ND	ND	93.1	97.3
Urine	0-24	2.4	0.4	18.9	1.5	24.8	ND	ND	0.8	1.9	49.3	100
Faeces	24-48	ND	15.7	0.9	7.9	17.2	9.2	25.7	5.1	11.4	6.9	100
Faeces	48-72	ND	14.5	0.7	4.9	14.9	12.2	23.5	2.5	23.3	3.5	100

(Source – Table 11-5, CSR112)

2.5.8 What are the characteristics of drug metabolism?

The proposed metabolic pathway for lesinurad is shown in Figure 14. In human in vitro evaluation, biotransformation of lesinurad was primarily mediated through cytochrome P450 (CYP) 2C9 with minimal contribution from CYP1A1, CYP2C19, and CYP3A. CYP2C9 is responsible for M3 formation and is also responsible for the metabolism of lesinurad to an epoxide intermediate (not detected in microsomal or hepatocyte incubation), which is rapidly hydrolyzed to M4 by microsomal epoxide hydrolase (mEH). M4 is mainly detected in urine likely due to its low protein binding (approximately 25%) and high renal clearance (CLR). It is considered to be a disproportionate human metabolite because a higher level (> 10% of dosing) was detected in human urine than in rat and monkey urine (< 0.5% of dosing). In human feces, the dominant components were debrominated metabolites, M2, M5, and M5b, indicating the role of intestinal microflora in lesinurad metabolism.

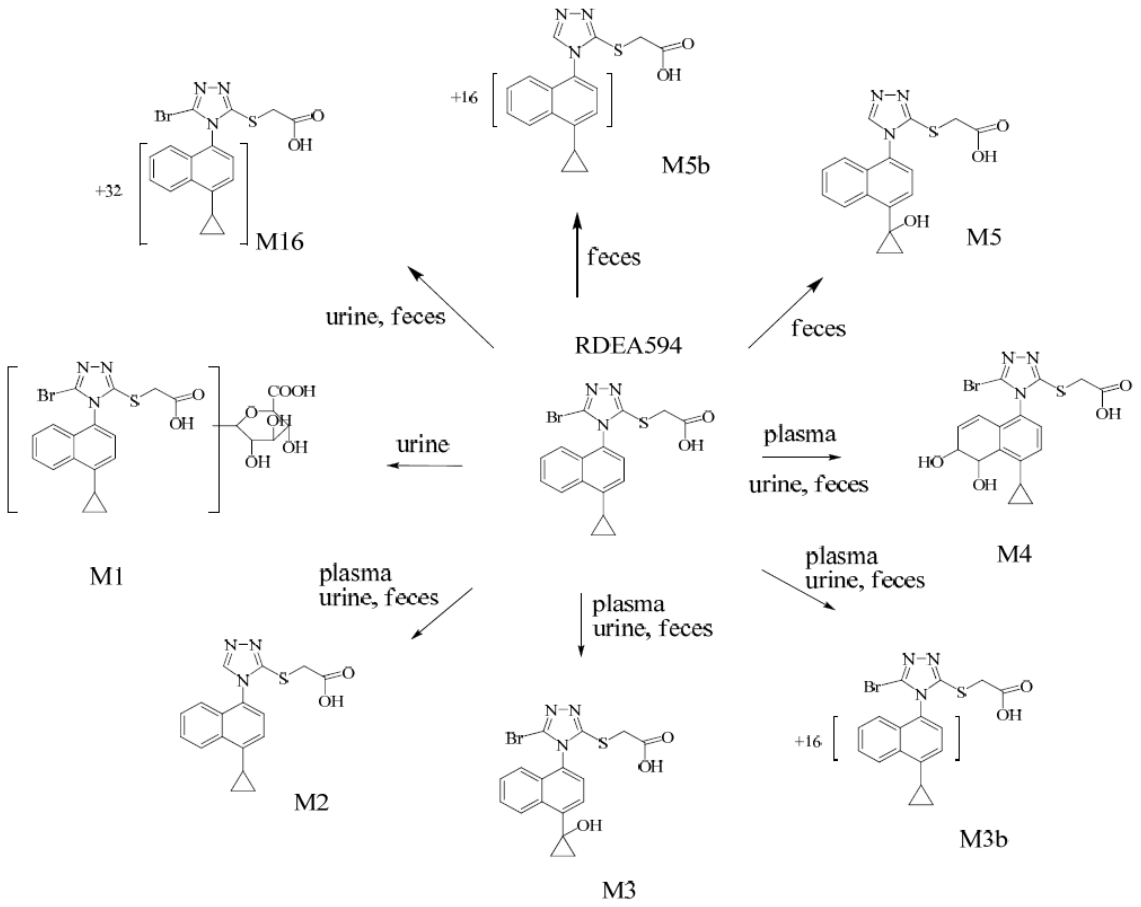


Figure 14: Proposed Metabolic Profile for lesinurad in Human Plasma
(Source – Figure 11-3, study report 112)

2.5.9 Is there evidence for excretion of parent drug and/or metabolites into bile?

Yes, some drug related material may be excreted via the bile.

In vitro studies determined that lesinurad is a minor substrate of BCRP, but not a substrate for P-gp or MRP2. In the mass balance study, feces sample were collected 0 - 144 h after oral dosing, and comprised 33.5% of the administered dose. Most of the radioactivity in feces was detected between 24-96 hour, with most of the total dose excreted as metabolites (see section 2.5.6). This indicated that some drug related material was excreted via the bile.

The glucuronide of lesinurad, M1, was detected in rat and monkey bile at much higher levels than in urine. However, M1 was not detected in feces in human, where only trace levels of M1 were detected in urine.

2.5.10 Is there evidence for enterohepatic recirculation for parent and/or metabolites?

For doses up to 1600 mg, there were no secondary peaks observed in plasma

concentration – time profiles of lesinurad (Figure 15). There is no evidence of enterohepatic recirculation at the proposed therapeutic dose of 200 mg qd.

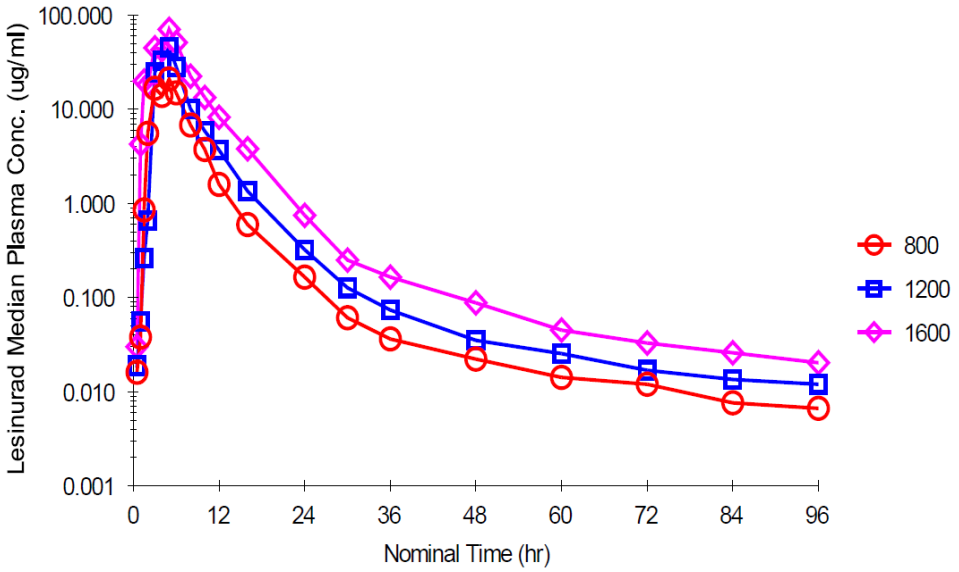


Figure 15: Median Plasma Concentration Profiles Following a Single Dose of Lesinurad 800, 1200, or 1600 mg to Healthy Male Subjects
(Source – Figure 11-1, study report 117)

2.5.11 What are the characteristics of drug excretion in urine?

In the human AME study (Study 112), a mean of 63.4% of the lesinurad dose was recovered in urine. Urinary recovery was essentially complete by 24 hours postdose (mean of 61.1% of the dose recovered). In urine, lesinurad was the major component excreted, accounting for 31.3% of the dose. The 2 most abundant metabolites, M3 and M4, accounted for 12.0% and 15.7% of the dose, respectively. A few other minor metabolites were also detected at lower than 3% of radioactivity. Among these minor metabolites, M1 (glucuronide conjugate of lesinurad) accounted for 2.4% of the 0-to-24-hour urine radioactivity, which is less than 2% of the dose.

2.5.12 Based on PK parameters, what is the degree of the proportionality of the dose-concentration relationship?

The dose proportionality of lesinurad under the fasted and fed conditions was assessed separately in pooled PK parameters from healthy volunteers receiving lesinurad alone. Proportionality analysis was performed using the power model (Peng 2004). Scatter plots of pooled Cmax and AUC∞ (100 mg to 1200 mg doses) under fed conditions are shown in Figure 16. Data were pooled from studies involving lesinurad (b) (4) IR capsules, and FA tablets for the dose-proportionality assessment.

Lesinurad exposure (AUC) increased more than dose proportionally for doses more than 1200 mg (Figure 17).

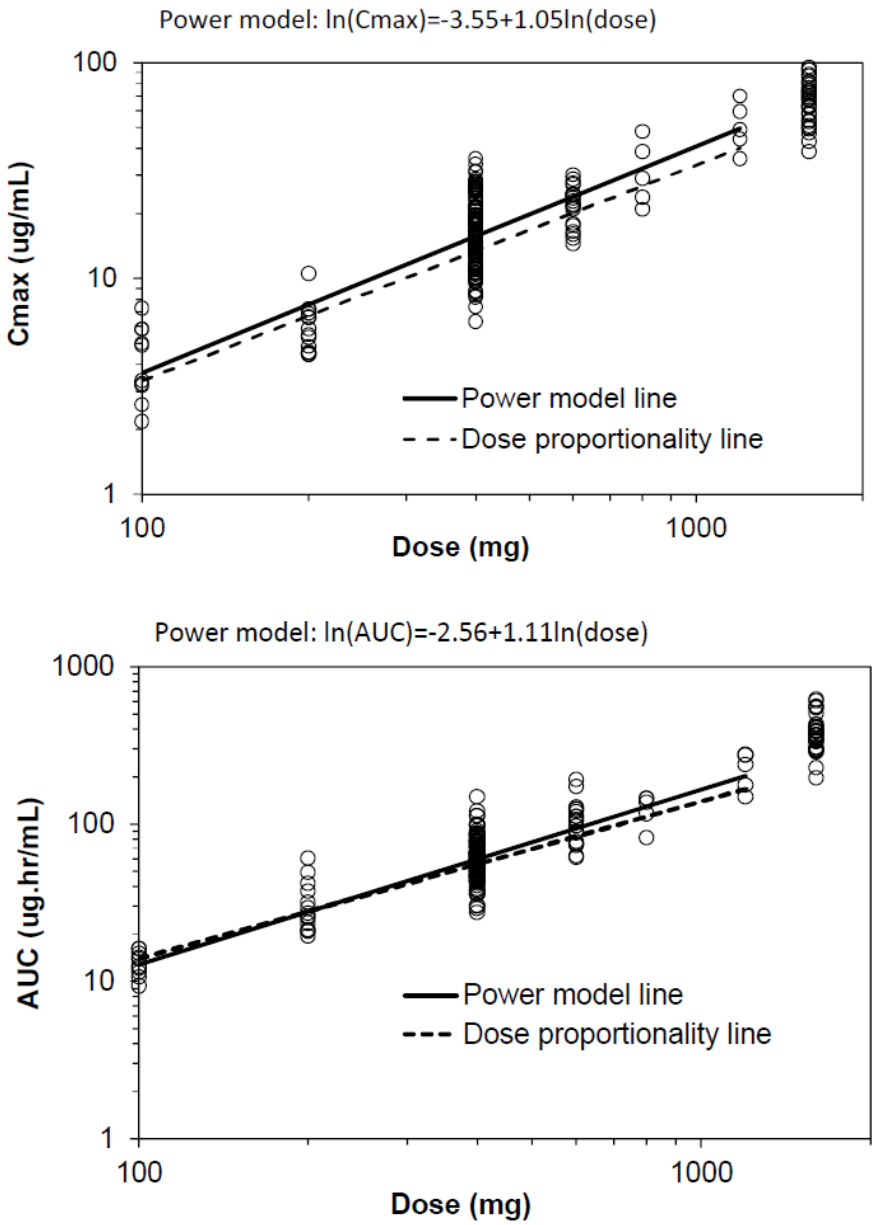


Figure 16. Dose Proportionality: Lesinurad Cmax and AUC Versus Dose Under Fed Conditions (100 mg to 1200 mg)
(Source: Figure 5, summary of clinical pharmacology)

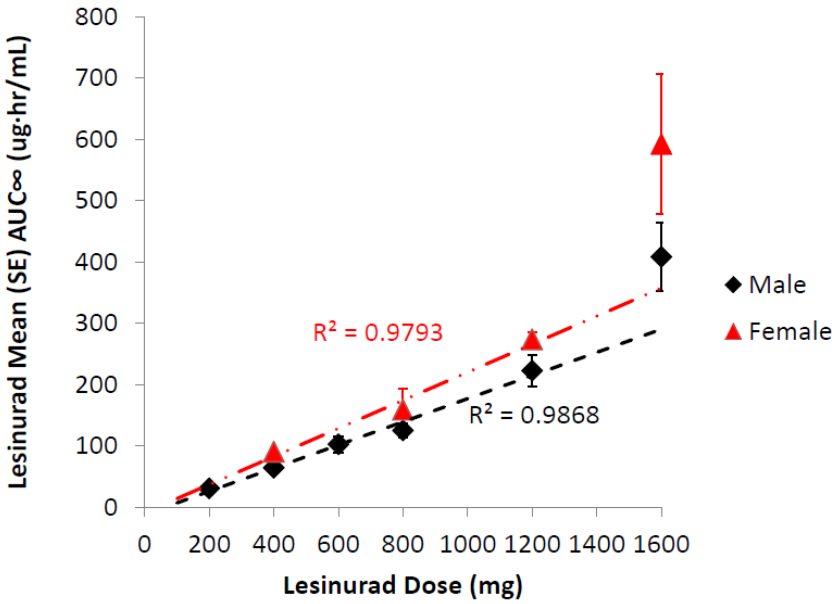


Figure 17. Dose Linearity Assessment Plot of AUC for Lesinurad in Males and Females (Source: Figure 11-4, study report 117)

2.5.13 How do the PK parameters change with time following chronic dosing?

$AUC_{0-\infty}$ for lesinurad after single dose is compared with $AUC_{\tau,ss\ (0-24h)}$ at steady state. CL/F(ss) of lesinurad did not change after multiple dosing compared to single dose administration. The linearity index, derived as dose normalized $AUC_{\tau,ss}/AUC_{0-\infty}$ was 0.95-1.07 (Table 13). The pharmacokinetics of lesinurad can therefore be considered time-independent. PK information was collected in Phase 2 and Phase 3 studies in gout patients. Trough (pre-dose) concentrations are similar over a 12-month period, indicating no time-dependency in PK of lesinurad after the concentration reached steady state.

Table 13: Exposure of lesinurad after single or multiple doses

Study	Subjects	Treatment	lesinurad AUC* (µg.h/mL)
101	Healthy	400 mg sd, fed	56.9
102	Healthy	400 mg (b) (4) qd, fed	53.9
		200 mg IR Qd, fed	30.3

N: Total subjects; SD: single dose; qd: once daily dose

* $AUC_{0-\infty}$ for SD; $AUC_{\tau,ss}$ for qd

(Source –Table 11-1, study report 101, Table 11-1, 11-2, study report 102)

2.5.14 Is there evidence for a circadian rhythm of the PK?

Lesinurad is recommended to be taken in the morning, and has not been dosed in the evening during development. Urine volume is substantially reduced at night (approx. 1/5 of morning). Therefore, the evening dosing may result in the highest concentrations of urinary uric acid, which would increase the potential for crystallization.

The PD effect of lesinurad during 24 hours postdose was evaluated in several studies. In general, the sUA lowering effect was more significant during the first few hours postdose, and sUA levels were higher when lesinurad concentrations were low (Figure 18). The protocol for phase 3 studies did not specify the sUA sampling timepoint relative to dose. The reviewer analysis shows that most serum uric acid samples were collected between 1-5 hour postdose at month 6 in phase 3 studies. The sampling time is similar among different arms in each study, and the sampling time distribution is similar in responders and non-responders (See pharmacometrics review).

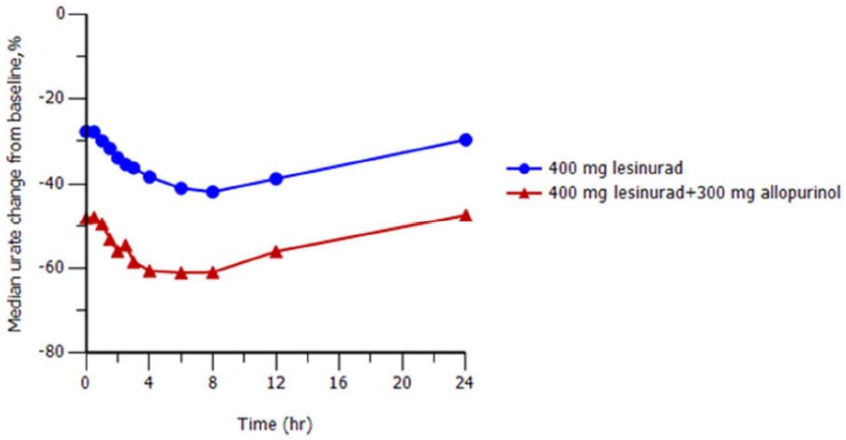


Figure 18. Median Plasma Uric Acid Change from Baseline Following Multiple QD Dosing of 400 mg Lesinurad on Steady State Day 7 (Study 110)
(Source: section 2.7.3, summary of clinical pharmacology, Figure 17)

2.6 Intrinsic Factors

2.6.1 What are the major intrinsic factors responsible for the inter-subject variability in exposure (AUC, Cmax, Cmin) in patients with the target disease and how much of the variability is explained by the identified covariates?

Based on sponsor's population PK analysis of gout patients and healthy subjects (N=1109), Creatine clearance, body weight, and disease status were identified as covariates influencing the PK of lesinurad. As shown in Figure 19, typical CL/F value in subjects in gout patients (Phase 3 studies) was approximately 18% lower than that observed in healthy subjects in (Phase 1 studies). Based on these decreases in CL/F, the estimated increases in lesinurad exposure would be approximately 12%, 31% and 65% in patients with mild, moderate, and severe renal impairment, respectively, compared with patients with normal renal function.

The most important covariate describing the variability was the effect of weight on Vc/F of lesinurad. Based on the body weight range in subjects in the Phase 3 studies (range: 46.7 to 239 kg), the Vc/F is expected to range from 19.6 to 45.1 L, but in a more typical

weight range (i.e., 60 to 120 kg), the Vc/F would range from 22.3 to 31.7 L.

Age, sex, and race/ethnicity were not found to be statistically significant covariates affecting PK parameters of lesinurad.

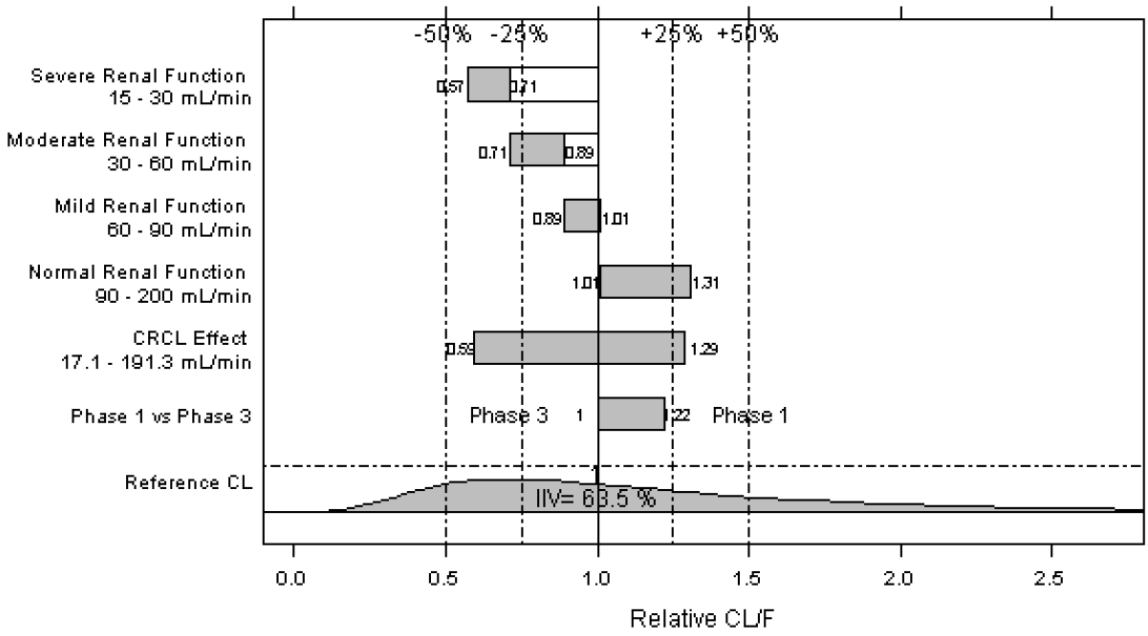


Figure 19. Effects of Renal Function and Disease Status (Phase 1-healthy; Phase 3-gout) on Apparent Clearance of Lesinurad
(Source: Figure 5.4-4, popPK lesinurad analysis)

2.6.2 Based upon what is known about E-R relationships in the target population and their variability, what dosage regimen adjustments are recommended for each group?

Lesinurad exposure is 50-74% higher in patients with moderate renal impairment, and may lead to potential safety concern. However, dose adjustment based on PK is not applicable here, due to changed PK/PD relationship in renal impairment patients. Considering the overall risk-benefit profile, we recommend approval of 200 mg in patients with eCRCL≥45 mL/min, and do not recommend lesinurad in patients with eCRCL <45 mL/min. See section 2.6.2.6 for further details.

2.6.2.1 Severity of Disease State

Plasma exposures in subjects with hyperuricemia were generally similar to those previously observed in healthy subjects.

2.6.2.2 Body Weight

Body weight was evaluated as a covariate in the population PK model (see Pharmacometrics Review, appendix 4.1), and was found to be a significant covariate on V/F .

2.6.2.3 Age

Age was evaluated as a covariate in the population PK model (see Pharmacometrics Review, appendix 4.1), and was found not to be a significant covariate. However, as CrCl was found to be a significant covariate and glomerular filtration rate (GFR) decreases with increasing age, there may be GFR-related changes in exposure with increased age.

2.6.2.4 Sex

After adjust for weight, gender does not have additional impact on lesinurad exposure (Table 14).

Table 14. Geometric Mean Ratios of Lesinurad Pharmacokinetics Between Female and Male Subjects (Study 117)

Dose (mg)	Parameter	N (Female/Male)	Geometric Mean Ratio % (90% CI)	Body Weight Normalized Geometric Mean Ratio % (90% CI)
			Female/Male	Female/Male
400	C_{max}	25/28	115% (99.4-134%)	98.4% (85.3-113%)
	AUC_{∞}	25/28	113% (99.8-127%)	95.9% (85.8-107%)
1600	C_{max}	26/28	116% (104-129%)	99.0% (88.8-110%)
	AUC_{∞}	26/28	116% (102-132%)	99.5% (88.1-112%)

(Source: Table 6, summary of clin pharm)

2.6.2.4 Pediatric Patients

Since gout is a disease of adults and has no pediatric correlate, sponsor is granted a full waiver (07 October 2014) from the requirement to conduct pediatric research with lesinurad for gout and hyperuricemia.

2.6.2.5 Race/Ethnicity

Race and ethnicity were evaluated as a covariate in the population PK model (see Pharmacometrics Review, appendix 4.1), and were found not to be significant covariates. Assessment of race included White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, Maori, and Other; ethnicity included Hispanic or Latino/non-Hispanic or non-Latino.

A Phase 1 study has been conducted in US with healthy male Japanese volunteers (Study 125) to study potential effects of lesinurad dosing on race. Based on cross-study comparisons of lesinurad PK in the fasted or fed condition after a 200 mg or 400 mg single dose of the FA tablet formulation in Japanese subjects, and in Western subjects who were drawn from the US population (Study 109 and Study 121), the time-course of lesinurad in plasma was similar across races. The geometric mean plasma Cmax and

AUC values were approximately 7% to 40% higher in Japanese subjects, but there was considerable overlap in 95% CIs around the exposure values in Japanese and Western subjects (Table 15).

Table 15. Comparison of Lesinurad Plasma Pharmacokinetic Parameters Following Single Doses (Fed) in Healthy Adult Male Japanese Subjects Versus Healthy Adult Male Western Subjects

Dose (mg)	Parameter		Western Subjects (Study 109) (N=8)	Japanese Subjects (Study 125) (N=6)	% Difference (Japanese Versus Western)
200	Body weight (kg)	Mean	78.5	78.4	NA
		SD	10.4	7.65	
		Range	62.2-97.0	69.0-90.1	
	AUC_{∞} (µg·hr/mL)	Geomean	28.5	30.4	6.7%
		95% CI	(20.9-38.7)	(26.6-34.7)	
	C_{max} (µg/mL)	Geomean	6.11	8.17	34%
		95% CI	(4.83-7.73)	(6.19-10.8)	
400	Body weight (kg)	Mean	78.5	71.4	NA
		SD	10.4	9.95	
		Range	62.2-97.0	60.2-85.1	
	AUC_{∞} (µg·hr/mL)	Geomean	61.6	86.2	40%
		95% CI	(48.1-78.9)	(66.8-111)	
	C_{max} (µg/mL)	Geomean	15.4	20.0	30%
		95% CI	(13.3-17.9)	(13.1-30.7)	
Dose (mg)	**Parameter**		**Western Subjects (Study 121) (N=15)**	**Japanese Subjects (Study 125) (N=6)**	**% Difference (Japanese Versus Western)**
400	Body weight (kg)	Mean	81.0	71.4	NA
		SD	12.7	9.95	
		Range	56.2-105	60.2-85.1	
	AUC_{∞} (µg·hr/mL)	Geomean	63.1	86.2	37%
		95% CI	(52.7-75.4)	(66.8-111)	
	C_{max} (µg/mL)	Geomean	16.3	20.0	23%
		95% CI	(12.9-20.4)	(13.1-30.7)	

(Source: Table 7, clin pharm summary)

2.6.2.6 Renal Impairment

Two studies in renal impaired subjects were conducted. Study 104 evaluated a single dose of lesinurad 200 mg in adult volunteers with mild (eCLcr 60 to less than 90 mL/min) or moderate renal impairment (eCLcr 30 to less than 60 mL/min). Study 120 evaluated a single dose of lesinurad 400 mg in adult volunteers with moderate or severe renal impairment (eCLcr less than 30 mL/min). Lesinurad exposure (AUC) increased by 31%, 50-74% and 113% respectively in subjects with mild, moderate and severe renal impairment (Table 16).

Table 16. Summary of lesinurad Pharmacokinetic Parameters, by renal impairment status

Study	PK	Renal	N	Mean (SD)	Ratio (vs

	parameter	impairment status			Normal)
104	AUCinf (μg.h/mL)	Normal	6	33.4 (10.7)	NA
		Mild	8	43.6 (9.7)	130.5%
		Moderate	10	58.0 (27.2)	173.5%
	Cmax (μg/mL)	Normal	6	8.5 (2.7)	NA
		Mild	8	11.6 (1.7)	135.6%
		Moderate	10	10.2 (3.9)	119.7%
120	AUCinf (μg.h/mL)	Normal	6	57 (17.6)	NA
		Moderate	6	85.6 (16.3)	150.2%
		Severe	6	121.3 (51.3)	212.9%
	Cmax (μg/mL)	Normal	6	15.9 (1.7)	NA
		Moderate	6	16.5 (7.7)	104.1%
		Severe	6	18.1 (2.7)	113.8%

(Source –Reviewer summary)

Creatinine clearance was found to be a significant covariate for lesinurad exposure in the Phase II/III PopPK analysis and in several supportive data sets (Figure 19, see Pharmacometrics Review, appendix 4.1) Data on severe renal impairment was too sparse to draw conclusions. There is apparent trend for lower creatinine clearance or estimated GFR to be associated with higher exposure to lesinurad in univariate analyses, and this does not inform on cause-effect relationship. The population PK analysis of the Phase 3 studies, which did not enroll subjects with severe renal impairment, yielded model-based estimates of lesinurad exposure increases of approximately 12%, 31%, and 65% in subjects with mild, moderate, and severe renal impairment, respectively, compared with subjects with normal renal function. Post hoc Cave of Lesinurad in subjects enrolled in Phase 3 studies are presented in Table 17 with stratification by renal function.

Table 17. Effects of Baseline Renal Function on Average Concentrations of Lesinurad Under Steady-State in Phase 3 Subjects (study 301, 302, and 304, dose of 200 mg QD, posthoc analysis)

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

(Source: Reviewer analysis, see pharmacometrics review)

The efficacy and safety of ZURAMPIC were evaluated in studies that included gout patients with mild and moderate renal impairment (see review by medical officer Dr. Rosemarie Neuner and statistic reviewer Dr. Yu Wang). The patients with CRCL<45mL/min had less overall efficacy. The patients with CRCL30-60mL/min had lower renal function reserve, and had a higher occurrence of renal related adverse

reactions compared to patients with mild renal impairment or normal renal function. As another uricosuric drug probenecid was not recommended in patients with eCRCL<50 mL/min by ACR guideline, and the data were sparse for patients with eCRCL between 45-50 mL/min in the lesinurad program, our analysis also supports similar recommendations for treatment with lesinurad(see section 2.4 for details).

2.6.2.7 Hepatic Impairment

As lesinurad undergoes hepatic metabolism, the effect of hepatic impairment on the metabolism of lesinurad was explored in Childs-Pugh Class A (mild impairment) and B (moderate impairment) subjects as compared with healthy volunteers following a 400 mg dose of lesinurad. In subjects with mild hepatic impairment, lesinurad Cmax and AUC were comparable to those from subjects with normal hepatic function (Table 18). Subjects with moderate hepatic impairment showed comparable Cmax values, while AUC was 33% greater when compared with subjects with normal hepatic function (Table 18). Plasma protein binding of lesinurad was unchanged in subjects with mild hepatic impairment (99.0% bound) and slightly lower in subjects with moderate hepatic impairment (98.8% bound) compared with subjects with normal hepatic function (99.0% bound), as shown in Table 19. The relative plasma exposure of M4, a major metabolite of lesinurad, was less than 8% in subjects with normal hepatic function and with mild to moderate hepatic impairment.

Overall, Sponsor's proposal for no dose adjustment of lesinurad in mild and moderate hepatic impaired patients is acceptable. Effect of severe hepatic impairment on lesinurad PK was not studied and hence sponsor is not recommending use of lesinurad in this population.

Table 18. Geometric Least Squares Means and Geometric Mean Ratios (90% Confidence Interval) of Total Lesinurad Pharmacokinetic Parameters between Hepatic Function Groups

Hepatic Function	N	Parameter	GeoLSM		Geomean Ratio (90% CI)
			Mild Impairment	Normal Function	(Impairment/Normal Function)
Mild Impairment versus Normal Function	8	C_{max} (µg/mL)	20.4	18.4	111% (90.2%-136%)
		AUC_{last} (µg·hr/mL)	66.2	61.9	107% (83.4%-137%)
		AUC_{∞} (µg·hr/mL)	66.5	62.0	107% (83.7%-137%)
		CL/F (L/hr)	6.02	6.45	93.3% (72.8%-120%)
		CL_{NR0-72} (mL/min)	4.93	4.91	100% (74.6%-135%)
Moderate Impairment versus Normal Function	8	C_{max} (µg/mL)	19.9	18.4	108% (77.9%-149%)
		AUC_{last} (µg·hr/mL)	82.4	61.9	133% (93.8%-189%)
		AUC_{∞} (µg·hr/mL)	82.6	62.0	133% (94.0%-189%)
		CL/F (L/hr)	4.84	6.45	75.0% (52.9%-106%)
		CL_{NR0-72} (mL/min)	3.74	4.91	76.3% (53.2%-110%)

(Source –Table 11-2, Study 118 report)

Plasma Protein Binding:
Analysis of protein binding in plasma from subjects with normal hepatic function, and mild and moderate hepatic impairment showed that lesinurad is highly bound (>98%) in all 3 groups (Table 19).

Table 19. Mean (Standard Deviation) Plasma Protein Binding (Percent) of Lesinurad

Normal Hepatic Function (N=8)	Mild Hepatic Impairment (N=8)	Moderate Hepatic Impairment (N=8)
99.0% (0.143)	99.0% (0.129)[a]	98.8% (0.217)

N = number of subjects.
Mean combining 1, 10, and 50 µM concentrations of lesinurad is presented.
[a] N = 7, plasma sample for protein binding assay was not available for Subject 001-010.

(Source –Table 11-5, Study 118 report)

2.6.3 Does genetic variation impact exposure and/or response?

Yes, CYP2C9 poor metabolizers (i.e., CYP2C9 *2/*2, *2/*3 or *3/*3) receiving 400 mg lesinurad had ~1.8-fold increase in lesinurad exposure relative to CYP2C9 extensive metabolizers (i.e., *1/*1). This is consistent with data from the drug interaction trial with a moderate CYP2C9 inhibitor (i.e., fluconazole) that showed similar exposure changes. Given that (1) higher lesinurad exposure has been associated with increased risk for adverse events (see exposure/response analysis, Section 2.4.3), and (2) increased exposure has been observed with concomitant use of moderate CYP2C9 inhibitors and in CYP2C9 poor metabolizers, usage recommendations should be consistent for CYP2C9 poor metabolizers and CYP2C9 inhibitors.

To evaluate the impact on CYP2C9 genotype on the PK of lesinurad, the applicant

assessed pharmacogenetic (CYP2C9 *1, *2, and *3 alleles) and pharmacokinetic data from five trials conducted in healthy subjects (RDEA594-109), or in patients with gout (RDEA594-110, RDEA594-111, RDEA594-202, and RDEA594-203) to perform a cross-study analysis. Genetic sampling rates in these trials were variable, and in combination with PK data, information was available from 67/435 (~15%) subjects. The reviewer classified the subjects' phenotype according to Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines to the following phenotype groups: (1) extensive metabolizers (genotype CYP2C9 *1/*1; EMs), (2) intermediate metabolizers (genotype CYP2C9 *1/*2, *1/*3; IMs), and (3) poor metabolizers (genotype CYP 2C9 *2/*2, *3/*3, *2/*3; PMs). Follow-up studies to further explore the potential impact of CYP2C9 genotype on lesinurad PK are not warranted at this time (See Appendix 4.2: Genomics Group review by Anuradha Ramamoorthy, Ph.D.).

2.7 Extrinsic Factors

2.7.1 Is there an *in vitro* basis to suspect *in vivo* drug-drug interactions?

Yes, lesinurad was primarily metabolized by CYP2C9. Lesinurad exhibited induction potential toward CYP3A, CYP2C8, and CYP2C9 *in vitro*. Lesinurad exhibited inhibitory potential toward CYP2C8 and CYP2C9.
Lesinurad is a substrate of OAT1 and OAT3 but not P-glycoprotein (P-gp). Among liver and kidney transporters evaluated in vitro, lesinurad potentially can inhibit OATP1B1, OCT1, OAT1, and OAT3.

2.7.2 Is the drug a substrate of CYP enzymes?

Biotransformation of lesinurad was primarily mediated through CYP2C9 with minimal contribution from CYP1A1, CYP2C19, and CYP3A.

CYP2C9 is responsible for M3 formation and also for the metabolism of lesinurad to an epoxide intermediate, which is rapidly hydrolyzed to M4 by mEH. Formation of M5 is mediated through the combination of CYP2C9 and gastrointestinal microflora. Formation of metabolite M6, the S-dealkylation metabolite, was catalyzed by CYP3A4 in the in vitro evaluation. Elimination of lesinurad in humans through this pathway is negligible *in vivo*.

2.7.3 Is the drug an inhibitor and/or an inducer of enzymes?

Lesinurad exhibited induction potential toward CYP3A, CYP2C8, and CYP2C9 *in vitro*. Lesinurad exhibited inhibitory potential toward CYP2C8 and CYP2C9.

2.7.4 Is the drug a substrate, an inhibitor and/or an inducer of transporter processes?

Lesinurad is a substrate of OAT1 and OAT3 but not P-glycoprotein (P-gp). Among liver and kidney transporters evaluated in vitro, lesinurad potentially can inhibit OATP1B1, OCT1, OAT1, and OAT3 (Table 20).

Table 20. Interaction of Lesinurad With Major Intestinal and Liver Transporters

Transporter	As a Substrate	IC_{50} (µM)	C_{max}/ IC_{50}[a]
P-gp	No	1000	0.02 1.98 (I_{gut}/ IC_{50})
BCRP	Minor	> 3000	< 0.006
OATP1B1	Yes	9.3	1.8
OATP1B3	Minor	43.1	0.4
OCT1	Yes	13.7	1.2

Abbreviations: BCRP, breast cancer resistance protein; C_{max}, maximum observed concentration; I_{gut}, estimated gastrointestinal concentration of lesinurad based on 400 mg dosing; IC_{50}, half maximal inhibitory concentration; OAT, organic anion transporter; OCT, organic cation transporter; P-gp, P-glycoprotein.

[a] From 200 mg dosing, C_{max} is approximately 17.1 µM and I_{gut} is 1.98 mM.

Transporter	As a Substrate	IC_{50} (µM)	$C_{max, free}$/ IC_{50}[a]
OAT1	Yes	4.3	0.06
OAT3	Yes	3.5	0.08
OCT2	No	> 300	< 0.001

Abbreviations: IC_{50}, half maximal inhibitory concentration; OAT, organic anion transporter; OCT, organic cation transporter.

[a] From 200 mg dosing, C_{max} is approximately 17.1 µM, using 98.4% as protein bound fraction for the calculation of free concentration.

(Source: Table 17, Table 18, section 2.6.4, pharmacokinetics written summary)

2.7.5 Are there other metabolic/transporter pathways that may be important?

No other metabolic enzyme or transported pathway is known to be important for disposition of lesinurad in addition to those already discussed in sections 2.7.2 and 2.7.4.

2.7.6 What extrinsic factors influence exposure and/or response, and what is the impact of any differences in exposure on effectiveness or safety responses?

The effect of extrinsic factors on lesinurad exposure was summarized in Table 21.

2.7.7 What are the drug-drug interactions?

-Effect of other drugs on Lesinurad

Effect of co-administration of CYP2C9 inducer and inhibitor, antacid, and NSAIDS on lesinurad exposure (AUC) and C_{max} was evaluated (Table 21).

Table 21. Extrinsic Factors

Co-administered drug	Rationale	Lesinurad		Dosing recommendation
		AUC_{inf}	C_{max}	
Fluconazole	Inhibitor of CYP2C9	↑ 56%	↑ 38%	Caution with moderate inhibitor of CYP2C9

Rifampicin	Inducer of CYP2C9	↓ 37.6%	↓ 23.9%	No dose adjustment based on limited impact on sUA lowering
NSAIDS • **Naproxen** • **Indomethacin**	Common Concomitant medicine	↓ 14.5% ↑ 10%	↓27.1% ↑ 18%	Not dose adjustment
Antacids • **Calcium carbonate** • **Aluminum-magnesium hydroxide** • **Ranitidine**	(b) (4) Concomitant medicine	↓ 10.9% ↓ 9.4% ↑ 9%	↓ 10.1% ↓ 15.1% ↑ 20%	Not dose adjustment

(Source: Reviewer summary)

Lesinurad is a substrate of CYP2C9. Coadministration of a single dose of lesinurad 400 mg and fluconazole (400 mg loading dose followed by 200 mg qd) increased lesinurad AUC by 56% and Cmax by 38%. Coadministration of a single dose of lesinurad 400 mg and rifampin (600 mg qd) decreased lesinurad AUC by 38% and Cmax by 24% (Table 21).

Lesinurad is planned to be routinely used with other gout therapies including NSAIDs for the treatment of pain and gout flares. Lesinurad AUC was comparable with or without coadministration of indomethacin or naproxen (Table 21). As renal toxicity is a major safety concern with lesinurad, and NSAIDs are also associated with development of kidney injury, coadministration of the two may pose additional risk. See medical officer Dr. Rosemarie Neuner's review for further details.

(b) (4)

Co-administration with histamine H2 antagonists or other antacids did not influence the exposure of lesinurad (Table 21).

1. *Coadministration with fluconazole significantly increased AUC and C_{max} of lesinurad by ~56% and 38%, respectively. Therefore, patients should be monitored closely for lesinurad related adverse events.*

2. *Coadministration with rifampicin significantly reduced AUC of lesinurad by ~50% 38%. A reduced uric acid lowering activity (30% vs 39%) was also observed in the dedicated DDI study. The data suggest that coadministration with rifampicin may decrease the efficacy of lesinurad.*

3. *No significant change in lesinurad exposure was observed following co-administration with antacids. Therefore, no dose adjustments are recommended.*

-Effect of Lesinurad on other drugs

A summary of studies conducted to examine the effect of lesinurad on other drugs for the treatment of gout is provided in Table 22.

Table 22. Effect of Lesinurad on Systemic Exposures of Coadministered Gout Drugs

Co-Administered Drug	Dose of Co-Administered Drug	Dose of Lesinurad	Analyte	Geometric Mean Ratio (90% CI)[a]	
				AUC	C_{max}
Febuxostat (Study 105)	40 mg qd x 7d	200 mg qd x 7d	Febuxostat	112 (109-115)	108 (94.9-122)
	40 mg qd x 7d	400 mg qd x 7d	Febuxostat	131 (124-139)	127 (104-155)
Febuxostat (Study 111)	40 mg qd x 7d	400 mg qd x 7d	Febuxostat	108 (98.9-117)	109 (83.2-143)
	40 mg qd x 7d	600 mg qd x 7d	Febuxostat	120 (109-132)	129 (109-154)
	80 mg qd x 7d	400 mg qd x 7d	Febuxostat	119 (112-126)	113 (104-123)
	80 mg qd x 7d	600 mg qd x 7d	Febuxostat	121 (107-137)	118 (93.4-148)
Allopurinol (Study 110)	300 mg qd x 7d	400 mg qd x 7d	Allopurinol Oxypurinol	90.5 (82.6-99.2) 74.2 (65.1-84.7)	78.8 (61.0-102) 79.4 (69.8-90.3)
	300 mg qd x 7d	600 mg qd x 7d	Allopurinol Oxypurinol	93.7 (83.8-105) 64.7 (61.3-68.3)	87.3 (62.9-121) 71.7 (67.8-75.7)
Colchicine (Study 110)	0.6 mg qd x 7d	400 mg qd x 7d	Colchicine	74.8 (67.4-83.0)	82.3 (73.0-92.7)
	0.6 mg qd x 7d	600 mg qd x 7d	Colchicine	67.0 (57.5-78.1)	75.6 (63.9-89.5)
Colchicine (Study 111)	0.6 mg qd x 7d	400 mg qd x 7d[b]	Colchicine	78.3 (71.1-86.3)	88.6 (78.2-100)
	0.6 mg qd x 7d	600 mg qd x 7d[b]	Colchicine	64.5 (58.8-70.7)	80.4 (69.5-93.0)
	0.6 mg qd x 7d	400 mg qd x 7d[c]	Colchicine	86.2 (74.9-99.2)	91.3 (78.0-107)
	0.6 mg qd x 7d	600 mg qd x 7d[c]	Colchicine	73.0 (58.7-90.7)	84.5 (67.3-106)
Naproxen (Study 126)	250 mg bid x 6d	400 mg	Naproxen	108 (107-109)	104 (99.4-109)
	250 mg bid x 13d	400 mg qd x 8d	Naproxen	101 (98.5-104)	102 (98.5-105)
Indomethacin (Study 126)	25 mg bid x 6d	400 mg	Indomethacin	135 (127-144)	118 (97.7-142)
	25 mg bid x 13d	400 mg qd x 8d	Indomethacin	131 (122-141)	120 (103-140)

(Source: Table 10, summary of clin pharm studies)

A summary of studies conducted to examine the effect of lesinurad on other drugs with potential for DDI is provided in Table 23.

Table 23. Effect of Lesinurad on Systemic Exposures of Coadministered Drugs

Co-Administered Drug	Dose of Co-Administered Drug	Dose of Lesinurad	Analyte	Geometric Mean Ratio[a] (90% CI)	
				AUC	C_{max}
CYP3A					
Sildenafil (Study 108)	50 mg single dose	200 mg qd x 9d[b] 400 mg qd x 9d[b]	Sildenafil Sildenafil	66.4 (55.9-78.8) 49.6 (34.2-72.0)	66.1 (45.3-96.5) 65.5 (39.7-108)
		400 mg qd x 10d[c]	Sildenafil	38.6 (30.8-48.3)	42.2 (31.0-57.3)
		600 mg qd x 10d[c]	Sildenafil	27.4 (21.2-35.5)	35.7 (26.2-48.7)
Atorvastatin (Study 113)	40 mg single dose	200 mg single dose	Atorvastatin total atorva[d]	96.2 (89.8-103) 107 (98.0-117)	91.9 (80.3-105) 101 (87.9-116)
		200 mg qd x 11d	Atorvastatin total atorva[d]	84.2 (74.2-95.6) 92.2 (82.9-103)	114 (92.0-141) 115 (91.7-144)
		400 mg single dose	Atorvastatin total atorva[d]	101 (91.3-111) 108 (100-118)	117 (94.0-146) 126 (105-150)
		400 mg qd x 11d	Atorvastatin total atorva[d]	72.7 (64.9-81.5) 86.1 (77.3-95.8)	99.5 (80.4-123) 117 (98.0-139)
Amlodipine (Study 114)	5 mg qd x 28d	400 mg qd x 14d	Amlodipine	57.5 (52.5-63.1)	60.4 (55.3-66.0)
CYP2C9					
Tolbutamide (Study 115)	500 mg single dose	400 mg single dose	Tolbutamide OH-tolbutamide	111 (107-115) 114 (111-118)	107 (104-110) 140 (129-151)
		400 mg qd x 13d	Tolbutamide OH-tolbutamide	106 (102-111) 111 (106-116)	102 (95.8-108) 124 (115-134)
Warfarin (Study 123)	25 mg single dose	400 mg qd x 21d	*S*-warfarin *R*-warfarin[e]	104 (99.6-109) 81.2 (77.3-85.3)	102 (97.0-108) 99.6 (94.5-105)
CYP2C8					
Repaglinide (Study 116)	0.5 mg single dose	400 mg single dose	Repaglinide	131 (124-139)	127 (108-148)
		400 mg qd x 12d	Repaglinide	111 (103-120)	101 (91.4-111)
OCT1					
Metformin (Study 128)	850 mg single dose	400 mg single dose	Metformin	103 (91.1-115)	106 (100-113)
OAT1/3					
Furosemide (Study 128)	40 mg single dose	400 mg single dose	Furosemide	69.3 (56.7-84.7)	48.9 (38.7-61.8)

(Source: Table 11, summary of clin pharm)

Reviewer's comments

1. *In interaction studies conducted in healthy subjects with lesinurad and CYP3A substrates, lesinurad reduced the plasma concentrations of sildenafil and amlodipine. When coadministered with sensitive CYP3A substrates, lesinurad may reduced efficacy of these drugs.*

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

exposure of oxypurinol, a URAT1 substrate, by 25%.

2.7.8 Does the label specify coadministration of another drug?

Yes, lesinurad should be used with XOI, and should not be used as monotherapy. There was no meaningful PK interaction of lesinurad with allopurinol, or lesinurad with febuxostat (Table 24 and Table 25).

Table 24. Effects of Coadministered XOI on Systemic Exposure of Lesinurad

Coadministered Drug	Dose of Coadministered Drug[a]	Dose of Lesinurad[a]	Geometric Mean Ratio (90% CI)[b]	
			AUC	C_{max}
Gout treatments				
Febuxostat (Study 105)	40 mg qd x 7 d	200 mg qd x 7 d 400 mg qd x 7 d	98.3 (95.6-101)[c] 105 (99.2-111)[c]	95.9 (88.1-104) 102 (90.6-115)
Allopurinol (Study 110)	300 mg qd x 7 d	400 mg qd x 7 d 600 mg qd x 7 d	107 (95.9-119)[c] 106 (98.2-115)[c]	117 (105-131) 104 (89.9-120)

(Source: Table 9, summary of clin pharm)

Table 25. Effect of Lesinurad on Systemic Exposures of Coadministered XOIs

Co-Administered Drug	Dose of Co-Administered Drug	Dose of Lesinurad	Analyte	Geometric Mean Ratio (90% CI)[a]	
				AUC	C_{max}
Febuxostat (Study 105)	40 mg qd x 7d	200 mg qd x 7d	Febuxostat	112 (109-115)	108 (94.9-122)
	40 mg qd x 7d	400 mg qd x 7d	Febuxostat	131 (124-139)	127 (104-155)
Febuxostat (Study 111)	40 mg qd x 7d	400 mg qd x 7d	Febuxostat	108 (98.9-117)	109 (83.2-143)
	40 mg qd x 7d	600 mg qd x 7d	Febuxostat	120 (109-132)	129 (109-154)
	80 mg qd x 7d	400 mg qd x 7d	Febuxostat	119 (112-126)	113 (104-123)
	80 mg qd x 7d	600 mg qd x 7d	Febuxostat	121 (107-137)	118 (93.4-148)
Allopurinol (Study 110)	300 mg qd x 7d	400 mg qd x 7d	Allopurinol Oxypurinol	90.5 (82.6-99.2) 74.2 (65.1-84.7)	78.8 (61.0-102) 79.4 (69.8-90.3)
	300 mg qd x 7d	600 mg qd x 7d	Allopurinol Oxypurinol	93.7 (83.8-105) 64.7 (61.3-68.3)	87.3 (62.9-121) 71.7 (67.8-75.7)

(Source: Table 9, summary of clin pharm)

As there is no DDI between lesinurad and allopurinol/febuxostat, the additional uric acid lowering activity observed in the combination therapy is due to synergestic PD effect of XOI and lesinurad, and not increased exposure to XOIs.

2.7.9 What other co-medications are likely to be administered to the target population?

Besides allopurinol, gout patients are likely to take lesinurad in background of other drugs to prevent flare such as NSAID, colchicine; other uric acid lowering agent such as pegloticase. As probenecid and lesinurad worked on similar mechanisms, co-administration of probenecid and lesinurad is not recommended.

Gout is more likely to occur in old age patients; therefore, there is a potential for other

drugs such as anti-hypertensives, anti-diabetic, anti-hyperlipidemic etc, to be administered with lesinurad.

2.7.10 Is there a known mechanistic basis for pharmacodynamic drug-drug interactions?

Salicylates at doses higher than 325 mg per day may decrease the serum uric acid lowering activity of ZURAMPIC in combination with allopurinol. Low doses of aspirin have been shown to increase URAT1 transport of uric acid. Subgroup analysis in study 301 and 302 suggested that low dose aspirin did not affect the efficacy of lesinurad.

Thiazide diuretics at Baseline: Thiazide diuretics increase sUA, likely through activation of OAT4 in the proximal tubule of the kidney, and as a result can make it more difficult to achieve sUA targets. Subgroup analysis in study 301 and 302 suggested that thiazide diuretics did not affect the efficacy of lesinurad.

Probenecid has similar mechanism of action as lesinurad. Therefore, lesinurad should not be used with probenecid.

2.8 General Biopharmaceutics

2.8.1 Based on the biopharmaceutic classification system principles, in what class is this drug and formulation? What solubility, permeability and dissolution data support this classification?

Sponsor proposed that lesinurad can be considered a BCS class 2 drug because of low aqueous solubility at lower pH.

Lesinurad is classified as a drug substance with low solubility according to BCS (Biopharmaceutical Classification System). The BCS solubility class boundary for lesinurad is not less than 0.8 mg/mL over the physiologically relevant pH range of 1 to 7.5. Lesinurad does not meet this criterion below approximately pH 5.3 (Figure 20). Lesinurad is highly permeable in the in vitro Caco-2 cell permeability assessment. The high permeability classification is further supported by results from an absolute bioavailability study, which show complete absorption of lesinurad and a bioavailability of approximately 100%. Thus, lesinurad can be classified as a BCS class 2 drug substance (low solubility – high permeability).

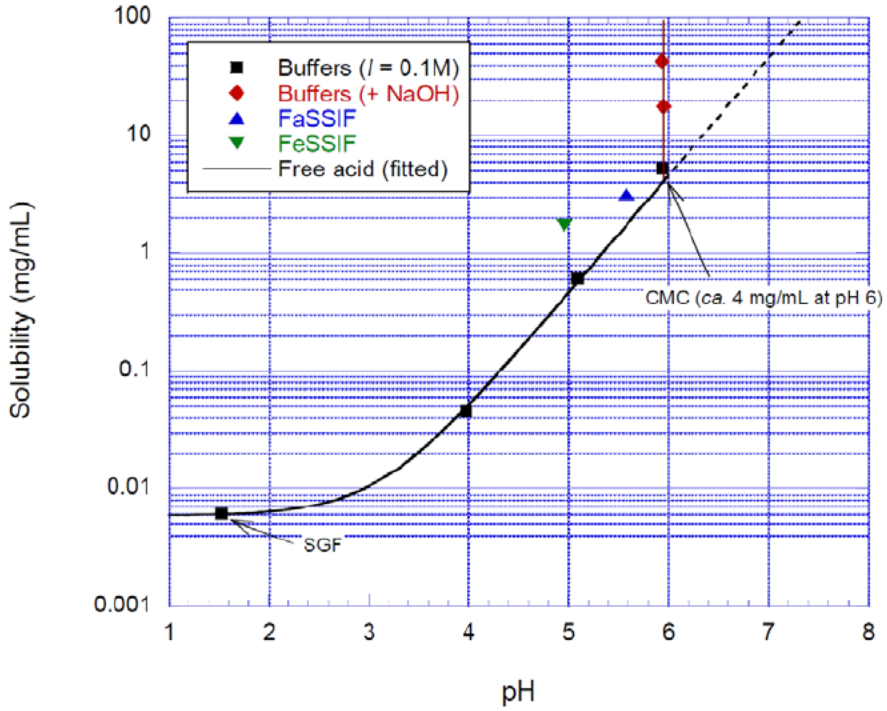


Figure 20. pH-dependent solubility profile lesinurad in aqueous media at 37°C
(Source: Figure 2, section 3.2.S.1.3)

2.8.2 How is the proposed to-be-marketed formulation linked to the clinical service formulation?

During its clinical development, lesinurad was formulated as an [(b) (4)] IR capsules, [(b) (4)] tablets, IR tablets, and an [(b) (4)]. Three forms of the drug substance have been evaluated: [(b) (4)] Whereas initial clinical trials were performed with the [(b) (4)] IR capsules, and assessed [(b) (4)] tablets, subsequent clinical trials were carried out with free acid tablet (Table 26). The relative bioavailability was assessed across different formulations. Please refer to review by Office of New Drug Quality Assessment (ONDQA) for further details regarding formulation changes.

