CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209203Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review
Clinical Review
Non-Clinical Review
Clinical Pharmacology Review

NDA/BLA Multi-disciplinary Review and Evaluation

Application Type	505(b)
Application Number(s)	NDA 209203
Priority or Standard	Standard
Submit Date(s)	October 20, 2016
Received Date(s)	October 20, 2016
PDUFA Goal Date	August 18, 2017 (actual August 20, 2017 Sunday)
Division/Office	DPARP
Review Completion Date	August 14, 2017
Established Name	Lesinurad/allopurinol fixed dose combination drug product
(Proposed) Trade Name	Duzallo
Pharmacologic Class	Combination URAT1 inhibitor (lesinurad) and XOI (allopurinol)
Applicant	Ardea Bioscience
Formulation(s)	Tablets
Dosing Regimen	Once daily
Applicant Proposed Indication(s)/Population(s)	Treatment of hyperuricemia associated with gout in patients who have not achieved target serum uric acid (sUA) levels with allopurinol alone
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Treatment of hyperuricemia associated with gout in patients who have not achieved target serum uric acid levels with a medically appropriate daily dose of allopurinol alone.

Table of Contents

Table of Tables

Table of Figures

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OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DHOT	Division of Hematology Oncology Toxicology
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Conference on Harmonization
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science

OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1 Executive Summary

1.1. Product Introduction

The applicant, Ardea Biosciences, Inc., submitted a new drug application (NDA) 209203 for the lesinurad/allopurinol 200/200 and 200/300 fixed-dose combination (FDC) tablets to be taken once daily for the treatment of hyperuricemia associated with gout in patients who have not achieved target serum uric acid (sUA) levels with allopurinol alone. This is a new drug application (NDA) for Duzallo, a proposed lesinurad/allopurinol fixed-dose combination (FDC) tablet comprised of two currently approved oral products at doses that are within the recommended dosing limits for both products:

- Lesinurad is a URAT1 inhibitor that decreases reabsorption of uric acid from the renal proximal tubule by inhibiting the function of carrier proteins that transport uric acid. URAT1 is responsible for the majority of the reabsorption of filtered uric acid from the renal tubular lumen. Lesinurad has been approved in the United Sates (US) since 2015 under NDA 207988 for the treatment of hyperuricemia associated with gout in patients who have not achieved target serum uric acid (sUA) levels with a xanthine oxidase inhibitor alone.
- Allopurinol is an inhibitor of xanthine oxidase, the enzyme responsible for the conversion of hypoxanthine to xanthine and of xanthine to uric acid. Allopurinol monocomponent has been approved in the United Sates since 1966 for the management of patients with signs and symptoms of primary or secondary gout (i.e., acute attacks, tophi, joint destruction, uric acid lithiasis, and/or nephropathy).

The FDC's proposed indication of hyperuricemia associated with gout in patients who have not achieved target serum uric acid levels with allopurinol alone is consistent with the approved indication for lesinurad. The Applicant states that they have developed these fixed dose combination tablets to mitigate the renal safety risk associated with lesinurad monotherapy, and has submitted this 505(b)(2) application which cross-references data reviewed previously in support of NDA 207988 Lesinurad (Zurampic) and the previous findings of safety and effectiveness of allopurinol (Zyloprim NDA 16084, and Aloprim, NDA 20298).

1.2. Conclusions on the Substantial Evidence of Effectiveness

The efficacy and safety data in support of this 505(b)(2) application for these proposed FDC tablets containing 200 mg/200 mg and 200 mg /300 mg of lesinurad and allopurinol, respectively, are derived from clinical studies reviewed previously in support of NDA 207988 lesinurad (Zurampic), where the addition of lesinurad monocomponent to medically appropriate doses of allopurinol was shown to have additional benefit over that of allopurinol alone for the reduction of serum uric acid in the intended patient population.

As the to-be marketed combination was not studied in these studies, the Applicant conducted a bioavailability/bioequivalence study RDEA594-501 (study 501) to provide the necessary pharmacokinetic data in support of a bridge between the combination of the monocomponents used in the clinical studies supporting NDA 207988 to the to-be-marketed lesinurad/allopurinol FDC. In that study, bioequivalence (BE) of the 200/300 FDC tablet to the coadministered single agents at corresponding doses was demonstrated. The 90% confidence intervals (CIs) for the geometric least squares mean ratios of AUC_{last}, AUC_{∞}, and C_{max} for lesinurad, allopurinol and oxypurinol, were within the conventional BE limits of 0.80 to 1.25 for the 200/300 FDC tablet. The 200/200 FDC tablet strength was evaluated and met BE criteria with respect to all 3 PK parameters for all 3 analytes, with the exception of allopurinol C_{max}; the upper limit of the 90% CI (1.28) was outside of the conventional BE limits. The efficacy and safety of allopurinol is primarily driven by oxypurinol as a result of its activity and longer elimination half-life compared to allopurinol (Zyloprim). Since oxypurinol PK parameters met the BE criteria, the observed differences in allopurinol C_{max} are not expected to affect the safety and efficacy profile of the FDC. These BE results were confirmed by in-house analysis and found to be acceptable from clinical pharmacology perspective. Overall, the results for both FDC tablet strengths fulfill the criteria to support the PK bridge between the lesinurad/allopurinol FDC product and coadministered lesinurad and allopurinol tablets in the fasted state.

In the same study, the effect of food on lesinurad and allopurinol PK was evaluated at the highest strength of 200/300 for the proposed FDC product. Lesinurad, allopurinol, and oxypurinol AUC, and oxypurinol C_{max}, were similar in the fed (high-fat, high-calorie) and fasted states following administration of the 200/300 FDC tablet, whereas C_{max} for lesinurad and allopurinol was reduced (by 46% and 18%, respectively) and T_{max} was extended following administration with food. The food effect observed with the approved lesinurad formulation was lower and only 18% reduction in C_{max} was observed (NDA 207988). To support the conclusion that the observed PK differences for the FDC in the fed state were not clinically meaningful the following analysis were submitted by the Applicant:

1. Plasma uric acid (pUA) concentration-time profile were evaluated following administration of the 200/300 FDC tablet in fasted and fed state demonstrating that pUA reductions was similar with and without food, indicating that the pharmacodynamics (PD) performance of the FDC was not affected by the C_{max} reductions in the healthy subjects.

2. A PK/PD model was developed by the Applicant to characterize the physiologic turnover of uric acid, including its production and clearance. Model validation was performed using the phase 3 studies for lesinurad development program from NDA 207988. Simulations for sUA lowering in various PK scenarios were performed using hyperuricemic patient characteristics for the proposed FDC product. The simulation results showed that steady-state lowering of sUA was not impacted by the PK differences observed for the lesinurad/ allopurinol FDC in the fed state in the hyperuricemic patients.

The PK/PD simulations were confirmed in-house and additional sensitivity analysis was performed to validate the model. The Office of Clinical Pharmacology senior leadership team concurred with the review team's assessment that food did not have a clinically meaningful effect on lesinurad, allopurinol and oxypurinol exposure from the 200/300 FDC tablet. Further, the observed clinical pharmacology differences are not likely to negatively impact safety.

The NDA also provides labeling consistent with the Pregnancy and Lactation Labeling Rule (PLLR).

1.3. Benefit-Risk Assessment

The efficacy and safety data supporting the favorable risk-benefit profile of the proposed fixed-dose combination tablets containing 200 mg/200 mg and 200 mg /300 mg of lesinurad and allopurinol, respectively, are derived from clinical studies reviewed previously in support of NDA 207988 lesinurad (Zurampic), where the addition of lesinurad monocomponent to medically appropriate doses of allopurinol was shown to have additional benefit over that of allopurinol alone for the reduction of serum uric acid in the intended patient population. The relevance of these data to the proposed to-be-marketed fixed-dose combination tablets of Duzallo is supported by the bioequivalence (BE) of the FDC tablet to the coadministered single agents at corresponding doses. Of note, administering Duzallo with food may result in reduced C_{max} of lesinurad by approximately 46% and extended T_{max}. However, the Applicant has provided data and results from modeling and simulation to support that the differences in C_{max} do not impact the pharmacodynamic effects of lesinurad in healthy subjects and treatment naïve or treatment-exposed hyperuricemic gout patients. Further, the observed clinical pharmacology differences observed in fed state are not likely to negatively impact safety. Thus, the overall risk-benefit profile of the to-be-marketed Duzallo tablets remains favorable.

I have reviewed this application and the contents of this document. I recommend approval of this NDA.

Nikolay P.
X Nikolov -S

Digitally signed by Nikolay P. Nikolov -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=0011314790, cn=Nikolay P. Nikolov -S
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Cross-Disciplinary Team Leader

2 Therapeutic Context

2.1. Analysis of Condition

Gout is a metabolic disorder characterized by reduced clearance or overproduction of uric acid leading to hyperuricemia, which in turn can result in monosodium urate (MSU) crystal formation around the joints and soft tissues, urate nephropathy, and nephrolithiasis. The prevalence of gout has been increasing over the past few decades, and has been recently estimated to affect approximately 3.9% of adults in the United States (8.3 million)[1]. The condition affects primarily middle-aged and older men and post-menopausal women. Obesity, hyperlipidemia, diabetes, hypertension, chronic renal insufficiency, metabolic syndrome, and cardiovascular disease are frequent comorbidities in patients with gout.

The course of gout is characterized by acute attacks of gouty arthritis alternating with attack-free periods of intercritical gout. A typical course of gouty arthritis attack (or gout flare) is characterized by acute inflammation of the affected joint and surrounding tissues associated with often excruciating pain, tenderness, erythema, and swelling. If left untreated, the acute inflammatory episode is self-limited, typically peaking within 24-48 hours and eventually subsiding within 7-10 days. Treatment of acute attacks utilizes anti-inflammatory treatment of various mechanisms, such as colchicine, nonsteroidal anti-inflammatory drugs (NSAIDS), or corticosteroids. It is common practice to use an agent to help reduce the frequency and severity of acute gout attacks, for which a patient is at increased risk during initiation of uric-acid lowering therapies. To this end, maintenance doses of either colchicine or an NSAID are continued as prophylaxis against gout flares; typically until the serum uric acid level has been maintained within the target range and there have been no acute attacks for 3 to 6 months.

The chronic management of gout is founded upon control of hyperuricemia, as only this approach treats the underlying pathology of the disorder. The mechanistic approaches to lowering serum uric acid (sUA) include:

- Lowering uric acid production. This is currently the most common approach to treatment, via xanthine oxidase inhibitors, i.e., allopurinol and febuxostat.
- Increasing urinary uric acid excretion (uricosurics). Uricosurics such as probenecid and lesinurad inhibit active renal reabsorption of uric acid through urate transporters in proximal tubule epithelial cells (predominantly URAT1), resulting in increased urinary uric acid excretion.
- Direct enzymatic breakdown of uric acid. Because humans do not possess an endogenous uricase, drugs such as pegloticase and rasburicase are derived from foreign

[1] Zhu Y, Pandya BJ, Choi HK, "Prevalence of gout and hyperuricemia in the US general population: the National Health and Nutrition Examination Survey 2007-2008." Arthritis Rheum 2011; 63:3136-3141.

proteins, and their use is limited by immunogenicity. Uricase breaks down uric acid into the much more soluble allantoin, which can then be excreted in the urine.

2.2. Analysis of Current Treatment Options

Table 1 lists the currently approved small molecule products as well as therapeutic biologic treatments for the management of hyperuricemia.

Table 1: Treatments for the Management of Hyperuricemia

Product	Year of Approval	Indication
Xanthine Oxidase Inhibitors (XOIs)		
Allopurinol	1966	Management of patients with signs and symptoms of primary or secondary gout (i.e., acute attacks, tophi, joint destruction, uric acid lithiasis, and/or nephropathy)
Febuxostat	2009	Chronic management of hyperuricemia in patients with gout
Uricosuric Agents[1]		
Probenecid	1951	Treatment of the hyperuricemia associated with gout and gouty arthritis
Sulfinpyrazone	1959 (Removed from market 2002)	Treatment of chronic gouty arthritis and intermittent gouty arthritis
Lesinurad	2015	Treatment of hyperuricemia associated with gout in patients who have not achieved target serum uric acid (sUA) levels with a xanthine oxidase inhibitor alone
Uricase		
Rasburicase	2002	Initial management of plasma uric acid levels in pediatric patients with leukemia, lymphoma, and sold tumor malignancies who are receiving anti-cancer therapy expected to result in tumor lysis and subsequent elevation of plasma uric acid
Pegloticase	2010	Treatment of chronic gout in adult patients refractory to conventional therapy

[1]Benzbromarone is a uricosuric agent that was never marketed in the U.S. but is available in other countries.

Benzbromarone, sulfinpyrazone, probenecid and lesinurad comprise the uricosuric class of drugs which can be used in patients who are underexcretors of urate. Probenecid and lesinurad are the only uricosuric currently available in the U.S. Like lesinurad, probenecid also interferes with renal absorption of uric acid by inhibiting URAT1. Probenecid also inhibits OAT1 and OAT3, as well as GLUT9. Based in part on concerns regarding urolithiasis and decreased efficacy in patients with creatinine clearance below 50 ml/min, American College of Rheumatology treatment guidelines include caveats such as not using uricosurics in patients with urolithiasis or in patients with a creatinine clearance below 50 ml/min, or in patients with elevated urine uric acid. The guidelines also recommend monitoring of urinary uric acid during therapy, and considering urine alkalinization and increasing fluid intake. In order to minimize

the risk of nephrotoxicity associated with lesinurad, patients prescribed this drug also need to take it with a concomitant xanthine oxidase inhibitor.

The xanthine oxidase inhibitors (XOI), allopurinol and febuxostat, are the agents most commonly used as first-line urate lowering therapy in patients with gout and in those with a history of nephrolithiasis (renal stones). The effectiveness of allopurinol is limited by a number of issues including the need to use lower doses in patients with renal insufficiency, and an adverse event profile that includes gastrointestinal, hepatic, renal, hematological and skin toxicities that occur in approximately 20% of patients who take this drug. In addition, hypersensitivity reactions occur in 2-4% of patients that in some instances have been fatal. Febuxostat's safety profile is similar to that of allopurinol but it does not require renal adjustment in dosing in patients with a creatinine clearance > 30 ml/minute. However, its current label carries warnings for both cardiovascular events and hepatotoxicity some of which have resulted in fatalities. Benzbromarone, sulfinpyrazone and probenecid comprise the uricosuric class of drugs which can be used in patients who are underexcretors of urate. Uricosuric agents are used as second-line therapy since their usefulness is limited by the risk for developing urate renal stones and crystalluria in patients who are overexcretors of urate, have decreased renal function (creatinine clearance of <50 mg/minute), and/or are not well hydrated to support good urine flow. Pegloticase is a pegylated formulation of recombinant (b) (4) urate oxidase that is administered intravenously. It is reserved as tertiary therapy as a treatment for patients with (b) (4) gout who are refractory to conventional therapy. The effectiveness of this therapeutic biologic is limited by the development of neutralizing antibodies and the occurrence of infusion reactions and anaphylaxis which requires patients to be premedicated prior to its administration. Additionally, patients with underlying congestive heart failure have to be monitored for exacerbations post-administration of pegloticase.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Lesinurad is an approved URAT1 inhibitor that is available and marketed in the U.S. (since 2015) and in Australia and the European Union (as of August 2016) as 200 mg-strength tablets when administered in combination with a xanthine oxidase inhibitor (XOI) for the treatment of hyperuricemia associated with gout inpatients who have not achieved target serum uric acid levels with a XOI alone. As a result of a nephrotoxicity safety signal, leinurad's USPI contains a box Warning regarding the risk for acute renal failure to occur particularly when this drug is administered as monotherapy. It also contains a Warnings and Precautions statement for monitoring renal function particularly in patients with eCLer below 60 ml/min and evaluate for signs and symptoms of acute uric acid nephropathy.

Allopurinol (Zyloprim®) is an approved XOI that is available as 100 mg and 200 mg tablets that has been marketed in this country since 1966 and is available generically for the management of patients with signs and symptoms of primary or secondary gout (i.e., acute attacks, tophi, joint destruction, uric acid lithiasis, and/or nephropathy) at daily doses of up to 800 mg. The USPI for Zyloprim® contains a number of Warning statements including one for severe skin hypersensitivity reactions for which patients with decreased renal function are at an increased risk. It also contains numerous Precaution statements including ones for rising BUNs during initiation of therapy and renal failure particularly in patients with pre-existing renal disease or poor urate clearance. There is a labeling recommendation to healthcare providers to start with a lower dose of Zyloprim® in these patients in order to minimize the safety risk associated with the prolong half-life of its active metabolite, oxypurinol.

In order to mitigate the renal safety risk associated with lesinurad monotherapy, the Applicant is proposing fixed dose combination (FDC) tablets containing 200 mg/200 mg and 200 mg/300 mg of lesinurad/allopurinol , respectively, as per the FDA's Combination Rule (21 CFR §300.50) and has submitted this 505(b)(2) application which cross-references data reviewed previously in support of NDA 207988 Lesinurad (Zurampic®).

3.2. Summary of Presubmission/Submission Regulatory Activity

In lieu of a face-to-face pre-IND meeting, written responses dated June 24, 2013 were shared with the Applicant that contain feedback comments regarding their proposed clinical development plans for fixed dose combination tablets containing the urate lowering agents, lesinurad and allopurinol, and applicability of the Combination Rule (21 CFR §300.50).

On Sept. 3, 2015, IND 119031 for lesinurad/allopurinol FDC tablets for use in the (b) (4) treatment of hyperuricemia associated with gout was opened by the Applicant.

- The opening study was RDEA594-501 which was a phase 1, bioavailability/bioequivalency, single-dose, cross-over pharmacokinetic (PK) study of lesinurad 200mg/allopurinol 300 mg tablets in healthy volunteers

At a Type C meeting held on January 13, 2016, the following items summarize agreements reached between the Applicant and the Division regarding the FDC lesinurad/allopurinol tablets clinical development program:

- Acceptability of LES200mg/ALLO300mg and LES200mg/ALLO200 mg FDC proportional similarity
- (b) (4) for LES200mg/ALLO200mg FDC strength
- Stability package for FDC non-functional coating change

An End-of-Phase 2 (EOP2) meeting with the Applicant was held on May 6, 2016. Agreements and discussion of key clinical and regulatory issues at that time included:

- Feedback on proposed in vitro dissolution test method
- Agreement on clinical package to support bridge for FDC to lesinurad and allopurinol monocomponents

A pre-NDA meeting was held on August 30, 2016. The following items summarize the understandings reached between the Applicant and the Division:

- Information to be contained in the FDC USPI
- Clinical data set information
- Formatting and technical issues related to application

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

Since clinical site inspections and an audit of the Applicant were conducted in support of NDA 207988 Lesinurad (Zurampic®), no additional inspections were required for this application.

4.2. Product Quality

Novel excipients: No
Any impurity of concern: No

The tablet drug product is a fixed dose combination of lesinurad, a URAT1 inhibitor, and allopurinol, a xanthine oxidase inhibitor (XOI), and is indicated for the (b) (4) treatment of hyperuricemia associated with gout in patients who have not achieved target serum uric acid (sUA) levels with allopurinol alone.

The lesinurad drug substance information for this application was provided by reference to the applicant's approved NDA 207988 for lesinurad tablets. Information for the allopurinol was provided by letter authorization to allow reference to (b) (4) type II DMF (b) (4) Refer to the reviews for those documents for information about the CMC for the two drug substances.

Lesinurad is a BCS class II compound and allopurinol is a BCS class IV compound. PSD for Allopurinol is controlled at D(v,0.5) NMT (b) (4) microns, and PSD for Lesinurad is controlled at NMT (b) (4) microns. Lesinurad is reported to possess two known (b) (4) crystal forms (b) (4) polymorphs), and other (b) (4).

The applicant supports two fixed-dose combinations (FDC) of 200/200 mg and 200/300 mg of lesinurad/allopurinol. These are light and dark orange debossed film coated tablets, respectively. The tablets include lactose, cellulose, hypromellose, crospovidone, and magnesium stearate as excipients. In both formulations, the % w/w for both APIs is greater (b) (4) %, thus achieving content uniformity is not difficult. This combination lesinurad/allopurinol tablet meets all of the quality standards targeted for it in its specification. The two different strengths are easily distinguished. The strengths of the two actives are well controlled, as are the excipients. The finished product in the commercial container-closure is stable enough to meet its specification at 24 months.

The drug product manufacturing process includes (b) (4)

The range of (b) (4) batch size is approximately (b) (4)

The proposed dissolution method, discriminating ability of the method, dissolution acceptance criterion, dissolution analytical method, PBPK modeling and simulation in support of the proposed PSD of both drugs and wider dissolution acceptance criterion for lesinurad, *in vitro* bridging for change in non-functional film coating for the proposed FDC IR tablet, were reviewed in detail and were found to be adequate. The Applicant adequately responded to the two biopharmaceutics information requests and PBPK questions discussed during the teleconference on 06-JUL-2017. It should be noted that although the proposed PBPK model is considered adequate for supporting PSD of drugs and wider dissolution acceptance criterion for lesinurad, further refinement of this model would be required if it were later proposed to broaden its application for lifecycle management (see letter to the applicant dated 20-JUL-2017).

There are five facilities associated with drug substance manufacture and three supporting drug product manufacture. The facilities team has found these to be adequate after a review of application and inspection documentation.

4.3. Clinical Microbiology

Not applicable.

4.4. Devices and Companion Diagnostic Issues

Not applicable.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

The proposed Lesinurad/Allopurinol fixed-dose combination (FDC) tablet is comprised of two currently approved oral products at doses that are within the recommended dosing limits for both products. Lesinurad is a URAT1 inhibitor that decreases reabsorption of uric acid from the renal proximal tubule by inhibiting the function of carrier proteins that transport uric acid; URAT1 is responsible for the majority of the reabsorption of filtered uric acid from the renal tubular lumen. Allopurinol is an inhibitor of xanthine oxidase, the enzyme responsible for the conversion of hypoxanthine to xanthine and of xanthine to uric acid. The FDC's proposed indication of hyperuricemia associated with gout in patients who have not achieved target serum uric acid levels with allopurinol alone is consistent with the approved indication for lesinurad.

There are complete nonclinical development programs for each component of the FDC, which have been reviewed previously (See NDA Pharmacology/Toxicology reviews for NDA 207988 [Lesinurad] and NDA 20298 [Allopurinol]). The sponsor has also conducted a 13-week lesinurad/allopurinol combination toxicology study in rats in support of the proposed FDC under IND 119031. No new or additive toxicities were observed in this study. No additional nonclinical studies were conducted (or required) to support approval.

The lesinurad portions of the nonclinical sections of the sponsor's proposed drug product labeling are considered adequate as currently presented. The Division has provided recommended changes to the allopurinol portions of the nonclinical sections of the proposed labeling to allow for alignment with the Pregnancy and Lactation Labeling Rule (PLLR) and current CDER labeling practices. Resources used to complete the revised allopurinol labeling included the following: (1) Language in the existing prescribing information for Zyloprim (oral allopurinol) and Aloprim (IV allopurinol), (2) Pharmacology/Toxicology review for Aloprim (NDA 20298, dated 5/17/96), and (3) published scientific literature.

The NDA is recommended for approval from the nonclinical perspective.

5.2. Referenced NDAs, BLAs, DMFs

NDA	Product	Approval
207988	Zurampic (Lesinurad)	2015
16084*	Zyloprim (Allopurinol [oral])	1966
20298	Aloprim (Allopurinol [IV])	1996

*The nonclinical review for NDA 20298 references the results of studies submitted in support of NDA 16084

5.3. Pharmacology

Primary pharmacology

Lesinurad

Lesinurad decreases the reabsorption of uric acid from the renal proximal tubule by inhibiting the function of carrier proteins that transport uric acid. Inhibition of URAT1 and OAT4, located on the apical surface of renal tubular epithelial cells, is likely to be principal mechanism of action. Lesinurad inhibits transporter function with potency in the 3 – 7 µM range. The Established Pharmacological Classification (EPC) for lesinurad is URAT1 inhibitor.

Allopurinol

Allopurinol is an inhibitor of xanthine oxidase, the enzyme responsible for the conversion of hypoxanthine to xanthine and of xanthine to uric acid, the end product of purine metabolism in humans. Allopurinol is metabolized to the corresponding xanthine analogue, oxypurinol (alloxanthine), which also is an inhibitor of xanthine oxidase. The Established Pharmacological Classification (EPC) for allopurinol is xanthine oxidase inhibitor.

5.4. ADME/PK

Lesinurad

- Lesinurad was orally bioavailable in rats (73%) and monkeys (41%).
- Lesinurad percent plasma protein binding values exceeded 94% in mouse, rat, dog, monkey, or human plasma.
- The major lesinurad metabolites, observed in humans, were also observed in at least one nonclinical species. Metabolites M3, a hydroxylated metabolite, and M4, a dihydrodiol, represent two disproportionate human metabolites (12.3% and 20.7% of the initial dose). M3 is formed at low levels in both rats and monkeys, while M4 is observed at low levels in monkeys only. The M4 metabolite was formed in humans via an epoxide intermediate termed M3c. Epoxide functional groups were known structural alerts for mutagenicity. M3c formation may represent a potential clinical concern given that lesinurad was to be administered chronically. M4 was not detected in rats suggesting that the M3c epoxide was not present at significant levels. However, cysteine conjugates (M9a and M9b) of the M3c epoxide were detected in monkeys. Based upon the 12-month monkey study, the human M3c metabolite, an epoxide intermediate, was qualified for safety with respect to general toxicity. Although the metabolite was not qualified for safety with respect to carcinogenicity, no additional nonclinical studies were required. This conclusion was based on the consideration that it was not technically feasible to directly administer M3c in a stand-alone carcinogenicity study due its chemical instability. Some concern with regard to the potential carcinogenic effects of M3c may be mitigated by its transient nature and the fact that, in humans, this molecule is detoxified to a didhydrodiol (M4).

Allopurinol

There is no oral pharmacokinetic data available in animals for allopurinol.

Lesinurad/allopurinol combination

- A 13 week oral combination toxicology study (Study SR11-002) was conducted in SD rats by Ardea in support of NDA 207988 and is cross-referenced in the current NDA application. The study was designed as follows:

Treatment group	Lesinurad (mg/kg)	Allopurinol (mg/kg)
1	0	0
2	100	0
3	0	25
4	300	0
5	0	100
6	100	25
7	100	100
8	300	25
9	300	100

- Results
  - PK parameters for lesinurad, allopurinol and oxypurinol (metabolite of allopurinol that also inhibits xanthine oxidase function) were measured at days 1, 29, and 91.
  - Lesinurad, allopurinol, and oxypurinol T_{max} values were between 1 – 8 hrs
  - Lesinurad C_{max} and AUC_{0-24} values were not affected by allopurinol co-administration
  - 100 mg/kg allopurinol AUC_{0-24} values were increased by 2 – 3-fold in the presence of 100 or 300 mg/kg lesinurad at day 91.

			Allopurinol			
			Males		Females	
	Lesinurad (mg/kg)	Allopurinol (mg/kg)	AUC_{0-24h} (µg*hr/ml)	C_{max} (µg/ml)	AUC_{0-24h} (µg*hr/ml)	C_{max} (µg/ml)
Day 1	0	25	5.51	4.08	6.96	5.80
	100	25	5.57	3.33	8.16	4.61
	300	25	3.33	1.71	3.99	1.21
	0	100	72.7	23.2	56.9	28.1
	100	100	83.9	22.9	105	32.0
	300	100	62.9	12.5	90.9	14.3
Day 91	0	25	13.8	7.92	15.1	9.31
	100	25	17.8	6.32	14.5	6.27
	300	25	11.3	2.99	13.4	4.40
	0	100	54.7	18.3	67.9	23.4
	100	100	153	27.8	141	31.5
	300	100	167	23.8	137	20.5

- The observed increase in allopurinol exposure in the presence of lesinurad is not considered to represent a significant clinical concern for the following reasons:
    - The existing clinical pharmacology data with the FDC has shown no such effects of lesinurad on allopurinol exposure in humans (See Section 6: Clinical Pharmacology).
    - The clinical lesinurad/allopurinol FDC tablet contains allopurinol at a maximum strength of 300 mg/day. This dose is well below the maximum recommended human dose of 800 mg/day allopurinol.
    - Allopurinol exposure in patients treated with the FDC is monitorable in the clinical setting.

5.5. Toxicology

5.5.1. General Toxicology

Lesinurad

Chronic toxicology studies conducted with oral lesinurad in rats and monkeys have been reviewed under NDA 207988 (see nonclinical review dated 9/3/15) and are briefly summarized below.

- Rats
    - In the 6 month repeat-dose rat toxicology study, animals were dosed orally with lesinurad at 0, 10, 30, 100, 300, and 600 mg/kg/d. An interim sacrifice was conducted at the 3 month time point. 13/60 high dose animals died within the first 3 weeks of dosing. These animals showed clear evidence of toxicity in the kidney (single cell necrosis (minimal – mild) and tubular degeneration) and gastrointestinal tract (single cell necrosis (minimal – moderate), congestion, and hemorrhage in stomach, duodenum, jejunum, ileum, cecum and colon). The remaining HD animals were euthanized on study day 23.

    - **Pancreas** (single cell necrosis) and **stomach** (erosion, hemorrhage) appeared to be potential target organs of toxicity at the 300 mg/kg dose at the 3 month time point, but not at the 6 month time point. Neither incidence nor severity of these findings increased between the 3 and 6 month time points. More specifically, the findings of pancreas single cell necrosis and stomach erosion were each limited to an incidence of 1/14 (separate animals) with a severity grading of minimal after 6 months of treatment.

    - Indicators of potential treatment-related **kidney** toxicity at 300 mg/kg/d included increased water consumption, increased urine volume (decreased ability to concentrate urine), increased serum creatinine, and decreased BUN:creatinine ratio. However, there was limited microscopic evidence for overt kidney pathology at either the 3 month or 6 month time points (limited to increased incidences of tubular dilation for males and females at 300 mg/kg/day).

- The no observed adverse effect level (NOAEL) was judged to be 100 mg/kg/day based on mortality observed at the 600 mg/kg dose and histopathological findings at 300 mg/kg/day in the pancreas (single cell necrosis) and stomach (erosion, hemorrhage) at the 3-month time point and kidneys at the 6-month time point. This dose was associated with an $AUC_{0\text{-}24h}$ of 415 µg*hr/ml.

- The $AUC_{0\text{-}24}$ at the NOAEL provides an exposure margin of 15 relative to the clinical exposure at the maximum recommended human dose of 200 mg/day.

- Monkeys
  - In the 12 month repeat dose monkey toxicology study, animals were dosed orally with LESINURAD at 0, 30, 100, 300, or 600 mg/kg/day. There were 5 premature deaths in HD animals (600 mg/kg/d). 4/5 deaths were due to treatment related severe diarrhea, emesis, and decreased food consumption.

