17 December 2015
EMA/6459/2016
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Zurampic

International non-proprietary name: lesinurad

Procedure No. EMEA/H/C/003932/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ACR	American College of Rheumatology
ADR	Adverse Drug Reaction
AE	adverse event
ALLO	allopurinol
ANCOVA	analysis of covariance
AUC	area under the concentration-time curve
BSR	British Society of Rheumatology
BCS	Biopharmaceutics Classification System
BMI	body mass index
BP	blood pressure
CEAC	Cardiovascular Endpoints Adjudication Committee
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CLEAR1/2	Study 301/302: lesinurad in combination with allopurinol
CL/F	apparent oral clearance
Cmax	maximum observed concentration
CR	complete resolution
CrCl	creatinine clearance
CR/PR	complete or partial resolution
CRYSTAL	Study 304: lesinurad in combination with febuxostat
CSR	Clinical Study Report
CV	cardiovascular
DDI	drug-drug interaction
ECG	electrocardiogram
eCrCl	Estimated creatinine clearance (calculated by the Cockcroft-Gault formula using ideal body weight at Screening)
EMA	European Medicines Agency
ESCISIT	EULAR Standing Committee for International Clinical Studies Including Therapeutics
EU	European Union
EULAR	European Union League Against Rheumatism
FBX	febuxostat
FDA	(United States) Food and Drug Administration
GCP	Good Clinical Practice
HAQ-DI	Health Assessment Questionnaire - Disability Index
IAE	Integrated Analysis of Efficacy
IAS	Integrated Analysis of Safety
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
ITT	intent-to-treat
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
LESU	lesinurad
LOCF	last observation carried forward
MACE	major adverse cardiovascular events
MCC	Medicines Control Council (South Africa)
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency (UK)
MI	myocardial infarction
MOA	mechanism of action
MPA	Medical Products Agency (Sweden)
n	number of subjects
NDA	New Drug Application
NRI	nonresponder imputation
NSAID	nonsteroidal anti-inflammatory drug
OAT	organic anion transporter
PBO	placebo
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)

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PRO	patient-reported outcome
PYE	person-years of exposure
qd	once daily
QOL	Quality of life
RDEA594	Lesinurad study-drug code
REAC	Renal Events Adjudication Committee
SAE	serious adverse event
SAP	Statistical Analysis Plan
sCr	serum creatinine
SD	standard deviation
SE	standard error
SI	International System of Units
SMQ	Standardised MedDRA Query
SOC	(MedDRA) system organ class
sUA	serum uric acid (also referred to as serum urate)
SURI	selective uric acid reabsorption inhibitor
TEAE	treatment-emergent adverse event
UK	United Kingdom
ULT	urate-lowering therapy
URAT1	uric acid transporter 1
US	United States
uUA	urinary uric acid
vs	versus
XO	xanthine oxidase
XOI	xanthine oxidase inhibitor

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1. Background information on the procedure

1.1. Submission of the dossier

The applicant AstraZeneca AB submitted on 7 January 2015 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Zurampic, through the centralised procedure under Article 3 (2) (a) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 23 January 2014.

The applicant applied for the following indication.

Zurampic is indicated for the chronic treatment of hyperuricaemia in combination with allopurinol or febuxostat in gout patients when additional therapy is warranted (i.e. not at target serum uric acid levels or with presence of tophus). Zurampic is indicated in adults.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application. The applicant indicated that lesinurad was considered to be a new active substance.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0153/2014 on the granting of a (product-specific) waiver.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Applicant's request for consideration

New active Substance status

The applicant requested the active substance lesinurad contained in the above medicinal product to be considered as a new active substance in itself, as the applicant claims that it is not a constituent of a product previously authorised within the Union.

Scientific Advice

The applicant received Scientific Advice from the CHMP on 29/11/2010, 1/04/2011, 17/11/2011 and 13/06/2014. The Scientific Advice pertained to quality, non-clinical and clinical aspects of the dossier.

Licensing status

The product was not licensed in any country at the time of submission of the application.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

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Rapporteur: Johann Lodewijk Hillege Co-Rapporteur: Greg Markey

- The application was received by the EMA on 7 January 2015.
- The procedure started on 21 January 2015.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 10 April 2015. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 10 April 2015.
- PRAC assessment overview, adopted by PRAC on 7 May 2015
- During the meeting on 21 May 2015, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 21 May 2015.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 17 August 2015.
- The following GLP inspection was requested by the CHMP and their outcome taken into consideration as part of the Quality/Safety/Efficacy assessment of the product:
  - A GLP inspection at a CRO site located in China and at an AstraZeneca subsidiary located in the USA have been conducted between July and September 2015. The summary inspection report of the inspections carried out was issued on 12 October 2015.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 30 September 2015.
- PRAC RMP Advice and assessment overview, adopted on 8 October 2015
- During the CHMP meeting on 22 October 2015, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 16 November 2015.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of outstanding issues to all CHMP members on 3 December 2015.
- PRAC RMP Advice and assessment overview, adopted on 3 December 2015
- During the meeting on 17 December 2015, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Zurampic

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2. Scientific discussion

2.1. Introduction

Problem statement

Gout is a chronic uric acid crystal deposition disease. It results from hyperuricemia, a metabolic disorder, which is mainly thought to be due to insufficient renal uric acid excretion, and to lesser extent a purine rich diet. Gout may be secondary to the intake of thiazide diuretics. Some families have a genetic predisposition, related to expression of uric acid transporter enzymes.

Hyperuricemia is defined typically as serum Uric Acid levels (sUA) > 6.8 mg/dL (> 400 µmol/L) based on the solubility limit of uric acid. When sUA exceeds the solubility limit, this can lead to deposition of urate crystals in body tissues. These crystals can accumulate in and around joints, which may cause painful and recurrent attacks of inflammatory arthritis. Eventually, subdermal deposits called tophi can occur. Tophi may be small and symptomless, or large and bothersome, causing chronic arthritis, malfunction of joints and rupture of the overlying skin ("leaking tophi"). Tophus forming in the kidney may lead to lithiasis and inflammation, and if uncontrolled, to renal failure.

Gout is the most common type of inflammatory arthritis (Doherty 2012). The prevalence of gout is estimated as 1-2 % in Europe. Gout is primarily diagnosed in middle-aged and elderly males. Patients with a genetic predisposition of hyperuricaemia, however, may develop severe gout and chronic topaceous arthritis at a young age. Women who develop gout are in general elderly using diuretics.

Common co-morbidities in gout are chronic kidney disorders and diabetes type 2, obesity, hypertension and cardiovascular (CV) disorders and alcohol dependence. Gout and asymptomatic hyperuricaemia is associated with an increased risk of CV death (Ioachimescu 2008, Kim 2008). Whether there is a causal relationship between hyperuricaemia and CV disease outcomes and hypertension is a matter of debate and not confirmed by interventional studies (Vinik, 2014).

Standard care of gout consist of urate-lowering therapy (ULT). In addition, acute gouty arthritis flares are treated symptomatically with analgesics and anti-inflammatory drugs. The therapeutic goal in the management of gout is to lower sUA levels with ULT below a target sUA of < 6 mg/dL (360 µmol/L) at minimum, to durably improve the signs and symptoms of gout. According to several international guidelines, including those from the British Society for Rheumatology and the American College of Rheumatology, lower target SUA levels < 5 mg/dL (300 µmol/L) are indicated for patients with tophi, as a larger gradient is required to obtain an adequate reduction in crystal deposition within a reasonable timeframe (Khanna, Fitzgerald, 2012, Richette 2014). The target of 5 mg/dL is based on the median sUA value of the general UK male population (Jordan et al, 2007).

Several ULTs are available for the prophylaxis of recurrent gouty attacks and reduction of tophi, which include:

(a) oral xanthine-oxidase inhibitors (XOI), allopurinol and febuxostat, which decrease the de novo synthesis of urate.

(b) oral uricosuric agents probenecid, benzbromarone, and sulphinpyrazone. Uricosuric agents increase excretion of uric acid into the urine, by inhibition of transporters mediating reabsorption of uric acid by the kidney. Lesinurad also belongs to the oral uricosuric agents.

(c) intravenous pegloticase, a pegylated recombinant uricase. Uricase is an enzyme which converts uric acid to more soluble allantoin for renal excretion.

Initiation of ULT could actually induce an arthritis gout attack, as instability of crystals deposits due to a sudden drop of sUA, may trigger an inflammatory reaction. According to clinical treatment guidelines,

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gout flare prophylaxis with colchicine or a NSAID is recommended in the first 3-6 months after starting ULT.