Table 26. Lesinurad Formulations Used in Clinical Safety and Efficacy Studies

Strength (Formulation Number)[a]	Doses (mg) Administered	Drug Product	Clinical Study No.
Phase 2b Studies			
100 mg (FN07)	200, 400, 600	Sodium Salt Capsule	202 (Main and Open Label Extension), 203 (Main and Double-blind Extension)
200 mg (FN14 and FN21)	200, 400, 600	Free Acid Tablet	203 (Open-label Extension)
Phase 3 Studies			
200 mg (FN21) 400 mg (FN22)	200, 400	Free Acid Tablet	301 (CLEAR 1), 302 (CLEAR 2), 304 (CRYSTAL)
400 mg (FN22)	400	Free Acid Tablet	303 (LIGHT)

(Source: Table 1, summary of biopharm)

2.8.3 What is the effect of food on the bioavailability of the drug when administered as (b) (4) or as drug product?

In the Phase 2 and Phase 3 studies, lesinurad was administered in the fed state.
The effect of food on the PK and PD of lesinurad has been examined in 5 studies using various lesinurad formulations (Table 29).

In Study 121, the pivotal study of food effects (Phase 3 formulation), administration with a high-fat meal decreases lesinurad Cmax by 18% but does not alter AUC as compared with fasted state (Table 27).

Table 27. Geometric Least Squares Means and Geometric Mean Ratios (90% Confidence Interval) of Lesinurad Plasma Pharmacokinetic Parameters under the Fed versus Fasting Condition

Parameter	N	GeoLSM		Geomean Ratio (90% CI)	p-value		
		Fed	Fasting	(Fed/Fasting)	Treatment[a]	Period	Sequence
C_{max} (µg/mL)	15[b]	16.2	19.9	81.6% (66.6%-99.8%)	0.0976	0.7728	0.3763
AUC_{last} (µg·hr/mL)	15[b]	62.7	68.0	92.2% (83.6%-102%)	0.1607	0.3278	0.4928
AUC_{∞} (µg·hr/mL)	15[b]	62.9	68.3	92.1% (83.6%-102%)	0.1589	0.3089	0.4905

(Source: Table 11.2, CSR121)

The sUA lowering effect of lesinurad was enhanced in the fed state (43% maximum reduction from baseline and 31% reduction at 24 hours postdose) as compared with the fasted state (36% maximum reduction from baseline and 26% reduction at 24 hours postdose, Table 28). The effect of food on sUA following treatment was also observed with various other formulations of lesinurad examined in Studies 101, 102, and 109 as shown in Table 29.

Table 28: Statistical Analysis of the Percentage Change from Baseline in Serum Urate Concentrations Following a Single 400 mg Oral Dose of Lesinurad to Healthy Adult Male Subjects Under Fed Versus Fasting Conditions

Lesinurad Dose (mg)	Parameter	Condition	LS Mean	N	Difference of LS Means (95% CI)[a]	P-value
400	$E_{max, CB}$ (%)	Fed	-43.05	15[b]	-7.07 (-10.00, -4.15)	< 0.001[c]
		Fasted	-35.98	16		
	$E_{24hr, CB}$ (%)	Fed	-31.10	15[b]	-5.56 (-8.93, -2.18)	0.001[c]
		Fasted	-25.54	16		

Abbreviations: CI, confidence interval; $E_{24hr, CB}$, 24 hour postdose percent change from baseline; $E_{max, CB}$, maximum observed percentage change from baseline in serum urate concentrations; LS, least squares; N, number of subjects

[a] Fed minus fasted.

[b] Subject 103 discontinued prior to Day 6 and was excluded from the statistical analysis.

[c] Statistically significant at 5% level.

(Source – Table 14.2.2.1, Study 121 CSR.)

Table 29: Effects of Food on Lesinurad AUC, Cmax, and Pharmacodynamics Observed Using Other Formulations of Lesinurad

Study	Dose/ Regimen	Formulation	AUC_∞ Geometric Mean Ratio (90% CI)	C_{max} Geometric Mean Ratio (90% CI)	$E_{max, CB}$ Ar. Mean (CV) Fed	$E_{max, CB}$ Ar. Mean (CV) Fasted
101	100 mg/ single dose	(b) (4)	92.3% (74.7-114%)[a]	58.3% (47.7-71.2)[a]	-22.3% (-15.0%)	-24.1% (-37.3%)
102	200 mg/ repeated dose	IR capsule	91.3% (73.5-113%)[b]	55.5% (45.1-68.3%)[c]	-40.5% (-21.0%)	-31.3% (-17.6%)
109	400 mg/ single dose	FA tablet	92.8% (85.1-101%)	76.3% (65.2-89.3%)	-41.4% (-12.9%)	-34.1% (-11.2%)
	400 mg/ single dose	IR capsule	82.1% (74.9-90.1%)	65.8% (53.9-80.5%)	-45.6% (-10.0%)	-39.9% (-9.0%)
	600 mg/ single dose	FA tablet	68.6% (54.7-86.1%)	54.6% (40.6-73.4%)	-44.3% (-12.2%)	-35.1% (-20.2%)

Abbreviations: Ar, arithmetic; AUC_∞, area under the concentration-time curve from time 0 to infinity; AUCτ, area under the concentration-time curve over the dosing interval; CI, confidence interval; C_{max}, maximum observed concentration; CV, coefficient of variation; $E_{max, CB}$, maximum observed percentage change from baseline in serum urate concentrations; FA, free acid; IR, immediate release.

[a] Geometric mean ratio for AUC fed relative to AUC fasted or C_{max} fed relative to C_{max} fasted after normalizing for dose.

[b] Geometric mean ratio determined using AUCτ fed relative to AUC τ fasted on Day 10. In Study 102, AUCτ is equivalent to AUC_{0-24}.

[c] Geometric mean ratio for C_{max} fed relative to C_{max} fasted on the last dosing day.

(Source – Table 20, Study 121 CSR.)

2.8.4 Was the bioequivalence of the different strengths of the to be marketed formulation tested? If so were they bioequivalent or not?

Phase 3 studies assessed two strengths: 200 and 400 mg tablets. Lesinurad tablets used in the Phase 3 studies were manufactured at (b) (4) . Another manufacturing site for lesinurad tablets, AstraZeneca AB (Södertälje, Sweden), is the proposed commercial manufacturing site. Associated with the AstraZeneca AB site were minor changes from (b) (4) site, including (b) (4) . There were no changes to quantitative or qualitative composition of the formulation, (b) (4) .

A bioequivalent (BE) study (study 129) demonstrated BE of the [redacted] 400 mg strength lesinurad tablet (manufactured at AstraZeneca AB) to Phase 3 tablets (manufactured at [redacted]). A summary of results from Study 129 is presented in Table 30.

Table 30. Summary of Results from Relative Bioavailability Study 129 –Manufacturing Site Comparison for Lesinurad 400 mg Tablets

Cohort (Food, N)	Manufacturing Site (Lot Number)	Comparison: Ratio of Geometric Least Squares Means (90% CI)		
		AUC_{∞}	AUC_{last}	C_{max}
Cohort 3 (Fasted, N=17)	Test: AstraZeneca AB (ELAD) Reference: [redacted] (12A015)	99.7% (89.9-111%)	99.8% (90.0-111%)	100% (85.0-118%)
Cohort 4 (Fed, N=18)	Test: AstraZeneca AB (ELAD) Reference: [redacted] (12A015)	95.3% (89.9-101%)	95.3% (89.9-101%)	101% (86.1-119%)

(Source: Table 5, summary of biopharm)

The strength of the to-be-marketed formulation is 200 mg tablet. A biowaiver is sought for the 200 mg strength lesinurad tablet. [redacted] Please refer to review by Office of New Drug Quality Assessment (ONDQA) reviewer for further details [redacted]

2.9 Analytical Section

2.9.1 How are parent drug and relevant metabolites identified and what are the analytical methods used to measure them in plasma and other matrices?

The concentrations of lesinurad and its metabolites were quantified in human EDTA plasma and urine samples. Nine bioanalytical reports/methods have been submitted to measure the parent drug, metabolites, and other analytes in different matrices (Table 31).

In plasma, the best lower limit of quantification (LLOQ) is 5 ng/mL for lesinurad, 1ng/mL for M1 and M6, and 2ng/mL for M4. At a single clinical dose of lesinurad (200 mg or 400 mg), plasma concentrations of lesinurad can be measure up to 24 h post dose.

In this review, we summarized the analytical method for the parent drug in plasma. SR09-041 was validated over the concentration range of 5 to 2000 ng/mL lesinurad, using a sample volume of 25 µL. The assay was developed and validated, and samples were analyzed in Ardea Biosciences (San Diego, CA).

The method involves [redacted] An

(b) (4)

Table 31: Summary of analytical methods for analysis of lesinurad and other analytes

Analytical Method	Analyte	Matrix	Method	Remark
SR07-105	M1, M6	Plasma	LC/MS/MS	1-1000 ng/mL
SR07-106	M6	Urine	LC/MS/MS	1-1000 ng/mL
SR09-017	Febuxostat	Plasma	LC/MS/MS	2-1000 ng/mL
SR09-041	RDEA594 (lesinurad)	Plasma	LC/MS/MS	5-2000 ng/mL
SR10-031	RDEA594 (lesinurad)	Urine	LC/MS/MS	50-10000 ng/mL
SR10-034	M6	Plasma	LC/MS/MS	5-2000 ng/mL
SR10-057	Uric acid	Plasma	LC/MS/MS	1-25 mg/dL
SR13-024	M4	Urine	LC/MS/MS	10-4000 ng/mL
SR13-025	M4	Plasma	LC/MS/MS	2-1000 ng/mL

(Source – Reviewer summary)

2.9.2 Which metabolites have been selected for analysis and why?

M1, M4 and M6 for lesinurad were selected for analysis because these were the predominant metabolites formed in humans (see section 2.5.8).

2.9.3 For all moieties measured, is free, bound, or total measured?

Total (bound + unbound) concentrations were measured in plasma PK samples.

2.9.4 What bioanalytical methods are used to assess concentrations of the measured moieties?

Table 31 presents a summary of analytical methods used for quantification of lesinurad and lists out the respective validation report numbers.

2.9.5 What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques were used?

Analytical method for lesinurad in plasma: report # SR09-041

The standard curves were validated over the concentration range of 5 to 2000 ng/mL for lesinurad. Calibration curves were constructed using the linear regression fit with a 1/x weighting from which concentrations of QC samples were interpolated.

2.9.5.1 What are the lower and upper limits of quantitation?

Analytical method for lesinurad in plasma: report # SR09-041

LLOQ and ULOQ for lesinurad were 5 and 2000 ng/mL, respectively, using sample volumes of 25 µL human plasma. Over-the-curve dilution was validated by diluting a 50 µg/mL RDEA594 plasma over the- curve dilution QC sample (DilQC) by a factor of 50.

2.9.5.2 What are the accuracy, precision, and selectivity at these limits?

The accuracy and precision of analytical method SR09-041 is listed in Table 32.

Table 32: Accuracy and Precision of Lesinurad Analytical LC/MS/MS Assay in human plasma (Validation Report # SR09-041)

Parameter	RDEA594
Intra-batch accuracy (% of nominal)	95.3 - 105
Intra-batch precision (% CV)	2.46 - 9.23
Inter-batch accuracy (% of nominal)	92.7 - 98.7
Inter-batch precision (% CV)	5.99 - 6.82

(Source – Table under 3.6, analytical report SR09-041)

The selectivity of all the methods was evaluated by extracting and analyzing blank human plasma from 6 individual sources. All lots were free from significant interfering peaks in the drug and internal standard regions. The co-administered drug interference from febuxostat, allopurinol, oxypurinol and colchicine was evaluated. The results show that there is no interference of any of these drugs at the RDEA594 and [D6]RDEA594 retention times.

2.9.5.3 What is the sample stability under conditions used in the study?

In human plasma, lesinurad was found to be stable for at least 24.5 hours at room temperature, for at least 10 days stored at nominal -70 °C and through seven freeze-thaw cycles.

Human plasma sample extracts in injection solvent containing lesinurad were stable at nominal 10 °C for up to 97 hours. Stock solution stability was also assessed for 22 hours at room temperature and 60 days at -20°C.

3. DETAILED LABELING RECOMMENDATIONS

The revised labeling language based on the preliminary review is as below. Based on the clinical pharmacology review, most revisions were on drug-drug interactions and recommendations for renal impairment patients. In addition, we have the following comment to the sponsor:

"**a.** Update your clinical pharmacology section based on the draft guidance "Clinical Pharmacology Labeling for Human Prescription Drug and Biological Products—Considerations, Content and Format."
(http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM109739.pdf)

b. You stated that [redacted (b) (4)] . Validate number and provide mean (CV%). Under the annotated label, provide the source study/data to support the claim in the label (not just general "see summary of clinical pharmacology").

HIGHLIGHTS OF PRESCRIBING INFORMATION

---------- **DOSAGE AND ADMINISTRATION** ----------

- [redacted (b) (4)] Access renal function before initiating ZURAMPIC. Do not initiate ZURAMPIC if eCLcr is below 45 mL/min (2.2)
- Discontinue ZURAMPIC if eCLcr falls below 45 mL/min. (2.2)

----------**USE IN SPECIFIC POPULATIONS**----------

- Renal impairment: [redacted (b) (4)] Not recommended for patients with eCLcr<45 mL/min. (2.2, 5.1, 8.6)
- Hepatic impairment: Not recommended with severe hepatic impairment. (8.7)

2 DOSAGE AND ADMINISTRATION

2.2 Patients with Renal Impairment

No dose adjustment is needed in patients with eCLcr of 45 mL/min or greater. ZURAMPIC should not be initiated in patients with an eCLcr less than 45 mL/min. Assessment of renal function is recommended prior to initiation of ZURAMPIC therapy and periodically thereafter. ZURAMPIC should be discontinued when eCLcr is persistently less than 45 mL/min [see Warnings and Precautions (5.1) and Use in Specific Populations (8.6)].

4 CONTRAINDICATIONS

The use of ZURAMPIC is contraindicated in the following conditions:

- Tumor lysis syndrome or Lesch-Nyhan syndrome [*see Use in Specific Populations (8.8)*].
- Severe renal impairment (eCLcr less than 30 mL/min), end stage renal disease or patients on dialysis [redacted (b) (4)] Use in Specific Populations (8.6)].

7 DRUG INTERACTIONS

7.1 CYP2C9 Inhibitors and inducers

Lesinurad exposure is increased when ZURAMPIC is co-administered with inhibitors of CYP2C9. ZURAMPIC should be used with caution in patients taking moderate inhibitors of CYP2C9 (eg, fluconazole, amiodarone). Lesinurad exposure is decreased when ZURAMPIC is co-administered with inducers of CYP2C9 (eg, rifampin), which may decrease the therapeutic effect of ZURAMPIC [see Clinical Pharmacology (12.3)]. .

7.5 [redacted] Aspirin

[redacted] Aspirin at doses higher than 325 mg per day may decrease the [redacted] efficacy of ZURAMPIC in combination with allopurinol. Aspirin at doses lower than 325 mg per day does not decrease the efficacy of ZURAMPIC. [redacted] -Aspirin of 325 mg or less per day (ie, for cardiovascular protection) can be coadministered with ZURAMPIC.

8 USE IN SPECIFIC POPULATIONS

8.6 Renal Impairment

The PK of ZURAMPIC was evaluated in studies that included patients with mild(eCLcr 60 to less than 90 mL/min), moderate (eCLcr 30 to less than 60 mL/min), and severe renal impairment (eCLcr less than 30 mL/min). Lesinurad exposure (AUC) increased by 3[redacted]%, 50-7[redacted]% and 113% respectively in subjects with mild, moderate and severe renal impairmen [see Clinical Pharmacology (12.3)].

The efficacy and safety of ZURAMPIC were evaluated in studies that included gout patients with mild and moderate renal impairment [see Clinical Studies (14)]. The patients with moderate renal impairment [redacted] had a higher occurrence of renal related adverse reactions compared to patients with mild renal impairment or normal renal function [see [redacted] Adverse Reactions (6.1)].The efficacy and safety of ZURAMPIC have not been evaluated in gout patients with severe renal impairment (eCLcr less than 30 mL/min), with ESRD, or receiving dialysis. ZURAMPIC is not expected to be effective in these patient populations [see Contraindications(4) and Clinical Pharmacology (12.3)].

[redacted]

[redacted]

8.7 Hepatic Impairment

No dose adjustment is necessary in patients with mild or moderate hepatic impairment (Child-Pugh classes A and B) [*see Clinical Pharmacology (12.3)*]. Lesinurad has not been studied in patients with severe hepatic impairment and is therefore not recommended .

12 CLINICAL PHARMACOLOGY

12.2 Pharmacodynamics

Effects on Serum Uric Acid and Urinary Excretion of Uric Acid

In gout patients, ZURAMPIC lowered sUA levels and increased renal clearance and fractional excretion of uric acid. Following single and multiple oral doses of ZURAMPIC to gout patients, dose-dependent decreases in sUA levels and increases in urinary uric acid excretion were observed. (b) (4)

12.3 Pharmacokinetics

Metabolism
Lesinurad undergoes oxidative metabolism mainly via the polymorphic cytochrome P450 CYP2C9 enzyme. Plasma exposure of metabolites is minimal (<10% of unchanged lesinurad). Metabolites are not known to contribute to the uric acid lowering effects of ZURAMPIC. A transient oxide metabolite is rapidly eliminated by microsomal epoxide hydrolase in the liver and not detected in plasma.

Patients who are CYP2C9 poor metabolizers are deficient in CYP2C9 enzyme activity. A cross-study pharmacogenomic analysis assessed the association between CYP2C9 polymorphism and lenisurad exposure in patients receiving single or multiple doses of lesinurad at 200 mg, 400 mg or 600 mg. At the 400 mg dose, lesinurad exposure was approximately 1.8-fold higher in CYP2C9 poor metabolizers (i.e., subjects with CYP2C9 *2/*2, *3/*3, (b) (4) genotype) compared to CYP2C9 extensive metabolizers (i.e., CYP2C9 *1/*1 genotype). Use with caution in CYP2C9 poor metabolizers, and in patients taking moderate inhibitors of CYP2C9 [see Drug Interactions (7.1)].

Specific Populations

Renal Impairment

Two dedicated studies were performed to assess PK in renal impairment (classified using the Cockcroft-Gault formula) subjects. In both studies, Cmax was comparable in renal impairment subjects compared to healthy subjects.

Study 1 was a single-dose, open-label study evaluating the pharmacokinetics of ZURAMPIC 200 mg in subjects with mild (eCrCL 60 to less than 90 mL/min) and moderate renal impairment (eCrCL 30 to less than 60 mL/min) compared to healthy subjects. Compared to healthy subjects (N=6; eCrCL greater than or equal to 90 mL/min), plasma AUC of lesinurad was increased by

approximately 3(b) (4)% and 7(b) (4)% in subjects with mild (N=8) and moderate (N=10) renal impairment, respectively.

Study 2 was a single-dose, open-label study evaluating the pharmacokinetics of ZURAMPIC 400 mg in subjects with moderate and severe renal impairment (eCrCL less than 30 mL/min) compared to healthy subjects. Compared to healthy subjects (N=6), plasma AUC of lesinurad was increased by approximately 50% and 113% in subjects with moderate (N=6) and severe (N=6) renal impairment, respectively.

4. APPENDIX

4.1 PHARMACOMETRIC REVIEW

OFFICE OF CLINICAL PHARMACOLOGY: PHARMACOMETRIC REVIEW

Application Number	NDA 207988
Submission Date	Dec 29, 2014
Compound	Lesinurad
Dosing regimen (route of administration)	200 mg QD (oral administration)
Indication	Gout
Clinical Division	DPARP
Primary PM Reviewer	Jianmeng Chen, Ph.D.
Secondary PM Reviewer	Yaning Wang, Ph.D.

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

1 SUMMARY OF FINDINGS

1.1 Key Review Questions

The purpose of this review is to address the following key questions.

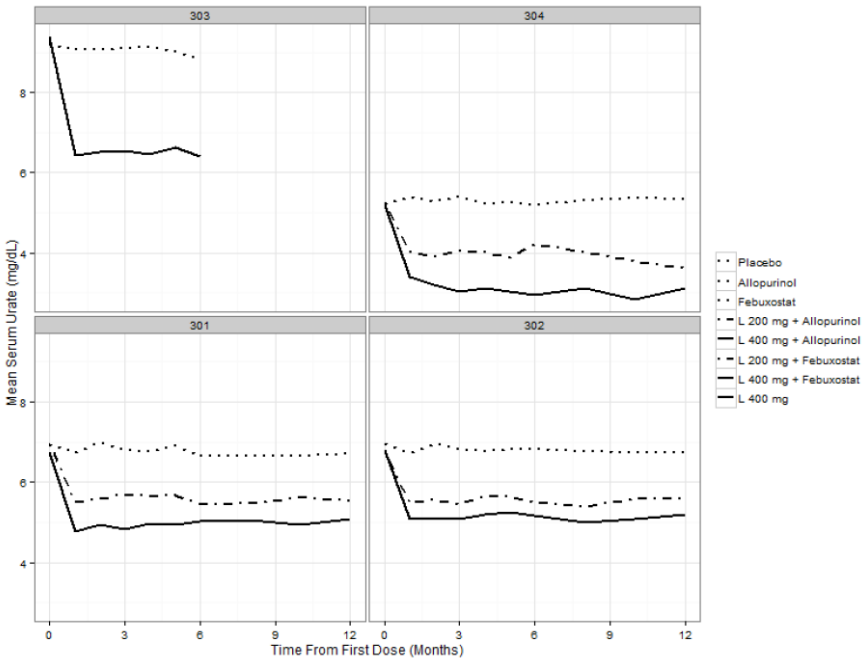
1.1.1.1 Is there a dose/exposure-response relationship for effectiveness?

There is dose response relationship for change from baseline in sUA in Phase 2 study 203 (200 mg, 400 mg, and 600 mg) and in Phase 3 studies (200 mg and 400 mg, Figure 21A). A trend for increase in efficacy with respect to change from baseline in sUA is observed with increasing dose.

An Emax model built to describe the change in serum uric acid identified lesinurad exposure and renal function as predictors of response. The sUA lowering effect with lesinurad 200 mg qd lies on the steep portion of the exposure-response curve and doses below 200 mg qd would be expected to have a clinically important decrement in efficacy.

Consistent with the dose-response, increased efficacy with respect to proportion of patients achieving target sUA is observed in the highest exposure (steady state Cave) quartile compared to lower quartiles (Figure 21B). The highest quartile corresponds to the exposures that are likely to be achieved with the 400 mg QD dose.

A. Time course of serum uric acid



B. sUA responder analysis

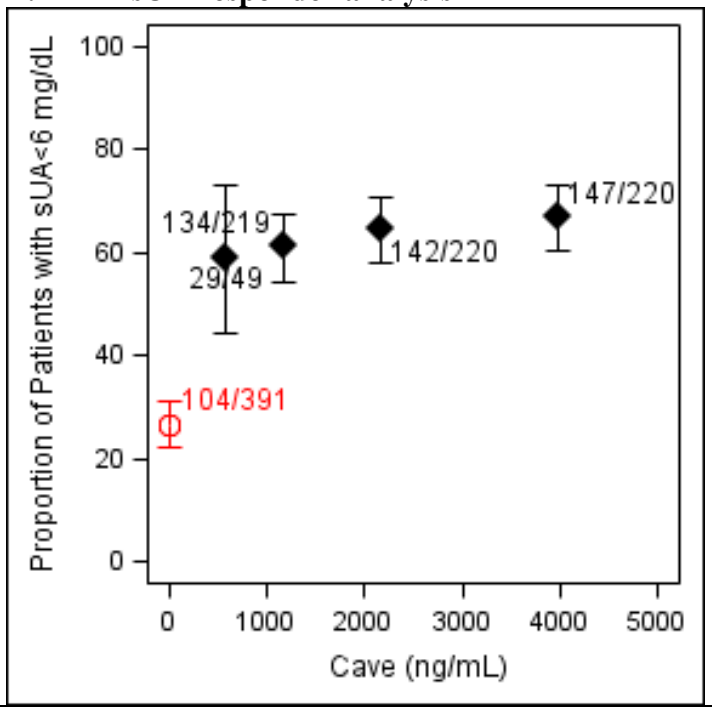


Figure 21: The Dose/exposure response for efficacy: A) Dose response for change in serum uric acid; B) serum uric acid responder analysis with steady state Cave. The black symbols represent the mean and 95% CI in each exposure quartile.

1.1.1.2 Is there impact of renal impairment on the efficacy of lesinurad?

Yes, renal function was identified as the only covariate that impacts the lesinurad efficacy. The final Emax model suggested that for a patient with CRCL of 30ml/min, 55% of the efficacy will be preserved at similar lesinurad exposure; For a patient with CRCL of 60ml/min, 80% of the efficacy will be preserved at similar lesinurad exposure. This is consistent with the observed efficacy data in Phase 3 studies. The evaluation of impact of renal function on lesinurad efficacy in study 301 and 302 demonstrate that:

- Consistent with the known mechanism of action of lesinurad, there appears to be a lower reduction in serum uric acid levels with increasing degree of renal impairment in subjects with gout. The reduction in sUA from baseline in subjects with creatinine clearance< 45mL/min was of lower magnitude (approximately half) when compared to the magnitude observed in the subjects with normal renal function or with mild renal impairment(Table 33).

- The responder analysis of pooled studies 301 and 302 also suggest that the efficacy in patients with creatinine clearance less than 45mL/min is minimal (Figure 22).

This impact of renal impairment on lesinurad efficacy is consistent with its mechanism of action. Lesinurad acts as an inhibitor of several transporters in kidney and inhibits the

reabsorption of uric acid. Its activity is dependent on the adequate glomerular filtration of uric acid.

Table 33. Effects of Baseline Renal Function on sUA decline compared to placebo (study 301and 302, dose of 200 mg QD, posthoc analysis)

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

(Source: Reviewer analysis, see statistical review by Dr. Yu Wang)

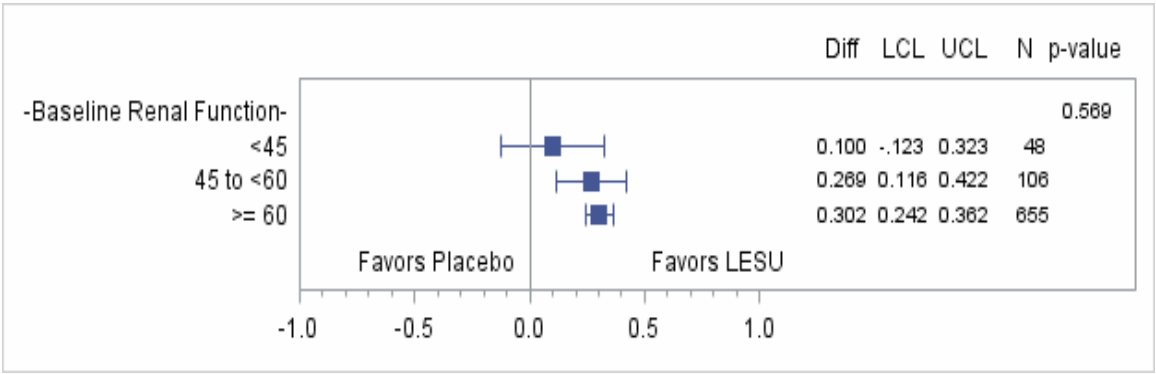


Figure 22. Pooled studies301 and 302 subgroup analysis of lesinurad 200 over placebo estimated sUA responder rate difference and 95% confidence interval. None responder imputation-ITT
(Source: Reviewer analysis by Dr. Yu Wang, Study 301 and 302)

1.1.1.2 Is there a dose/exposure-response relationship for safety?

Yes, there is a dose-response relationship for renal toxicity. Dose-safety analysis revealed that:

- Lesinurad decreased eCRCL from baseline in a dose-dependent manner. This decrease in eCRCL was observed in all categories of renal impairment patients (Figure 23). On average, the decline in eCRCL appeared to stabilize after month 1. However, at individual level, more patients have serum creatinine elevations with longer lesinurad treatment durations (Figure 24).

- A dose dependent eCRCL decline was observed in all categories of renal impairment patients and patients with normal renal function. However, the decline of renal function led to more severe consequence in patients with worse baseline renal function. In 5% (5/101) of patients with moderate renal impairment at baseline, the eCRCL declined to <30mL after 6 to 12 months treatment of lesinurad 200mg+allopurinol, compared to 1% (1/101)in the placebo+allopurinol

group (Table 34). Some of these patients end up requiring dialysis as the renal function declined in the Phase 3 studies.

See Dr. Rosemarie Neuner's clinical review for detailed information on safety analysis.

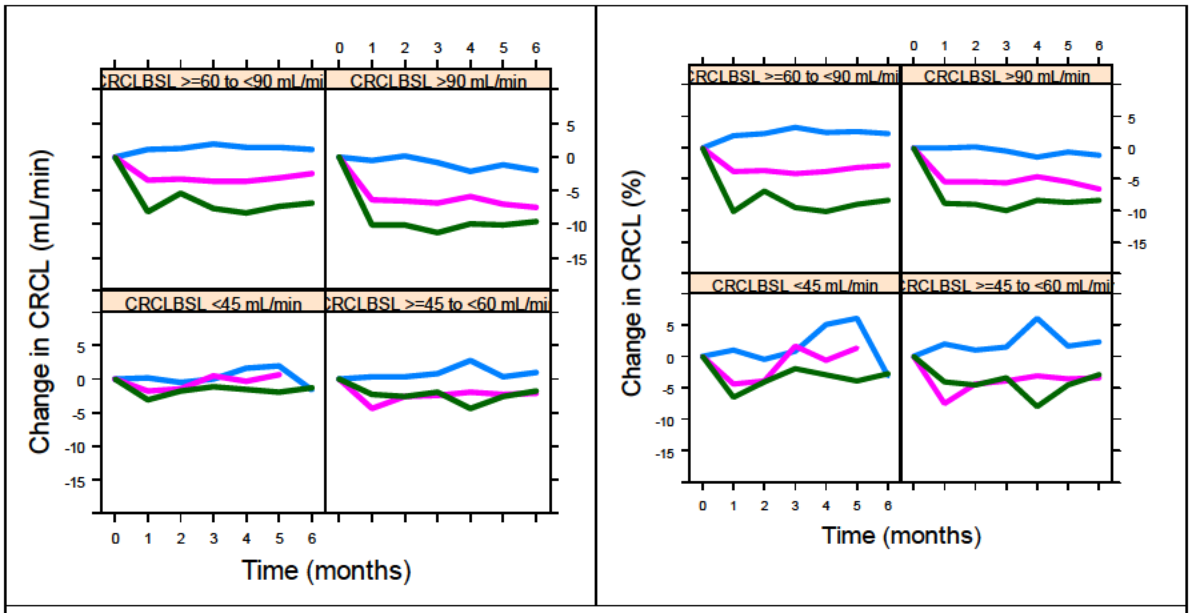


Figure 23. Mean change in eCRCL (mL/min) and relative change in Ecrcl(%)from baseline over time in patients with different baseline CRCLs. Blue: Placebo+Allo, Pink: Lesinurad 200mg+Allo, Green: Lesinurad 400mg+Allo
(Source: Reviewer analysis, Study 301 and 302)

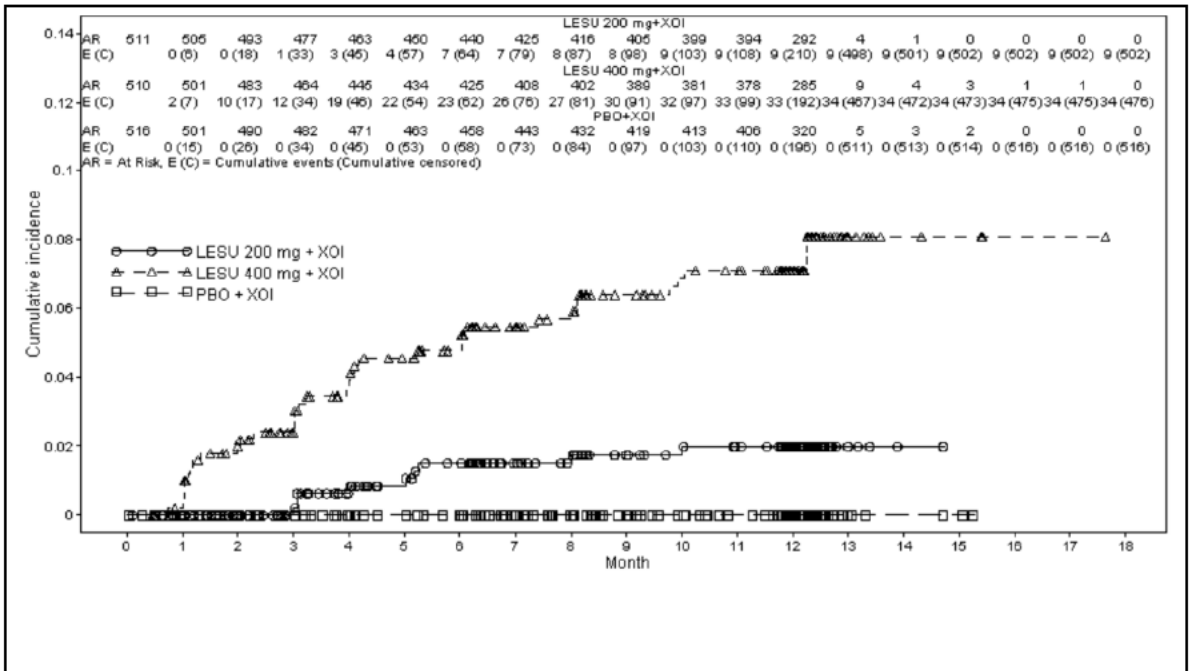


Figure 24: Cumulative Incidence of Serum Creatinine Elevations≥2.0 x Baseline in the Pivotal Phase 3 Studies (12-Month Studies 301, 302, and 304)

(source: Figure 5, lesinurad renal safety report)

Table 34. Shift From Baseline to Last Post-Baseline Estimated Creatinine Clearance Category During Core Study (Studies 301, 302, and 304)

Placebo (n=516)

	Last eCrCl (mL/min)					
Baseline eCrCl (mL/min)	>=90 n (%)	>=60-<90 n (%)	>=30-<60 n (%)	<30 n (%)	Missing n (%)	Total n (%)
>=90	154 (30.0)	19 (3.7)	1 (0.2)	0	6 (1.2)	180 (35.0)
>=60-<90	45 (8.8)	171 (33.3)	8 (1.6)	0	5 (1.0)	229 (44.6)
>=30-<60	0	29 (5.6)	68 (13.2)	1 (0.2)	3 (0.6)	101 (19.6)
<30	0	0	4 (0.8)	0	0	4 (0.8)
Total	199 (38.7)	219 (42.6)	81 (15.8)	1 (0.2)	14 (2.7)	514 (100)

Lesinurad 200mg+XOI (n=511)

	Last eCrCl (mL/min)					
Baseline eCrCl (mL/min)	>=90 n (%)	>=60-<90 n (%)	>=30-<60 n (%)	<30 n (%)	Missing n (%)	Total n (%)
>=90	167 (32.7)	29 (5.7)	0	0	4 (0.8)	200 (39.2)
>=60-<90	31 (6.1)	153 (30.0)	15 (2.9)	0	9 (1.8)	208 (40.8)
>=30-<60	0	21 (4.1)	75 (14.7)	5 (1.0)	0	101 (19.8)
<30	0	0	0	1 (0.2)	0	1 (0.2)
Total	198 (38.8)	203 (39.8)	90 (17.6)	6 (1.2)	13 (2.5)	510 (100)

Lesinurad 400mg+XOI (n=510)

	Last eCrCl (mL/min)					
Baseline eCrCl (mL/min)	>=90 n (%)	>=60-<90 n (%)	>=30-<60 n (%)	<30 n (%)	Missing n (%)	Total n (%)
>=90	152 (29.9)	45 (8.9)	1 (0.2)	0	5 (1.0)	203 (40.0)
>=60-<90	24 (4.7)	162 (31.9)	24 (4.7)	2 (0.4)	1 (0.2)	213 (41.9)
>=30-<60	1 (0.2)	17 (3.3)	70 (13.8)	3 (0.6)	1 (0.2)	92 (18.1)
<30	0	0	0	0	0	0
Total	177 (34.8)	224 (44.1)	95 (18.7)	5 (1.0)	7 (1.4)	508 (100)

(Source: Table 9.5.4.1, ias-16)

1.1.1.3 Does the dose-response relationship for effectiveness and safety support the proposed doses of 200 mg QD in gout patients with normal renal function, mild renal impairment, or moderate renal impairment?

OCP recommends the following regulatory and labeling actions. An Advisory Committee meeting will be held on Oct 23, 2015 to discuss the review team's recommendations.

I Dosing in gout patients with normal renal function (eCRCL ≥ 90mL/min) and mild renal impairment (eCRCL = 60-<90 mL/min):

The sponsor proposes lesinurad 200 mg be administered with food and water. OCP review team recommends approval in this population.

II Dosing in moderate renal impaired patients with an estimated creatinine clearance of 30-<60 mL/min:

Lesinurad acts as an inhibitor of several transporters in kidney, and inhibits the reabsorption of uric acid. Activity of lesinurad is dependent on the renal function of patients. There appears to be an attenuated uric acid lowering activity in patients with eCRCL less than 45mL/min based on the integrated PK/PD analysis, which is supported by the subgroup analysis (see section 1.1.1.1 and 2.2.2).

The renal safety evaluation also suggested that the decline of renal function led to more severe consequence in patients with worse baseline renal function (see section 1.1.1.2).

Given the lower response of lesinurad in eCRCL<45 mL/min group and the increased risk of decline in renal function (eCRCL) from baseline, we consider benefit-risk of lesinurad not favorable in eCRCL<45 mL/min group. As another uricosuric drug probenecid was not recommended in patients with eCRCL<50mL/min by ACR guideline, and the data were sparse for patients with eCRCL between 45-50 mL/min in the lesinurad program, our analysis also supports similar recommendations for treatment with lesinurad. This risk benefit analysis has been communicated to clinical team.

Overall, we recommends:

In patients with eCRCL ≥45 mL/min

- Recommend for approval.
- Labeling explicitly cautioning language for adverse events, and renal function monitoring.

In patients with eCRCL<45 mL/min

- Do not use lesinurad because of unfavorable benefit-to-risk ratio.

1.1.1.4 Are the effects of intrinsic factors on exposure significant from either efficacy or safety perspective?

Based on sponsor's population PK analysis of gout patients and healthy subjects (N=1109), Creatine clearance, body weight, and disease status were identified as covariates influencing the PK of lesinurad. As shown in Figure 25, typical CL/F value in subjects in gout patients (Phase 3 studies) was approximately 18% lower than that observed in healthy subjects in (Phase 1 studies). Based on these decreases in CL/F, the estimated increases in lesinurad exposure would be approximately 12%, 31% and 65% in patients with mild, moderate, and severe renal impairment, respectively, compared with patients with normal renal function.

The most important covariate describing the variability was the effect of weight on Vc/F of lesinurad. Based on the body weight range in subjects in the Phase 3 studies (range: 46.7 to 239 kg), the Vc/F is expected to range from 19.6 to 45.1 L, but in a more typical weight range (i.e., 60 to 120 kg), the Vc/F would range from 22.3 to 31.7 L.

Age, sex, and race/ethnicity were not found to be statistically significant covariates affecting PK parameters of lesinurad.

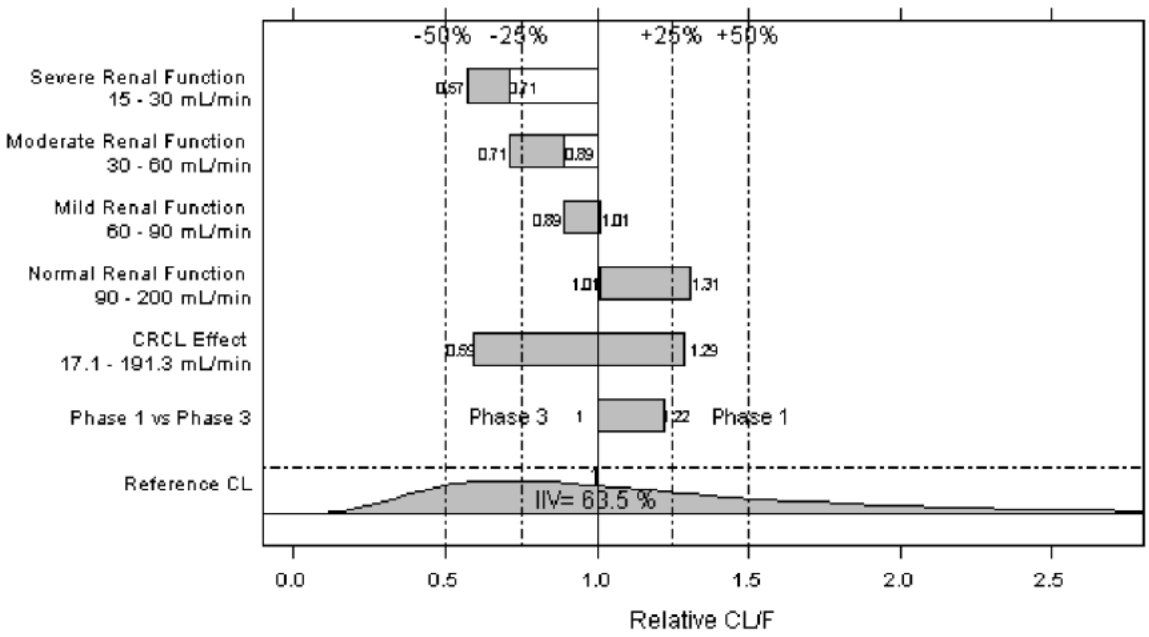


Figure 25. Effects of Renal Function and Disease Status (Phase 1-healthy; Phase 3-gout) on Apparent Clearance of Lesinurad
(Source: Figure 5.4-4, popPK lesinurad analysis)

1.2 Recommendations

Considering the overall risk-benefit profile, we recommend approval of 200 mg in patients with eCRCL>=45mL/min, and do not recommend lesinurad in patients with eCRCL <45mL/min. See section 1.1.1.3 for further details.

1.3 Label Statements

The following are the labeling recommendations relevant to clinical pharmacology for NDA 207988. The ~~red strikeout font~~ is used to show the proposed text to be deleted and underline blue font to show text to be included or comments communicated to the sponsor.

12 CLINICAL PHARMACOLOGY

12.3 Pharmacokinetics

Special Populations

Renal Impairment

(b) (4)

Hepatic Impairment

Following administration of a single dose of ZURAMPIC at 400 mg in patients with mild (Child-Pugh class A) or moderate (Child-Pugh class B) hepatic impairment, lesinurad C_{max} was comparable and lesinurad AUC was 7% and 33% higher, respectively, compared to individuals with normal hepatic function. There is no clinical experience in patients with severe (Child-Pugh class C) hepatic impairment.

Effect of Age, Gender, Race/Ethnicity and Body Weight on Pharmacokinetics

Based on the population pharmacokinetic analysis, age, gender, race and ethnicity do not have a clinically meaningful effect on the pharmacokinetics of lesinurad [*see Use in Specific Populations (8.5)*].

Reviewer's Comments:
The sponsor did two dedicated renal impairment study. The PK data in renal impairment patients from population PK study is complicated by sparse sampling time and model assumptions.

2 RESULTS OF SPONSOR'S ANALYSIS

2.1 Population PK Analysis

Primary objective of sponsor's population PK analysis were:
1. To describe the PK of lesinurad in Phase 1(healthy) and Phase 3 (gout patients) studies.
2. To describe variability in PK parameters of lesinurad and identify clinically relevant covariates.

2.1.1 Methods

Data

A dataset consisting of available plasma concentration-time data of lesinurad in 1136 subjects enrolled in Phase 1 (Protocols RDEA594-118, RDEA594-120, RDEA594-121, RDEA594-122, RDEA594-126 and RDEA594-127) and Phase 3 studies (RDEA594-301, RDEA594-302, RDEA594-303, RDEA594-304) was constructed. The PK analysis dataset included 989 gout patients and 120 healthy subjects. One to 60 plasma samples collected after lesinurad administration were available for each subject, resulting in a total of 9936 plasma samples that were included for the population PK analysis.

Phase 1 subjects were generally younger (mean age value of 41 years old) than Phase 3 subjects (mean age value of 52 years old). The body weight of Phase 1 subjects was similarly distributed across the Phase 1 studies with mean value of 85 kg. Subjects in Phase 3 were slightly obese with mean body weight of 106 kg and BMI of approximately 34 kg/m2. Creatinine clearance at baseline was lower in subjects in Phase 3 studies (86.6 mL/min) compared to subjects in Phase 1 studies (100 mL/min) except those in the renal impairment study RDEA594-120 (53 mL/min). Of the 1109 subjects, 95.4% were male

and 4.6% were female. A majority of subjects were White (77.4%) and were not Hispanic/Latino (90.6%).

The Phase 1 studies had rich sampling. Most PK samples for the Phase 3 studies were collected within 5 hour postdose.

Model Development

The population PK model of lesinurad was first developed based on data collected in Phase 1 studies (RDEA594-118, RDEA594-120, RDEA594-121, RDEA594-122, RDEA594-126 and RDEA594-127) in which subjects received the same formulation as in Phase 3 studies. In order to identify the base model in Phase 1 studies, various compartmental model with linear elimination (2- and 3-compartment) and absorption models (first-, zero- and mixed-order), structures of omega of CL/F, Vc/F and Ka (diagonal and block) were tested. Overall, a 2-compartment model with first-order absorption (run014) with a shared eta between CL/F and Vc/F (i.e., correlation of 1) was retained with an additive and proportional error model selected.

Age, sex, weight, creatinine clearance as well as markers of liver function (AST and ALT) and baseline sUA were selected for the formal covariate analysis. Based on the stepwise covariate testing, only time-varying CrCl on CL/F and body weight on V/F remained in the Phase I population PK model of lesinurad.

The population PK model developed based on Phase 1 data was used for a population PK analysis of PK data collected in Phase 1 and 3 studies (RDEA594-301, RDEA594-302, RDEA594-303 and RDEA594-304). An inter-occasion variability (IOV) term was implemented for Vc/F. Since lower values of posthoc CL/F were observed in subjects in Phase 3 (i.e., CL/F median of 6.48 L/h in subjects in Phase 3 versus 8.31 L/h in subjects from Phase 1 – refer to Figure 25), effect of disease status on CL/F was included in the population PK model, in addition to body weight on V/F and CRCL on CL/F. Finally, model parameters were re-estimated on the full combined data set of Phase 1 and Phase 3 data.

2.1.2 Results

The plasma concentration-time profiles for lesinurad were adequately described by a a 2-compartment model with first-order absorption rate and lag time for absorption. Inter-individual variability (IIV) terms could be implemented for the apparent volume of distribution (V2/F), relative bioavailability (F1) and absorption rate constant (KA). An inter-occasion variability (IOV) term was implemented for Vc/F. The parameter estimates from the final model are shown in **Table 36**. The goodness of fit plots for the model is shown in **Figure 26**.

Effect of covariates on the exposure of lesinurad are discussed in section 1.1.1.4.

Table 35: Population PK Parameters of Lesinurad - Final Population PK Model Based on Phase 1

Data Only

Population Pharmacokinetic Parameter	Typical Values	Between Subject Variability (%)	Shrinkage (%)
Clearance and Volume Parameters			
CL/F (L/h)	$7.02 \times (CRCL/87)^{0.269}$	29.8%	1.26%
Vc/F (L)	$18.5 \times (WT/70)^{0.413}$	13.3%	Shared ETA
CL2/F (L/h)	6.65	0 Fix	NA
V2/F (L)	0.453	19.9%	27.0%
Absorption Parameters			
Ka (h^{-1})	1.22	67.6%	8.55%
Tlag (h)	0.165 Fix	85.1%	41.1%
Error Model			
Proportional (%)	46.2	NA	
Additive Error (ng/mL)	4.650	NA	

Note: ALT was removed since the positive effect of ALT on CL/F was deemed not physiologically plausible, based on the results of Study 118 (liver impairment study)
ALT = alanine aminotransferase; CL/F = apparent clearance; CL2/F = clearance of second compartment; Ka = first-order rate of absorption; CRCL = creatinine clearance; NA= not applicable; PK = pharmacokinetic; TLag = lag time; Vc/F = apparent central volume of distribution; V2/F = volume of second compartment, WT = weight.

(Source: Table 4.3 from population PK lesinurad analysis report, appendix 2.)

Table 36: Population PK Parameters of Lesinurad - Final Population PK Model Based on Phase 1 and 3 Studies

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Population Pharmacokinetic Parameters	Typical Values	Between Subject Variability (%)	IOV
CL/F (L/h)	$6.99 \times (CrClT/87)^{0.322}$ x 0.82 in Phase 3 subjects	63.4%	NA
Vc/F (L)	$24.1 \times (WT/70)^{0.511}$	12.2%	13.6%
CL2/F (L/h)	0.448	0 Fix	NA
V2/F (L)	8.30	20.5%	NA
Ka (h^{-1})	0.690	121.7%	NA
Tlag (h)	0.233	38.9%	NA
Error Model			
Proportional (%) Additive Error (ng/mL)	46.5 6.98	NA	NA

Abbreviations: CL/F, apparent clearance; CL2/F, clearance of second compartment; CrClT, time-varying creatinine clearance; IOV, inter-occasion variability; Ka, first-order rate of absorption; NA, not applicable; PK, pharmacokinetic; Tlag, lag time of absorption; Vc/F, apparent central volume of distribution; V2/F, volume of second compartment.

(Source: Table 5.4-1 from population PK lesinurad analysis report.)

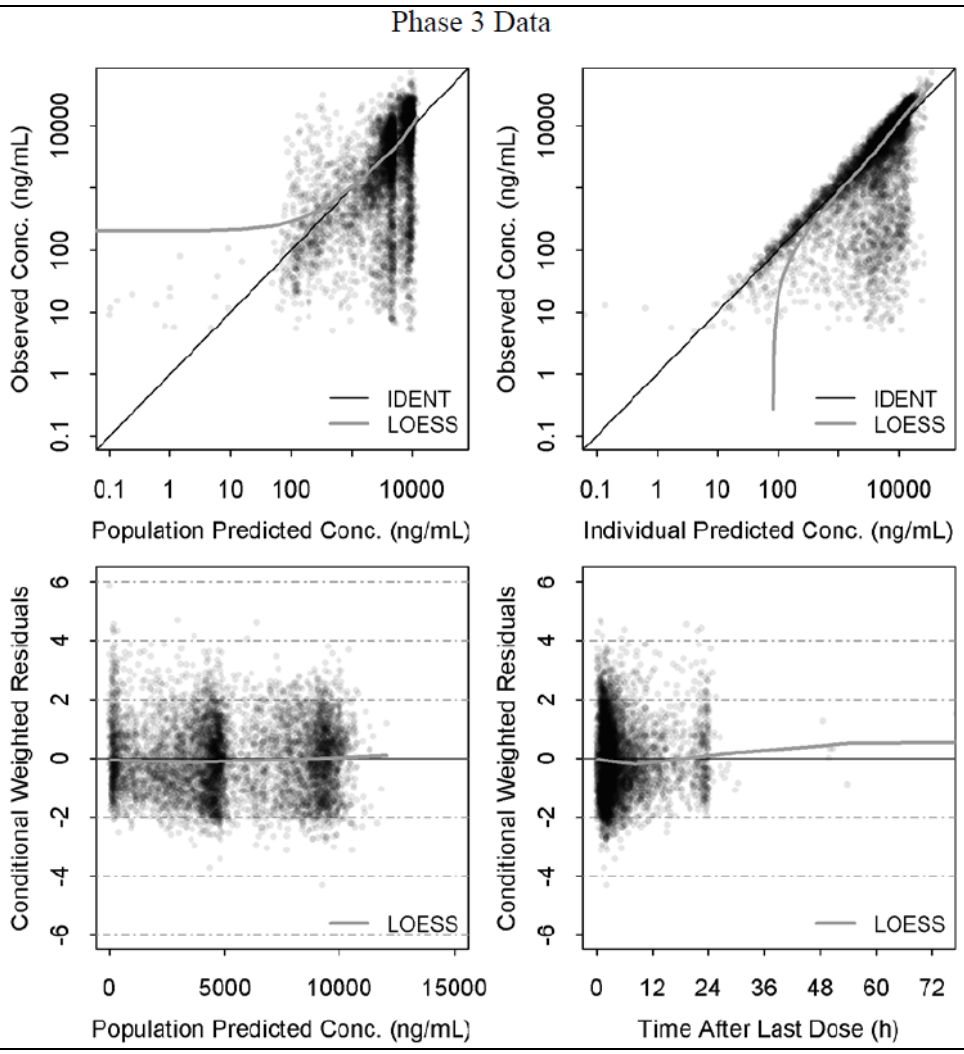


Figure 26: Goodness of Fit of Lesinurad for Phase 3 Data- Final Population PK Model Derived with Phase 1 and 3 Studies
(Source: Figure 5.4-3 from population PK lesinurad analysis report.)