  - **Bile duct** hyperplasia in 300 mg/kg/d males and 600 mg/kg/d M & F with correlating increases in gamma glutamyltransferase levels in affected animals was considered to be dose limiting. The NOAEL was judged to be 100 mg/kg/day. This dose was associated with an $AUC_{0\text{-}24h}$ of 82.6 µg*hr/ml.

  - The $AUC_{0\text{-}24}$ at the NOAEL provides an exposure margin of 3 relative to the clinical exposure at the maximum recommended human dose of 200 mg/day.

Allopurinol
Based upon the 13-week toxicology study in rats, described below, the kidneys were the target organ of toxicity.

Lesinurad + allopurinol combination

Study title/ number: RDEA 594 and Allopurinol: A 13-week repeat combination oral dose toxicity and toxicokinetic study in Sprague-Dawley rats / SR11-002

Key Study Findings
- 100 mg/kg allopurinol $AUC_{0\text{-}24}$ values were increased by 2 – 3-fold in the presence of 100 or 300 mg/kg lesinurad at day 91.
- There were no additive effects of combining lesinurad + allopurinol with respect to toxicologic findings
- Observed treatment-related findings in stomach and kidney were expected based on previous toxicology studies conducted in rats with lesinurad or allopurinol alone.

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Methods

Dose and frequency of dosing:

Treatment group	Lesinurad (mg/kg)	Allopurinol (mg/kg)
1	0	0
2	100	0
3	0	25
4	300	0
5	0	100
6	100	25
7	100	100
8	300	25
9	300	100

Once daily dosing

Route of administration: Oral gavage

Formulation/Vehicle: Lesinurad & allopurinol used the same vehicle: (b) (4)

Species/Strain: Rat/Sprague-Dawley [Crl: CD (SD)]

Number/Sex/Group: Main study: 10

Age: 7 – 8 weeks

Satellite groups: TK animals: 6/sex/group

Unique design: Complete histopathology conducted in groups 1, 4, 5, and 9 only

Deviation from study protocol affecting interpretation of results: No

Observations and Results: changes from control

Parameters	Major findings

Mortality

The cause of death for male #73671 was characterized by the sponsor as Renal tubular degeneration. Observations included tubular epithelium attenuation, loss, and basophilia as well as single cell necrosis of many tubular cells. Tubules were frequently dilated. Affected tubules were in a diffuse zone largely in the outer stripe and continuing into the outer medulla. The observed tubular degeneration in the current study is consistent with observations in rats treated with lesinurad alone. The causes of death for other animals appeared to have no or questionable relationships to treatment.

Dose group	Dose (mg/kg/d)	Sex	Animal no.	Mode of death	Day of death	Cause of death
7	LES 100/AL 100	M	73726	Found dead	60	*Potential gavage error.* Dyspnea & convulsions ~ 1 min post dose. Foam at the mouth & nose.
8	LES 300/AL 25	F	73825	Found dead	80	*Undetermined* Mammary gland: benign fibroadenoma Thymus: mild hemorrhage; marked lymphoid depletion in cortex Spleen (white pulp): mild lymphoid depletion Bone marrow sternum: mild hypocellularity Lymph node (mandibular, mesenteric): lymphoid depletion; minimal *Gross findings* (no microscopic correlates): Stomach: gas filled (mild) Ovary: diffuse gray discoloration, mild Uterus: diffuse gray discoloration, Mild
8	LES 300/AL 25	M	73671	Moribund sacrifice	18	*Cause of death: renal tubule degeneration* **Kidney**: Renal tubule degeneration (moderate) Adrenal: vacuolation, mild Pancreas: zymogen granule depletion: minimal Thymus: marked lymphoid depletion- cortex Lymph node (mandibular, mesenteric): lymphoid depletion, minimal *Gross findings* Stomach: gas filled (marked) GI tract: gas filled (marked)

Clinical Signs	No effects of lesinurad, allopurinol, or combination
Body Weights	No effects of lesinurad, allopurinol, or combination
Ophthalmoscopy	No effects of lesinurad, allopurinol, or combination
Hematology	No effects of lesinurad, allopurinol, or combination

Clinical Chemistry

Slight increases in liver enzymes (ALT, AST, ALP) and cholesterol values were observed in HD Lesinurad alone treated males and females. These observations appear to generally be consistent with the microscopic evidence of hepatocellular hypertrophy observed in HD Lesinurad treated animals. There was not a clear increase in effect size between days 28 and 92. There was no clear effect of allopurinol on liver enzyme levels. The increase in liver enzyme levels in HD/HD animals appeared to be largely driven by the effects of Lesinurad alone. There was no evidence for a clear additive effect of lesinurad + allopurinol on liver enzyme levels.

Small increases of kidney markers (BUN and creatinine) were consistent with the minimal – mild severity of renal pathology observed in HD animals

		Males				Females			
		Control	HD Les	HD Allo	HD Les/Allo	Control	HD Les	HD Allo	HD Les/Allo
Day 28	ALT (U/L)	38.1	+26%	-15%	+8%	33.2	4%	+56%	+0%
	AST (U/L)	141.7	+7%	-9%	+0%	118.7	+9%	+19%	+11%
	ALP (U/L)	178.9	+45%	-6%	+36%	84.8	+48%	+12%	+41%
	CHOLESTEROL (mM)	1.47	+51%	+24%	+52%	2.04	+18%	-7%	+10%
	BUN (mM)	4.88	+12%	+20%	+7%	6.42	-2%	+1%	-2%
	CREATININE (µM)	25.8	+31%	+6%	+38%	31.7	+11%	+1%	+12%
Day 92	ALT (U/L)	35.1	+26%	+1%	+23%	34.4	-7%	+22%	-8%
	AST (U/L)	131.9	+5%	-7%	+1%	119.3	+0%	+6%	+0%
	ALP (U/L)	84.2	+75%	+1%	+55%	39.9	+28%	+24%	+24%
	CHOLESTEROL (mM)	1.77	+55%	+5%	+53%	2.25	+15%	-10%	+19%
	BUN (mM)	5.86	-4%	+11%	+6%	6.58	-8%	+7%	+2%
	CREATININE (µM)	31.5	+24%	+15%	+44%	37.0	+2%	+8%	+16%

Urinalysis

No effects of lesinurad, allopurinol, or combination

Gross Pathology

Stomach: discoloration (HD/LD; HD/HD females)
Kidney: rough surface, bilateral (HD allopurinol males)

Organ Weights

Increased mean absolute liver weight in HD Lesinurad M (+14%) & F (+20%)
No additive effect of Lesinurad + Allopurinol on liver weight

Histopathology

Adequate battery: Yes

Histopathological findings attributed to lesinurad were observed in the liver (hepatocellular hypertrophy), kidneys (cysts), and glandular stomach (erosion). Findings attributed to allopurinol were observed in the kidneys (tubular nephropathy). Hepatocellular hypertrophy is considered to be an adaptive response to drug administration, brought about by the need for increased metabolic activity. Stomach & kidney findings were expected based on toxicology studies with individual components of the combination. There was no evidence of additive effects with the combination of lesinurad and allopurinol. Findings were consistent with the individual components.

	Males									Females								
Group	1	2	3	4	5	6	7	8	9	1	2	3	4	5	6	7	8	9
	Individual Components					Combinations (LES/Allo)				Individual Components					Combinations (LES/Allo)			
	Ctrl	LD LES	LD Allo	HD LES	HD Allo	LD/ LD	LD/H D	HD/ LD	HD/ HD	Ctrl	LD LES	LD Allo	HD LES	HD Allo	LD/ LD	LD/H D	HD/ LD	HD/ HD
LES/ALLO (mg/kg/day)	0/0	100 /0	0/2 5	300 /0	0/ 100	100 /25	100/ 100	300 /25	300/ 100	0/ 0	100 /0	0/2 5	300 /0	0/1 00	100 /25	100/ 100	300 /25	300/ 100
LIVER (# examined)	10	10	10	10	10	10	10	9	10	9	10	10	10	9	9	10	9	10

Hypertrophy, hepatocellular, centrilobular																			
minimal	0	7	0	0	0	8	7	1	0	0	0	0	2	0	2	5	3	2	
mild	0	3	0	9	0	2	3	8	10	0	0	0	8	0	0	0	6	8	
TOTAL	0	10	0	9	0	10	10	9	10	0	0	0	10	0	2	5	9	10	
STOMACH (# examined)	10	10	10	10	10	10	10	9	10	9	10	10	10	9	9	10	9	10	
Erosion; glandular																			
minimal	0	0	0	0	0	0	0	0	0	0	1	0	1	0	0	0	1	3	
KIDNEY (# examined)	10	10	10	10	10	10	10	9	10	9	10	10	10	9	9	10	9	10	
cyst																			
minimal	0	1	1	1	1	0	1	0	0	0	0	0	4	0	0	0	1	2	
tubular nephropathy																			
minimal	0	0	3	0	2	2	3	1	5	0	0	0	0	5	0	5	1	3	
mild	0	0	0	0	5	0	5	0	3	0	0	0	0	4	0	2	0	1	
moderate	0	0	0	0	3	0	2	0	1	0	0	0	0	0	0	0	0	0	
TOTAL	0	0	3	0	10	2	10	1	9	0	0	0	0	9	0	7	1	4	

LD: low dose; MD: mid dose; HD: high dose.
-: indicates reduction in parameters compared to control.

5.5.2. Genetic Toxicology

No genetic toxicology studies were conducted with the combination of lesinurad and allopurinol as they are not required. Studies have been conducted with its individual components.

Lesinurad
Lesinurad tested negative in the following genotoxicity assays: the in vitro Ames assay, in vitro chromosomal aberration assay in Chinese hamster ovary cells, and in vivo rat bone marrow micronucleus assay (see NDA 207988 nonclinical review dated 9/3/15).

Allopurinol
Allopurinol tested negative in the following genotoxicity assays: the in vitro Ames assay, in vitro mouse lymphoma assay, and in vivo rat bone marrow micronucleus assay (see product label).

5.5.3. Carcinogenicity

No carcinogenicity studies were conducted with the combination of lesinurad and allopurinol as they are not required. Studies have been conducted with its individual components.

Lesinurad
The carcinogenic potential of lesinurad was evaluated in a 2-year study conducted in Sprague-Dawley rats and a 26-week study in TgRasH2 mice. No evidence of tumorigenicity was observed in male or female rats at oral doses up to 200 mg/kg/day (approximately 35 times the MRHD on an AUC basis). No evidence of tumorigenicity was observed in TgRasH2 mice at oral doses up to 125 and 250 mg/kg/day in male and female mice, respectively (see NDA 207988 nonclinical review dated 9/3/15).

Allopurinol
The carcinogenic potential of allopurinol has been evaluated in mice and rats. No evidence of tumorigenicity was observed in male or female mice or rats that received oral allopurinol for the majority of their life spans (greater than 88 weeks) at doses up to 20 mg/kg/day. This dose is equivalent to 0.3 and 0.6 times the maximum recommended human dose on a mg/m^2 basis in mice and rats respectively.

5.5.4. Reproductive and Developmental Toxicology

No reproductive and developmental toxicology studies were conducted with the combination of lesinurad and allopurinol. Studies have been conducted with its individual components.

Fertility and Early Embryonic Development

Lesinurad
Lesinurad was tested at oral doses of 0, 75, 150, and 300 mg/kg/day. Male rats were dosed for at least 10 weeks prior to scheduled sacrifice, including 4 weeks prior to mating and throughout the cohabitation period through the day prior to scheduled sacrifice. Female rats were dosed for 2 weeks prior to mating and throughout the cohabitation period, and Gestation Days 0 through 7.

Female rats that received oral lesinurad at 300 mg/kg/day exhibited prolonged estrous cycles and a slight increase in mean number of days to mate, compared to the control group. In addition, slightly decreased mean numbers of corpora lutea and implantation sites were observed in this dose group in the presence of overt toxicity (mortality, adverse clinical signs, and decrease in mean body weight gain and mean food consumption).

However, fertility and reproductive performance were unaffected in male or female rats that received lesinurad at oral doses up to 300 mg/kg/day. This dose is equivalent to approximately 15 times the MRHD on a mg/m^2 basis (see NDA 207988 nonclinical review dated 9/3/15).

Allopurinol
Dedicated studies evaluating the effects of allopurinol on fertility and early embryonic development were not conducted. However, studies were conducted in rats and rabbits in which oral allopurinol (20 mg/kg) was dosed for 6 weeks prior to mating, throughout pregnancy, and until weaning. There was no evidence of impairment to fertility in these studies (see product label).

Embryo-Fetal Development

Lesinurad
Rats at 300 mg/kg/day exhibited maternal toxicity, including mortality, adverse clinical signs, decrease in mean food consumption and mean body weight gains. There were no test article-

related effects on post-implantation loss or fetal parameters including body weight, sex ratio, external, visceral or skeletal observations. The NOAEL for maternal toxicity was 150 mg/kg/day, whereas the NOAEL for embryofetal developmental toxicity was 300 mg/kg/day. Thus, lesinurad was not teratogenic in rats at oral doses up to 300 mg/kg/day.

A NOAEL for maternal toxicity in the rabbit EFD study was not identified due to mortality in all lesinurad-dosed groups. Lesinurad was not teratogenic in rabbits at oral doses up to 75 mg/kg/day (see NDA 207988 nonclinical review dated 9/3/15).

Allopurinol
Embryofetal development studies were conducted in rats and rabbits. Females were dosed orally from gestational days 8 – 16 at up to 200 mg/kg/d (rats) or 100 mg/kg/day (rabbits). There was no evidence of teratogenic effects in either species (see product label).

In a published report of an embryofetal development study with pregnant mice[2], single doses of allopurinol on gestation days 10 or 13 produced significant increases in fetal deaths and teratogenic effects (cleft palate, harelip, and digital defects) at maternal intraperitoneal doses of 50 or 100 mg/kg. It is uncertain whether the findings in mice represented fetal effects or effects secondary to maternal toxicity.

Gieling et al.[3] examined the effects of orally administered allopurinol (15 mg/kg/d) in pregnant pigs during the final trimester of pregnancy (GD 86 – delivery; approximately 30 days of treatment). Allopurinol was found to cross the placental barrier and was detectable in fetal plasma in this study.

Prenatal and Postnatal Development

Lesinurad
Pregnant female rats were dosed orally with lesinurad at 0, 100, 200, or 300 mg/kg/day from gestational day 7 (GD 7) – lactation day 20 (LD 20). Lesinurad was highly maternally toxic at ≥ 200 mg/kg/day, with target organs including the stomach, kidney, and liver. The milk: plasma ratio was ≥ 1 in all treatment groups, showing that lesinurad distributes approximately evenly between plasma and milk. There was no NOAEL identified with respect to maternal toxicity based on statistically significant, dose-dependent decreases in body weight gain >10% at all doses.

Lesinurad at ≥ 200 mg/kg evoked multiple adverse effects on F1 offspring. 200 mg/kg/day lesinurad treatment resulted in significantly reduced viability index, mean number of surviving

[2] Fujii & Nishimura (1972). Comparison of teratogenic action of substances related to purine metabolism in mouse embryos. *Japanese Journal of Pharmacology*. 22, 201 – 206.
[3] Gieling, E. et al. (2014). Chronic allopurinol treatment during the last trimester of pregnancy in sows: Effects on low and normal birthweight offspring. *PLOS One*. 9, 1 – 15.

pups per litter at PND 21, and mean pup weight at birth & PND 21 vs. controls. The litter size at PND 21 value and mean pup weight value were both outside of the range observed in historical control animals.

Viability index (# of live pups on d 4/ # of live pups on d 1) and lactation index (# of live pups on d 21/ # of live pups on d 4) were significantly lower in the 300 mg/kg dose group vs. controls. The mean number of surviving pups at day 21 and mean pup weight at birth & day 21 were also significantly reduced in the 300 mg/kg group vs. controls. Litter size at day 21 value and mean pup weight values were outside of the range observed in historical control animals.

Mean time to vaginal patency was significantly delayed in F1 females in the 200 mg/kg and 300 mg/kg groups. There were no treatment-related effects on learning and memory or mating and reproduction performance in the F1 generation. The NOAEL for fetal developmental toxicity was 100 mg/kg/day. Lesinurad did not induce gross external changes in F2 generation fetuses.

Allopurinol

There was no evidence of maternal toxicity, or fetal toxicity in rats and rabbits receiving oral doses of 20 mg/kg allopurinol for 6 weeks prior to mating, throughout pregnancy, and until weaning. This dose is approximately 0.6 and 1.3 times the maximum recommended human on a mg/m^2 basis in rats and rabbits respectively (see NDA 20298 action package dated 5/17/96).

X Matthew T. Whittaker -S
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Primary Reviewer

Team Leader

6 Clinical Pharmacology

6.1. Executive Summary

The applicant, Ardea Biosciences, Inc., has submitted NDA 209203 for the lesinurad/allopurinol 200/200 and 200/300 fixed-dose combination (FDC) tablets to be taken once daily (qd) for the treatment of hyperuricemia associated with gout in patients who have not achieved target serum uric acid (sUA) levels with allopurinol alone.

Lesinurad is a selective uric acid reabsorption inhibitor (SURI) that inhibits uric acid transporter 1 (URAT1). ZURAMPIC® (lesinurad 200 mg tablets, qd) is indicated in combination with a xanthine oxidase inhibitor (XOI: allopurinol or febuxostat) for the treatment of hyperuricemia associated with gout in patients who have not achieved target sUA levels with a XOI alone (NDA 207988, approved 2015). Allopurinol decreases production of uric acid by inhibiting xanthine oxidase, the enzyme responsible for the conversion of hypoxanthine to xanthine and of xanthine to uric acid, the end product of purine metabolism in humans. Allopurinol is rapidly metabolized to the corresponding xanthine analogue, oxypurinol, which also is an inhibitor of xanthine oxidase. ZYLOPRIM® (allopurinol) was first approved in the US in 1966; allopurinol 100 mg and 300 mg tablets are commercially available. Allopurinol is approved, at daily doses up to 800 mg, for multiple indications, including the management of patients with signs and symptoms of gout.

6.2. Summary of Clinical Pharmacology Assessment

The Office of Clinical Pharmacology/Divisions of Clinical Pharmacology 2 (OCP/DCP2) and Pharmacometrics (OCP/DPM) have reviewed Clinical Pharmacology data submitted under NDA 209203 (10/20/2016, 3/28/2017, 5/25/2017 and 06/05/2017) and recommend approval.

6.2.1. Pharmacology and Clinical Pharmacokinetics

The clinical development plan for the lesinurad/allopurinol FDC product included one pivotal study - RDEA594-501 (study 501). Study 501 was a Phase 1, randomized, open-label, single-dose, crossover study to assess the bioavailability (BA) of lesinurad/allopurinol 200/300 and 200/200 FDC tablets relative to that of coadministered lesinurad and allopurinol tablets, and the effect of a high-fat/high-calorie meal on the PK of lesinurad /allopurinol FDC tablets in healthy adult subjects. The study comprised of 3 parts and the results from the study are discussed below.

Pivotal bioequivalence results: In part 1, bioequivalence (BE) of the 200/300 FDC tablet to the coadministered single agents at corresponding doses was evaluated. 90% confidence intervals (CIs) for the geometric least squares mean ratios of AUC_{last}, AUC_{∞}, and C_{max} for lesinurad, allopurinol and oxypurinol, were within the conventional BE limits of 0.80 to 1.25 for the

200/300 FDC tablet. In part 3, the 200/200 FDC tablet strength was evaluated and met BE criteria with respect to all 3 PK parameters for all 3 analytes, with the exception of allopurinol C_{max}; the upper limit of the 90% CI (1.28) was outside of the conventional BE limits. The efficacy and safety of allopurinol is primarily driven by oxypurinol as a result of its activity and longer elimination half-life compared to allopurinol (Zyloprim, package insert). Since oxypurinol PK parameters met the BE criteria, the observed differences in allopurinol C_{max} are not expected to affect the safety and efficacy profile of the FDC. These BE results were confirmed by in-house analysis and found to be acceptable from clinical pharmacology perspective. Overall, the results for both FDC tablet strengths fulfill the criteria to support the PK bridge between the lesinurad/allopurinol FDC product and coadministered lesinurad and allopurinol tablets in the fasted state.

Food effect results: The effect of food on lesinurad and allopurinol PK was evaluated in part 2 of Study 501 at the highest strength of 200/300 for the proposed FDC product. Lesinurad, allopurinol, and oxypurinol AUC, and oxypurinol C_{max}, were similar in the fed (high-fat, high-calorie) and fasted states following administration of the 200/300 FDC tablet, whereas C_{max} for lesinurad and allopurinol was reduced (by 46% and 18%, respectively) and T_{max} was extended following administration with food. The food effect observed with the approved lesinurad formulation was lower and only 18% reduction in C_{max} was observed (NDA 207988). To show that the observed PK differences for the FDC in the fed state were not clinically meaningful the following analysis were submitted by the sponsor:

1. Plasma uric acid (pUA) concentration-time profile were evaluated following administration of the 200/300 FDC tablet in fasted and fed state demonstrating that pUA reductions was similar with and without food, indicating that the pharmacodynamics (PD) performance of the FDC was not affected by the C_{max} reductions in the healthy subjects.
2. A PKPD model was developed by the sponsor to characterize the physiologic turnover of uric acid, including its production and clearance. Model validation was performed using the phase 3 studies for lesinurad development program from NDA 207988. Simulations for sUA lowering in various PK scenarios were performed using hyperuricemic patient characteristics for the proposed FDC product. The simulation results showed that steady-state lowering of sUA was not impacted by the PK differences observed for the lesinurad/ allopurinol FDC in the fed state in the hyperuricemic patients.

The PKPD simulations were confirmed in-house and additional sensitivity analysis was performed to validate the model. These data and analyses were discussed with Office of Clinical Pharmacology senior leadership team (SLT) on June 6th, 2017. The SLT concurred with the review team's assessment that food did not have a clinically meaningful effect on lesinurad, allopurinol and oxypurinol exposure from the 200/300 FDC tablet.

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

The recommended dose is one 200 mg lesinurad/300 mg allopurinol tablet per day (or one 200 mg lesinurad/200 mg allopurinol for patients with renal impairment).

Therapeutic Individualization

Lesinurad/allopurinol FDC tablets should be taken in the morning with food and water.

Outstanding Issues

None.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Lesinurad is a SURI that inhibits URAT1. URAT1 is responsible for the majority of the reabsorption of filtered uric acid (UA) from the renal tubular lumen. By inhibiting URAT1, lesinurad increases UA excretion and thereby lowers sUA. Lesinurad also inhibits organic anion transporter 4 (OAT4), a UA transporter involved in diuretic-induced hyperuricemia. Lesinurad C_{max} was attained within 1 to 4 hours. C_{max} and AUC exposures of lesinurad increased proportionally with single doses of lesinurad from 5 to 1200 mg. Administration with a high-fat meal (800 to 1000 calories with 50% of calories being derived from fat content) decreases C_{max} by approximately 18% but does not alter AUC as compared with fasted state. In clinical trials, lesinurad was administered with food. The elimination half-life (t½) of lesinurad is approximately 5 hours. Lesinurad does not accumulate following multiple doses. The total body clearance is approximately 6 L/hr. Refer to clinical and clinical pharmacology reviews under NDA 207988 for detailed information on studies conducted with lesinurad alone and lesinurad in combination with allopurinol (DARRTS date 09/03/2015).

Allopurinol decreases production of UA by inhibiting xanthine oxidase, the enzyme responsible for the conversion of hypoxanthine to xanthine and of xanthine to UA, the end product of purine metabolism in humans. Allopurinol is rapidly metabolized to the corresponding xanthine analogue, oxypurinol (alloxanthine), which also is an inhibitor of xanthine oxidase. Oxypurinol has a longer plasma half-life than allopurinol (approximately 15 hours vs 1 - 2 hours) and is responsible for sustained sUA lowering over a 24-hour period with single daily doses of allopurinol. Peak plasma levels generally occur at 1.5 hours and 4.5 hours for allopurinol and oxypurinol, respectively. Refer to Zyloprim package insert for additional details on allopurinol.

6.3.2. Clinical Pharmacology Questions

What are the Clinical Pharmacology and Biopharmaceutics studies submitted under this NDA?
Clinical studies conducted in the lesinurad/allopurinol FDC development program are listed in Table 1. RDEA594-501 is the pivotal BE study reviewed under the current NDA.

Table 2. Overview of Clinical Studies in the FDC Clinical Development Program

Protocol Number	Title	Objectives
RDEA594-501	A Phase 1, Randomized, Open-Label, Crossover Study to Assess the Relative BA of Lesinurad/Allopurinol FDC Tablets and Coadministered Lesinurad and Allopurinol Tablets and the Effect of Food on the PK of Lesinurad/Allopurinol FDC Tablets in Healthy Adult Subjects	1. To assess the BA of lesinurad/allopurinol 200/300 FDC tablets and lesinurad/allopurinol 200/200 FDC tablets relative to coadministered lesinurad and allopurinol tablets in healthy adult subjects. 2. To assess the effect of a high-fat/high-calorie meal on the PK of lesinurad/allopurinol 200/300 FDC tablets in healthy adult subjects. 3. To assess the safety and tolerability of lesinurad/allopurinol 200/300 FDC tablets, lesinurad/allopurinol 200/200 FDC tablets, and lesinurad coadministered with allopurinol in healthy adult subjects.
ALLO-101	In Vitro-In Vivo Relationship Study to Assess the Impact of the In Vitro Dissolution Profile of Allopurinol on the PK Parameters Used to Establish BE	4. To determine whether defined and limited changes in in vitro dissolution impact the in vivo PK and relative BA of allopurinol and the active metabolite oxypurinol. 5. To provide additional safety information on allopurinol in healthy subjects.

Source: Module 2.5. Clinical Summary, Page 17.

What is the composition of the to-be-marketed formulation of lesinurad/allopurinol FDC?
Lesinurad is a Class II weak acid based on the Biopharmaceutics Classification System (BCS) designation, with low solubility at lower pH and high permeability. Absorption of lesinurad from the gastrointestinal tract is complete and oral BA is approximately 100%. Allopurinol is highly soluble across the physiological pH range (highly soluble by BCS classification up to 200 mg dose), and exhibits a permeability that suggests approximately 85% BA. Allopurinol is a BCS Class IV compound at the 300 mg dosage strength. Allopurinol shows pH independent solubility in the physiological pH range at 0.8 – 0.9 mg/mL at 37 °C. Allopurinol is rapidly metabolized to the active metabolite, oxypurinol. A weak PK drug-drug interaction was observed when lesinurad and allopurinol were coadministered but was not considered clinically meaningful (Refer to clinical pharmacology review for NDA 207988).

Were the to-be-marketed lesinurad/allopurinol FDC tablets used for pivotal study?
Drug product commercial formulation lots that were manufactured at the (b) (4) commercial scale at AstraZeneca AB by the proposed commercial process were used in relative BA clinical Study 501 and registration stability studies. Batch size (b) (4) range is approximately (b) (4) (b) (4) kg, which corresponds to approximately (b) (4) tablets. Two lesinurad /allopurinol FDC strengths, 200/200 and 200/300, were developed for the clinical/commercial formulation. (b) (4) were formulated for each FDC strength containing both active ingredients to provide immediate release of lesinurad and allopurinol. The nonfunctional film coating composition was initially a (b) (4) dosed in relative BA clinical Study 501 and primary stability lots. The film coating composition of the commercial formulation was later changed to a (b) (4) formulation. Refer to CMC review for details.

What are the findings from OSIS inspection?
Office of Study Integrity and Surveillance (OSIS) inspection was requested for the clinical and analytical sites for the pivotal BE study. The clinical site was not inspected based on the past inspection history. OSIS recommended accepting data after on-site inspection for the bioanalytical site (Refer to OSIS review dated 03/08/2016 in DARRTS).

Are the single-dose exposures from lesinurad/allopurinol FDC comparable to the individual components coadministered together in the fasted state?
Yes, the single dose exposures for lesinurad/allopurinol FDC were comparable to the individual components coadministered together in the fasted state.

In Study 501, Part 1, BE in the fasted state between the lesinurad/allopurinol 200/300 FDC tablets and the coadministered single agents was established based on the exposure data for lesinurad, allopurinol, and oxypurinol. All 90% CIs for the ratios of the test and reference products for both AUC and C_{max} were contained within the conventional BE limits of 0.80 to 1.25 (Table 3). In Part 3, the 200/200 FDC tablet met the BE criteria with respect to all 3 PK parameters for all 3 analytes, with the exception of allopurinol C_{max}; the upper limit of the 90% CI (1.28) was outside of the conventional BE limits and the geometric mean was 18% higher (Table 4). The efficacy and safety of allopurinol is mainly driven by oxypurinol and because the FDC tablet demonstrated BE to the single agents with respect to oxypurinol, the increase in allopurinol C_{max} are not expected to be clinically important for efficacy and safety of the FDC drug product. Overall, the results for both FDC tablet strengths fulfill the criteria to support the PK bridge between the lesinurad/allopurinol FDC tablet and coadministered lesinurad and allopurinol tablets in the fasted state.

Table 3. Comparison of Geometric Mean Pharmacokinetic Parameters: Lesinurad/Allopurinol 200/300 FDC Tablets Versus the Coadministered Single Agents (Study 501, Part 1; N=35)

Parameter	Analyte	GLSMR (90% CI)	Variability (CV%)	
			Intra-subject	Inter-subject
C_{max}	Lesinurad	1.1026 (1.0056-1.2090)	23.1	25.7
	Allopurinol	1.0758 (0.9837-1.1766)	22.4	23.0
	Oxypurinol	0.9914 (0.9653-1.0183)	6.6	15.5
AUC_{last}	Lesinurad	0.9895 (0.9501-1.0306)	10.1	31.9
	Allopurinol	1.0045 (0.9675-1.0428)	9.3	27.7
	Oxypurinol	0.9967 (0.9771-1.0168)	4.9	16.5
AUC_{∞}	Lesinurad	0.9889 (0.9494-1.0299)	10.1	31.6
	Allopurinol	1.0054 (0.9683-1.0440)	9.3	26.9
	Oxypurinol	1.0022 (0.9804-1.0245)	5.4	19.4

Source: Module 2.7.1, Summary of Biopharmaceutics Studies and Associated Analytical Methods, Page 17.

Table 4. Comparison of Geometric Mean Pharmacokinetic Parameters: Lesinurad/Allopurinol 200/200 FDC Tablets Versus the Coadministered Single Agents (Study 501, Part 3; N=53)

Parameter	Analyte	GLSMR (90% CI)	Variability (CV%)	
			Intra-subject	Inter-subject
C_{max}	Lesinurad	0.9881 (0.9248-1.0558)	20.5	17.3
	Allopurinol	1.1823 (1.0905-1.2817)	25.2	23.9
	Oxypurinol	1.0260 (1.0046-1.0479)	6.5	18.0
AUC_{last}	Lesinurad	0.9816 (0.9439-1.0208)	12.1	27.7
	Allopurinol	1.0914 (1.0520-1.1324)	11.3	25.7
	Oxypurinol	1.0175 (1.0003-1.0349)	5.2	16.4
AUC_{∞}	Lesinurad	0.9825 (0.9452-1.0214)	11.9	27.4
	Allopurinol	1.0760 (1.0387-1.1147)[a]	10.6	25.3
	Oxypurinol	1.0175 (0.9991-1.0363)	5.6	20.0

Source: Module 2.7.1, Summary of Biopharmaceutics Studies and Associated Analytical Methods, Page 18.