Approximately 40% to 80% of patients do not achieve recommended sUA goals with current first line XOI, and warrant additional treatment to control their disease (Schumacher 2008, Becker 2005, Becker 2010, Edwards 2009). Urocosic agents have their limitations regarding safety, and are not overall available in the EMA member states. E.g. benzbromarone is associated with hepatotoxicity. Probenecid causes multiple drug-drug interactions and has to be frequently dosed over the day, whereas sulphinpyrazone has been associated with rash and gastric bleeding. Pegloticase is highly effective, however, its use is limited to last line because of the risk of serious infusion reactions.

In conclusion, though several ULT options are available, there is a need for other effective oral ULTs with a favourable safety profile.

About the product

Zurampic is a solid tablet containing 200 mg of lesinurad. Lesinurad is an uricosuric Urate Lowering Therapy (ULT) that inhibits specifically Uric Acid Transporter 1 (URAT1). URAT1 is thought to be responsible for the majority of the reabsorption of filtered uric acid from the renal tubular lumen. By inhibiting URAT1, lesinurad increases uric acid excretion and thereby lowers sUA. In addition, lesinurad is an inhibitor of OAT4 (organic anion transporter), which is considered to be involved in hyperuricemia secondary to the use thiazide diuretics.

The initially proposed indication was “chronic treatment of hyperuricaemia in combination with allopurinol or febuxostat in gout patients when additional therapy is warranted (i.e. not at target serum uric acid levels or with presence of a tophus” in adults.

The recommend indication is “Zurampic, in combination with a xanthine oxidase inhibitor, is indicated in adults for the adjunctive treatment of hyperuricaemia in gout patients (with or without tophi) who have not achieved target serum uric acid levels with an adequate dose of a xanthine oxidase inhibitor”.

According to the SmPC of Zurampic, the treatment target sUA level is less than 6 mg/dL (360 µmol/L). In patients with tophi or persistent symptoms, the target is less than 5 mg/dL (300 µmol/L). Testing for the target sUA level may be performed as early as 4 weeks after initiating Zurampic treatment.

The recommended dose of Zurampic is 200 mg once daily in the morning, to be taken with food and water. No dose adjustments are proposed for elderly, patients with mild-moderate renal impairment, and patients with hepatic impairment. A statement has been included in the SmPC that Zurampic should not be initiated in patients with severe renal impairment (CrCL less than 30 mL/min).

Several precautionary measures are recommended in the SmPC to prevent hyperuricosuria when using lesinurad, such as sufficient hydration (2 litres of liquid per day), and morning intake. Zurampic must be taken at the same time as the xanthine oxidase inhibitor (XOI) of choice (allopurinol or febuxostat), since it has been show that XOI reduce the urinary uric acid load and the risk of renal events of lesinurad.

Gout flare prophylaxis with either colchicine or NSAIDs is recommended for at least 5 months when starting lesinurad therapy, in order to reduce the risk of ULT-induced gouty arthritis flares.

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2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as film-coated tablet containing 200 mg of lesinurad as active substance.

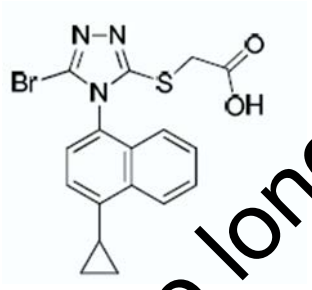
Other ingredients are hypromellose, microcrystalline cellulose, lactose monohydrate, crospovidone and magnesium stearate for the tablet core and hypromellose, titanium dioxide, triacetin, indigo carmine and brilliant blue FCF in the tablet coat.

The product is available in a clear (PCTFE/PVC/Aluminium) blister.

2.2.2. Active Substance

General information

The structure of lesinurad is depicted below:



Lesinurad is a white to off-white powder and is not hygroscopic. Sufficient information on the solublility in aqueous and organic solvents has been provided. Regarding aqueous solvents, solubility increases with increasing pH (0.0041 mg/mL at pH 1.1 in 0.1 N HCl to 117 mg/mL at pH 6.0 in 0.3N NaOH). Lesinurad does not contain any chiral centres but is provided as racemic mixture of 2 atropisomers (ratio of 50:50) on which sufficient information has been provided. There are 2 known non-solvated crystal forms (free acid polymorphs) of lesinurad: form 1 (metastable) and form 2 (thermodynamically stable). Form 2 is the desired thermodynamically stable form which is consistently manufactured and does not change upon storage.

The structure has been elucidated using elemental analysis, Nuclear Magnetic Resonance Spectroscopy (^{1}H and ^{13}C), Mass Spectrometry, UV/Vis Spectroscopy, Infrared Spectroscopy and X-ray crystallography (Form 2). Additional supporting evidence for the structure of lesinurad comes from the route of synthesis, process controls during manufacturing, and from the use of well characterized starting materials.

In accordance with article 8.3 of Directive 2001/83/EC, New Active Substance status was claimed. The information provided in the dossier shows that lesinurad is not an isomer, mixture of isomers, a complex or derivative or salt of a chemical substance previously authorised as a medicinal product in the European Union. Lesinurad is also not a chemical entity already used in a medicinal product. Therefore lesinurad is considered a new active substance from a quality perspective.

Manufacture, characterisation and process controls

The active substance is manufactured at three locations.

Lesinurad is synthesized in 3 synthetic steps. The commercial manufacturing process for the synthesis of the active substance was sufficiently detailed including quantities and operating conditions.

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Starting materials have been adequately described and justified on the basis of the Reflection Paper on requirements for selection and justification of starting materials for the manufacture of chemical active substances (EMEA/H448443/2014). Sufficient information on raw materials, synthesis and specifications of lesinurad have been provided. Reprocessing consists of repetition of the regular process.

The process comprises 2 isolated intermediates and their specifications are acceptable based on the provided control strategy which is in line with ICH Q11. Critical quality attributes have been discussed, although the application is not a Quality by Design application. The critical steps have been adequately justified and critical parameters have been determined and described sufficiently.

The development of the control strategy for the manufacture of lesinurad followed a science and risk-based approach. Analytical procedures which are considered critical for the quality of the active substance and intermediate control have been adequately validated.

Thorough discussion of impurities (that have been divided into organic, inorganic / heavy metals, solvents and genotoxic) comprising several spike and purge studies show adequate control of impurities in lesinurad. The residual solvents are all class 2 and 3 solvents. Genotoxic / mutagenic impurities have been studied according to ICH M7 and their purge and control is acceptable.

The active substance is stored in double low density polyethylene (LPDE) bags individually closed with plastic tie wraps. This primary packaging complies with 21CFR 177.1520 and EC directive 10/2011 as amended and the specification contains tests for description (colourless translucent bag) and identification by IR (spectrum of reference standard provided).

Specification

The active substance specification includes tests for description, identification (by FTIR and HPLC), assay (by HPLC), sulfated ash (according to Ph. Eur.), water content (according to Ph. Eur.), organic impurities (amino impurity, hydroxy impurity, des-bromo impurity, chloro impurity, individual, unspecified impurity, total impurities) by HPLC and residual solvents (ethyl acetate, n-heptane, toluene, tetrahydrofuran) by GC headspace.

The justification for tests and limits of description, identification, inorganic impurities and residual solvents has been provided. Impurities present higher than the qualification threshold according to ICH Q3A were toxicologically qualified.

The specification limit follows the ICH Q3D (Draft, July 2013) Class 2B oral permitted daily exposures limits (option 1) for elemental impurities.

The analytical procedures have been described in sufficient detail and the in-house analytical procedures have been adequately validated in accordance with the ICH guidelines. The reference standard for the active substance (manufactured with the commercial process) and impurity standards have been characterised and are suitable for their intended use.

Batch analyses data of eight batches manufactured at commercial site using the commercial process were provided and demonstrate compliance with the proposed specification.

Stability

Stability data on 3 commercial batches of lesinurad active substance stored in double LPDE bags (intended package) for 24 months under long term conditions at 25 °C / 60% RH and for up to 6 months under accelerated conditions at 40 °C / 75% RH according to the ICH guidelines were provided. In addition, data of two pilot scaled batches with a previously used manufacturing process have been provided, stored at 25 °C / 60% RH (36 months) and 40 °C / 75% RH (6 months). The

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material was packed in double LDPE bags, closed with tie wraps as those proposed for commercial packaging.

Stability data for all batches of lesinurad active substance met the proposed commercial specification criteria at all storage conditions studied.

The overall data is sufficient to grant the proposed re-test period of 36 months, when stored below 30°C, although the storage restriction does not have to be applied.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

The finished product corresponds to a film-coated tablet intended for immediate release. Market authorisation is sought for a strength of 200 mg of the active substance lesinurad. The finished product is presented as film-coated tablet containing 200 mg of lesinurad as the active substance. Other ingredients are hypromellose, microcrystalline cellulose, lactose monohydrate, crospovidone and magnesium stearate for the tablet core and hypromellose, titanium dioxide, triacetin, indigo carmine and brilliant blue FCF in the tablet coat. The product is available in a clear (PCTFE/PVC/Aluminium) blister.