Reviewer's comments:

- *Sponsor's population PK model adequately characterized the observed concentrations of lesinurad 0-24-hr post dose and slightly underestimated the lesinurad concentrations beyond 24 hour postdose. This could be potentially attributed to the analytical method limitations (LLOQ is 5 ng/mL), as all BQL data were excluded from the analysis.*
- *The reviewer agrees with sponsor's assessment that no dose adjustment based on body weight, age or gender is warranted.*

2.2 Exposure Response Analysis (efficacy): PK-PD modeling for serum uric acid

The objectives of the exposure-response analyses for efficacy were

- To develop a population pharmacokinetic-pharmacodynamic (PK-PD) model suitable for describing the time course of sUA as a function of lesinurad exposure

and background medication used for the treatment of gout (i.e., allopurinol, febuxostat);

- To explore the sources of variability in PD parameters and identify clinically relevant covariates.

2.2.1 Methods

Data

Data collected from studies RDEA594-301, RDEA594-302, RDEA594-303 and RDEA594-304 were used in the exposure-response analysis. All measureable sUA concentrations were included in the population PK-PD analysis. A total of 13763 samples from a total of 1638 subjects with measurable concentrations of uric acid in serum (>1.00 mg/dL) were included in the population PK-PD analysis. Cave was imputed from the population PK individual prediction at each occasion where sUA measurement was made. In 15.5% of the cases, no measurable lesinurad concentration matched the sUA concentration. For the latter case, when posthoc parameter estimates were not available due to lack of PK information, last observation carried forward (LOCF) was performed. Values of Cave in subjects treated with placebo were imputed to 0.

Model Development

The PK-PD model included an Emax-type effect model to characterize the changes in sUA driven by the extent exposure and/or time of exposure of lesinurad. This model can be described by

$$F_{ij} = f_{placebo}(t_{ij,}\theta) + f_{DrugEffect}(x_i, t_{ij}, \theta) + \varepsilon_{ij}$$

With

$$f_{placebo}(t_{ij,}\theta) = \text{Intercept} + Slope * \left(\frac{t_{ij}}{2500}\right)$$

And

$$f_{DrugEffect}(x_i, t_{ij}, \theta) = \left(\frac{E_{\max,i} x_i}{E_{50,i} + x_i}\right)$$

PD parameters of lesinurad and key covariates were explored for a preliminary assessment of sources of variability. Age, sex, race, ethnicity, weight, baseline creatinine clearance (based on C-G formula) as well as time-varying creatinine clearance were selected for the covariate analysis.

2.2.2 Results

Exploratory Data Analysis of Lesinurad

In a first step, an exploratory analysis of the mean effect of lesinurad on sUA level was evaluated using graphical tools. The mean sUA were plotted over time by study and

treatment group in Figure 27. Based on study RDEA594-301 and RDEA594-302, a 200 mg dose of lesinurad in combination with allopurinol resulted in significant decrease in sUA vs. allopurinol alone. Moreover, a dose-response of lesinurad was observed, whereby the 400 mg dose of lesinurad resulted in a more pronounced decrease in sUA than 200 mg. The combination of allopurinol and lesinurad (200 or 400 mg) resulted in a maximum effect at approximately 30 days (i.e., 1 month) after the start of treatment.

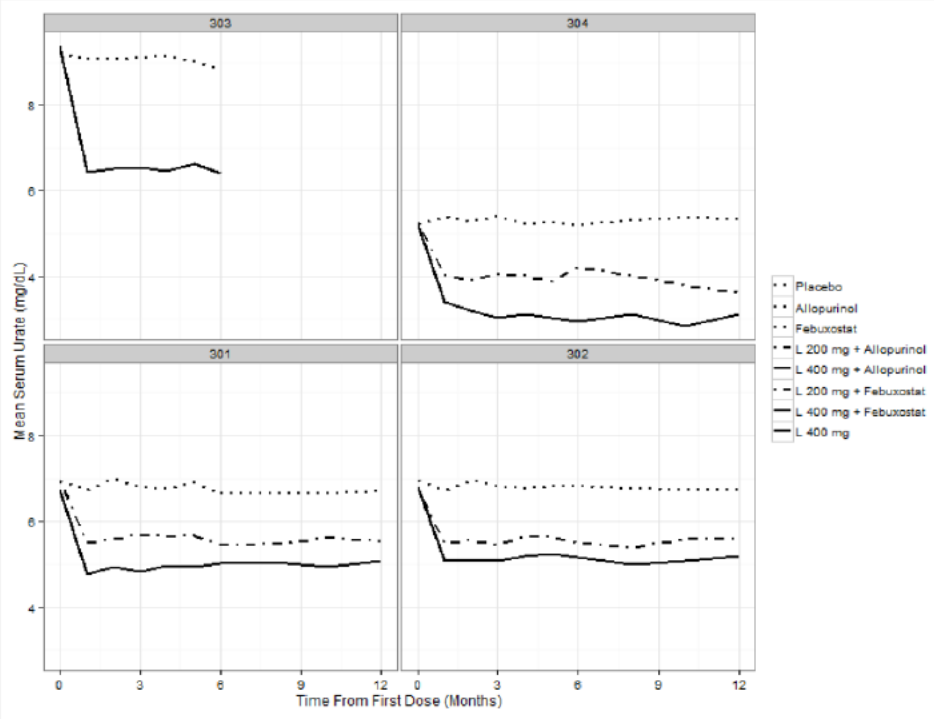


Figure 27. Time Profiles of Serum Urate by Study and Treatment
(Source: Figure 5.2-1, popPKPD sUA report)

Exposure response model of Lesinurad

Exposure of lesinurad (Cave) and serum uric acid data from Phase 3 studies were fit in an Emax model. A PK-PD model was constructed by including a baseline component (E0) specific to each study to take into account the differences in background treatments at baseline. The effect of lesinurad was modeled using a maximum effect model (Emax) with effective concentrations associated with 50% of the maximum effect (EC50). The effect of time-varying creatinine clearance on Emax was included in the final PK-PD model. Additive contribution of placebo and allopurinol or febuxostat treatment was modeled as linear function of time (Table 37).

$$F = \mathrm{E}_{0\ 301/302} + Slope_p * \left(\frac{time}{2500}\right) + \frac{E_{\max} * \left(\frac{CrCl}{87}\right)^{0.564} * C_{ave}}{E_{50} + C_{ave}}$$

Table 37. Population PK-PD Parameters of Lesinurad and sUA

Population Pharmacodynamic Parameter	Typical Value (RSE%)	Between Subject Variability (%) (RSE%)
$E_{0\ 301/302}$ (mg/dL)	6.77 (0.5)	13.9 (5.2)
$E_{0\ 303}$ (mg/dL)	8.82 (1.1)	
$E_{0\ 304}$ (mg/dL)	5.12 (1.5)	25.6 (9.3)
E_{50} (ng/mL)	974 (9.6)	0 Fix (NA)
E_{max} (mg/dL)	-2.55 (3.2)	34.6 (12.5)
$Slope_P$ (mg/dL/2500 h)*	-0.137 (6.0)	237 (70.9)
$Slope_A$ (mg/dL/2500 h)	0.0284 (6.0)	1146 (71.2)
$Slope_F$ (mg/dL/2500 h)	-0.00305 (19.7)	10675 (202.2)
Effect of CrCl on E_{max}	0.564 (4.7)	NA
Error Model		
Proportional Error (%)	13.1	NA
Additive Error (mg/dL)	0.498	NA

Abbreviations: CrCl, creatinine clearance; E_{max}, parameter that contributes to the maximum effect of the E_{max} model for lesinuard; $E_{0\ 301/302}$, sUA level at baseline (studies 301 and 302); $E_{0\ 303}$, sUA level at baseline (study 303 only); $E_{0\ 304}$, sUA level at baseline (study 304 only); E_{50}, parameter that contributes to the 50% of maximum effect of the E_{max} model for lesinurad; NA, not applicable; PK-PD, pharmacokinetic/pharmacodynamic; RSE, relative standard error; $Slope_A$, slope for allopurinol treatment group; $Slope_F$, slope for febuxostat treatment group; $Slope_P$, slope for placebo treatment group.
*Slope (mg/dL/h) = $-0.137/2500 = 5.48*10^{-5}$. Same applies for the other slopes.

(Source: Table 5.6-1, popPK-PD sUA report)

Table 38. Descriptive Statistics of posthoc Lesinurad Cave Derived from the Final population PK Model

Study	C_{ave} (ng/mL) Geometric Mean (Geometric CV%) Median [Minimum, Maximum]	
	Lesinurad 200 mg	Lesinurad 400 mg
RDEA594-301	1523.1 (68.5) 1418.9 [198.4-11636.9]	3106.5 (75.8) 3030.3 [271.4-23473.5]
RDEA594-302	1302.8 (71.5) 1264.2 [78.9-9289.9]	2816.7 (68.9) 2816.7 [122.1-18679.6]
RDEA594-303	---	3400.8 (69.4) 3346.6 [226.9-22174.8]
RDEA594-304	1576.1 (45.1) 1541.2 [418.4-4870.1]	3366.3 (66.2) 3104.7 [736.6-24146.1]

(Source: Table 5.2-1, popPK-PD sUA report)

The sUA lowering effect with lesinurad 200 mg qd lies on the steep portion of the exposure-response curve and doses below 200 mg qd would be expected to have a clinically important decrement in efficacy. Typical Cave values associated with the 200 and 400 mg dose levels (refer to Table 38) were markedly higher than the EC50 (974

ng/mL). For example, typical Cave values associated with the 200 and 400 mg dose levels (Table 38) would correspond to 62% and 78% of the maximum effect of lesinurad.

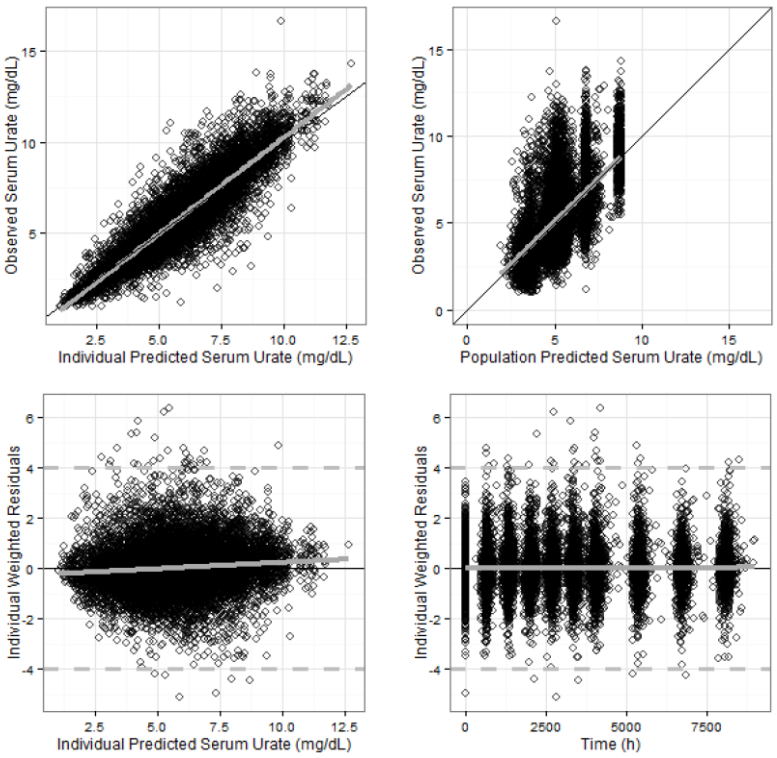


Figure 28: Goodness of Fit of sUA - Final Population PK-PD Model
(Source: Figure 5.4-3 from population PK lesinurad analysis report.)

Reviewer's comments:

- *Sponsor's Emax model adequately describe and exposure-response relationship between lesinurad and serum uric acid (***Figure 28***).*
- *Sponsor's ER analysis suggested that lesinurad 200 mg qd lies on the steep portion of the exposure-response curve, and this is consistent with the dose response observed in Phase 2 and Phase 3 studies.*
- *Renal function was identified as the only covariate that impact the lesinurad efficacy. The final model suggested that for a patient with CRCL of 30ml/min, 55% of the efficacy will be preserved at similar lesinurad exposure; For a patient with CRCL of 60ml/min, 80% of the efficacy will be preserved at similar lesinurad exposure. This is consistent with the observed efficacy data in Phase 3 studies.*

2.3 Exposure Response Analysis for safety (serum creatinine elevation)

The objectives of the exposure-response analyses for safety was to explore the relationship between lesinurad plasma concentrations and the sCr concentrations within the core Phase 3 studies (RDEA594-301, RDEA594-302, RDEA594-303, and RDEA594-304).

2.3.1 Methods

Data

Dataset used for the exploratory PK-sCr analysis were based on datasets for the population PK analysis of plasma lesinurad, with the addition of information on sCr in placebo subjects. A dataset consisting of available plasma concentration-time data of lesinurad collected for up to 12 months in 1614 subjects (989 treated with lesinurad and 625 treated placebo) (Studies RDEA594-301, RDEA594-302, RDEA594-303 and RDEA594-304) was constructed. A total of 14378 values of sCr were available for the analysis (9039 in lesinurad and 5339 in placebo treatment group). Baseline sCr value is defined as the highest value within the 14 days prior to the first dose of lesinurad.

Exploratory analysis

Exploratory analysis of PK-sCr relationship was performed. The graphical assessment was considered using three different definitions of the sCr endpoint:

1. sCr at any time point within individual; or maximum sCr across all observations within the same individual
2. change from Baseline for sCr at any time point or maximum value within the same individual;
3. binary endpoint for all observations or maximum within the same individual: sCr $< 1.5 \times$ Baseline value and sCr $\geq 1.5 \times$ Baseline value.

2.3.2 Results

Exploratory Data Analysis of Lesinurad PK-Serum creatinine in Phase 3 studies

The exploratory population exposure-sCr analysis revealed higher median lesinurad exposure with sCr values ≥ 1.5 x Baseline than with sCr values < 1.5 x Baseline, and is consistently seen across all Phase 3 studies(Figure 29).

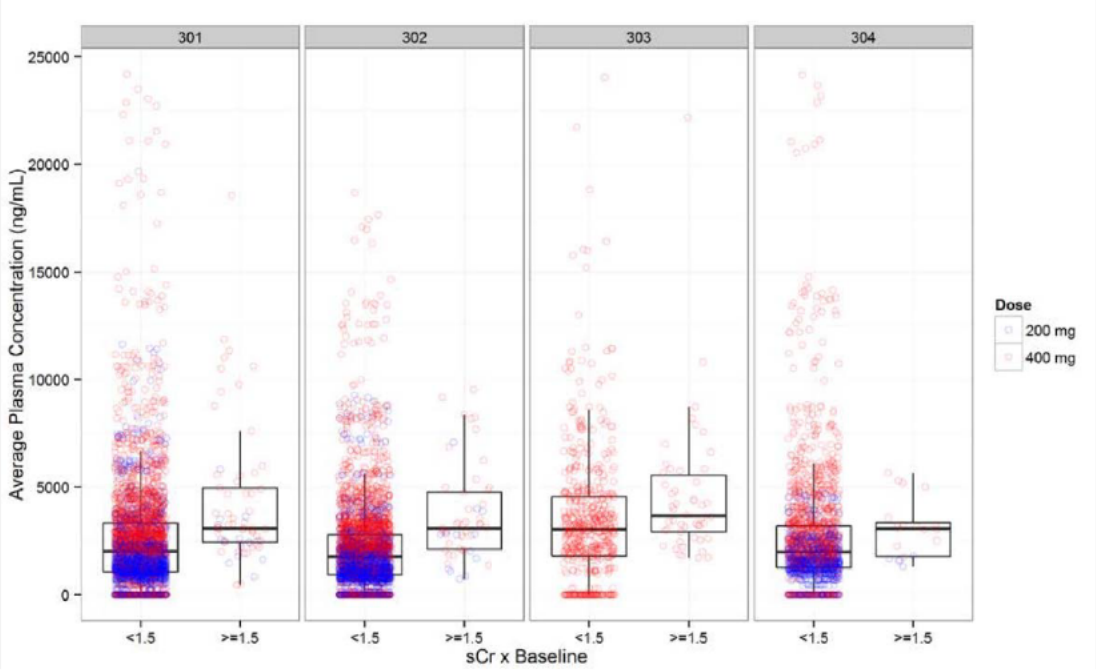


Figure 29. Average plasma concentration of lesinurad in patients with different sCr elevations relative to baseline sCr
(Source: Figure 5.2-1, popPKPD sUA report)

There was a weak trend for increased sCr with increased Cave in pooled allopurinol combination Studies RDEA594-301 and RDEA594-302 (Figure 30) and study 303 and 304 (data not shown). Although there were weak relationships noted between Cave and sCr, this analysis does not inform on cause and effect (ie, whether higher Cave was a cause or a result of higher sCr).

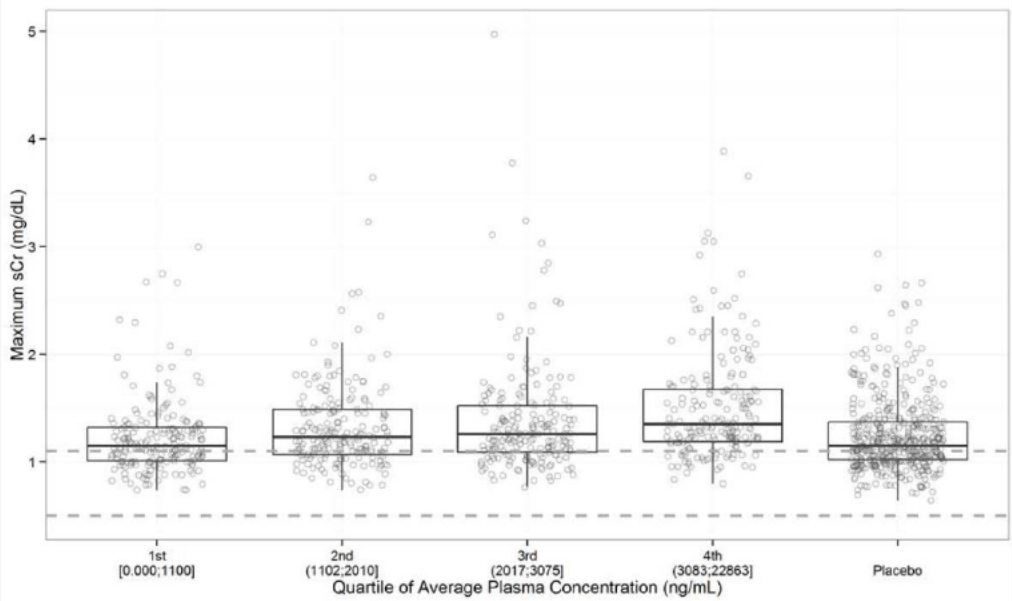


Figure 30. Box Plot of Maximum sCr Binned by Cave Quartile (Studies 301 and 302). Dashed gray lines correspond to normal limits of sCr values (0.5-1.1 mg/dL)
(Source: Appendix 7.12, popPKPD sCR report)

3 RESULTS OF REVIEWER'S ANALYSIS

3.1 Dose/Exposure Response Analysis for efficacy

The primary objective of reviewer's dose/exposure response analysis was to ascertain that the sponsor's proposed dose of 200 mg QD and dose modification scheme (temporarily interrupt or reduce to 100 mg BID if patient experiences AEs) is appropriate.

3.1.1 Methods

Data sets used are summarized in **Table 39**. Exploratory analysis of PK-responder (primary endpoint for phase 3 studies 301 and 302) relationship was performed. The graphical assessment was done in overall population and patients with various degrees of renal impairment.

The analysis was conducted in S-PLUS.

Table 39: Analysis Data Sets

Name	Link to EDR
pkdatp13.xpt	\\cdsesub1\evsprod\nda207988\0000\m5\datasets\final-poppk-lesinurad-anlaysis\analysis\adam\datasets\pkdatp13.xpt
pksua.xpt	\\cdsesub1\evsprod\nda207988\0000\m5\datasets\poppk-pd-sua\analysis\adam\datasets\pksua.xpt
pkscr.xpt	\\cdsesub1\evsprod\nda207988\0000\m5\datasets\scrcorrelations\analysis\adam\datasets\pkscr.xpt

3.1.2 Results

See section 1.1.1.1 for dose/exposure response results for efficacy.

There was increased efficacy with respect to the rate of responders for the 400 mg QD compared to a dose of 200 mg QD or lower in Phase 2 studies, and in Phase 3 studies (Figure 27).
Consistent with the dose-response, increased efficacy with respect to rate of sUA responders is observed in the highest exposure (steady state Cave) quartile (67%) compared to lower quartiles (59, 61, and 65%, Figure 31). The highest quartile corresponds to the exposures that are likely to be achieved with the 400 mg QD dose.

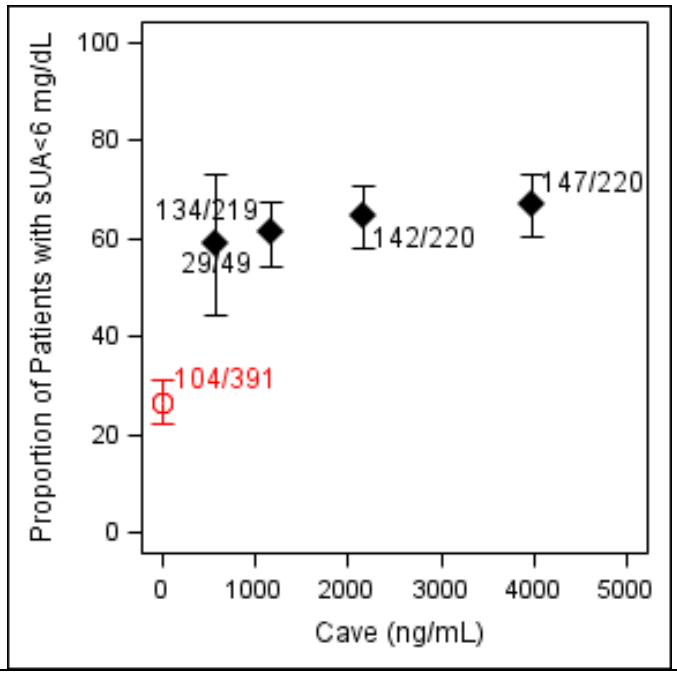


Figure 31. The relationship of proportion of patients who achieved sUA<6 mg/dL with steady state average concentration. The black symbols represent the mean and 95% CI in each exposure quartile. The blue and green horizontal lines represent the exposure range achieved upon administration of 200 mg QD and 400 mg QD doses
(Source: Reviewer analysis, study 301 and 302)

3.2 Effect of creatinine clearance on efficacy

A post-hoc analysis was also conducted for study 301 and 302, evaluating efficacy in subgroups with an eCRCL cut-off of 45 mL/min (predefined by sponsor). Table 40 describes the mean change in sUA from baseline to 6 months across treatment groups (placebo+Allo, and lesinurad 200 mg+Allo) and baseline renal function subcategories. Overall, in moderate renal impairment subjects with creatinine clearance 45-60mL/min, the sUA lowering effect size is similar to the effect in patients with normal renal function or mild renal impairment (~1-1.2 mg/dL). However, magnitude of change in sUA from baseline in subjects with eCRCL< 45 mL/min is much smaller (~0.6-0.7 mg/dL). The responder analysis of pooled studies 301 and 302 also suggest that the efficacy in patients with creatinine clearance less than 45mL/min is minimal (Figure 32).

Table 40. Effects of Baseline Renal Function on Baseline sUA and efficacy (study 301and 302, dose of 200 mg QD, posthoc analysis)

		Placebo+Allo (n=407)				Lesinurad 200 mg+Allo (n=405)			
Study	**Renal function**	**N**	**Baseline sUA (mg/dL)**	**Mon 6 sUA (mg/dL)**	**Responder (%)**	**N**	**Baseline sUA (mg/dL)**	**Mon 6 sUA (mg/dL)**	**Responder (%)**
301	**≥60mL/min**	160	6.94 (1.22)	6.66 (1.99)	26.9% (43/160)	155	6.95 (1.33)	5.70 (1.77)	55.5% (86/155)
	45 - < 60	20	7.26	6.48	35%	33	7.00	5.82 (1.14)	57.6%

	mL/min		(1.39)	(1.14)	(7/20)		(1.04)		(19/33)
	< 45 mL/min	20	7.15 (1.44)	6.84 (1.64)	30% (6/20)	12	7.85 (1.68)	7.13 (1.95)	25% (3/12)
302	**≥60mL/min**	165	6.98 (1.30)	6.99 (1.50)	23% (38/165)	175	6.85 (1.14)	5.82 (1.95)	54.9% (96/175)
	45 - < 60 mL/min	30	6.65 (0.96)	6.52 (1.23)	30% (9/30)	23	6.78 (1.00)	5.58 (1.04)	60.9% (14/23)
	< 45 mL/min	10	8.07 (1.02)	7.89 (1.70)	10% (1/10)	6	6.87 (0.57)	6.22 (1.05)	50% (3/6)

(Source: Reviewer analysis, see statistical review by Dr. Yu Wang)

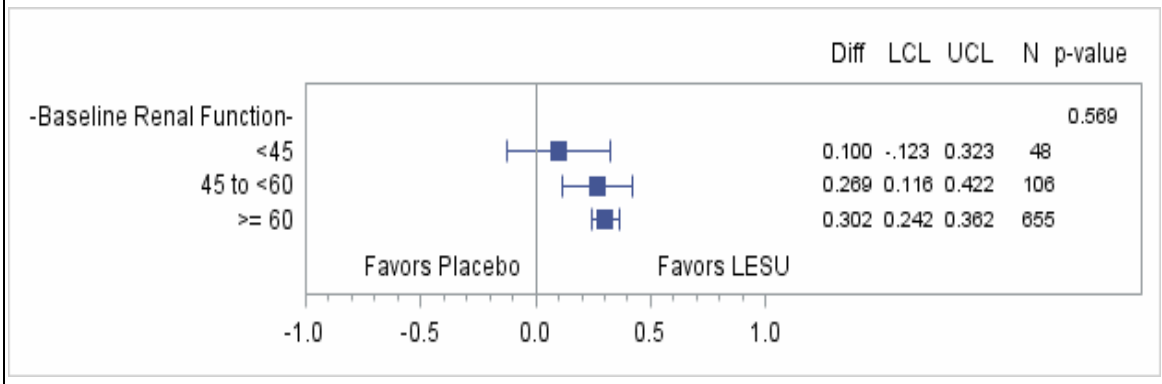


Figure 32. Pooled studies301 and 302 subgroup analysis of lesinurad 200 over placebo estimated sUA responder rate difference and 95% confidence interval. None responder imputation-ITT
(Source: Reviewer analysis by Dr. Yu Wang, study 301 and 302)

3.3 Dose/Exposure Response Analysis-safety

Data sets used are summarized in **Table 39**. Effect of lesinurad on renal function was evaluated based on longitudinal change from baseline in eCRCL, and by evaluating the reduction in eCRCL as a function of baseline renal function. The exploratory graphical assessment was done in overall population and patients with various degrees of renal impairment.

See section 1.1.1.2 for safety results.

3.4 Daily variation of serum uric acid level relative to lesinurad dose

The PD effect of lesinurad during 24 hours postdose was evaluated in several studies. In general, the sUA lowering effect was more significant during the first few hours postdose, and sUA levels were higher when lesinurad concentrations were low (Figure 33). The protocol for Phase 3 studies did not specify the sUA sampling timepoint relative to dose, and there is a concern that the daily variation of serum uric acid may add to the variability of endpoints.

The sUA sampling time relative to the last dose was documented in the dataset pksua. Xpt (**Table 39**). The sUA sampling information was summarized by individual studies, and responder/non responders in Figure 34. The analysis shows that most serum uric acid

samples were collected between 1-5 hour postdose. The sampling time is similar among different arms in each study, and the sampling time distribution is similar in responders and non-responders. Therefore, the sampling time should not affect the study outcomes in the Phase 3 studies.

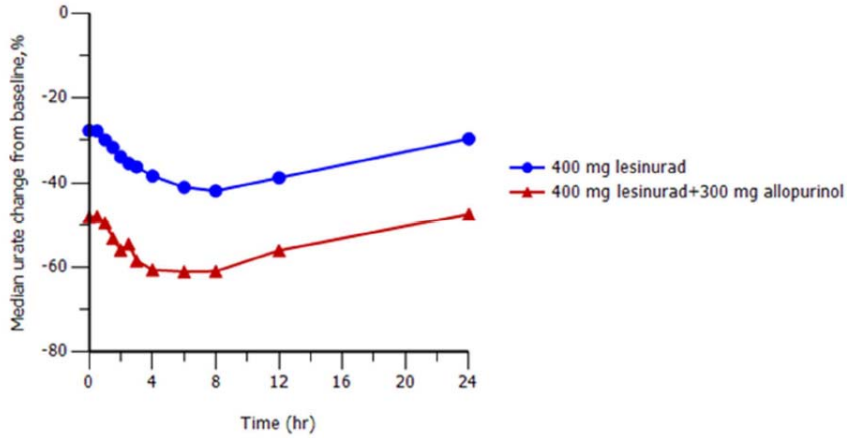
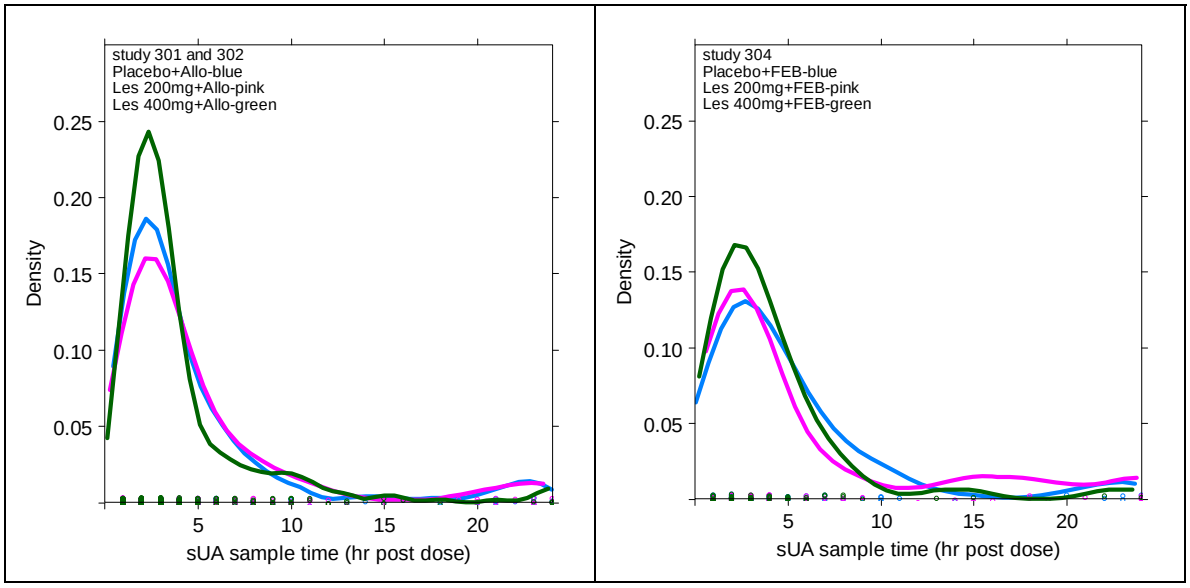
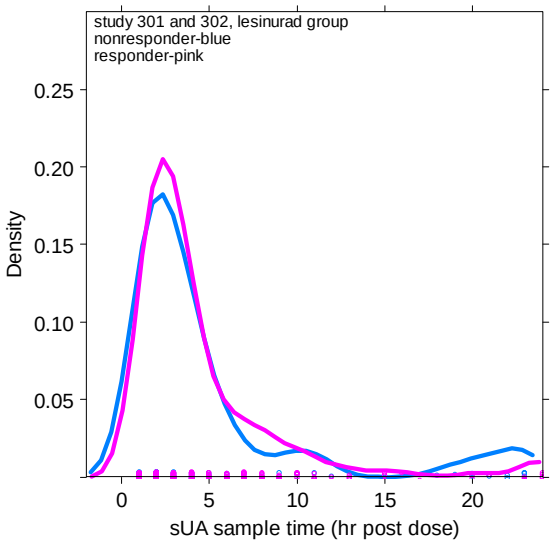


Figure 33. Median Plasma Uric Acid Change from Baseline Following Multiple QD Dosing of 400 mg Lesinurad on Steady State Day 7 (Study 110)
(Source: section 2.7.3, summary of clinical pharmacology, Figure 17)





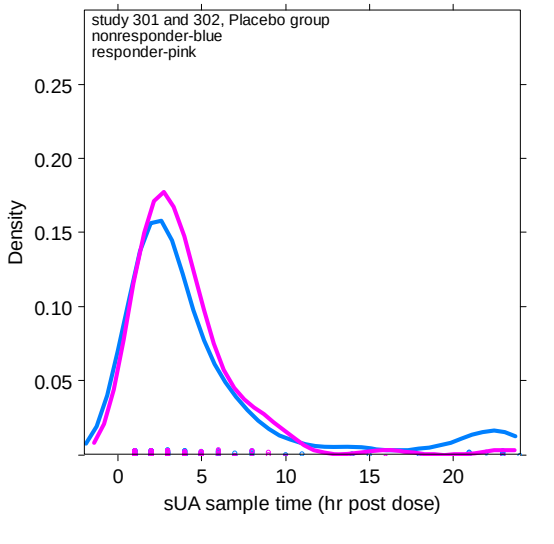


Figure 34. Distribution of serum uric acid sampling time relative to last dose
(Source: Reviewer analysis, study 301 and 302)

4.2 GENOMICS GROUP REVIEW

OFFICE OF CLINICAL PHARMACOLOGY
GENOMICS GROUP REVIEW

NDA Number	207988
Submission Date	12/29/2014
Applicant Name	Ardea Biosciences
Generic Name	Lesinurad
Proposed Indication	Treatment of hyperuricemia associated with gout
Primary Reviewer	Anuradha Ramamoorthy, Ph.D.
Secondary Reviewer	Christian Grimstein, Ph.D.

1. Background

The proposed indication for lesinurad is treatment of hyperuricemia associated with gout in combination with a xanthine oxidase (XO) inhibitor. According to the applicant, lesinurad is a selective uric acid reabsorption inhibitor that inhibits urate transporter 1 (URAT1), and thereby regulates reabsorption and urinary excretion of uric acid. Lesinurad also inhibits the uric acid transporter, organic anion transporter 4 (OAT4), which is associated with diuretic-induced hyperuricemia. The applicant further states that combining lesinurad with a XO inhibitor leads to increased excretion, as well as, decreased production of uric acid.

Approximately half of the oral dose of lesinurad is expected to be cleared via CYP2C9 metabolism. Therefore CYP2C9 genotype/phenotype may impact the pharmacokinetics (PK) of lesinurad. In drug interaction trials, fluconazole (a moderate CYP2C9 inhibitor) increased the AUC of lesinurad by 56%. Rifampin (a moderate CYP2C9 inducer) decreased the AUC of lesinurad by 38%, and also decreased the maximal lowering of serum uric acid (sUA) from 39% to 30%. Similarly, polymorphisms in the CYP2C9 gene may affect CYP2C9 enzyme activity, and consequently affect lesinurad exposure.

The purpose of this review is to evaluate the potential impact of CYP2C9 genetic variations on lesinurad exposure, and whether labeling changes, or additional pharmacogenetic studies are indicated on the basis of these results.

2. Submission Contents Related to Genomics

The applicant collected genotype data in five Phase 1 and Phase 2 trials, and PK data in four of those trials (Table 1). To evaluate the effect of CYP2C9 polymorphism on the PK of lesinurad, the applicant combined cross-study pharmacogenetic data, and submitted a dedicated pharmacogenetic summary report (SR13-015). CYP2C9 genotype information was collected in 118 subjects, including healthy subjects (from RDEA594-109), and patients with gout (from RDEA594-110, RDEA594-111, RDEA594-202 and RDEA594-203). Genotyping for CYP2C9 was performed by [redacted] (b) (4). The applicant did not submit information on the assay used for CYP2C9 genotype analysis.

Table 1: Trials included in the evaluation of associations between CYP2C9 genotype and lesinurad PK.					
Trial	**Design**	**Dose/ Regimen**	**Objective**	**DNA sampling N (%)**	**Genotype and PK N (%)**
RDEA594-109	Phase 1, OL, relative BA, CO, trial in HV	Single dose of lesinurad – 200, 400, and 600 mg	PK, BA	8/23 (~35%)	8/23 (~35%)
RDEA594-110	Phase 1b, OL, PK and PD drug interaction trial in gout patients	Multiple doses of lesinurad - 400 and 600 mg qd; Multiple doses of allopurinol; Multiple doses of colchicine	PK, DDI	20/21 (~95%)	20/21 (~95%)
RDEA594-111	Phase 1b, PK and PD drug interaction trial in gout patients	Multiple doses of lesinurad - 400 and 600 mg qd; Multiple doses of febuxostat; Multiple doses of colchicine	PK, DDI	19/21 (~90%)	19/21 (~90%)
RDEA594-202	Phase 2, DB, placebo controlled, dose response trial to evaluate safety and efficacy in gout patients	Multiple doses of lesinurad – 200, 400, and 600 mg qd; Placebo; Multiple doses of colchicine	Response	7/143 (~5%)	0/143 (0%)
RDEA594-203	Phase 2 trial to evaluate safety, efficacy and potential PK interaction in gout patients	Multiple doses of lesinurad – 200, 400, and 600 mg qd; Placebo; Multiple doses of allopurinol; Multiple doses of colchicine	Response	64/227 (~28%)	20/227 (~9%)
Total				**118/435 (~27%)**	**67/435 (~15%)**

Note: BA – bioavailability, CO – cross-over, DB – double-blind, HV – healthy volunteers, OL – open-label, PD – pharmacodynamics, PK – pharmacokinetics.

Reviewer comments:

1. Genotyping data was available for 118 subjects from five trials; this represents only 27% of the participants in these trials (Table 1). Both CYP2C9 genotype information and PK data was available for only 15% (n=67) of the subjects (Table 1).
2. CYP2C9 was genotyped for only *2 and *3 alleles, though other alleles can alter the

enzyme activity as well.

3. The frequency of CYP2C9 genotypes reported by the applicant for Caucasians (n=93), and Blacks (n=17) is roughly consistent with that reported for the respective racial groups in the 1000 Genomes population [PMID: 25099164], with some exceptions (e.g., under-representation of *3/*3 in Caucasians). Other racial groups were represented in the data set, but in small numbers (i.e., Asians (n=5), Native Hawaiians or other Pacific Islanders (n=2), and American Indians or Alaska Natives (n=1)).
4. The pharmacogenetics summary report does not include data from two additional trials that have potentially relevant CYP2C9 genotype/phenotype information: (1) Trial RDEA594-115 assessed drug interaction with a CYP2C9 substrate (tolbutamide) and performed CYP2C9 genotyping analysis; only CYP2C9 wildtype (*1/*1; extensive metabolizer) subjects were eligible to participate in the trial, and (2) Trial RDEA594-122 assessed the effect of co-administering a CYP2C9 inducer (rifampin), or a CYP2C9 inhibitor (fluconazole); no CYP2C9 genotyping analysis was performed.

3. Key Questions and Summary of Findings

3.1. Does genetic polymorphisms in CYP2C9 affect the PK of lesinurad?

Applicant's analysis:

The applicant genotyped for CYP2C9*2 and *3 alleles, and categorized subjects into the following CYP2C9 phenotype groups based on their genotype: extensive (EMs; *1/*1), slow extensive (*1/*2 or *2/*2), intermediate (IMs; *1/*3 or *2/*3), and poor (PMs; *3/*3) metabolizers. Genotype data was available in 118 subjects, 72.9% of whom are extensive, 12.7% are slow extensive (10.2% for CYP2C9 *1/*2 and 2.5% for CYP2C9 *2/*2), 12.7% are intermediate (10.2% for CYP2C9 *1/*3 and 2.5% of CYP2C9 *2/*3), and 1.7% are poor (PMs; CYP2C9 *3/*3) metabolizers. Only 67 out of 118 subjects had both genotype and PK data.

Based on the applicant's analysis (Table 2), at the 400 mg dose, when compared to the extensive metabolizers (*1/*1), the *1/*2 slow extensive metabolizers (n=6; 4% higher AUC_{0-24} and 10% lower C_{max}) showed no meaningful differences in drug exposure. However, one subject with *2/*2 who is also classified as a slow extensive metabolizer by the applicant had inconsistent changes in AUC_{0-24} and C_{max}, with 81% higher AUC_{0-24} and 25% lower C_{max}. Lesinurad exposure showed no meaningful difference in intermediate metabolizers (*1/*3 (n=7); 22% higher AUC_{0-24} and 3% higher C_{max}). Lesinurad exposure was increased in a poor metabolizer (*3/*3 (N=1); 111% higher $AUC_{0-24,}$ and 75% higher C_{max}), though it was within the range observed in the extensive metabolizer group (*1/*1).

Table 2: (A) Geometric mean of lesinurad PK, and (B) percent differences (%) in geometric mean of lesinurad PK at various dose levels (pooled across studies).

(A)

Lesinurad dose (mg)	n; PK parameter	CYP2C9 Genotype; Geomean of PK Parameter				
		*1/*1	*1/*2	*2/*2	*1/*3	*3/*3
200	n	12	0	0	1	0
	AUC_{0-24} (µg·hr/mL)	25.4	NA	NA	42.9	NA
	C_{max} (µg/mL)	4.88	NA	NA	4.33	NA
	Ae_{0-24} (mg)	46.5	NA	NA	85.1	NA
400	n	55	6	1	7	1
	AUC_{0-24} (µg·hr/mL)	47.9	49.6	86.8	58.5	101
	C_{max} (µg/mL)	10.1	9.09	7.63	10.4	17.7
	Ae_{0-24} (mg)	66.0	70.1	20.6	109	245
600	n	39	3	3	0	1
	AUC_{0-24} (µg·hr/mL)	88.2	85.2	93.3	NA	158
	C_{max} (µg/mL)	19.0	15.4	12.7	NA	32.3
	Ae_{0-24} (mg)	149	104	87.7	NA	334

(B)

Lesinurad dose (mg)	n; PK parameter	CYP2C9 Genotype; Difference in PK Parameter Compared to *1/*1 Metabolizers (%)				
		*1/*1	*1/*2	*2/*2	*1/*3	*3/*3
200	n	12	0	0	1	0
	AUC_{0-24}	NA	NA	NA	68.9↑	NA
	C_{max}	NA	NA	NA	11.3 ↓	NA
	Ae_{0-24}	NA	NA	NA	83.0 ↑	NA
400	n	55	6	1	7	1
	AUC_{0-24}	NA	3.55 ↑	81.2 ↑	22.1 ↑	111 ↑
	C_{max}	NA	10.0 ↓	24.5 ↓	2.97 ↑	75.2 ↑
	Ae_{0-24}	NA	6.21 ↑	68.8 ↓	65.2 ↑	271 ↑
600	n	39	3	3	0	1
	AUC_{0-24}	NA	3.40 ↓	5.78 ↑	NA	79.1 ↑
	C_{max}	NA	18.9 ↓	33.2 ↓	NA	70.0 ↑
	Ae_{0-24}	NA	30.2 ↓	41.1 ↓	NA	124 ↑

(Source: Applicant's table 3 and 4 from SR13-015 study report.)

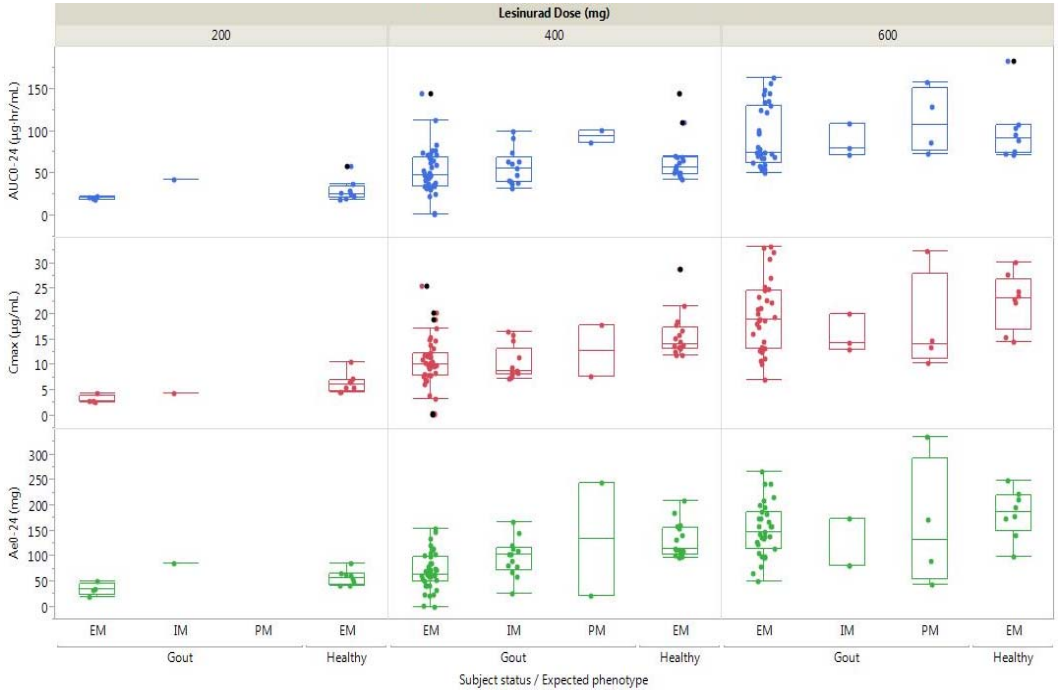
The applicant concluded that: (1) no meaningful association between CYP2C9*2 allele and lesinurad PK was observed, and (2) the association between CYP2C9 gene polymorphism and lesinurad exposure appears to be confined to CYP2C9*3. The applicant notes that because of the small sample size in some of the genotypes, the result should be cautiously interpreted.

Reviewer comments:

1. In clinical practice, multiple approaches may be used to determine CYP2C9 phenotype based on the genotype information. In contrast to the CYP2C9 phenotype classification performed by the applicant, the Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines defines intermediate metabolizers as *1/*3 or *1/*2, and poor metabolizers as *2/*2 or *3/*3 or *2/*3) [PMID: 25099164].

2. To assess the effect of CYP2C9 phenotype on lesinurad exposure (AUC_{0-24} and C_{max}), the reviewer's analysis pooled subject-level data from the 4 trials (RDEA594-109, RDEA594-110, RDEA594-111, and RDEA594-203) and used the CPIC CYP2C9 genotype-to-phenotype classification: extensive (*1/*1), intermediate (*1/*2, *1/*3), and poor (*2/*2, *3/*3, *2/*3) metabolizers.
3. The reviewer's evaluation identified a graded effect of CYP2C9 genotype on lesinurad PK (Figure 1). In general, poor metabolizers had higher exposure to lesinurad. This analysis is limited by the small sample size in some of the metabolizer groups.
4. These results are consistent with the results from the drug interaction trial using the CYP2C9 inhibitor fluconazole (RDEA594-122). Higher lesinurad exposure (~1.5 fold increase) was reported with concomitant use of CYP2C9 inhibitor fluconazole.
5. Some differences in the exposure were observed between healthy subjects and gout patients (Figure 1). However, the numbers are small, and the results should be interpreted with caution.

Figure 1: Effect of CYP2C9 metabolizer status on the pharmacokinetics of lesinurad.



Source: Reviewer analysis using data submitted in the pharmacogenomic study report (SR13-015). Note: All healthy subjects were extensive metabolizers; this includes data from both single and multiple dose studies; EM: Extensive Metabolizer (*1/*1); IM: Intermediate Metabolizer (*1/*2, *1/*3); PM: Poor Metabolizer (*2/*2, *3/*3, *2/*3).

4 Summary and Conclusions

Poor metabolizers (i.e., CYP2C9 *2/*2, *3/*3, *2/*3; CPIC classification) who received lesinurad 400 mg in single or multiple dose studies had ~1.8-fold increase in lesinurad exposure relative to CYP2C9 extensive metabolizers. This is consistent with data from the drug interaction trial with a moderate CYP2C9 inhibitor (i.e., fluconazole) that

showed similar exposure changes.

Given that (1) higher lesinurad exposure has been associated with increased risk for adverse events (for a review of the exposure/response analysis, refer to the Clinical Pharmacology review by Dr. Jianmeng Chen), and (2) increased exposure has been observed with concomitant use of moderate CYP2C9 inhibitors and in CYP2C9 poor metabolizers, labelling should adequately reflect this information, and recommendations should be consistent for CYP2C9 poor metabolizers and CYP2C9 inhibitors.

Since no recommendation for CYP2C9 poor metabolizers has been proposed by the applicant in the labeling, the reviewer recommends modifications to the labelling to include information on CYP2C9 poor metabolizers (See section 5.2).

5 Recommendations

The submission is acceptable from a Genomics and Targeted Therapy Group perspective. The labelling should be modified to accommodate dosing modification based on CYP2C9 genotype.

5.1 Post-marketing studies

No postmarketing commitments or requirements are recommended at this time.

5.2 Label Recommendations

Recommended label additions are noted in underlined red text, deletions are noted in ~~blue strikethrough~~ text.

DRUG INTERACTIONS
Moderate Cytochrome P450 2C9 (CYP2C9) Inhibitors [redacted (b) (4)]:
Use with caution. (7.1)

FULL PRESCRIBING INFORMATION: CONTENTS*
7 DRUG INTERACTIONS
7.1 CYP2C9 Inhibitors and CYP2C9 Poor Metabolizers
Lesinurad exposure is increased when ZURAMPIC is co-administered with inhibitors of CYP2C9 and in CYP2C9 poor metabolizers. ZURAMPIC should be used with caution in patients taking moderate inhibitors of CYP2C9 (eg, fluconazole, amiodarone) and in CYP2C9 poor metabolizers [see Clinical Pharmacology (12.3)].

12 Clinical Pharmacology
12.3 Pharmacokinetics
Metabolism
Lesinurad undergoes oxidative metabolism mainly via the polymorphic cytochrome P450 CYP2C9 enzyme. Plasma exposure of metabolites is minimal (<10% of unchanged lesinurad). Metabolites are not known to contribute to the uric acid lowering effects of ZURAMPIC. A transient oxide metabolite is rapidly eliminated by microsomal epoxide hydrolase in the liver and not detected in plasma.

Patients who are CYP2C9 poor metabolizers are deficient in CYP2C9 enzyme activity. A cross-study pharmacogenomic analysis assessed the association between CYP2C9 polymorphism and lenisurad exposure in patients receiving single or multiple doses of lesinurad at 200 mg, 400 mg or 600 mg. At the 400 mg dose, lesinurad exposure was approximately 1.8-fold higher in CYP2C9 poor metabolizers (i.e., subjects with CYP2C9 *2/*2, *3/*3, (b) (4) genotype) compared to CYP2C9 extensive metabolizers (i.e., CYP2C9 *1/*1 genotype). Use with caution in CYP2C9 poor metabolizers, and in patients taking moderate inhibitors of CYP2C9 [see Drug Interactions (7.1)].

4.3 INDIVIDUAL STUDY REVIEW

Note –
In this review, early development names RDEA594 is also used to refer to lesinurad. All clinical pharmacology studies listed in Table 2 were reviewed in this section, except for study 103, 106 and 107 (early formulation studies).

IN VITRO STUDIES

The brief summary of *in vitro* studies was listed in Table 41.

Table 41. Lesinurad (RDEA594) and Its Major Metabolites M4 and M6 In Vitro Studies Using Human Biomaterials

ADME	Conclusions	Study/Report
Absorption	High permeability, actively transported across Caco-2 monolayers, not a substrate for P-gp	8ARDEP3R1
		SR09-066
Distribution	Mean plasma protein binding of lesinurad was equal to or greater than 97.7% at concentrations ≤ 50 μM in all species tested except mice, where the binding was at least 94.0%. In human plasma, the binding was primarily due to interaction with albumin with minimal contribution from α-1-acid glycoprotein.	SR08-045, SR12-039
Metabolism	Lesinurad was stable with at least 92% of parent remaining following incubation with human liver microsomes (1h)or hepatocytes (4h). Major metabolites were M3 and M4.	SR08-056
	In human, the major circulating component was unchanged lesinurad. Lesinurad and 2 oxidation metabolites, M3 and M4, were major components in human urine. In human feces, the dominant component was debrominated metabolites, M2, M5, and M5b.	RDEA594-112-MET, RDEA594-105-MET-M4
	In humans, CYP2C9 played a major role in the formation of oxidative metabolites (M+16) and to a lesser extent by other enzymes including CYP1A1, CYP2C19, and CYP3A. Formation of M4 is believed to occur through an epoxide intermediate that was quickly converted to the dihydrodiol metabolite M4 by mEH. As such, the epoxide intermediate was detected only in incubation with CYP2C9 recombinant enzyme, but not in either microsomal or hepatocyte incubations.	SR08-038
		SR11-031
	Glutathione conjugates were detected for RDEA594	SR12-027
	Glucuronidation of lesinurad in human liver appeared to be catalyzed by UGT1A1, UGT2B7, and to a lesser extent by UGT1A3.	SR10-002
	There is epoxide intermediate (M3c) in the metabolism of RDEA594 to M4	SR12-026
DDI	Lesinurad inhibited CYP2C8 and CYP2C9 with half maximal	SR08-048, SR12-

potential	inhibitory concentration (IC50) values of 16.2 and 40.7 µM, respectively. The IC50 values for CYP1A2, CYP2B6, CYP2C19, CYP2D6, and CYP3A4 were all greater than 100 µM	043
		SR10-001
	The in vitro results predicted in vivo induction potential according to the following rank order: CYP3A > CYP2C8 > CYP2C9 > CYP2C19 > CYP2B6.	SR08-026, SR10-063
	For valproic acid and progabide, the conversion of M3c to M4 was not affected. However, valpromide inhibited approximately 20% of the M3c to M4 conversion.	SR12-044
Transporter	RDEA594 appeared to be a substrate of OATP1B1, and perhaps OATP1B3 and BCRP. RDEA594 is not a substrate of P-gp.	SR11-044
	RDEA594 appeared to be an inhibitor of OATP1B1 (IC50= 9.29uM) and OATP1B3 (IC50=43.1uM). RDEA594 is not an inhibitor for P-gp and BCRP.	SR11-045
	RDEA594 is not an inhibitor for BCRP.	SR11-053
	RDEA594 demonstrated concentration dependent inhibition of OCT1(IC50 = 13.7 µM). RDEA594 is not an inhibitor for OCT2	SR11-054, SR11-028
	RDEA594 is a substrate for OCT1. RDEA594 is not a substrate for OCT2.	SR11-055, SR11-029
	Lesinurad stimulated human MRP2 (ABCC2) mediated transport and inhibit the human MRP4 (ABCC4) efflux	SR11-099
	RDEA594 was a substrate of hOAT1 and hOAT3. RDEA594 is an inhibitor for OAT1 (39%-46% inhibition at 5 µM, 82%-92% at 50 µM) and OAT3 (64%-80% inhibition at 5 µM, 95% at 50 µM).	SR08-018
	RDEA594 was transported by OAT1 and OAT3 with Km values 0.85 and 1.96 µM, respectively, but not by URAT1. RDEA594 inhibited uptakes of uric acid by URAT1, para-aminohippurate (PAH) by OAT1 and esutrone-3-sulfate (E13S) by OAT3 with IC50 values of 52.5, 4.34 and 3.54 µM, respectively.	SR10-006
	lesinurad-M4 is not an inhibitor of human OCT2, MATE1 or MATE2-K	SR14-007
	Lesinurad has some inhibition (62% inhibition at 100 uM) against BCRP and some inhibition (76% at 100 uM) against NPT1 and negligible effects on MATE1 and MATE2K activity.	SR11-020
	Lesinurad-M6 is not a substrate of human MRP2 and MRP4, Lesinurad-M6 is not an inhibitor of human MRP2. Lesinurad-M6 inhibits MRP4 with IC50 of 29 µM.	SR13-006

(Source – reviewer summary)

PHARMACOKINETICS

1. Mass Balance Study

Study # 112

Title: An AME (Absorption, Metabolism and Excretion) Study of [14C]RDEA594 Orally Administered to Healthy Adult Male Volunteers

- **Objective:**
  - To determine the characteristics of absorption, metabolic profile, and excretion of a single oral 600 mg dose of [14C]lesinurad in humans.