How does food affect the bioavailability of lesinurad/allopurinol FDC?

The effect of food on lesinurad and allopurinol PK was evaluated in Study 501, Part 2. Healthy volunteers received a single dose of the 200/300 FDC tablet under fasted conditions (fasted at least 10 hours prior to dosing) and a single dose under fed conditions (30 minutes after a high calorie, high-fat meal [800 to 1000 Kcal with at least 50% of the calories from fat]), with a 7-day washout period between the 2 doses. All patients were given a standard meal 4 hours after FDC tablet administration. Exposure results from the fasted and fed treatments are compared in Table 5.

Table 5. Comparison of Lesinurad, Allopurinol, and Oxypurinol Exposures in Fed Versus Fasting States (Study 501, Part 2; N=28)

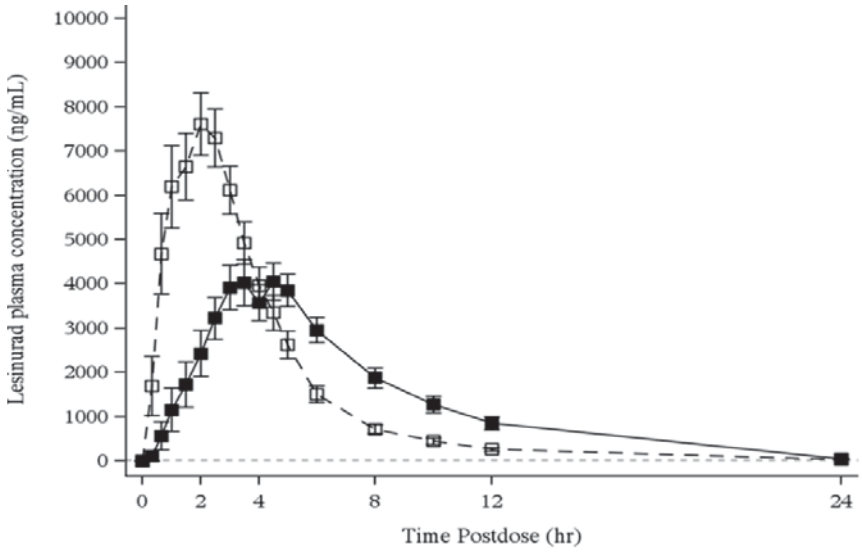
Parameter	Analyte	GLSMR (90% CI)	Variability (CV%)	
			Intra-subject	Inter-subject
C_{max}	Lesinurad	0.5450 (0.4703-0.6316)	33.2	15.6
	Allopurinol	0.8166 (0.7030-0.9486)	33.8	12.0
	Oxypurinol	0.8633 (0.8315-0.8964)	8.2	10.3
AUC_{last}	Lesinurad	0.9796 (0.9272-1.0350)	12.1	31.0
	Allopurinol	0.8750 (0.8331-0.9191)	10.8	22.6
	Oxypurinol	0.8471 (0.8267-0.8680)	5.4	16.2
AUC_{∞}	Lesinurad[a]	0.9642 (0.9182-1.0125)	10.3	30.9
	Allopurinol[a]	0.8835 (0.8399-0.9294)	10.7	21.8
	Oxypurinol	0.8476 (0.8248-0.8711)	6.0	20.8

Source: Module 2.7.1, Summary of Biopharmaceutics Studies and Associated Analytical Methods, Pages 19.

Lesinurad plasma AUC was similar in the fed and fasted states following administration of the FDC tablet, whereas C_{max} was reduced by 46% in the fed state and median T_{max} was extended

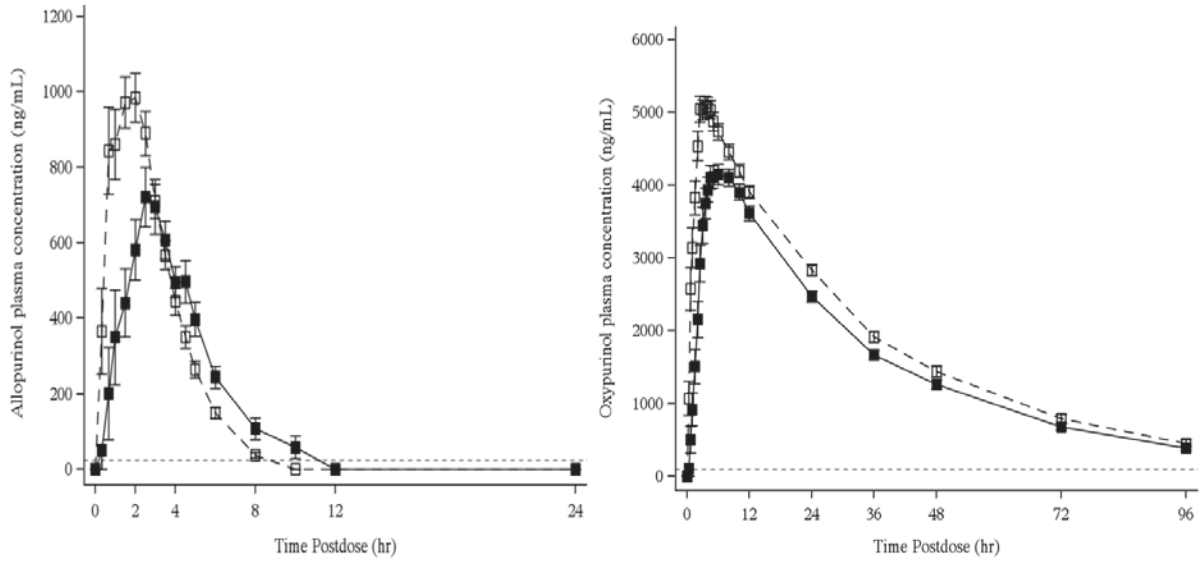
from 2.00 hours to 4.50 hours (Figure 1). Similarly, allopurinol plasma AUC was similar in the fed and fasted states following administration of the FDC tablet, whereas C_{max} was reduced by 18% in the fed state and median T_{max} was extended from 1.25 hours to 3.00 hours (Figure 2). The 90% CIs for the fed/fasted ratios of oxypurinol C_{max} and AUC were within the 0.80 to 1.25 BE limits; the point estimates were reduced by approximately 15% in the fed state compared with the fasted state.

Figure 1. Mean (Standard Error) 0 to 24-Hour Plasma Concentrations of Lesinurad Following Single Oral Doses of Lesinurad/Allopurinol 200/300 FDC Tablets Under Fasted and Fed Conditions



Source: Module 5.3.1.1, RDEA594-501 - Lesinurad/Allopurinol 200/300 and 200/200 FDC Tablets Bioavailability, Pages 75.

Figure 2. Mean (Standard Error) Plasma Concentrations of Allopurinol (left) and Oxypurinol (right) Following Single Oral Doses of Lesinurad/Allopurinol 200/300 FDC Tablets Under Fasted and Fed Conditions



Source: Module 5.3.1.1, RDEA594-501 - Lesinurad/Allopurinol 200/300 and 200/200 FDC Tablets Bioavailability, Pages 80-81.

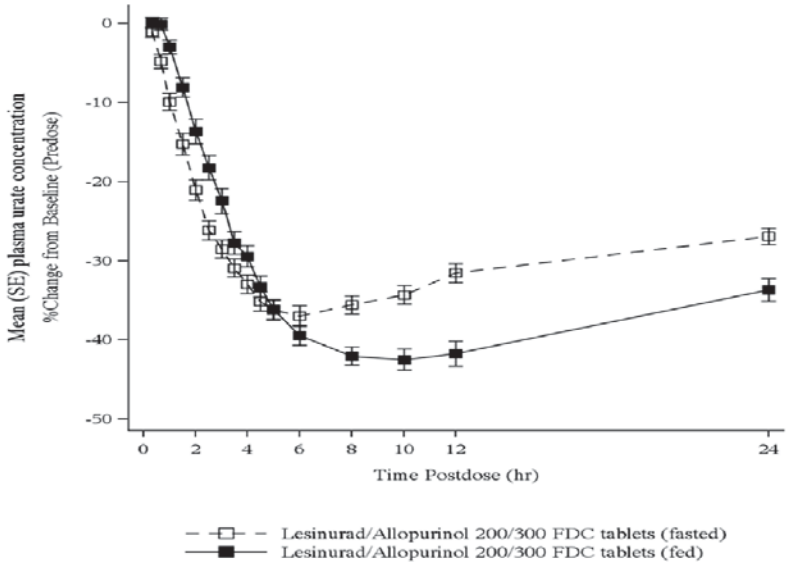
In view of the observed PK differences in the food effect study with the FDC tablet, additional questions and the supportive data submitted thereof by the sponsor were evaluated; these questions are discussed below.

1. ***Do the observed PK differences in the food effect study have an impact on the pharmacodynamics when lesinurad/allopurinol FDC is administered in the fed state in the healthy subjects?***

The effect of differences in PK profiles between FDC and coadministered single agents on PD performance was evaluated by measurement of plasma uric acid (pUA) concentrations in samples collected from Study 501, Part 2 comparing the fed and fasted states (Figure 3). The mean percent change in pUA was similar through the first 6 hours postdose and separated between 6 and 24 hours postdose, with a more prolonged maximal lowering effect thereafter in the fed state. This demonstrates that the UA lowering in the healthy subjects was not impacted by the PK differences observed in the fed state with the FDC tablet.

While the effect of food on lesinurad C_{max} following administration of the lesinurad/allopurinol FDC tablet in Study 501 (46%) was within the range observed in the lesinurad PK studies with different pilot formulations (18-58%), it was greater than that cited in the Zurampic® label (18%, Study 121, refer to clinical pharmacology and clinical reviews for NDA 207988). The applicant speculates that this difference may be attributable to the mass of the FDC tablet and the impact of prolonged gastric emptying on lesinurad absorption. The applicant states that the larger mass of the FDC tablet as compared to the lesinurad tablet (Zurampic®) may contribute to the observed difference in the effect of food on the lesinurad concentration-time profile. Lesinurad from the FDC tablet may take longer than lesinurad from the Zurampic tablet to completely transit through the stomach at a fixed gastric emptying rate leading to a decrease in C_{max}. As the solubility profile of lesinurad is pH-dependent, the delays in gastric emptying may impact C_{max} while not influencing the AUC. While the exact mechanism for the observed difference in C_{max} from FDC as compared to lesinurad tablet remains unclear, these differences did not translate in to PD differences in the healthy subjects.

Figure 3. Mean Percentage Change From Predose in pUA Following Single Oral Dose of Lesinurad/Allopurinol 200/300 FDC Tablets Under Fasted and Fed Conditions (Study 501)



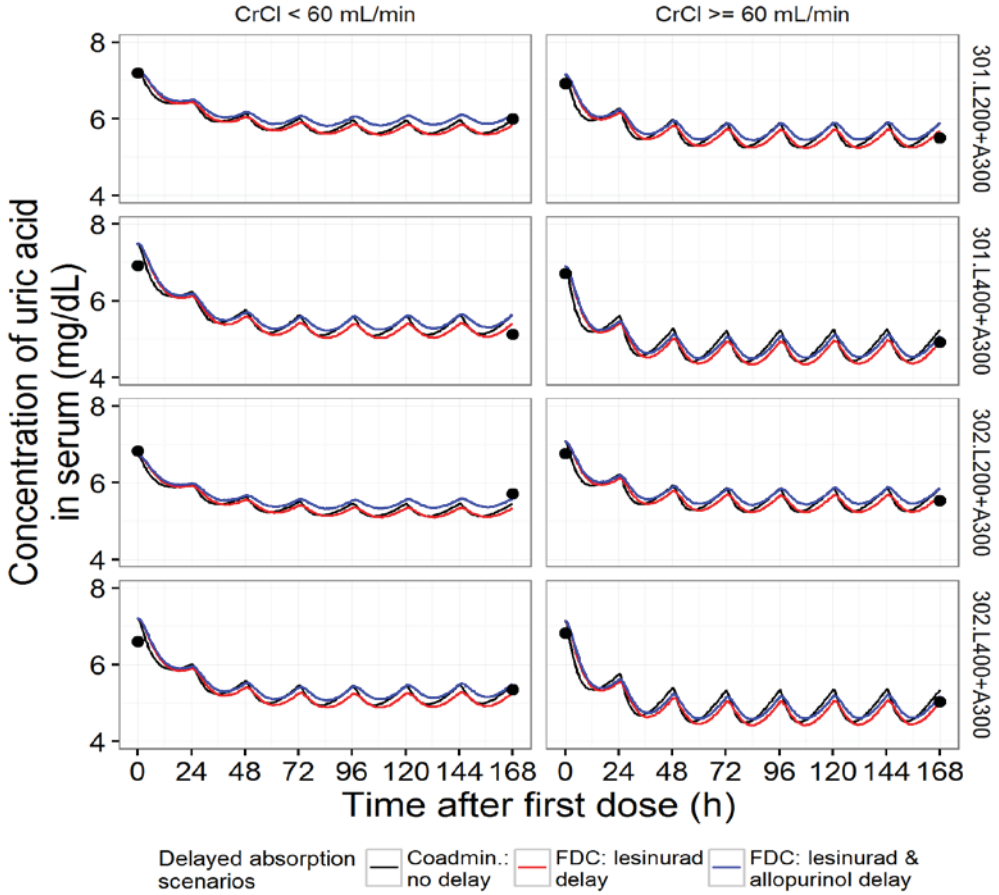
Source: Module 5.3.1.1, RDEA594-501 - Lesinurad/Allopurinol 200/300 and 200/200 FDC Tablets Bioavailability, Pages 89.

2. Do the observed PK differences in the food effect study when lesinurad/allopurinol FDC was administered in the fed state in healthy subjects have an impact on the pharmacodynamics in the hyperuricemic patients?

A physiology based PKPD model capturing the uric acid turnover including its production and clearance and the pharmacological effect of lesinurad and allopurinol on uric acid disposition was used for simulating the uric acid lowering effect from the FDC tablet in the patients. The PK/PD dataset used for model building and parameter estimation consisted of data from 17 Phase 1 studies (NDA 207988). Out of the 17 studies, RDEA594-110 and study RDEA594-111 were Phase 1b studies conducted in gout patients with hyperuricemia. The developed PK/PD model was externally validated using data from core lesinurad (NDA 207988) Phase 3 studies (RDEA594-301, RDEA594-302, RDEA594-303, and RDEA594-304) and 2 published febuxostat Phase 3 studies APEX and FACT. The validation results showed that the model is able to adequately predict the serum UA profiles following lesinurad, allopurinol, and febuxostat treatment in the hyperuricemic patients. In addition, the model validation also accounted for the dependence of UA disposition and dynamic responses of the UA handing system to lesinurad treatment on renal function by stratifying the validation results by creatinine clearance (CrCl) levels. Results showed that the model is able to accurately predict serum UA profiles in patients with mild and moderate renal impairment. With the developed and validated PK/PD model, simulations were conducted to evaluate the food effect induced lesinurad and allopurinol absorption delay on the ability of the FDC tablet to maintain UA lowering. Simulation results demonstrated that there are no clinically meaningful differences in the serum UA lowering effect of the FDC tablet in the hyperuricemic patients over a range of lesinurad and allopurinol absorption rate and BA changes; in other words, the PD effect of the FDC tablet is independent of the lesinurad and allopurinol C_{max} changes as long as AUCs are

unchanged. The sponsor's simulation was conducted for typical hyperuricemic patients who are naïve to allopurinol and lesinurad treatment. However, the FDC tablet is proposed for the treatment of hyperuricemia associated with gout in patients who have not achieved target serum uric acid levels with allopurinol alone. To verify the robustness of the sponsor's simulation results and conclusion, independent simulation in patients who are already on allopurinol treatment and have not achieved target serum UA levels were conducted in-house. In this analysis patient characteristics in the lesinurad Phase 3 study 301 and 302 were used for the simulation to represent the target population for the FDC tablet, i.e. hyperuricemic patients who have not achieved target serum UA levels with allopurinol alone. Three scenarios were simulated including 1) a reference scenario where lesinurad and allopurinol are co-administered as evaluated in the Phase 3 studies; 2) a scenario where the FDC tablet is administered with food which results in reduced C_{max} of lesinurad; 3) a scenario where the FDC tablet is administered with food which not only reduced the absorption rate of lesinurad but also reduced the absorption rate and bioavailability of allopurinol. The factors for delay of lesinurad and allopurinol absorption were selected to mimic the observed changes in lesinuard and allopurinol PK in the food effect study 501 part 2 conducted with the lesinurad/allopurinol FDC tablet. The simulated sUA profiles demonstrate that food-effect-induced lesinurad and allopurinol PK changes following the FDC tablet administration in hyperuricemic patients who have not achieved target sUA levels with allopurinol alone has negligible effect on serum UA lowering, as shown in Figure 4. Refer to pharmacometrics review in Appendix 13.4 for details of the PKPD model and the validation and simulation results.

Figure 4. Simulated Concentration Time Profiles of Serum Uric Acid under Different Scenarios



Source: Figure 24 from Pharmacometrics review in appendix 13.4.

The lesinurad C_{max} reduction from the FDC tablet in the presence of food was considered significant from PK perspective. However, modeling and simulation data showed that these PK differences would not result in clinically meaningful differences in the serum uric acid lowering effect in the hyperuricemic patients. Hence, it was concluded that the observed food effect is not expected to compromise the efficacy of lesinurad/allopurinol FDC tablet in the hyperuricemic patients.

Are the bioanalytical methods properly validated to measure PK and PD in plasma samples?
PK measurement: Bioanalytical methodology employed stable isotope-labeled internal standardization and liquid chromatography with tandem mass spectrometric detection (LC/MS/MS) for analyses of lesinurad and allopurinol/oxypurinol concentrations in plasma. Method validation and sample analysis supporting the clinical studies were according to the US FDA guidance (US FDA Bioanalytical Method Validation, 2001) and all acceptance criteria as specified in those guidelines were met. Accuracy, expressed as percent bias from the theoretical concentrations, was within ±20% at the lower limit of quantification and ±15% at all other concentration levels. Precision, expressed as percent coefficient of variation, was ≤20% at the lower limit of quantification and ≤15% at all other concentration levels. The lesinurad

analysis in the plasma assay was initially validated in Study SR09-041 (BAM2009.03); the method was subsequently modified to alter the curve range to more appropriately match the expected plasma concentration profile based upon the intended dosing. The new method (BAM2015-05), which was used in FDC Study 501, was partially validated in Study SR15-019. Supporting stock and working solution stability can be found in Study SR09-045. The allopurinol and oxypurinol analysis in plasma assay (BAM2011-03) was validated in Study SR11-076. Supporting stock and working solution stability can be found in Study SR11-077. An overview of lesinurad, allopurinol, and oxypurinol bioanalytical methods used and validation study reports is presented in Table 6.

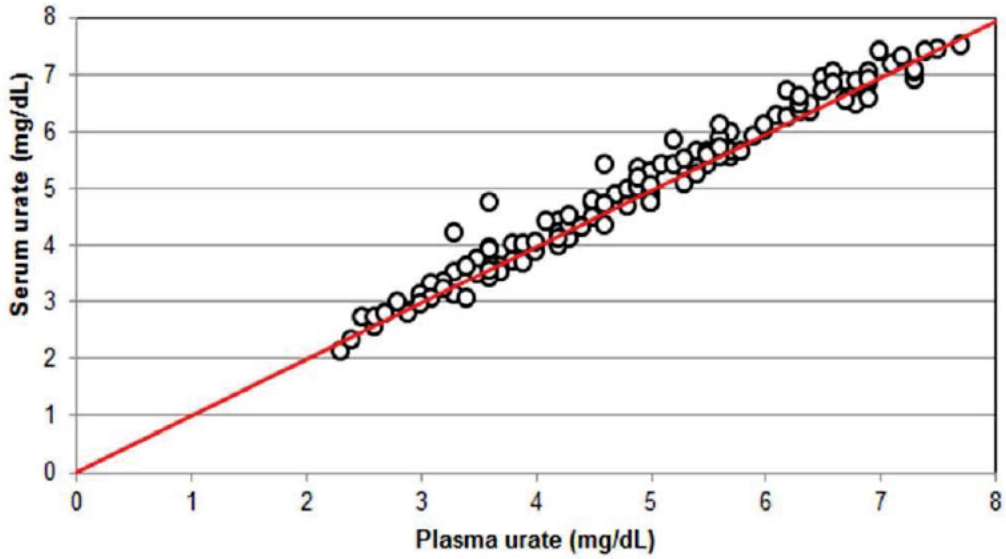
Table 6. Summary of Bioanalytical Assay for Pivotal Biopharmaceutical Study 501

Study Number	Analyte(s)	Method	Matrix	Analytic Technique	LLOQ(s)	Linear Range(s)	Method Validation Reports
RDEA594-501	Allopurinol, oxypurinol	BAM2011-03	Plasma	LC/MS/MS	25.0 (allo), 100 (oxy) ng/mL	25.0-2000 (allo), 100-25000 (oxy) ng/mL	SR11-076 original issuance and Amendment 1; SR11-077 original issuance and Amendment 1
	Lesinurad	BAM2015-05	Plasma	LC/MS/MS	20.0 ng/mL	20.0-10000 ng/mL	SR15-019 original issuance; SR09-041 original issuance and Amendment 1; SR09-045 original issuance and Amendment 1

Source: Module 2.7.1., Summary of Biopharmaceutic Studies and Associated Analytical Methods, Page 11.

PD measurement: Plasma uric acid concentrations were measured using a validated methodology (BAM2010-05-3.0). The method involved the addition of [1,3-$^{15}N_2$]uric acid as internal standard and extraction by protein precipitation using dilution solvent (1% ammonium hydroxide solution in methanol:water, 3:1, v/v). An aliquot of the extract was further diluted with injection solvent (0.1% ammonium hydroxide solution in water) and analyzed by high-performance liquid chromatography with tandem mass spectrometry (LC/MS/MS). A triple quadrupole mass spectrometer, operated in negative TurboIonSpray® mode, was used to monitor the precursor → product ion transitions of m/z 167 →124 and m/z 169 →125 for uric acid and [1,3-^{15}N]uric acid, respectively. The calibration curves were linear over the concentration range between 1.00 mg/dL and 25.0 mg/dL with a lower limit of quantitation (LLOQ) of 1.00 mg/dL. While sUA concentrations were determined by enzymatic method for PD assessment in NDA 207988, the sponsor did not collect serum samples in study 501 and hence pUA was measured. pUA concentrations determined by LC/MS/MS were shown to highly correlated with sUA in the validation studies as shown in Figure 5 (Study 125 bioanalytical report SR13-041).

Figure 5. Correlation between plasma uric acid and serum uric acid (Study 125, NDA 207988).



Source: NDA 207988, Study 125, bioanalytical report SR13-041, Figure 38.

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Renu Singh (Clinical Pharmacology Primary Reviewer)

X Xiaofeng Wang -S (Affiliate)

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Anshu Marathe (Clinical Pharmacology Team Leader)

7 Statistical and Clinical and Evaluation

Duzallo is a fixed dose combination (FDC) product that consists of two previously approved urate lowering agents, lesinurad (Zurampic®) and allopurinol (Zyloprim®). As a result of a nephrotoxicity signal observed in the safety database reviewed in support of NDA 207988, lesinurad's USPI contains Box Warnings regarding the risk for acute renal failure to occur particularly when this drug is administered as monotherapy and the need to use it in combination with a xanthine oxidase inhibitor. According to the Applicant, they have developed this FDC urate lowering product under the FDA's Combination Rule (21 CFR §300.50) in order to mitigate the renal safety risk of lesinurad monotherapy. The efficacy and safety data in support of this 505(b)(2) application for these proposed FDC tablets containing 200 mg/200 mg and 200 mg /300 mg of lesinurad and allopurinol, respectively, is primarily predicated on data reviewed previously in support of NDA 207988 lesinurad (Zurampic®), which included combination studies that evaluated the co-administration of these two urate lowering agents. As no new clinical efficacy data were submitted in this NDA, for details on the efficacy data supporting this FDC product, the reader is referred to the efficacy data reviewed previously in support of NDA 207988 lesinurad (Zurampic®). Additionally, the Applicant conducted a bioavailability/bioequivalence study to provide the necessary pharmacokinetic data in support of a bridge between the combination studies contained in the lesinurad NDA (207988) to the lesinurad/allopurinol FDC NDA (209203), which was reviewed and commented above in Section 6 Clinical Pharmacology by the Office of Clinical Pharmacology/Division of Clinical Pharmacology II reviewer.

7.1. Sources of Clinical Data and Review Strategy Table of Clinical Studies

Table 7 summarizes the clinical development program for the FDC lesinurad/allopurinol tablets which includes two new phase 1 clinical pharmacology studies and three phase 3 studies which were previously reviewed under lesinurad NDA 207988.

Table 7 – Key Design Features of Lesinurad/Allopurinol Trials

Study /Objectives	Study Design/ Duration/ No. Sites	Dosage Regimen/ Route of Adm.	No. of Subjects	Diagnosis/ Entry Criteria	End Points
Phase 1 study (New studies)					
RDEA594-501; Objectives: 1. Evaluate the bioavailability of lesinurad/allopurinol 200/300 and 200/300 FC tablets relative to coadministration of lesinurad and allopurinol; 2. Evaluate effect of high-fat/high calorie	R,OL, 3-part, cross-over, relative bioavailability and food effect study	Single dose: Part 1: LES200mg/ALLO 300 FDC tablets Part 2: LES200/ALLO200 FDC tablets Part 3: LES200 mg tablets with ALLO 100 mg and 300mg	Part 1: N= 36 Part 2: N=28 Part 3: N=55	Healthy volunteers	PK Parameters

meal on PK of lesinurad/allopurinol 200/300 FDC tablets; 3. Evaluate the safety and tolerability of lesinurad/allopurinol 200/300 and 200/300 FDC tablets and lesinurad coadministered with allopurinol		tablets			
ALLO-101; Objectives: 1. Determine whether defined and limited changes in *in vitro* dissolution impact the *in vivo* PK and relative bioavailability of allopurinol and the active metabolite oxypurinol; 2. Evaluate the safety of allopurinol	OL, sequential dose, 4-period in vitro dissolution study (fasted state)	Zyloprim 300 mg tablet; ALLO 300 mg tablet of varying hardness (23, 25, and 26 kp)	N=22	Healthy volunteers	PK Parameters
Phase 3 Studies (Previously reviewed under NDA 207988)					
RDEA594-301; Objectives: Evaluate lesinurad's efficacy at Month 6 when used in combination with allopurinol compared to allopurinol monotherapy	12-month, MC, R, DB, PC, combination study	Multiple doses of 200 mg and 400 mg qd lesinurad crystalline free acid tablets in fed state Multiple daily doses of 100-800 mg allopurinol in fed state Colchicine 0.5-0.6 mg qd or NSAID ± PPI in fed state	N=603	Subjects with gout with an inadequate hypo-uricemic response to standard of care allopurinol	Efficacy and Safety
RDEA594-302; Objectives: Evaluate lesinurad's efficacy at Month 6 when used in combination with allopurinol compared to allopurinol monotherapy	12-month, MC, R, DB, PC, combination study	Multiple doses of 200 mg and 400 mg qd lesinurad crystalline free acid tablets in fed state Multiple daily doses of 100-900 mg allopurinol in fed state Colchicine 0.5-0.6 mg qd or NSAID ± PPI in fed state	N=610	Subjects with gout with an inadequate hypo-uricemic response to standard of care allopurinol	Efficacy and Safety
RDEA594-306; Objectives: Evaluate the long-term efficacy and safety of lesinurad in combination with allopurinol	Long-term, uncontrolled, OL extension study for subjects who completed Studies 301 and 302	Multiple doses of 200 mg and 400 mg qd lesinurad crystalline free acid tablets in fed state Multiple daily doses of 100-900 mg allopurinol in fed state	N=714	Subjects with Gout	Efficacy and Safety (Ongoing Month 12)

		Colchicine 0.5-0.6 mg qd or NSAID ± PPI in fed state			

7.1.2. Review Strategy

The Applicant conducted two adequate and well-controlled phase 3 trials, RDEA594-301 and RDEA594-302, which evaluated the efficacy and safety of the co-administration of 200 mg and 400 mg of lesinurad with doses of up to 800 mg of allopurinol in hyperuricemic patients with gout. The results from these two pivotal trials were reviewed by this medical officer for efficacy in support of NDA 207988 Lesinurad (Zurampic®). Additionally, the Applicant submitted the interim results from one ongoing extension trial, RDEA594-306. Since this study was not designed to evaluate efficacy but to support the safety of chronic administration of the lesinurad/allopurinol, it was not reviewed to support the FDC lesinurad/allopurinol 200/200 mg and 200/300 mg tablets ability to treat hyperuricemia associated with gout but was included previously in the overall review of safety in support of lesinurad's NDA 207988.

7.2. Review of Relevant Individual Trials Used to Support Efficacy

7.2.1. Studies RDEA594-301 and RDEA594-302

The reader is referred to the review dated September 14, 2015 of NDA 207988 for additional information regarding these two clinical studies.

7.2.2. Study Results

Refer to the review for NDA 207988 lesinurad (Zurampic®) dated September 14, 2015.

7.3. Integrated Review of Effectiveness

7.3.1. Assessment of Efficacy Across Trials

Refer to the review for NDA 207988 lesinurad (Zurampic®) dated September 14, 2015.

7.3.2. Integrated Assessment of Effectiveness

The clinical data submitted in support of the FDC lesinurad /allopurinol tablets as a treatment of hyperuricemia associated with gout in adults was generated from two, 12-month, phase 3 trials, RDEA594-301 and RDEA504-302, which were previously reviewed in support of lesinurad's NDA 207988. These were multiregional, randomized, double-blind, placebo-controlled, parallel group studies in 1,213 patients who failed to achieve serum uric acid (sUA) levels of <6 mg/dL despite treatment with a minimum of 8 weeks of allopurinol (at least 300 mg/day or 200 mg /day in subjects with eCrCl ≥45-60 mL/min). These trials evaluated the urate lowering effect of 200 mg and 400 mg doses of lesinurad administered once daily with concomitant allopurinol. In studies RDEA594-301 and RDEA594-302, a greater proportion of

patients achieved the primary endpoint (sUA <6 mg/dL at Month 6) in the lesinurad 200 mg + allopurinol treatment groups (study RDEA594-301: 54%; study RDEA594-302: 55%) and the lesinurad 400 mg + allopurinol treatment groups (study RDEA594-301:59%; study RDEA594-302: 67%) as compared to placebo + allopurinol (study: RDEA594-301: 28%; Study RDEA594-302: 23%). The differences between each of the lesinurad + allopurinol treatment groups and the placebo+ allopurinol groups were statistically significant for both trials (Study 301: p<0.0001; Study 302: p<0.001) but a dose-response effect between the two lesinurad groups + allopurinol was only demonstrated in study RDEA594-302. Over the 12-month courses of both studies, these differences in treatment responses between the lesinurad + allopurinol groups versus placebo + allopurinol were consistently maintained and support the durability of the combination's urate lowering effects. However, the magnitude of lesinurad's urate lowering effect was modest in both of these trials. (The adjusted difference in mean change over baseline for the lesinurad 200 mg + allopurinol treatment groups versus placebo + allopurinol groups ranged from 1.01-1.09 mg/dL at Month 6 to 0.89-0.93 mg/dL at Month 12; for the lesinurad 400 mg + allopurinol treatment groups versus placebo + allopurinol groups this difference ranged from 1.23-1.36 mg/dL at Month 6 to 1.18-1.25 mg/dL at Month 12.)