The proposed commercial packaging is push-through blister packs formed from a clear laminated plastic film made of PVC and PCTFE and sealed to aluminium foil with heat seal lacquer.

All excipients meet Ph. Eur. compendial specifications and in-house specifications (where applicable). An acceptable in-house specification is provided for the coating material. Non-compendial colouring excipients in the tablet coating (FD&C Blue #1 Indigo Carmine Aluminium Lake and FD&C Blue #2/Brilliant Blue FCF Aluminium Lake) are in compliance with Commission Regulation No 231/2012. Excipients and packaging are usual for this type of dosage form.

Various pharmaceutical forms and polymorphic forms of the active substance were explored during pharmaceutical development. The proposed commercial formulation is identical to that used in Phase 3, i.e., an immediate release tablet containing 200 mg of crystalline lesinurad free acid. Bioequivalence studies were carried out to compare the various forms.

Development of the routine QC dissolution testing method was adequately described and was shown to discriminate between batches of acceptable bioavailability and batches with a slower rate and extent of absorption.

Manufacture of the product and process controls

The manufacturing process is a standard manufacturing process involving high shear granulation including dry mixing and wet granulation, wet milling, fluidized bed drying, milling, blending including lubrication, compression, and film-coating. The manufacturing process is described in sufficient detail.

Major steps of the manufacturing process have been validated by a number of studies. The critical steps are defined and suitable controls are applied. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form.

An acceptable process validation protocol for three consecutive batches has been provided, which will be completed prior to sales of drug product.

Product specification

The product release and shelf life specification includes tests for description (visual inspection), identification of lesinurad (HPLC spectrum and retention time/UV spectrum), assay (HPLC),

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degradation products (HPLC), dissolution (Ph. Eur.), uniformity of dosage units by mass variation (Ph. Eur.), and microbiological quality (Ph. Eur.).

Analytical methods are adequately described and validated in accordance with the ICH guidelines. Additional validation data have been provided for the dissolution (cross-validation of the HPLC and UV methods) and microbiological quality methods (demonstration of the absence of growth inhibition by the drug product). Satisfactory information on the reference standards has been presented.

Batch analytical data of the intended commercial manufacturing site are presented for one commercial scale and four pilot scale batches of the 200 mg strength, demonstrating compliance with the release specification.

Stability of the product

Stability data on the product have been provided for three pilot scale batches of the 200 mg strength stored at 25 °C / 60% RH (36 months), 30 °C / 75% RH (36 months) and 40 °C / 75% RH (six months). The conditions and products used in the stability studies are according to the ICH stability guideline. The batches were manufactured at the development site. Stability studies of batches manufactured at the intended commercial manufacturing site have been initiated. The batches are stored in PVC/PCTFE blister packs, representative of the commercial container closure system. Samples were tested for description, assay, degradation products, dissolution and microbial limit tests (at least annually at release). In addition hardness and water content were tested. The analytical procedures were sufficiently described and shown to be stability indicating.

No significant changes were observed at any storage condition. Increasing trends in the levels of a specified degradation product and water content have been observed. Updated stability data have been provided and results were within specification.

Photostability of unpacked tablets was demonstrated according to ICH Q1B and indicate that the finished product is not light sensitive.

Stability of the finished product in bulk packs (4-layer aluminium foil bag) has been shown for three months at 25°C/60% RH, 30°C/75% RH and 40°C/75% RH.

Therefore the proposed shelf-life of 36 months in Aclar blisters with no specific storage restrictions seems justified.

Adventitious agents

Magnesium stearate is sourced from vegetable origin. Lactose monohydrate is manufactured from milk that has been sourced from healthy cows in the same conditions as milk collected for human consumption. This pharmaceutical grade lactose complies with the requirements for Europe per Directive 75/318/EEC and EMEA/410/01. A statement of compliance from the supplier of lactose monohydrate has been provided.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions

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defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendations for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

Lesinurad is a selective uric acid reabsorption inhibitor (SURI) that inhibits the uric acid transporter 1 (URAT1). URAT1 is responsible for the majority of the reabsorption of filtered uric acid from the renal tubular lumen. By inhibiting URAT1, lesinurad increases uric acid excretion and thereby lowers serum uric acid. Lesinurad also inhibits Organic Anion Transporter 4 (OAT4), a uric acid transporter involved in diuretic induced hyperuricemia.

The nonclinical safety profile of lesinurad was characterised in a testing programme that included assessment of primary and secondary pharmacodynamics (PD), safety pharmacology, pharmacokinetics (PK) including drug-drug interaction (DDI) with major liver enzymes and liver/kidney transporters, metabolism, distribution, excretion, and a complete toxicology package to support the chronic administration of lesinurad in adult patients.

Scientific advice was received from the CHMP on 29 November 2010 and 1 April 2011. The non-clinical advice concerned the adequacy of the embryofetal developmental studies in rats and rabbits.

2.3.2. Pharmacology

Primary pharmacodynamic studies

The inhibitory effects of lesinurad on human URAT1-mediated transport of uric acid were studied in two independent experiments in *Xenopus laevis* oocytes. An IC_{50} of 52.5 µM and 41 µM was calculated. In human embryonic kidney cells stably expressing the human URAT1 transporter, lesinurad suppressed uptake of [^{14}C] uric acid with an IC_{50} value of 7.3 µM.

Both *cis*-inhibition (due to high luminal lesinurad concentrations in the proximal tubuli) as well as *trans*-inhibition (due to basolateral transport by OAT1 and OAT3) may contribute to the inhibition of uric acid transport by URAT1.

When rat and mice URAT1 transfected cells were used, it appeared that lesinurad did not inhibit these rodent orthologs at relevant concentrations (up to 100 µM).

Besides, hURAT1, lesinurad also inhibits hOAT4 with an average EC_{50} value for lesinurad of 3.7 µM. Human OAT4 (hOAT4) is a recently characterized urate transporter involved in human urate transport in the kidney. Human SLC2A9v1 and SLC2A9v2 (the GLUT9 transporter) located at the basolateral membrane of renal tubular cells, however, are not affected by lesinurad.

Lesinurad and its metabolites M1, M2, M3 and M6 were tested for potential inhibition of xanthine oxidase using either xanthine or hypoxanthine as a substrate. No inhibition of xanthine oxidase conversion of xanthine or hypoxanthine to uric acid was observed at relevant concentration.

Similarly, no inhibition of purine nucleoside phosphorylase was observed.

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Considering the lower concentrations of the metabolites and the higher IC_{50} values for URAT1 and OAT4 of the metabolites M2, M3, M4 and M6, it is not expected that these metabolites contribute to the pharmacological activity of lesinurad.

The primary pharmacological activity of lesinurad was studied in the New World monkey *Cebus apella* (Brown capuchin). Urinary excretion of uric acid increased from baseline, suggesting that lesinurad likely shares the same mechanism of action as benzbromarone, although the presence of URAT1 transporter in *Cebus* monkeys has not been established. Serum uric acid levels did not change in animals treated with lesinurad or benzbromarone. At baseline, significant amounts of allantoin were detected in both plasma (mean concentration of 0.432 mg/dL) and urine (mean concentration of 17.6 mg/dL), suggesting the existence of uricase in *Cebus* monkeys, which significantly reduces the value of the *Cebus* monkey as an *in vivo* model.

Secondary pharmacodynamic studies

Secondary pharmacological targets of lesinurad were assessed by measuring its ability (at 100 µM) to inhibit binding of radiolabeled ligands to 169 pharmacological targets that comprise transporters, receptors, and enzymes. Ligand binding of 10 targets was inhibited more than 50% and subsequently tested to obtain an IC_{50}. The only ligands that were inhibited with an IC_{50} below 30 µM were the human prostanoid thromboxane A2 (TP) receptor and DP1 receptor. However, additional in vitro pharmacology data, ex vivo models, cardiovascular safety pharmacology, and toxicological studies indicate that lesinurad is not a functional antagonist of the arachidonic acid biosynthetic pathway or of the major prostaglandin receptors in vivo. The evidence of weak in vitro activities, a lack of tissue-based activity, and the absence of relevant toxicity findings at supratherapeutic dosing in chronic nonclinical studies indicates that there are no clinically relevant PD interactions with these pathways.

Other targets investigated included neuropeptide Y (NPY)4 and NPY5, which showed no clinically relevant inhibition from either lesinurad or the M6 metabolite of lesinurad. A battery of nuclear receptors was also tested, and at the 100 µM concentration of lesinurad only 2 fold activation of peroxisome proliferator-activated receptor (PPAR) γ and weak inhibition (20%) of thyroid hormone receptor (TR) α was seen, and no significant activity was seen at $\leq$ 25 µM.