- To evaluate the pharmacokinetic profile of [14C]lesinurad in healthy adult male volunteers.

- **Study design:** This was a single-center, open-label, single-dose study.

- **Test drug and sample size:** 600 mg lesinurad containing 500 μCi of [14C]-lesinurad administered (b) (4) in 6 healthy adult male volunteers.

- **Samples:**
  - Blood: sampling for PK pre-dose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36, 48, 60, 72, 96, 120 144, 168, 192, 216, 240, 264, 288, and 312 hours post-dose or until Discharge Criteria were met; blood sampling for metabolic profiling pre-dose, 1, 3, 6, 10, 12, 24 and 48 hours after study drug administration.
  - Urine sampling intervals: pre-dose (single void collected at approximately 0 Hour); and 0 to 6, 6 to 12, 12 to 24, 24 to 48, 48 to 72, 72 to 96, 96 to 120, 120 to 144, 144 to 168, 168 to 192, 192 to 216, 216 to 240, 240 to 264, 264 to 288, and 288 to 312 hours post-dose or until Discharge Criteria were met.
  - Feces sampling intervals: pre-dose and 0 to 6, 6 to 12, 12 to 24, 24 to 48, 48 to 72, 72 to 96, 96 to 120, 120 to 144, 144 to 168, 168 to 192, 192 to 216, 216 to 240, 240 to 264, 264 to 288, and 288 to 312 hours post-dose or until Discharge Criteria were met.

- **Results**

The overall recovery of the administered dose was approximately 95.6% by day 6 (144 hr). Cumulative total, urine, and fecal recovery of [^{14}C] radioactivity following oral administration is shown in Figure 35.

Absorption:
Following a single oral dose of 600 mg [14C]lesinurad to healthy male volunteers, radioactivity was readily absorbed with median Tmax occurring at 0.5 hours post-dose in both whole blood and plasma.

Distribution:
Mean volume of distribution at steady state (Vss/F) was 27.9 L. Plasma-to-blood radioactivity ratios over the observed course indicated that radioactivity was largely contained in the plasma space and did not penetrate or partition extensively into red blood cells.

Metabolism:
Mean plasma lesinurad to plasma radioactivity ratios of AUC0-24 and AUC∞ were 0.618 and 0.463, respectively, indicating that the majority of circulating radioactivity in plasma in the first 24 hours postdose was attributed to lesinurad but after 24 hours was mainly due to metabolites.

Two oxidative metabolites, M3 and M4, were low in amount relative to unchanged lesinurad (less than 3% of [14C]lesinurad-derived radioactivity at 3 hours postdose).

Some additional minor metabolites were observed in 3-hour plasma samples, with detectable levels of M2 and M3b only by mass spectrum analysis.

Elimination:
A mean of 63.4% of the dose was recovered in urine and 32.3% was recovered in faeces. Most of the administered radioactivity was recovered in the first 72 hours post-dose (mean of 87.3%) and urinary recovery was essentially complete by 24 hours post-dose (Figure 35).

In urine, lesinurad was the major component excreted, accounting for 31.3% of the dose. The 2 most abundant metabolites, M3 and M4, accounted for 12.0% and 15.7% of the dose, respectively. A few other minor metabolites were also detected at lower than 3% of radioactivity. Among these minor metabolites, M1 (glucuronide conjugate of lesinurad) accounted for 2.4% of the 0-to-24- hour urine radioactivity, which is less than 2% of the dose.

The majority of radioactivity in feces was attributed to minor metabolites, namely debrominated products (M2, M5, and M5b) and oxidative products (M3, M3b, M4, and M16). M6 was not detectable in samples from this study.

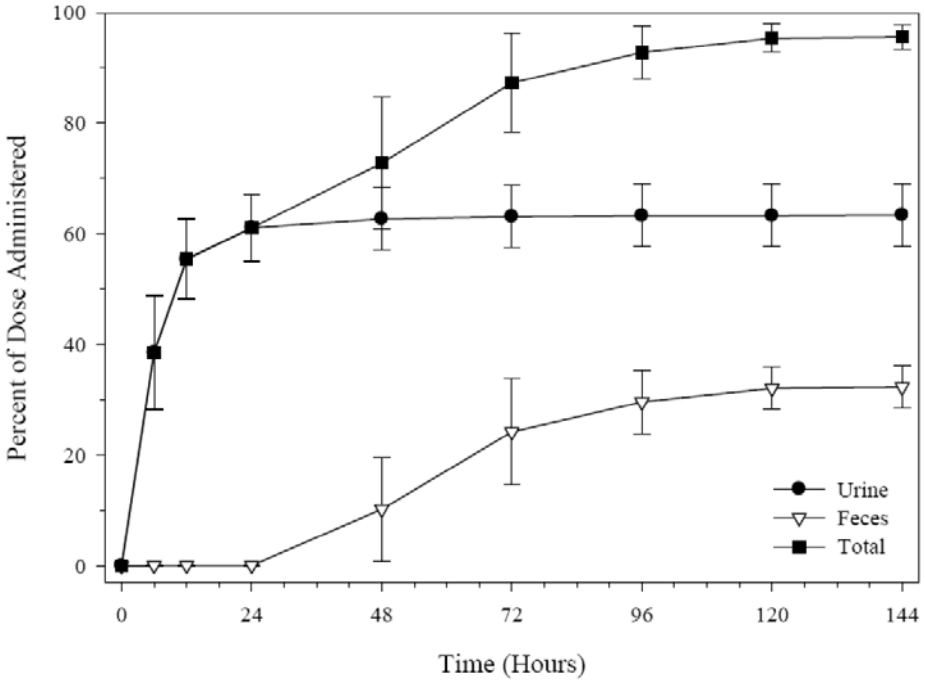


Figure 35: Mean cumulative excretion of total radioactivity in percent of dose in urine, feces and total recovery after single oral administration of 600 mg lesinurad (b) (4)
(Source: Figure 11-1, CSR 112)

Table 42: Metabolic Balance of Urine and Faeces Samples Following a Single Dose of 600 mg [14C]lesinurad

Matrix	Time (hr)	Dose %										
		M1	M2	M3	M3b	M4	M5	M5b	M16	Others	Lesinurad	Total
Urine	0-144	1.5	0.3	12.0	1.0	15.7	ND	ND	0.5	1.2	31.3	63.4
Faeces	0-144	ND	4.8	0.3	1.9	5.0	3.6	7.8	1.1	7.5	1.5	33.5

(Source: Table 11-8, CSR 112)

Table 43: Concentration of [14C]lesinurad Derived Radioactivity, Free Lesinurad, Tightly Bound Lesinurad or Covalently Bound Metabolites (Non-extractable by Acetonitrile)

Fraction		AUC_{0-24} (µg.hr/mL)	Fraction of AUC_{0-24} (%)
Total ^{14}C		197[a]	
ACN extract	Total	177[b]	89.8
	Lesinurad	123[a]	62.4
	M2, M3, M3b, M4	54	27.4
FA extract		10 (187)[a,c]	5.1
KOH extract		1 (188)[b,d]	0.5

(Source – Table 11-7, CSR112)

Table 44: Metabolic Profiles of Pooled Human Plasma, Urine, and Faeces Samples Following a Single Dose of 600 mg [14C]lesinurad

Matrix	Time (hr)	Radioactivity %										
		M1	M2	M3	M3b	M4	M5	M5b	M16	Others	Lesinurad	Total
Plasma	3	ND	ND	2.2	ND	2.0	ND	ND	ND	ND	93.1	97.3
Urine	0-24	2.4	0.4	18.9	1.5	24.8	ND	ND	0.8	1.9	49.3	100
Faeces	24-48	ND	15.7	0.9	7.9	17.2	9.2	25.7	5.1	11.4	6.9	100
Faeces	48-72	ND	14.5	0.7	4.9	14.9	12.2	23.5	2.5	23.3	3.5	100

(Source – Table 11-5, CSR112)

Conclusion

Renal excretion is an important route of elimination for lesinurad. Lesinurad was the predominant compound in plasma and urine, and did not penetrate or partition extensively into red blood cells. The majority of radioactivity in feces was attributed to minor metabolites. Metabolite M4 was only a minor fraction of circulating components.

2. Single Rising Dose (101, 117)

Trial # 101

Title: A Phase 1, Randomised, Double-Blind, Placebo-Controlled, Single Rising Dose Study of RDEA594, a Novel Uricosuric Agent, in Healthy Adult Male Volunteers

- **Objective:** To evaluate
  - The single-dose pharmacokinetics of RDEA594 after oral administration of a (b) (4) formulation;
  - The single-dose uricosuric effects of RDEA594 after oral administration of a (b) (4) formulation;
  - The effect of food on the pharmacokinetic profile of RDEA594.

- **Study design:** A double-blind, placebo-controlled, randomised, ascending single oral dose, sequential group study. It was planned to study a total of 35 subjects, in 7 groups, with 5 subjects per group. In Groups 1, 2, 3 and 4, RDEA594 was administered in the fasted state at dose levels of 5, 25, 100 and 200 mg, respectively.
  - In Groups F, 5 and 6, RDEA594 was administered in the fed state at approximately 30 minutes after starting to consume a standard breakfast at dose levels of 100, 400 and 600 mg, respectively.

- **Test product:** All doses were administered as (b) (4)

- **Sampling Schedule**

PK Sampling Schedule

- Plasma samples were collected at the following time-points in relation to dosing on Day 1: pre-dose (within 30 minutes before dosing) and at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 24, 30, 36, 48, 54, 60, and 72 hours postdose.
- Urine (total catch) were collected over the following intervals in relation to dosing on Day 1: -24 to -18, -18 to -12, -12 to 0, 0 to 6, 6 to 12, 12 to 24, 24 to 30, 30 to 36, 36 to 48, 48 to 54, 54 to 60, and 60 to 72 hours post-dose.

PD Sampling Schedule

Blood and urine samples for the analysis of serum and urinary concentrations of urate and creatinine. Serum samples for uric acid and creatinine measurement were collected at screening and at the following time-points in relation to dosing on Day 1: -24, -18, and -12 hours (pre-treatment), 0 hours (within 30 minutes before Day 1 dosing), and at 6, 12, 24, 30, 36, 48, 54, 60, and 72 hours after Day 1 dosing. Urine samples from each of the pharmacokinetic collections were assayed for uric acid and creatinine.

Results:

Pharmacokinetic results

The mean plasma concentration-time profile is shown in Figure 36. Following oral administration, lesinurad was readily absorbed with a median Tmax ranging between

0.5 to 0.75 hours in the fasted state (5 mg to 200 mg) and 0.25 to 1.5 hours in the fed state (100 mg to 600 mg). Lesinurad appears to follow bi-exponential disposition kinetics in healthy male volunteers (Figure 36). The terminal half-life after single dose was 2.73 to 34.6 hours across the different dose groups (Table 45). However, the large majority of lesinurad was eliminated within the first 24 hours postdose. The mean residence time of lesinurad in plasma after oral dosing was approximately 2.91 to 5.94 hours. PK parameters after single dose of lesinurad under fasting and fed conditions are summarized in Table 45.

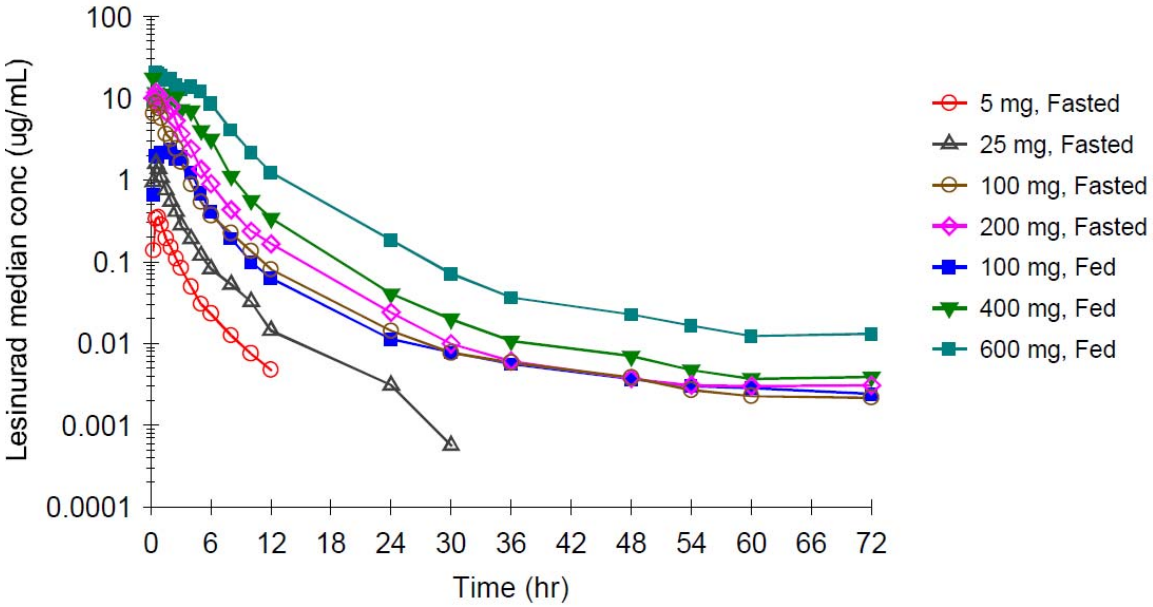


Figure 36: Median Plasma Concentration Profiles of Lesinurad Following Single Oral Doses of Lesinurad (b) (4) Under Fasted and Fed Conditions
(Source – Figure 1, summary of clin pharm)

Table 45: Summary of the Pharmacokinetic Parameters for RDEA594 Following Single Oral Doses

	Dose of RDEA594						
Parameter	5 mg (fasted) (N=4)	25 mg (fasted) (N=4)	100 mg (fasted) (N=4)	200 mg (fasted) (N=4)	100 mg (fed) (N=4)	400 mg (fed) (N=4)	600 mg (fed) (N=4)
$AUC_{(0\text{-}24\ h)}$ (µg·h/mL)	0.787 0.407, 1.52	3.12 2.45, 3.98	17.5 10.7, 28.8	31.9 21.0, 48.5	10.9 8.33, 14.2	56.4 34.9, 91.2	106 53.8, 209
$AUC_{(0\text{-}\infty)}$ (µg.h/mL)	0.779 0.396, 1.53	3.15 2.46, 4.03	17.9 10.8, 29.6	32.2 21.2, 49.1	11.2 8.65, 14.5	56.9 35.2, 92.1	108 54.1, 216
C_{max} (µg/mL)	0.303 0.134, 0.685	1.54 1.17, 2.04	7.68 4.46, 13.2	11.8 9.16, 15.2	3.21 1.62, 6.33	17.7 13.5, 23.2	22.0 16.1, 30.1
T_{max}[a] (h)	0.75 0.50-1.00	0.50 0.50-0.50	0.50 0.50-1.00	0.50 0.25-0.50	1.50 0.25-2.50	0.25 0.25-1.00	0.875 0.50-5.00
$AUC_{(0\text{-}\infty)}$ (norm)	10.2 6.44, 16.2	10.6 8.22, 13.6	12.4 6.07, 25.5	12.5 8.39, 18.5	8.89 6.47, 12.2	11.7 7.94, 17.2	15.7 7.67, 32.3
C_{max} (norm)	3.97 2.26, 6.97	5.18 4.59, 5.85	5.34 2.39, 11.9	4.56 2.89, 7.18	2.54 1.52, 4.26	3.64 2.92, 4.54	3.21 2.04, 5.06
$t_{½}$ (h)	2.73 1.46, 5.09	3.99 3.40, 4.68	12.7 4.64, 34.6	5.97 4.63, 7.70	34.6 17.3, 69.3	5.19 5.03, 5.35	8.04 2.61, 24.8
MRT (h)	2.93 2.33, 3.70	2.91 2.21, 3.82	3.76 2.51, 5.64	3.09 2.40, 3.99	5.74 4.86, 6.78	3.70 2.96, 4.63	4.82 3.08, 7.56
CL/F (mL/min)	107 54.4, 210	132 103, 169	93.1 56.3, 154	103 67.9, 157	149 115, 193	117 72.4, 190	92.5 46.3, 185
V_z/F (L)	25.3 20.1, 31.8	45.7 31.6, 66.1	102 24.4, 427	53.4 27.7, 103	445 232, 854	52.6 33.4, 82.8	64.4 17.2, 242

(Source – 11-1, Study 101 report)

Pharmacodynamic results

A dose-dependent decrease in sUA concentrations resulted from the oral administration of lesinurad over the 100 mg (fed/fasted) to 600 mg (fed) dose range, with maximum suppression of sUA occurring at the first sampling timepoint of 6 hours postdose (Figure 37). The duration of the suppression of sUA concentrations in serum increased with increasing lesinurad dose, from approximately 12 hours at 100 mg (fed/fasted) to beyond 24 hours postdose at the highest dose level (600 mg [fed]).

Excretion of uUA appeared to increase with increasing dose with the majority of statistically significant differences to placebo found across the 0 to 6 hour interval for the amount of uric acid recovered in urine (Aeur, 600 mg), renal clearance of uric acid (CLur; 100 mg, 400 mg, and 600 mg [fed]) and fractional excretion of uric acid (FEUA, 100 mg [fasted] and 100 mg to 600 mg [fed]).

The administration of RDEA594 did not appear to affect creatinine clearance (CLCr), urine flow rate or mean daily fluid consumption.

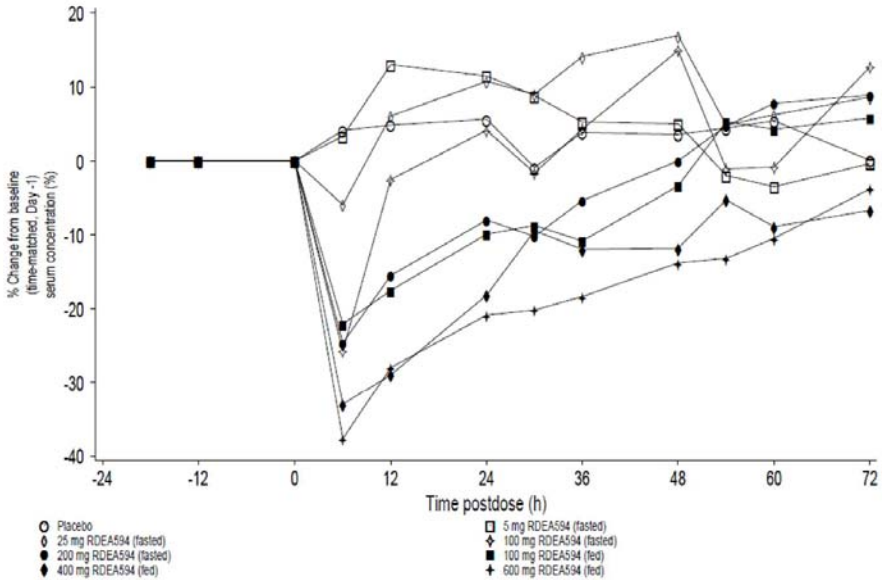


Figure 37. Median Percent Time-Matched Changes from Baseline (Day -1) in Serum Urate Concentrations Following Single Ascending Oral Doses of Lesinurad in Healthy Volunteers (Study 101)
(Source: Figure 11, summary of clin pharm)

Conclusions:

Overall lesinurad exposure was dose proportional up to 600 mg. Food effect of lesinurad is minimal. A dose-dependent decrease in sUA concentrations over the 100 mg (fed/fasted) to 600 mg (fed) dose range was observed, as an increase in excretion of uUA in urine. The creatinine clearance was not affected by single dose of lesinurad, indicating that the transporter inhibition in kidney did not directly change the clearance of creatinine.

Trial # 117

Title: A Double-Blind Randomized Crossover Trial to Define the ECG Effects of Lesinurad Using the Highest Therapeutic and a Supratherapeutic Dose of Lesinurad Compared to Placebo and Moxifloxacin (a Positive Control) in Healthy Men and Women: a Thorough QT Study

- **Objective:**
  - To assess the single-dose pharmacokinetics (PK) and pharmacodynamics (PD) of lesinurad in healthy adult male and female subjects following single doses of lesinurad up to 1600 mg.
  - To investigate the effects of lesinurad on the heart rate corrected QT interval (QTcF).

QT data were not reviewed here. For QT results, please refer to QT-IRT review by Dr. Janice Brodsky (DARRTS date 10/23/2012, IND102128).

- **Study design:** This was a 2-segment study designed to assess the safety, tolerability, and PK of supratherapeutic doses of lesinurad.Segment A assessed lesinurad at 800, 1200, and 1600 mg to allow selection of the supratherapeutic dose for the thorough QT portion of the study (Segment B, 400 mg and 1600 mg). 89 subjects entered the study, with 35 subjects entering Segment A and 54 subjects entering Segment B.

- **Test product:** All doses were administered as lesinurad 400 mg tablets

- **Sampling Schedule**

PK Sampling Schedule

In Segment A, plasma samples were collected at the following time points in relation to dosing on Day 1: predose and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, 30, 36, 48, 60, 72, 84, and 96 hours postdose. In Segment B, plasma samples were collected at the following time points in relation to dosing on Day 1 of each treatment period: predose and at 1, 2, 3, 4, 5, 6, 8, 10, 12, 16, and 23 hours postdose.

In Segment A, urine (total catch) was collected over the following intervals in relation to dosing on Day 1: -24 to -18, -18 to -12, -12 to 0, 0 to 6, 6 to 12, 12 to 24, 24 to 48, 48 to 72, and 72 to 96 hours postdose. In Segment B, urine (total catch): subjects voided within approximately 30 minutes prior to lesinurad dosing, and subsequent total catch urine was collected on Day 1 over the 0 to 6 and 6 to 12 hour postdose intervals).

PD Sampling Schedule

Urate and creatinine concentrations were measured at Screening and at the following time points in relation to dosing on Day 1: -24, -18, -12, and -8 hours (pre-treatment), 0 hours (within 30 minutes before Day 1 dosing), and at 6, 12, 16, 24, 30, 36, 48, 60, 72, 84, and 96 hours after Day 1 dosing. Urine samples from each of the pharmacokinetic collections were assayed for uric acid and creatinine.

Genotyping

Whole blood was collected for CYP2C9 genotyping.

Results:

Pharmacokinetic results

In Segment A, median Tmax (4-5 hours) was similar following single dosing of lesinurad in both genders, with mean half-life generally between 15 and 31 hours. Plasma AUC exposure of lesinurad increased linearly with dose up to 1200 mg in both male and female subjects. At 1600 mg, more than proportional increases were observed for AUC but not Cmax in all subjects (Table 46).

Assessment of geometric mean ratios of female to male Cmax and AUC values demonstrated that in both Segments A and B, plasma Cmax and AUC exposures were

slightly higher in female subjects than male subjects at all dose levels. However, these differences diminished after body weight normalization, suggesting that gender difference in lesinurad plasma exposures was mainly due to the difference in subject body weights(Table 47 and Table 48).

Following single supratherapeutic doses ranging from 800 to 1600 mg in Segment A, approximately 30% to 40% of lesinurad was excreted in urine. The majority of excretion occurring at 0 to 24 hours postdose and there was no apparent gender difference across doses. Slightly lower renal clearance of lesinurad was observed at 1600 mg in male and female subjects. In Segment B, urine excretion and renal clearance of lesinurad within 12 hours postdose at 400 and 1600 mg were consistent with the values reported in previous studies.

The evaluation of the plasma PK profiles of the M4 and M6 metabolites in Segment A showed a median Tmax for M4 of 5 to 6 hours postdose for all groups, and the median Tmax of M6 was at 8 to 10 hours postdose in all groups. M4 and M6 were minor components of systemic circulation of lesinurad (<1% for M6 and <3% for M4). In urine, M4 was efficiently removed through high renal clearance (approximately 200-370 mL/min). Excretion of M4 in urine was approximately 10% to 15% of dose.

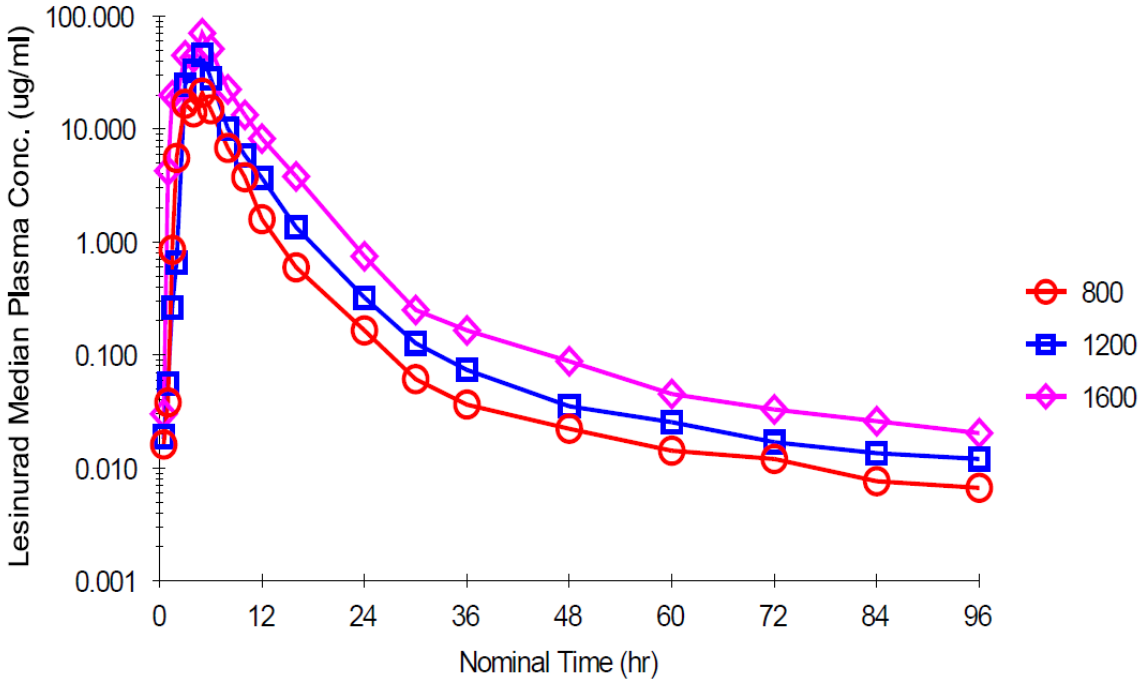


Figure 38: Median Plasma Concentration Profiles Following a Single Dose of Lesinurad 800, 1200, or 1600 mg to Healthy Male Subjects in Segment A
(Source – Figure 11-1, CSR117)

Table 46: Plasma Pharmacokinetics of Lesinurad Following a Single Dose of Lesinurad 800, 1200, or 1600 mg to Healthy Male and Female Subjects

			Median (range)	Geometric Mean (95% CI)					
Dose (mg)	Gender	N	T_{max}[a] (h)	C_{max} (µg/mL)	$AUC_{0\text{-}24}$ (µg·h/mL)	$AUC_{0\text{-}96}$ (µg·h/mL)	AUC_{∞} (µg·h/mL)	CL/F (L/h)	$t_{1/2}$ (h)
800	Male	5	5.00 (3.00-5.00)	30.6 (20.0-46.8)	120 (89.0-162)	122 (90.3-165)	122 (90.5-166)	6.54 (4.83-8.84)	34.4 (23.2-51.1)[b]
	Female	4	4.00 (1.50-5.00)	40.9 (30.2-55.3)	147 (79.3-273)	149 (80.0-278)	150 (80.2-279)	5.35 (2.87-9.98)	24.7 (19.0-32.0)
	All Subjects	9	5.00 (1.50-5.00)	34.8 (27.4-44.1)	132 (103-167)	133 (105-170)	134 (105-170)	5.98 (4.70-7.61)	29.7 (23.5-37.5)[b]
1200	Male	5	5.00 (2.00-5.00)	50.3 (36.5-69.3)	212 (151-297)	216 (153-304)	216 (154-305)	5.55 (3.94-7.82)	27.7 (15.3-50.3)
	Female	5	5.00 (2.00-6.00)	59.9 (49.0-73.2)	268 (235-306)	272 (239-310)	273 (239-310)	4.40 (3.87-5.02)	14.9 (7.33-30.2)
	All Subjects	10	5.00 (2.00-6.00)	54.9 (46.8-64.3)	238 (202-281)	242 (205-286)	243 (206-286)	4.94 (4.19-5.83)	20.3 (13.3-31.1)
1600	Male	5	5.00 (2.00-6.00)	70.2 (51.6-95.3)	386 (275-543)	394 (280-555)	395 (280-557)	4.05 (2.87-5.71)	33.2 (20.5-53.9)[b]
	Female	5	4.00 (2.00-5.00)	84.0 (59.4-119)	536 (362-794)	545 (367-809)	558 (356-876)	2.87 (1.83-4.50)	83.8 (14.8-473)[b]
	All Subjects	10	5.00 (2.00-6.00)	76.8 (63.5-92.8)	455 (360-576)	463 (366-586)	470 (365-605)	3.41 (2.64-4.39)	52.8 (24.3-114)[b]

(Source – 11-1, Study 117 report)

Table 47: Assessment of Dose Proportionality of Lesinurad at 800, 1200, and 1600 mg

Gender	Parameter	a*	b*	95% CI around b
Male	C_{max}	0.0101	1.20	(0.661-1.74)
	AUC_{∞}	0.00166	1.67	(1.16-2.19)
Female	C_{max}	0.0395	1.04	(0.594-1.48)
	AUC_{∞}	0.000460	1.89	(1.25-2.54)

(Source – Table 11-2, Study 117 report)

Table 48. Geometric Mean Ratios of Lesinurad Pharmacokinetics Between Female and Male Subjects (Study 117)

Dose (mg)	Parameter	N (Female/Male)	Geometric Mean Ratio % (90% CI)	Body Weight Normalized Geometric Mean Ratio % (90% CI)
			Female/Male	Female/Male
400	C_{max}	25/28	115% (99.4-134%)	98.4% (85.3-113%)
	AUC_{∞}	25/28	113% (99.8-127%)	95.9% (85.8-107%)
1600	C_{max}	26/28	116% (104-129%)	99.0% (88.8-110%)
	AUC_{∞}	26/28	116% (102-132%)	99.5% (88.1-112%)

(Source: Table 6, summary of clin pharm)

Pharmacodynamic results

In Segment A, decreases in mean sUA concentrations were greater and the time to maximum decrease was longer as the dose of lesinurad was increased up to 1200 mg. Thereafter, no further meaningful increases in sUA levels were observed. Also, the urinary clearance of uric acid and FEUA has plateaued beyond lesinurad 1200 mg (Figure 40).

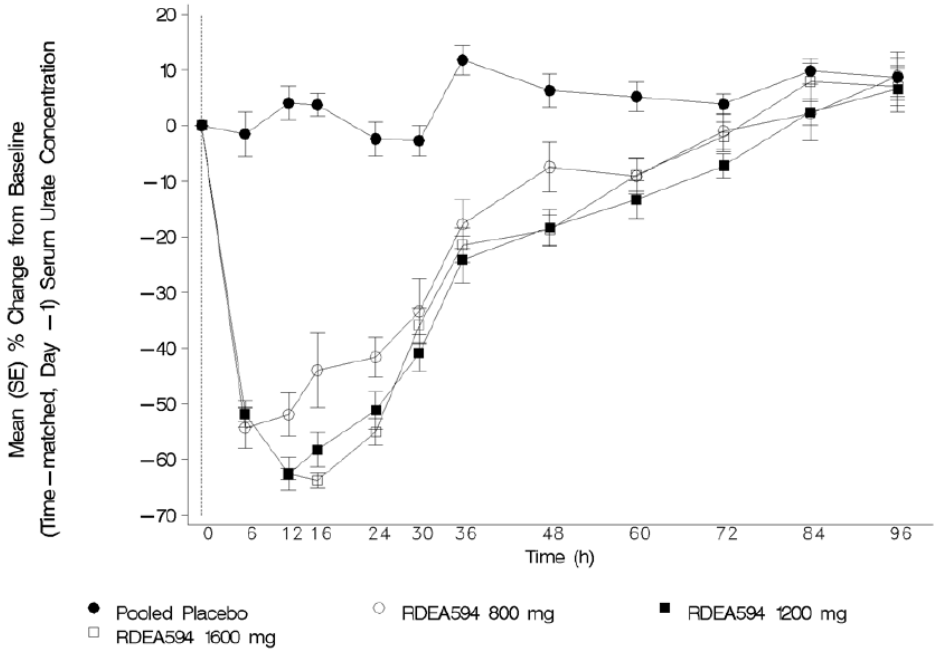


Figure 39. Mean Percent Changes from Baseline (Time-matched Day -1) in Serum Concentrations of Urate Following Single Oral Doses of Lesinurad or Placebo (Segment A)
(Source: Figure 11-15, CSR117)

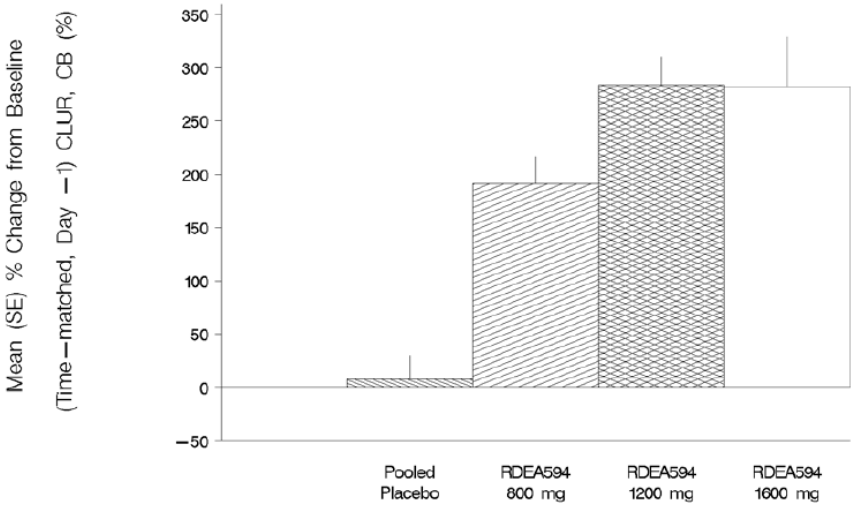


Figure 40. Mean Percent Changes from Baseline (Time-matched Day -1) in Uric Acid Renal Clearance on Day 1 Following Single Oral Doses of Lesinurad or Placebo (Segment A)
(Source: Figure 11-18, CSR117)

Conclusions:

Lesinurad exposure was more than dose proportional beyond 1200 mg. The dose-dependent decrease in sUA concentrations has plateaued beyond lesinurad 1200 mg.

3. Multiple Rising Dose (102)

Trial # 102

Title: A Phase 1, Randomized, Double-Blind, Placebo-Controlled, Multiple Ascending
Dose Study of RDEA594, a Novel Uricosuric Agent, in Healthy Adult Male Volunteers

- **Objective:**
  - To To evaluate the safety and tolerability of the developmental drug candidate RDEA594 when administered as rising multiple oral doses for 7 or 10 days.
  - To evaluate the multiple-dose pharmacokinetics of RDEA594 when orally administered for 7 or 10 days.
  - To evaluate the uricosuric effects of RDEA594 when orally administered for 7 or 10 days.
  - To evaluate the potential induction effect of RDEA594 on the urinary ratio of 6-beta-hydroxycortisol to free cortisol (marker for CYP3A activity) when orally administered for 7 or 10 days.

- **Study design:** This was a Phase 1, randomized, double-blind, placebo-controlled, multiple rising oral dose, study of RDEA594 in healthy adult male subjects. The 4 dose groups in Segment I (Groups 1, 2, 3 and 4) were administered RDEA594 qd for 10 days as 100 mg (b) (4) (fed), 200 mg and 400 mg as IR capsules (fasted) and 200 mg as IR capsules (fed). In Segment II, 3 groups (Groups 5, 6 and 7) were administered RDEA594 qd for 7 days as (b) (4) capsules (b) (4) at 200 mg, 400 mg and 600 mg qd (fed).

Table 49. Treatments and Subject Numbers

	Group	Treatment	Dietary St
Segment I	1 (N=8)	100 mg qd (b) (4) RDEA594/placebo Days 1 to 10	Fed[a]
	2 (N=8)	200 mg qd IR capsules RDEA594/placebo Days 1 to 10	Fasted
	3 (N=8)	400 mg qd IR capsules RDEA594/placebo Days 1 to 10	Fasted
	4 (N=8)	200 mg qd IR capsules RDEA594/placebo Days 1 to 10	Fed[b]
Segment II	5 (N=8)	200 mg qd (b) (4) capsules RDEA594/placebo Days 1 to 7	Fed[c]
	6 (N=8)	400 mg qd (b) (4) capsules RDEA594/placebo Days 1 to 7	Fed[a]
	7 (N=8)	600 mg qd (b) (4) capsules RDEA594/placebo Days 1 to 7	Fed[c]
	8 (N=8)	200 mg qd (b) (4) tablets RDEA594/placebo Days 1 to 7	Fed[b]

N = Number of subjects studied
[a] Low fat breakfast (17.9% fat, 618.78% kcal)
[b] Moderate fat breakfast (36.4% fat, 984.53 kcal)
[c] Low fat breakfast Days 1 to 4, moderate fat breakfast Days 5 to 7

(Source: Table 9-1, CSR102)

- **Test product:** lesinurad was administered as [redacted] (b) (4) capsules [redacted] (b) (4) as shown in Table 49.

- **Sampling Schedule**

PK Sampling Schedule

- Serial plasma samples for RDEA594 assays were collected at the following time-points in relation to dosing on Days 1, 6, and 10: pre-dose (within 30 minutes before dosing) and at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, and 24 hours post-dose. Additional samples were collected on Days 11 and 12 at 36 and 48 hours after the final dose.
- Urine (total catch) for assays of RDEA594, uric acid, and creatinine were collected over the -24 to -12 hour and -12 to 0 hour intervals on Day -1 (24-hour baseline period prior to first dose of study drug) and over the 0 to 12 and 12 to 24 hour intervals in relation to dosing on Days 1, 6, and 10.

PD Sampling Schedule

Serum sampling for uric acid and creatinine measurement were collected at the -24 hour and -12 hour time-points on Day -1 (during the 24-hour baseline period prior to first dose of study drug) and at the 0 hour (within 30 minutes before dosing) and 12 hour time-points on Days 1, 6, and 10. In addition, 0 hour samples were collected on Days 2, 4, and 7, and samples were also collected on Day 11 at 24 and 36 hours after the final dose and on Day 12 at 48 hours after the final dose.

Results:

Pharmacokinetic results

Lesinurad PK after multiple doses was consistent with the single dose PK. The median T_{max} was about 0.75-5 hr and mean apparent terminal $t_{1/2}$ ranged from 3.77-10.6 hrs. Accumulation after multiple doses was minimal. Mean accumulation ratio for all doses ranged from 0.85 to 1.27, which was as expected based on short half-life and QD dosing regimen. The steady state was reached after one dose. Mean plasma PK profiles are shown in Figure 41 and summary PK parameters are listed in Table 50. From other studies, measurement of trough concentrations indicated that steady-state was achieved within 24-48 hrs after initiating repeat dosing.

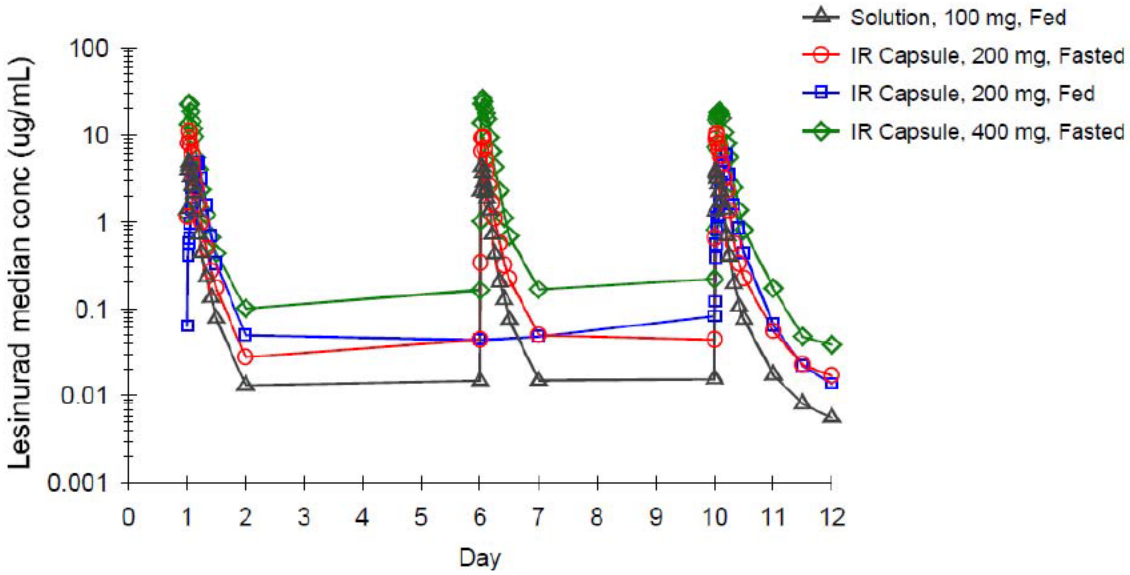


Figure 41: Median Plasma Concentration Profiles of Lesinurad Following Once Daily Multiple Oral Doses of Lesinurad (b) (4) or Immediate-Release Capsules
(Source – Figure 7, Summary of clin pharm)

Table 50: Summary of the Pharmacokinetic Parameters for RDEA594 Following Multiple Oral Doses (Segment I)

Parameter	Dose of RDEA594							
	100 mg (b) (4) fed) (N=6)		200 mg (IR capsules, fasted) (N=6)		400 mg (IR capsules, fasted) (N=6)		200 mg (IR capsules, fed) (N=6)	
	Day 1	Day 10	Day 1	Day 10	Day 1	Day 10	Day 1	Day 10
AUC_τ (µg.h/mL)	14.2 (12.4, 16.2)	12.1 (10.6, 13.7)	28.7 (24.1, 34.1)	33.1 (28.1, 39.1)	70.5 (52.0, 95.8)	89.8 (67.1, 120)	29.8 (20.7, 43.0)	30.3 (23.3, 39.2)
AUC_∞ (µg.h/mL)	14.2 (12.5, 16.2)	NA	28.9 (24.2, 34.5)	NA	71.2 (52.4, 96.8)	NA	30.2 (20.8, 43.9)	NA
C_{max} (µg/mL)	4.74 (3.41, 6.59)	4.02 (2.86, 5.67)	10.8 (9.26, 12.5)	11.7 (9.27, 14.9)	23.1 (16.9, 31.6)	21.9 (18.3, 26.2)	5.54 (4.44, 6.91)	6.51 (5.46, 7.76)
T_{max}[a] (h)	0.750 (0.25-2.50)	0.625 (0.50-2.50)	0.750 (0.75-1.50)	0.750 (0.50-2.00)	1.00 (0.75-1.50)	2.00 (1.00-4.00)	5.00 (4.00-6.00)	4.50 (3.00-5.00)
AUC_τ (norm)	10.1 (8.90, 11.4)	8.56 (7.33, 9.99)	11.4 (8.23, 15.7)	13.1 (9.88, 17.5)	14.2 (10.7, 18.8)	18.1 (13.6, 24.0)	11.7 (7.76, 17.5)	11.8 (8.75, 16.0)
AUC_∞ (norm)	10.1 (8.95, 11.4)	NA	11.5 (8.27, 15.9)	NA	14.3 (10.8, 19.0)	NA	11.8 (7.80, 17.9)	NA
C_{max} (norm)	3.36 (2.48, 4.56)	2.86 (2.03, 4.01)	4.27 (3.69, 4.94)	4.66 (3.35, 6.49)	4.65 (3.65, 5.92)	4.41 (3.57, 5.44)	2.16 (1.59, 2.95)	2.55 (2.16, 3.00)
$t_{½}$ (h)	4.23 (3.74, 4.78)	10.6 (7.43, 15.1)	4.72 (4.03, 5.53)	8.91 (7.59, 10.5)	5.03 (4.33, 5.85)	7.48 (6.22, 8.99)	3.77 (3.38, 4.20)	8.20 (5.85, 11.5)
MRT (h)	3.19 (2.68, 3.80)	3.92 (3.34, 4.60)	3.35 (2.81, 4.00)	4.26 (3.90, 4.65)	3.60 (2.97, 4.37)	4.67 (3.80, 5.75)	6.45 (5.08, 8.19)	7.20 (6.44, 8.06)
CL/F or CL_{ss}/F (L/h)	7.02 (6.16, 8.00)	8.29 (7.27, 9.46)	6.92 (5.80, 8.25)	6.04 (5.11, 7.13)	5.61 (4.13, 7.63)	4.46 (3.33, 5.97)	6.62 (4.55, 9.62)	6.61 (5.10, 8.57)
V_{ss}/F (L)	22.4 (17.8, 28.2)	32.5 (25.4, 41.6)	23.2 (21.3, 25.3)	25.7 (21.6, 30.6)	20.2 (15.1, 27.1)	20.8 (17.5, 24.7)	42.7 (34.0, 53.5)	47.6 (39.7, 57.0)
$R_{AUC\tau}$	NA	0.851 (0.729, 0.992)	NA	1.09 (0.765, 1.56)	NA	0.949 (0.628, 1.43)	NA	1.18 (0.819, 1.69)
R_{Cmax}	NA	0.849 (0.633, 1.14)	NA	1.16 (0.968, 1.38)	NA	1.27 (1.01, 1.61)	NA	1.01 (0.850, 1.21)

	Dose of RDEA594							
	(b) (4) 200 mg capsules, fed (N=6)		(b) (4) 400 mg capsules, fed (N=6)		(b) (4) 600 mg capsules, fed (N=6)		(b) (4) 200 mg tablets, fed (N=6)	
Parameter	Day 1	Day 7	Day 1	Day 7	Day 1	Day 7	Day 1	Day 7
AUC_τ (µg.h/mL)	26.1 (20.4, 33.3)	25.1 (21.2, 29.7)	51.8 (40.8, 65.7)	53.9 (44.6, 65.1)	73.0 (61.3, 87.0)	84.9 (73.5, 98.1)	20.9 (17.3, 25.3)	21.2 (18.7, 24.1)
AUC_∞ (µg.h/mL)	26.3 (20.6, 33.7)	NA	52.3 (41.3, 66.3)	NA	73.7 (61.9, 87.7)	NA	21.1 (17.4, 25.5)	NA
C_{max} (µg/mL)	8.18 (5.49, 12.2)	7.71 (5.91, 10.0)	13.8 (11.5, 16.7)	15.7 (13.9, 17.7)	20.1 (17.3, 23.3)	20.8 (16.4, 26.4)	6.16 (4.60, 8.25)	5.57 (4.24, 7.31)
T_{max}[a] (h)	3.00 (1.00, 3.00)	3.50 (2.00-5.00)	3.00 (1.50, 3.00)	2.50 (1.50-4.00)	2.50 (1.50, 5.00)	3.50 (1.00-5.00)	1.75 (1.00, 5.00)	4.50 (2.00-6.00)
AUC_τ (norm)	10.4 (7.93, 13.6)	9.98 (7.99, 12.5)	11.0 (7.94, 15.2)	11.4 (8.77, 14.9)	9.62 (8.08, 11.5)	11.2 (10.0, 12.5)	8.79 (8.05, 9.61)	8.92 (7.58, 10.5)
AUC_∞ (norm)	10.5 (8.00, 13.7)	NA	11.1 (8.03, 15.4)	NA	9.72 (8.17, 11.6)	NA	8.87 (8.10, 9.71)	NA
C_{max} (norm)	3.25 (2.12, 4.98)	3.07 (2.35, 4.01)	2.94 (2.31, 3.75)	3.33 (2.71, 4.10)	2.65 (2.18, 3.20)	2.74 (2.22, 3.39)	2.59 (1.96, 3.43)	2.34 (1.66, 3.30)
$t_{½}$ (h)	4.56 (4.24, 4.90)	6.98 (6.04, 8.06)	4.01 (2.94, 5.47)	8.40 (6.80, 10.4)	4.14 (2.78, 6.17)	7.89 (5.22, 11.9)	4.11 (3.83, 4.41)	5.65 (5.28, 6.05)
MRT (h)	4.67 (4.09, 5.33)	5.90 (5.21, 6.69)	4.94 (4.33, 5.64)	5.50 (4.80, 6.29)	4.71 (3.85, 5.77)	5.95 (5.12, 6.90)	4.71 (3.48, 6.37)	6.67 (5.50, 8.07)
CL/F or CL_{ss}/F (L/h)	7.59 (5.94, 9.70)	7.97 (6.74, 9.43)	7.65 (6.03, 9.69)	7.43 (6.15, 8.97)	8.14 (6.84, 9.69)	7.06 (6.12, 8.16)	9.50 (7.85, 11.5)	9.44 (8.31, 10.7)
V_{ss}/F (L)	35.5 (26.0, 48.3)	47.1 (36.9, 60.0)	37.8 (28.1, 50.9)	40.8 (37.0, 45.1)	38.4 (31.2, 47.2)	42.0 (38.9, 45.4)	44.7 (30.4, 65.8)	62.9 (52.0, 76.1)
$R_{AUC\tau}$	NA	0.961 (0.855, 1.08)	NA	1.04 (0.861, 1.26)	NA	1.16 (1.07, 1.26)	NA	1.01 (0.815, 1.26)
R_{Cmax}	NA	0.943 (0.633, 1.41)	NA	1.13 (0.964, 1.33)	NA	1.04 (0.877, 1.22)	NA	0.904 (0.670, 1.22)

(Source – Table 11-1, 11-2, study report 102)

Pharmacodynamic results

A statistically significant treatment-dependent decrease in sUA concentrations was found, compared with placebo, following multiple qd oral administration of lesinurad as IR formulations (100 mg to 400 mg over 10 days, Figure 42) and (b) (4) formulations (200 mg to 600 mg over 7 days). Similarly, excretion of uUA increased with increasing doses of lesinurad. Maximum suppression of sUA occurred at the first sampling timepoint of 12 hours postdose, which corresponded with maximal uUA excretion at the earliest time interval of 0 to 12 hours postdose. The effects of sUA reduction were observed through 24 hours postdose at 100 mg to 600 mg dosing, with some daily variation relative to lesinurad dose (Figure 42).

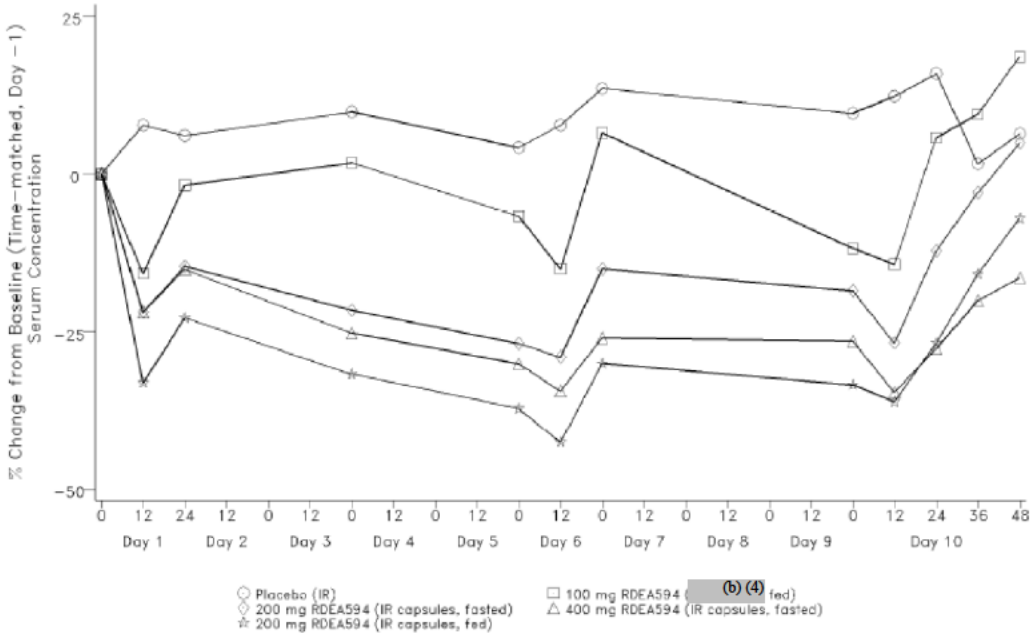


Figure 42. Median Percent Changes from Baseline (Time-Matched, Day -1) in Serum Urate Concentrations Following Multiple Oral Immediate-Release Doses of Lesinurad (Day 1 to Day 10) in Healthy Volunteers (Study 102)
(source: Figure 12, summary of clin pharm)

- **Conclusions**

PK results indicate that the (b) (4) and IR capsule had similar bioavailability. A dose-dependent decrease in sUA concentrations over the 100 mg to 600 mg qd dose range was observed. The effects of sUA reduction were observed through 24 hours postdose with some daily variation relative to lesinurad dose.