Since the primary endpoints for the pivotal studies were based on serum uric acid, additional support for a clinical benefit for treatment with lesinurad was to have been derived from a number of clinical major secondary endpoints that assessed gout flares and tophus resolution. No additional clinical benefit in terms of decreasing gout flares or the resolution or size of tophi was demonstrated with either the 200 mg or 400 mg lesinurad + allopurinol treatment groups in these two studies. There was also no improvement in the assessments for disability that were conducted in these studies, but this was probably due to the low level of disability at baseline for the patient populations in these trials.

The results from subpopulation analyses for age, race and region on pooled data for studies RDEA594-301 and RDEA594-302 did not identify differences in efficacy across these groups. A lack of treatment effect with lesinurad + allopurinol was observed for female gender in these analyses for the pooled studies RDEA594-301 and RDEA594-302. However, the small sample size for females precluded definitive conclusions about these findings. No statistically significant differences in treatment effect were observed for subgroups by baseline renal function (eCrCl: <45 mL/min, 45 to <60 mL/min, and > 60 mL/min) or for baseline allopurinol dose (<300 mg/d, 300 mg/d, and >300 mg/d) for these studies. Additional subgroup analyses in patients using low dose (< 325 mg/day) aspirin and thiazide and thiazide-like diuretics, which are known to affect uric acid levels, did not identify differences in the efficacy of lesinurad + allopurinol.

Based on these previously findings, there appears to be adequate statistical evidence to support the efficacy of the proposed FDC tablets comprised of 200 mg dose of lesinurad with either 200 mg or 300 mg of allopurinol as a treatment of hyperuricemia associated with gout.

7.4. Review of Safety

7.4.1. Safety Review Approach

Similar to the efficacy data, the safety data in support of the FDC lesinurad /allopurinol tablets is primarily predicated on the safety data that was submitted and reviewed previously in support of lesinurad's NDA 207988. (The reader is referred to the clinical review for NDA 207988 Lesinurad [Zurampic®] dated September 14, 2015 for additional information.) For completeness, the Applicant also submitted the safety data collected from the phase 1, bridging bioavailability/bioequivalency study RDEA594-501 and a 120-day safety update that contained supportive safety data from the following sources:

- Postmarketing safety data (2016 annual report) for Zurampic®
- Exposure adjusted data from pooled studies RDEA594-301, RDEA594-302, RDEA594-304 (lesinurad + febuxostat), RDEA594-306, and REDA594-307 (lesinurad-febuxostat) (cutoff date: 04 November 2014)
- Final study report for open-label continuation studies RDEA594-306 and RDEA594-307 (lesinurad + febuxostat)
- Updated 30-month summary of serious adverse events (SAEs) and serious adverse events of interest (SAEI) (e.g., renal and cardiovascular adverse events) from the open-label extension studies RDEA594-306 (lesinurad + allopurinol) and RDEA594-307 (lesinurad + febuxostat) and RDEA594- 203 (phase 2 dose ranging study evaluating lesinurad + allopurinol)

Since assessment of pooled safety data that included data from studiesRDEA594-304 and RDEA594-307 could result in a mischaracterization of the FDC lesinurad/allopurinol tablets as these two studies evaluated lesinurad with concomitant febuxostat which is a xanthine oxidase inhibitor with a different safety profile from allopurinol particularly in patients with underlying renal insufficiency, this data was not included in this safety assessment. Safety data from studies RDEA594-301, RDEA594-302 and the open-label extension study RDEA594-306 were all previously reviewed in support of lesinurad's NDA 207988 and will not be re-discussed in this review. The following safety review will only discuss the postmarketing safety data and updated 30-month summary of SAEs and SAEI as it relates to the FDC lesinurad + allopurinol tablets contained in the 120-day safety update.

7.4.2. Review of the Safety Database

Refer to the clinical review for NDA 207988 Lesinurad (Zurampic®) dated September 14, 2015.

7.4.3. Safety Results

Review of the safety data collected from the phase 1 study RDEA594-501 did not reveal any new safety signals. There were no deaths or SAEs reported in this trial. All treatment-emergent adverse events in this trial were Rheumatology Common Toxicity Criteria Grade 1 or 2. The commonly reported TEAEs in study associated with FDC lesinurad/allopurinol 200 mg/300 mg tablets were constipation, headache, anal hemorrhage, arthralgia, decreased appetite, fatigue, infrequent bowel movements, back pain, balance disorder, and gingival swelling.

7.4.4. Analysis of Submission-Specific Safety Issues

There were no new deaths reported in the completed study reports for the pivotal studies RDEA594-301 and RDEA594-302, or in the open-label extension study RDEA594-306 contained in the 120-day safety update. Review of the SAEs revealed no new safety issues pertaining to the coadministration of lesinurad with allopurinol. Since renal risk was minimized by numerous amendments to these ongoing study protocols, no new serious renal adverse events (e.g., acute renal failure, kidney stones or increases in serum creatinine) or major adverse cardiovascular events (MACE) events were reported.

7.4.5. Safety Analyses by Demographic Subgroups

Refer to clinical review for NDA 207988 Lesinurad (Zurampic®) dated September 14, 2015.

7.4.6. Specific Safety Studies/Clinical Trials

Refer to the clinical review for NDA 207988 Lesinurad (Zurampic®) dated September 14, 2015.

7.4.7. Additional Safety Explorations

Refer to the clinical review for NDA 207988 Lesinurad (Zurampic®) dated September 14, 2015.

7.4.8. Safety in the Postmarket Setting

This application crossed referenced postmarketing data contained in the previously reviewed 2016 annual report for NDA 207988. Since lesinurad had been marketed for a very short period of time in this country (since October 2016) at the time this report was submitted, review of the latter did not reveal any new safety issues associated with lesinurad 200 mg in combination with a xanthine oxidase inhibitor as it did not contain any 15-day expedited reports of unexpected SAEs. The Applicant also submitted the results of an updated literature search for lesinurad monotherapy for the time period December 23, 2015 to December 22, 2016 that utilized Embase.com and or Medline for literature citations and abstracts in the 120-day safety update. Review of the results from this exercise did not identify any new safety information concerning lesinurad when co-administered with allopurinol.

7.4.9. Integrated Assessment of Safety

Specific safety concerns raised during the review of the safety database submitted in support of lesinurad's NDA 207988 included a higher rate of deaths, a higher rate of MACE events, a higher rate of serious adverse events and a higher rate of serious and non-serious renal-related adverse events associated with the administration of lesinurad. Additionally, the serious and serious renal-related adverse events (e.g., acute and chronic renal failure as well as kidney stones) observed occurred in a dose-dependent manner and correlated with safety findings from the lesinurad 400 mg monotherapy dose which was evaluated separately in a 6-month, randomized, placebo-controlled trial (study RDEA596-303). As a result of these safety findings, the risk/benefit assessment favored the 200 mg dose of lesinurad in combination with a xanthine oxidase inhibitor. The identified safety concerns were conveyed to healthcare providers as a box Warning regarding the increased risk for acute renal failure particularly when lesinurad is administered as monotherapy and Warnings and Precaution statements that included the occurrence of major adverse cardiovascular events in the USPI and Medication Guide for lesinurad. (Reader is referred to the clinical review for NDA 207988 Lesinurad [Zurampic®] dated September 14, 2015 for additional information.) Although no new safety signals were identified on review of the new safety data contained in the 120-day safety update or on review of the limited postmarketing data associated with the coadministration of lesinurad with allopurinol, the same safety concerns noted during the review of lesinurad's NDA 207988 continue to apply to the FDC lesinurad/allopurinol tablets.

SUMMARY AND CONCLUSIONS

7.5. Statistical Issues

The reader is referred to section 7.3.2 above and the statistical review for NDA 207988 lesinurad (Zurampic®) dated October 8, 2015 for additional information regarding statistical issues.

7.6. Conclusions and Recommendations

Based on the safety data contained in the 120-day safety update for this application coupled with the efficacy and safety results from the adequate and well-controlled studies RDEA594-301 and RDEA594-302 which evaluated the co-administration of the two monocomponents lesinurad 200 mg with 200 mg and 300 mg doses of allopurinol reviewed previously under NDA 207,988, the risk/benefit assessment favors approval of the lesinurad/allopurinol fixed-dose combination (FDC) tablets at strengths of 200 mg/200 mg and 200 mg/300 mg, respectively, administered once daily for the treatment of hyperuricemia associated with gout in patients who have not achieved target serum uric acid (sUA) levels with allopurinol alone.

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Primary Clinical Reviewer

Clinical Team Leader

8 Advisory Committee Meeting and Other External Consultations

An Arthritis Advisory Committee (AAC) meeting was held on October 23, 2015 at which the risk/benefits associated with the use of lesinurad based on the efficacy and safety issues identified during the agency's review of the data submitted in support of NDA 207,988 Lesinurad (Zurampic®) were discussed. An AAC meeting was not held for this 505(b)(2) application for the FDC lesinurad/allopurinol tablets since this application relies on data submitted and reviewed previously in support of NDA 207,988. The reader is referred to the minutes from the October 23, 2015 AAC meeting at which NDA 207,988 Lesinurad (Zurampic®) was discussed for additional information.

9 Pediatrics

As per provisions of the Pediatric Research Equity Act (PREA), the Applicant submitted a request for a full waiver not to conduct studies in birth to 18 years of age in pediatric patients with gout and hyperuricemia since such studies would be impossible or highly impractical. Based on discussions held at the March 30, 2017 meeting of the Pediatric Review Committee (PeRC), it was agreed that the Applicant's proposed request for a full pediatric waiver was acceptable.

10 Labeling Recommendations

10.1. Prescribing Information

Given that Duzallo is a combination product drug consisting of allopurinol and lesinurad (Zurampic) components, the Applicant proposed a labeling that accommodated language from previously approved labeling for the single components. However, there were several aspects of the Applicant's proposal that generated additional discussions. Specifically, in the proposed labeling, the Applicant proposed to:

- (b) (4) a Boxed Warning was included in the Duzallo labeling consistent with that in the lesinurad single ingredient labeling.
- (b) (4). Given that the product is a combination of the approved dose of Zurampic but relatively low doses of allopurinol, the Agency had concerns that since the proposed fixed-combination drug only offers allopurinol up to 300 mg, (b) (4) the use of allopurinol as follows "…who have not achieved target serum uric acid levels with *a medically appropriate daily dose of* allopurinol alone."
- (b) (4)
- Include a statement limiting the use of Duzallo to only one tablet given the increased risk of toxicity with higher doses. This was considered appropriate.
- Include multiple drug-drug interactions for allopurinol. The Agency limited this information to drug-drug interactions available in the labeling of the reference listed allopurinol products.
- (b) (4) The Agency did not agree with presenting this information as it is not necessary to inform the safe or effective use of Duzallo (b) (4) doses rather than optimizing allopurinol, as a first line therapy.

The above labeling changes were discussed with the Applicant at t-cons on August 01, 2017 and on August 14, 2017.

The proposed labeling for Duzallo was in a format and content consistent with the Pregnancy

and Lactation Labeling Rule (PLLR) based on the labeling for lesinurad which is in a PLLR format and content. Labeling for the allopurinol component was adapted to be compliant with the PLLR. With reference to allopurinol, data was added for an EFD study in mice and placental transport in pregnant pigs demonstrating fetal drug exposure.

10.2. Patient Labeling

A consultative review of the Applicant's proposed package insert (PI) and container label for the FDC tablets of lesinurad and allopurinol in 200 mg/200 mg and 200 mg/300 mg strengths was completed on June 16, 2017 by the agency's Office of Medication Error Prevention and Risk Management (OMEPRM)/ Division of Medication Error Prevention and Analysis (DMEPA) who made the following recommendations for changes to the proposed PI and container label in order to increase the clarity of information to promote the safe use of the product as follows:

1. Proposed package insert
    a. Full Prescribing Information – Section 2.1 Recommended Dosing
        i. Consider Using only metric measurements to prevent medication errors in the sentence: TRADENAME should be taken once daily by mouth, in the morning with food and water. Patients should be instructed to stay well hydrated (e.g., 2 liters (b) (4) of liquid per day).
2. Container label (30 count and 90 count)
    a. Move the manufacturer information to the side panel or reduce the size as it competes with the proprietary name for prominence and takes readers' attention away from important information such as proprietary and proper names and strength.
    b. Ensure the lot number and expiration date is printed on the container labels.

11 Risk Evaluation and Mitigation Strategies (REMS)

This submission did not contain a Risk Evaluation Minimization Strategy (REMS) proposal for review.

11.1. Safety Issue(s) that Warrant Consideration of a REMS

None.

11.2. Conditions of Use to Address Safety Issue(s)

Not applicable.

11.3. Recommendations on REMS

A REMS is not necessary for the FDC tablets of lesinurad and allopurinol in 200 mg/200 mg and 200 mg/300 mg strengths since its safety profile appears to be similar to that of the marketed monotherapy component lesinurad (Zurmapic®). However, this requirement may be reconsidered if future postmarketing evidence identifies a safety risk that cannot be managed by labeling.

12 Postmarketing Requirements and Commitments

The Applicant has an ongoing postmarketing required randomized, controlled, clinical study (RDEA594-401) of 2-years duration evaluating the safety of lesinurad 200 mg on a background of concomitant xanthine oxidase inhibitors, with respect to renal function and renal adverse events, in gout patients who have not achieved target serum uric acid with a xanthine oxidase inhibitor alone under NDA 207,988. The patient population for this study is being enriched with patients with moderate renal impairment (creatinine clearance 30 to 60 ml/min) and also includes an assessment of cardiovascular (CV) safety based on an independent adjudication of prospectively defined and collected CV events. Of note, the EMA has required a postmarketing study of lesinurad monotherapy with an XOI to assess the risk for major adverse cardiac events (MACE). In view of the ongoing moderate renal insufficiency study, no additional postmarketing required clinical studies or commitments should be required for the FDC lesinurad/allopurinol tablets.

13 Appendices

13.1. References

[1] Zhu Y, Pandya BJ, Choi HK, "Prevalence of gout and hyperuricemia in the US general population: the National Health and Nutrition Examination Survey 2007-2008." Arthritis Rheum 2011; 63:3136-3141.

13.2. Financial Disclosure

The financial disclosure information for this application was reviewed previously in support of NDA 207,988 Lesinurad (Zurampic®). The reader is referred to the clinical review dated September 14, 2015 for that application regarding information on this issue.

13.3.Nonclinical Pharmacology/Toxicology

The Division has provided recommended changes to the allopurinol portions of the nonclinical sections of the proposed labeling to allow for alignment with the Pregnancy and Lactation Labeling Rule (PLLR) and current CDER labeling practices.

Current labeling practices compare dose values from nonclinical studies with the maximum recommended human dose (MRHD) on a mg/m^2 basis. The allopurinol MRHD of 300 mg/d is equivalent to 5 mg/kg based on an average human weight of 60 kg. Doses in humans and nonclinical species are converted from mg/kg to mg/m^2 using established conversion factors found in the FDA Guidance for Industry: Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers, Table 3. Allopurinol exposure ratios based on mg/m^2 comparisons between doses in animal studies and the MRHD are used throughout the revised labeling.

Allopurinol exposure multiple calculations are found in the following table.

		Doses referenced in labeling		
Study	**Species**	**mg/kg**	**mg/m^2**	**Fold MRHD**
Clinical dose	Human	5[a]	185[b]	-
Fertility	Rat	20	120[c]	0.65
	Rabbit	20	240[d]	1.3
Embryofetal development	Rat	200	1200[c]	6.5
	Rabbit	100	1200[d]	6.5
Single dose IP study (Fujii et al. 1972)	Mouse	50	150[e]	0.8
		100	300[e]	1.6
Carcinogenicity	Mouse	20	60[e]	0.32
	Rat	20	120[c]	0.65

[a] Max allopurinol dose in FDC = 300 mg / 60 kg human weight = 5 mg/kg
[b] K_m = 37 kg/m^2 for humans
[c] K_m = 6 kg/m^2 for rats
[d] K_m = 12 kg/m^2 for rabbits
[e] K_m = 3 kg/m^2 for mice

13.4.OCP Appendices (Technical documents supporting OCP recommendations)

OFFICE OF CLINICAL PHARMACOLOGY:

PHARMACOMETRIC REVIEW

Application Number	NDA209203
Submission Date	10/20/2016
Compounds	Lesinurad/Allopurinol (fixed dose combination)
Dosing regimen (route of administration)	200 mg lesinurad/300 mg allopurinol tablet per day (or one 200 mg lesinurad/200 mg allopurinol for patients with renal impairment)
Indication	For the treatment of hyperuricemia associated with gout in patients who have not achieved target serum uric acid levels with allopurinol alone
Clinical Division	Division of Pulmonary, Allergy, and Rheumatology Products
Primary PM Reviewers	Xiaofeng Wang, Ph.D.; Jiang Liu, Ph.D.
Secondary PM Reviewer	Yaning Wang, Ph.D.

Table of Contents

Yes, available PK/PD data supports the bridging of the lesinurad/allopurinol FDC formulation to the established benefit-risk profile of the co-administrated mono-products.

The results from a Phase 1, randomized, open-label, single-dose, crossover study in healthy adult subjects (RDEA594-501 part 1 and 3) demonstrate that PK of lesinurad, allopurinol, and oxypurinol are comparable between the FDC tablet and the co-administrated mono-products at corresponding doses in the fasted state. As shown in Table 8, bioequivalence (BE) was established between the 200/300 FDC tablet and the co-administrated mono-products in the fasted state; and the 200/200 FDC tablet and the co-administered mono-products were found to be bioequivalent in the fasted state with respect to all parameters (Cmax, AUC_{last}, and AUC_{∞}) for lesinurad, allopurinol, and oxypurinol, with the exception of allopurinol C_{max}. The upper limit of the 90% CI (1.2817) for allopurinol C_{max} was outside the 0.80 to 1.25 BE limits. However, this is not considered to be clinically relevant for either safety or efficacy because the majority of xanthine oxidase inhibition is believed to be due to the active metabolite, oxypurinol.

Therefore, the PK bridging between the FDC formulation and the co-administrated mono-products in the fasted state is considered well established (Refer to the Clinical Pharmacology Section 6.3.2 in the multidisciplinary review for details about study 501).

Table 8: Bioavailability of Lesinurad/Allopurinol FDC Tablets Relative to the Co-administered Mono-Products at Corresponding Doses in the Fasted State

PK Parameter	Analyte	Geometric Least Squares Mean Ratio (90% CI)	
		200/300 mg FDC tablet (N=35)	200/200 mg FDC tablet (N=53)
C_{max}	Lesinurad	1.1026 (1.0056-1.2090)	0.9881 (0.9248-1.0558)
	Allopurinol	1.0758 (0.9837-1.1766)	1.1823 (1.0905-1.2817)
	Oxypurinol	0.9914 (0.9653-1.0183)	1.0260 (1.0046-1.0479)
AUC_{last}	Lesinurad	0.9895 (0.9501-1.0306)	0.9816 (0.9439-1.0208)
	Allopurinol	1.0045 (0.9675-1.0428)	1.0914 (1.0520-1.1324)
	Oxypurinol	0.9967(0.9771-1.0168)	1.0175 (1.0003-1.0349)
AUC_{∞}	Lesinurad	0.9889 (0.9494-1.0299)	0.9825 (0.9452-1.0214)
	Allopurinol	1.0054 (0.9683-1.0440)	1.0760 (1.0387-1.1147)[a]
	Oxypurinol	1.0022 (0.9804-1.0245)	1.0175 (0.9991-1.0363)

Abbreviations: AUC_{∞}, area under the concentration-time curve from time zero to infinity; AUC_{last}, area under the concentration-time curve from time zero to the last quantifiable sampling timepoint; C_{max}, maximum observed concentration; CI, confidence interval; FDC, fixed-dose combination; N, number of evaluable subjects; PK, pharmacokinetic.
[a] N=51.

Source: Sponsor's Clinical Overview, Table 3 on Page 17

The PK bridging between the FDC formulation and the co-administrated mono-products in the fed state, which is more relevant due to the requirement of administration of both lesinurad in combination with allopurinol and lesinurad/ allopurinol FDC tablet with food, cannot be established due to lack of direct PK comparison between the FDC formulation and the co-administrated mono-products in the fed state.

For lesinurad mono-product, administration with a high-fat meal decreases lesinurad C_{max} by up to 18% but does not alter AUC as compared with fasted state based on the lesinurad (ZURAMPIC®) label. However, the results from Study 501 part 2 showed that lesinurad C_{max} was decreased by ~45% on average and T_{max} of lesinurad was increased by about 2 hours when the lesinurad/allopurinol 200/300 FDC tablet was given with food compared to when it was given fasted. At the same time the AUC of lesinurad was unchanged (Table 9). The difference in the magnitude of the food-induced change in C_{max} and T_{max} between lesinurad and FDC tablets in the absence of a change in the AUC suggests that absorption of lesinurad may be delayed (i.e., its absorption rate decreased) for the FDC tablet compared to lesinurad tablet when both are given with food.

Study 501, Part 2, also showed that allopurinol C_{max} was decreased by approximately 18%, T_{max} was increased about two-fold, and its AUC decreased by about 12% when the FDC tablet was given with food compared to fasted state. The decrease of C_{max} and increase in T_{max} suggest that absorption of allopurinol from the FDC tablet may be delayed in the presence of food. The decrease of AUC suggests that bioavailability (BA) of allopurinol is likely decreased due to

incomplete absorption. Both C_{max} and AUC of oxypurinol decreased by about 15% and T_{max} slightly increased, which may also reflect changes in the absorption of allopurinol (Refer to the Clinical Pharmacology Section 6.3.2 in the multidisciplinary review for details about study 501).

Table 9: Bioavailability of Lesinurad 200 mg/Allopurinol 300 mg FDC Tablet: Fed Versus Fasted State (N=28)

PK Parameter	Analyte	Fed/Fasted Geometric Least Squares Mean Ratio (90% CI)
C_{max}	Lesinurad	0.5450 (0.4703-0.6316)
	Allopurinol	0.8166 (0.7030-0.9486)
	Oxypurinol	0.8633 (0.8315-0.8964)
AUC_{last}	Lesinurad	0.9796 (0.9272-1.0350)
	Allopurinol	0.8750 (0.8331-0.9191)
	Oxypurinol	0.8471 (0.8267-0.8680)
AUC_{∞}	Lesinurad[a]	0.9642 (0.9182-1.0125)
	Allopurinol[a]	0.8835 (0.8399-0.9294)
	Oxypurinol	0.8476 (0.8248-0.8711)

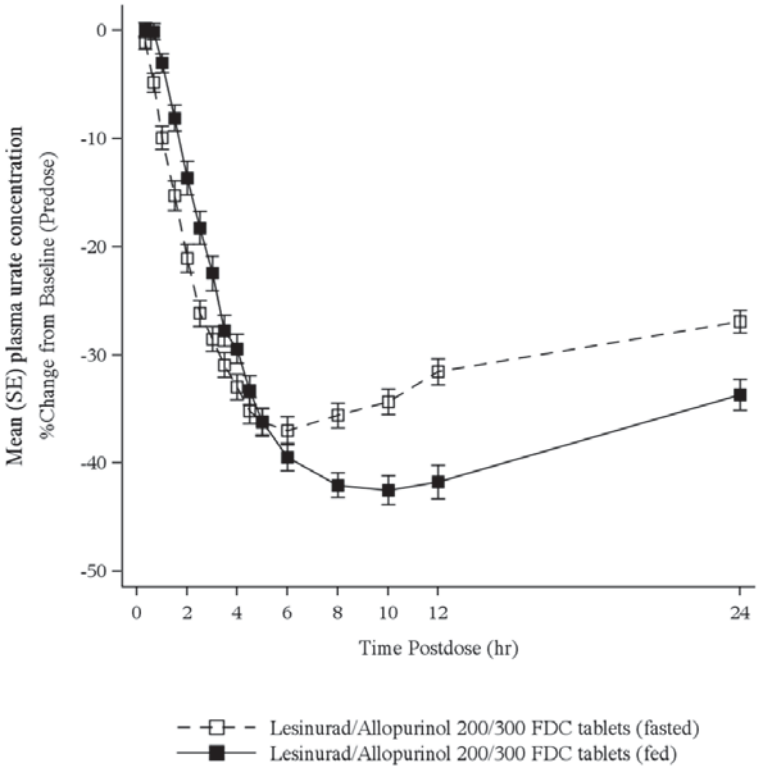
Abbreviations: AUC_{∞}, area under the concentration-time curve from time zero to infinity; AUC_{last}, area under the concentration-time curve from time zero to the last quantifiable sampling timepoint; C_{max}, maximum observed concentration; CI, confidence interval; FDC, fixed-dose combination; N, number of evaluable subjects; PK, pharmacokinetic.
[a] N=26.

Source: Sponsor's Clinical Overview, Table 4 on Page 18

Given the possibility that administration with a high-fat meal may significantly delay absorption of lesinurad and mildly delay/decrease absorption of allopurinol for the FDC formulation comparing with the co-administration of mono-products, its impacts on the clinical pharmacodynamics (PD) domain of serum uric acid were evaluated based on both observed PD data and modeling and simulation results that are discussed below.

First, evaluation of the PD performance of the FDC formulation in Study RDEA594-501, Part 2 demonstrated that the reduction in lesinurad C_{max} in the fed state was not associated with a reduced PD effect with respect to plasma/serum Uric Acid (UA) lowering. As shown in Figure 6, up to 6 hours post dose, the mean change in plasma UA concentrations was similar under fed and fasted conditions. Between 6 and 24 hours post dose, FDC in the fed state resulted in a more prolonged maximal plasma UA lowering compared with that in the fasted state. Such findings on the influence of food effect on plasma/serum UA lowering are consistent with those observed in the lesinurad development program.

Figure 6: Comparison of Mean Plasma Uric Acid Reduction Following Fed and Fasted FDC Tablet Administration (Study 501)



Source: Sponsor's Summary of Biopharmaceutic Studies, Figure 2 on Page 23

Second, PKPD modeling and simulation was employed to evaluate the effect of the significant delay in the absorption of lesinurad and the mild delay/decrease in the absorption of allopurinol (mimicking the PK changes as observed in Study RDEA594-501, Part 2) on the ability of the FDC formulation to maintain UA lowering. The developed PKPD model adequately described the physiologic turnover of UA and the pharmacological effect of lesinurad and allopurinol on UA disposition. Moreover, the PKPD model was qualified to predict serum UA concentration in hyperuricemic patients following lesinurad and allopurinol administration using Phase 3 study data in the lesinurad clinical development program and published data. Simulation using the developed PKPD model was conducted by varying the absorption rate constant of lesinurad, and the absorption rate constant and bioavailability (BA) of allopurinol, in ranges covering the observed changes on C_{max} and AUC of lesinurad and oxypurinol in Study RDEA594-501, Part 2. Simulation results demonstrated that there are no clinically meaningful differences in the serum UA lowering effect of the FDC tablet in hyperuricemic patients over a range of lesinurad and allopurinol absorption rate and BA changes which could represent the changes in lesinurad and allopurinol C_{max} and AUC following FDC administration in the fed state or in even more extreme scenarios (Refer to Section 3 and Section 4 of this review for detailed information about PKPD modeling and simulation).

In summary, the PK/PD bridging between the FDC formulation and the co-administrated mono-products in the fed state is adequately established based on modeling and simulation. The lesinurad and allopurinol PK following administration of the FDC tablet in the fed state would

result in a comparable PD profile to that of the co-administered mono-products and the observed food effect is not expected to compromise the efficacy of the FDC tablet in hyperuricemic patients.

2 Pertinent regulatory background

Allopurinol (ZYLOPRIM®), a xanthine oxidase inhibitor, was approved in 1966 for the management of patients with signs and symptoms of primary or secondary gout. Lesinuard (ZURAMPIC®), a URAT1 inhibitor, was approved in December 2015 in combination with a xanthine oxidase inhibitor for the treatment of hyperuricemia associated with gout in patients who have not achieved target serum uric acid levels with a xanthine oxidase inhibitor alone.

In the current submission, the sponsor is seeking approval of the Lesinurad/Allopurinol Fixed-Dose Combination (FDC) tablets, 200mg/300mg and 200mg/200mg under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act with Allopurinol (ZYLOPRIM®) and Lesinuard (ZURAMPIC®) as the reference listing drugs.

3 Results of Sponsor's Analysis

3.1 Uric acid (UA) PKPD modeling and simulation

Objective

The objective of this analysis was to develop and qualify a pathophysiologically-based PK/PD model of UA and the pharmacological effects of lesinurad, allopurinol, and febuxostat on UA disposition.

Overview

A PK/PD model characterizing the physiology of UA and the pharmacological effects of lesinurad, allopurinol, and febuxostat on UA disposition was developed in a sequential manor. The modeling strategy was to develop a mean response PK/PD model where mean time courses of UA concentration in serum and amount excreted in urine were modeled as a function of the mean drug concentration-time profile. For modeling purposes, the time courses of drug concentration and serum UA (sUA) concentration from individual subjects were pooled and grouped by treatment and dose of drug (
Table 10). First, the mean PK model parameters were estimated for each treatment group, and then mean PK/PD parameters were estimated given mean values of PK parameters. Model simulations were performed using the mean values of the UA model parameters and typical values of PK parameters from previously developed population PK models for each drug. Figure 7 shows the overall work flow for model development and simulation.