As lesinurad is a metabolite of RDEA806, which is an HIV-1 non-nucleoside reverse transcriptase inhibitor (NNRTI) compound, anti-HIV activity was investigated. Lesinurad did not exhibit any clinically significant antiviral activity against HIV. Lesinurad was also tested for activity against the human DNA polymerases α, β, and γ. The IC_{50} against human DNA polymerase α was 98.4 µM, while the IC_{50} against human DNA polymerases β and γ was > 100 µM, suggesting little potential for toxicity by this mechanism.

The potential for cytotoxicity of lesinurad was evaluated by determining the 50% cytotoxic concentration (CC_{50}) in HeLa-JC53 cells and the human HepG2 cell line. The CC_{50} value in HeLa-JC53 was > 40 µM, whereas the CC_{50} in HepG2 was above 100 µM. Furthermore, while benzbromarone and menadione (a positive control) were extremely potent at inducing mitochondrial toxicity, lesinurad was inactive at clinically relevant concentrations. Yet, it should also be considered that HeLa and HepG2 cells have only limited metabolic activity and therefore insufficiently cover any potential role of metabolites (see also discussion on DILI in toxicology section).

A study on muscle cell toxicity did not reveal muscle toxicity potential of lesinurad in Rat L6 cells *in vitro* at a concentration of 10 µM.

In 2 monosodium urate (MSU) dependent rodent acute gout flare models, lesinurad was efficacious in reducing inflammation from injected MSU crystals. The mechanism for this result in animals is not understood.

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Safety pharmacology programme

No important safety pharmacology effects on parameters of the CNS, cardiovascular system, respiratory system, gastrointestinal tract and renal/urinary system were observed.

Effects of a single dose 30, 100 or 300 mg/kg lesinurad on a functional observation battery were tested in rats. No test article related effects were observed up to 300 mg/kd, corresponding to a C_{max} and AUC 165x and 101x times higher than at the human MRHD, respectively.

The effect of 10, 30, 100 and 200 µM lesinurad on hERG channel current expressed in HEK293 cells was tested. The IC_{50} was determined to be 198 µM, while the human C_{max} at MRHD was 12 µg/mL. Considering the 98% protein binding of lesinurad in human plasma, the IC_{50} would be estimated at 9.9mM, whereas human total plasma concentration is 17µM at MRHD.

Male Cynomolgus monkeys were exposed to lesinurad (30, 100, 300 mg/kg) and cardiovascular parameters were determined using telemetry. QTcR values (QT corrected for heart rate) were similar to control values. The NOAEL for cardiovascular effects was 300 mg/kg, which corresponded with 21x C_{max} and 38x AUC of the human MRHD.

No effects on respiratory parameters induced by lesinurad (30, 100, 300 mg/kg) were observed in male Cynomolgus monkeys 2 and 24 hours after dosing. The NOAEL for respiratory effects was 300 mg/kg, which corresponded with 21x C_{max} and 38x AUC at the human MRHD.

Rats were exposed to 30, 100, 300 and 1000 mg/kg lesinurad. At 1000 mg/kg gastrointestinal motility was statistically significant decreased and an increase of watery feces was observed. At the NOAEL of 300 mg/kg, C_{max} and AUC were 165 and 101 fold higher than at the MRHD.

Rats were exposed to lesinurad up to a dose of 1000 mg/kg. Mildly increased urinary creatinine and urinary excretion of uric acid and minimal increases in serum blood urea nitrogen and creatinine were observed at 1000 mg/kg. At the NOAEL of 300 mg/kg, C_{max} was 24-fold and AUC 101-fold compared to the MRHD.

Pharmacodynamic drug interactions

No pharmacodynamic drug interactions studies were submitted in support of this application.

2.3.3. Pharmacokinetics

Pharmacokinetics of lesinurad after single and repeated administration were investigated in rats, dogs, and monkeys. In addition, in vitro studies were performed to investigate plasma protein binding, blood cell/plasma partitioning, potential drug-drug interactions, drug metabolism and transporter characteristics. The pharmacokinetics of the main metabolite M4 and the metabolite M6 (in monkeys) were also investigated.

Absorption

In vitro

Permeability Evaluation in Caco-2 Monolayer Assay (8ARDEP3R1, SR09-066)

In-vitro permeability of lesinurad was evaluated in bidirectional experiments using Caco-2 monolayers and [^{14C}]-lesinurad. In these studies, lesinurad showed higher basolateral to apical (B-A, approximately 12-16 10^{-6} cm/s) permeability than apical to basolateral (A-B, approximately 4-5 10^{-6} cm/s) with efflux ratios greater than 2 at 1, 10, and 100 µM, indicating that lesinurad was actively transported across Caco-2 monolayers. However, verapamil or PSC833, known P-glycoprotein (P-gp) inhibitors, had either no effect or only partially inhibited the basolateral to apical transport of lesinurad.

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In vivo

Single-Dose Pharmacokinetic Studies

The single-dose PK studies were conducted by oral or IV dosing of lesinurad in mice (oral only), rats, dogs, and monkeys. Lesinurad was rapidly absorbed in all species following oral dosing. Bioavailability ranged from highest in dogs (100%) to lowest in monkeys (41.1%). Mean plasma lesinurad-to-total-radioactivity ratios were >than 50% in rats and monkeys, suggesting that the majority of systemic exposure to [14C] lesinurad was in the form of the parent compound lesinurad. The PK parameters determined from these studies are summarised in **Table 1**.

Table 1. Pharmacokinetic Parameters of Total 14C Radioactivity and Lesinurad Following Single Oral Administration (SR08-058, SR08-059, SR08-060)

Species	Gender	Dose (mg/kg)	Absorption (%)	F (%)	$t_{1/2}$ (hr)	AUC_{inf} (µg-eq·hr/g or µg·hr/mL)[a]	C_{max} (µg-eq/g or µg/mL)[b]	T_{max} (hr)
Total ^{14}C Radioactivity								
Rat	Male	20	85.8	NE	6.44	99.5	34.2	0.250
	Female	20	70.0	NE	1.96	96.6	26.0	0.250
Monkey	Male	20	45.9	NE	61.5	111	17.8	1.33
Lesinurad								
Rat	Male	20	NE	75.3	3.39	[illegible]	33.3	0.250
	Female	20	NE	71.1	3.98	[illegible]1.8	28.7	0.250
Dog	Male	20	NE	100	6.45	156	60.9	0.438
Monkey	Male	20	NE	41.1	21.8	50.1	16.2	1.33

Abbreviations: F, bioavailability; NE, not estimated
[a] µg-eq·hr/g for total 14C and µg·hr/mL for lesinurad.
[b] µg-eq/g for total 14C and µg/mL for lesinurad

Dose Proportionality Study Following Single Dosing of Lesinurad to Sprague Dawley Rats (SR08-071)

A single-dose PK study was conducted in male Sprague Dawley rats prior to the start of the 14-day toxicology study in rats. Dose proportionality was evaluated following a single oral dose of lesinurad at 20, 100, 300, or 1000 mg/kg to male rats. The rate of absorption, as measured by Tmax, increased from 2.33 to 16.5 hours as the dose increased from 20 to 1000 mg/kg. Between 20 and 300 mg/kg, exposure (as measured by AUC0-24) increased in a more than dose-proportional manner. At the 1000 mg/kg dose, absorption was delayed and exposure increased in less than a dose-proportional manner within 24 hours post-dose.

Distribution

***In vitro* Protein Binding**

In vitro binding of lesinurad to plasma proteins was evaluated using radio-labelled lesinurad at concentrations of 1, 10, and 50 µM in all species, and at higher concentrations in rats and monkeys using equilibrium dialysis (**Table 2)**.

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Table 2. Protein binding of lesinurad in plasma across species (SR08-045)

Species	% Protein Binding (Mean ± SD, N=3)					
	1 µM	10 µM	50 µM	200 µM	500 µM	1000 µM
Mouse	95.2 ± 0.45	94.9 ± 0.35	94.0 ± 0.15	NM	NM	NM
Rat	97.7 ± 0.34	98.1 ± 0.09	97.7 ± 0.01	97.6 ± 0.11	96.4 ± 0.06	95.1 ± 0.18
Dog	98.3 ± 0.06	98.2 ± 0.11	98.1 ± 0.13	NM	NM	NM
Monkey	98.2 ± 0.15	98.3 ± 0.03	98.2 ± 0.10	97.8 ± 0.06	97.3 ± 0.02	NM
Human	98.5 ± 0.06	98.4 ± 0.02	97.9 ± 0.17	NM	NM	NM

Abbreviations: NM, not measured; SD, standard deviation

Quantitative Tissue Distribution of Lesinurad-Derived Radioactivity in Rats (SR08-046)

The distribution and concentrations of total radioactivity in male albino rats and male pigmented rats were similar following oral administration, and the general patterns of distribution of radioactivity in albino rats were similar following oral and IV administration. Following oral administration, high concentrations of radioactivity were observed in the contents of the GI tract. Urinary concentrations were also high, with a maximum level recorded at 2 hours post-dose. There was no preferential uptake of lesinurad-derived radioactivity into the brain.