SPECIFIC POPULATION

4. Hepatic Impairment

Trial # 118

Title: A Phase 1, Single-Dose, Pharmacokinetic and Pharmacodynamic Study of Lesinurad in Male Subjects with Various Degrees of Hepatic Impairment.

Objective:

- To determine the PK of a single dose of lesinurad in subjects with various degrees of hepatic impairment compared to matched control subjects.
- To determine the safety profile of a single dose of lesinurad in subjects with various degrees of hepatic impairment compared to matched control subjects.
- To evaluate the serum uric acid lowering effects of a single dose of lesinurad in subjects with various degrees of hepatic impairment.

Study design: Open-label, single-dose study

Patient groups and sample size:

- Cohort 1: Child-Pugh A (5 to 6 points; mild impairment, n=8).
- Cohort 2: Child-Pugh B (7 to 9 points; moderate impairment, n=8).
- Cohort 3: Normal hepatic function (control subjects matched to mild and moderate impairment subjects, n=8).

Cohort 3 (normal hepatic function) was enrolled after the mild and moderate hepatic impairment subjects, in order to match baseline characteristics of age, body mass index (BMI), and CYP2C9 genotype.

Treatment: Lesinurad was to be orally administered as a 400 mg tablet.

PK Sampling Schedule

- **Blood –** 5 Plasma PK samples were collected at the following timepoints in relation to doing of lesinurad on Day 1: predose (within 30 minutes before dosing) and at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, 30, 36, 48, 54, 60, and 72 hours postdose.
- **Urine –**6 Urine PK samples were to be collected at the following intervals in relation to dosing of lesinurad on Day 1: -12-0, 0-6, 6-12, 12-24, 24-36, 36-48, 48-60, and 60-72 hours postdose.
- **PD-**7 Serum samples for uric acid and creatinine measurement (enzymatic method) were to be collected at Screening and at the following timepoints in relation to dosing of lesinurad on Day 1: -24, -18, -12, -8 (pre-treatment), 0 hours (within 30 minutes before Day 1 dosing), and at 6, 12, 16, 24, 36, 48, 60 and 72 hours postdose.

Results:

Pharmacokinetic results

Summary statistics of PK parameters are presented in Table 51. Plasma exposures (Cmax and AUC), total clearance (CL/F), and non-renal clearance (CLNR0-72) of lesinurad in subjects with mild hepatic impairment were comparable to those in subjects with normal hepatic function. The geometric mean ratios were within the 80-125% interval generally used to establish bioequivalence and close to 100%, indicating that mild hepatic impairment had no effect on lesinurad pharmacokinetics.

In subjects with moderate hepatic impairment, Cmax was comparable to those in subjects with normal hepatic function, while AUC was 33% greater than in subjects with normal hepatic function (**Table 52**). Total clearance and non-renal clearance of lesinurad were reduced by 25% and 24%, respectively (**Table 52**).

Table 51. Summary of Plasma Pharmacokinetics of Total Lesinurad Following a Single Oral Dose of Lesinurad 400 mg to Subjects with Various Degrees of Hepatic Function

Hepatic Function	N	T_{max}[a] (hr)	C_{max} (µg/mL)	T_{last}[a] (hr)	AUC_{last} (µg·hr/mL)	AUC_{∞} (µg·hr/mL)	CL/F (L/hr)	CL_{NR0-72} (L/hr)	V_{ss}/F (L)	$t_{½}$ (hr)
Normal Function	8	1.75 (1.00-2.00)	18.4 (16.0-21.2)	72.0 (54.0-72.0)	61.9 (54.4-70.4)	62.0 (54.5-70.5)	6.45 (5.67-7.34)	4.91 (4.09-5.89)	28.8 (24.9-33.3)	11.3 (7.57-16.9)
Mild Impairment	8	1.50 (1.00-2.00)	20.4 (16.1-25.8)	72.0 (54.0-72.0)	66.2 (48.7-90.0)	66.5 (48.9-90.3)	6.02 (4.43-8.18)	4.93 (3.45-7.03)	29.6 (22.6-38.7)	20.3[b] (11.3-36.3)
Moderate Impairment	8	1.75 (1.50-5.00)	19.9 (13.2-29.9)	72.0 (48.0-72.0)	82.4 (52.5-129)	82.6 (52.6-130)	4.84 (3.08-7.60)	3.74 (2.39-5.87)	26.3 (16.5-41.9)	15.0 (9.85-22.9)

AUC_{last} = area under the plasma concentration-versus-time curve (AUC) from time zero to the last sampling time with quantifiable observation; AUC_{∞} = AUC from time zero to infinity; CL/F = apparent total plasma clearance; CL_{NR} = non-renal clearance; C_{max} = maximum observed plasma concentration; N = number of subjects; T_{last} = time of last quantifiable plasma concentration observed; T_{max} = time of C_{max}; $t_{½}$ = apparent plasma terminal half-life; V_{ss}/F = volume of distribution at steady state.

[a] T_{max} and T_{last} are represented by median (range).

[b] More than half of the subjects have terminal $t_{½}$ calculated from a period of less than two fold of the calculated $t_{½}$ value.

(Source –Table 11-1, Study 118 report)

Table 52. Geometric Least Squares Means and Geometric Mean Ratios (90% Confidence Interval) of Total Lesinurad Pharmacokinetic Parameters between Hepatic Function Groups

Hepatic Function	N	Parameter	GeoLSM		Geomean Ratio (90% CI)
			Mild Impairment	Normal Function	(Impairment/Normal Function)
Mild Impairment versus Normal Function	8	C_{max} (µg/mL)	20.4	18.4	111% (90.2%-136%)
		AUC_{last} (µg·hr/mL)	66.2	61.9	107% (83.4%-137%)
		AUC_{∞} (µg·hr/mL)	66.5	62.0	107% (83.7%-137%)
		CL/F (L/hr)	6.02	6.45	93.3% (72.8%-120%)
		CL_{NR0-72} (mL/min)	4.93	4.91	100% (74.6%-135%)
Moderate Impairment versus Normal Function	8	C_{max} (µg/mL)	19.9	18.4	108% (77.9%-149%)
		AUC_{last} (µg·hr/mL)	82.4	61.9	133% (93.8%-189%)
		AUC_{∞} (µg·hr/mL)	82.6	62.0	133% (94.0%-189%)
		CL/F (L/hr)	4.84	6.45	75.0% (52.9%-106%)
		CL_{NR0-72} (mL/min)	3.74	4.91	76.3% (53.2%-110%)

(Source –Table 11-2, Study 118 report)

Plasma Protein Binding:

Analysis of protein binding in plasma from subjects with normal hepatic function, and mild and moderate hepatic impairment showed that lesinurad is highly bound (>98%) in all 3 groups (**Table 53**).

Table 53. Mean (Standard Deviation) Plasma Protein Binding (Percent) of Lesinurad

Normal Hepatic Function (N=8)	Mild Hepatic Impairment (N=8)	Moderate Hepatic Impairment (N=8)
99.0% (0.143)	99.0% (0.129)[a]	98.8% (0.217)

N = number of subjects.
Mean combining 1, 10, and 50 µM concentrations of lesinurad is presented.
[a] N = 7, plasma sample for protein binding assay was not available for Subject 001-010.

(Source –Table 11-5, Study 118 report)

Pharmacodynamic results

The sUA lowering effect following a lesinurad 400 mg dose was consistent across the 3 cohorts (Figure 43), with no statistically significant differences between hepatic function groups in maximum observed percentage change from baseline in serum urate, or the change from baseline in sUA concentrations at any of the timepoints.

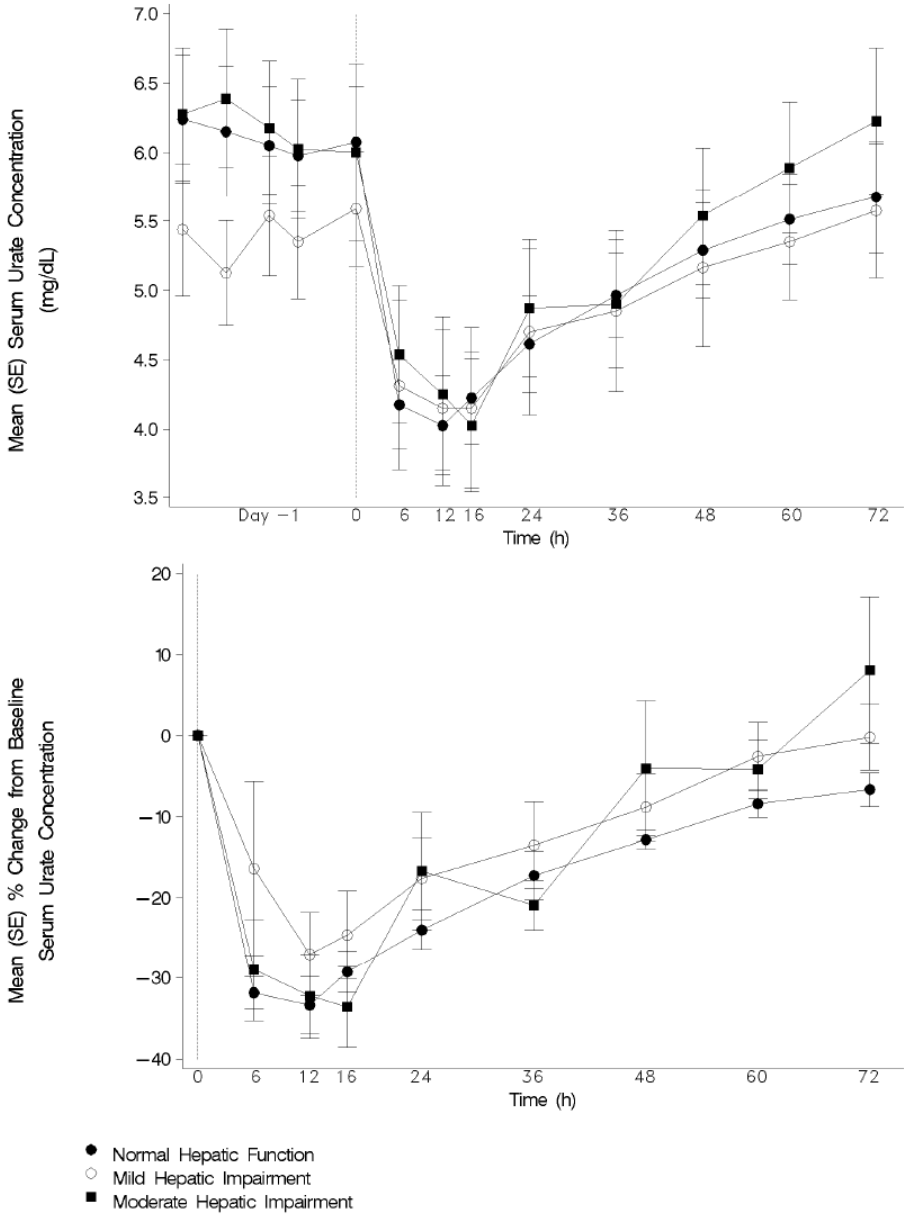


Figure 43. Mean Absolute and Percent Change from Baseline in Serum Concentrations of Urate Following a Single Oral Dose of Lesinurad 400 mg to Subjects with Various Degrees of Hepatic Function
(Source: Figure 11-1, study report 118)

Conclusions:
Lesinurad plasma exposures were comparable in subjects with mild hepatic impairment, and exposure was 33% greater in subjects with moderate hepatic impairment when compared with subjects with normal hepatic function. Reductions in sUA were comparable for subjects with normal hepatic function and mild and moderate hepatic impairment.
Therefore, no dose adjustment is necessary for patients with mild or moderate hepatic impairment.

5. Renal Impairment (104, 120)

Trial # 104
Title: A Phase 1, Single Dose, Pharmacokinetic and Pharmacodynamic Study of RDEA594 in Adult Volunteers with Various Degrees of Renal Insufficiency

Objective:
- To evaluate the PK of an orally administered single dose of RDEA594 in subjects with various degrees of renal insufficiency.
- To evaluate the safety profile of an orally administered single dose of RDEA594 in subjects with various degrees of renal insufficiency.
- To evaluate the uricosuric effects of an orally administered single dose of RDEA594 in subjects with various degrees of renal insufficiency.

Study design: multicentre, open-label, single dose study of RDEA594 in subjects with various degrees of renal insufficiency. Twenty-four subjects entered the study: 8 subjects for each of the 3 cohorts defined in the protocol based upon Cockcroft-Gault CrCL using actual body weight at Screening:
Cohort 1: CrCL > 50 to 80 mL/min (Mild Renal Impairment, n=8)
Cohort 2: CrCL > 30 to 50 mL/min (Moderate Renal Impairment, n=8)
Cohort 3: CrCL > 80 mL/min (Normal Renal Function, n=8)

In the final study report, the subjects were categorized for renal function based upon Day -1, 24-hour measured urine CrCL normalized for BSA, 5 subjects were classified as having normal renal function, and 10, 7, and 2 subjects were classified as having mild, moderate, and severe renal impairment, respectively.

Reviewer comment:
As recommended in "the guidance for industry, pharmacokinetics in patients with impaired renal function-study design, data analysis, and impact on dosing and labeling", classification of renal function should be based on estimated GFR (MDRD equation) or estimated creatinine clearance (C-G equation). Also, in phase 3 studies, the patients were screened based on C-G CrCL. Therefore, this reviewer reassigned

*the patients to different renal impairment groups based on the C-G CrCL at screening (***Table 54***).*

Cohort 1: CrCL 60 to 89 mL/min (Mild Renal Impairment, n=8)
Cohort 2: CrCL 30 to 59 mL/min (Moderate Renal Impairment, n=10)
Cohort 3: CrCL ≥ 90 mL/min (Normal Renal Function, n=6)

Table 54. List of subjects with baseline renal function

Subject ID	Cmax (ug/ml)	AUCinf (ug.hr/ml)	CrCL (mL/min) at screening	Reviewer's Group	Sponsor's group
100-302	8.69	24.7	149	normal	nomal
100-303	4.31	17	126	normal	nomal
200-301	9.94	42.9	122	normal	nomal
200-302	12.4	42.4	106	normal	mild
100-301	8.89	32.7	101	normal	nomal
200-303	6.99	40.8	92	normal	mild
200-305	10.9	45.4	89	mild	nomal
100-105	11.7	41.6	86	mild	moderate
200-304	12.8	36	83	mild	mild
200-103	12.5	54.2	82	mild	mild
100-104	10.3	27.5	74	mild	mild
200-104	14.8	39.3	73	mild	mild
200-101	10	47.5	61	mild	mild
100-101	9.6	57.3	61	mild	mild
100-102	13.3	34.5	58	moderate	mild
100-204	8.25	87.1	56	moderate	moderate
100-202	6.55	36.4	54	moderate	mild
200-105	14.9	104	53	moderate	moderate
100-203	2.78	31	50	moderate	moderate
200-201	11.7	80.3	47	moderate	moderate
200-204	11.2	74.7	41	moderate	moderate
100-201	9.49	32.5	36	moderate	severe
200-203	8.82	36	35	moderate	severe
200-202	15.2	63.4	34	moderate	moderate

(source: reviewer summary of Table 18.1, study report of study 104; Table 14-1, 14-2, 14-3, RDEA594-104 compliance and drug concentration data amend1)

- **Test product:** The study drug was orally administered as RDEA594 capsules, 200 mg (2 x 100 mg)

- **Sampling Schedule**

PK Sampling Schedule

Blood samples for the analysis of plasma RDEA594 and metabolite M4 concentrations were collected at the following timepoints in relation to dosing on Day 1: pre-dose (within 30 minutes before dosing) and at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5,

6, 8, 10, 12, 16, 24, 30, 36, 48, 54, 60, and 72 hours post-dose. In addition, blood samples for evaluation of plasma total protein and protein binding of RDEA594.

Urine (total catch) samples for the analysis of RDEA594 were collected over the following intervals in relation to dosing on Day 1: -24 to -18, -18 to -12, -12 to 0, 0 to 6, 6 to 12, 12 to 24, 24 to 36, 36 to 48, 48 to 60, and 60 to 72 hours post-dose.

PD Sampling Schedule

Blood samples were collected measurement ofr serum urate and creatinine concentrations on Days -1 to 4 in the morning at the following times in relation to dosing on Day 1; -24, -18, -12, -8, 0, 6, 12, 16, 24, 36, 48, 60, and 72 hours postdose. Urine samples from each of the pharmacokinetic collections were assayed for urate and creatinine.

Genotyping

Whole blood was collected for possible CYP2C9 genotyping.

Results:

Pharmacokinetic results

After a single-dose administration of lesinurad 200 mg following an overnight fast, lesinurad rapidly reached systemic circulation in all subjects regardless of renal impairment status. The mean Cmax was comparable among different renal impairment groups (Table 55). Total plasma exposure (AUC0-∞) values were 33.4, 43.6, and 58.0 ug*h/mL for normal, mild, and moderate renal impairment groups, respectively (Table 55).

Table 55. Summary of lesinurad Pharmacokinetic Parameters, by renal impairment status

PK parameter	Renal impairment status	N	Mean (SD)	Ratio (vs Normal)
AUCinf (µg.h/mL)	Normal	6	33.4 (10.7)	NA
	Mild	8	43.6 (9.7)	130.5%
	Moderate	10	58.0 (27.2)	173.5%
Cmax (µg/mL)	Normal	6	8.5 (2.7)	NA
	Mild	8	11.6 (1.7)	135.6%
	Moderate	10	10.2 (3.9)	119.7%

(Source –Reviewer summary)

Conclusions:

Compared to healthy subjects, plasma AUC of lesinurad was increased by approximately 31% and 74% in subjects with mild and moderate renal impairment, respectively.

Trial # 120

Title: A Phase 1, Single-Dose, Pharmacokinetic Study of Lesinurad in Male Subjects with Moderate and Severe Renal Impairment

Objective:

- To assess the pharmacokinetics of a single-dose of lesinurad in subjects with moderate and severe renal impairment compared to matched control subjects with normal renal function.
- To assess the safety profile of a single-dose of lesinurad in subjects with moderate and severe renal impairment compared to matched control subjects with normal renal function.

Study design: Multicenter, open-label, single dose study in adult male subjects with moderate and severe renal impairment and subjects with normal renal function. Eighteen subjects entered the study: 6 subjects for each of the 3 cohorts defined in the protocol based upon Cockcroft-Gault using ideal body weight (CrCl = [(140-age) x ideal body weight (kg)] / [72 x sCr (mg/dL)]; ideal body weight = 50 kg + 2.3 kg for each inch of height greater than 60 inches):
• Cohort 1: Moderate renal impairment (30 to < 60 mL/min, n=6).
• Cohort 2: Severe renal impairment (15 to < 30 mL/min, n=6).
• Cohort 3: Matched control subjects with normal renal function (≥ 90 mL/min, n=6).

In the final study report, the subjects were categorized for renal function based upon Day -1, 24-hour measured urine CrCL normalized for BSA, 6 subjects were classified as having normal renal function, and 2, 5, and 5 subjects were classified as having mild, moderate, and severe renal impairment, respectively.

Reviewer comment:
*As recommended in "the guidance for industry, pharmacokinetics in patients with impaired renal function-study design, data analysis, and impact on dosing and labeling", classification of renal function should be based on estimated GFR (MDRD equation) or estimated creatinine clearance (C-G equation). Also, in phase 3 studies, the patients were screened based on C-G CrCL. Therefore, this reviewer reassigned the patients to different renal impairment groups based on the C-G CrCL at screening (***Table 56***).*

Cohort 1: CrCL 60 to 89 mL/min (Mild Renal Impairment, n=6)
Cohort 2: CrCL 30 to 59 mL/min (Moderate Renal Impairment, n=6)
Cohort 3: CrCL ≥ 90 mL/min (Normal Renal Function, n=6)

Table 56. List of subjects with baseline renal function

Subject ID	Cmax (ug/ml)	AUCinf (ug.hr/ml)	CrCL (mL/min) at screening	Reviewer's Group	Sponsor's group
003-010	16.5	43.8	116.85	normal	normal
002-009	18.3	87	106.5	normal	normal

002-007	13.7	59.8	99.5	normal	normal
001-013	15.1	45.2	93.6	normal	normal
003-013	15.1	65.3	91.5	normal	mild
001-008	17.2	40.9	90.8	normal	normal
001-003	9.71	104	52.6	moderate	mild
003-005	14.9	75.2	51.8	moderate	moderate
001-001	15.6	77.4	47.7	moderate	moderate
003-003	21.3	72.1	44.03	moderate	normal
002-004	29.2	109	35.4	moderate	moderate
002-003	8.41	76.1	30.6	moderate	severe
001-005	13.3	89.2	29.2	severe	moderate
003-009	18.6	54	25.7	severe	moderate
003-004	17.6	84.8	22.97	severe	severe
001-014	19.1	169	22.2	severe	severe
003-008	18.2	173	21.64	severe	severe
001-006	21.6	158	15.1	severe	severe

(Source: reviewer summary of Table 10.1, study report of study 120; Table 12, 13, 14, 15 RDEA594-120 compliance and drug concentration data)

- **Test product:** The study drug was orally administered as a 400 mg tablet

- **Sampling Schedule**

PK Sampling Schedule

Blood samples for the analysis of plasma RDEA594 and metabolite M4 concentrations were collected at the following timepoints in relation to dosing on Day 1: pre-dose (within 30 minutes before dosing) and at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, 30, 36, 48, 54, 60, and 72 hours post-dose. In addition, blood samples for evaluation of plasma total protein and protein binding of RDEA594.

Urine (total catch) samples for the analysis of RDEA594 were collected over the following intervals in relation to dosing on Day 1: -24 to -18, -18 to -12, -12 to 0, 0 to 6, 6 to 12, 12 to 24, 24 to 36, 36 to 48, 48 to 60, and 60 to 72 hours post-dose.

PD Sampling Schedule

Serum samples for urate and creatinine measurement (enzymatic method) were to be collected at Screening and at the following timepoints in relation to dosing of lesinurad: -24, -18, -12, -8 (pre-treatment), 0 hours (within 30 minutes before Day 1 dosing), and at 6, 12, 16, 36, and 60 hours post-dose.Urine samples from each of the pharmacokinetic collections were assayed for
urate and creatinine.

Genotyping

Whole blood was collected for possible CYP2C9 genotyping.

Results:

Pharmacokinetic results

After a single-dose administration of lesinurad 400 mg following an overnight fast, lesinurad rapidly reached systemic circulation in all subjects regardless of renal

impairment status. The mean Cmax was comparable among different renal impairment groups (Table 57). Total plasma exposure (AUC0-∞) values were 57, 85.6, and 121.3 ug*h/mL for normal, mild, and moderate renal impairment groups, respectively (Table 57).

Table 57. Summary of lesinurad Pharmacokinetic Parameters, by renal impairment status

PK parameter	Renal impairment status	N	Mean (SD)	Ratio (vs Normal)
AUCinf (µg.h/mL)	Normal	6	57 (17.6)	NA
	Moderate	6	85.6 (16.3)	150.2%
	Severe	6	121.3 (51.3)	212.9%
Cmax (µg/mL)	Normal	6	15.9 (1.7)	NA
	Moderate	6	16.5 (7.7)	104.1%
	Severe	6	18.1 (2.7)	113.8%

(Source –Reviewer summary)

Conclusions:
Compared to healthy subjects, plasma AUC of lesinurad was increased by approximately 50% and 113% in subjects with moderate and severe renal impairment, respectively.

6. Japanese subjects

Trial # 125

Title: A Phase 1, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Single and Multiple Doses of Lesinurad in Healthy Male Japanese Subjects

Objective:

- To evaluate the safety and tolerability of lesinurad when administered as single and multiple doses in Japanese subjects.
- To evaluate the single-dose and multiple-dose PK of lesinurad in Japanese subjects.
- To evaluate the single-dose and multiple-dose PD of lesinurad in Japanese subjects.

Study design: This was a randomized, double-blind, placebo-controlled study in healthy male, Japanese subjects, designed to evaluate single and multiple doses of lesinurad. It was planned for the study to enroll up to 5 cohorts of 8 subjects per cohort; 6 subjects were randomized to receive lesinurad and 2 subjects were randomized to receive placebo in each cohort.

Study medication was to be administered to subjects as a single dose on Day 1 in the fasted condition, and as multiple daily doses for 7 days; under the fed condition from Days 6 to 11; and in the fasted condition on Day 12. The following dose cohorts were planned:
• Cohort 1: lesinurad 200 mg or placebo.
• Cohort 2: lesinurad 400 mg or placebo.
• Cohort 3: lesinurad 100 mg or placebo.
• Cohort 4 (Optional): lesinurad 600 mg or placebo.
• Cohort 5 (Optional): lesinurad 50 mg or placebo.

- **Test Product:** Lesinurad was to be orally administered as 50 mg tablets and 200 mg tablets.

- **Sampling Schedule**

PK Sampling Schedule

- Blood samples for the analysis of plasma RDEA594 were collected on Day 1 and Day 12: Pre-dose (within 30 mins before dosing), 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 24, 30, 36, 48, and 72 hours post dose; on Day 6: Pre-dose (within 30 mins before dosing), 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 24 hours post dose; on Day 7-11: Pre-dose (within 30 mins before dosing).

- Urine (total catch) samples for the analysis of RDEA594 were collected at Day -1: -24 to -18, -18 to -12, -12 to 0 hours. Day 1: 0 to 6, 6 to 12, 12 to 24, 24 to 30, 30 to 36, 36 to 48, 48 to 60 and 60 to 72 hours post dose. Day 6: 0 to 6, 6 to 12, 12 to 24 hours post dose. Day 12: 0 to 6, 6 to 12, 12 to 24, 24 to 30, 30 to 36, 36 to 48, 48 to 60 and 60 to 72 hours post dose.

PD Sampling Schedule

Blood samples for serum urate and creatinine measurements were collected at Screening, on Day 1 and Day 12: Pre-dose (within 30 mins before dosing), 6, 12, 24, 30, 36, 48, and 72 hours post dose. Day 6: Pre-dose (within 30 mins before dosing), 6, 12, and 24 hours post dose. Day 7-11: Pre-dose (within 30 mins before dosing). Urine samples from each of the pharmacokinetic collections were assayed for urate.

Results:

Pharmacokinetic results

Following administration of single oral doses of lesinurad ranging from 50 mg to 600 mg under the fasted condition to healthy male Japanese subjects, lesinurad was readily absorbed with a median Tmax ranging from 1.50 to 2.0 hours after which plasma concentrations of lesinurad declined with average half-life values ranging between 3 to 14 hours. Following qd multiple oral doses of lesinurad ranging from 50 mg to 400 mg, there was no accumulation of
lesinurad observed across all dose groups, and the exposure of lesinurad increased approximately dose proportional.

Food effect was evaluated between the fasted state on Day 1 and fed state on Day 6 following single oral dosing at 50 mg to 400 mg. Under the fed condition, absorption was

slightly delayed with median Tmax ranging from 1.75 to 3.0 hours, but the difference was considered non-significant. Food reduced approximately 18% to 52% of lesinurad plasma Cmax and approximately 11% to 26% of lesinurad plasma AUC.

Table 58. Summary of Plasma Pharmacokinetics of Lesinurad Following Administration of Various Lesinurad Dose Levels to Healthy Japanese Male Subjects (Geometric Mean [95% Confidence Intervals])

Lesinurad Dose (mg)	Food/ N	Day	T_{max}[a] (hr)	C_{max} (µg/mL)	AUC_{0-24} (µg·hr/mL)	AUC_{∞} (µg·hr/mL)	$t_{1/2}$ (hr)	CL/F[b] (L/hr)	V_{ss}/F (L)
50	Fasted N=6	1	2.00 (1.00-4.00)	1.90 (1.09-3.29)	7.47 (5.46-10.2)	7.51 (5.48-10.3)	3.05 (2.11-4.42)	6.66 (4.85-9.13)	30.0 (19.1-47.0)
	Fed N=6[c]	6	2.00 (1.00-5.00)	1.53 (1.08-2.16)	6.66 (5.71-7.77)	6.76 (5.83-7.84)	3.87[d] (2.79-5.36)	7.40 (6.38-8.58)	39.7 (25.4-61.8)
	Fasted N=6[c]	12	2.00 (1.50-4.00)	1.85 (1.46-2.35)	7.18 (5.86-8.79)	NA	4.66 (4.22-5.15)	6.97 (5.69-8.53)	32.4 (22.2-47.3)
100	Fasted N=6	1	1.75 (1.50-4.00)	6.41 (5.22-7.86)	21.3 (17.5-26.0)	21.5 (17.7-26.2)	4.39 (4.16-4.63)	4.65 (3.82-5.66)	19.6 (15.1-25.5)
	Fed N=6	6	2.25 (1.00-5.00)	3.07 (2.19-4.29)	15.8 (13.3-18.7)	15.9 (13.4-18.9)	3.59[d] (3.10-4.16)	6.29 (5.29-7.47)	32.1 (27.2-37.9)
	Fasted N=6	12	2.00 (1.00-3.00)	5.85 (4.79-7.15)	17.0 (13.1-22.1)	NA	17.9 (5.68-56.6)	5.88 (4.53-7.63)	27.8 (21.3-36.1)
200	Fasted N=6	1	2.00 (0.500-4.00)	12.6 (11.6-13.7)	33.7 (28.7-39.5)	34.0 (28.9-40.1)	5.25 (3.67-7.52)	5.87 (4.99-6.92)	24.0 (19.6-29.4)
	Fed N=6	6	3.00 (1.00-4.00)	8.17 (6.19-10.8)	30.0 (26.6-33.8)	30.4 (26.6-34.7)	4.30[d] (3.81-4.86)	6.59 (5.77-7.52)	35.4 (28.2-44.3)
	Fasted N=6	12	1.00 (0.500-2.00)	12.3 (9.26-16.2)	32.6 (28.3-37.6)	NA	24.8[e] (12.0-51.4)	6.14 (5.32-7.08)	26.8 (22.3-32.2)
400	Fasted N=6	1	1.50 (1.00-5.00)	24.6 (18.7-32.3)	102 (82.1-126)	103 (83.2-129)	14.1 (6.96-28.7)	3.87 (3.11-4.81)	20.2 (17.3-23.4)
	Fed N=6	6	1.75 (1.00-5.00)	20.0 (13.1-30.7)	85.2 (66.4-109)	86.2 (66.8-111)	3.57[d] (3.03-4.22)	4.64 (3.60-5.99)	26.2 (18.4-37.2)
	Fasted N=6	12	3.00 (1.00-4.00)	19.5 (15.3-24.7)	79.5 (56.3-112)	NA	32.9[e] (21.4-50.5)	5.03 (3.57-7.10)	28.9 (20.7-40.3)
600	Fasted N=6	1	2.00 (0.500-3.00)	32.2 (26.7-38.9)	154 (123-191)	157 (126-196)	12.1 (10.1-14.4)	3.83 (3.06-4.78)	20.9 (18.0-24.3)

(Source –Table 11-1, Study 125 report)

Table 59. Geometric Mean Ratio (90% Confidence Interval) of Lesinurad Plasma Pharmacokinetic Parameters under the Fed versus Fasted Condition

Treatment	N	Parameter	Geomean Ratio (90% CI) (Fed/Fasted)
50 mg lesinurad, fed (Day 6) versus 50 mg lesinurad, fasted (Day 1)	6[a]	C_{max}	76.8% (51.8%-114%)
		AUC_{0-24}	82.1% (71.4%-94.3%)
		AUC_{∞}	82.7% (72.1%-94.8%)
100 mg lesinurad, fed (Day 6) versus 100 mg lesinurad, fasted (Day 1)	6	C_{max}	47.9% (37.7%-60.7%)
		AUC_{0-24}	74.0% (63.8%-85.9%)
		AUC_{∞}	74.0% (63.7%-85.9%)
200 mg lesinurad, fed (Day 6) versus 200 mg lesinurad, fasted (Day 1)	6	C_{max}	64.9% (53.4%-78.8%)
		AUC_{0-24}	88.8% (80.7%-97.9%)
		AUC_{∞}	89.2% (80.8%-98.5%)
400 mg lesinurad, fed (Day 6) versus 400 mg lesinurad, fasted (Day 1)	6	C_{max}	81.5% (62.6%-106%)
		AUC_{0-24}	83.8% (70.3%-99.9%)
		AUC_{∞}	83.3% (69.6%-99.7%)

(Source –Table 11-3, Study 125 report)

Pharmacodynamic results

Upon administration of single doses of lesinurad from 50 mg to 600 mg and multiple doses of lesinurad from 50 mg to 400 mg, dose-dependent decreases in sUA were observed, with maximal sUA reductions being consistently greater with increased lesinurad doses.

As observed in the fasted states, maximum sUA reductions under the fed state were consistently greater with increased lesinurad doses. The observed sUA lowering effect was enhanced in the fed state compared with the fasting state for all lesinurad dose groups.

Over the first 24 hours postdose, urinary excretion of uric acid (Aeur and FEUA) and renal clearance of uric acid (CLur) were increased for all lesinurad treatments compared to placebo (Figure 44).

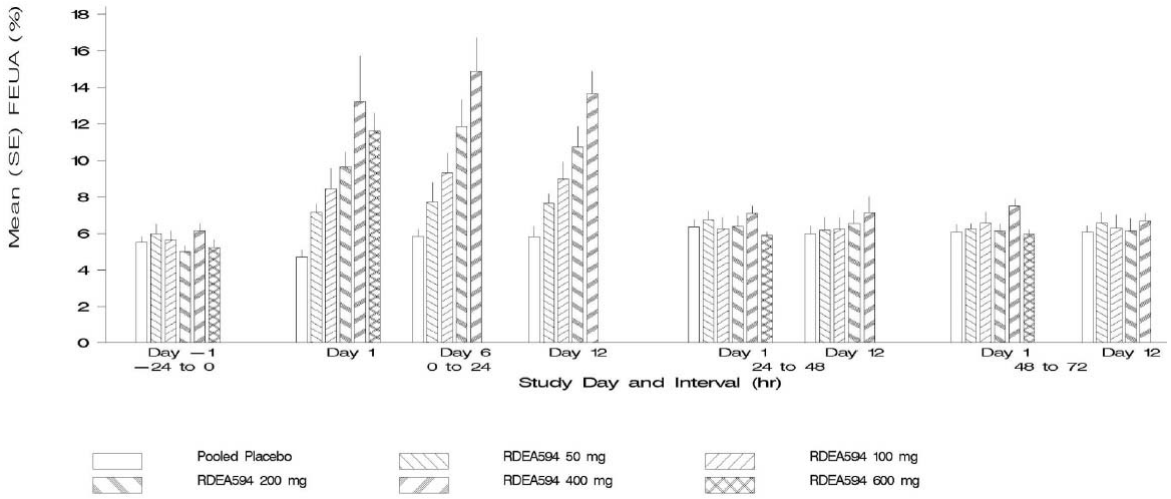


Figure 44. Mean 24 Hour Absolute Fractional Excretion of Uric Acid Following Administration of Various Lesinurad Dose Levels to Healthy Japanese Male Subjects
(Source –Figure 11.1, Study 125 report)

Conclusions:
Following single doses of lesinurad at 200 and 400 mg under the fed state, plasma exposures of lesinurad were slightly higher in Japanese subjects than in Western subjects, possibly due to smaller body mass.

Dose-responsiveness was observed in reductions of sUA (Emax, CB) and renal handling of uric acid (FEUA). The observed sUA lowering effect was enhanced in the fed state compared with the fasting state.

DRUG-DRUG INTERACTIONS

7. DDI with Febuxostat (105, 111)

Trial # 105

Title: A Phase 1 Study to Evaluate the Potential Pharmacokinetic and Pharmacodynamic Interaction Between RDEA594 and Febuxostat in Healthy Adult Volunteers

- **Objective:**

The primary objectives were to compare the multiple-dose pharmacokinetics (PK) of febuxostat in the absence versus presence of RDEA594 co-administration and to

compare the multiple-dose PK of RDEA594 in the absence versus presence of febuxostat co-administration.
The secondary objectives were to measure the effects of RDEA594 and febuxostat, both alone and in combination, on serum urate (sUA) concentrations and amounts of urate excreted into urine and to evaluate the safety and tolerability of multiple-doses of RDEA594 and febuxostat, both alone, or in combination.

- **Study design and treatment schedule:**

This was a single-centre, double-blind, placebo-controlled, randomised, cross-over PK and pharmacodynamics (PD) drug interaction study in healthy adult subjects. 36 subjects were sequentially enrolled into 2 panels, starting with Panel 1 (200 mg once-daily [qd] dose of RDEA594 or placebo), followed by Panel 2 (400 mg qd dose of RDEA594 or placebo). Subjects in each panel were randomly assigned to one of two treatment sequences (Sequence A or B), as shown in Table 60.

Table 60: Treatment Sequences

Sequence	Study Days	Treatment
A	1 to 7	Febuxostat, 40 mg (qd)
	8 to 14	RDEA594 or placebo in combination with febuxostat (qd)
	15 to 21	RDEA594 or placebo (qd)
B	1 to 7	RDEA594 or placebo (qd)
	8 to 14	RDEA594 or placebo in combination with febuxostat (qd)
	15 to 21	Febuxostat, 40 mg (qd)

(Source: Table 9-1, CSR 105)

- **Test product:** The study drug, RDEA594, was administered as orally as capsules containing 100 mg RDEA594

- **Sampling Schedule**

PK Sampling Schedule

- Blood samples for the analysis of plasma RDEA594 and/or febuxostat were collected on Days 7, 14, and 21 at pre-dose, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16 and 24 hours postdose. In addition, 0-hour samples were collected on Days 1 to 6, 9 to 13, and 16 to 20.
- Urine (total catch) samples for the analysis of RDEA594 were collected at pre-treatment over the following intervals on Day -1 at -24 to -18, -18 to -12, -12 to 0 hours (time of first dose); and on Days 7, 14, and 21 at 0 to 6, 6 to 12 and 12 to 24 hours postdose.

PD Sampling Schedule

Blood samples for serum urate and creatinine measurements were collected at Screening, on Day -1 at -24, -18, -12, -8, and 0 hours; and on Days 7, 14, and 21 at 0, 6, 12, 16 and 24 hours postdose. In addition, 0-hour samples were collected on Days 2 to 6, 9 to 13, and 16 to 20. Urine samples from each of the pharmacokinetic collections were assayed for urate and creatinine.

- **Results and Conclusions:**

PK results

The pharmacokinetics of RDEA594 were similar following multiple oral doses of RDEA594 administered alone and in combination with febuxostat. Mean AUC0-24 and Cmax were similar following 200 mg RDEA594 alone or in combination with febuxostat, and were similar following 400 mg RDEA594 alone or in combination with febuxostat. The 90% CIs of geometric mean ratios for Cmax and AUC0-24 at both doses were between 80 and 125%, indicating bioequivalence at 200 mg and 400 mg.

The pharmacokinetics of febuxostat were similar following multiple oral doses of febuxostat when administered alone, and in combination with 200 mg RDEA594. Geometric mean ratios for Cmax and AUC0-24 were 108% and 112%, respectively, suggesting an approximately 10% increase in plasma exposure following febuxostat with 200 mg RDEA594, however 90% CI fell within 80 to 125%, indicating bioequivalence.

Mean AUC0-24 and Cmax were higher following 40 mg febuxostat administered in combination with 400 mg RDEA594 compared to when administered alone; mean ratios were 127% (90% CI 104 to 155%) and 131% (90% CI 124 to 139%), respectively, suggesting mild drug-drug interaction between febuxostat and RDEA594. There was approximately a 25 to 30% increase in plasma exposure of febuxostat when administered in combination with 400 mg RDEA594.

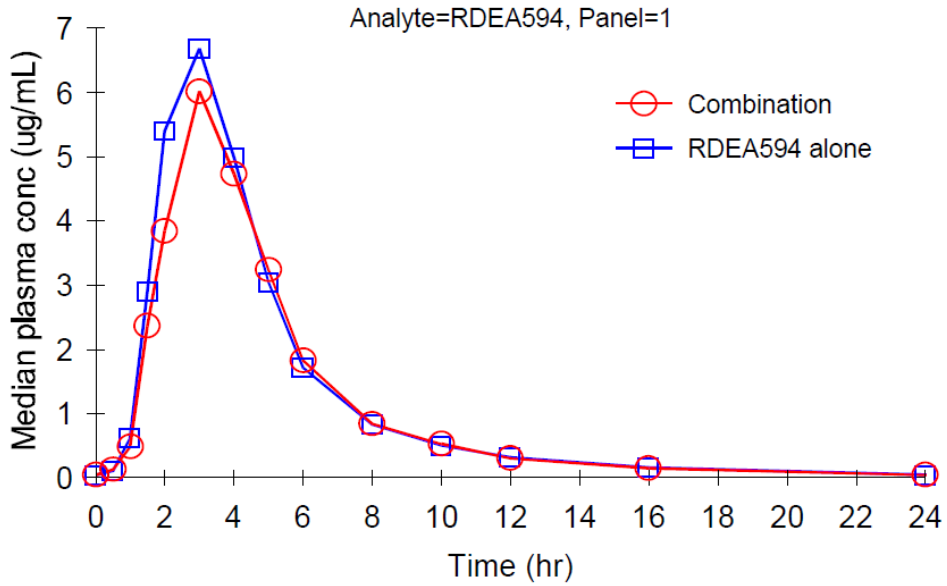


Figure 45: Median Plasma Concentrations of RDEA594 Following Once Daily Oral Administration of RDEA594 (200 mg) Alone or in Combination with Febuxostat (40 mg) (Linear Scale)
(Source: Figure 11- 1 CSR105)

Table 61: Summary of the Pharmacokinetic Parameters for Febuxostat Following Multiple Oral Doses, with or without lesinurad

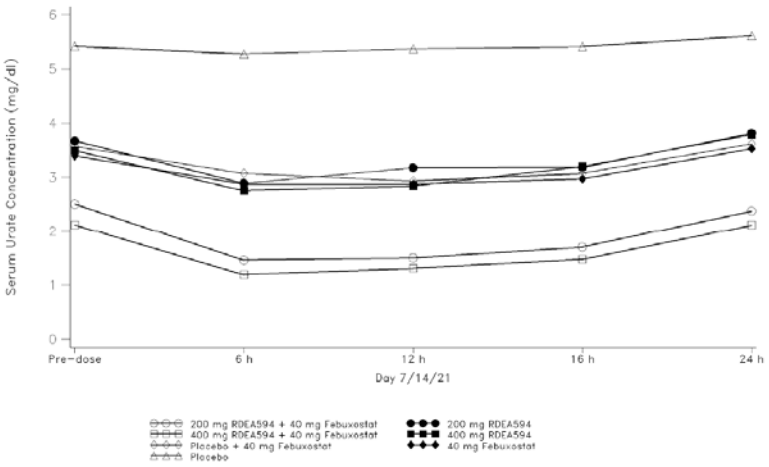
	Panel 1		Panel 2	
Parameter	Febuxostat 40 mg (N=12)	RDEA594 200 mg + Febuxostat 40 mg (N=12)	Febuxostat 40 mg (N=12)	RDEA594 400 mg + Febuxostat 40 mg (N=11)
AUC_{0-24} (hr·µg/mL)	3.17 (19.1)	3.55 (19.1)	3.62 (24.8)	4.85 (32.7)
C_{max} (µg/mL)	0.740 (26.8)	0.796 (28.0)	0.794 (26.7)	1.03 (29.5)
t_{max} (hr)	2.29 (35.4)	2.54 (44.7)	1.77 (4.44)	2.14 (63.7)
$t_{½}$ (hr)	6.02 (41.7)	6.34 (51.1)	5.68 (38.5)	5.56 (46.4)
CL_{ss}/F (L/hr)	13.0 (18.0)	11.6 (18.4)	11.7 (24.6)	8.98 (28.9)
V_{ss}/F (L)	87.8 (23.7)	79.7 (29.7)	77.4 (28.6)	55.9 (30.8)
MRT (hr)	6.73 (16.0)	6.78 (17.8)	6.61 (10.1)	6.33 (18.0)

(Source: Table 11-3, CSR 105)

PD results

Median serum urate concentrations decreased on all assessment days following multiple qd dosing of 200 mg or 400 mg RDEA594 administered alone or in combination with 40 mg febuxostat. Mean maximum % changes from baseline (time-matched Day -1) in serum urate levels (Emax,CB) were most pronounced for the combination treatments of 400 mg RDEA594 plus febuxostat (81%) and 200 mg RDEA594 plus febuxostat
(72%). The decreases in median serum urate concentrations were less pronounced (compared to combination dosing) following single agent qd dosing of 200 and 400 mg RDEA594 (46% and 59%, respectively) and qd dosing of 40 mg febuxostat with or without placebo (48% and 51%, respectively).

A



B.

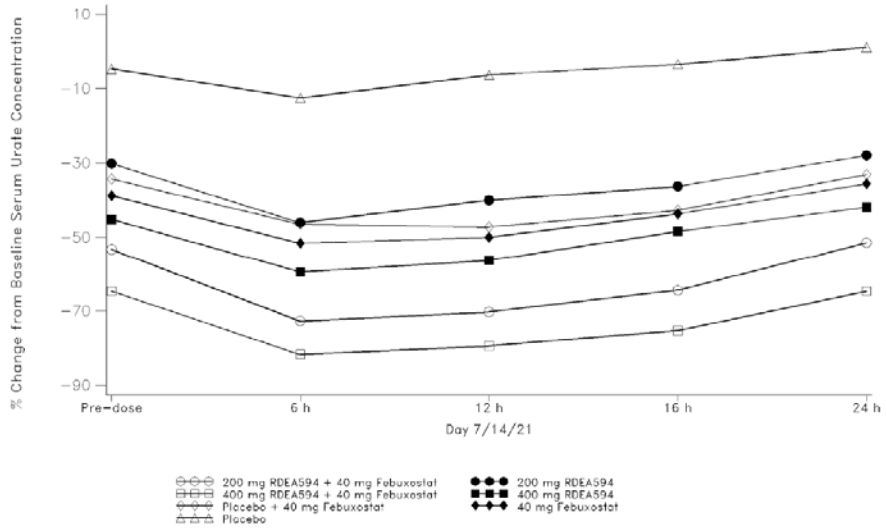


Figure 46: (A) Median Serum Concentrations of Urate and (B) Median % Changes from Baseline sUA Following Multiple Oral Doses of RDEA594 and Febuxostat (0 to 24 hours)
(Source: Figure 11- 5, Figure 11-7 CSR105)

- **Conclusions:**

There was no PK interaction between RDEA594 200 mg and febuxostat 40 mg. The additional uric acid lowering activity observed in the combination therapy is due to synergestic PD effect of febuxostat and lesinurad, and not increased exposure to febuxostat.

Trial # 111

Title: A Phase 1b Study to Evaluate the Potential Pharmacokinetic and Pharmacodynamic Interaction Between RDEA594 and Febuxostat in Gout Patients with Hyperuricemia

- **Objective:**

The primary objectives were

- To compare the multiple-dose pharmacokinetics (PK) of febuxostat in the absence versus presence of RDEA594 co-administration.
- To compare the multiple-dose PK of RDEA594 in the absence versus presence of febuxostat co-administration.
- To evaluate the multiple-dose plasma PK of colchicine alone and in combination with febuxostat or both febuxostat and RDEA594.

The secondary objectives were to measure the effects of RDEA594 and febuxostat, both alone and in combination, on serum urate (sUA) concentrations and amounts of urate excreted into urine and to evaluate the safety and tolerability of multiple-doses of RDEA594 and febuxostat, both alone, or in combination.

- **Study design and treatment schedule:**

This was a Phase 1b, multi-centre, open-label, multiple-dose, PK and PD drug interaction study of RDEA594 in gout patients with hyperuricemia. Twenty-one

subjects entered the study, with 12 subjects entering Panel 1 and 9 subjects entering Panel 2. A schematic of the study design is presented in Figure 47.

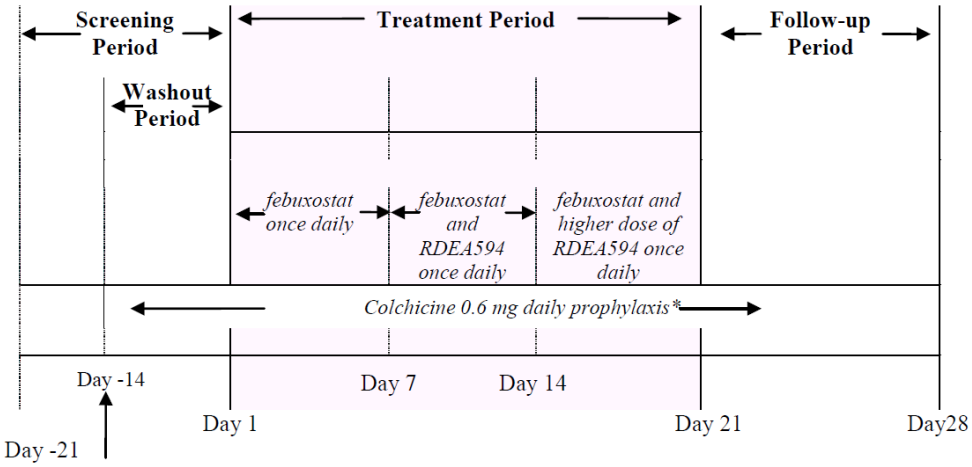


Figure 47: Study Schematic
(Source: Figure 9-1, CSR 111)

- **Test product:** The study drug, RDEA594, was administered as orally as capsules containing 100 mg RDEA594

- **Sampling Schedule**

PK Sampling Schedule

- Blood samples for the analyses of plasma RDEA594, febuxostat, and colchicine concentrations were collected at the following timepoints on Days -1, 7, 14, and 21 relative to RDEA594 dosing: pre-dose and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12 and 24 hours.
- Urine (total catch) samples for the analysis of RDEA594 were collected over the 0 to 6, 6 to 12 and 12 to 24 hour intervals on Days -1, 7, 14, and 21.

PD Sampling Schedule

Serial PD serum samples for the analyses of urate and creatinine were collected at the following time-points on Days -1, 7, 14, and 21 relative to RDEA594 dosing: pre-dose, 6, 12 and 24 hours post-dose. Urine (total catch) samples for the analyses of xanthine and hypoxanthine were collected over the 0 to 6, 6 to 12 and 12 to 24 hour intervals on Days -1, 7, 14, and 21.

- **Results:**

PK results

Cross-panel comparisons showed that RDEA594 plasma exposures were not meaningfully altered by coadministration with febuxostat at either 40 or 80 mg. As expected, plasma RDEA594 exposures were increased when the dose of RDEA594 within a panel was increased from 400 to 600 mg.

Table 62: Geometric Mean (95% CI) Plasma Pharmacokinetics of RDEA594 at 400 and 600 mg in Combination with Febuxostat in Panels 1 and 2

Panel	RDEA594 Dose (mg)	N	T_{max}[a] (hr)	C_{max} (µg/mL)	AUC_{0-24} (µg·hr/mL)	$t_{1/2}$ (hr)
1 FBX 40 mg	400	11	4.00 (2.50-6.00)	10.5 (7.58-14.6)	54.5 (39.8-74.7)	4.49 (4.11-4.90)
	600	11	3.00 (0.500-6.00)	17.9 (13.6-23.6)	89.6 (68.0-118)	4.43 (4.03-4.88)
2 FBX 80 mg	400	9	3.00 (0.500-6.00)	10.9 (8.42-14.1)	55.1 (42.8-71.0)	3.84 (3.45-4.28)
	600	9	4.00 (1.00-4.00)	16.4 (11.8-22.6)	78.2 (57.0-107)	3.87 (3.50-4.27)

(Source: Table 11-1, CSR 111)

Plasma febuxostat exposures were higher in Panel 2 than in Panel 1. The within-panel comparisons showed that febuxostat plasma AUC0-24 was increased approximately 8% to 21% by concomitant RDEA594 treatment. The extent of increase in febuxostat exposure did not appear dependent on the dose of febuxostat (40 or 80 mg) or RDEA594 (400 or 600 mg). The t1/2 of febuxostat in plasma appeared to be unaffected by RDEA594 co-administration.

Table 63: Geometric Mean Ratios (90% CI) of Febuxostat in the Absence or Presence of Escalated Doses of RDEA594

FBX dose	RDEA594 dose (mg)	Parameters	Combination/Alone		
			Ratio (%)[a]	90% CI (Lower)	90% CI (Upper)
40 mg	400	C_{max}	109	83.2	143
	600		129	109	154
	400	AUC_{0-24}	108	98.9	117
	600		120	109	132
80 mg	400	C_{max}	113	104	123
	600		118	93.4	148
	400	AUC_{0-24}	119	112	126
	600		121	107	137

(Source: Table 11-4, CSR 111)

The within-panel comparisons showed that colchicine plasma AUC0-24 was unaffected by febuxostat, but was mildly decreased by RDEA594 treatment. The effect of RDEA594 on colchicine exposure was dependent on RDEA594 dose level, with less change in colchicine exposure at the lower 400 mg dose (colchicine AUC0-24 decreased by ~20%) than at the higher 600 mg dose (colchicine AUC0-24 decreased by ~30%). The effect of RDEA594 on colchicine is consistent with CYP3A4 induction by RDEA594.