(b) (4)

Table 10: Description of Treatment Groups in the Modeling Dataset

Group Number	Group Label	Description
1	LES-0	Placebo
2	LES-600	Lesinurad 600 mg single dose
3	LES-100	Lesinurad 100 mg single dose
4	LES-200	Lesinurad 200 mg single dose
5	LES-400	Lesinurad 400 mg single dose
6	LES-800	Lesinurad 800 mg single dose
7	LES-1200	Lesinurad 1200 mg single dose
8	LES-1600	Lesinurad 1600 mg single dose
9	LES-50	Lesinurad 50 mg single dose
10	ALL-P1	Allopurinol 300 mg Day 1-14 and lesinurad 400 mg Day 7-21
11	ALL-P2	Allopurinol 300 mg Day 1-14 and lesinurad 600 mg Day 7-21
12	FX-P1-A	Febuxostat 40 mg Day 1-14 and lesinurad 200 mg Day 7-21
13	FX-PP-A	Febuxostat 40 mg Day 1-14 and placebo Day 14-21
14	FX-P1-B	Lesinurad 200 mg Day 1-14 and febuxostat 40 mg Day 7-21
15	FX-PP-B	Placebo Day 1-7 and febuxostat 40 mg Day 7-21
16	FX-P2-B	Lesinurad 400 mg Day 1-14 and febuxostat 40 mg Day 7-21
17	FX-P2-A	Febuxostat 40 mg Day 1-14 and lesinurad 400 mg Day 7-21
18	FX-P2	Febuxostat 80 mg Day 1-21 and lesinurad 400 mg Day 7-14 and 600 mg Day 14-21
19	FX-P1	Febuxostat 40 mg Day 1-21 and lesinurad 400 mg Day 7-14 and 600 mg Day 14-21

Source: Sponsor's study report: Model of Uric Acid handling; Table 2 on Page 12

3.1.1 Model Development

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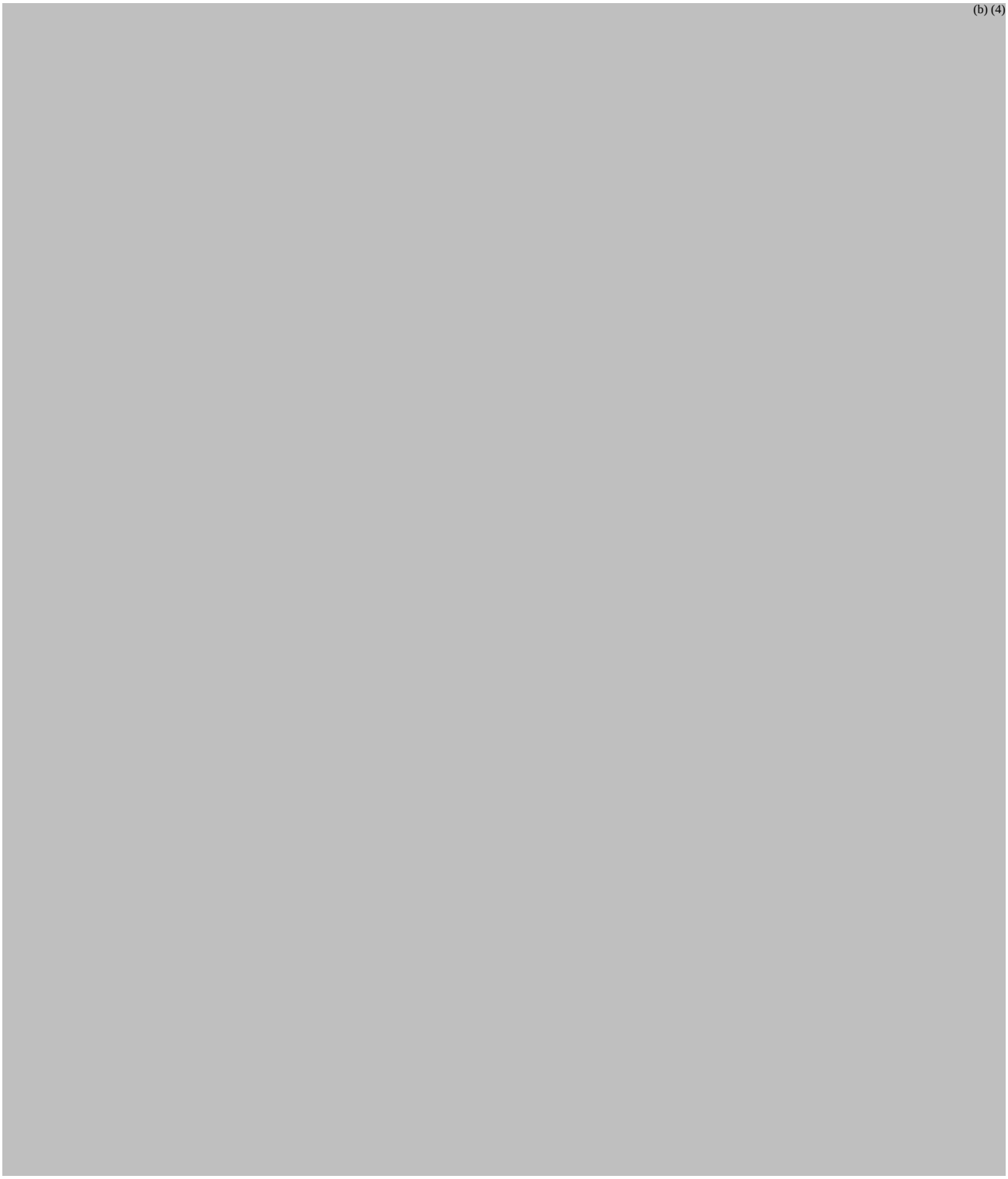

Model Fitting Results

The model was fitted in NONMEM and Model parameter estimates are listed in Table 11. Goodness-of-fit plots for serum uric acid are shown in Figure 10 -Figure 13. Figure 14 shows mean fit of serum UA concentration for each treatment group. Goodness-of-fit plots for urine uric acid are shown in Figure 15 - Figure 18. Figure 19 shows mean fit of urine UA amount for

each treatment group.

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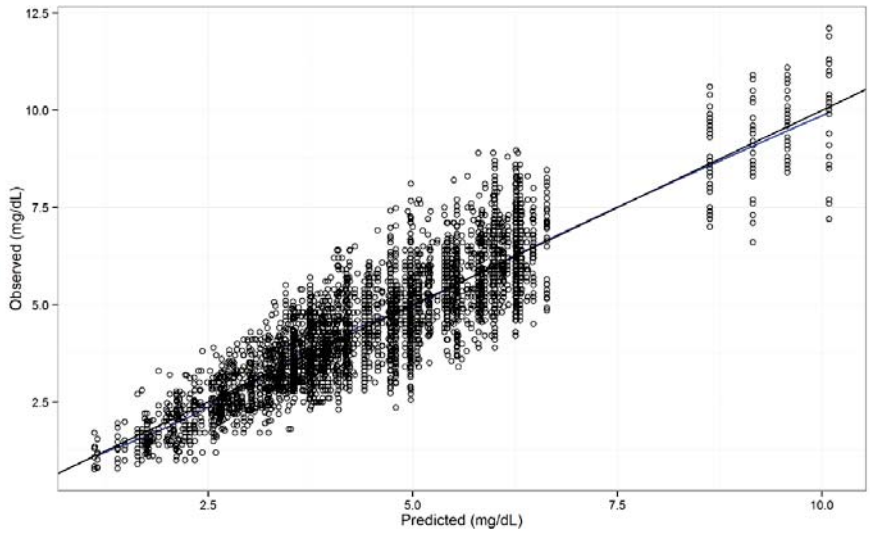
Table 11: PKPD Model Parameter Estimates

Parameter Name	Estimated Value	Relative SE	Literature Value[a]
Production rate of uric acid (mg/h), k_1	40 (normal) – 576 mg/day urinary excretion corresponding to fractional excretion 0.06 and CrCl = 124 mL/min 52 (hyperuricemia)	NA (precision not calculated)	687 mg/day urinary excretion in normal subjects with CrCl = 124 mL/min
Baseline fractional excretion, $1 - E_0$	0.06 (normal) 0.03 (hyperuricemia)	NA (precision not calculated)	0.04 (hyperuricemia)
Volume of distribution of uric acid (L), V_1	16.6	NA (precision not calculated)	14-27
Intestinal clearance of uric acid (L/h), k_2	0.29	NA (precision not calculated)	0.30
Lesinurad E_{max}	0.38	NA (precision not calculated)	NA
Lesinurad EC_{50} (ng/mL)	6424 (healthy volunteers) 13690 (hyperuricemia)	0.38 0.11	NA
Oxypurinol E_{max}	0.83	0.05	NA
Oxypurinol EC_{50} (ng/mL)	6700 (healthy volunteers) 13740 (hyperuricemia)	0.19 0.11	NA
Febuxostat E_{max}	1	NA (parameter fixed)	NA
Febuxostat EC_{50} (ng/mL)	84 (healthy volunteers) 130 (hyperuricemia)	NA (precision not calculated) 0.17	65 (relative SE 0.05) 207 (relative SE 0.06)

Abbreviations: NA, not available; SE, standard error.

Source: Sponsor's study report: Model of Uric Acid handling; Table 4 on Page 26

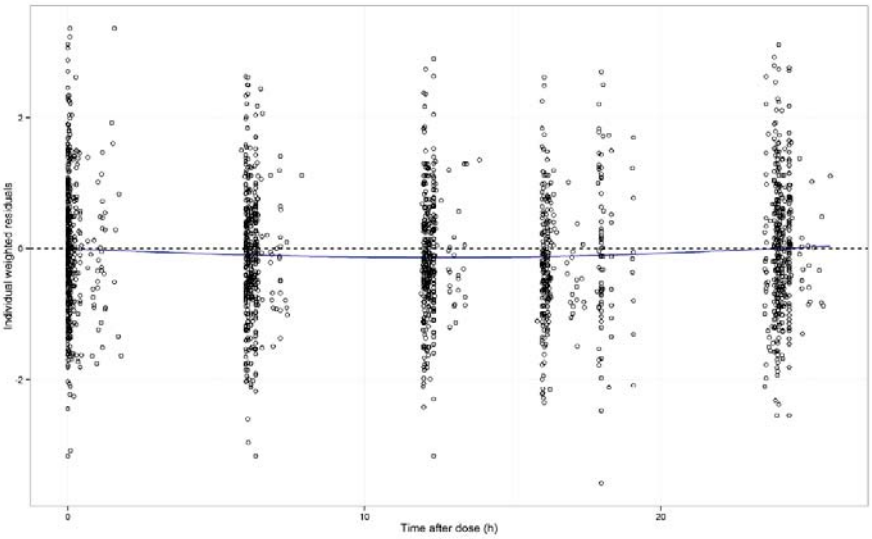
Figure 10: Predicted Serum Uric Acid Concentrations Versus Observed Values



Blue line – Loess Smooth. Black line – Line of Identity.

Source: Sponsor's study report: Model of Uric Acid handling Appendix F, Figure 2 on Page 8

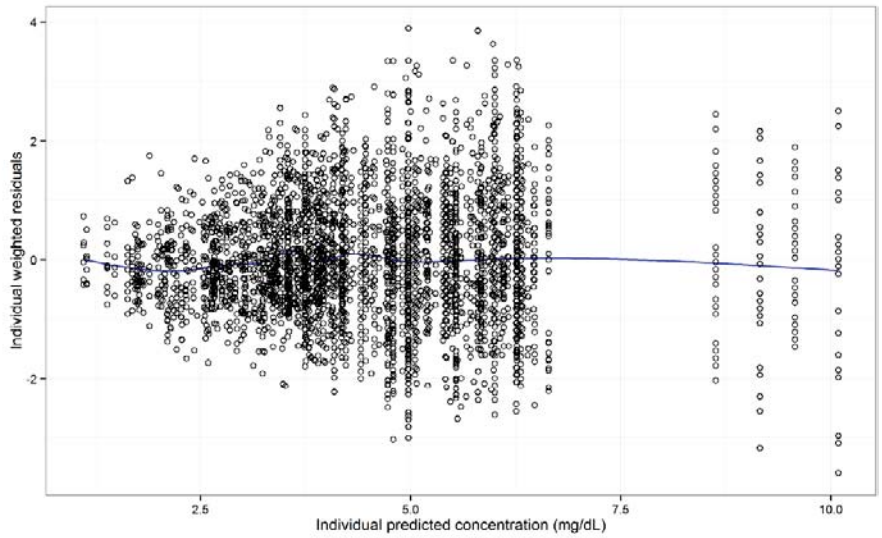
Figure 11: Individual Weighted Residuals for Serum Uric Acid Concentrations Versus Time After Dose



Dashed line – Reference line for mean residual = 0. Blue line – Loess Smooth.

Source: Sponsor's study report: Model of Uric Acid handling Appendix F, Figure 14 on Page 20

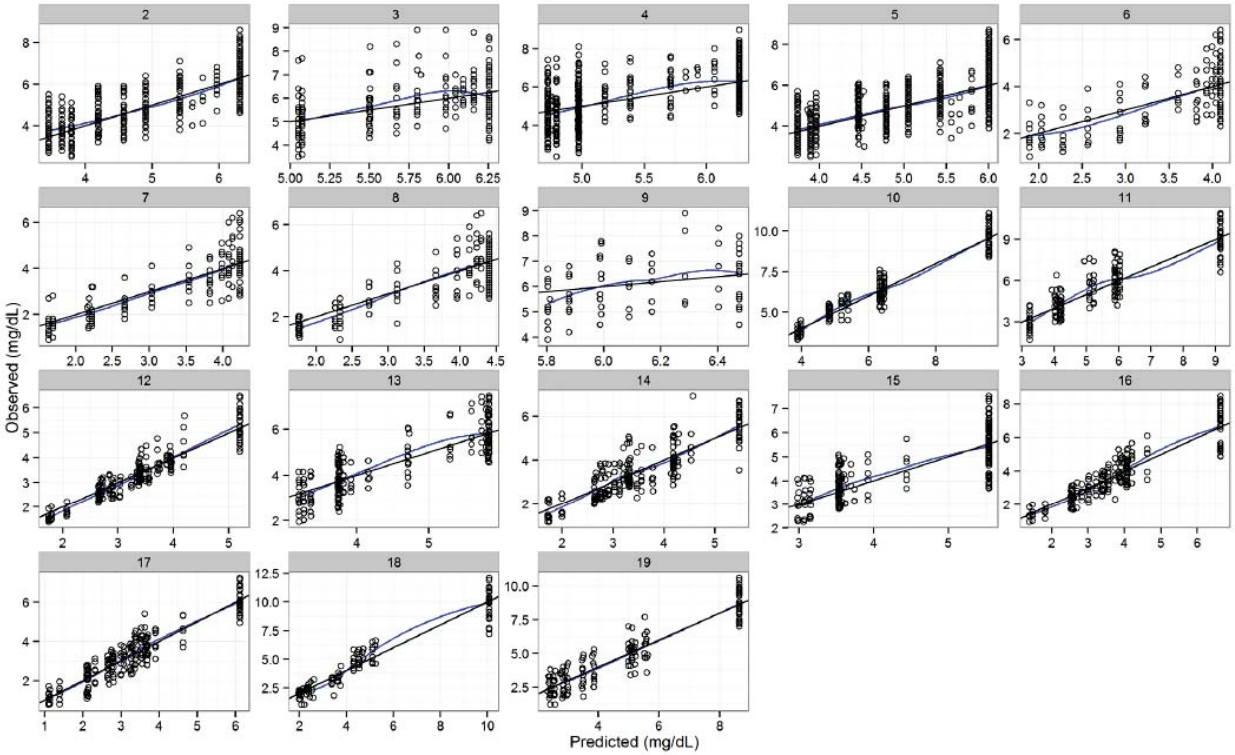
Figure 12: Individual Weighted Residuals for Serum Uric Acid Concentrations Versus Predictions



Dashed line – Reference line for mean residual = 0. Blue line – Loess Smooth.

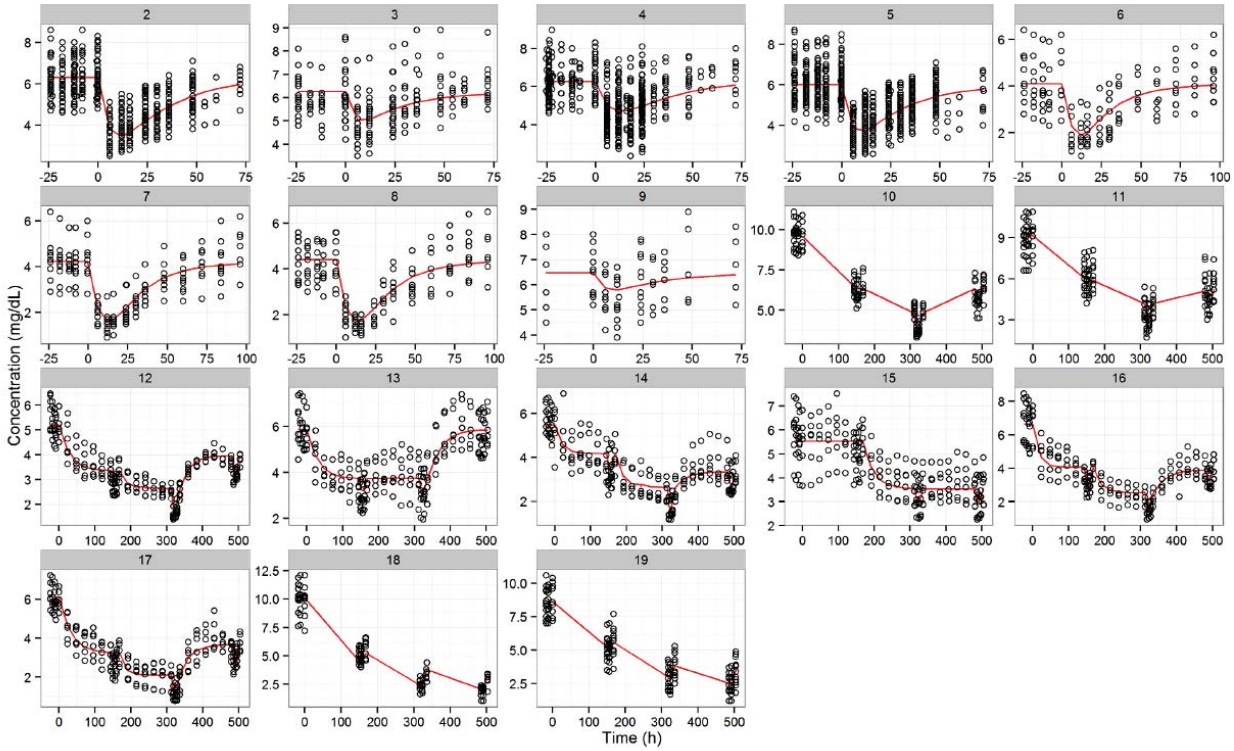
Source: Sponsor's study report: Model of Uric Acid handling Appendix F, Figure 16 on Page 22

Figure 13: Model Predicted Serum Uric Acid Concentrations Versus Observed Values by Treatment Group



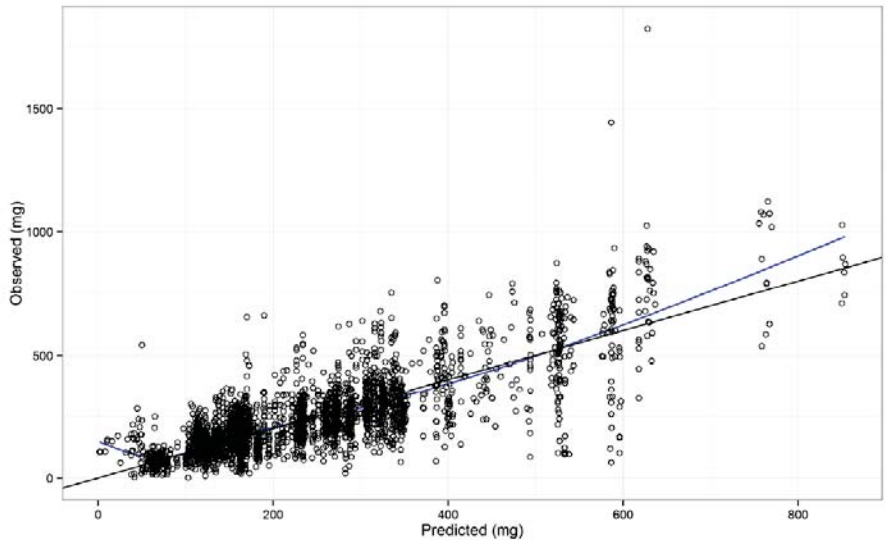
Source: Sponsor's study report: Model of Uric Acid handling Appendix F, Figure 1 on Page 7

Figure 14: Observed and Predicted Serum Uric Acid Concentration Versus Time By Treatment Group



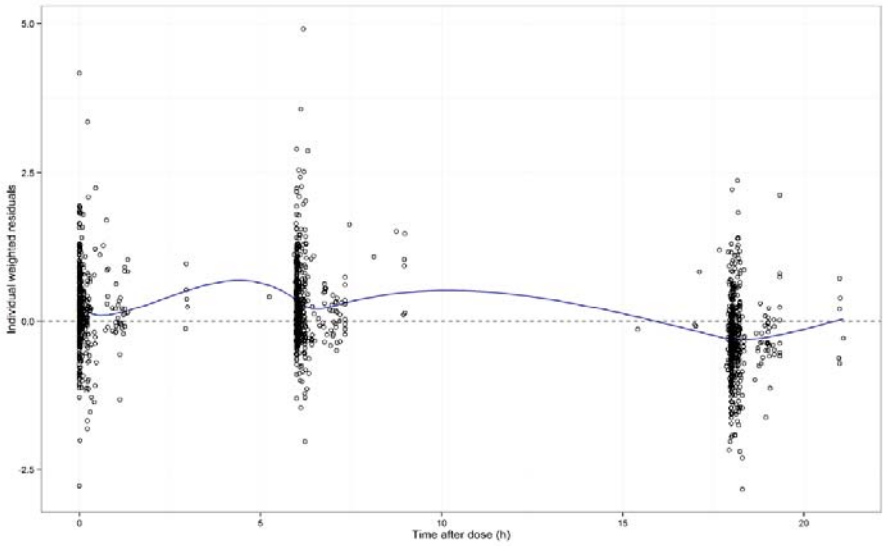
Note: Each panel represents 1 of the 19 treatment groups, excluding Group 1 (placebo).
Symbols are individual serum uric acid values.
Red lines are mean model predictions.
Source: Sponsor's study report: Model of Uric Acid handling; Figure 5 on Page 24

Figure 15: Predicted Urine Uric Acid Amount Versus Observed Values



Blue line – Loess Smooth. Black line – Line of Identity.
Source: Sponsor's study report: Model of Uric Acid handling Appendix F, Figure 4 on Page 10

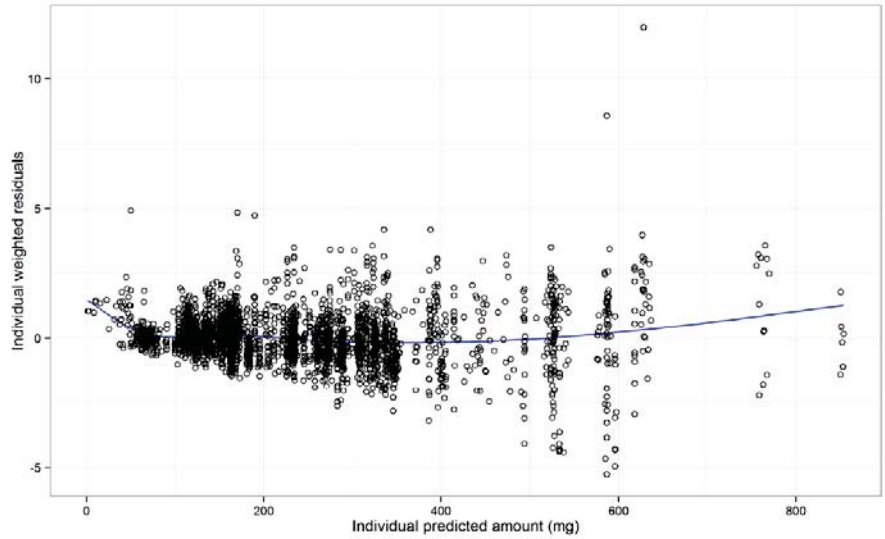
Figure 16: Individual Weighted Residuals for Urine Uric Acid Amount Versus Time After Dose



Dashed line – Reference line for mean residual = 0. Blue line – Loess Smooth.

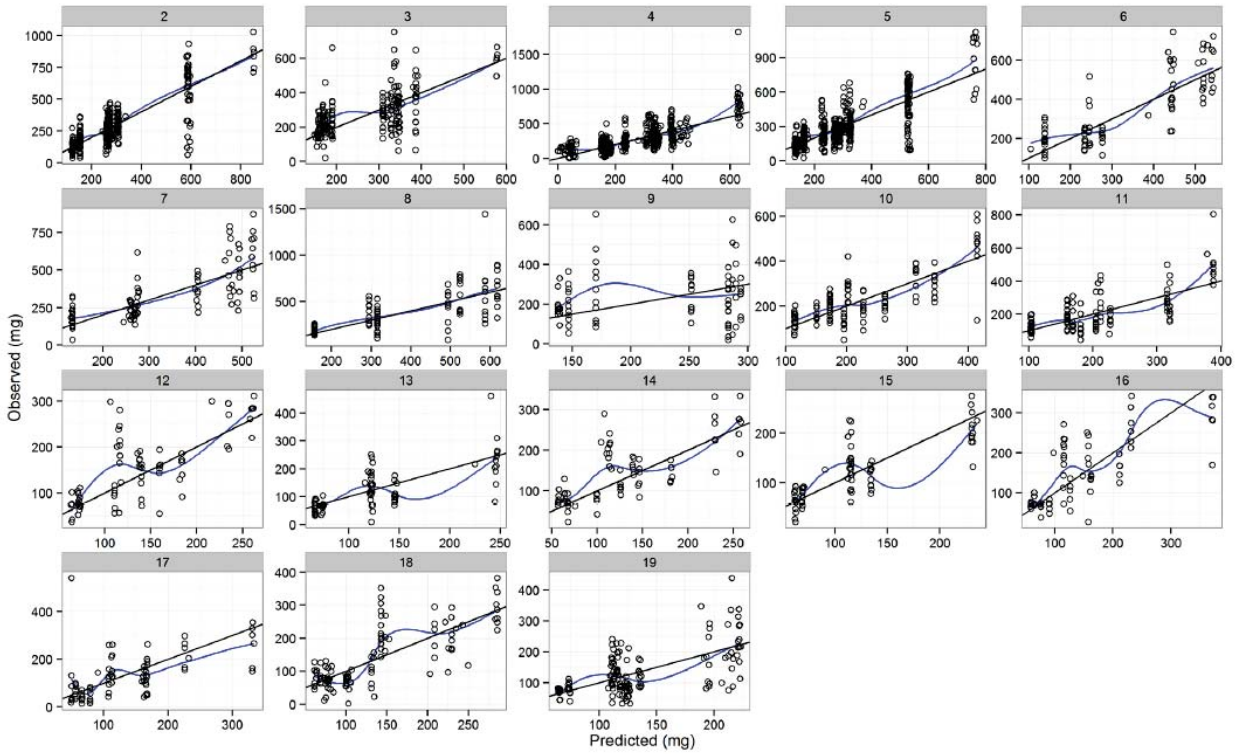
Source: Sponsor's study report: Model of Uric Acid handling Appendix F, Figure 18 on Page 24

Figure 17: Individual Weighted Residuals for Urine Uric Acid Amonut Versus Predictions



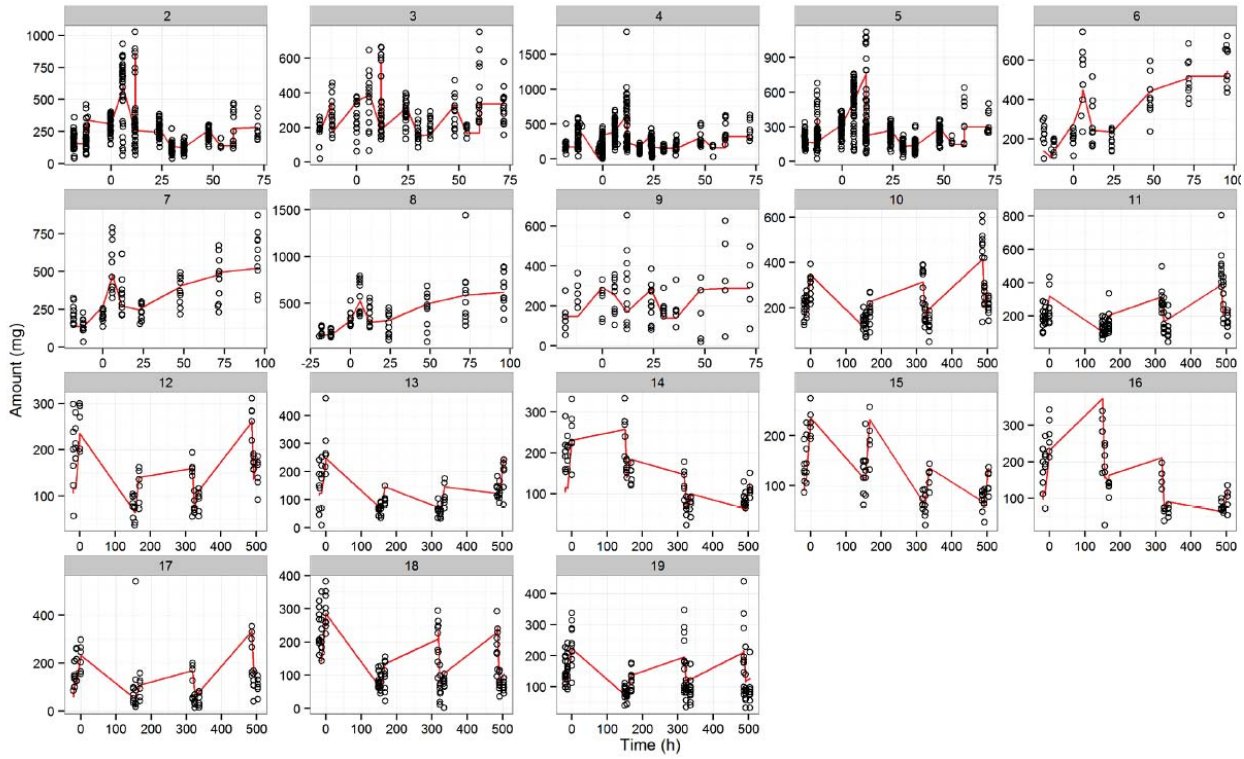
Dashed line – Reference line for mean residual = 0. Blue line – Loess Smooth.
Source: Sponsor's study report: Model of Uric Acid handling Appendix F, Figure 20 on Page 26

Figure 18: Model Predicted Urine Uric Acid Amount Versus Observed Values by Treatment Group



Source: Sponsor's study report: Model of Uric Acid handling Appendix F, Figure 3 on Page 9

Figure 19: Observed and Predicted Urine Uric Acid Concentration Versus Time By Treatment Group



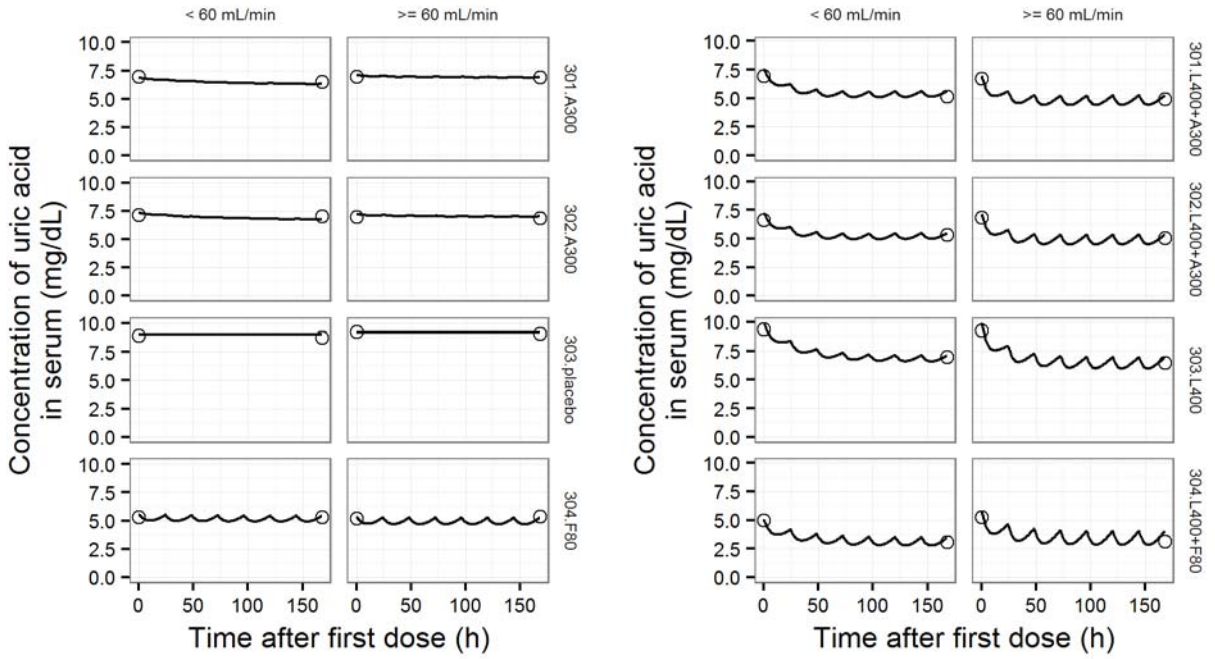
Note: Each panel represents 1 of 19 treatment groups, excluding Group 1 (placebo).
Symbols are individual amounts of uric acid excreted in urine shown at the time of end of urine collection interval.
Red lines are mean model predictions.