Elimination of radioactivity from tissues following oral administration was generally rapid in albino and pigmented rats. Decreased tissue radioactivity levels were observed in all of the measured tissues at 24 hours post-dose, and elimination was completed by 168 hours in the pigmented rat. Tissues associated with metabolism and elimination (e.g., liver and kidney) were the only tissues to have maximum concentrations of radioactivity greater than in cardiac blood, suggesting limited uptake of radioactivity into tissues.

***In vivo* Partition Between Plasma and Red Blood Cells (SR08-028, SR08-017)**

In general, following oral or IV administration of [14C] lesinurad to rats, the blood-to-plasma ratios of [14C] lesinurad-derived radioactivity were between 0.5 to 0.9 over the first 12 hours of the study and between 0.5 to 0.9 in monkeys over the first 48 hours of the study.

Metabolism

In Vitro Metabolic Profiles in Liver Microsomes and Cryopreserved Hepatocytes (SR08-038, SR08-056, SR11-031)

Lesinurad was the predominant component following incubation of [14C] lesinurad with liver microsomes and cryopreserved hepatocytes. The majority of the radioactivity (> 92%) was attributed to unchanged parent compound. Two oxidative metabolites, M3 and M4, were detected after incubation with both monkey and human hepatocytes. Following incubation in cryopreserved rat and dog hepatocytes, no metabolite was detected. In human and monkey hepatocytes, the M3 and M4 metabolites were present at low levels, with 92.1% and 98.1% of parent drug remaining, respectively, following 4-hour incubation.

Figure 1 shows the proposed metabolic pathways for metabolites higher than 10% of parent in circulation or 10% of dose in excreta.

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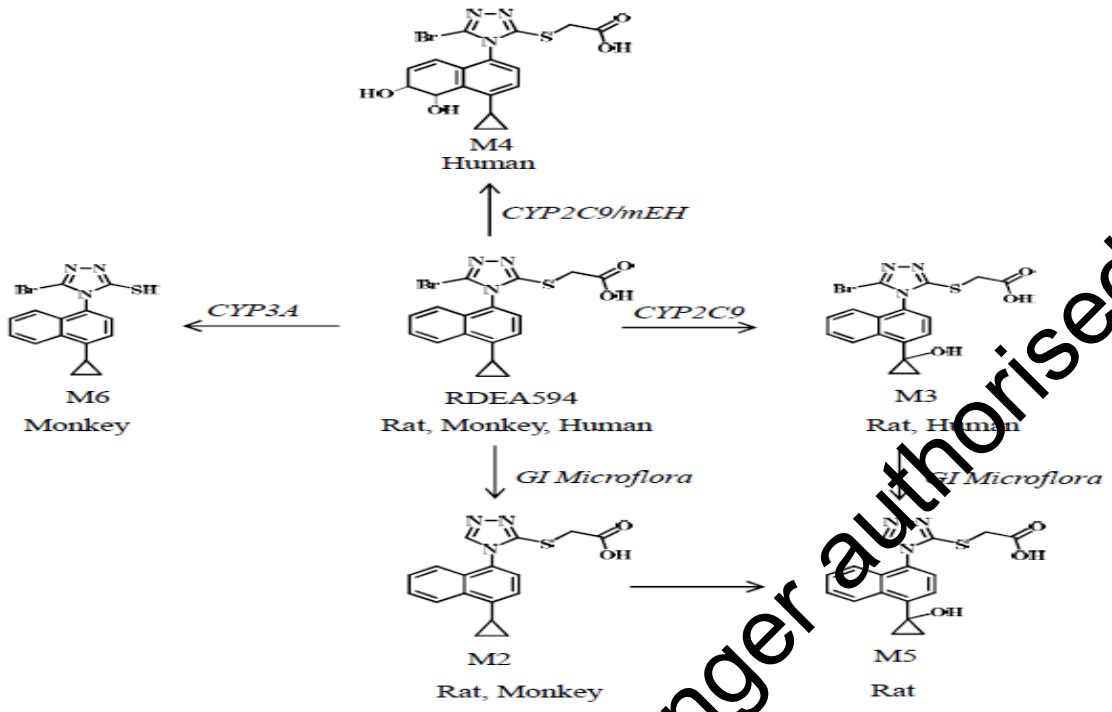
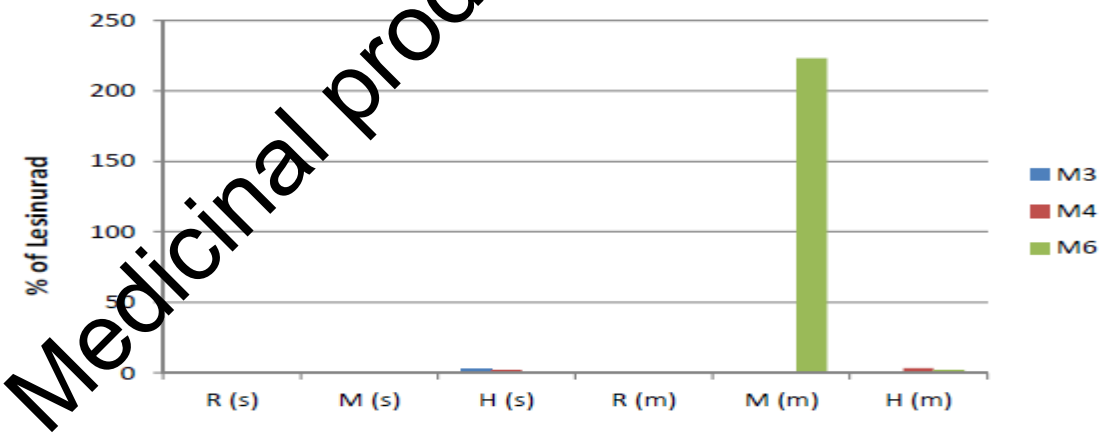
Figure 1. Proposed Metabolic Pathways for Metabolites Higher than 10% of Parent in Circulation or 10% of Dose in Excreta



Abbreviations: CYP, cytochrome P450; GI, gastrointestinal; mEH, microsomal epoxide hydrolase

The relative abundance of major metabolites in plasma and urine is presented in **Figures 2 and 3.**

Figure 2. Relative Abundance of Metabolites in Plasma Following Single or Multiple Doses of lesinurad



Abbreviations: m, multiple doses; PO, oral; qd, once daily; s, single dose
R (s): Rat 20 mg/kg, PO, 1 hour post-dose (SR08-120)
M (s): Monkey 20 mg/kg, PO, 2 hours post-dose (SR08-119)
H (s): Human 600 mg, 3 hours post-dose (Study 112 CSR)
R (m): Rat 300 mg/kg/day, PO, Day 36, 1 hour post-dose (SR10-021)
M (m): Monkey 600 mg/kg/day, PO, Week 50, AUC0-24 ratio (SR08-094)
H (m): Human 600 mg qd, Week 44, AUClast ratio (Study 202 extension CSR)

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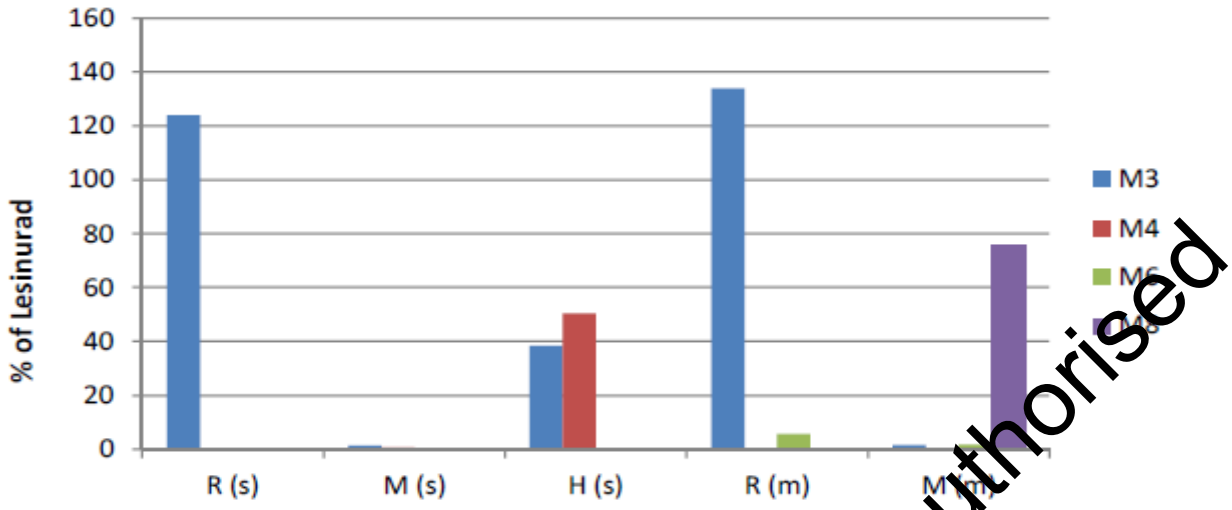
Figure 3. Relative Abundance (Percent of Lesinurad) of Metabolites in Urine Following Single or Multiple Doses of Lesinurad