Table 64: Geometric Mean Ratios (90% CI) of Colchicine in Combination with Febuxostat Plus RDEA594 Relative to Colchicine Alone in Panels 1 and 2

FBX dose (mg)	RDEA594 dose (mg)	Parameters	Combination/alone		
			Ratio (%)[a]	90% CI (Lower)	90% CI (Upper)
40	400	C_{max}	88.6	78.2	100
	600		80.4	69.5	93.0
	400	AUC_{0-24}	78.3	71.1	86.3
	600		64.5	58.8	70.7
80	400	C_{max}	91.3	78	107
	600		84.5	67.3	106
	400	AUC_{0-24}	86.2	74.9	99.2
	600		73.0	58.7	90.7

(Source: Table 11-7, CSR 111)

PD results

Once-daily administration of RDEA594 400 or 600 mg with febuxostat resulted in a further decrease of the mean and % change from baseline in serum concentrations of urate beyond that achieved with 40 or 80 mg febuxostat alone in gout patients with high baseline sUA levels of ≥ 8 mg/dL.

Febuxostat alone and in combination with RDEA594 reduced mean sUA across all timepoints (trough [predose], and 6, 12 and 24 hours post-dose) at Day 7, Day 14 and Day 21 compared with baseline. Greater reductions were seen with combination treatment compared with febuxostat alone at each timepoint regardless of dose.

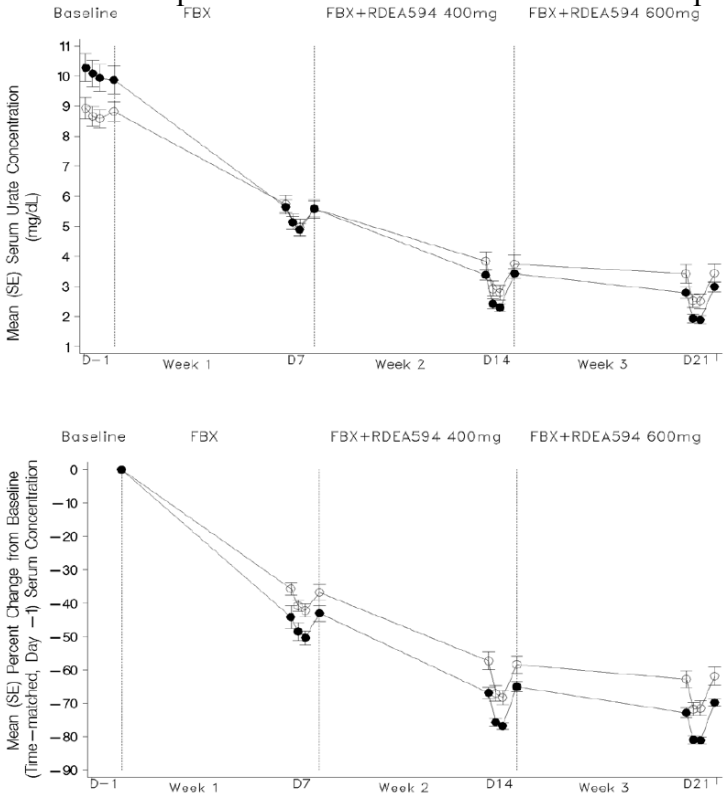


Figure 48: Mean and Mean Percent Change from Baseline (Time-Matched Day -1) in Serum Concentrations of Urate Following Multiple Oral Doses of Febuxostat Alone and in Combination with RDEA594 (Day -1 to Day 21)

(Source: Figure 11- 1, CSR111)

Fractional excretion values and urate renal clearance were increased by RDEA594 administered in combination with febuxostat and decreased with febuxostat alone.

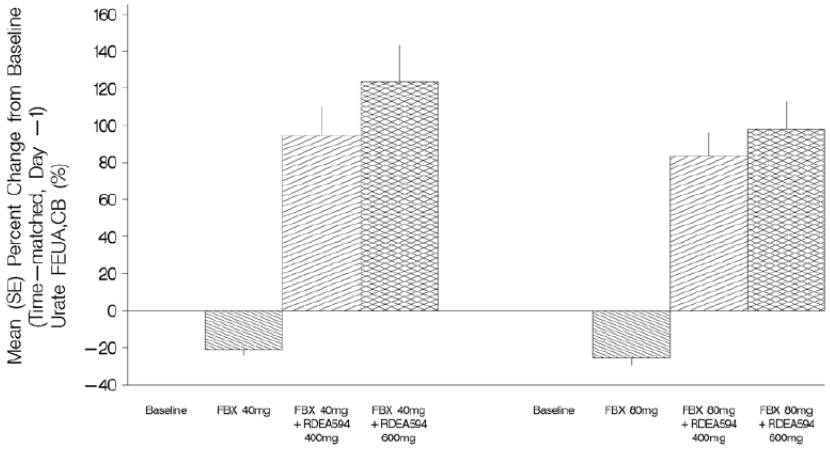


Figure 49: Mean Percent Changes from Baseline (Time-Matched Day -1) in Fractional Excretion of Urate in Urine Following Multiple Oral Doses of Febuxostat as a Single Agent and in Combination with RDEA594
(Source: Figure 11-3, CSR111)

- **Conclusions:**

There was no significant PK interaction between RDEA594 and febuxostat. The additional uric acid lowering activity observed in the combination therapy is due to synergestic PD effect of febuxostat and lesinurad, and not increased exposure to febuxostat.

8. DDI with Allopurinol

Trial # 110

Title: A Phase 1b Study to Evaluate the Potential Pharmacokinetic and Pharmacodynamic Interaction Between RDEA594 and Allopurinol in Gout Patients with Hyperuricemia

- **Objective:**

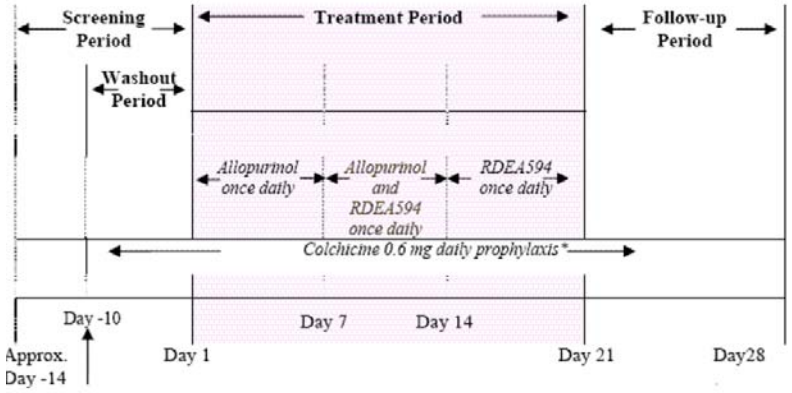
Primary:

- To evaluate the multiple-dose plasma PK and urinary excretion of allopurinol and oxypurinol alone and in combination with RDEA594.
- To evaluate the multiple-dose plasma PK and urinary excretion of RDEA594 alone or in combination with allopurinol.
- To evaluate the multiple-dose plasma PK of colchicine alone and in combination with RDEA594, allopurinol or both allopurinol and RDEA594.

Secondary:

- To measure the effect of RDEA594, alone and in combination with allopurinol, on sUA concentrations and urinary urate excretion.

- **Study design –** This was a multi-centre open-label, multiple-dose, PK and PD drug interaction study of RDEA594 in gout patients with hyperuricemia. It was planned to evaluate 2 panels (Panels 1 and 2), with up to 12 subjects in each panel. Allopurinol, RDEA594, or the combination of allopurinol and RDEA594 were administered each morning on Days 1 to 21. Colchicine (0.6 mg qd) was given as a prophylactic treatment (
- Figure 50).



* Colcrys® (colchicine) prophylaxis begins at Day -7 in patients not on ULT

Figure 50. Study schematic
(Source: Figure 9.1, CSR110)

- **Test product:** The study drug, RDEA594, was administered as orally as capsules containing 100 mg RDEA594.

- **Sampling Schedule**

PK Sampling Schedule

- Blood samples for the analysis of plasma RDEA594, allopurinol, oxypurinol and colchicine were collected on Days -1, 7, 14, and 21 at 0, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, and 24 hour time-points.

- Urine (total catch) samples for the analysis of RDEA594, allopurinol and oxypurinol were collected over the -24 to -18, -18 to -12, and -12 to 0 hour intervals on Day -1 and over the 0 to 6, 6 to 12, and 12 to 24 hour intervals on Days 7, 14, and 21.

PD Sampling Schedule

Blood and urine samples were collected for the measurement of serum and urinary concentrations of urate and creatinine. Blood samples for were collected on Days -1, 14, and 21 at 0, 6, 12, and 24 hour time-points. Urine samples obtained for pharmacokinetic analysis were also analysed for concentrations of xanthine and hypoxanthine to evaluate the impact of RDEA594 on the activity of allopurinol/oxypurinol.

- **Results and Conclusions:**

PK results

The RDEA594 plasma PK profile was unaffected when co-administered with allopurinol 300 mg qd (Table 65). As expected, plasma RDEA594 exposures were dose related, with higher plasma exposures at the 600 mg dose level (Panel 2) than at the 400 mg dose level (Panel 1).

The allopurinol within-panel comparisons showed that plasma exposures were not meaningfully altered by RDEA594 co-administration, with geometric mean ratios and 90% CI values within bioequivalence limits of 80% to 125% for AUC0-24 values. The oxypurinol within-panel comparisons showed that plasma exposures were mildly decreased by approximately 25% to 35% during co-administration of RDEA594 400 mg and 600 mg, respectively(Table 66).

The within-panel comparisons showed that colchicine plasma AUC0-24 was unaffected by allopurinol treatment and was minimally to mildly decreased by RDEA594 treatment (Table 67).

Table 65: Geometric Mean (95% CI) Plasma Pharmacokinetics of RDEA594 Alone or in Combination with Allopurinol in Panels 1 and 2

Panel	RDEA594 Dose (mg)	Allopurinol (mg)	N	T_{max}[a] (hr)	C_{max} (µg/mL)	AUC_{0-24} (µg·hr/mL)
1	400	300	10	2.25 (1.00-4.00)	9.84 (8.16-11.8)	46.6 (35.6-61.1)
		0	10	3.00 (1.50-6.00)	8.40 (6.48-10.9)	43.7 (33-57.9)
2	600	300	10	3.00 (1.50-4.00)	18.2 (13.7-24.3)	92.8 (72.9-118)
		0	9[b]	4.00 (2.50-4.00)	18.0 (14-23.1)	90.2 (71.4-114)

(Source: Table 11-1, CSR 110)

Table 66: Geometric Mean (95% CI) Plasma Pharmacokinetics of allopurinol and oxypurinol, Alone or in Combination with RDEA594 in Panels 1 and 2

Analyte	RDEA594 dose (mg)	PK Parameters	(RDEA594+allopurinol/allopurinol)		
			Ratio (%)	90% CI Lower	90% CI Upper
Allopurinol	400 Panel 1	C_{max}	78.8	61.0	102
		AUC_{0-24}	90.5	82.6	99.2
	600 Panel 2	C_{max}	87.3	62.9	121
		AUC_{0-24}	93.7	83.8	105
Oxypurinol	400 Panel 1	C_{max}	79.4	69.8	90.3
		AUC_{0-24}	74.2	65.1	84.7
	600 Panel 2	C_{max}	71.7	67.8	75.7
		AUC_{0-24}	64.7	61.3	68.3

(Source: Table11-4, 11-6, CSR 110)

Table 67: Geometric Mean Ratios (90% CI) of Colchicine Plus Allopurinol or/and RDEA594 Relative to Colchicine Alone in Panels 1 and 2

Panel	Colchicine PK	(colchicine+allopurinol/colchicine)		
		Ratio (%)	90% CI Lower	90% CI Upper
1	C_{max}	111	91.0	135
	AUC_{0-24}	102	93.1	112
2	C_{max}	104	94.9	115
	AUC_{0-24}	107	100	114
Panel	**Colchicine PK**	**(colchicine+RDEA594/colchicine)**		
		Ratio (%)	**90% CI Lower**	**90% CI Upper**
1	C_{max}	82.3	73.0	92.7
	AUC_{0-24}	74.8	67.4	83.0
2	C_{max}	75.6	63.9	89.5
	AUC_{0-24}	67.0	57.5	78.1

(Source: Table11-8, 11-9, CSR 110)

PD results

RDEA594 400 or 600 mg in combination with allopurinol 300 mg resulted in a further decrease of the mean and % change from baseline in serum concentrations of urate beyond that achieved with allopurinol or RDEA594 alone (Figure 51). Allopurinol or RDEA594 alone and in combination reduced mean sUA across all timepoints (trough [pre-dose], and 6, 12, and 24 hours post-dose) at Day 7, Day 14, and Day 21 compared with baseline. Greater reductions were seen with combination treatment compared with allopurinol and RDEA594 alone at each timepoint regardless of dose (Table 68).

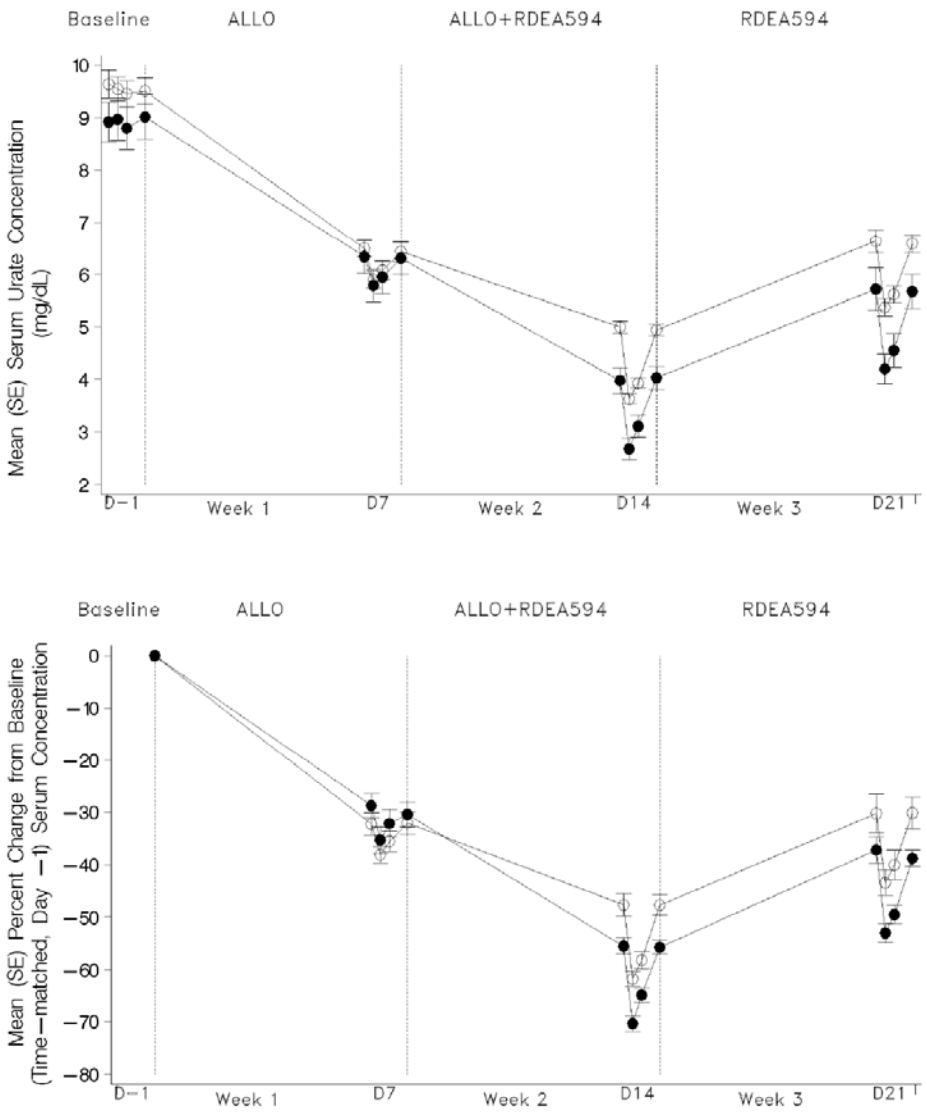


Figure 51: Mean and Percent Change from Baseline (Time-Matched Day -1) in Serum Concentrations of Urate Following Multiple Oral Doses of Allopurinol and RDEA594, Administered Alone and in Combination (Day -1 to Day 21)
(Source: Figure 11- 1, CSR110)

Table 68: Statistical Analysis of Mean Percent Changes from Baseline (Time-Matched Day -1) in Serum Urate Concentrations Following Multiple Oral Doses of Allopurinol and RDEA594 as Single Agents and in Combination

			Difference of LS mean (95% CI) Test vs. Comparator			
Test	**Comparator**	**Day**	**Pre-dose**	**6 hour**	**12 hour**	**24 hour**
300 mg allo + 400 mg RDEA	300 mg allo (Panel 1)	Day 14/ Day 7	-15.43* (-22.40, -8.46)	-23.66* (-29.14, -18.17)	-22.64* (-28.56, -16.73)	-15.61* (-21.56, -9.67)
300 mg allo + 600 mg RDEA	300 mg allo (Panel 2)	Day 14/ Day 7	-26.75* (-33.72, -19.78)	-35.10* (-40.58, -29.61)	-32.68* (-38.59, -26.76)	-25.31* (-31.25, -19.36)
300 mg allo + 400 mg RDEA	400 mg RDEA	Day 14/ Day 21	-17.40* (-24.38, -10.43)	-18.37* (-23.85, -12.89)	-18.14* (-24.06, -12.23)	-17.54* (-23.48, -11.59)
300 mg allo + 600 mg RDEA	600 mg RDEA	Day 14/ Day 21	-18.40* (-25.57, -11.23)	-18.42* (-24.09, -12.75)	-15.43* (-21.51, -9.35)	-17.07* (-23.18, -10.95)

(Source: Table 11-14, CSR 110)

Dosing with RDEA594 400 mg or 600 mg alone or in combination with allopurinol increased fractional excretion of urate, whereas treatment with allopurinol alone showed no notable effects.

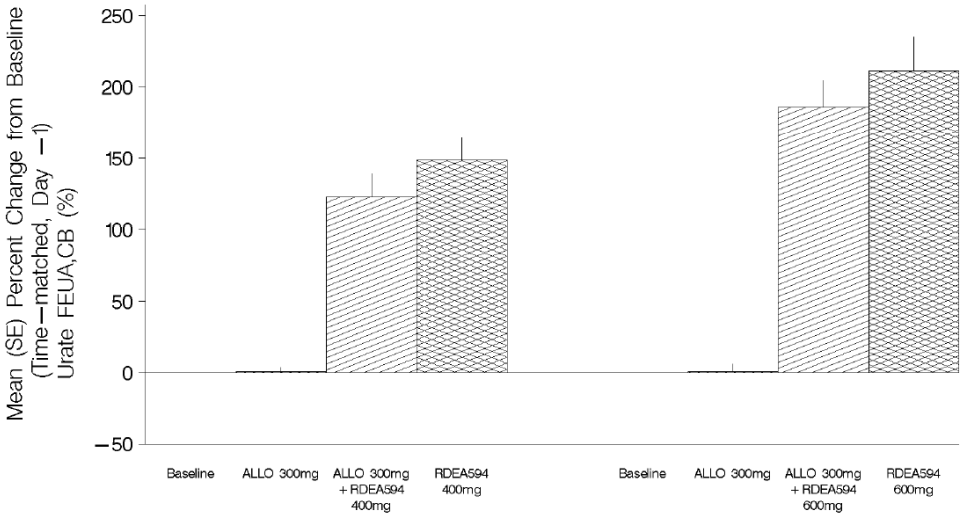


Figure 52: Mean Percent Changes from Baseline (Time-Matched Day -1) in Fractional Excretion of Urate in Urine Following Multiple Oral Doses of Allopurinol and RDEA594 as Single Agents and in Combination
(Source: Figure 11-3, CSR110)

- **Conclusions:**

Additional uric acid lowering activity was observed in the combination therapy of allopurinol and lesinurad, compared to lesinurad or allopurinol alone. There is sUA variation during 24 hour postdose, relative to lesinurad dosing. As expected given the mechanism of action of lesinurad, FEUA was increased at all lesinurad doses administered.

There was no significant PK interaction between lesinurad up to 600 mg and

allopurinol. The most notable aspect of the PK interaction between RDEA594 and allopurinol/oxypurinol in this study was the mild decrease in oxypurinol plasma exposures. The additional uric acid lowering activity observed in the combination therapy is due to synergestic PD effect of allopurinol and lesinurad, and not increased exposure to allopurinol or oxypurinol.

The effect of RDEA594 on colchicine was minimal (<25% decrease) at the lower 400 mg daily dose of RDEA594.

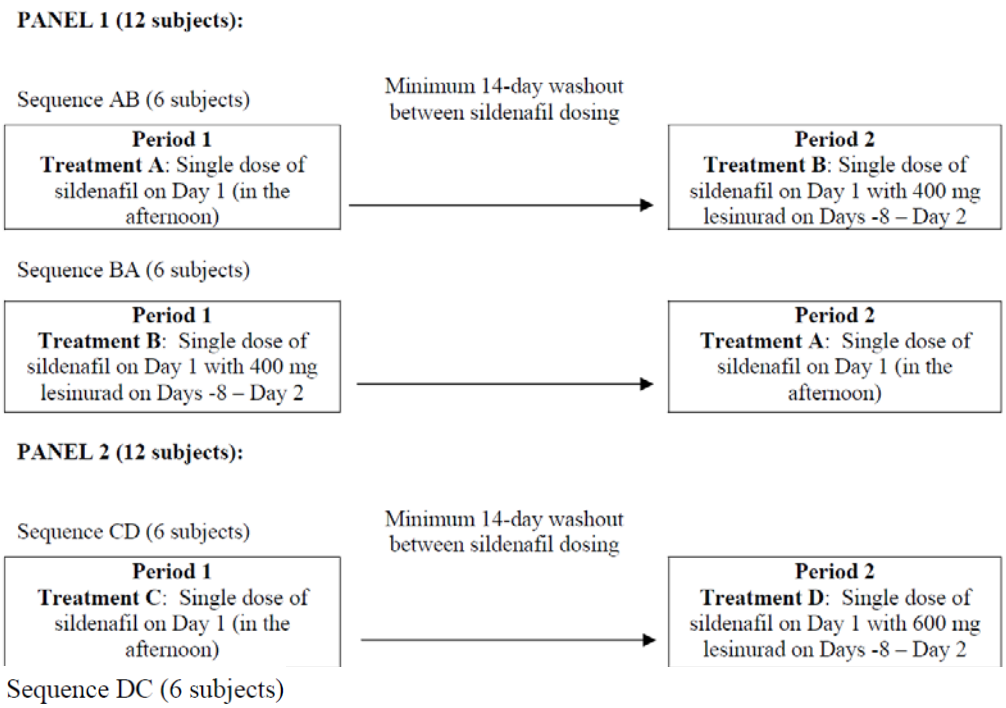
9. DDI with Sildenafil

Trial # 108

Title: A Phase 1 Study to Evaluate the Potential Pharmacokinetic Interaction Between Lesinurad and Sildenafil in Healthy Adult Male Volunteers

- **Objective:**
  - To evaluate the effect of lesinurad multiple doses on the single dose PK of sildenafil and the pharmacologically active N-desmethyl metabolite of sildenafil.
  - To evaluate the effect of multiple doses of lesinurad in combination with allopurinol on the single dose PK of sildenafil and the pharmacologically active N-desmethyl metabolite of sildenafil.

- **Study design –** This was an open-label, two-way crossover PK study to evaluate the drug-drug interaction. 12 subjects entered each of Panels 1 to 4.



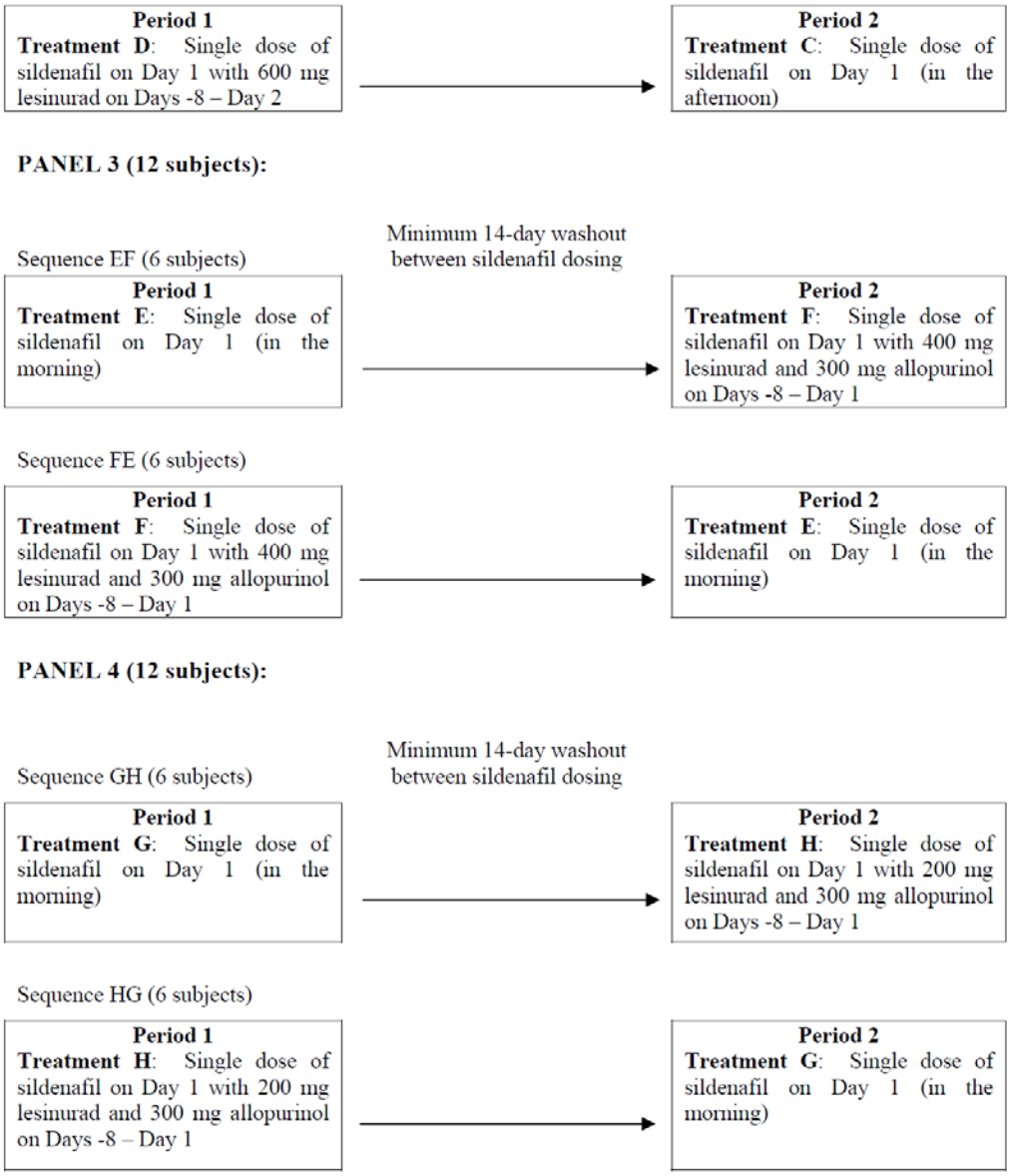


Figure 1. Study design scheme
(Source: Figure 1. CSR 108)

- **PK Sampling Schedule**

Plasma samples for Panels 1 and 2 were collected at the following time-points in relation to sildenafil dosing on Day 1: pre-dose (within 30 minutes before dosing) and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 16, 20, and 24 hours post-dose.
Plasma samples for Panels 3 and 4 were to be collected at the following time-points in relation to sildenafil dosing on Day 1: pre-dose (within 30 minutes before dosing) and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 20, and 24 hours post-dose.

- **Results**

In Panel 4, a 50 mg sildenafil dose was taken alone or coadministered with a 200 mg lesinurad dose and a 300 mg allopurinol dose in the morning in the fed state. During coadministration, sildenafil Cmax and AUC∞ both decreased by approximately 34%

(Table 69). Sildenafil exposure was more affected by 400 mg lesinurad (Panel 3) than 200 mg lesinurad (Panel 4) with allopurinol combination in both panels. Cmax decrease remained constant between Panels 3 and 4. In Panels 3 (400 mg lesinurad) and 4 (200 mg lesinurad), sildenafil AUC∞ decreased approximately 50% and 34%, respectively, suggesting that the lower dose of lesinurad in Panel 4 had less impact on sildenafil exposure.

Comparison of Panel 1 versus 2, and Panel 3 versus 4, indicate that sildenafil exposure was decreased at higher lesinurad dose levels. This observation is likely due to increased induction of CYP3A.

Table 69: Statistical Assessment of Pharmacokinetics of Sildenafil Dosed Alone versus Coadministration with Lesinurad in Panel 4

			Geometric Mean Ratio (Combo/Alone)			P value		
Variable	Treatment[a]	GeoLSM	Ratio (%)	90% CI (lower)	90% CI (upper)	Treatment	Sequence	Period
C_{max}	50 mg Sildenafil	0.116						
(µg/mL)	50 mg Sildenafil + 200 mg Lesinurad + 300 mg Allopurinol	0.0765	66.1	45.3	96.5	0.0734	0.6931	0.8832
AUC_{last}	50 mg Sildenafil	0.459						
(µg.hr/mL)	50 mg Sildenafil + 200 mg Lesinurad + 300 mg Allopurinol	0.303	66.2	55.6	78.8	0.0020	0.5306	0.4329
AUC_{∞}	50 mg Sildenafil	0.464						
(µg.hr/mL)	50 mg Sildenafil + 200 mg Lesinurad + 300 mg Allopurinol	0.308	66.4	55.9	78.8	0.0020	0.5400	0.4139
CL/F	50 mg Sildenafil	108						
(L/hr)	50 mg Sildenafil + 200 mg Lesinurad + 300 mg Allopurinol	162	151	127	179	0.0020	0.5400	0.4139
		Median	Min	Max		Wilcoxon test P		
T_{max}	50 mg Sildenafil	1.25	0.250	5.00				
(hr)	50 mg Sildenafil + 200 mg Lesinurad + 300 mg Allopurinol	2.00	0.500	5.00			0.0469	

(Source: Table 11-5, CSR108)

- **Conclusions:**

Lesinurad was a weak to moderate inducer of CYP3A. Treatment with sidenafil and lesinurad may result in lower plasma exposures of sildenafil, potentially decreasing sildenafil's therapeutic effect in some individuals. The lesinurad induction effect was slightly reduced when lesinurad was coadministered with sildenafil than when lesinurad was administered at a different time of day than sildenafil.

10.DDI with Atorvastatin

Trial # 113

Title: A Phase 1 Study to Evaluate the Potential Pharmacokinetic Interaction Between Lesinurad and the CYP3A4 Substrate Atorvastatin in Healthy Adult Male Volunteers

- **Objective:**
  - To evaluate the potential inhibitory effect of lesinurad treatment on single dose PK of atorvastatin upon initiation of lesinurad qd dosing in healthy adult male subjects.
  - To evaluate the potential induction effect of lesinurad multiple dose treatment for 11 to 13 days on the single dose PK of atorvastatin in healthy adult male subjects.

- **Study design –** This was an open-label study in healthy male subjects. It was planned to evaluate 2 cohorts (Cohort 1: lesinurad 200 mg + atorvastatin 40 mg; Cohort 2: lesinurad 400 mg + atorvastatin 40 mg), with up to 14 subjects in each cohort. Subjects were to receive a single dose of atorvastatin 40 mg on Day 1, Day 4 and Day 14. In addition, subjects were to receive multiple qd doses of lesinurad from Days 4 to 16, inclusive. Plasma PK samples were to be collected from 30 minutes pre-dose to 72 hours post-dose on Days 1, 4, and 14.Subjects were to receive study medication in the morning in the fed state.

- **PK Sampling Schedule**
  - **For atorvastatin - Plasma –**day 1, day 4 and day 14 : pre-dose (within 30 minutes before dosing) and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12 16, 24, 30, 36, 48, 60 and 72 hour post-dose.

- **Results**

Coadministration of a single dose of lesinurad (200 or 400 mg) did not significantly alter the single dose PK (AUC and Cmax) of atorvastatin and total atorvastatin (the sum of atorvastatin and its 2-OH and 4-OH metabolites), although a small increase (34%) in maximal levels of 2-OH-atorvastatin was observed when given with lesinurad 400 mg (Table 70).

Total systemic exposure of atorvastatin (as assessed by AUC) was decreased by approximately 27% during multiple dosing with lesinurad 400 mg (Table 71), and was associated with a corresponding minimal increase in maximal levels of 2-OH-atorvastatin, consistent with mild CYP3A4 induction.

Table 70: Geometric Mean Ratios (90% Confidence Interval) of Pharmacokinetics of Atorvastatin, Total Atorvastatin, 2-OH-atorvastatin, and 4-OH-atorvastatin in the Presence versus Absence of a Single Dose of Lesinurad

Lesinurad Single Dose	Analyte	Parameter	Geometric Mean Ratio (90% CI) (Day 4)
Cohort 1: 200 mg (N=14)	Atorvastatin	C_{max}	91.9 (80.3-105)
		AUC_{∞}	96.2 (89.8-103)
	Total atorvastatin	C_{max}	101 (87.9-116)
		AUC_{∞}	107 (98.0-117)
	2-OH-atorvastatin	C_{max}	116 (99.1-136)
		AUC_{∞}	120 (108-134)
	4-OH-atorvastatin	C_{max}	115 (85.1-155)
		AUC_{0-24}	155 (105-230)
Cohort 2: 400 mg (N=14)	Atorvastatin	C_{max}	117 (94.0-146)
		AUC_{∞}	101 (91.3-111)
	Total atorvastatin	C_{max}	126 (105-150)
		AUC_{∞}	108 (100-118)
	2-OH-atorvastatin	C_{max}	134 (115-155)
		AUC_{∞}	117 (107-127)
	4-OH-atorvastatin	C_{max}	160 (147-175)
		AUC_{0-24}	280 (160-490)

(Source: Table 11-5, CSR113)

Table 71: Geometric Mean Ratios (90% Confidence Interval) of Pharmacokinetics of Atorvastatin, Total Atorvastatin, 2-OH-atorvastatin, and 4-OH-atorvastatin in the Presence versus Absence of Multiple Doses of Lesinurad

Lesinurad Multiple Dose	Analyte	Parameter	Geometric Mean Ratio (90% CI) (Day 14)
Cohort 1: 200 mg qd (N=13)[a]	Atorvastatin	C_{max}	114 (92.0-141)
		AUC_{∞}	84.2 (74.2-95.6)
	Total Atorvastatin	C_{max}	115 (91.7-144)
		AUC_{∞}	92.2 (82.9-103)
	2-OH-atorvastatin	C_{max}	120 (93.4-154)
		AUC_{∞}	101 (90.8-112)
	4-OH-atorvastatin	C_{max}	102 (65.8-158)
		AUC_{0-24}	90.2 (58.3-140)
Cohort 2: 400 mg qd (N=13)[a]	Atorvastatin	C_{max}	99.5 (80.4-123)
		AUC_{∞}	72.7 (64.9-81.5)
	Total Atorvastatin	C_{max}	117 (98.0-139)
		AUC_{∞}	86.1 (77.3-95.8)
	2-OH-atorvastatin	C_{max}	134 (113-159)
		AUC_{∞}	101 (90.4-112)
	4-OH-atorvastatin	C_{max}	138 (115-167)
		AUC_{0-24}	157 (115-215)

(Source: Table 11. 2, CSR113)

- **Conclusions:**

Exposure of total atorvastatin was unaffected by multiple doses of lesinurad 200 mg or 400 mg, suggesting no clinically relevant pharmacological effect. *In vivo* activity of OATP1B1 was not affected by lesinurad.

11.DDI with Amlodipine

Trial # 114

Title: A Phase 1 Open Label Study to Evaluate the Potential Pharmacokinetic Interaction Between Lesinurad and the CYP3A4 Substrate Amlodipine in Healthy Adult Male Volunteers

- **Objective:**
  - To evaluate the potential CYP3A4 induction effect of lesinurad multiple-dose treatment on the steady-state PK of amlodipine in healthy adult male subjects.

- **Study design –** This was an open-label study in healthy male subjects. Subjects were to receive amlodipine 5 mg qd from Day 1 to Day 28, inclusive. In addition, subjects were to receive multiple qd doses of lesinurad 400 mg in conjunction with amlodipine 5 mg from Day 15 to Day 28, inclusive. The steady-state PK of amlodipine was to be assessed on study Day 14 (pre-lesinurad) and Day 28 (with lesinurad). Subjects were to receive study medication in the morning in the fed state

- **PK Sampling Schedule**
  - **For amlodipine - Plasma** –day 14 and day 28 : pre-dose (within 30 minutes before dosing) and at 1, 2, 3, 4, 5, 6, 8, 10, 12, 16, and 24 hours post-dose

- **Results**

The steady-state PK parameters of amlodipine 5 mg before (Day 14) and after (Day 28) initiating lesinurad 400 mg qd in healthy adult male subjects under the fed state are presented in Table 72. The decrease (approximately 40%, Table 73) in amlodipine exposure at steady state with once daily doses of lesinurad 400 mg in this study was consistent with weak induction of CYP3A4, and also was consistent with results from other clinical studies, which indicated that lesinurad was a weak to moderate inducer of CYP3A.

Table 72: Steady-State Plasma Pharmacokinetics of Amlodipine Following Once Daily Doses of Amlodipine 5 mg in the Absence or Presence of Lesinurad 400 mg (Geometric Mean with 95% Confidence Interval)

Day	Treatment	N	T_{max}[a] (hr)	C_{max} (ng/mL)	AUC_{τ} (ng•hr/mL)	CL_{ss}/F (L/hr)	$t_{½}$ (hr)
14	Amlodipine alone	14	4.50 (3.00 - 8.00)	9.93 (8.21 - 12.0)	186 (153 - 225)	26.9 (22.3 - 32.6)	33.0[c] (28.9 - 37.7)
28	Amlodipine + lesinurad	13[b]	5.00 (4.00 - 10.0)	6.07 (5.12 - 7.19)	108 (91.8 - 126)	46.4 (39.6 - 54.5)	25.1[c] (21.8 - 28.7)

(Source: Table 11. 1, CSR114)

Table 73: Amlodipine Pharmacokinetic Parameters Following Amlodipine Dosing in the Presence versus Absence of Multiple Doses of Lesinurad (Geometric Mean Ratios with 90% Confidence Interval)

Treatment	Amlodipine Parameter	Day	N	Geometric Least Squares Mean	Geometric Mean Ratio (90% CI) Day 28/Day 14
Amlodipine alone (Day 14) versus Amlodipine + lesinurad (Day 28)	C_{max} (ng/mL)	14	14	10.0	60.4 (55.3 - 66.0)
		28	13[a]	6.07	
	AUC_{τ} (ng•hr/mL)	14	14	187	57.5 (52.5 - 63.1)
		28	13[a]	108	

(Source: Table 11. 2, CSR114)

- **Conclusions:**

Lesinurad was a weak to moderate inducer of CYP3A. Treatment with amlodipine and lesinurad may result in lower plasma exposures of amlodipine, potentially decreasing amlodipine's therapeutic effect in some individuals.

12.DDI with Tolbutamide

Trial # 115

Title: A Phase 1 Study to Evaluate the Potential Pharmacokinetic Interaction Between Lesinurad and the CYP2C9 Probe Substrate, Tolbutamide, in Healthy

Volunteers

- **Objective:**
  - To evaluate the potential inhibitory effect of lesinurad treatment on single-dose PK of tolbutamide upon initiation of lesinurad qd dosing in healthy subjects.
  - To evaluate the potential induction effect of lesinurad multiple-dose treatment for 11 to 13 days on the single-dose PK of tolbutamide in healthy subjects.

- **Study design –** This was an open-label study in healthy subjects. Single doses of tolbutamide 500 mg were to be administered in the morning of Day 1, Day 4, and Day 14. Lesinurad 400 mg qd was to be administered in the morning from Day 4 to Day 16. After informed consent was obtained, blood cells were to be collected from subjects at Screening to determine the subject's CYP2C9 genotype. Only subjects who were homozygous wild-type (*1/*1) CYP2C9 were eligible to participate in this study.

- **PK Sampling Schedule**
  - **For Tolbutamide - Plasma –**day 1, day 4 and day 14 : pre-dose (within 30 minutes before dosing) and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36, 48, 60, and 72 hours post-dose

- **Results**

Results from in vitro studies suggest that lesinurad may affect activity of the drug metabolizing enzyme CYP2C9 by weak inhibition and/or by weak induction. These effects may result in altered plasma exposures and altered safety and efficacy for concomitant medications that are predominantly cleared by CYP2C9. The present study evaluated the effect of lesinurad on the PK of the oral blood glucose-lowering agent tolbutamide, which is predominantly metabolized by CYP2C9. The study was designed to assess the potential for acute inhibition of CYP2C9 (at the time of the first dose of lesinurad) as well as for the potential effect of CYP2C9 induction on tolbutamide PK.

No significant change in tolbutamide exposure was observed (i.e., ~11%, Table 74) with administration of a single dose of lesinurad, which indicates no inhibition of CYP2C9 activity following a single dose of lesinurad. After 14 days of lesinurad 400 mg dosing, no changes were observed in plasma AUC for tolbutamide (~6%, Table 74) and for hydroxytolbutamide (11%), establishing that lesinurad is not an inducer of CYP2C9.

Table 74: Plasma Pharmacokinetics of Tolbutamide Following a Single Dose of Tolbutamide 500 mg in the Absence or Presence of Lesinurad (Geometric Mean with 95% Confidence Interval)

Day	Treatment	N	T_{max}[a] (hr)	C_{max} (µg/mL)	T_{last}[a] (hr)	AUC_{last} (µg•hr/mL)	AUC_{∞} (µg•hr/mL)	CL/F (L/hr)	$t_{1/2}$ (hr)
1	Tolbutamide alone	14	4.00 (3.00-12.0)	48.5 (44.4-53.0)	60.0 (60.0-72.0)	684 (596-785)	688 (598-792)	0.727 (0.632-0.837)	7.46 (6.57-8.48)
4	Tolbutamide + single dose lesinurad	13[b]	4.00 (2.00-8.00)	51.2 (46.5-56.4)	72.0 (60.0-72.0)	757 (636-902)	763 (638-913)	0.655 (0.548-0.784)	8.46 (7.40-9.66)
14	Tolbutamide + multiple doses lesinurad	13[b]	6.00 (3.00-12.0)	48.7 (44.0-53.9)	72.0 (60.0-72.0)	727 (637-830)	731 (638-837)	0.684 (0.597-0.784)	8.19 (7.34-9.14)

(Source: Table 11. 1, CSR115)

- **Conclusions:**

This study demonstrated that lesinurad did not inhibit CYP2C9 following a single dose or induce CYP2C9 following multiple doses.

13.DDI with Repaglinide

Trial # 116

Title: A Phase 1 Study to Evaluate the Potential Pharmacokinetic Interaction Between Lesinurad and the CYP2C8 Probe Substrate, Repaglinide, in Healthy Volunteers

- **Objective:**
  - To evaluate the potential inhibitory effect of lesinurad treatment on single-dose PK of repaglinide upon initiation of lesinurad qd dosing in healthy subjects.
  - To evaluate the potential induction effect of lesinurad multiple-dose treatment for 12 days on the single-dose PK of repaglinide in healthy subjects.

- **Study design –** This was an open-label study in healthy subjects. Single doses of repaglinide 0.5 mg were to be administered in the morning of Day 1, Day 4, and Day 14 in the morning in the fed state. Lesinurad 400 mg qd was to be administered in the morning from Day 4 to Day 16. After informed consent was obtained, blood cells were to be collected from subjects at Screening for possible analysis of the subject's CYP2C8 genotype.

- **PK Sampling Schedule**
  - **For repaglinide - Plasma –** day 1, day 4, and day 14 : pre-dose (within 30 minutes before dosing) and at 20, 40, 60, 80, and 100 minutes, and at, 2, 2.5, 3, 4, 5, 6, 8, 12, 16, 24, and 30 hours postdose.

- **Results**

Results from in vitro studies suggest that lesinurad may affect activity of the drug

metabolizing enzyme CYP2C8 by weak inhibition and/or by weak induction. These effects may result in altered plasma exposures and altered safety and efficacy for concomitant medications that are predominantly cleared by CYP2C8. The present study evaluated the effect of lesinurad on the PK of the oral hypoglycemic agent repaglinide, which is predominantly metabolized by CYP2C8. The study was designed to assess the potential for acute inhibition of CYP2C8 (at the time of the first dose of lesinurad) as well as for the potential effect of CYP2C8 induction on repaglinide PK.

A small increase (10-31%) in repaglinide plasma AUC exposure was observed with administration of a single dose and multiple doses of lesinurad, which may indicate weak inhibition of CYP2C8. Repaglinide exposure after multiple daily doses of lesinurad was essentially unchanged as compared with repaglinide administered without concomitant lesinurad, indicating there was no clinically significant interaction of lesinurad with the CYP2C8 substrate repaglinide (Table 75).

Table 75: Plasma Pharmacokinetics of Repaglinide Following a Single Dose of Repaglinide 0.5 mg in the Absence or Presence of Lesinurad (Geometric Mean with 95% Confidence Interval)

Day	Treatment	N	T_{max}[a] (hr)	C_{max} (ng/mL)	T_{last}[a] (hr)	AUC_{last} (ng•hr/mL)	AUC_{∞} (ng•hr/mL)	CL/F (L/hr)	$t_{1/2}$ (hr)
1	Repaglinide alone	14	1.33 (0.333-3.00)	3.49 (3.09-3.94)	5.00 (3.00-6.00)	8.09 (6.61-9.90)	8.49 (6.98-10.3)	58.9 (48.4-71.6)	0.856 (0.767-0.954)
4	Repaglinide + single dose lesinurad	14	1.33 (0.417-3.00)	4.42 (3.46-5.64)	6.00 (5.00-8.00)	10.6 (8.65-12.9)	11.1 (9.15-13.5)	45.0 (37.0-54.7)	1.13 (0.968-1.31)
14	Repaglinide + multiple doses lesinurad	13[b]	1.33 (0.333-2.50)	3.45 (2.83-4.20)	6.00 (3.00-8.00)	8.66 (6.99-10.7)	9.30 (7.54-11.5)	53.8 (43.6-66.3)	1.25 (0.927-1.70)

(Source: Table 11. 1, CSR116)

- **Conclusions:**

No dose adjustment is necessary for CYP2C8 substrate when coadministered with lesinurad.

14.DDI with Fluconazole and Rifampin

Trial # 122

Title: A Phase 1 Drug-Drug Interaction Study to Evaluate the Potential Effect of CYP2C9 Inhibition and Induction on the Pharmacokinetics of Lesinurad in Healthy Adult Male Subjects

- **Objective:**
  - To evaluate the potential effect of fluconazole, a CYP2C9 inhibitor, on the PK of lesinurad, in healthy adult male subjects.
  - To evaluate the potential effect of rifampin, a CYP2C9 inducer, on the PK of lesinurad in healthy adult male subjects.

- To measure the PD effects of lesinurad on sUA and fractional excretion of uric acid with and without concurrent administration of fluconazole or rifampin in healthy adult male subjects.

- **Study design –** This was a Phase 1, open-label, single-center, sequential DDI study in healthy adult male subjects. 12 subjects were assigned to each of the following cohorts:
  - Cohort 1: Lesinurad and fluconazole.
  - Cohort 2: Lesinurad and rifampin.

As demonstrated in Figure 53, subjects in Cohort 1 were to receive single doses of lesinurad 400 mg on Days 1 and 5, a loading dose of fluconazole 400 mg on Day 4, and fluconazole 200 mg on each of Days 5 and 6; subjects in Cohort 2 were to receive single doses of lesinurad 400 mg on Days 1 and 15, and qd doses of rifampin 600 mg from Days 4 to 17, inclusive.

Reviewer's comment:
Rifampicin dosing at 600 mg QD for seven days is considered adequate for CYP induction and is preferred over use of lower doses. Inducers may take several days to exert their effects on CYP and dosing for several days ascertains that CYP induction is achieved before evaluating its effect on PK of lesinurad.

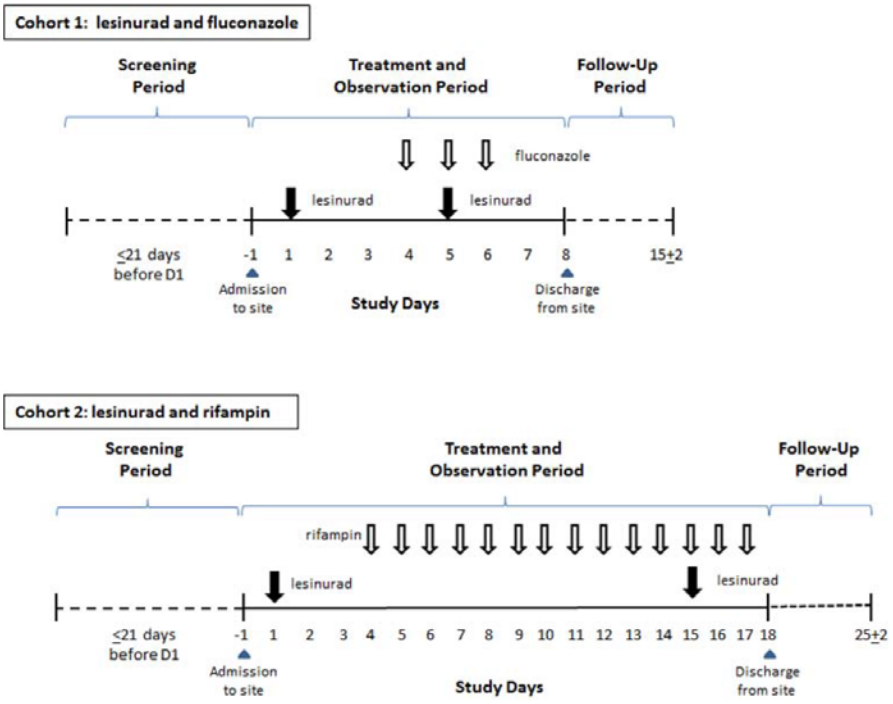


Figure 53. Study Design Diagram for Cohort 1 and 2
(Source: Figure 9-1, CSR122)

- **Test product:** Lesinurad was administered as a 400 mg tablet.

- **Sampling Schedule**

PK Sampling Schedule

Blood samples were to be collected on Day 1 and Day 5 (Cohort 1) or Day 1 and Day 15 (Cohort 2): Predose (within 30 minutes before dosing), 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 16, 24, 30, 36, 48, 54, 60, and 72 hours postdose.

Urine (total catch) samples were to be collected at the following timepoints:

- Day -1: -12 to 0 hours before Day 1 lesinurad dose.
- Day 1 and Day 5 (Cohort 1) or Day 1 and Day 15 (Cohort 2): 0 to 6, 6 to 12, 12 to 24, 24 to 36, 36 to 48, 48 to 60, and 60 to 72 hours postdose.

PD Sampling Schedule

Blood samples were to be collected for the analysis of serum urate (sUA) at Screening and at the following timepoints in relation to dosing of lesinurad: -24, -18, -12, -8, 0 hours predose (within 30 minutes before dosing), and at 6, 12, 16, 24, 36, 48, 60, and 72 hours postdose. Urine samples from each of the pharmacokinetic collections were assayed for uric acid and creatinine.

Genotyping

Whole blood was collected for possible CYP2C9 genotyping.

- **Results**

PK results:

Plasma PK parameters of lesinurad following a single dose of 400 mg lesinurad in the absence and presence of fluconazole and rifampin are presented in Table 76.

Fluconazole: Following a single oral dose of 400 mg lesinurad alone in Cohort 1 (Day 1), lesinurad was absorbed at a median Tmax of 3 hours postdose. In the presence of fluconazole, lesinurad appeared to be more rapidly absorbed, with median Tmax occurring at 1.5 hours postdose. In the presence of fluconazole, lesinurad plasma exposures Cmax and AUC increased by 38% and 56%, respectively, when compared to dosing lesinurad alone (Table 77). In the presence of fluconazole, RDEA594-M4 plasma Cmax and AUC decreased by 40% and 28%, respectively.

Rifampin: Following a single oral dose of 400 mg lesinurad alone in Cohort 2, lesinurad was readily absorbed at a median Tmax of 2 hours postdose. A similar median Tmax (1.75 hours) was observed in the presence of rifampin, indicating that rifampin does not significantly alter the absorption rate of lesinurad. In the presence of rifampin, lesinurad plasma exposures Cmax and AUC decreased by approximately 24% and 38%, respectively, when compared to dosing lesinurad alone (Table 77). In the presence of rifampin, RDEA594-M4 Cmax increased by 12% while AUC showed no change.