Source: Sponsor's study report: Model of Uric Acid handling; Figure 6 on Page 25

3.1.2 Model Validation and Qualification

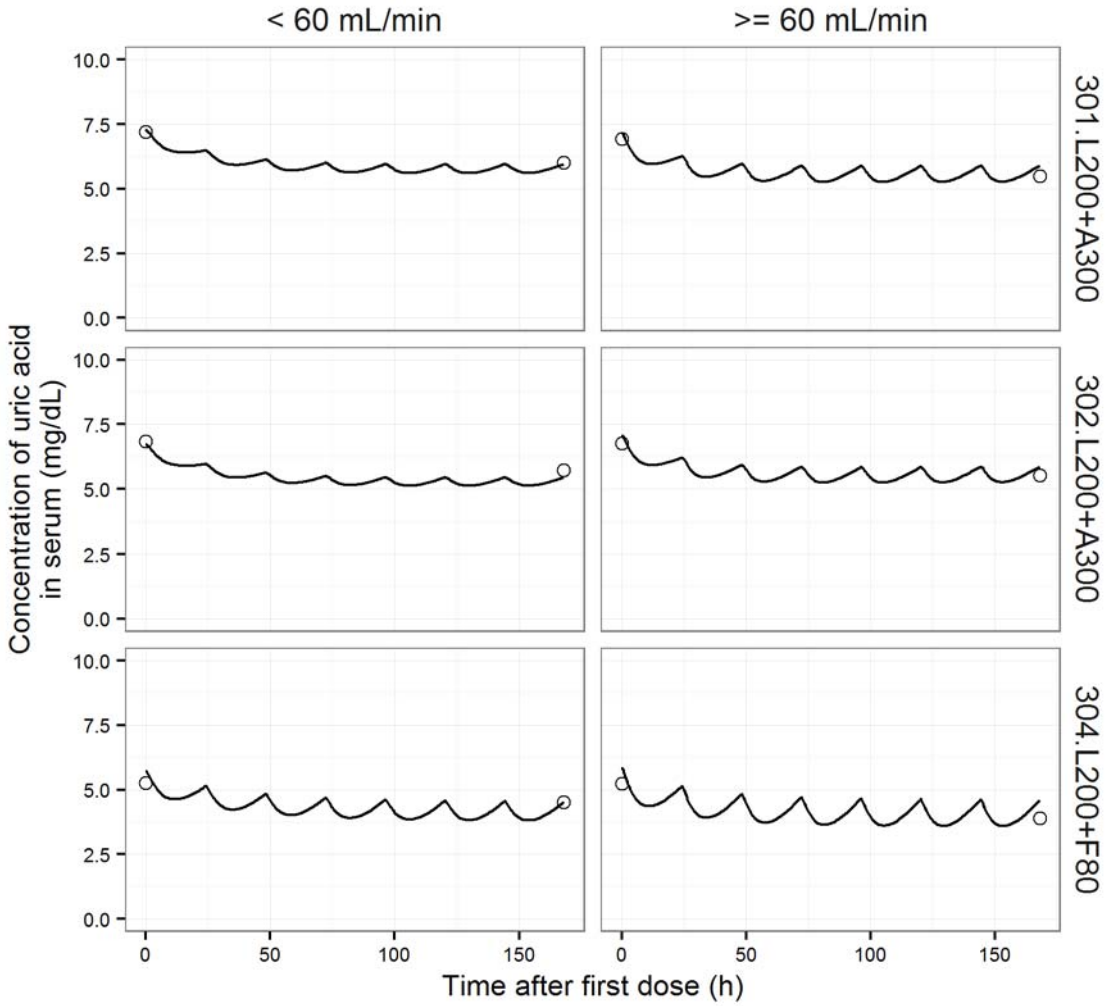
Serum UA concentration data from core lesinurad Phase 3 studies (RDEA594-301, RDEA594-302, RDEA594-303, and RDEA594-304) and 2 published febuxostat Phase 3 studies APEX and FACT were used to externally validate and qualify the model for subjects with hyperuricemia. Typical serum UA concentration time profiles for subsets of subjects with mild and normal renal function (CrCl > 60 mL/min) and subjects with moderate renal impairment (CrCl < 60 mL/min) within each treatment group of the 5 Phase 3 studies were simulated using the developed UA PKPD model and compared with observed values. Results show that model predictions agreed with observed serum UA concentrations in the Phase 3 studies of lesinurad alone, febuxostat alone, allopurinol alone, and combination of lesinurad and allopurinol, and combination of lesinurad and febuxostat (Figure 20,
Figure **21**, and Figure 22).

Figure 20: Model Predicted Serum Uric Acid Concentration Time Profile Versus Observed Values in the Lesinurad Phase 3 Studies for Lesinurad 400 mg Daily and Placebo



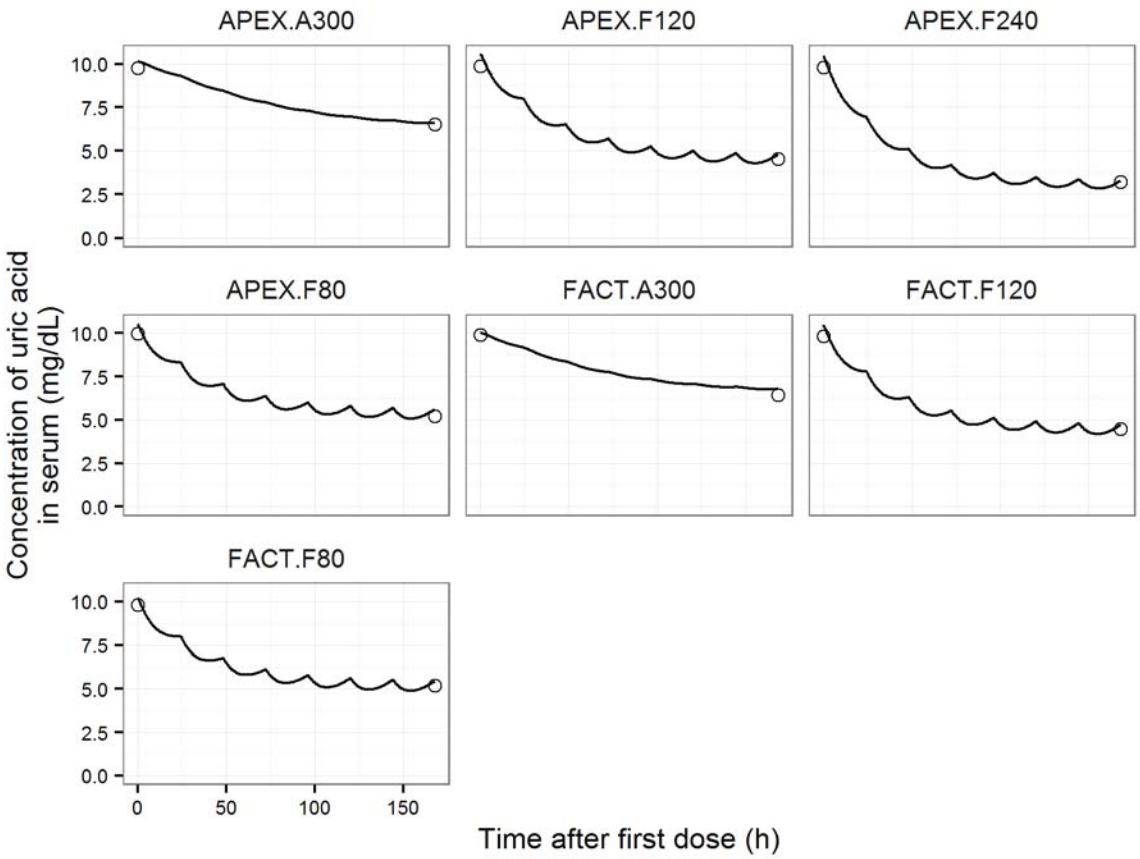
Line: model prediction. Symbols: mean baseline and on treatment concentration of serum uric acid.
Columns show subsets of subjects by creatinine clearance. Rows show subsets of subjects by treatment group: labels 301, 302, 303 and 304 refer to Studies RDEA594-301, 302, 303 and 304; L400 refers to lesinurad 400 mg daily; A300 refers to allopurinol 300 mg daily; and F80 refers to febuxostat 80 mg daily.
Source: Sponsor's study report: Model of Uric Acid handling; Figure 11 on Page 34

Figure 21: Model Predicted Serum Uric Acid Concentration Time Profile Versus Observed Values in the Lesinurad Phase 3 Studies for Lesinurad 200 mg Daily



Line: model prediction. Symbols: mean baseline and on treatment concentration of serum uric acid.
Columns show subsets of subjects by creatinine clearance. Rows show subsets of subjects by treatment group: labels 301, 302 and 304 refer to Studies RDEA594-301, 302 and 304; L200 refers to lesinurad 200 mg daily; A300 refers to allopurinol 300 mg daily; and F80 refers to febuxostat 80 mg daily.
Source: Sponsor's study report: Model of Uric Acid handling; Figure 12 on Page 35

Figure 22: Model Predicted Serum Uric Acid Concentration Time Profile Versus Observed Values in the Phase 3 Studies APEX and FACT



Line: model prediction. Symbols: mean baseline and on treatment concentration of serum uric acid.
Panels are labeled with APEX and FACT for APEX and FACT studies; A300 refers to allopurinol 300 mg daily; and F80, F120 and F240 refer to febuxostat 80 mg, 120 mg and 240 mg daily.
Source: Sponsor's study report: Model of Uric Acid handling; Figure 13 on Page 38

3.1.3 Simulation of the Effect of Changes in Absorption of Lesinurad and Allopurinol on Serum Uric Acid Lowering

Objective

The objective of the model simulation was to compare the serum UA lowering effect in hyperuricemic patients for a range of lesinurad and allopurinol absorption rates and BA changes representative of the potential differences in C_{max} and AUC between the FDC tablet and co-administered lesinurad and allopurinol in the fed state.

Method

To represent delayed absorption of lesinurad in the FDC tablet given with food, the absorption rate of lesinurad was varied between 0.1 and 1 times the value estimated in the population PK

model of lesinurad. The factor 1 represents the reference scenario of co-administered lesinurad and allopurinol when there is no difference in absorption of lesinurad between co-administration and the FDC tablet. The conservative lower value of the factor 0.1 was chosen to represent a larger decrease of C_{max} between the FDC tablet and the co-administered combination than what can be estimated comparing decreases of 45% for FDC fed vs fasted (Study 501, Part 2) and 18% for lesinurad tablets fed vs fasted (Study 121).

To represent delayed absorption of allopurinol the absorption rate of allopurinol was varied between 0.1 and 1 times the value estimated in the population PK analysis of allopurinol. The factor 1 represents the reference scenario of co-administered lesinurad and allopurinol when there is no difference in absorption of allopurinol between co-administration and the FDC tablet. The conservative lower value of the factor 0.1 was chosen to result in a larger decrease of C_{max} of allopurinol between the FDC tablet and the co-administered combination than what can be estimated using data from Study 501, Part 2. The BA of allopurinol was varied between 1 and 0.7 times the value estimated in the population PK analysis of allopurinol. A factor of 1 represents the reference scenario of co-administered lesinurad and allopurinol when there is no difference in BA of allopurinol between co-administration and the FDC tablet. The lower value of 0.7 was chosen to simulate a larger decrease of C_{max} and AUC of allopurinol and oxypurinol than what can be estimated using data from Study 501, Part 2.

Factors for absorption parameter changes for each simulation scenario are listed in Table 12.

Table 12: Factors for Absorption Parameters for Simulation Scenarios for Fixed-Dose Combination Relative to Co-administered Combination

Scenario	Lesinurad PK parameters	Allopurinol PK parameters
1. Coadministration: no change in absorption	$k_L\|_1 = 1 \times k_L$	$k_A\|_1 = 1 \times k_A$ $F_A\|_1 = 1 \times F_A$
2. FDC:small delay of absorption	$k_L\|_2 = 0.5 \times k_L$	$k_A\|_2 = 0.5 \times k_A$ $F_A\|_2 = 0.9 \times F_A$
3. FDC moderate delay of absorption	$k_L\|_3 = 0.2 \times k_L$	$k_A\|_3 = 0.2 \times k_A$ $F_A\|_3 = 0.8 \times F_A$
4. FDC large delay of absorption	$k_L\|_4 = 0.1 \times k_L$	$k_A\|_4 = 0.1 \times k_A$ $F_A\|_4 = 0.7 \times F_A$

Lesinurad parameter: absorption rate, k_L. Allopurinol parameters: absorption rate k_A, BA F_A.

Source: Sponsor's study report: Simulation of Uric Acid Lowering; Table 3 on Page 13

Parameter values of the lesinurad population PK model, the allopurinol and oxypurinol population PK model, and the UA model for simulation are summarized in

Table 13: Parameter Values for the Lesinurad Population PK Model for Simulation

Parameter (units)	Value	Source
Absorption rate constant k_L (1/h)	1.22	Aksenov 2016
Lag time of absorption t_L (h)	0.16	Aksenov 2016
Central volume of distribution $V_{1L,typ}$ (L)	22.86	Aksenov 2016
Peripheral volume of distribution V_{2L} (L)	6.65	Aksenov 2016
Intercompartmental clearance Q_L (L/h)	0.45	Aksenov 2016
Systemic clearance $CL_{L,typ}$ (L/h)	7.56	Aksenov 2016

Source: Sponsor's study report: Simulation of Uric Acid Lowering; Table 1 on Page 10

Table 14: Parameter Values for the Allopurinol and Oxypurinol Population PK Model for Simulation

Parameter (units)	Value	Source
Absorption rate constant of allopurinol k_A (1/h)	1.6	Wright 2013
Central volume of distribution of allopurinol V_{1A} (L)	11.4	Wright 2013
Peripheral volume of distribution of allopurinol V_{2A} (L)	90.7	Wright 2013
Intercompartmental clearance of allopurinol Q_A (L/h)	142	Wright 2013
Systemic clearance of allopurinol CL_A (L/h)	49.6	Wright 2013
Fraction of allopurinol metabolized into oxypurinol p_{AX}	0.8	Wright 2013
Bioavailability of allopurinol F_A	0.85	Wright 2013
Coefficient for effect of lesinurad dose on oxypurinol clearance a (1/mg lesinurad dose)	0.0017	Aksenov 2016

Source: Sponsor's study report: Simulation of Uric Acid Lowering; Table 2 on Page 12

Table 15: Parameter Values for the UA Model for Simulation

Parameter (units)	Value	Source
Volume of distribution of uric acid V_1 (L)	16.6	Aksenov 2016
Intestinal clearance of uric acid k_2 (L/h)	0.29	Aksenov 2016
Lesinurad E_{max}	0.38	Aksenov 2016
Lesinurad EC_{50} (ng/mL)	13691	Aksenov 2016
Oxypurinol E_{max}	0.83	Aksenov 2016
Oxypurinol EC_{50} (ng/mL)	13740	Aksenov 2016
Production rate of uric acid (mg/h), k_1		Calculated from pre-treatment sUA, k_2, E_0 and *GFR*
Baseline $FEUA = 1 - E_0$	0.03-0.06	Set in the simulation
Creatinine clearance *CrCl* (mL/min)	45-90	Set in the simulation
[a]Actual body weight (kg)	80	Set in the simulation
[a]Body-mass index (kg/m^2)	25	Set in the simulation
[a]Sex	Male	Set in the simulation

[a] Body-mass index, sex and body weight were used to calculate oxypurinol clearance.

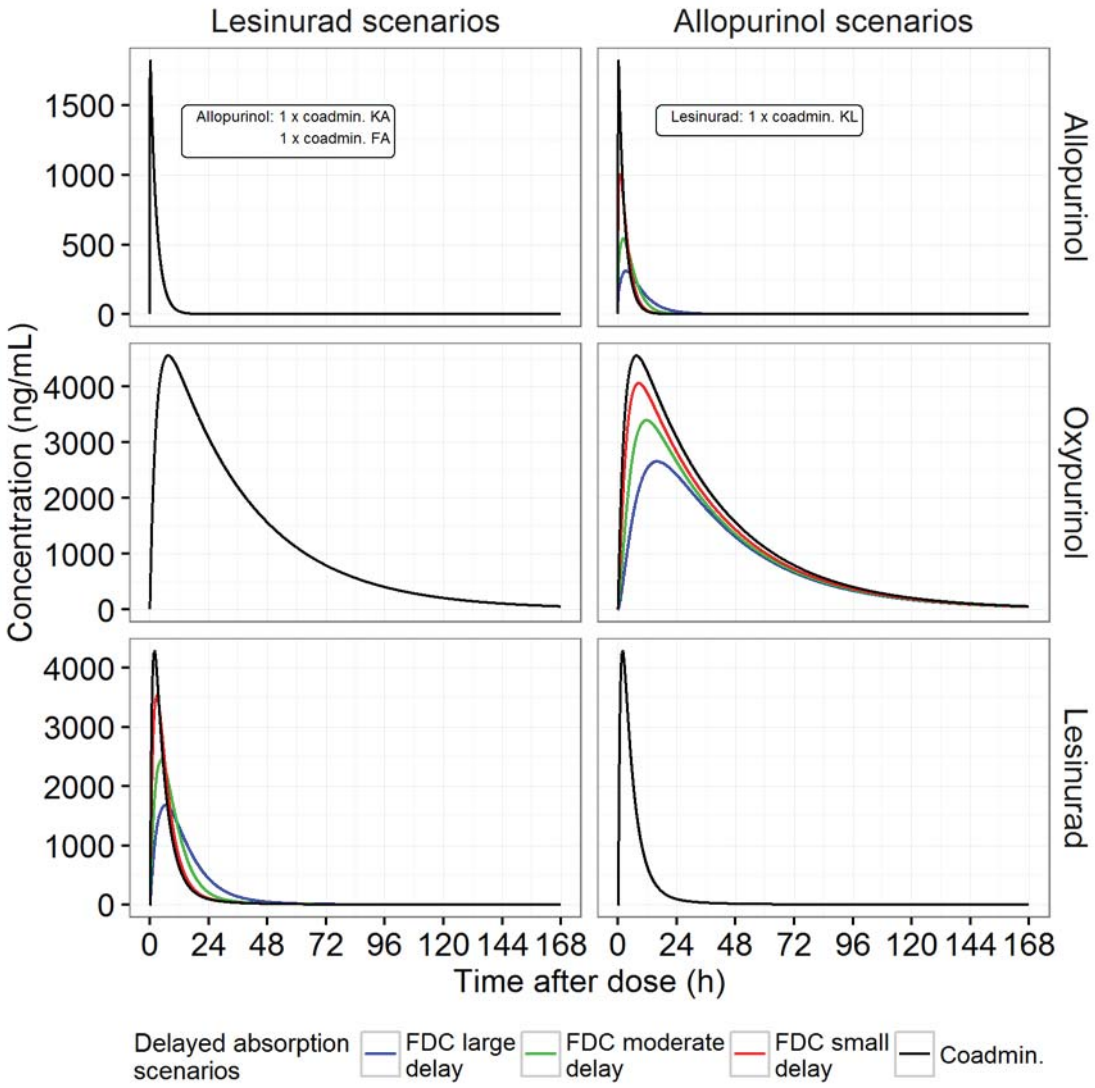
Source: Sponsor's study report: Simulation of Uric Acid Lowering; Table 4 on Page 13. Model simulation was performed using R (version 3.3.1).

Results

Simulated typical concentration time profiles of lesinurad, allopurinol, and oxypurinol following a single dose of lesinurad/allopurinol 200/300 FDC tablet in fed state for delayed absorption scenarios are shown in Figure 23, in which the left panel demonstrates the effect of delayed absorption of lesinurad on lesinurad, allopurinol, and oxypurinol PK while holding the absorption rate and bioavailability of allopurinol at their reference values of the co-administration scenario (ratio of 1); and the right panel demonstrates the effect of reduced absorption rate and bioavailability of allopurinol on lesinurad, allopurinol, and oxypurinol PK while holding the absorption rate of lesinurad at its reference value of the co-administration scenario (ratio of 1). The corresponding simulated ratios of C_{max}, AUC, and T_{max} for the delayed absorption scenarios relative to the reference co-administration scenario are listed in Table 16.

Simulated concentration time profiles of serum UA following a single dose of lesinurad/allopurinol 200/300 FDC tablet for delayed absorption scenarios for a typical hyperuricemic patient with baseline untreated serum UA of 10 mg/dL, excretion rate of UA in urine of 600 mg/day and GFR of 90 mL/min are shown in Figure 24, which demonstrates the effect of delayed absorption for a single dose of lesinurad/allopurinol 200/300 FDC tablet on serum UA concentration.

Figure 23: Simulated Concentration Time Profiles of Lesinurad, Allopurinol, and Oxypurinol following a Single Dose of Lesinurad/Allopurinol 200/300 FDC Tablet for Delayed Absorption Scenarios



Note: The corresponding FEUA is 0.046 and production rate is 54 mg/h, calculated from steady state model equations. KL – absorption rate of lesinurad; KA – absorption rate of allopurinol; FA – BA of allopurinol.

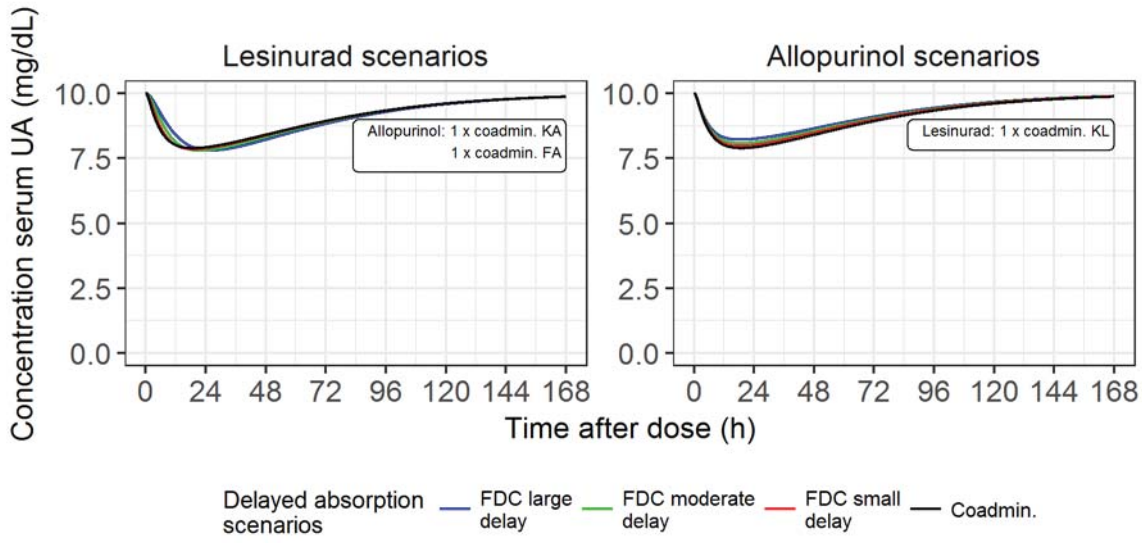
Source: Sponsor's study report: Simulation of Uric Acid Lowering; Figure 2 on Page 15

Table 16: Simulated Ratios of C_{max}, T_{max}, and $AUC_{0\text{-}168h}$ After Single Dose of Lesinurad/Allopurinol 200/300 Fixed-Dose Combination

Drug and scenario	C_{max} ratio to coadministration	T_{max} ratio to coadministration	$AUC_{0\text{-}168h}$ ratio to coadministration
Lesinurad 1. Coadministration: no change in absorption	1	1	1
Lesinurad 2. FDC:small delay of absorption	0.82	1.5	1.0
Lesinurad 3. FDC:moderate delay of absorption	0.57	2.4	1.0
Lesinurad 4. FDC:large delay of absorption	0.39	3.4	1.0
Allopurinol 1. Coadministration: no change in absorption	1	1	1
Allopurinol 2. FDC:small delay of absorption	0.55	3.6	0.90
Allopurinol 3. FDC:moderate delay of absorption	0.30	9.6	0.80
Allopurinol 4. FDC:large delay of absorption	0.17	15	0.70
Oxypurinol 1. Coadministration: no change in absorption of allopurinol	1	1	1
Oxypurinol 2. FDC:small delay of absorption of allopurinol	0.90	1.1	0.90
Oxypurinol 3. FDC:moderate delay of absorption of allopurinol	0.75	1.6	0.80
Oxypurinol 4. FDC:large delay of absorption of allopurinol	0.58	2.1	0.70

Source: Sponsor's study report: Simulation of Uric Acid Lowering; Table 5 on Page 17

Figure 24: Simulated Concentration Time Profiles of Serum Uric Acid Following A Single Dose of Lesinurad/Allopurinol 200/300 FDC Tablet for Delayed Absorption Scenarios

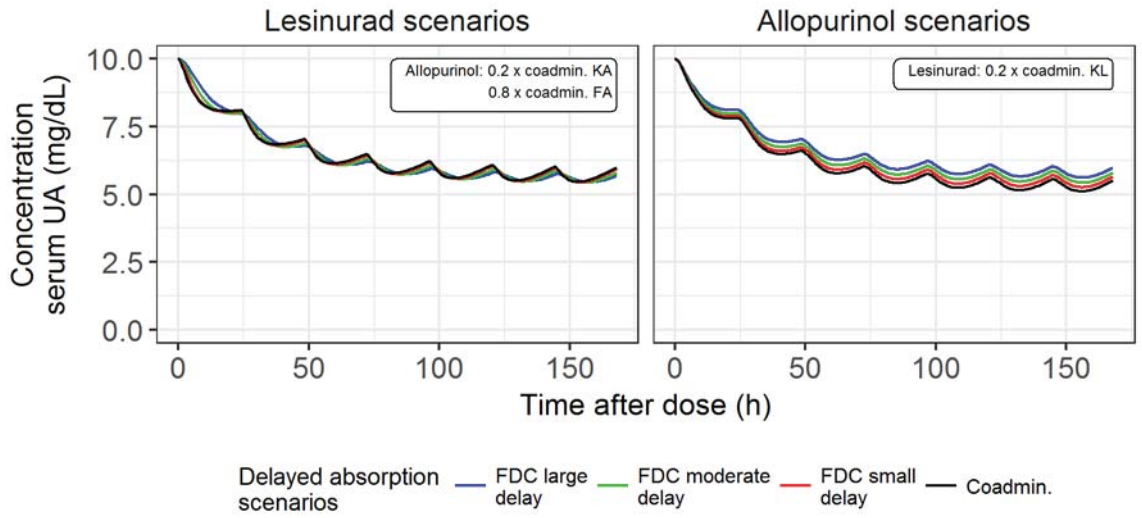


Note: KL – absorption rate of lesinurad; KA – absorption rate of allopurinol; FA – BA of allopurinol.

Source: Sponsor's study report: Simulation of Uric Acid Lowering; Figure 3 on Page 16

In addition, concentration time profiles of serum UA following multiple doses of lesinurad/allopurinol 200/300 FDC tablets were simulated for a typical hyperuricemic patient with baseline untreated serum UA of 10 mg/dL, excretion rate of UA in urine of 600 mg/day and GFR of 90 mL/min receiving 7 daily doses of lesinurad/allopurinol 200/300 FDC in fed state. Figure 25 shows the simulate results, illustrating the effect delayed absorption on concentration of serum UA at steady state.

Figure 25: Simulated Concentration Time Profiles of Serum Uric Acid Following Multiple Doses of Lesinurad/Allopurinol 200/300 FDC Tablet for Delayed Absorption Scenarios



Note: The corresponding FEUA is 0.046 and production rate is 54 mg/h, calculated from steady state model equations. KL – absorption rate of lesinurad; KA – absorption rate of allopurinol; FA – BA of allopurinol.

Source: Sponsor's study report: Simulation of Uric Acid Lowering; Figure 4 on Page 19

FDA Reviewer's Comments:

The sponsor's modeling and simulation appears reasonable and is adequate and qualified for its purpose, i.e. to evaluate the influence of food-effect-induced PK changes on the PD performance.

This PK/PD model of UA integrated key elements of UA physiology and described the pharmacological effect of lesinurad and allopurinol on the disposition of UA. For the PK/PD model development, phase 1 study data containing not only data healthy subject data, but also hyperuricemic patient data were used. A sequential PK/PD modeling approach was employed. First, the mean PK parameters for each drug were estimated for each treatment group, and then mean PK/PD parameters were estimated given mean values of PK parameters. Model parameters were estimated with acceptable precision and are consistent with literature values. Goodness-of-fits plots indicate reasonable model fitting.

The developed PK/PD model was then externally validated using data from core lesinurad Phase 3 studies (RDEA594-301, RDEA594-302, RDEA594-303, and RDEA594-304) and 2 published febuxostat Phase 3 studies APEX and FACT. The validation results showed that the model is able to adequately predict the serum UA profiles following lesinurad, allopurinol, and febuxostat treatment in hyperuricemic patients. In addition, the model validation also accounted for the dependence of UA disposition and dynamic responses of the UA handing system to lesinurad treatment on renal function by stratifying the validation results by CrCl levels. Results showed

that the model is able to accurately predict serum UA profiles in patients with mild and moderate renal impairment.