Abbreviations: m, multiple doses; PO, oral; qd, once daily; s, single dose
R (s): Rat 20 mg/kg, 0 – 24 hours post-dose (SR08-120)
M (s): Monkey 20 mg/kg, 0 – 24 hours post-dose (SR08-119)
H (s): Human 600 mg, 0 – 24 hours post-dose (Study 112 CSR)
R (m): Rat 300 mg/kg/day, Day 36, 0 – 24 hours post-dose (SR10-021)
M (m): Monkey 600 mg/kg/day, Week 52, ~7 – 24 hours post-dose (SR08-094)

***In vitro* reaction phenotyping (SR11-082, SR12-027, SR12-028, SR08-038, SR11-031, SR10-002, SR12-026)**

Phenotyping of CYP enzymes responsible for lesinurad oxidative metabolism revealed that in humans, CYP2C9 played a major role in the formation of oxidative metabolites (M+16) and to a lesser extent by other enzymes including CYP1A1, CYP2C19, and CYP3A. *S*-dealkylation of lesinurad to form metabolite M6 appeared to be catalyzed by CYP3A. Metabolite M4 was detected following incubation with human liver microsomes but not with CYP2C9 recombinant enzyme. Conversely, metabolite M3c (an epoxide) was detected following incubation in CYP2C9 recombinant enzyme but not in human liver microsomes. In separate experiments, mEH was identified as the enzyme responsible for conversion of the epoxide to M4 metabolite. Similar results were seen in animals, where CYP3A was responsible for *S*-dealkylation and CYP2C was responsible for oxidation.

Glucuronidation of lesinurad in human liver appeared to be catalyzed by UGT1A1, UGT2B7, and to a lesser extent by UGT1A3. The glutathione conjugate of lesinurad was detected in monkey and human liver microsomal incubations in the presence of glutathione.

Excretion

Excretion patterns were evaluated for lesinurad following administration of single doses of [14C] lesinurad to rats and monkeys and are presented in **Table 3.**

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Table 3. Excretion Patterns in Rats, Monkeys, and Humans Following a Single Dose of [14C] lesinurad (SR08-028, SR08-017, Study RDEA594-112)

Species	Sex	Route	Duration (hr)	Dose (mg/kg)	Recovery of Dose (%)				
					Urine	Feces	Other[a]	Carcass	Total
Rat	M	PO	120	20	11.9	75.3	1.35	0	88.5
Rat	M	IV	120	20	8.14	92.4	2.71	3.00	106
Rat	F	PO	120	20	36.3	44.2	2.58	0.14	83.2
Rat	F	IV	120	20	34.1	38.6	16.0	5.69	94.4
Monkey	M	PO	120	20	32.6	41.7	16.9	NA	91.2
Monkey	M	IV	120	10	25.7	45.0	13.2	NA	83.9
Human	M	PO	144	600 mg	63.4	32.3	NA	NA	95.6

Abbreviations: F, female; IV, intravenous; M, male; NA, data not available since animals were not sacrificed for radioactivity counting; PO, oral

[a] *Cage wash and cage wipe*

Enterohepatic circulation in rat (SR09-056)

Following a single 20 mg/kg oral dose of [14C] lesinurad to BDC male rats, recovery of total radioactivity in bile and urine suggested that approximately 50 % of radioactivity was absorbed through enterohepatic circulation.

Excretion to rat milk (SR11-068)

In lactating rats in a perinatal and postnatal rat reproduction toxicology study, at 4 hours post-dose of lesinurad at 100, 200, or 300 mg/kg on Lactation Day 10, lesinurad was detected in the milk and had similar concentrations to that detected in plasma.

Enzyme inhibition (SR08-048, SR12-043, SR10-001)

Lesinurad inhibited CYP2C8 and CYP2C9 with IC50 values of 16.2 and 40.7 µM, respectively in human liver microsomes. The IC50 values for CYP1A2, CYP2B6, CYP2C19, CYP2D6, and CYP3A4 were all >100 µM. No mechanism-based inhibition by lesinurad (10 µM) was observed for any P450 isozymes tested with a 30-minute pre-incubation.

Lesinurad also inhibited metabolism of β-estradiol (at 50 µM) and AZT (at 1000 µM) with IC50 values of 148 and 384 µM for UGT1A1 and 2B7, respectively.

Enzyme induction (SR08-026, SR10-063)

The induction effects of lesinurad have been evaluated in in vitro studies using cultured human hepatocytes for CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP3A4/5.

With a 400 mg daily dose, lesinurad was identified as a mild to moderate CYP3A inducer and caused weak to no induction of CYP2C8 and CYP2C9 (**Table 4**).

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Table 4. *In vitro* and *in vivo* evaluation of P450 induction potential of lesinurad

CYP Enzyme	Relative Effectiveness In Vitro (10 µM)		Predicted In Vivo Induction With 400 mg Daily Dose		Clinical Phase 1 DDI Results (with 400 mg daily dose of lesinurad)
	Based on CYP Activity	Based on CYP mRNA	Predicted Effects on Plasma AUC of a Sensitive In Vivo Probe	Predicted Induction Potential	
CYP3A	67.4%	NA	50%-80%	Moderate	Sildenafil (moderate) Atorvastatin (weak) Amlodipine (weak)
CYP2C8	15.1%	50.0%	15%-50%	None-Weak	Repaglinide (no effect)
CYP2C9	4.87%	40.1%	5%-50%	None-Weak	Tolbutamide S-warfarin (no effect)
CYP2C19	20.1%	162%[a]	≤ 20%	None-Weak	Not assessed
CYP2B6	17.6%	12.6%	< 20%	None	Not assessed
CYP1A2	NA	NA	< 20%	None	Not assessed

Abbreviations: AUC, area under the concentration-time curve; CYP, cytochrome P450; DDI, drug-drug interaction; mRNA, messenger ribonucleic acid; NA, not applicable.

[a] *Due to unknown reasons, treatment of positive control caused no effect on the mRNA expression of CYP2C19.*

Assessment of lesinurad pharmacokinetics in the presence of OAT inhibitors in rats (SR11-059)

Urinary excretion of lesinurad in female Sprague Dawley rats was evaluated following a single IV dose of lesinurad at 20 mg/kg with vehicle (control) or inhibitors of OAT, cimetidine (40 mg/kg), or probenecid (50 mg/kg). Probenecid is known to inhibit OAT1, OAT2, OAT3, and OAT4. Cimetidine is also known to inhibit OAT3 in addition to the OCTs. Renal secretion of lesinurad was slightly inhibited (nearly half of the excretion compared to vehicle) by probenecid while minimal inhibition was observed by cimetidine.

In vivo assessment of potential interactions with allopurinol in monkeys (SR09-065)

Because oxypurinol, the active moiety of allopurinol, is a substrate of URAT1, potential DDI effects on PK were investigated in monkeys (**Table 5**).

Table 5. Summary of Mean Pharmacokinetic Parameters of Lesinurad, Allopurinol, and Oxypurinol in Male Monkeys Following Single Doses Alone or Combination Dosing (SR09-065)

Analyte	Dose Regimen[a] (1 eg/Group)	N	T_{max} (hr)	C_{max} (µg/mL)	T_{last} (hr)	AUC[b] (µg·hr/mL)	$t_{1/2}$ (hr)	Combo/Alone C_{max}	Combo/Alone AUC[b]
Lesinurad	Lesinurad alone (1/1)	4	1.00	18.7	48.0	61.7	11.0	NA	NA
	Allopurinol[c]/lesinurad (2/1)	4	1.25	14.2	48.0	46.4	7.63	0.885	0.810
Allopurinol	Allopurinol alone (1/2)	4	1.13	1.15	6.00	3.05	1.07	NA	NA
	Lesinurad[c]/allopurinol (2/2)	3	1.33	0.545	4.00	1.23	0.756	0.572	0.552
Oxypurinol	Allopurinol Alone (1/2)	4	2.00	6.18	39.0	27.5	7.84	NA	NA
	Lesinurad[c]/allopurinol (2/2)	3	2.00	8.46	36.0	35.6	6.30	1.46	1.26

Abbreviation: NA, not applicable

a When listed, allopurinol was dosed at 12 mg/kg and lesinurad was dosed at 25 mg/kg.

b AUClast was reported and used for ratio calculations for allopurinol; AUC0-48 was reported and used for ratio calculations for lesinurad and oxypurinol.

c Compound was administered 1 hour before analyte dosing.