Table 76: Summary of Plasma Pharmacokinetics of Lesinurad Following Administration of a Single Oral Dose of 400 mg Lesinurad in the Absence or Presence of Fluconazole or Rifampin to

Healthy Subjects (Geometric Mean [95% Confidence Interval])

Treatment	Day	n	T_{max}[a] (hr)	C_{max} (µg/mL)	T_{last}[a] (hr)	AUC_{last} (µg·hr/mL)	AUC_{∞} (µg·hr/mL)	$t_{1/2}$ (hr)	CL/F (L/hr)	V_{ss}/F (L)
400 mg lesinurad alone	1	13	3.00 (1.00-5.00)	16.6 (13.4-20.6)	72.0 (72.0-72.0)	61.6 (52.2-72.7)	62.0 (52.6-73.2)	24.8[b] (16.1-38.2)	6.45 (5.47-7.61)	40.4 (34.3-47.5)
400 mg lesinurad + 200 mg fluconazole	5	12[c]	1.50 (0.750-2.50)	22.2 (19.4-25.3)	72.0 (72.0-72.0)	94.8 (77.9-115)	95.4 (78.4-116)	17.6[b] (12.0-25.7)	4.19 (3.45-5.10)	27.3 (22.8-32.8)
400 mg lesinurad alone	1	14	2.00 (1.00-5.00)	16.6 (14.4-19.2)	72.0 (36.0-72.0)	56.4 (47.6-66.8)	56.6 (47.8-67.1)	19.3 (13.7-27.2)	7.06 (5.96-8.37)	34.0 (28.6-40.3)
400 mg lesinurad + 600 mg rifampin	15	14	1.75 (0.750-5.00)	12.6 (10.4-15.3)	60.0 (30.0-72.0)	35.1 (29.8-41.3)	35.3 (30.0-41.6)	16.3 (10.2-26.0)	11.3 (9.61-13.4)	55.6 (44.1-70.1)

(Source: Table 11. 1, CSR122)

Table 77: Geometric Least Squares Mean and Geometric Mean Ratio (90% Confidence Interval) of Lesinurad Plasma Pharmacokinetic Parameters in the Presence versus Absence of Fluconazole or Rifampin

Treatment	n	Parameter	Geometric LS Mean	Geomean Ratio (90% CI)
400 mg lesinurad + fluconazole versus 400 mg lesinurad alone	12[a]	C_{max} (µg/mL)	22.2 16.0	138% (120% - 158%)
		AUC_{last} (µg·hr/mL)	94.8 60.6	156% (141% - 173%)
		AUC_{∞} (µg·hr/mL)	95.4 61.1	156% (141% - 173%)
400 mg lesinurad + rifampin versus 400 mg lesinurad alone	14	C_{max} (µg/mL)	12.6 16.6	76.1% (69.6% - 83.3%)
		AUC_{last} (µg·hr/mL)	35.1 56.4	62.2% (57.7% - 67.1%)
		AUC_{∞} (µg·hr/mL)	35.3 56.6	62.4% (57.8% - 67.2%)

(Source: Table 11. 1, CSR122)

PD results:

Changes in sUA concentrations, following a single dose of 400 mg lesinurad in the absence and presence of fluconazole and rifampin, were evaluated in healthy adult male subjects. Mean absolute and mean percentage change from baseline (Time-matched, Day -1) in sUA concentrations are presented in Figure 54 and Figure 55, respectively. The Emax, CB and the percentage change from baseline (Time-matched, Day -1) in sUA at 24 hours postdose are presented in Table 78.

The observed sUA lowering effect was similar following administration of 400 mg lesinurad in the presence and absence of fluconazole, with a maximum reduction in sUA of 43%, and a reduction in sUA at 24 hours postdose of 29% (Table 78).

The maximum reduction in sUA was slightly lower in the presence of rifampin (30%) compared to when lesinurad was administered alone (39%). The reduction in sUA at 24 hours postdose was similar following administration of lesinurad alone (22%) and in the presence of rifampin (20%) (Table 78).

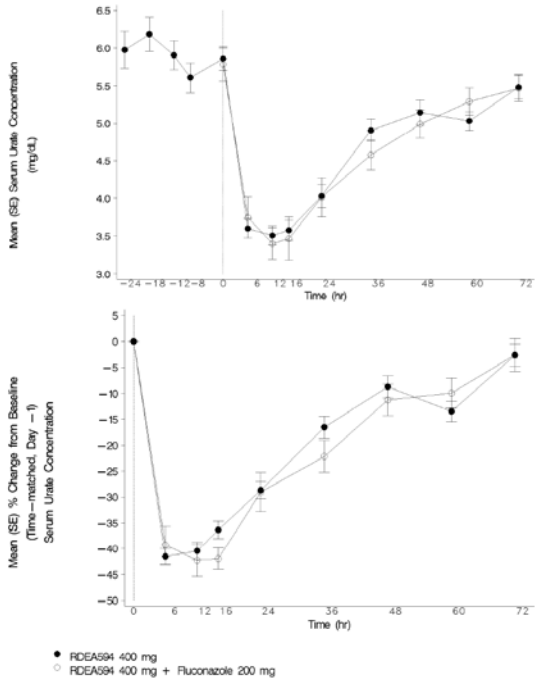


Figure 54. Mean Absolute and Mean Percentage Change from Baseline (Time-matched, Day -1) in Serum Urate Concentrations Following Administration of a Single Oral Dose of 400 mg Lesinurad in the Absence or Presence of Fluconazole to Healthy Subjects
(Source: Figure 11.1, CSR122)

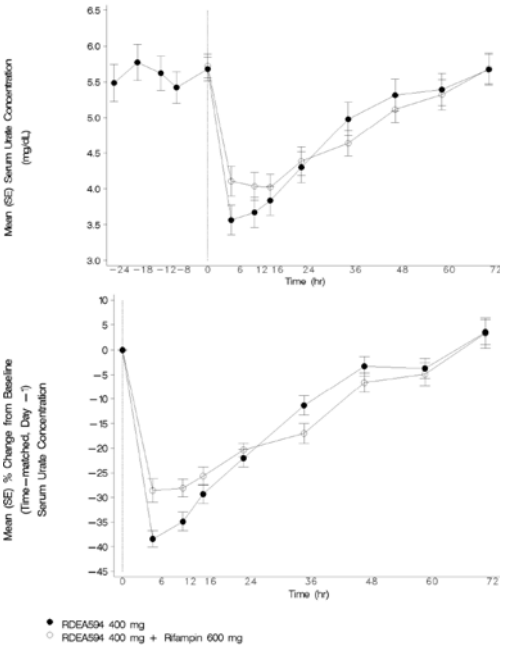


Figure 55. Mean Absolute and Mean Percentage Change from Baseline (Time-matched, Day -1) in Serum Urate Concentrations Following Administration of a Single Oral Dose of 400 mg Lesinurad in the Absence or Presence of Rifampin to Healthy Subjects
(Source: Figure 11.2, CSR122)

Table 78: Statistical Analysis of the Percentage Change From Baseline (Time-matched, Day -1) in Serum Urate Concentrations Following Administration of a Single Oral Dose of 400 mg Lesinurad in the Absence or Presence of Fluconazole or Rifampin to Healthy Subjects

Maximum Observed Percentage Change From Baseline (Time-matched, Day -1) in Serum Urate Concentrations ($E_{max, CB}$)

Test	Comparator	Test LS Mean (n)	Comparator LS Mean (n)	Difference of LS Means (95% CI) Test versus Comparator	p-value
400 mg lesinurad + 200 mg fluconazole	400 mg lesinurad	-42.72 (13)[a]	-42.56 (13)	-0.16 (-6.49, 6.17)	0.9574
400 mg lesinurad + 600 mg rifampin	400 mg lesinurad	-29.86 (14)	-38.88 (14)	9.02 (5.87, 12.18)	<0.0001[b]

Percentage Change from Baseline (Time-matched, Day -1) in Serum Urate Concentrations at 24 hours

Test	Comparator	Test LS Mean (n)	Comparator LS Mean (n)	Difference of LS Means (95% CI) Test versus Comparator	p-value
400 mg lesinurad + 200 mg fluconazole	400 mg lesinurad	-28.98 (13)[a]	-28.61 (13)	-0.37 (-9.12, 8.37)	0.9306
400 mg lesinurad + 600 mg rifampin	400 mg lesinurad	-20.38 (14)	-22.05 (14)	1.67 (-3.14, 6.48)	0.4803

(Source: Table 11.10, CSR122)

- **Conclusions:**

Lesinurad exposure is increased when lesinurad is co-administered with inhibitors of CYP2C9. ZURAMPIC should be used with caution in patients taking moderate inhibitors of CYP2C9. Treatment with rifampin and lesinurad may result in lower plasma exposures of lesinurad, potentially decreasing lesinurad's uric acid lowering effect in some individuals.

Reviewer's comment:

- *Based on the PK and PD result, we recommend "Lesinurad exposure is decreased when ZURAMPIC is co-administered with inducers of CYP2C9 (eg, rifampin), which may decrease the therapeutic effect of ZURAMPIC [see Clinical Pharmacology (12.3)]."in the section 7 of the label.*

15.DDI with Warfarin

Trial # 123

Title: A Phase 1, Open-Label, Drug-Drug Interaction Study to Evaluate the Potential Effect of Lesinurad on the Pharmacokinetics of Warfarin in Healthy Adult Male Subjects

- **Objective:**

- To evaluate the potential effect of lesinurad on the pharmacokinetics of warfarin (R-warfarin and S-warfarin enantiomers) in healthy adult male subjects.
- To measure the potential effect of lesinurad on the pharmacodynamics of warfarin in healthy adult male subjects.

- **Study design –** This was a Phase 1, open-label, single-center, DDI study in healthy adult male subjects. All subjects were to be dosed with lesinurad 400 mg qd on Day 8 to Day 28, and 2 single doses of warfarin 25 mg on Day 1 and Day 22. After informed consent was obtained, a whole blood sample was to be collected from subjects at Screening to determine the subject's CYP2C9 and vitamin K epoxide reductase complex 1 (VKORC1) genotype.

- **Test product:** Lesinurad was administered as 400 mg tablets.

- **Sampling Schedule**

PK Sampling Schedule

Plasma samples were to be collected at the following timepoints in relation to dosing of warfarin on Days 1 and 22: predose (within 0.75 hours of dosing) and 0.5, 1, 2, 4, 8, 12, 24, 36, 48, 72, 96, 120, 144, and 168 hours postdose.

PD Sampling Schedule

Plasma PD samples were to be collected at Screening, Day -1, Days 1 to 8, Days 21 to 29, and at Follow-up. PT, INR, aPTT, and Factor VII clotting activity (%) were to be included in PD and safety analyses.

- **Results**

PK results:

Plasma PK parameters of S-warfarin and R-Warfarin following a single dose of 25 mg warfarin in the absence and presence of multiple doses of lesinurad are presented in Table 79. The Cmax and AUC of S-warfarin or R-warfarin were comparable with or without lesinurad coadministration.

Table 79: Plasma Pharmacokinetics of Warfarin Following a Single Oral Dose of 25 mg Warfarin in the Absence (Day 1) or Presence (Day 22) of 400 mg Lesinurad (Geometric Mean [95% Confidence Interval])

Enantiomer	Day	N	T_{max}[a] (hr)	C_{max} (ng/mL)	T_{last}[a] (hr)	AUC_{last} (ng·hr/mL)	AUC_{∞} (ng·hr/mL)	CL/F (L/hr)	V_{ss}/F (L)	$t_{½}$ (hr)
S-Warfarin	1[b]	18	4.00 (1.00-8.00)	1130 (1050-1220)	168 (168-168)	41100 (36100-46800)	42700 (36900-49300)	0.586 (0.507-0.677)	25.5 (23.8-27.4)	34.7 (31.0-38.8)
	22[c]	18	4.00 (4.00-8.00)	1160 (1080-1240)	168 (168-168)	42800 (38800-47100)	44400 (40000-49400)	0.563 (0.507-0.625)	25.4 (23.9-27.1)	36.1 (32.8-39.7)

Enantiomer	Day	N	T_{max}[a] (hr)	C_{max} (ng/mL)	T_{last}[a] (hr)	AUC_{last} (ng·hr/mL)	AUC_{∞} (ng·hr/mL)	CL/F (L/hr)	V_{ss}/F (L)	$t_{½}$ (hr)
R-Warfarin	1[b]	18	4.00 (2.00-12.0)	1180 (1100-1280)	168 (168-168)	67200 (60000-75300)	72900 (64000-83000)	0.343 (0.301-0.391)	22.0 (20.4-23.7)	44.1 (39.9-48.8)
	22[c]	18	4.00 (4.00-8.00)	1180 (1100-1260)	168 (168-168)	56200 (50100-63100)	59200 (52000-67400)	0.422 (0.371-0.481)	22.4 (21.0-24.0)	37.2 (33.6-41.3)

(Source: Table 11. 1 and 11.4, CSR123)

PD results
There was no significant impact of lesinurad on INR or Factor VIImax (% inhibition).

- **Conclusions:**

Lesinurad had no effect on CYP2C9 activity. No dose adjustment is necessary for Warfarin when coadministered with lesinurad.

16.DDI with NSAIDS

Trial # 126

Title: A Phase 1 Study to Evaluate the Potential Two-Way Pharmacokinetic Interaction Between Lesinurad and Naproxen and Between Lesinurad and Indomethacin in Healthy Adult Male Subjects

- **Objective:**
  - To evaluate the effect of multiple doses of naproxen on the single-dose pharmacokinetics of lesinurad in healthy adult male subjects.
  - To evaluate the effect of multiple doses of indomethacin on the single-dose pharmacokinetics of lesinurad in healthy adult male subjects.
  - To evaluate the effect of multiple doses of lesinurad on the multiple-dose pharmacokinetics of naproxen in healthy adult male subjects.
  - To evaluate the effect of multiple doses of lesinurad on the multiple-dose pharmacokinetics of indomethacin in healthy adult male subjects.

- **Study design –** This was a Phase 1, open-label, sequential, drug-drug interaction (DDI) study in healthy adult male subjects. A total of 20 subjects were enrolled in the study; 10 subjects in Cohort 1 (Lesinurad and naproxen) and 10 subjects in Cohort 2 (Lesinurad and indomethacin).

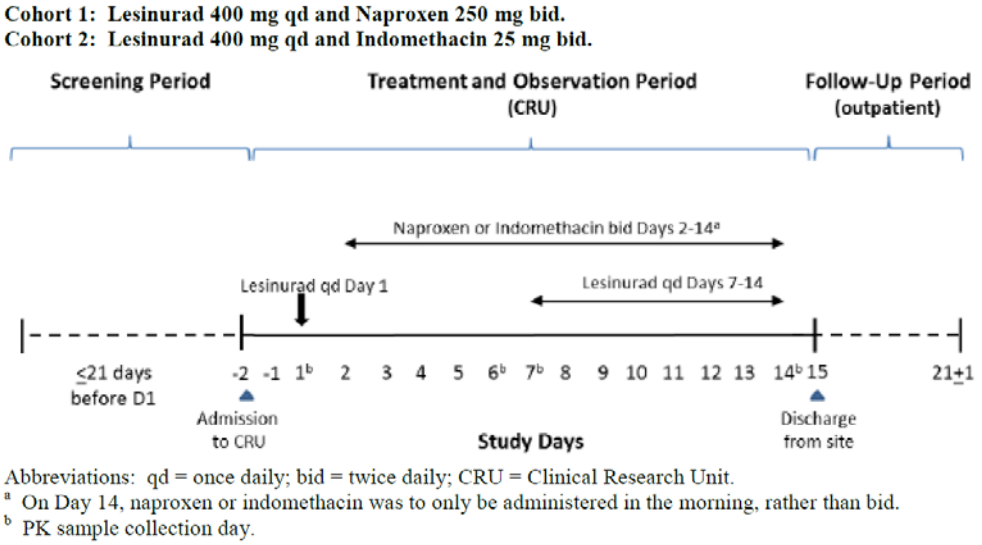


Figure 56. Study Design Diagram for Cohort 1 and 2
(Source: Figure 9-1, CSR126)

- **Test product:** Lesinurad was administered as 400 mg tablets.

- **Sampling Schedule**

PK Sampling Schedule

Plasma samples were to be collected on Day 1, Days 6 to 7, and Day 14 at the following timepoints: predose (within 30 minutes before dosing) and 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, and 24 hours postdose.

PD Sampling Schedule

Not collected.

- **Results**

PK results

In the presence of multiple doses of naproxen, plasma exposures of a single dose of lesinurad (Day 7) decreased by approximately 27% and 15% for Cmax and AUC, respectively, as compared to lesinurad dosed alone (Day 1, Table 80). Multiple-dose plasma Cmax and AUC exposures of lesinurad on Day 14 appeared to show no discernible difference compared to Day 7 following continued dosing in combination with naproxen, suggesting naproxen showed similar impact on single or multiple doses of lesinurad. In the presence of a single or multiple doses of lesinurad, naproxen plasma Cmax and AUC exposures were unchanged.

In the presence of multiple doses of indomethacin, plasma lesinurad exposures of a single dose of lesinurad showed an increase by approximately 18% for Cmax and no change for AUC. Multiple-dose plasma Cmax and AUC exposures of lesinurad on Day 14 appeared to show no difference compared to Day 7 following continued dosing in combination with indomethacin, suggesting indomethacin showed similar impact on multiple doses of lesinurad as it had on single dosing. In the presence of a single dose of lesinurad (Day 7), plasma indomethacin Cmax and AUC increased to 18% and 35%, respectively, when compared to indomethacin dosing alone. A similar increase in plasma Cmax (20%) and AUC (31%) was observed following multiple doses of lesinurad with indomethacin (Day 14).

Table 80: Geometric Mean Ratio (90% Confidence Interval) of Lesinurad Pharmacokinetic Parameters Following a Single Dose of 400 mg Lesinurad in the Absence (Day 1) or Presence of Multiple Dose of 250 mg Naproxen bid or 25 mg Indomethacin bid (Day 7)

Treatment	n	Parameter	Geomean Ratio (90% CI)
Multiple-dose naproxen + single-dose lesinurad (Day 7) vs. single-dose lesinurad alone (Day 1)	10	C_{max}	72.9% (57.6%-92.2%)
		AUC_{0-24}	85.5% (79.7%-91.8%)
Multiple-dose indomethacin + single-dose lesinurad (Day 7) vs. single-dose lesinurad alone (Day 1)	11	C_{max}	118% (103%-136%)
		AUC_{0-24}	110% (103%-119%)

(Source: Table 11. 2, CSR126)

- **Conclusions:**

Lesinurad AUC was comparable with or without coadministration of indomethacin or naproxen.

NSAIDs may lower the GFR, thus may affect the uric acid lowering effect of lesinurad. This potential PD interaction was not assessed in this study. In phase 3, less than 10% patients used NSAIDs during the studies, and the data is too limited to draw any conclusion on NSAIDs' impact on lesinurad efficacy.

As renal toxicity is a major safety concern with lesinurad, and NSAIDs are also associated with the development of kidney injury, coadministration of the two may pose additional risk. See medical officer Dr. Rosemarie Neuner's review for further details.

17.DDI with Ranitidine

Trial # 127

Title: A Phase 1, Open-Label, Drug-Drug Interaction Study to Evaluate the Potential Effects of Ranitidine on the Pharmacokinetics of Lesinurad in Healthy Adult Male Subjects.

- **Objective:**
  - To evaluate the potential effect of ranitidine on the single-dose pharmacokinetics of lesinurad in healthy adult male subjects under the fasted state.

- **Study design –** This was a Phase 1, randomized, open-label, crossover, drug-drug interaction (DDI) study in healthy adult male subjects. A total of 16 subjects were randomized and entered the Cohort 1 (8 in Sequence 1 and 8 in Sequence 2, Figure 57). Cohort 2 was not studied.

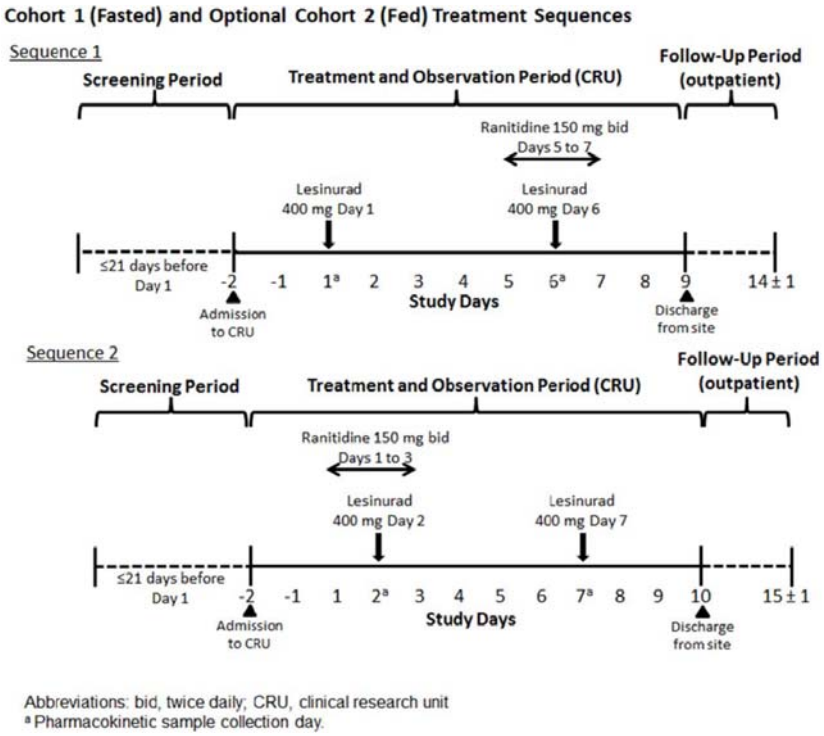


Figure 57. Study Design Diagram for Cohort 1 and 2
(Source: Figure 9-1, CSR127)

- **Test product:** Lesinurad was administered as a 400 mg tablet.

- **Sampling Schedule**

PK Sampling Schedule

Blood samples were to be collected for the analysis of plasma concentrations of lesinurad at the following timepoints in relation to dosing of lesinurad: predose (within 30 minutes before dosing) and at 30 minutes and 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, 48, 60, and 72 hours postdose.

PD Sampling Schedule

Blood samples were to be collected for the analysis of serum urate (sUA) at Screening and at the following timepoints in relation to dosing of lesinurad: -24, -18, -12, 0 hours predose (within 30 minutes before dosing), and at 6, 12, 24, 36, 48, 60, and 72 hours postdose.

- **Results**

PK results

In the presence of ranitidine, lesinurad plasma AUC exposure was unchanged as the geometric mean ratio was ~110% and the corresponding 90% confidence intervals (103% to 116%, Table 82) were wholly contained within the 80% to 125% interval. Plasma Cmax was increased by approximately 20% when compared to dosing lesinurad alone (90% confidence interval 101% to 143%, Table 82).

Table 81: Summary of Plasma Pharmacokinetics of Lesinurad Following a Single 400 mg Oral Dose of Lesinurad in the Absence or Presence of Ranitidine in Healthy Adult Male Subjects (Geometric Mean [95% Confidence Intervals])

Treatment	N	T_{max}[a] (hr)	C_{max} (µg/mL)	T_{last}[a] (hr)	AUC_{0-24} (µg·hr/mL)	AUC_{last} (µg·hr/mL)	AUC_{∞} (µg·hr/mL)	CL/F (L/hr)	V_{ss}/F (L)	$t_{1/2}$ (hr)
lesinurad 400 mg	16	2.00 (1.00-6.00)	14.0 (12.1-16.2)	60.0 (36.0-72.0)	43.8 (39.2-48.9)	44.5 (39.8-49.7)	44.6 (39.9-49.9)	8.97 (8.02-10.0)	38.3 (33.7-43.5)	9.92 (6.96-14.2)
lesinurad 400 mg + ranitidine	16	1.50 (1.00-3.00)	16.8 (14.5-19.5)	60.0 (36.0-72.0)	48.0 (41.5-55.5)	48.7 (42.1-56.3)	48.8 (42.2-56.4)	8.20 (7.09-9.48)	33.2 (28.3-39.0)	11.5 (8.17-16.3)

(Source: Table 11. 1, CSR127)

Table 82: Geometric Least Squares Mean and Geometric Mean Ratio (CI90%) of Lesinurad Plasma Pharmacokinetic Parameters in the Presence versus Absence of Ranitidine

Treatment	N	Parameter	Geometric LS Mean	Geomean Ratio (90% CI)
lesinurad 400 mg + ranitidine versus lesinurad 400 mg	16	C_{max}	16.8 14.0	120% (101% - 143%)
		AUC_{0-24}	48.0 43.8	110% (103% - 116%)
		AUC_{last}	48.7 44.5	109% (103% - 116%)
		AUC_{∞}	48.8 44.6	109% (103% - 116%)

(Source: Table 11. 2, CSR127)

PD results

The observed sUA lowering effect was similar following administration of lesinurad 400 mg in the absence and presence of ranitidine, with maximum reductions in sUA of approximately 34% and 33%, and reductions in sUA at 24 hours postdose of approximately 16% and 19%, respectively.

- **Conclusions:**

No dose adjustment is necessary when lesinurad is coadministered with ranitidine.

18.DDI with Metformin, Forosemide

Trial # 128

Title: A Phase 1, Randomized, Open-Label, Single-Dose Study to Evaluate the Potential Pharmacokinetic Interaction Between Lesinurad and Metformin and Between Lesinurad and Furosemide in Healthy Adult Male Subjects

- **Objective:**
  - To evaluate the effect of a single dose of lesinurad on the single-dose pharmacokinetics of metformin in healthy adult male subjects.
  - To evaluate the effect of a single dose of lesinurad on the single-dose pharmacokinetics of furosemide in healthy adult male subjects.

- **Study design –** This was a Phase 1, randomized, open-label, crossover, drug-drug interaction (DDI) study in healthy adult male subjects. A total of 24 subjects were randomized and entered the study; 12 subjects in Cohort 1 (6 in Sequence A and 6

in Sequence B) and 12 subjects in Cohort 2 (6 in Sequence C and 6 in Sequence D). In Cohort 1 subject received lesinurad ± metformin 850 mg and in Cohort 2 subjects received lesinurad ± furosemide 40 mg.

- Cohort 1 (lesinurad + metformin)
  - Sequence A (6 subjects):
    - Day 1: Metformin 850 mg
    - Day 5: Lesinurad 400 mg + metformin 850 mg
  - Sequence B (6 subjects):
    - Day 1: Lesinurad 400 mg + metformin 850 mg
    - Day 5: Metformin 850 mg
- Cohort 2 (lesinurad + furosemide)
  - Sequence C (6 subjects):
    - Day 1: Furosemide 40 mg
    - Day 5: Lesinurad 400 mg + furosemide 40 mg
  - Sequence D (6 subjects):
    - Day 1: Lesinurad 400 mg + furosemide 40 mg
    - Day 5: Furosemide 40 mg

- **Test product:** Lesinurad was administered as a 400 mg tablet.

- **Sampling Schedule**
  - Plasma Day 1 and Day 5: predose (within 30 min before dosing) and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 14, and 24 hours postdose.

- **Results**

PK results

In the presence of lesinurad, metformin plasma AUC exposure and Cmax were unchanged (≤ 6% difference), as the 90% CIs around the geometric least squares mean ratios for both AUC and Cmax were wholly contained within the 80% to 125% interval.

In the presence of lesinurad, furosemide plasma AUC exposure and Cmax were decreased by approximately 31% and 51%, respectively (Table 83).

Table 83: Summary of Plasma Pharmacokinetics of Furosemide Following a Single 40 mg Oral Dose of Furosemide in the Absence or Presence of Lesinurad 400 mg in Healthy Adult Male Subjects (Geometric Mean [95% Confidence Interval])

Treatment	N	T_{max}[a] (hr)	C_{max} (µg/mL)	T_{last}[a] (hr)	AUC_{last} (µg·hr/mL)	AUC_{∞} (µg·hr/mL)	CL/F (L/hr)	V_{ss}/F (L)	$t_{1/2}$ (hr)
furosemide 40 mg	11	1.00 (0.500-5.00)	0.938 (0.654-1.35)	14.0 (14.0-24.0)	2.41 (1.89-3.09)	2.56 (1.99-3.29)	15.6 (12.1-20.1)	69.8 (39.5-124)	4.81 (2.66-8.67)
furosemide 40 mg + 400 mg lesinurad	11	2.00 (0.500-4.00)	0.463 (0.338-0.634)	24.0 (14.0-24.0)	1.69 (1.40-2.03)	1.77 (1.48-2.12)	22.6 (18.8-27.0)	129 (96.3-173)	5.62 (3.66-8.63)

(Source: Table 11. 3, CSR128)

PD results

Urine PD parameters were evaluated following a single dose of furosemide in the absence and presence 400 mg lesinurad. There was no apparent impact of lesinurad

on the activity of furosemide based on an assessment of urine volume, urine specific gravity, and urine sodium.

- **Conclusions:**

lesinurad has no effect on OCT1, or OAT1 and 3 *in vivo*. No dose adjustment is necessary when metformin or furosemide is coadministered with lesinurad.

19.DDI with Antacid

Trial # 130

Title: A Phase 1, Randomized, Open-Label, Drug-Drug Interaction Study to Evaluate the Potential Pharmacokinetic and Pharmacodynamic Interaction Between Lesinurad and Calcium Carbonate and Aluminum/Magnesium Hydroxide-Containing Antacids in Healthy Adult Male Subjects

- **Objective:**
  - To assess the effect of a calcium carbonate-containing antacid on the pharmacokinetics and pharmacodynamics of lesinurad in healthy adult male subjects under fed conditions.
  - To assess the effect of a magnesium hydroxide- and aluminum hydroxide-containing antacid on the pharmacokinetics and pharmacodynamics of lesinurad in healthy adult male subjects under fed conditions.

- **Study design –** This was a Phase 1, randomized, open-label, crossover, drug-drug interaction (DDI) study in healthy adult male subjects. A total of 24 subjects were randomized and entered the study; 12 subjects in Cohort 1 (6 in Sequence A and 6 in Sequence B) and 12 subjects in Cohort 2 (6 in Sequence C and 6 in Sequence D).In Cohort 1 subject received lesinurad ± calcium carbonate 1250 mg (Tums®) and in Cohort 2 subjects received lesinurad ± aluminum hydroxide 800 mg/magnesium hydroxide 800 mg/simethicone 80 mg (MINTOX).

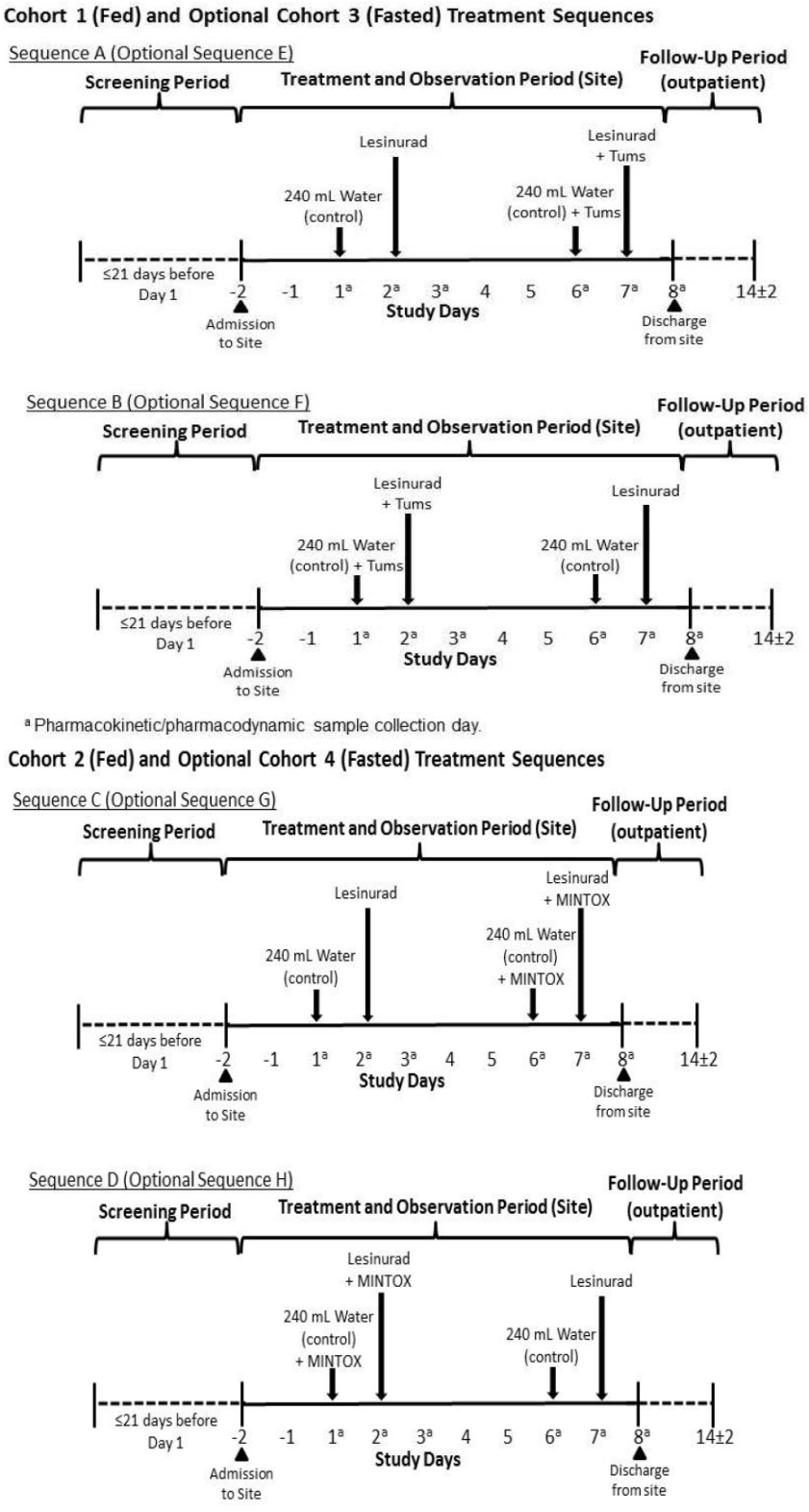


Figure 58. Study Design Diagram for Cohort 1 and 2
(Source: Figure 9-1, 9-2, CSR130)

- **Test product:** Lesinurad was administered as a 400 mg tablet

- **Sampling Schedule**
    - Plasma Day 2 and Day 7: Predose (within 30 minutes before dosing) and at 30 minutes and 1, 1.5, 2, 3, 4, 6, 8, 10, 12, and 24 hours postdose.

- **Results**

PK results

In the presence of Tums (Cohort 1), lesinurad plasma AUC0-24, AUC∞, and Cmax geometric mean ratios (90% CIs) were 89.0% (83.8% to 94.5%), 89.1% (83.9% to 94.7%), and 89.9% (77.6% to 104%), respectively.
In the presence of MINTOX (Cohort 2), lesinurad plasma AUC0-24, AUC∞, and Cmax geometric mean ratios (90% CIs) were 90.4% (81.4% to 100%), 90.6% (81.8% to 100%), and 84.9% (68.0% to 106%), respectively.

PD results

Differences in sUA levels were less than 2% following administration of control alone and control with Tums or MINTOX.

- **Conclusions:**

Coadministration with antacid does not alter the PK or PD of lesinurad. No dose adjustment is necessary when lesinurad is coadministered with antacid.

BIOPHARMACEUTICS

20.Absolute Bioavailability

Trial # 131

Title: A Phase 1, Open-Label Study to Assess the Absolute Bioavailablility of a Single Oral Dose of Lesinurad with Respect to an Intravenous Micro Tracer Dose of [14C]Lesinurad in Healthy Adult Male Subjects

- **Objective:**
    - To assess the absolute bioavailability of a single oral dose of lesinurad.
    - To evaluate the pharmacokinetic parameters of lesinurad and [14C]lesinurad in healthy adult male subjects.

- **Study design and treatment schedule:**

    This was a Phase 1, open-label study performed in 10 healthy, adult male subjects. A single oral dose of lesinurad (400 mg tablet) and a single IV micro tracer dose of [14C]lesinurad were administered to subjects on Day 1 of this study. A single, 15 minute, IV infusion of [14C]lesinurad (100 µg; 810 nCi) was given such that the infusion ended 2 hours after the oral dose was administered.

- **PK Sampling Schedule**

- Plasma: Day 1: Predose (within 30 minutes before oral dosing), 30, 60, 90, 105, 110, 115, 120, 125, 130, 135, 140, 145, and 150 minutes, and 3, 3.5, 6, 9, 12, 18, 24, 30, 36, 48, 72, and 96 hours post oral lesinurad dose.

- Urine: 0 to 6, 6 to 12, 12 to 24, 24 to 36, 36 to 48, 48 to 60, 60 to 72, and 72 to 96 hours post oral dose.

- **Results**

Plasma PK parameters of lesinurad, [14C]lesinurad, and total radioactivity were evaluated following a single oral dose of lesinurad 400 mg and 15-minute 100 µg IV infusion of [14C]lesinurad under the fasted condition. Median overlaid dose-normalized plasma concentrations profiles of lesinurad and [14C]lesinurad are presented in Figure 59. The summary of absolute bioavailability of lesinurad is presented in Table 84.

Absolute bioavailability for each subject was determined based on the dose normalized AUCinf for lesinurad, comparing oral administration with iv administration. The mean actual IV dose administered was 108.45 µg, and oral dose was 400 mg. The absolute bioavailability was estimated to be 101% (Table 84).

Table 84: Summary Absolute Bioavailability of Lesinurad Following a Single Oral Dose of 400 mg Lesinurad and Intravenous Infusion of 100 µg [14C]Lesinurad (Geometric Mean [90% Confidence Interval])

	AUC_∞ (IV) (ng·hr/mL)	AUC_∞ (oral) (µg·hr/mL)	Absolute bioavailability (%)
N	10	10	10
Geomean	18.1	67.3	101
CI 90% lower	15.0	55.5	95.4
CI 90% upper	22.0	81.7	106

(Source – Table 11-4, Study 131 report)

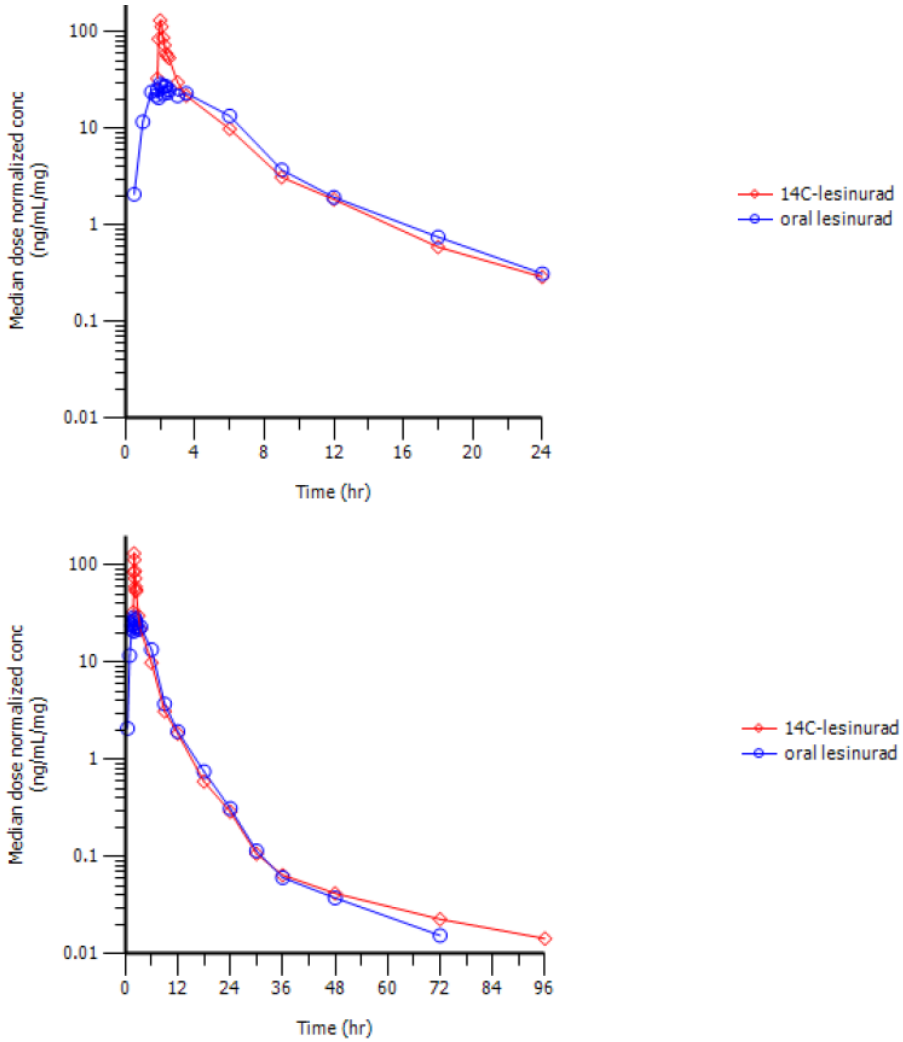


Figure 59. Median Dose-Normalized Concentration (ng/mL/mg) Profiles of Lesinurad and [14C]Lesinurad in Plasma Following a Single Oral Dose of Lesinurad 400 mg with 100 µg Intravenous Infusion of [14C]Lesinurad
(Source: Figure 11-1 , study report 131)

The median overlaid plasma concentrations profiles of [14C]lesinurad and total radioactivity are presented in Figure 60. The geometric mean plasma lesinurad-to-total radioactivity ratio for AUC∞ was 0.571, indicating that the majority of circulating material was lesinurad.

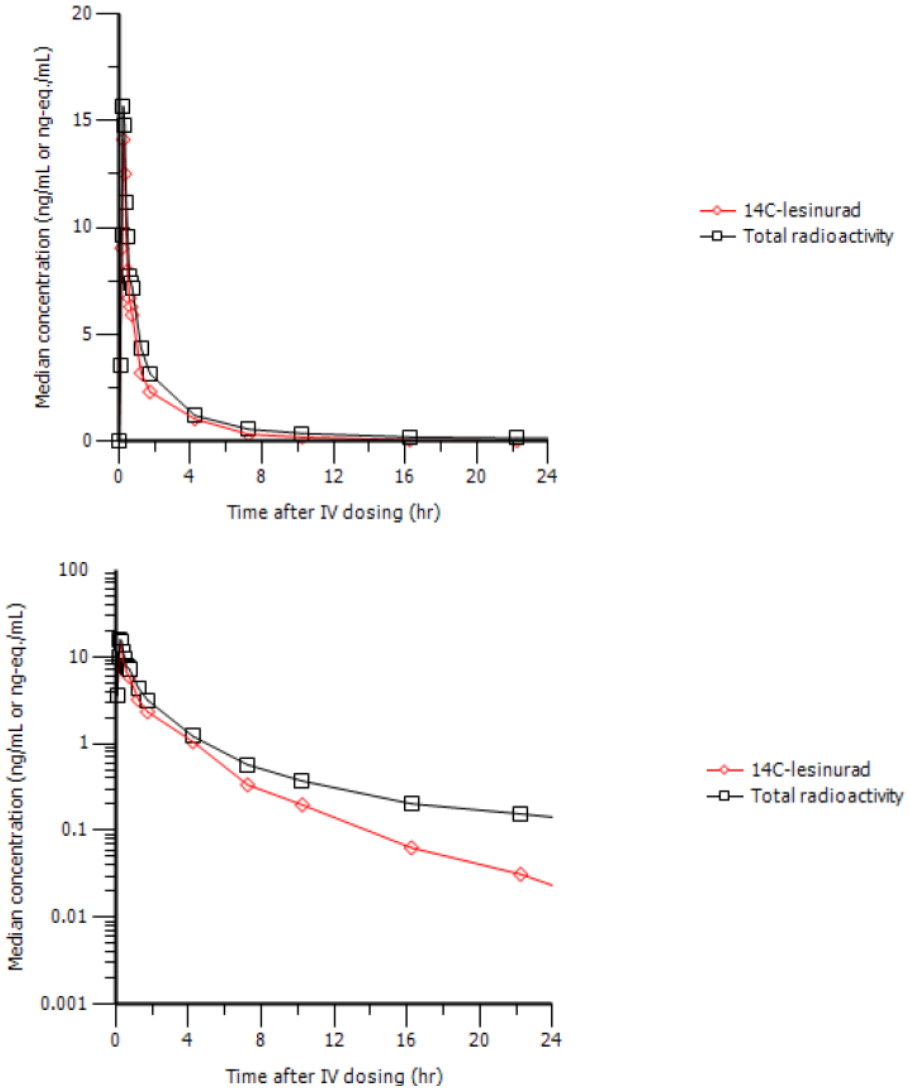


Figure 60. Median Concentration Profiles of [14C]Lesinurad (ng/mL) and Total Radioactivity (ng-eq./mL) in Plasma Following 100 µg Intravenous Infusion of [14C]Lesinurad (0 to 24 Hours Postdose)
(Source: Figure 11-2, study report 131)

- **Conclusions**

The absolute oral bioavailability for lesinurad was determined to be approximately 101% (90% CI: 95.4% to 106%), indicating that lesinurad is completely absorbed into the system with a lack of gut wall and hepatic first pass metabolism.

21.Relative Bioavailability (129, 132, 109)

Trial # 129

Title: A Phase 1, Randomized, Open-Label, Crossover Study in Healthy Adult Male Subjects to Assess the Relative Bioavailability of Lesinurad Tablets Manufactured at Two Different Sites

- **Objectives**

- To assess the relative bioavailability of lesinurad tablets, manufactured at 2 different sites, in fed and fasted states based on the PK evaluation in adult male subjects.

- **Study design and treatment schedule:**

A Phase 1, randomized, open-label, 2-treatment, 2-sequence, 2-period, balanced single-dose, crossover, PK study in 72 healthy, adult male subjects (18 subjects per cohort) designed to assess the relative bioavailability of lesinurad tablets, manufactured at 2 different sites.

- **PK Sampling Schedule**

Day 1 and Day 5: Predose (≤ 30 minutes prior to breakfast [or before lesinurad dose in fasting cohorts]), 20, 40, 60, 80, 100, 120, 140, 160, 180, 200, and 220 minutes, and 4, 4.5, 5, 5.5, 6, 8, 10, 12, 14, 24, 36, 48, 60, and 72 hours postdose.

- **Results and Conclusions**

Lesinurad Lot B manufactured at Site 2 (AstraZeneca AB) demonstrated comparable bioavailability with the Site 1 lot under both fasted and fed conditions (Table 85). The geometric mean ratios for Cmax and AUC of Lot B relative to the Site 1 lot were both approximately 100% under the fasted condition. Under the fed condition, the geometric mean ratios for Cmax and AUC were approximately 101% and 95%, respectively. The 90% CIs for the geometric mean ratios for both Cmax and AUC were wholly contained within the 80% to 125% bioequivalence limits under both fasted and fed conditions.

Table 85. Summary of Results from Relative Bioavailability Study 129 – Manufacturing Site Comparison for Lesinurad 400 mg Tablets

Cohort (Food, N)	Manufacturing Site (Lot Number)	Comparison: Ratio of Geometric Least Squares Means (90% CI)		
		AUC_{∞}	AUC_{last}	C_{max}
Cohort 3 (Fasted, N=17)	Test: AstraZeneca AB (ELAD) Reference: (b) (4) (12A015)	99.7% (89.9-111%)	99.8% (90.0-111%)	100% (85.0-118%)
Cohort 4 (Fed, N=18)	Test: AstraZeneca AB (ELAD) Reference: (b) (4) (12A015)	95.3% (89.9-101%)	95.3% (89.9-101%)	101% (86.1-119%)

(Source: Table 5, summary of biopharm)

- **Conclusions**

Evaluation of results from Cohorts 3 and 4 indicate that the drug product produced at both manufacturing sites, when manufactured within the proposed manufacturing process parameters, were bioequivalent.

Trial # 132

Title: A Phase 1, Randomized, Open-Label, Crossover Study to Assess the Bioequivalence of Lesinurad Tablets from Two Manufacturing Sites in Healthy Adult

Male Subjects

- **Objectives**

  To assess the bioequivalence of lesinurad tablets, manufactured at 2 different sites, in the fasted state based on the pharmacokinetic evaluation in healthy adult male subjects.

- **Study design and treatment schedule:**

a Phase 1, randomized, open-label, 2-treatment, 2-sequence, 2-period, balanced single-dose, crossover, PK study in healthy adult male subjects designed to assess the bioequivalence of lesinurad tablets, manufactured at 2 different sites. Subjects were randomized to 1 of 2 treatment sequences as follows:
Sequence A (n = 27):
Day 1: Lesinurad 400 mg (manufactured at Site 1)
Day 5: Lesinurad 400 mg (manufactured at Site 2)
Sequence B (n = 27):
Day 1: Lesinurad 400 mg (manufactured at Site 2)
Day 5: Lesinurad 400 mg (manufactured at Site 1)
All doses of study medication were administered in the fasted state orally with 240 mL water.

- **Test product:** Subjects received lesinurad 400 mg tablets manufactured at Site 1 ([redacted] (b) (4); reference product) and lesinurad 400 mg tablets manufactured at Site 2 (AstraZeneca AB; test product) according to the treatment sequences.

- **Sampling Schedule**

PK Sampling Schedule

Blood samples were collected at the following timepoints in relation to dosing of oral lesinurad on Days 1 and 5: Predose (≤ 30 minutes prior to dosing), 20, 40, 60, 80, 100, 120, 140, 160, 180, 200, and 220 minutes, and 4, 4.5, 5, 5.5, 6, 8, 10, 12, 14, 24, 36, 48, 60, and 72 hours postdose.

Genotyping:

For those subjects who gave informed consent to optional genetic testing, a whole blood sample was collected for possible single gene and whole genome genetic sequencing and single nucleotide polymorphism analysis.

- **Results and Conclusions**

Due to a significant Group-by-Treatment interaction for Cmax (p = 0.0263), bioequivalence was assessed for each dosing group. In Group 1, the 90% CIs around the geometric mean ratios for both Cmax and AUC∞ were wholly contained within the bioequivalence limits (80% to 125%, Table 86). In Group 2, the 90% CIs around the geometric mean ratios for AUC were wholly contained within the 80% to 125% bioequivalence limits, but not for Cmax as the lower limit was 79.95%. The results from the subgroup analyses were generally consistent with results of the full analysis of all subjects, and are supportive of conclusions based on the full analysis.

Table 86. Geometric Least Squares Mean and Geometric Mean Ratio (90% Confidence Interval) of Key Lesinurad Plasma Pharmacokinetic Parameters for Lesinurad Manufactured at Site 2 Relative to Site 1 Following Administration of Lesinurad 400 mg in Healthy Adult Male Subjects

Group	n	Site (Lot)	Parameter	Geometric LS Mean	Geomean Ratio (90% CI)
All	53	Site 2 (ELAD) relative to Site 1 (12A015-P1)	C_{max} (µg/mL)	21.8 22.5	96.79% (90.42% - 103.61%)
			AUC_{∞} (µg·hr/mL)	73.7 74.1	99.34% (94.82% - 104.07%)
Group 1	26	Site 2 (ELAD) relative to Site 1 (12A015-P1)	C_{max} (µg/mL)	23.2 21.8	106.13% (97.37% - 115.68%)
			AUC_{∞} (µg·hr/mL)	72.2 69.3	104.18% (97.58% - 111.22%)
Group 2	27	Site 2 (ELAD) relative to Site 1 (12A015-P1)	C_{max} (µg/mL)	20.5 23.1	88.61% (79.95% - 98.20%)
			AUC_{∞} (µg·hr/mL)	75.2 79.2	94.90% (88.69% - 101.54%)

Abbreviations: AUC_{∞} = AUC from time zero to infinity; CI = confidence interval; C_{max} = maximum observed concentration; LS = least squares; n = number of subjects with data.
(Source: Table 1, study 132 synopsis)

- **Conclusions**

The drug product produced at both manufacturing sites were bioequivalent.

Trial # 109, capsule vs crystalline free acid tablet

Title: A Phase 1, Open-Label, Single Dose, Relative Bioavailability Cross-Over Study to Assess the Free Acid and the Immediate Release Dose Formulations of Lesinurad in Healthy Adult Male Volunteers

- **Objectives**
  - To investigate the single-dose pharmacokinetic (PK) profile and relative bioavailability of the free acid (FA) dose formulation of lesinurad (RDEA594) and immediate release (IR) formulation in healthy adult male volunteers.
  - To evaluate the effect of a low-fat meal on the PK profile of lesinurad formulations.

- **Study design and treatment schedule:**

A single-center, open-label, cross-over study in healthy adult male volunteers. The study was to include 3 segments (Segments A, B, and C) with 4 treatment periods per segment. 8 subjects were randomized to each segment.

- **Test product:** In each study segment, an FA tablet formulation was evaluated relative to the sodium salt IR capsule formulation. FA tablet formulation used in Segment C was later used in the Phase 3 clinical trials. Therefore, PK result in Segment C was reviewed here.

- **Sampling Schedule**

PK Sampling Schedule

Blood samples were collected for the analysis of plasma concentrations of lesinurad at the following timepoints on Day 1: predose, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, 30, 36, and 48 hours post dose.

Urine samples were collected for the analysis of urinary concentrations of lesinurad at the following timepoints on Day 1: 0 to 6, 6 to 12, 12 to 24, 24 to 30, 30 to 36, and 36 to 48 hours postdose.

Pharmacodynamics:

Blood samples were collected for the analysis of serum urate and creatinine at the following timepoints on Day 1: predose, 6, 12, 16, 24, 30, 36, and 48 hours post dose.

Urine samples were collected for the analysis of uric acid and creatinine at the following timepoints on Day 1: 0 to 6, 6 to 12, 12 to 24, 24 to 30, 30 to 36, and 36 to 48 hours postdose.

- **Results**

PK results

In Segment C, Cmax for lesinurad 400 mg in the fed state was 15.4 and 15.2 µg/mL for the FA tablet and sodium salt IR capsule formulations, respectively. In Segment C, AUC0-∞ for lesinurad 400 mg in the fed state was 61.6 and 63.0 µg·hr/mL for the FA tablet and sodium salt IR capsule formulations, respectively (Table 87).

Table 87. Plasma Pharmacokinetics of Lesinurad Following Single Doses of Lesinurad Administered in Segments C

Segment/ Period	Dose, Formulation, Meal Status	Median (range)	Geometric Mean (95% CI)			
		T_{max}[a] (hr)	C_{max} (µg/mL)	AUC_{0-24} (µg·hr/mL)	AUC_{∞} (µg·hr/mL)	$t_{1/2}$ (hr)
C/1	200 mg FA, fed	4.00 (1.50-6.00)	6.11 (4.83-7.73)	28.1 (20.8-37.9)	28.5 (20.9-38.7)	4.94 (3.93-6.21)
C/2	400 mg FA, fed	3.00 (1.50-4.00)	15.4 (13.3-17.9)	60.7 (47.7-77.3)	61.6 (48.1-78.9)	6.91 (4.88-9.79)
C/3	400 mg IR, fed	2.00 (1.50-3.00)	15.2 (11.9-19.5)	61.9 (45.0-85.2)	63.0 (45.6-86.9)	9.48[b] (6.39-14.1)
C/4	600 mg FA, fed	4.00 (2.00-5.00)	21.9 (17.6-27.3)	95.6 (74.1-123)	97.7 (75.1-127)	8.36[b] (6.19-11.3)

(Source: Table11-1, study 109 CSR)

PD results

Lowering of sUA following administration of the FA tablet was similar to that of the sodium salt IR capsule in both the fed and fasted states, respectively. Dosing in the fed state modestly increased the sUA lowering effect of all lesinurad formulations tested.