With the developed and validated PK/PD model, simulations were conducted to evaluate the effect of food-effect-induced delayed lesinurad and allopurinol absorption on the ability of the FDC formulation to maintain UA lowering. Simulation results demonstrated that there are no clinically meaningful differences in the serum UA lowering effect of the FDC formulation in hyperuricemic patients over a range of lesinurad and allopurinol absorption rate and BA changes; in other words, the PD effect of the FDC formulation is independent of the lesinurad and allopurinol C_{max} changes as long as AUCs are unchanged.

The simulated allopurinol absorption delay scenarios did show marginally lower serum UA lowering effects with larger allopurinol absorption delay, which should be attributed to decreased allopurinol and oxypurinol AUC (up to 30% reduction) due to reduced allopurinol availability. However, this should not be a concern because food effect study results from study 501 part 2 demonstrated that allopurinol and oxypunirol AUCs are comparable under fed and fasted conditions with 90% CIs for the fed/fasted geometric mean ratios within the BE limits of 0.80 to 1.25, even though the geometric mean ratios are on the lower end of the BE limits.

The sponsor's simulation was conducted for typical hyperuricemic patients who are naïve to allopurinol and lesinurad treatment. However, the FDC formulation is proposed for the treatment of hyperuricemia associated with gout in patients who have not achieved target serum uric acid levels with allopurinol alone. To verify the robustness of the sponsor's simulation results and conclusion, the reviewer conducted independent simulation in patients who are already on allopurinol treatment and have not achieved target serum UA levels, which serves a sensitivity analysis. The reviewers' analysis results are consistent with the sponsor's and presented in section 4 of this review.

4 Reviewer's analysis

4.1 Introduction

Modeling and simulation is of critical importance in evaluating of the effect of food-effect-induced C_{max} decrease of lesinurad on serum UA lowering, thus is the key component for establishing the PKPD bridging between the FDC formulation and the co-administrated mono-products in the fed state. The pharmacometrics reviewers performed independent simulation analysis as sensitivity analysis to verify the sponsor's analysis results. To make the simulated scenarios consistent with real clinical settings, patient characteristics in the lesinurad Phase 3 studies 301 and 302 in which lesinurad and allopurinol were co-administered were employed for our simulation.

4.2 Objectives

The objective of the reviewer's analysis was to assess the robustness of the sponsor's modeling and simulation results and the conclusion that the serum UA lowering effect of the FDC tablet is independent of the rate of absorption of lesinurad.

4.3 Methods

Lesinurad and allopurinol PK profiles and UA PD profiles under hypothesized scenarios, where the FDC formulation is hypothesized to be administered with food to hyperuricemic patients in the lesinurad Phase 3 study 301 and study 302, who have not achieved target serum UA levels with allopurinol alone, were simulated based on the sponsor's PKPD model. The simulated PK and PD profiles under the hypothesized scenarios were compared with the reference levels following co-administration of lesinurad and allopurinol, as well as with the observed UA levels.

4.3.1 Data Sets

Data sets used in the reviewer's analysis are summarized in the table below.

Study Number	Name	Link to Sharedrive
Study 301 Study 302 Study 303 Study 304	Pkscr.csv	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\LesinuradAllopurinolFDC_NDA 209203_RS_XW\E-R Analysis\Phase 3 model validation
Study 301 Study 302 Study 304	baseline-feua-594-301-302-304.csv	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\LesinuradAllopurinolFDC_NDA 209203_RS_XW\E-R Analysis\Phase 3 model validation
Study 303	303-baseline-feua.csv	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\LesinuradAllopurinolFDC_NDA 209203_RS_XW\E-R Analysis\Phase 3 model validation
APEX FACT	febuxostat-ph3.csv	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\LesinuradAllopurinolFDC_NDA 209203_RS_XW\E-R Analysis\Phase 3 model validation

4.3.2 Software

NONMEM (version 7.3) and R (version 2.15.3) were used for the analyses and graphics generation.

4.4 Results and discussion

Patient characteristics in the lesinurad Phase 3 study 301 and 302 were used for the simulation to represent the target population for the FDC formulation, i.e. hyperuricemic patients who have not achieved target serum UA levels with allopurinol alone. Three scenarios were simulated including 1) a reference scenario where lesinurad and allopurinol are co-administered as evaluated in the Phase 3 studies; 2) a scenario where the FDC formulation is administered with food which results in reduced absorption rate and C_{max} of lesinurad; 3) a scenario where the FDC formulation is administered with food which not only reduced the absorption rate of lesinurad but also reduced the absorption rate and bioavailability of allopurinol. The factors for absorption parameter changes for each simulation scenario are listed in Table 17. The factors for delay of lesinurad and allopurinol absorption were selected to

mimic the observed changes in lesinuard and allopurinol PK in the food effect study 501 part 2.

Table 17: Absorption Parameters for Simulation Scenarios for Fixed Dose Combination Relative to Co-administered Combination

Scenario	Lesinurad PK Parameter	Allopurinol PK Parameter
1: Co-administration: no change in absorption (reference scenario)	$k_L \mid_1 = k_L \times 1$	$k_A \mid_1 = k_A \times 1$ $F_A \mid_1 = F_A \times 1$
2: FDC: delay of lesinurad absorption	$k_L \mid_1 = k_L \times 0.2$	$k_A \mid_1 = k_A \times 1$ $F_A \mid_1 = F_A \times 1$
3: FDC : delay of lesinurad and allopurinol absorption	$k_L \mid_1 = k_L \times 0.2$	$k_A \mid_1 = k_A \times 0.2$ $F_A \mid_1 = F_A \times 0.85$

k_L : absorption rate of lesinurad; k_A : absorption rate of allopurinol; F_A : bioavailability of allopurinol

Simulations were stratified by treatment group and renal function within each treatment group to account for the dependence of UA disposition and the response of UA handling system to lesinurad treatment on renal function. The simulated PK profiles of lesinurad, allopurinol, and oxypurinol are presented in Figure 26, showing decreased C_{max} but unchanged AUC for lesinurad and decreased C_{max} and AUC for allopurinol and oxypurinol. The simulated serum UA profiles demonstrate that food-effect-induced lesinurad and allopurinol PK changes following the FDC tablet administration in hyperuricemic patients who have not achieved target serum UA levels with allopurinol alone has negligible effect on serum UA lowering, as shown in Figure 29. In addition, the results also show that the simulated serum UA profiles are consistent with the observed serum UA levels in study 301 and 302, which again verifies the predictability of the PKPD model.

In conclusion, the reviewer's sensitivity analysis results are consistent with the sponsor' results. The conclusion that the lesinurad and allopurinol PK following administration of the FDC tablet in the fed state would result in a comparable PD profile to that of the co-administered mono-products and the observed food effect is not expected to compromise the efficacy of the FDC tablet in hyperuricemic patients is considered to be robust.

Figure 26: Simulated Lesinurad PK Profiles under Different Scenarios

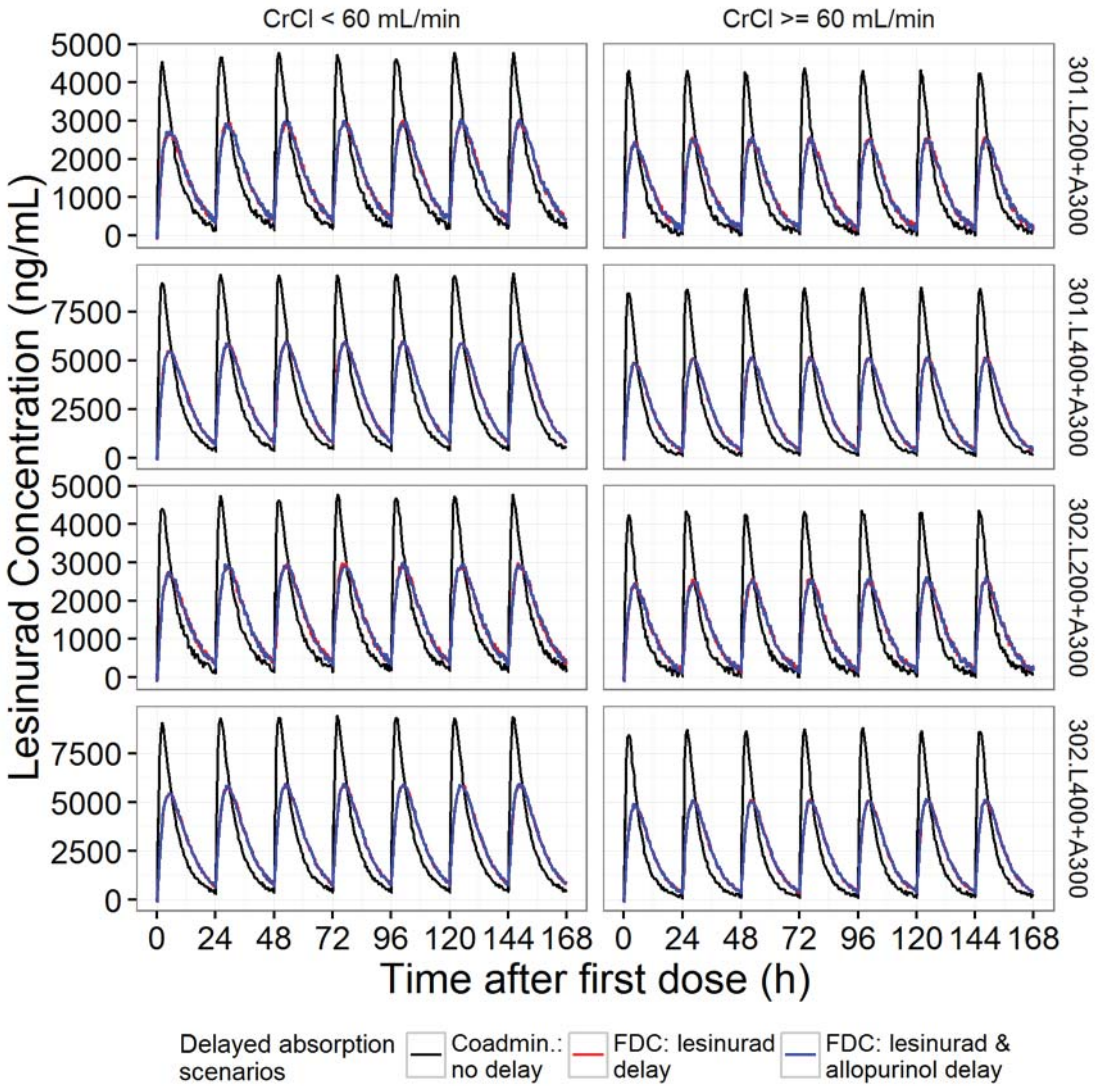


Figure 27: Simulated Allopurinol PK Profiles under Different Scenarios

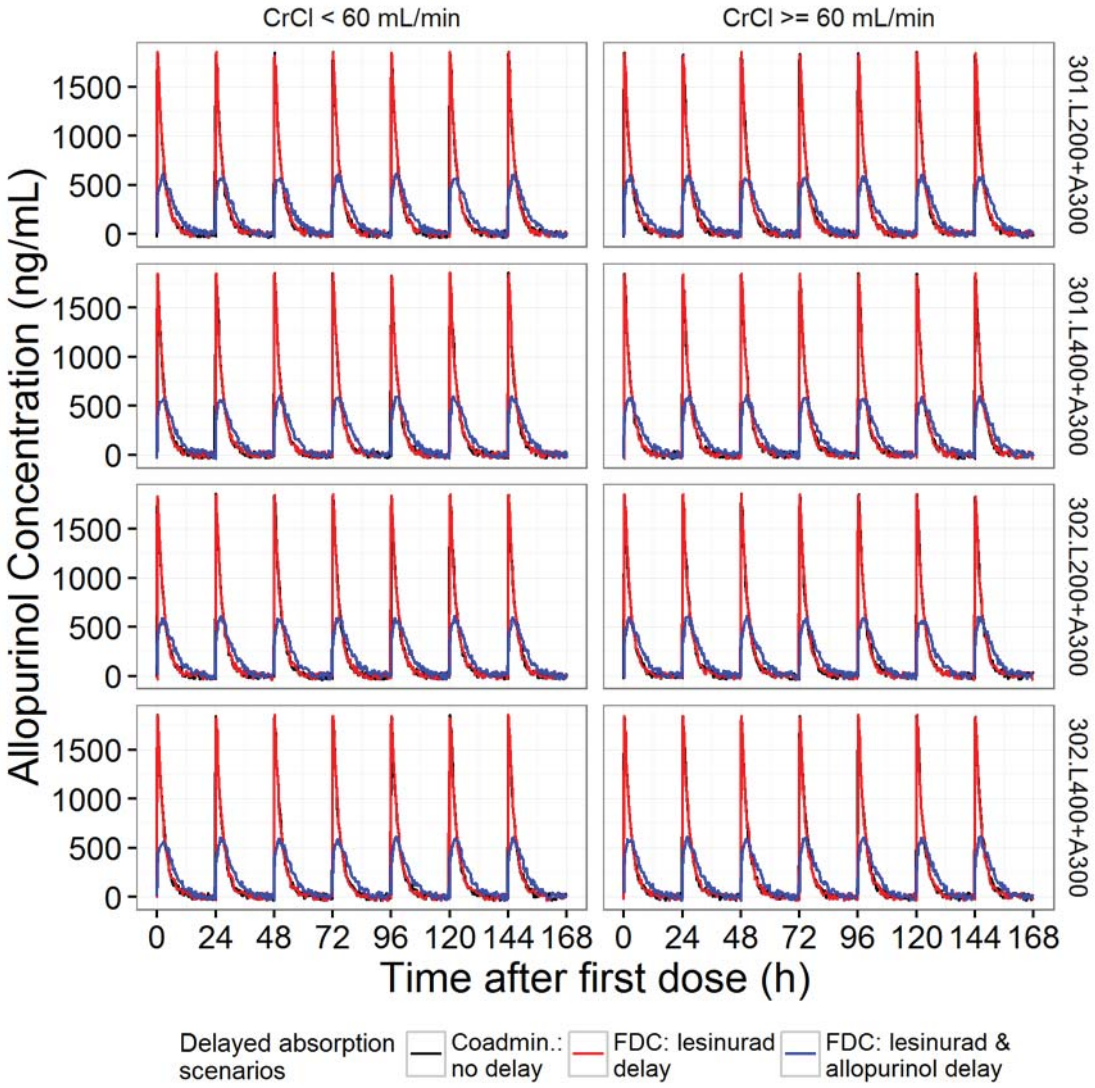


Figure 28: Simulated Oxypurinol PK Profiles under Different Scenarios

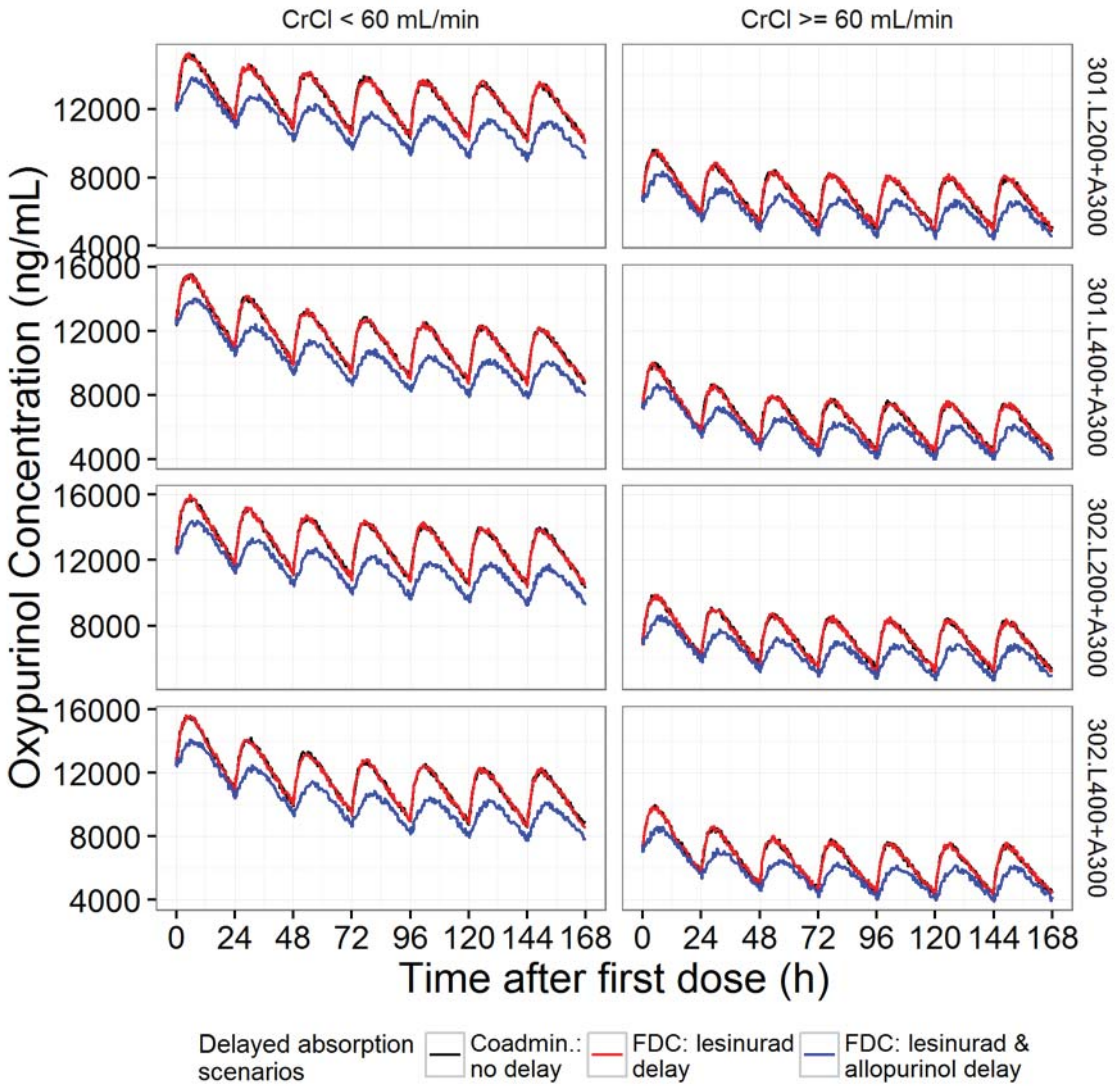
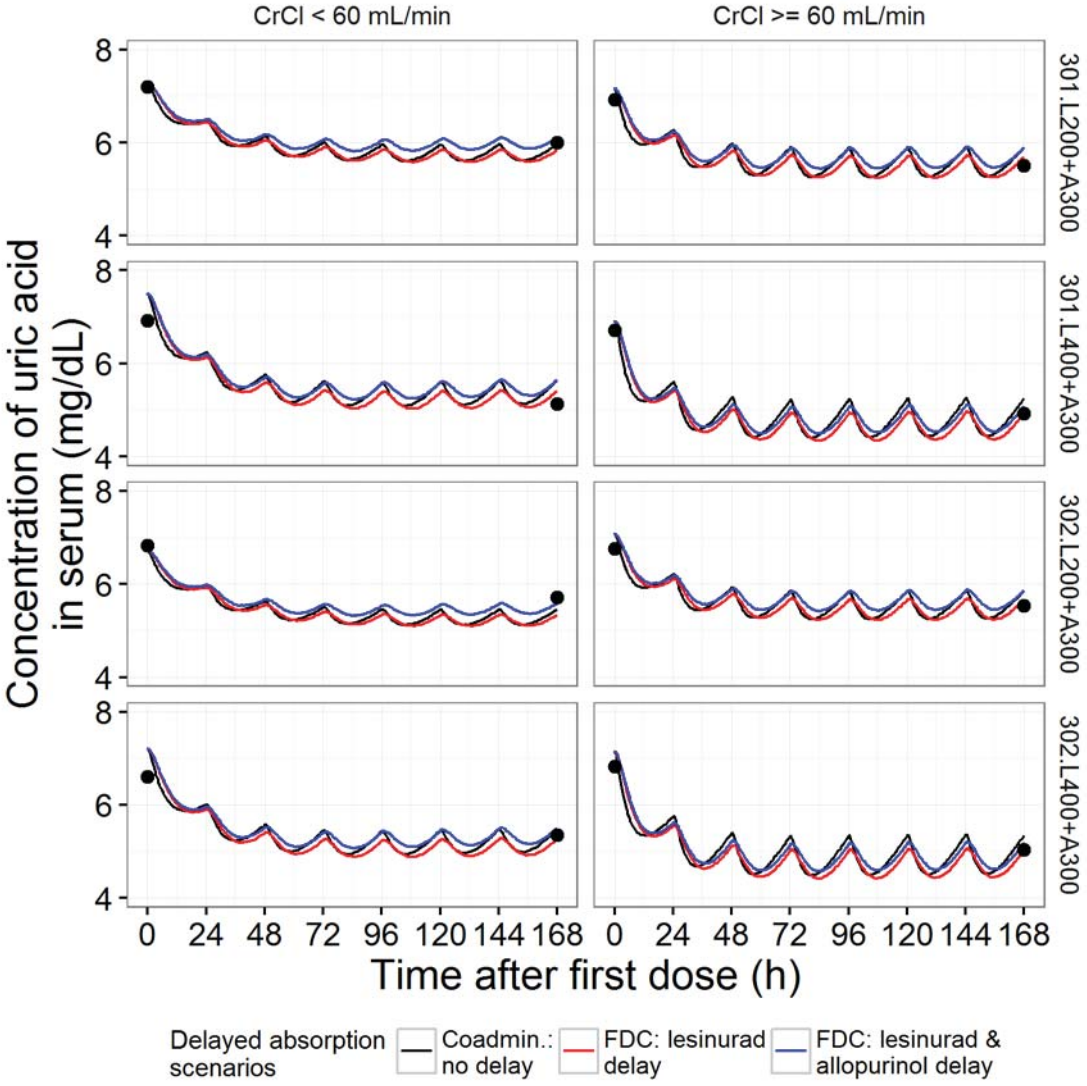


Figure 29: Simulated Concentration Time Profiles of Serum Uric Acid under Different Scenarios



4.5 Listing of Analyses Codes and Output Files

File Name	Description	Location in \\cdsnas\pharmacometrics\
ph3-predict_yw.R	R program to simulate lesinurad PK and serum UA for the reference scenario	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\LesinuradAllopurinolFDC_NDA 209203_RS_XW\E-R Analysis\Simulation by YW
ph3-predict_yw2.R	R program to simulate lesinurad PK and serum UA for the scenario of delayed lesinurad absorption	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\LesinuradAllopurinolFDC_NDA 209203_RS_XW\E-R Analysis\Simulation by YW

ph3-predict_yw3.R	R program to simulate lesinurad PK and serum UA for the scenario of delayed lesinurad and allopurinol absorption	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\LesinuradAllopurinolFDC_NDA 209203_RS_XW\E-R Analysis\Simulation by YW

14 Division Director (DPARP)

I have reviewed the application and the document and concurred with recommendation from the teams. The action on this application will be Approval.

X Badrul A. Chowdhury -S

Digitally signed by Badrul A. Chowdhury -S
DN: c=US, o=U S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300127299, cn=Badrul A. Chowdhury -S
Date: 2017.08.15 11:50:45 -04'00'

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/s/

BADRUL A CHOWDHURY
08/15/2017

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 07/21/2017

FROM: Timothy W. Robison, Ph.D., D.A.B.T.

TO: File for NDA 209203 dated October 20, 2016

SUBJECT: Nonclinical Secondary Review

APPLICATION/DRUG: NDA 209203 for DUZALLO® (Fixed dose combination product of lesinurad and allopurinol)

Refer to Dr. Matthew Whittaker's Nonclinical Primary Review Memo dated July 5, 2017 as well as the NDA Multi-disciplinary Review and Evaluation.

Ardea Bioscience submitted NDA 209203 dated October 20, 2016 for DUZALLO®, a fixed dose combination product of lesinurad and allopurinol.

The proposed Lesinurad/Allopurinol fixed-dose combination (FDC) tablet is comprised of two currently approved oral products at doses that are within the recommended dosing limits for both products. Lesinurad is a URAT1 inhibitor that decreases reabsorption of uric acid from the renal proximal tubule by inhibiting the function of carrier proteins that transport uric acid; URAT1 is responsible for the majority of the reabsorption of filtered uric acid from the renal tubular lumen. Allopurinol is an inhibitor of xanthine oxidase, the enzyme responsible for the conversion of hypoxanthine to xanthine and of xanthine to uric acid. The FDC's proposed indication of hyperuricemia associated with gout in patients who have not achieved target serum uric acid levels with allopurinol alone is consistent with the approved indication for lesinurad.

There are complete nonclinical development programs for each component of the FDC, which have been reviewed previously (See Pharmacology/Toxicology Reviews for NDA 207988 [Lesinurad] and NDA 20298 [Allopurinol]). The Sponsor has also conducted a 13-week lesinurad/allopurinol combination toxicology study in rats in support of the proposed FDC under IND 119031. No new or additive toxicities were observed in this study. Observed findings were consistent with individual components. No additional nonclinical studies were conducted (or required) to support approval.

Changes to the product label are recommended for Sections 8.1 (Pregnancy), 8.2 (Lactation), 12.1 (Mechanism of Action), and 13 (Nonclinical Toxicology). Nonclinical information for lesinurad was taken directly from the ZURAMPIC® label. Dr. Whittaker

provided recommended changes to the nonclinical information for allopurinol to allow for alignment with the Pregnancy and Lactation Labeling Rule (PLLR) and current CDER labeling practices. Resources used to complete the revised allopurinol labeling included the following: Language in the existing prescribing information for ZYLOPRIM® (oral allopurinol) and ALOPRIM® (IV allopurinol) and published scientific literature. The Pharmacology/Toxicology Review for ALOPRIM® (NDA 20298, dated 1/4/96) was examined, although no information was referenced or transferred into the present application.

I concur with Dr. Whittaker's recommendation that the application be approved from the nonclinical perspective.

Refer to the Multi-disciplinary Review and Evaluation for additional details.

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/s/

TIMOTHY W ROBISON
07/21/2017
See Dr. Whittaker's Primary Review dated 7-5-17

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 7/14/2017

TO: File for NDA 0209203

THROUGH: Anshu Marathe, Ph.D.

FROM: Renu Singh, Ph.D.

SUBJECT: Clinical Pharmacology Primary Review

APPLICATION/DRUG: NDA 209203/ Duzallo (Lesinurad/allopurinol fixed dose combination)

The applicant, Ardea Biosciences, Inc., has submitted NDA 209203 for the lesinurad/allopurinol 200/200 and 200/300 fixed-dose combination (FDC) tablets taken once daily (qd) for the treatment of hyperuricemia associated with gout in patients who have not achieved target serum uric acid (sUA) levels with allopurinol alone. The NDA submission included one pivotal bioequivalence (BE) study RDEA594-501 (study 501) report and PKPD modeling and simulation reports. Study 501 demonstrated BE between lesinurad/allopurinol 200/300 and 200/200 FDC tablets and coadministered single agents in healthy subjects in the fasted state. Study 501 also evaluated the food effect for the 200/300 FDC tablet. Food effect study results showed that lesinurad, allopurinol, and oxypurinol AUC, and oxypurinol C_{max}, were similar in the fed (high-fat, high-calorie) and fasted states following administration of the 200/300 FDC tablet, whereas C_{max} for lesinurad and allopurinol was reduced (by 46% and 18%, respectively) and T_{max} was extended following administration with food.

Similar to dosing instructions for approved lesinurad tablet (Zurampic, 200 mg), the applicant proposed that the lesinurad/allopurinol FDC tablets should be taken in the morning with food and water. Modeling and simulation using a physiologic uric acid turnover model demonstrated that the food-effect-induced lesinurad and allopurinol C_{max} reductions following the FDC tablet administration in hyperuricemic patients who have not achieved target sUA levels with allopurinol alone are likely to have negligible effect on sUA lowering. This was consistent with the observations in healthy subjects where reductions in C_{max} due to food did not lead to PD (plasma uric acid) differences. After reviewing the submitted data, the Office of Clinical Pharmacology/Divisions of Clinical Pharmacology 2 (OCP/DCP2) and Pharmacometrics (OCP/DPM) recommends approval of the lesinurad/allopurinol fixed dose combination.

From a clinical pharmacology perspective, this supplement NDA is approvable provided that the applicant and the FDA reach an agreement regarding the labeling language.

Refer to the multi-disciplinary review and evaluation for additional details.

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/s/

RENU SINGH
07/14/2017

BHAWANA SALUJA
07/14/2017

XIAOFENG WANG
07/14/2017

JIANG LIU
07/14/2017

YANING WANG
07/14/2017

ANSHU MARATHE
07/15/2017

Medical Officer Review

Date: July 14, 2017

To: NDA 209203 Lesinurad/Allopurinol Fixed Dose Combination (FDC) Tablets (Duzallo®)

From: Rosemarie Neuner, MD, MPH
Medical Reviewer, CDER/ODEII/DPARP

Through: Nikolay Nikolov, MD
Clinical Team Leader, CDER/ODEII/DPARP

Sponsor: Ardea Bioscience

Subject: Clinical Review of NDA

Background

Duzallo® is a fixed dose combination (FDC) product that consists of two previously approved urate lowering agents, lesinurad (Zurampic®) and allopurinol (Zyloprim®). According to the Applicant, they have developed this FDC urate lowering product under the FDA's Combination Rule (21 CFR §300.50) in order to mitigate the renal safety risk associated with lesinurad monotherapy. The efficacy and safety data in support of this 505(b)(2) application for these proposed FDC tablets containing 200 mg/200 mg and 200 mg /300 mg of lesinurad and allopurinol, respectively, is primarily predicated on clinical trial data reviewed previously by this medical officer in support of NDA 207988 lesinurad (Zurampic®), which included combination studies that evaluated the co-administration of these two urate lowering agents. Additionally, the Applicant submitted the results of a bioavailability/bioequivalence study they had conducted to provide the necessary pharmacokinetic data in support of a bridge between the combination studies contained in the lesinurad NDA (207988) to the lesinurad/allopurinol FDC NDA (209203), which was reviewed by the Office of Clinical Pharmacology/Division of Clinical Pharmacology II. The Applicant also submitted updated postmarketing data for lesinurad in support of this application. For additional information regarding the reviews and discussions of the data contained in this application, the reader is referred to the Multi-Disciplinary Review and Evaluation which will be filed at a later date.

Final Recommendation: Pending agreement on the lesinurad/allopurinol FDC tablets' final labeling, this clinical reviewer recommends approval of this new drug application.

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/s/

ROSEMARIE NEUNER
07/14/2017

NIKOLAY P NIKOLOV
07/14/2017

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: July 5, 2017

FROM: Matthew Whittaker, Ph.D.

THROUGH: Timothy W. Robison, DABT, Ph.D.