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2.3.4. Toxicology

Single dose toxicity

No single dose toxicity study was submitted with lesinurad. Assessment of acute toxicity was evaluated in repeat dose toxicity studies.

Repeat dose toxicity

Lesinurad was tested in repeated dose toxicity studies in rats up to 6 months and monkeys up to 12 months. Kidney was the main target organ in rats, where severe kidney toxicity was the cause of early deaths in the high dose group in the 14 day study. In every dose group animals suffered from tubular degeneration in the kidney. It appears that kidney toxicity is transient in nature, as no tubular degeneration was seen after longer duration of treatment at similar doses. After 4 weeks of treatment kidney effects were limited to increased kidney weight (still evident after 2 weeks recovery) and after 6 months to tubular dilation. Other target organs in the rat were the liver and the thyroid with hepatocellular hypertrophy occurring at 100 mg/kg/day in the 6-month study, and hypertrophy of the follicular epithelium in the thyroid. The liver effect was not completely recovered in females after a month recovery period. The mammary gland adenocarcinomas seen in the high dose group after 6 months of dosing were likely a chance finding, as no increase in tumour incidence was seen in the carcinogenicity study. No effects were observed in the lowest dose tested, which provides a safety margin for males of 1.3 after 4 week and 4 after 6 months, and for females 5 after 4 weeks and 3 after 6 months.

Limited toxicity was seen in monkeys, with some effects on the gastro-intestinal tract in the form of inflammation. Bilirubin was consistently reduced, and after 12 months of dosing bile duct hyperplasia occurred as well as increased kidney weight. The bile duct hyperplasia might be the result of accumulation of metabolite M6 which is excreted via bile, which does not occur in humans.

Another hypothesis to explain the development of bile duct hyperplasia is the presence of an epoxide intermediate M3c, which is converted into M9 present in monkey bile. In humans, the same epoxide intermediate is formed and subsequently converted into M4, present mainly in urine

Genotoxicity

The genotoxic potential of lesinurad was assessed in vitro in a bacterial mutation assay and a mammalian cell cytogenetic test, both in the presence and absence of a metabolic activation system (S9), and in vivo in a rat bone marrow micronucleus study. Lesinurad has no genotoxic potential.

Carcinogenicity

The carcinogenic potential of lesinurad was assessed in a 6-month transgenic (TgrasH2) mouse study and in a 2-year Sprague Dawley rat study (**Table 6**).

Table 6 Carcinogenicity studies performed with lesinurad

Study ID /GLP	Dose / Route	Exposure (AUC)	Species / No. of animals	Major findings
SR10-019 GLP	0, 15,45, 125 (M), 0, 30, 90, 250 (F) mg/kg/day Oral gavage	89.9, 260, 926 (M), 232, 724, 1760 (F) µg.hr/ml	TgrasH2 Mice, 25/sex/dose	**No neoplastic findings** **≥ low**: ↓ kidney weight **≥ mid**: ↓ liver weight, hepatocellular hypertrophy (M) **= high**: ↓ uterus weight, hepatocellular hypertrophy (F)
SR09-070 GLP	25, 75, 200	Day 72: 123, 431, 909 (M), 104, 679, 1040 (F), µg.hr/ml	SD rat, 60/sex/dose	**No neoplastic findings** **≥25**: hyperplasia urothelium (F) **≥75**: necrosis mucosa small intestine, bile duct hyerplasia **=200**: kidney cyst, papilla necrosis and inflammation,

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	mg/kg/day Oral gavage		hyperplasia collecting ducts, hyperplasia urothelium (M), tubular necrosis and dilation, cortical inflammation, tubular casts, necrosis mucosa large intestine

The average lesinurad exposure (gender combined AUC0-24hr) established from Day 1 to Week 72 at a dose of 200 mg/kg/day in this study was 1469 µg.hr/mL, which is slightly higher than the average exposure (AUC0-24hr of 1193 µg.hr/mL) obtained from the 6-month rat study at a dose of 300 mg/kg/day, the NOAEL for 6 months of dosing.

Exploratory plasma metabolic profiling in rats following dosing for up to 52 weeks at 200 mg/kg/day showed metabolite M2, and to a lesser extent metabolite M3, at greater than 1% of the parent compound on Day 1. At Weeks 26 and 52, metabolites M6, M8, M13, and M20 were detected in addition to M2 and M3. However, metabolite M4, which is formed via hydrolysis of an epoxide intermediate (M3c) and a major human metabolite in human urine, was not detected in rat plasma.

There was no test article-related increase in mortality as compared to control animals in either males or females. Microscopic evaluation indicated that there were no lesinurad-related neoplasms in males and females at any dose. Treatment-related non-neoplastic findings were present in the kidney, liver, and GI tract. In the kidney, papillary necrosis (minimal to marked severity) at 200 mg/kg/day was considered to be an adverse effect of lesinurad. In the liver, there was an increase in the incidence of BDH, a common background observation in aged rats across all the doses. The incidence of BDH was higher in males than females, although females had higher lesinurad exposures at the highest dose. Therefore, the relationship of lesinurad or its metabolites to BDH in rats is uncertain.

Reproduction Toxicity

A summary of the reproductive and developmental toxicity studies and the main findings of these studies are presented in **Table 7**.

Table 7. Reproduction toxicity studies performed with lesinurad

Study type / Study ID / GLP	**Species; Number Female / group**	**Route & dose**	**Dosing period**	**Major findings**	**NOAEL (mg/kg &AUC)**
SR10-007 Male and female fertility GLP	SD rat 22/sex/ dose	0, 75, 150, 300 mg/kg/day Oral gavage	M: 10wks F: 2wks prior – GD7	**M**: **=300**: ↓ BW **F**: **=300**: 3 mortalities, ↓ BW gain **No effect on fertility**	300 mg/kg/day No TK performed
SR09-009 Embryo-fœtal development DRF	SD rat 6F/dose	0, 100, 300, 450, 600 mg/kg/day Oral gavage	GD6-17	**=300**: 2 mortalities **450 and 600**: Groups removed due to toxicity **No effects on F1**	F1: 300 mg/kg/day AUC: 1040 µg.h/ml
SR10-008 Embryo-fœtal development GLP	SD rat 25F/dose	0, 75, 150, 300 mg/kg/day Oral gavage	GD6-17	F0: **=300**: 5 mortalities, ↓ BW gain, kidney toxicity F1**: no effect**	F0: 150 mg/kg/day F1: 300 mg/kg/day AUC: 1300 µg.h/ml

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SR09-068 Embryo-fœtal development DRF	NZW rabbit 3-6F/dose	Non-pregnant: 0, 100, 200, 300, 400 Pregnant: 0, 100, 150, 200, 250 mg/kg/day Oral gavage	7 days GD7-20	Non-pregnant: **300 and 400** removed due to toxicity Pregnant: **100**: 1 mortality **150**: 2 mortalities **200 and 250** removed due to toxicity **No effects on F1**	F1: 150 mg/kg/day AUC: 3220 µg.h/ml
SR10-009 Embryo-fœtal development GLP	NZW rabbit 20F/dose	0, 25, 75, 125 mg/kg/day Oral gavage	GD7-20	F0: **25**: 1 mortality **75**: 2 mortalities, ↓ pregnancies and **125**: 7 mortalities, group removed F1: **75**: ↓ viable foetuses	F0: <25 mg/kg/day F1: foetus viability: 25 g/kg/day AUC: 193 µg.h/ml foetal development: 75 mg/kg/day AUC: 357 µg.h/ml
SR11-068 Peri & postnatal GLP	SD rat 25F-dose	0, 100, 200, 300 mg/kg/day	GD7-LD20	F0: **100**: ↓ BW from GD17 **200**: 4 mortalities, ↓ BW, poor condition, ↓ gestation index **300**: 10 mortalities F1: **≥ 200**: dead pups LD1-4, ↓ viable foetuses, ↓ BW, cold dehydrated pups, no milk in stomach F1 development: **≥200**: ↑vaginal patency No effects on behaviour and reproduction performance of F1	F0: <100 mg/kg/day F1: pup development: 100 mg/kg/day AUC: 397 µg.h/ml Behaviour and reproduction: 300 mg/kg/day AUC: 1113 µg.h/ml

Local Tolerance

No local tolerance studies were submitted.