- **Conclusions**

Systemic exposure of lesinurad was similar following oral administration of the sodium salt IR capsule and the phase 3 FA tablet formulation.

22.Food Effect with phase 3 formulation

Trial # 121

Title: A Phase 1, Open Label Study Assessing the Effect of Food and Antacids on

the Pharmacokinetics and Pharmacodynamics of Lesinurad in Healthy Adult Male Subjects

- **Objective**
  - To assess the effect of a high fat/high calorie meal on the PK of lesinurad in healthy, adult male subjects.
  - To assess the effect of a high fat/high calorie meal on the PD of lesinurad in healthy, adult male subjects.

- **Study design –** This was a randomized, open-label single-dose study in healthy adult male subjects with a required Food Effect Phase and Antacid Effect Phase, and an Optional Exploratory Phase. Sixteen subjects were randomized and entered the study; 15 subjects completed the Food and Antacid Effect Phases and 13 subjects completed the Optional Exploratory Phase.

  The Food Effect Phase was a 2-period, 2-treatment, 2-sequence balanced, single-dose, crossover design. Only results related to food effect are reviewed here. The antacid effect was evaluated under fast state in this study. See study 130 for review of DDI with antacid under fed condition.

  Subjects received single doses of lesinurad in the morning on Days 1 and 6 for food Effect assessment.

- **Test product:** Lesinurad was administered as a 400 mg tablet

- **Sampling Schedule**

PK Sampling Schedule

- Plasma samples were to be collected at the following timepoints in relation to dosing of lesinurad: predose (within 30 minutes before dosing) and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, 48, 60, and 72 hours postdose.

- Urine samples (total catch) were to be collected over the following timed intervals in relation to dosing of lesinurad: -12-0 hours predose and 0-6, 6-12, 12-24, 24-36, 36-48, 48-60, and 60-72 hours postdose.

PD Sampling Schedule

Blood tests to measure concentrations of creatinine and uric acid were to be collected at the following timepoints in relation to dosing of lesinurad: -12 hours predose, 0, 6, 12, 24, 36, 48, 60, and 72 hours postdose. Urine (total catch) for evaluating concentrations of creatinine, uric acid and possibly other measurements were to be collected over the following timed intervals in relation to dosing of lesinurad: -12-0 hours predose and 0-6, 6-12, 12-24, 24-36, 36-48, 48-60, and 60-72 hours postdose.

Genotyping

Blood samples were collected for possible analysis of cytochrome P450 2C9 genotype.

- **Results and Conclusions**

PK results

Administration with a high-fat meal decreases lesinurad Cmax by 18% but does not alter AUC as compared with fasted state (Table 88). Under the fed condition, median Tmax occurred at 2 hours, approximately 0.5 hours slower compared to the fasting condition (Figure 61).

Table 88. Geometric Least Squares Means and Geometric Mean Ratios (90% Confidence Interval) of Lesinurad Plasma Pharmacokinetic Parameters under the Fed versus Fasting Condition

Parameter	N	GeoLSM		Geomean Ratio (90% CI)	p-value		
		Fed	Fasting	(Fed/Fasting)	Treatment[a]	Period	Sequence
C_{max} (µg/mL)	15[b]	16.2	19.9	81.6% (66.6%-99.8%)	0.0976	0.7728	0.3763
AUC_{last} (µg·hr/mL)	15[b]	62.7	68.0	92.2% (83.6%-102%)	0.1607	0.3278	0.4928
AUC_{∞} (µg·hr/mL)	15[b]	62.9	68.3	92.1% (83.6%-102%)	0.1589	0.3089	0.4905

(Source: Table 11.2, CSR121)

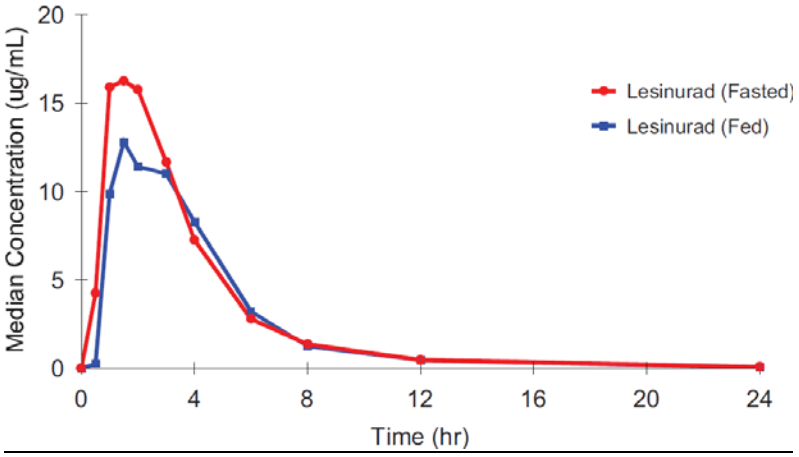


Figure 61. Median Plasma Concentration Profiles of Lesinurad (µg/mL) Following a Single 400 mg Oral Dose of Lesinurad to Healthy Male Subjects under Fed or Fasting Condition from 0 to 24 Hours Postdose

(Source: Figure 1, Compliance and drug concentration data, study 121)

PD results

The sUA lowering effect of lesinurad was enhanced in the fed state (43% maximum reduction from baseline and 31% reduction at 24 hours postdose) as compared with the fasted state (36% maximum reduction from baseline and 26% reduction at 24 hours postdose, Table 89). The effect of food on sUA following treatment was also observed with various other formulations of lesinurad was examined in Studies 101, 102, and 109.

Table 89: Statistical Analysis of the Percentage Change from Baseline in Serum Urate Concentrations Following a Single 400 mg Oral Dose of Lesinurad to Healthy Adult Male Subjects Under Fed Versus Fasting Conditions

Lesinurad Dose (mg)	Parameter	Condition	LS Mean	N	Difference of LS Means (95% CI)[a]	P-value
400	$E_{max, CB}$ (%)	Fed	-43.05	15[b]	-7.07 (-10.00, -4.15)	< 0.001[c]
		Fasted	-35.98	16		
	$E_{24hr, CB}$ (%)	Fed	-31.10	15[b]	-5.56 (-8.93, -2.18)	0.001[c]
		Fasted	-25.54	16		

Abbreviations: CI, confidence interval; $E_{24hr, CB}$, 24 hour postdose percent change from baseline; $E_{max, CB}$, maximum observed percentage change from baseline in serum urate concentrations; LS, least squares; N, number of subjects
[a] Fed minus fasted.
[b] Subject 103 discontinued prior to Day 6 and was excluded from the statistical analysis.
[c] Statistically significant at 5% level.

(Source – Table 14.2.2.1, Study 121 CSR)

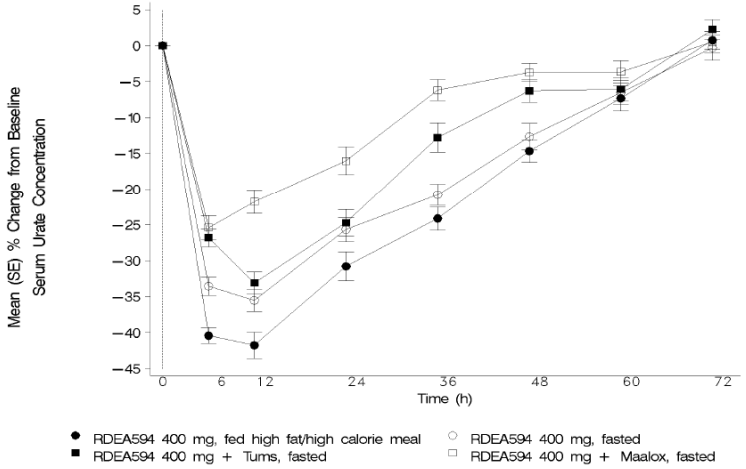


Figure 62. Mean Serum Urate Concentration % Change from Baseline
(Source: Figure 14.2.2, CSR121)

The renal handling of UA following lesinurad administration was shown in Table 90. The FEUA and CLur appear to slightly higher under fed states compared to fast states during 6-12 h post dose. Consistent with the time course of lesinurad upon sUA values, both the FEUA and CLUR were maximally increased over the 0 to 6 hour period following lesinurad administration with significant pharmacologic effects still observed 6 to 12 hours following dosing before declining to baseline levels at 12 to 24 hours following dosing.

Table 90: Summary of Fractional Excretion of Uric Acid in Urine and Renal Clearance of Uric Acid Following a Single 400 mg Oral Dose of Lesinurad to Healthy Adult Male Subjects under the Fed versus Fasting Condition

Fractional Excretion of Uric Acid (FEUA, %)				
Treatment	**-12 to 0 h**	**0 to 6 h**	**6 to 12 h**	**12 to 24 h**
Lesinurad, 400 mg fasted (N=16)	5.08 (4.57, 5.59)	26.3 (23.4, 29.3)	14.1 (11.6, 16.6)	5.51 (4.87, 6.15)
Lesinurad, 400 mg fed (N=15[a])	5.26 (4.70, 5.82)	25.6 (21.4, 29.8)	16.6 (12.7, 20.6)	6.03 (4.77, 7.28)
Uric Acid Renal Clearance (CL_{UR}, mL/min)				
Treatment	**-12 to 0 h**	**0 to 6 h**	**6 to 12 h**	**12 to 24 h**
Lesinurad, 400 mg fasted (N=16)	5.74 (4.81, 6.67)	32.7 (28.2, 37.3)	16.4 (14.7, 18.2)	6.41 (5.41, 7.40)
Lesinurad, 400 mg fed (N=15[a])	6.26 (5.50, 7.01)	37.7 (31.4, 44.0)	22.0 (16.2, 27.9)	7.31 (5.67, 8.95)

(Source – Table 11.10, Study 121 CSR.)

- **Conclusions**

The sUA lowering effect of lesinurad was enhanced in the fed state as compared with the fasted state. Therefore, lesinurad was administered in the fed state in all Phase 2 and Phase 3 studies.

PHARMACODYNAMICS

23.Monotherapy

Study # 201

Title: Randomized, Double-Blind, Multicenter, Placebo-Controlled, Dose Titration, Safety and Pharmacodynamics Pilot Study of RDEA594 Versus Placebo and Open-Label Allopurinol in Hyperuricemic Subjects with Symptomatic Gout

- **Objective:**
  - To compare the proportion of subjects whose sUA level is <6.0 mg/dL following 2 weeks of continuous treatment with RDEA594 compared to allopurinol and placebo for Cohort 1.
  - To evaluate the percent reduction from baseline in sUA levels following 2 weeks of continuous treatment with RDEA594 in combination with allopurinol for Cohort 2.
  - To evaluate the pharmacokinetics, safety and tolerability of RDEA594 in combination with allopurinol in subjects with gout for Cohort 2 only.

- **Study design –** This was a randomized, double-blind, multicenter, placebo-controlled, dose titration, safety and pharmacodynamics pilot study of RDEA594 versus placebo and open-label allopurinol (Cohort 1) and RDEA594 in combination with allopurinol versus continued allopurinol alone (Cohort 2) in hyperuricemic subjects with symptomatic gout. A total number of 26 subjects

were planned to be enrolled and randomized to receive treatment in one of following cohorts:

- Cohort 1: 21 subjects were randomized to receive RDEA594 200 mg, placebo, or allopurinol 300 mg in a 2:1:1 ratio for 2 weeks
- Cohort 2: 5 subjects were randomized to receive RDEA594 200 mg x 1 week followed by RDEA594 400 mg + allopurinol 300mg x 1 week, or placebo + allopurinol x 2 weeks in a 5:1 ratio

- **Test product:** Lesinurad was provided as 50 mg capsules for cohort 1 and 100 mg capsules for cohort 2.

- **Sampling Schedule**

PK Sampling Schedule

- Blood samples for the analysis of RDEA594, allopurinol, or oxypurinol at Baseline (Day 1: 1 hour and 8 hours postdose), Day 8 (trough, 1 hour and 8 hours postdose), Day 9 (24 hours after the Day 8 dose), Day 14 (trough and 8 hours postdose), and Day 15 (24 hours after the Day 14 dose).

- Twenty-four hour urine collections began on Day -1, Day 8, and Day 14.

PD Sampling Schedule

Serum urate levels were obtained at Screening, Day -7 (for Cohort 2 subjects prior to the first dose of allopurinol), Days 1 and 8 (predose and 1 and 8 hours postdose), Day 9 (24 hours after the Day 8 dose), Day 14 (predose and 8 hours postdose), Day 15 (24 hours after the Day 14 dose), and at follow-up 1 week postdose or upon early discontinuation from the study. The 24-hour urine samples were used to measure urine urate excretion and were collected on Day -1 (ending on Day 1), Day 8 (ending on Day 9), and Day 14 (ending on Day 15).

- **Results and Conclusions:**

PK results

Median RDEA594 plasma concentrations increased with increased dose, as concentrations at the 400 mg dose level were higher than observed at corresponding sample collection time points at the 200 mg dose level.

Median trough plasma concentration of allopurinol was below detectable levels across all sampling days in both single-agent treatments as well as when combined with RDEA594. Median trough plasma concentrations of oxypurinol decreased by approximately 30% and 40% at Day 8 and 14, respectively, when RDEA594 was added to allopurinol treatment (Table 91).

Table 91: Summary of Plasma Allopurinol and Oxypurinol Concentrations (µg/mL) in Cohort 2

	Day 1[a]			Day 8[a]				Day 14[a]		
	0 hours	1 hour	8 hours	0 hours	1 hour	8 hours	24 hours	0 hours	8 hours	24 hours
	Analyte= allopurinol, Treatment = RDEA594+allopurinol, Cohort 2									
N	5	5	4	5	5	3	5	5	5	5
Median (range)	BLQ (BLQ, BLQ)	0.898 (0.112, 1.97)	0.0812 (0.0595, 0.0903)	BLQ (BLQ, BLQ)	0.737 (0.178, 1.92)	0.0542 (BLQ, 0.126)	BLQ (BLQ, 0.151)	BLQ (BLQ, BLQ)	0.0502 (BLQ, 0.151)	BLQ (BLQ, BLQ)
	Analyte= allopurinol, Treatment = allopurinol, Cohort 2									
N	1	1	1	1	1	1	1	0	0	0
value	BLQ	0.928	BLQ	BLQ	1.29	BLQ	BLQ	NA	NA	NA
	Analyte = oxypurinol, Treatment = RDEA594+allopurinol, Cohort 2									
N	5	5	4	5	5	4	5	5	5	5
Median (range)	9.08 (6.70, 12.6)	11.2 (8.04, 14.4)	10.9 (8.69, 15.4)	6.16 (4.70, 13.1)	7.95 (6.39, 14.2)	9.03 (6.83, 13.7)	6.04 (4.87, 9.52)	5.15 (4.54, 8.09)	7.75 (7.02, 12.4)	4.97 (4.02, 8.99)
	Analyte = oxypurinol, Treatment = allopurinol, Cohort 2									
N	1	1	1	1	1	1	1	0	0	0
value	9.22	10.2	13.8	12.4	14.0	15.7	10.6	NA	NA	NA

[a] RDEA594 dosing for the combination treatment (RDEA594 + allopurinol) was as follows: Day 1, initial RDEA594 200 mg dose; Day 8, initial escalated RDEA594 400 mg dose; and Day 14, final RDEA594 400 mg dose.

(Source: Table 11:2, CSR 201)

PD results

In cohort 1, Lesinurad 200 mg QD monotherapy and allopurinol 300 mg QD were compared with placebo over 14 days of treatment. The sUA levels were decreased by 34% and 45% after 2 weeks of treatment with RDEA594 and allopurinol, respectively, while treatment with placebo resulted in only a minor change in sUA levels (4%). Also, 46% and 100% of subjects receiving RDEA594 and allopurinol, respectively, achieved serum urate levels < 6.0 mg/dL after 2 weeks of treatment; no subjects (0%) receiving placebo achieved serum urate levels < 6.0 mg/dL.

In Cohort 2, 5 (100%) subjects in the RDEA594 + allopurinol treatment group had sUA levels < 6.0 mg/dL at Day 14; the one subject in the placebo + allopurinol treatment group did not achieve sUA levels < 6.0 mg/dL at study endpoint (Table 92).

Table 92: Proportion of Subjects With Serum Urate < 6.0 mg/dL, < 5.0 mg/dL, and < 4.0 mg/dL at Day 14 (Predose)

	Cohort 1			Cohort 2	
n (%)	Placebo N = 5	RDEA594 N = 11	Allopurinol N = 5	Placebo + Allopurinol N = 1	RDEA594 + Allopurinol N = 6
Serum urate < 6.0 mg/dL	0	5 (45.5)	5 (100)*	0	5 (100)[a]
Serum urate < 5.0 mg/dL	0	1 (9.1)	2 (40.0)	0	3 (60.0)[a]
Serum urate < 4.0 mg/dL	0	1 (9.1)	1 (20.0)	0	0

(Source: Table 11:5, CSR 201)

Table 93: Baseline Values and Percent Change From Baseline in Serum Urate at Day 14 (Predose)

	Cohort 1			Cohort 2	
	Placebo N = 5	RDEA594 N = 11	Allopurinol N = 5	Placebo + Allopurinol N = 1	RDEA594 + Allopurinol N = 6
Baseline Mean (SD) actual value (mg/dL)	9.16 (1.18)	9.15 (1.22)	8.94 (1.11)	11.80 (NA)	10.72 (0.82)
Day 14 Mean % change (SD)	3.54 (8.31)	-34.13 (6.71)	-44.77 (10.54)	-47.46 (NA)	-53.88 (7.31)
Least square mean Diff (95% CI)	-	-37.69 (-48.2; -27.2)*	-48.63 (-60.9; -36.3)*	-	-

(Source: Table 11:6, CSR 201)

The summary of mean % changes from baseline in fractional excretion of urate in urine on Days 9 and 15 is presented in **Table 94**. Mean % changes from baseline in FEUA (over the 0 to 24 hour interval) were increased following 8 days (102.3%) and 14 days (88.8%) of qd dosing with RDEA594 as a single agent. The addition of allopurinol did not appreciably alter the effects of RDEA594 on FEUA after 8 days (161.4%) or 14 days (90.6%). Mean % changes from baseline in FEUA were similar for subjects who received placebo or allopurinol, ranging from approximately 7-9% and 6-8%, respectively, across both time points.

Table 94: Summary of the Mean Percent Changes from Baseline in Fractional Excretion of Urate in Urine

Cohort	Treatment	Day	n	Mean FEUA% from Baseline 0-24 hour	95%CI
1	Placebo	9	5	9.0	-15.3, 33.4
		15	4	7.0	-38.0, 51.9
	RDEA594	9	11	102.3	57.8, 146.9
		15	8	88.8	47.1, 130.4
	Allopurinol	9	4	6.4	-41.5 54.3
		15	3	8.2	-110.9, 127.2
2	Placebo + Allopurinol	9	1	-11.2	NA
		15	0	NA	NA
	RDEA594 + Allopurinol	9	4	161.4	-31.1, 353.9
		15	5	90.6	54.6, 126.6

(Source: Table 11:9, CSR201)

- **Conclusions:**

Based on limited data of this study, lesinurad 200mg qd monotherapy has moderate uric acid lowering effect, but not as good as allopurinol 300 mg qd. Additional uric acid lowering activity was observed in the combination therapy of allopurinol and lesinurad, compared to lesinurad or allopurinol alone.

There was no significant PK interaction between lesinurad and allopurinol.

24.Combination therapy

Study # 203

Title: Randomized, Double-Blind, Multicenter, Placebo-Controlled, Combination Study to Evaluate the Safety, Efficacy and Potential Pharmacokinetic Interaction of RDEA594 and Allopurinol in Gout Patients with an Inadequate Hypouricemic Response with Standard Doses of Allopurinol (RDEA594-203)

- **Objective:**
  - To assess the percent reduction from Baseline in serum uric acid (sUA) levels following 4 weeks of continuous treatment with lesinurad (RDEA594) in combination with allopurinol compared to allopurinol alone (the placebo group) in gout patients with documented inadequate hypouricemic response with standard doses of allopurinol.
  - To compare the multiple-dose pharmacokinetics (PK) of allopurinol and oxypurinol in the absence versus presence of lesinurad co-administration.

Only results related to PK/PD are reviewed here. For efficacy and safety results, please refer to clinical review by Dr. Rosemarie Neuner.

- **Study design –** This was a randomized, double-blind, multicenter, placebo-controlled combination study with core study for 4 weeks. 136 subjects were treated with lesinurad (46, 42, and 48 in the 200 mg, 400 mg, and 600 mg qd groups, respectively) +allopurinol, and 72 subjects were treated with placebo+placebo. The PK substudy included 54 subjects: 10, 9, and 14 in the 200 mg, 400 mg, and 600 mg groups, respectively, and 21 in the placebo group.

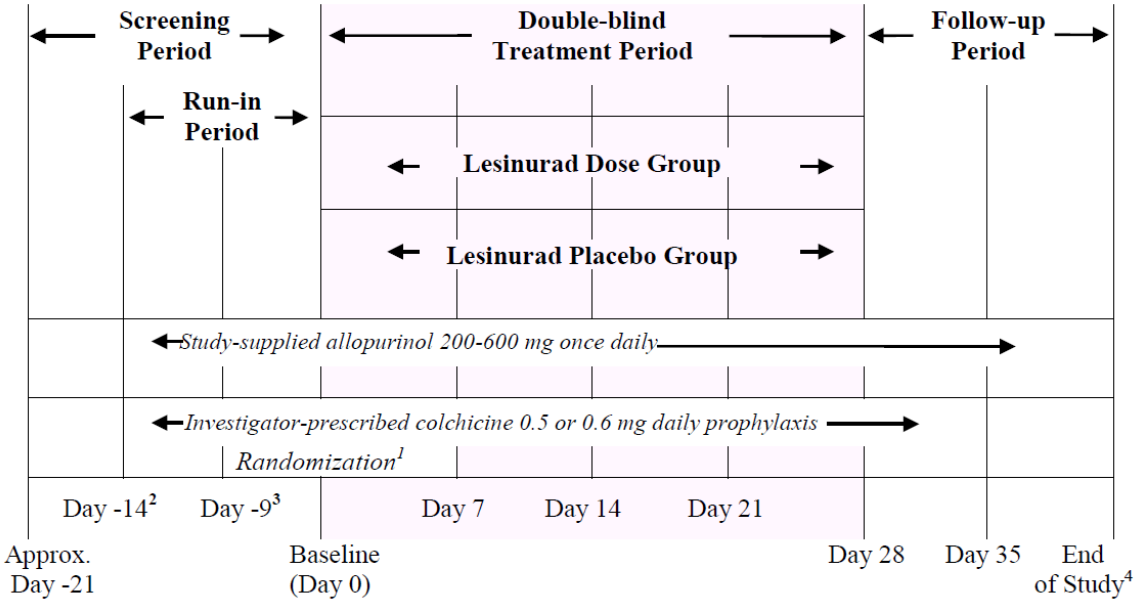


Figure 63. Study Design Diagram for Core Study
(Source: Figure 1, CSR203)

- **Test product:** Lesinurad was provided as 100 mg capsules.

- **Sampling Schedule**

PK Sampling Schedule

- Blood samples for the analysis of plasma RDEA594, allopurinol, oxypurinol and colchicine were collected on Days -1, 7, 14, and 21 at 0, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, and 24 hour time-points.

- Urine (total catch) samples for the analysis of RDEA594, allopurinol and oxypurinol were collected over the -24 to -18, -18 to -12, and -12 to 0 hour intervals on Day -1 and over the 0 to 6, 6 to 12, and 12 to 24 hour intervals on Days 7, 14, and 21.

PD Sampling Schedule

Blood and urine samples were collected for the measurement of serum and urinary concentrations of urate and creatinine. Blood samples for were collected on Days -1, 14, and 21 at 0, 6, 12, and 24 hour time-points. Urine samples obtained for pharmacokinetic analysis were also analysed for concentrations of xanthine and hypoxanthine to evaluate the impact of RDEA594 on the activity of allopurinol/oxypurinol.

- **Results and Conclusions:**

PK results

Following 4-week multiple qd doses of lesinurad, median trough plasma concentration of lesinurad in subjects receiving the final dose at 200 mg, 400 mg, or 600 mg on Day 28 showed variable lesinurad exposures that appeared to be roughly proportional to dose. The median lesinurad M6 metabolite to lesinurad molar ratios for Cmax and AUC0-24 were less than 0.5%, indicating that conversion of lesinurad to M6 is not a favored pathway for elimination of lesinurad in humans.

Based on comparison of the Day 13 and Day -1 results, lesinurad treatment (200 or 400 mg qd) did not appear to affect plasma PK or urinary excretion of allopurinol. Lesinurad treatment increased renal clearance of oxypurinol and reduced oxypurinol plasma exposure by approximately one-third (Table 95).

An effect of lesinurad on colchicine plasma exposure was not discernible in this study.

Table 95: Geometric Mean Ratios of Pharmacokinetics of Oxypurinol following Administration of 300 mg Allopurinol in the Absence or Presence of lesinurad (200 mg treatment group)

Allo	Treatment Group	RDEA594 dose	Day	N	Parameters	Geometric LSM	Geometric mean ratio (Day 13/Day-1)		
							Ratio (%)	90% CI Lower	90% CI Upper
300 mg	Placebo	0 mg	-1	14	C_{max}	11.3			
			13	14	(µg/mL)	13.4	118	89.9	156
		0 mg	-1	14	AUC_{0-24}	220			
			13	14	(µg·hr/mL)	255	116	90.5	148
	200 mg	0 mg	-1	9	C_{max}	14.0			
		200 mg	13	8	(µg/mL)	10.7	76.2	55.6	104
		0 mg	-1	9	AUC_{0-24}	289			
		200 mg	13	7	(µg·hr/mL)	196	67.8	46.7	98.3

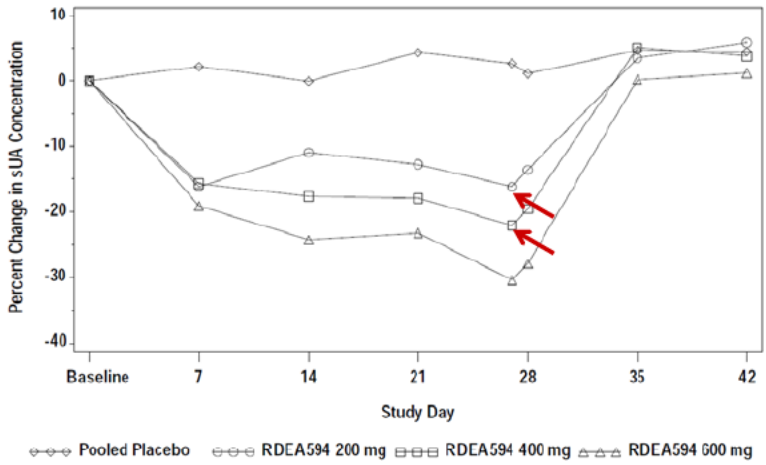
(Source: Table 12, CSR 203)

PD results

Three doses of lesinurad (200 mg QD, 400 mg QD, and 600 mg QD) were compared with placebo over 28 days of treatment. The percent change from baseline in sUA following 4 weeks of treatment (primary efficacy endpoint) was statistically significant for lesinurad plus allopurinol compared with placebo plus allopurinol (Figure 64, -22.09%, -26.53%, and -32.90% in the 200 mg, 400 mg, and 600 mg dose groups, respectively, compared with -2.51% in the placebo group; $p < 0.0001$ for all comparisons).

In the non-responder imputation analysis, 63.0%, 73.8%, and 79.2% of subjects in the 200 mg, 400 mg, and 600 mg groups, respectively, and 25.0% in the placebo group had sUA < 6.0 mg/dL at Day 27 ($p < 0.0001$ for all comparisons), suggesting that the 600 mg dose did not provide much added benefit compared with 400 mg in attaining target sUA values. Therefore, two doses of lesinurad (200 mg QD, 400 mg QD) were included in the Phase 3 program.

A.



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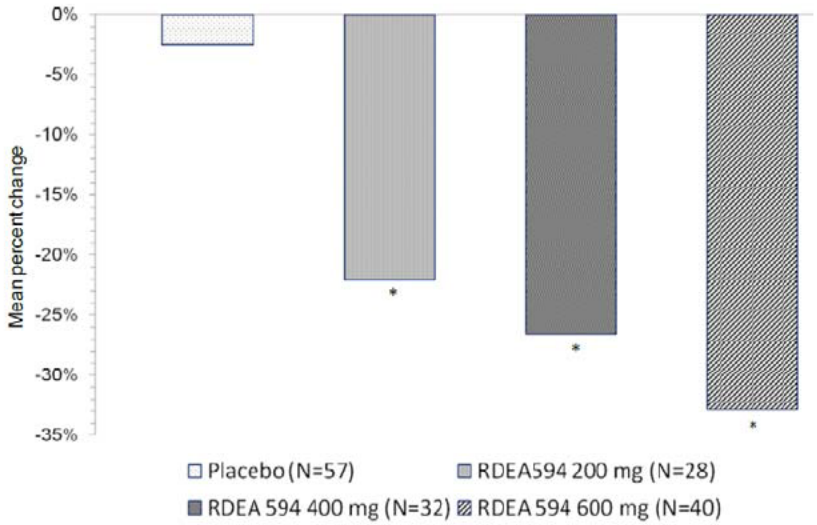

Figure 64. Mean Percent Change from Baseline in sUA Concentration (A) by Study Visit and (B) at day 27.

(Source: CSR rdea594-203, Fig 4, Fig5)

Results for the other 24-hour urine assessments of renal handling of uric acid are summarized as the mean percent change from Baseline to Day 28 in the ITT population in Table 96 below and are described briefly as follows.

Table 96: Summary of Selected 24-Hour Urine Collection Parameters as Mean Percent Change from Baseline to Day 28 (ITT Population)

Parameter (units as measured)	Lesinurad			Pooled Placebo
	200 mg (Cohorts 1A/1B/4)	400 mg (Cohort 2)	600 mg (Cohort 3)	
Urine urate (mg/24 hr)	22.3% (n=40)	33.5%[1] (n=38)	38.3% (n=41)	6.7% (n=63)
Urate clearance (mL/min)	43.72%[2] (n=38)	84.88%[1,2] (n=35)	118.82%[1,2] (n=40)	7.95% (n=61)
Fractional excretion of urate (%)[3]	50.73%[1,2] (n=38)	110.77%[1,2] (n=35)	128.97%[1,2] (n=40)	5.28% (n=61)

(Source: Table 7, CSR203)

- **Conclusions:**

Reductions in sUA and response rates increased with increasing dose. There is sUA variation during 24 hour postdose, relative to lesinurad dosing. As expected given the mechanism of action of lesinurad, FEUA was increased at all doses administered.

There was no significant PK interaction between lesinurad up to 600 mg and allopurinol. The additional uric acid lowering activity observed in the combination therapy is due to synergestic PD effect of allopurinol and lesinurad, and not increased exposure to allopurinol or oxypurinol.

4.3 FILING MEMO

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information about the Submission

	Information		Information
NDA/BLA Number	**207988**	**Brand Name**	**ZURAMPIC**
OCP Division (I, II, III, IV, V)	**II**	**Generic Name**	**lesinurad**
Medical Division	**Pulmonary, Allergy, and Rheumatology Products**	**Drug Class**	**URAT1 inhibitor**
OCP Reviewer	**Jianmeng Chen**	**Indication(s)**	**Gout**
OCP Team Leader	**Satjit Brar**	**Dosage Form**	**Tablet (200 mg)**
Pharmacometrics Reviewer	**Jianmeng Chen**	**Dosing Regimen**	**200 mg QD**
Pharmacometrics Team Leader	**Liang Zhao**		
Date of Submission	**12/29/2014**	**Route of Administration**	**Oral**
Estimated Due Date of OCP Review	**9/3/2015**	**Sponsor**	**Ardea Biosciences**
PDUFA Due Date	**12/29/2015**	**Priority Classification**	**N**

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**x**			
Tabular Listing of All Human Studies	**x**			
HPK Summary	**x**			
Labeling	**x**			
Reference Bioanalytical and Analytical Methods	**x**	**9**		
I. Clinical Pharmacology				
Mass balance:	**X**	**1**		Study 112
Isozyme characterization:	**X**			
Blood/plasma ratio:				
Plasma protein binding:	**X**			
Transporter specificity:	**X**			
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	**X**	**1**		Study 101
multiple dose:	**X**	**1**		Study 102
Patients-				
single dose:				
multiple dose:	**X**	**3**		Study 202, 203, 204
Dose proportionality -				
fasting / non-fasting single dose:	**X**	**1**		Study 101
fasting / non-fasting multiple dose:	**X**	**2**		Study 102, Study 117
Drug-drug interaction studies -				
In-vivo effects on primary drug:	**X**	**3+5**		Study 105 (febuxostat), 115(Tolbutamide), 121 (Antacid), 122 (fluconazole), 127(ranitidine), 130 (Antacid), 110 (allopurinol, colchicine), 111 (febuxostat)

In-vivo effects of primary drug:	X	10		Study 105 (febuxostat), 108 (sildenafil), 113 (Atorvastatin), 114 (Amlodipine), 116(Repaglinide), 123 (Warfarin), 126 (naproxen, indomethacin), 128 (metformin, furosemide), 110 (allopurinol, colchicine), 111 (febuxostat)
In-vitro:	X	18		
Subpopulation studies -				
ethnicity:	X	1		Study 125 (Japanese subjects)
gender:				
pediatrics:	X			
geriatrics:				
renal impairment:	X	2+1		Study 104, 120, 204
hepatic impairment:	X	1		Study 118
PD -				
Phase 2:	X	3		Study 202, 203, 204
Phase 3:	X	3		Study 301, 302, 304
PK/PD -				
Phase 1 and/or 2, proof of concept:	X			
Phase 3 clinical trial:	X			
Population Analyses -				
Data rich:				
Data sparse:	X	3		
II. Biopharmaceutics				
Absolute bioavailability	X	1		Study 131
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	X	3+2		Study 106 ((b) (4) formulation), 107 (sodium salt IR tablets vs capsule), 109(sodium salt IR vs FA IR tablet), 129 (AstraZeneca site vs (b) (4) site), 132 (AstraZeneca site vs (b) (4) site)
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies	X	3		Study 101, 102, and 109
Bio-waiver request based on BCS				
BCS class	X			BCS Class II weak acid
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies	X			Polymorphism in CYP2C9 assessed
QT studies	X	1		Study 117
Chronopharmacokinetics				
Pediatric development plan	NA			
Literature References				
Total Number of Studies		35		35 clinical studies (Including 30 clin pharm studies, 3 phase III studies, number of studies in black, and 2 studies assessing different formulation that will not be reviewed, number of studies in gray), and also in vitro studies and analytical report (number of studies in blue); duplicated study numbers shown in red

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/s/

JIANMENG CHEN
09/03/2015

ANURADHA RAMAMOORTHY
09/03/2015

CHRISTIAN GRIMSTEIN
09/03/2015

YANING WANG
09/03/2015

PING JI
09/03/2015

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information about the Submission

	Information		Information
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Isozyme characterization:	**X**			
Blood/plasma ratio:				
Plasma protein binding:	**X**			
Transporter specificity:	**X**			
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	**X**	**1**		Study 101
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Patients-				
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hepatic impairment:	**X**	**1**		Study 118
PD -				
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Phase 1 and/or 2, proof of concept:	**X**			
Phase 3 clinical trial:	**X**			
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Absolute bioavailability	**X**	**1**		Study 131
Relative bioavailability -				
solution as reference:				
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BCS class	**X**			BCS Class II weak acid
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QT studies	**X**	**1**		Study 117
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On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			X	
2	Has the applicant provided metabolism and drug-drug interaction information?	X			
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	X			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?	X			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?	X			
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	X			
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	X			
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	X			
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?		X		

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?
_____Yes__

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

- None

Submission in brief:

Indication and mechanism of action
Ardea Biosciences has submitted the NDA 207988 seeking the marketing approval for lesinurad, to be used as "*the treatment of hyperuricemia associated with gout in combination with a xanthine oxidase inhibitor."*

Lesinurad is a small molecule URAT1 inhibitor. Recommended dose is 200mg QD taken in the morning with food and water.

There have been several interactions between Agency and Sponsor to discuss clinical pharm program for the proposed product as listed in Table 1.

Table 1. Summary of Regulatory history relevant to clinical pharmacology

PNDA (Sep 2014)	Agreed on general clinical pharm studies adequate to support NDA filing
Communication (Nov 2013)	Agree on the DDI plan, no need for DDI studies with CYP2B6 and CYP2C19
EOP2 (Aug 2011)	• Agreed that sufficient information on characterization of elimination • Recommend subgroup analysis in phase 3 studies to assess risk benefit in renal impairment patients

Summary of information submitted
NDA 207988 consists of 22 in vitro studies with human materials, 30 Phase 1 studies (including 15 drug-drug interaction trials), 2 Phase 2b, and 3 Phase 3 studies (301, 302, and 304) in gout patients, and 3 meta-analysis and PopPK/PD reports. The clinical pharmacology information for lesinurad is mainly derived from Phase 1 studies as well as in vitro studies evaluating permeability, plasma protein binding, role of transporters, and potential for CYP 450 metabolic enzymes inhibition and induction. Population based modeling analyses including population pharmacokinetics analysis were performed to assess the effect of covariates and to understand the PK in special populations such as renal impairment patients. In addition, 9 bioanalytical reports have been submitted to measure the levels of parent compound and main metabolites.

Rational for 200 mg QD dose selection

-Dose frequency

The once daily dosing regimen is based on the PD effect of lesinurad. The PK half-life of lesinurad is 5 hours. The normal urate half-life (in absence of URAT1 inhibitor) ranges from approximately 20 hours to 56 hours. when lesinurad was administered alone, approximately 70% of the maximum effect was maintained at 24 hours. Maximal lowering of plasma uric acid (pUA) during steady state administration occurs at approximately 8 hours post-dose with a sustained urate lowering effect for 24 hours after dosing (Figure 1).

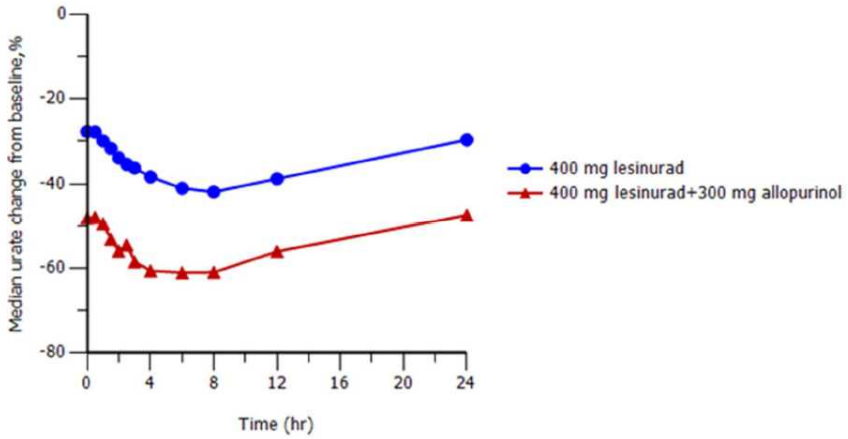


Figure 1. Median Plasma Uric Acid Change from Baseline Following Multiple QD Dosing of 400 mg Lesinurad on Steady State Day 7 (Study 110)

(Source: section 2.7.3, summary of clinical pharmacology, Figure 17)

-Dose

The doses for the phase III trials (200 mg QD, 400 mg QD) was selected based on the results from the phase II dose-finding studies 202 (monotherapy) and 203 (in combination with allopurinol). Phase 1 and 2 studies of lesinurad showed a direct relationship between lesinurad dose and sUA lowering, with doses of 100 mg qd and lower being relatively inactive and doses of 200 mg, 400 mg, and 600 mg qd showing dose-related effects on sUA and uUA. In study 203, 3 doses of lesinurad (200 mg QD, 400 mg QD, and 600 mg QD) were compared with placebo over 28 days of treatment.

The percent change from baseline in sUA following 4 weeks of treatment (primary efficacy endpoint) was statistically significant for lesinurad plus allopurinol compared with placebo plus allopurinol (-16.12%, -22.07%, and -30.35% in the 200 mg, 400 mg, and 600 mg dose groups, respectively, compared with +2.63% in the placebo group; $p < 0.0001$ for all comparisons, Figure 2). In the non-responder imputation analysis, 63.0%, 73.8%, and 79.2% of subjects in the 200 mg, 400 mg, and 600 mg groups, respectively, and 25.0% in the placebo group had sUA < 6.0 mg/dL at Day 27 ($p < 0.0001$ for all comparisons), suggesting that the 600 mg dose did not provide much added benefit compared with 400 mg in attaining target sUA values. Therefore, two doses of lesinurad (200 mg QD, 400 mg QD) were included in the phase III program.

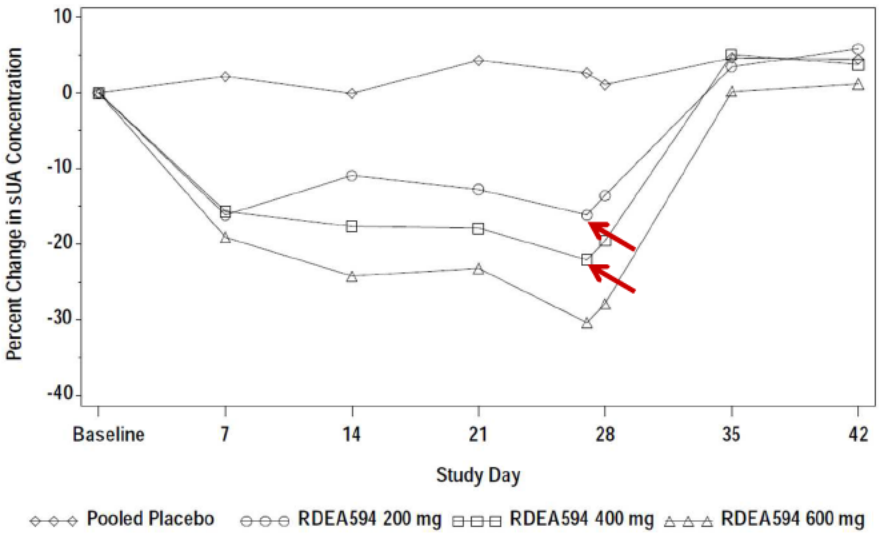


Figure 2. Mean Percent Change from Baseline in sUA Concentration by Study Visit
(Source: CSR rdea594-203, Fig 4)

Phase III studies indicated that lesinurad 400 mg qd was associated with acute uric acid nephropathy as evidenced by an increased incidence of sCr elevations and AEs of acute renal failure. Thus, it is concluded that lesinurad 200 mg is the most appropriate strength for which to seek approval.

Efficacy in Phase 3 trials

There are three Phase 3 studies supporting the efficacy and safety of lesinurad in gout patients (study 301, 302, and 304). All studies are randomized, double-blind, placebo controlled studies with primary endpoints at months 6. Study 301 and 302 assessed lesinurad in combination with allopurinol, and study 304 assessed lesinurad in combination with febuxostat. The submission of phase 3 efficacy and safety results is summarized in the medical (Dr. Rosemarie Neuner) and biostatistics (Dr. Yu Wang) reviews.

Effect of intrinsic/extrinsic factors

As per sponsor's proposal, lesinurad is recommended to be administered in the morning with food. No dose adjustments have been proposed based on studied intrinsic factors (Figure 3). Based on the population pharmacokinetic analysis, age, gender, race and ethnicity do not have a clinically meaningful effect on the pharmacokinetics of lesinurad. For hepatic impairment, no dose adjustment of is recommended. For renal impairment, sponsor recommended no dose adjustments for mild or moderate cases, and patients with severe renal impairment were not included in the phase 3 studies. As the risk/benefit is different in the renal impairment patients, the recommendation of lesinurad use in this population will be a major issue in the clinical pharmacology NDA review.

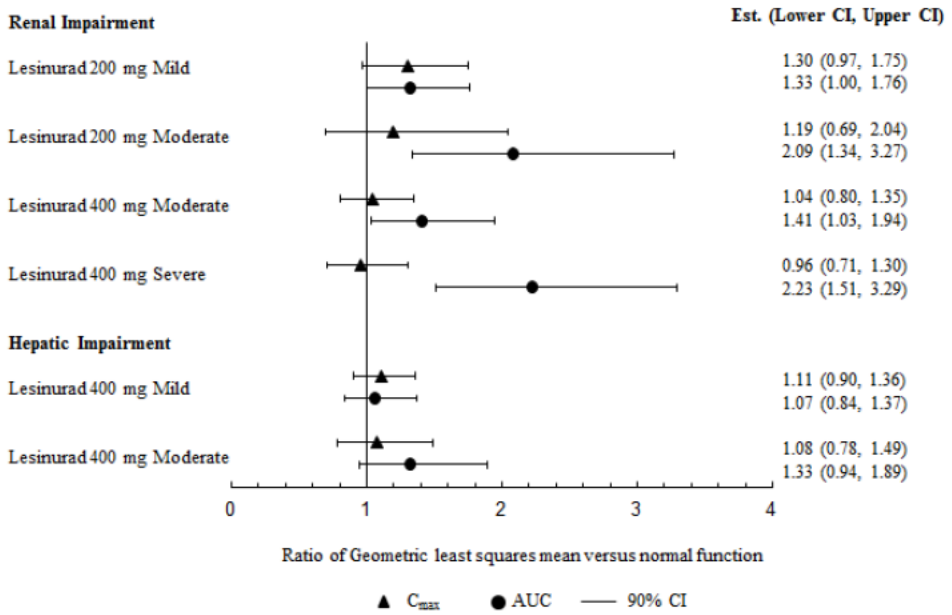
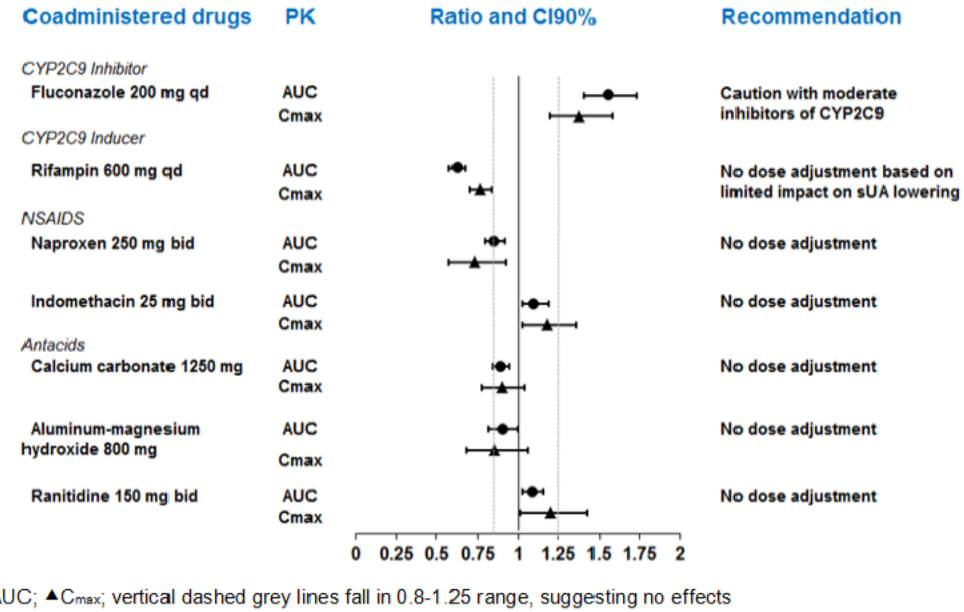


Figure 3. Effect of Renal and Hepatic Impairment on Lesinurad Pharmacokinetics: Point Estimates and 90% Confidence Intervals for Lesinurad Cmax and AUC

Summary of drug-interaction studies

-Effect of other drugs on Lesinurad

Lesinurad is a substrate of OAT1, OAT3, and CYP2C9. Figure 4 shows the effect of co-administered drugs on the pharmacokinetics of lesinurad.



● AUC; ▲Cmax; vertical dashed grey lines fall in 0.8-1.25 range, suggesting no effects

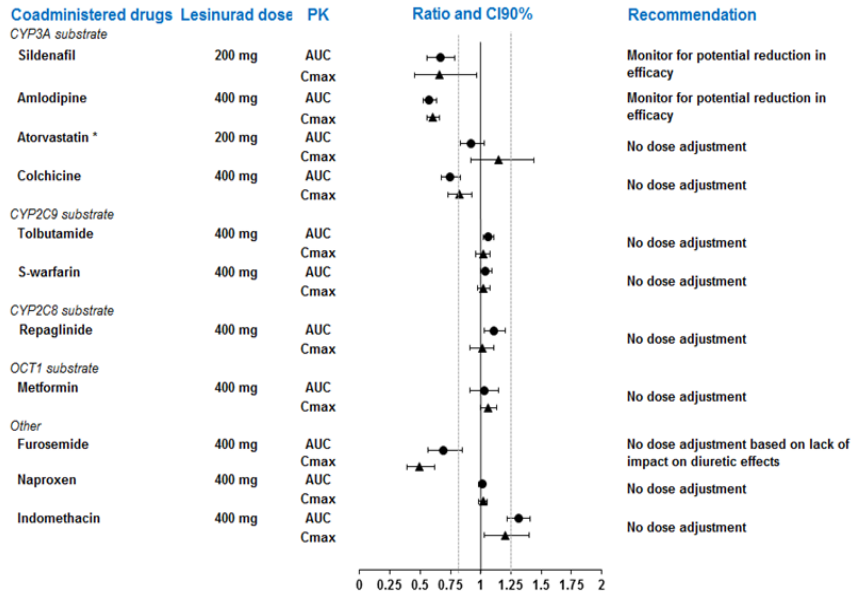
Figure 4: Effect of Co-Administered Drugs on the Pharmacokinetics of Lesinurad

-Effect of Lesinurad on other drugs

Lesinurad is an inducer of CYP3A and has no relevant effect on any other CYP enzyme for induction (CYP1A2, CYP2C8, CYP2C9, CYP2B6, or CYP2C19) or inhibition (CYP1A2, CYP2B6, CYP2D6, CYP2C8, CYP2C9, CYP2C19, or CYP3A4).

Lesinurad has no relevant effect on major drug transporters such as P-glycoprotein and organic anionic or cationic transporters (OAT1, OAT 3, OCT1, OCT2, OATP1B1, OATP1B3) and BCRP (breast cancer resistance protein).

Figure 5 shows the effect of lesinurad on co-administered drugs.



● AUC; ▲C_{max}; vertical dashed grey lines fall in 0.8-1.25 range, suggesting no effects; *total atorvastatin (atorvastatin and its active metabolites) were measured.

Figure 5: Effect of Lesinurad on the Pharmacokinetics of Co-Administered Drugs

Effect on QT interval

As per QT-IRT review (by Dr. Janice Brodsky, DARRT date 10/23/2012, IND102128), a thorough QT study (study 117) demonstrated the lack of effect of either a therapeutic or supratherapeutic dose of 400 mg and 1600 mg, respectively, in healthy subjects. The largest upper bounds of the 2-sided 90% CI for the mean difference between lesinurad and placebo were below 10 ms (Table 1), the threshold for regulatory concern as described in ICH E14 guidelines.

Table 1: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for Lesinurad and the Largest Lower Bound for Moxifloxacin (FDA Analysis)

Treatment	Time (h)	ΔΔQTcI (ms)	90% CI (ms)
Lesinurad 400 mg	2	2.9	(1.0, 4.8)
Lesinurad 1600 mg	6	3.5	(1.4, 5.7)
Moxifloxacin 400 mg	3	9.8	(7.9, 11.6)

* Multiple endpoint adjustment was not applied. The largest lower bound after Bonferroni adjustment for 4 timepoints is 7.9 ms.

Pediatrics development plan
Since gout is a disease of adults and has no pediatric correlate, sponsor is granted a full waiver (07 October 2014) from the requirement to conduct pediatric research with lesinurad for gout and hyperuricemia.

Summary of Lesinurad PK
Per sponsor, Lesinurad was readily absorbed following a single dose of free acid (FA) tablets with a median Tmax at 1.5 hours under fasted conditions and 2.0 hours under fed conditions. The absolute bioavailability of lesinurad is approximately 100%, and plasma exposure of lesinurad is similar in subjects with gout and healthy subjects.

Lesinurad is highly protein bound (approximately 98%, mainly to albumin) with limited extravascular distribution (volume of distribution of 20.3 L), and [14C]lesinurad-derived radioactivity was largely contained in the plasma space and did not partition extensively into red blood cells.

Lesinurad undergoes oxidative metabolism mainly via cytochrome P450 CYP2C9. Plasma exposure of metabolites is minimal (< 10% of unchanged lesinurad). Metabolites are not known to contribute to the uric acid lowering effects of lesinurad.

Approximately 63.4% of administered dose gets excreted in urine and of which almost half was unchanged lesinurad, confirming that renal excretion is an important route of elimination. and 32% of administered radioactive dose was recovered in faeces. Metabolites accounted for the majority (64.1%) of the total radioactivity in the excreta, and approximately half of the oral dose is cleared via cytochrome P450 (CYP) 2C9 metabolism. The elimination half-life (t½) of lesinurad was approximately 5 hours following a single 200 mg dose. Lesinurad exhibited dose proportionality (Cmax and AUC) up to a dose of 1200 mg. Following once daily (qd) dosing, there is no evidence for accumulation.

Summary of Exposure Response Analysis
Sponsor conducted exposure response analysis for efficacy (UA) and for safety endpoints (CrCL). Sponsor reported findings from these analyses in three pop PK/PD reports.
- UA: Based on the Emax model with realtime concentration, 200 mg qd is on the steep portion of the E-R curve; baseline CrCL has no significant impact on efficacy.
- CrCL: higher exposure is related to higher elevation of sCr, but this does not inform on cause-effect.

<u>Mid-Cycle Deliverables</u>
Following are the Mid-Cycle Deliverables;
- Any approvability issues
- Dose Selection
- Exposure-Response Evaluation for Efficacy and Safety
- Drug-drug Interaction and Extrinsic/Intrinsic Factors
- Labeling

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/s/

JIANMENG CHEN
02/20/2015

SATJIT S BRAR
02/20/2015