TO: File for NDA 209203

SUBJECT: Nonclinical Primary Review

APPLICATION/DRUG: NDA 209203 / Lesinurad + Allopurinol Fixed Dose Combination
Ardea Biosciences submitted NDA 209203 on October 20, 2016. The proposed Lesinurad/Allopurinol fixed-dose combination (FDC) tablet is comprised of two currently approved oral products at doses that are within the recommended dosing limits for both products. Lesinurad decreases reabsorption of uric acid from the renal proximal tubule by inhibiting the function of carrier proteins that transport uric acid (e.g. URAT1). Allopurinol is an inhibitor of xanthine oxidase, the enzyme responsible for the conversion of hypoxanthine to xanthine and of xanthine to uric acid. The FDC's proposed indication of hyperuricemia associated with gout in patients who have not achieved target serum uric acid levels with allopurinol alone is consistent with the approved indication for lesinurad.

The nonclinical development programs for each component of the FDC have been reviewed previously (See NDA Pharmacology/Toxicology reviews for NDA 207988 [Lesinurad] and NDA 20298 [Allopurinol]). The sponsor has also conducted a 13-week lesinurad/allopurinol combination toxicology study in rats in support of the proposed FDC. No additive toxicity was observed in this study. No additional nonclinical studies were conducted (or required) to support approval.

The lesinurad portions of the nonclinical sections of the sponsor's proposed drug product labeling are considered adequate as currently presented. The Division has provided recommended changes to the allopurinol portions of the nonclinical sections of the proposed labeling to allow for alignment with the Pregnancy and Lactation Labeling Rule (PLLR) and current CDER labeling practices. Resources used to complete the revised allopurinol labeling included the following: (1) Language in the existing prescribing information for Zyloprim (oral allopurinol) and Aloprim (IV allopurinol), (2) Pharmacology/Toxicology review for Aloprim (NDA 20298, dated 1/4/96), and (3) published scientific literature.

The NDA should be approved from the nonclinical perspective with recommended changes to the labeling. Refer to the Multi-disciplinary Review and Evaluation for labeling recommendations and additional details.

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/s/

MATTHEW T WHITTAKER
07/05/2017

TIMOTHY W ROBISON
07/05/2017
I concur

CLINICAL PHARMACOLOGY FILING FORM

Application Information

NDA/BLA Number	209203	**SDN**	0000
Applicant	Ardea Biosciences	**Submission Date**	10/20/2016
Generic Name	Lesinurad/Allopurinol FDC	**Brand Name**	Duzallo
Drug Class	Fixed dose combination of selective uric acid reabsorption inhibitor and xanthine oxidase inhibitor		
Indication	treatment of hyperuricemia associated with gout in patients who have not achieved target serum uric acid levels with allopurinol alone		
Dosage Regimen	Once daily		
Dosage Form	Tablet	**Route of Administration**	Oral
OCP Division	DCP 2	**OND Division**	DPARP

OCP Review Team	**Primary Reviewer(s)**	**Secondary Reviewer/ Team Leader**
Division	Renu Singh, PhD	Anshu Marathe, PhD
Pharmacometrics		
Genomics		

Review Classification	☑ Standard ☐ Priority ☐ Expedited		
Filing Date	12/19/2016	**74-Day Letter Date**	1/2/2017
Review Due Date	7/14/2017	**PDUFA Goal Date**	8/20/2017

Application Fileability

Is the Clinical Pharmacology section of the application fileable?

☑ Yes

☐ No

If no list reason(s)

Are there any potential review issues/ comments to be forwarded to the Applicant in the 74-day letter?

☑ Yes

☐ No

If yes list comment(s)

We note that the upper limit of 90% CI of allopurinol C_{max} for 200/200 mg FDC tablet (study RDEA594-501) was outside the BE limits of 0.80 to 1.25. We also note that food effect study showed 46% lower C_{max} for lesinurad from the FDC tablet in the fed state. The observed C_{max} reduction is more than the reported C_{max} reduction as per the approved lesinurad label. The acceptability of these results will be a review issue.

Is there a need for clinical trial(s) inspection?

☑ Yes

☐ No

If yes explain: OSIS consult request sent as this is the pivotal BE study (RDEA-594-501) for the proposed FDC product

Clinical Pharmacology Package

Tabular Listing of All Human Studies	☑ Yes ☐ No	Clinical Pharmacology Summary	☑ Yes ☐ No
Bioanalytical and Analytical Methods	☑ Yes ☐ No	Labeling	☑ Yes ☐ No

Clinical Pharmacology Studies			
Study Type		**Count**	**Comment(s)**
In Vitro Studies			
☐ Metabolism Characterization			
☐ Transporter Characterization			
☐ Distribution			
☐ Drug-Drug Interaction			
In Vivo Studies			
Biopharmaceutics			
☐ Absolute Bioavailability			
☐ Relative Bioavailability			
☑ Bioequivalence		1	RDEA594-501 (Module 5.3.1.1) (pivotal BE effect study)
☑ Food Effect		1	RDEA594-501 (Module 5.3.1.1) (pivotal BE effect study)
☐ Other			
Human Pharmacokinetics			
Healthy Subjects	☑ Single Dose	1	RDEA594-501 (Module 5.3.1.1) (pivotal BE effect study)
	☐ Multiple Dose		
Patients	☐ Single Dose		
	☐ Multiple Dose		
☐ Mass Balance Study			
☐ Other (e.g. dose proportionality)			
Intrinsic Factors			
☐ Race			
☐ Sex			
☐ Geriatrics			
☐ Pediatrics			
☐ Hepatic Impairment			
☐ Renal Impairment			
☐ Genetics			
Extrinsic Factors			
☐ Effects on Primary Drug			
☐ Effects of Primary Drug			
Pharmacodynamics			
☐ Healthy Subjects			
☐ Patients			
Pharmacokinetics/Pharmacodynamics			
☐ Healthy Subjects			
☐ Patients			
☐ QT			
Pharmacometrics			
☐ Population Pharmacokinetics			

☐ Exposure-Efficacy					
☐ Exposure-Safety					
Total Number of Studies	**1**				1
Total Number of Studies to be Reviewed	**1**	**In Vitro**		**In Vivo**	1

Criteria for Refusal to File (RTF)		
RTF Parameter	**Assessment**	**Comments**
1. Did the applicant submit bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	☑Yes ☐No ☐N/A	The sponsor claims that tablets of the proposed commercial formulations (except for non-function coating), were used in the pivotal BE studies.
2. Did the applicant provide metabolism and drug-drug interaction information? (Note: RTF only if there is complete lack of information)	☐Yes ☐No ☑N/A	Cross- reference to NDA 207988
3. Did the applicant submit pharmacokinetic studies to characterize the drug product, or submit a waiver request?	☑Yes ☐No ☐N/A	
4. Did the applicant submit comparative bioavailability data between proposed drug product and reference product for a 505(b)(2) application?	☑Yes ☐No ☐N/A	Comparative study information provided for FDC and individual components of the combination in the 505(b)(2) application.
5. Did the applicant submit data to allow the evaluation of the validity of the analytical assay for the moieties of interest?	☑Yes ☐No ☐N/A	
6. Did the applicant submit study reports/rationale to support dose/dosing interval and dose adjustment?	☐Yes ☐No ☑N/A	
7. Does the submission contain PK and PD analysis datasets and PK and PD parameter datasets for each primary study that supports items 1 to 6 above (in .xpt format if data are submitted electronically)?	☑Yes ☐No ☐N/A	
8. Did the applicant submit the module 2 summaries (e.g. summary-clin-pharm, summary-biopharm, pharmkin-written-summary)?	☑Yes ☐No ☐N/A	
9. Is the clinical pharmacology and biopharmaceutics section of the submission legible, organized, indexed and paginated in a manner to allow substantive review to begin? If provided as an electronic submission, is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work leading to appropriate sections, reports, and	☑Yes ☐No ☐N/A	

appendices?		
Complete Application **10.** Did the applicant submit studies including study reports, analysis datasets, source code, input files and key analysis output, or justification for not conducting studies, as agreed to at the pre-NDA or pre-BLA meeting? If the answer is 'No', has the sponsor submitted a justification that was previously agreed to before the NDA submission?	☑Yes ☐No ☐N/A	
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality) Checklist		
Data		
1. Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	☑Yes ☐No ☐N/A	
2. If applicable, are the pharmacogenomic data sets submitted in the appropriate format?	☐Yes ☐No ☑N/A	
Studies and Analysis		
3. Is the appropriate pharmacokinetic information submitted?	☑Yes ☐No ☐N/A	
4. 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)?	☐Yes ☐No ☑N/A	
5. Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	☐Yes ☐No ☑N/A	Cross- reference to NDA 207988
6. 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?	☐Yes ☐No ☑N/A	Cross- reference to NDA 207988
7. Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?	☐Yes ☐No ☑N/A	Request for a waiver of studies in children ages 0 to less than 18 years.
General		
8. Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	☑Yes ☐No ☐N/A	
9. Was the translation (of study reports or other study information) from another language needed and provided in this submission?	☐Yes ☐No ☑N/A	

Filing Memo

Attachment: File & Plan meeting Clinical Pharmacology presentation.

FDA U.S. FOOD & DRUG ADMINISTRATION

NDA 209203 Filing Meeting

Lesinurad/Allopurinol FDC
Sponsor: Ardea Biosciences Inc.
Submitted: 20th October 2016

OCP Review Team:
Clin Pharm Reviewer: Renu Singh, Ph.D.
Clin Pharm Team Leader: Anshu Marathe, Ph.D.

Overview

Type of Submission: 505(b)(2)

- Lesinurad 200 md qd approved in 2015
- Allopurinol 100 mg and 300 mg tablets marketed (approved in 1966) - Max dose 800 mg/day.

Proposed Indication:

- Indicated for the (b) (4) treatment of hyperuricemia associated with gout in patients who have not achieved target serum uric acid (sUA) levels with allopurinol alone

Formulation:

- FDC tablets - 200mg/300 mg and 200mg/200 mg

Administration:

- Oral

Proposed dose:

- once daily use of lesinurad/allopurinol fixed dose combination (200/200 and 200/300) tablets
- Dose recommended with food and water in the morning – same as lesinurad

Overview

Table 1: Dosing regimen examples

(b) (4)

Overview

Table 2: Summary of studies in the FDC clinical development program

Protocol Number	Title	Objectives
RDEA594-501	A Phase 1, Randomized, Open-Label, Crossover Study to Assess the Relative BA of Lesinurad/Allopurinol FDC Tablets and Coadministered Lesinurad and Allopurinol Tablets and the Effect of Food on the PK of Lesinurad/Allopurinol FDC Tablets in Healthy Adult Subjects	1. To assess the BA of lesinurad allopurinol 200/300 FDC tablets and lesinurad allopurinol 200/200 FDC tablets relative to coadministered lesinurad and allopurinol tablets in healthy adult subjects. 2. To assess the effect of a high-fat high-calorie meal on the PK of lesinurad allopurinol 200/300 FDC tablets in healthy adult subjects. 3. To assess the safety and tolerability of lesinurad allopurinol 200/300 FDC tablets, lesinurad allopurinol 200/200 FDC tablets, and lesinurad coadministered with allopurinol in healthy adult subjects.
ALLO-101	In Vitro-In Vivo Relationship Study to Assess the Impact of the In Vitro Dissolution Profile of Allopurinol on the PK Parameters Used to Establish BE	4. To determine whether defined and limited changes in in vitro dissolution impact the in vivo PK and relative BA of allopurinol and the active metabolite oxypurinol. 5. To provide additional safety information on allopurinol in healthy subjects.

Abbreviations: BA, bioavailability; BE, bioequivalence; FDC, fixed-dose combination; PK, pharmacokinetics.

Sponsor claims adequate bridging of Lesinurad and Allopurinol exposure from FDC tablet in pivotal BE study

Table 3: Bioavailability of Lesinurad/Allopurinol FDC Tablets Relative to the Coadministered Single Agents at Corresponding Doses (Study 501, Parts 1 and 3)

PK Parameter	Analyte	Geometric Least Squares Mean Ratio (90% CI)	
		200/300 mg FDC tablet (N=35)	200/200 mg FDC tablet (N=53)
C_{max}	Lesinurad	1.1026 (1.0056-1.2090)	0.9881 (0.9248-1.0558)
	Allopurinol	1.0758 (0.9837-1.1766)	1.1823 (1.0905-1.2817)
	Oxypurinol	0.9914 (0.9653-1.0183)	1.0260 (1.0046-1.0479)
AUC_{last}	Lesinurad	0.9895 (0.9501-1.0306)	0.9816 (0.9439-1.0208)
	Allopurinol	1.0045 (0.9675-1.0428)	1.0914 (1.0520-1.1324)
	Oxypurinol	0.9967(0.9771-1.0168)	1.0175 (1.0003-1.0349)
AUC_{∞}	Lesinurad	0.9889 (0.9494-1.0299)	0.9825 (0.9452-1.0214)
	Allopurinol	1.0054 (0.9683-1.0440)	1.0760 (1.0387-1.1147)*
	Oxypurinol	1.0022 (0.9804-1.0245)	1.0175 (0.9991-1.0363)

Abbreviations: AUC_{∞}, area under the concentration-time curve from time zero to infinity; AUC_{last}, area under the concentration-time curve from time zero to the last quantifiable sampling timepoint; C_{max}, maximum observed concentration; CI, confidence interval; FDC, fixed-dose combination; N, number of evaluable subjects; PK, pharmacokinetic.
*N=51.

Oxypurinol – active metabolite of Allopurinol

5

Fed C_{max} in FDC lower than the approved lesinurad formulation

Table 4: Bioavailability of Lesinurad 200 mg/Allopurinol 300 mg FDC Tablets: Fed Versus Fasted State (Study 501, Part 2; N=28)

PK Parameter	Analyte	Fed/Fasted Geometric Least Squares Mean Ratio (90% CI)
C_{max}	Lesinurad	0.5450 (0.4703-0.6316)
	Allopurinol	0.8166 (0.7030-0.9486)
	Oxypurinol	0.8633 (0.8315-0.8964)
AUC_{last}	Lesinurad	0.9796 (0.9272-1.0350)
	Allopurinol	0.8750 (0.8331-0.9191)
	Oxypurinol	0.8471 (0.8267-0.8680)
AUC_{∞}	Lesinurad*	0.9642 (0.9182-1.0125)
	Allopurinol*	0.8835 (0.8399-0.9294)
	Oxypurinol	0.8476 (0.8248-0.8711)

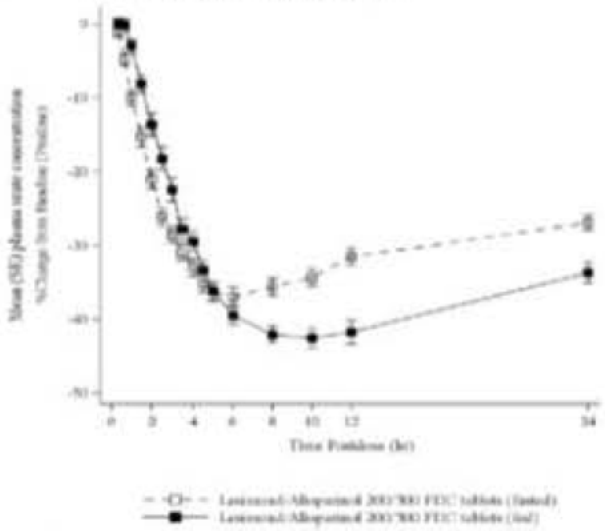
Abbreviations: AUC_{∞}, area under the concentration-time curve from time zero to infinity; AUC_{last}, area under the concentration-time curve from time zero to the last quantifiable sampling timepoint; C_{max}, maximum observed concentration; CI, confidence interval; FDC, fixed-dose combination; N, number of evaluable subjects; PK, pharmacokinetic.
*N=26.

T_{max} delayed by 2 hr under fed conditions

6

Study-501 (food effect)

Figure 2: Comparison of Mean Plasma Urate Reduction Following Fed and Fasted FDC Tablet Administration (Study 501)



Sponsor's Top Line Results

- The lesinurad/allopurinol 200/300 and 200/200 FDC tablet met the criteria for BE to the coadministered single agents with respect to all 3 PK parameters for all 3 analytes, with the exception of allopurinol C_{max} for 200/200 FDC tablet; the upper limit of the 90% CI (1.2817) was outside of the BE limits.

- Lesinurad, allopurinol, and oxypurinol AUC, and oxypurinol C_{max}, were similar whether the lesinurad/allopurinol 200/300 FDC tablet was administered under fed or fasted conditions. Under fed conditions, C_{max} for lesinurad and allopurinol was reduced (by 46% and 18%, respectively) and T_{max} was increased. These effects of food on the PK profiles of lesinurad and allopurinol were not associated with a reduction in the percentage change in plasma urate concentration of the FDC tablet in the fed state and not considered clinically important.

- Single doses of lesinurad/allopurinol FDC tablets, and of coadministered lesinurad and allopurinol tablets, were generally safe and well tolerated.

Review Focus

Do the results of BE studies support sponsor's claim for Lesinurad /Allopurinol FDC?

- adequacy of data to support bridging **to individual components**
- adequacy of data to support food effect claim
- specifics of data analysis – data exclusions and analysis methods

9

Filing Status and Consults

- Clin Pharm recommends NDA 209203 to be ***fileable***
- OSIS consult:
  - Yes, for the clinical and analytical sites for pivotal BE study-501
- Request for Sponsor:
  - None

10

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RENU SINGH
12/20/2016

ANSHU MARATHE
12/21/2016

CLINICAL FILING CHECKLIST FOR NDA 209203
Lesinurad/Allopurinol Fixed Dose Combination (FDC) Tablets

NDA Number: 209203 **Applicant:** Andrea Biosciences **Stamp Date:** Oct. 20, 2016

Drug Name: Lesinurad/Allopurinol Fixed Dose Combination (FDC) Tablets **NDA Type:** Standard

On initial overview of the NDA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic common technical document (eCTD).	X			
2.	Is the clinical section legible and organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
LABELING					
6.	Has the applicant submitted a draft prescribing information that appears to be consistent with the Physician Labeling Rule (PLR) regulations and guidances (see http://www.fda.gov/Drugs/GuidanceComplianceRegulatory Information/LawsActsandRules/ucm084159 htm	X			
SUMMARIES					
7.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
8.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
9.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
10.	Has the applicant submitted a benefit-risk analysis for the product?	X			
11.	Indicate if the Application is a 505(b)(1) or a 505(b)(2).				505(b)(2)
505(b)(2) Applications					
12.	If appropriate, what is the relied upon listed drug(s)?				Lesinurad (Zurampic®) and Allopurinol (Zyloprim®)
13.	Did the applicant provide a scientific bridge demonstrating the relationship between the proposed product and the listed drug(s)/published literature?	X			
14.	Describe the scientific bridge (e.g., BA/BE studies)	X			BA/BE Study RDEA594-501
DOSAGE					
15.	If needed, has the applicant made an appropriate attempt to determine the correct dosage regimen for this product (e.g., appropriately designed dose-ranging studies)? Study Number: Study Title:			X	

CLINICAL FILING CHECKLIST FOR NDA 209203
Lesinurad/Allopurinol Fixed Dose Combination (FDC) Tablets

	Content Parameter	Yes	No	NA	Comment
	Sample Size: Treatment Arms: Location in submission:				
EFFICACY					
16.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1 Indication:			X	This 505(b)(2) application cross-references efficacy data reviewed in support of NDA 207988 Lesinurad (Zurampic®)
17.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?			X	This 505(b)(2) application cross-references efficacy data reviewed in support of NDA 207988 Lesinurad (Zurampic®)
18.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.			X	This 505(b)(2) application cross-references efficacy data reviewed in support of NDA 207988 Lesinurad (Zurampic®)
19.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	
SAFETY					
20.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
21.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?			X	This 505(b)(2) application cross-references the QT interval study reviewed in support of NDA 207988 Lesinurad (Zurampic®)
22.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
23.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dosage (or dosage range) believed to be efficacious?			X	This 505(b)(2) application cross-references exposure data reviewed in support of NDA 207988 Lesinurad (Zurampic®)
24.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	This 505(b)(2) application cross-references exposure data reviewed in

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

CLINICAL FILING CHECKLIST FOR NDA 209203
Lesinurad/Allopurinol Fixed Dose Combination (FDC) Tablets

	Content Parameter	Yes	No	NA	Comment
					support of NDA 207988 Lesinurad (Zurampic®)
25.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	X			
26.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?			X	This 505(b)(2) application cross-references exposure data reviewed in support of NDA 207988 Lesinurad (Zurampic®)
27.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
OTHER STUDIES					
28.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			
29.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
30.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			
PREGNANCY, LACTATION, AND FEMALES AND MALES OF REPRODUCTIVE POTENTIAL USE					
31.	For applications with labeling required to be in Pregnancy and Lactation Labeling Rule (PLLR) format, has the applicant submitted a review of the available information regarding use in pregnant, lactating women, and females and males of reproductive potential (e.g., published literature, pharmacovigilance database, pregnancy registry) in Module 1 (see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm)?	X			
ABUSE LIABILITY					
32.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
33.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	
DATASETS					
34.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
35.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA 209203
Lesinurad/Allopurinol Fixed Dose Combination (FDC) Tablets

	Content Parameter	Yes	No	NA	Comment
36.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
37.	Are all datasets to support the critical safety analyses available and complete?	X			
38.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
39.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
40.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			
FINANCIAL DISCLOSURE					
41.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
42.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? ____Yes____

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Refer to the appended slides from the December 7, 2016 filing meeting for additional information regarding this application.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

1. According to the draft labeling included in your submission, you are proposing to include under Section 14 Clinical Studies efficacy data generated from phase 3 studies previously reviewed and described in the lesinurad product labeling. Inclusion of these data in the lesinurad/allopurinol fixed dose combination (FDC) tablet proposed labeling will be a review issue.

2. We have concerns that the information you have included under Subsection 2.1 Recommended Dosing of the draft label regarding patients who are taking higher doses of allopurinol than contained in the lesinurad/allopurinol FDC tablets may be confusing to healthcare providers and patients. The content of the information under Section 2 Dosing and Administration of the FDC tablet's label will also be a review issue.

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Reviewing Medical Officer Date

Electronic signature

Clinical Team Leader Date

NDA 209203 Lesinurad/Allopurinol FDC
Sponsor: Ardea Biosciences

Filing Meeting: Dec. 7, 2016

Medical Reviewer: Rosemarie Neuner, MD, MPH

Overview

- **Product:** Lesinurad/Allopurinol Fixed-Dose Combination (FDC) Tablets
- **MOA:** Combination URAT1 inhibitor (lesinurad) and XOI (allopurinol)
- **Dose and ROA:**
  - LES200mg/ALLO300mg po once daily **and**
  - LES200mg/ALLO200mg po once daily
- **Indication:** Treatment of hyperuricemia associated with gout in patients who have not achieved sUA levels with allopurinol alone
- **Application Type:** 505(b)(2)
  - RLDs Zurampic (lesinurad) 200 mg tablet and Zyloprim® (Allopurinol)
  - Cross-references safety and efficacy data to NDA 207988 Lesinurad (Zurampic®) 200 mg tablet
- **Final Recommendation:** Application is fileable from a clinical perspective

Regulatory History

- PreIND WR June 24, 2013
  - Feedback on proposed clinical development plans and applicability of the Combination Rule
- IND 119031 for lesinurad/allopurinol FDC tablets for use in the (b) (4) treatment of hyperuricemia associated with gout was opened on Sept. 3, 2015
  - Initial Study RDEA594-501 was a P1, BA/BE single-dose, x-over PK study of LES200mg/ALLO300 mg tablets in HV
- Type C meeting held on Jan. 13, 2016
  - Acceptability of LES200mg/ALLO300mg and LES200mg/ALLO200 mg FDC proportional similarity
  - (b) (4) for LES200mg/ALLO200mg FDC strength
  - Stability package for FDC non-functional coating change
- EOP2 meeting held on May 6, 2016
  - Feedback on proposed in vitro dissolution test method
  - Agreement on clinical package to support bridge for FDC to lesinurad and allopurinol monocomponents
- PreNDA meeting on Aug. 30, 2016
  - FDC label info
  - Clinical data set info
  - Formatting and technical issues related to application

Lesinurad/Allopurinol FDC Tablets Studies

Study	Design	No. Pts.	Dose Regimen	Status
RDEA594-501	P1, R, OL, 3-part, x-over, relative BA and food effect PK study of LES/ALLO FDC tablets and LES and ALLO tablets	Pt. 1: N= 36 HV Pt. 2: N=28 HV Pt. 3: N=55 HV	LES200mg/ALLO 300 FDC tablets LES200/ALLO200 FDC tablets LES200 mg tablets ALLO 100 mg and 300mg tablets	Completed
ALLO-101	P1, OL, sequential dose , 4-period in vitro dissolution study (fasted state)	N=22	Zyloprim 300 mg tablet ALLO 300 mg tablet of varying hardness (23, 25 and 26 kp)	Completed
RDEA594-306 EXT	P3, OLE of Studies 301 and 302	N=714 subjects with gout	LES200 mg with ALLO 100 mg and 300 mg tablets (dose range: 100-900 mg) qd	Ongoing (Month 12)
RDEA594-307 EXT	P3, OLE of Study 304	N=196 hyperuricemic subjects with gout	LES200 mg with FEB 80 mg qd	Ongoing (Month 12)

Lesinurad/Allopurinol FDC Tablets Studies

- Efficacy data
  - Cross-referenced efficacy data previously reviewed in support of NDA 207988 Lesinurad (Zurampic®) 200 mg tablets
    - Does not need to be re-reviewed
- Safety data
  - Safety data from BA/BE study RDEA594-501
    - Single dose safety data
  - 12-month safety data from ongoing OLE studies 306 and 306 of patients who completed pivotal phase 3 studies reviewed in support of NDA 207988
    - Supportive data
    - No new postmarketing safety data since Zurampic® (lesinurad) only marketed since Oct. 2016
  - Cross-referenced safety data previously reviewed in support of NDA 207988 Lesinurad (Zurampic®) 200 mg tablets
    - Does not need to be re-reviewed

Proposed Labeling and REMS

- REMS
  - None provided (and not needed!)

- Label
  - Draft USPI contains references to “lesinurad in combination with allopurinol”
    - Retained safety info on lesinurad 400mg in combination with allopurinol to emphasize dose dependent safety concerns with higher doses of lesinurad in the Warnings and Precautions and AE sections
    - No info regarding lesinurad in combination with febuxostat
    - Info on lesinurad monotherapy included in the Warnings section for renal risk and clin pharm section
    - PLLR format provided for both drug components
      - Sponsor converted information for Zyloprim® (allopurinol) into PLR format and added updated information based on literature, the USPI for IV allopurinol (Aloprim®) and EMA labeling (Zyloric® UK)

Proposed Draft FDC Label: Dosing Regimen Examples

- Concerns regarding “user friendliness” of conveying dosing in this format
  - Do you think it is confusing?

Midcycle Deliverables

- Efficacy
  - Nothing to be done since it has been previously reviewed
- Integrated Safety Summary
  - Review of safety data from BA/BE study RDEA594-501
  - Review of the supportive safety data from the OLE studies 301 and 302

(b) (4)

- Maybe will have figured out how to complete the clinical reviewer's template
  - Not 505(b)(2) friendly

Consult List/Fileability

- Consults to the following have been sent:
  - DMETS/OSE: proprietary name review
    - Sponsor has proposed “Duzallo”
  - OPDP/DDMAC / DMPP/et al: USPI and MG review
  - PeRC
    - iPSP submitted to IND 119031 requesting full waiver for neonates, infants, children and adolescents between ages birth to <18 years due to rarity of disease
    - Need to submit iPSP for concurrence for NDA

- Consult to DPMH?
  - Review of PLLR content for Zyloprim® (allopurinol) – (not sure this is necessary)

- No consults
  - DSI: single BA/BE study does not require site audit
  - DRISK: REMS not necessary since same WARNINGs in Zurampic® (lesinurad) PI apply to Lesinurad/Allopurinol FDC

- Application is fileable from a clinical perspective


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ADMINISTRATION

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/s/

ROSEMARIE NEUNER
12/15/2016

NIKOLAY P NIKOLOV
12/15/2016

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA

NDA Number: 209203 **Applicant:** Ardea Biosciences **Stamp Date:** 10/20/16

Drug Name: Lesinurad/Allopurinol fixed dose combination **NDA Type:** 505(b)(2)

On **initial** overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	X		
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	X		
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	X		
4	Are all required and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	X		The nonclinical data for lesinurad is cross-referenced to the approved product Zurampic (Lesinurad, NDA 207988, approved in 2015). The nonclinical data for allopurinol is derived from the current prescribing information for Zyloprim (allopurinol, approved in 1966) as well as the published literature. The adequacy of the allopurinol nonclinical data for completion of the prescribing information for the fixed dose combination product will be a review issue.
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).	X		Ardea has conducted a GLP 13-week combination toxicology study in SD rats with oral lesinurad and allopurinol (Study SR11-002).
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant submitted a rationale to justify the alternative route?	X		Yes, toxicology studies were conducted using the oral gavage route. The clinical route of administration is oral.

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA

	Content Parameter	Yes	No	Comment
7	Has the applicant submitted a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations?	X		All relevant nonclinical studies with lesinurad were conducted under GLP conditions. Study SR11-002 (lesinurad/allopurinol combination study) was conducted under GLP conditions.
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			Not applicable.
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?	X		The draft labeling format for the fixed dose combination product is consistent with the guidelines established in the Physician Labeling Rule (PLR) and the Pregnancy and Lactation Labeling Rule (PLLR).
10	Have any impurity, degradant, extractable/leachable, etc. issues been addressed? (New toxicity studies may not be needed.)	X		Will consult with CMC Reviewers on any impurity issues.
11	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			Not applicable.
12	If the applicant is entirely or in part supporting the safety of their product by relying on nonclinical information for which they do not have the right to the underlying data (i.e., a 505(b)(2) application referring to a previous finding of the agency and/or literature), have they provided a scientific bridge or rationale to support that reliance? If so, what type of bridge or rationale was provided (e.g., nonclinical, clinical PK, other)?	X		Ardea owns the underlying data related to lesinurad but not allopurinol. The scientific rationale for combining allopurinol (xanthine oxidase inhibitor) with lesinurad (URAT1 inhibitor) in a fixed dose tablet for treatment of hyperuricemia associated with gout is reasonable. The nonclinical content of the current prescribing information for Zyloprim (allopurinol) is not consistent with the Physician Labeling Rule (PLR) or Pregnancy and Lactation Labeling Rule (PLLR). Therefore, reference to the published literature to complete the nonclinical sections of the labeling for the fixed dose combination product is considered acceptable.

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? Yes.

If the NDA/BLA is not fileable from the pharmacology/toxicology perspective, state the reasons and provide comments to be sent to the Applicant.
The NDA is fileable from the pharmacology/toxicology perspective.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.
There are no potential nonclinical review issues to be forwarded to the sponsor in the 74-day letter.

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/s/

MATTHEW T WHITTAKER
12/06/2016

TIMOTHY W ROBISON
12/07/2016
I concur