Other toxicity studies

Metabolite Assessment

Metabolism of lesinurad in humans was mediated mainly by CYP2C9 with minimal contributions from CYP1A2, CYP2C19, and CYP3A. CYP2C9 was responsible for the formation of the oxidative M3 metabolite from lesinurad. Additionally, CYP2C9 metabolized lesinurad to form an epoxide intermediate M3c, which was rapidly hydrolyzed to the dihydrodiol M4 metabolite by mEH. Therefore, M3c was only detected when *in vitro* incubation was conducted using CYP2C9 recombinant enzyme, which lacks the expression of mEH, or in microsomes with the presence of mEH inhibitors. In microsomes or hepatocytes where mEH was present, and in the absence of mEH inhibitors, only M4 was detected.

The applicant stated that there was no detectable epoxide intermediate in human plasma, urine, or faeces samples. In humans, M3 and M4 were detected in urine at a proportion >10% of dose. In rats, M3 is the primary metabolite in urine (approximately 50% in male rats and 18% in female rats; thus M3 is qualified in the repeated-dose and carcinogenicity studies. In rats and monkeys, M4 is present at

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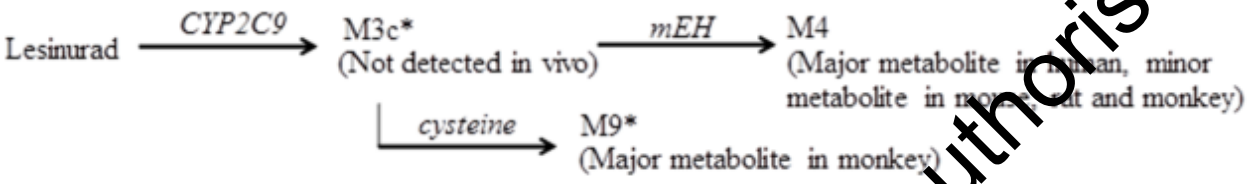
much lower levels in urine (< 0.5% of dose), thus M4 is considered to be a disproportionate metabolite in humans. M3 and M4 have no structural alerts beyond those observed with lesinurad for genotoxicity (lesinurad was negative for genotoxicity) and are not pharmacologically active.

In contrast to humans, monkeys have only small amounts of M4 detected in urine and bile. This

is because in monkeys the epoxide hydrolase pathway was a minor route of detoxification of M3c, which reacts mainly with cysteine to form a cysteine adduct metabolite M9, presumably via a nucleophilic attack (**Figure 4**). The presence of a significant amount of M9 in monkey bile along with the detection of M4 in rat and mouse supports the hypothesis that metabolism involving epoxide formation occurs in all toxicology species investigated.

Figure 4. *In vivo* elimination of epoxide intermediate M3c



Abbreviations: CYP2C9, cytochrome P450 2C9; mEH, microsomal epoxide hydrolase

Although not measurable or quantifiable, the amount of the M3c epoxide intermediate can be calculated based on the M4 and M9 levels detected in each species. Since M4 or M9 were not measured in the pivotal toxicity studies, data generated from single or repeated-dose oral radio-labelled lesinurad studies in mice, rats, or monkeys were used to calculate the amount of epoxide intermediate. Interspecies comparison of calculated epoxide amount is presented in **Table 8**.

Table 8. Interspecies Comparison of Multiples of Human Exposure for Calculated Epoxide Intermediate M3c

Species	Dose	Calculated Epoxide Amount (0-24 hours)			Multiples Over Human Calculated Epoxide (per body weight)
		Total (mg)	Per Body Weight (mg/kg)	Per Liver Weight (mg/g)	
Mouse[a]	100 mg/kg	Trace	NC	NC	NC
Rat[b]	200 mg/kg[c]	0.074	0.27	0.006[d]	0.79
Monkey[e]	300 mg/kg/day[f]	63.5	25	1.1	74
Human[g]	200 mg	29.5	0.34	0.014	NA

a Data from a [14C]lesinurad single oral dose study in wild type TgrasH2 mice (SR11-037);

b Values were calculated based on the data from a [14C]lesinurad single oral dose rat study (SR12-032);

Total (mg) = % of Dose in urine × mean dose administrated (mg/kg) x mean body weight (kg) x molar ratio of M3c (MW)/lesinurad (MW);

c No observed effect level (NOEL) for rat carcinogenicity;

d Actual liver weight was not measured in the study; 45 g liver/kg rat body weight (Houston 1994)was used for the calculation;

e Data from a [14C]lesinurad 28-day oral repeated-dose monkey study (SR10-029);

f No observed adverse effect level (NOAEL) for 12-month monkey;

g Human absorption, metabolism, and excretion study (Study 112 CSR) and clinical study (Study 105 CSR).

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Calculated total epoxide amount estimated from M4 levels in human urine and faeces (Study 112 CSR) was 129.3 mg, or 1.5 mg/kg (per body weight), or 0.06 mg/g (per liver weight) following a single oral 600 mg [14C]lesinurad dosing in liquid formulation, which resulted in disproportionally higher systemic exposure (AUC=123 µg•hr/mL) of lesinurad compared to AUC=28.0 µg•hr/mL at 200 mg in Study 105 CSR, where the lesinurad IR capsules were used. The epoxide in humans at the dose of 200 mg was adjusted using a correction factor of 4.39 (123/28) and calculated to be 29.5 mg for the IR capsule form.

The mean calculated amount of M3c per body weight at the NOEL (200 mg/kg/day) in rats for carcinogenicity was 0.79 times the estimated amount in humans at the MRHD. A value for M3c could not be calculated for mice, as only trace M4 was detected in TgrasH2 mice. The calculated amount of M3c at the NOAEL (300 mg/kg/day) in monkeys (12 -month study) was 74 times the estimated amount in humans at the MRHD. Thus, M3c has been evaluated for potential general toxicity in both rats and monkeys along with carcinogenicity in rats. The negative results for carcinogenicity in the rat including the liver, where M3c conversion to M4 occurs, support the conclusion that there are no safety concerns associated with the levels of M3c that occur following a lifetime exposure to lesinurad at the MTD.

In human plasma, M4 was not detected at a proportion >10% of parent, but it was detected in human urine at a proportion >10% of dose. The mean calculated amount of M4 per body weight at the NOEL (200 mg/kg/day) in rats for carcinogenicity was 0.78 times the estimated amount in humans at the MRHD. A value for M4 could not be calculated for mice, as only trace M4 was detected in TgrasH2 mice. The calculated amount of M4 per body weight at the NOAEL (300 mg/kg/day) in monkeys (12-month study) was 3.1 times the estimated amount in humans at the MRHD. Therefore, M4 has been adequately assessed for chronic toxicity and carcinogenicity. Since the rat carcinogenicity was negative, there is no need to evaluate M4 in a genotoxicity battery. Furthermore, at a high dose of 1000 mg/kg in the rat micronucleus test, no increase in micronucleus was observed. Evaluation for reproductive toxicity would not be required given that M4 was only a disproportionate metabolite in urine. Further, the reproductive toxicity studies in rats tested at a top dose of 300 mg/kg/day of lesinurad, which conceivably would have resulted in higher M4 exposures than the high dose of 200 mg/kg/day used in the carcinogenicity study, thus contribute to the overall reproductive toxicity testing of M4.

Studies on impurities

Key intermediates and potential impurities in the synthetic pathway for lesinurad that require qualification according to ICH guidelines were adequately qualified using repeated-dose studies. As part of the genotoxic impurity control strategy, *in silico* evaluation and Ames testing of the impurities were carried out. Intermediates or starting material impurities and reagent formylhydrazine which were identified as genotoxic impurities were under the threshold of toxicological concern of (TTC) 1.5 µg/day at a concentration of 7.5 ppm in the 200 mg tablet (once daily) of lesinurad.

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Phototoxicity

Lesinurad is able to absorb UVB light. However, due to insufficient distribution to skin and eyes, lesinurad is unlikely to have phototoxic potential.

2.3.5. Ecotoxicity / environmental risk assessment

Table 9. Summary of main study results

Substance (INN / Invented Name): lesinurad					
CAS-number (if available): 878672-00-5					
PBT screening		Result			**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	Log D_{ow} = 1.9 at pH 5 Log D_{ow} = 0.34 at pH 7 Log D_{ow} = -0.061 at pH 9			Potential PBT (N)
PBT-assessment					
Parameter	**Result relevant for conclusion**				**Conclusion**
Bioaccumulation	log K_{ow}	Log D_{ow} = 1.9 at pH 5 Log D_{ow} = 0.34 at pH 7 Log D_{ow} = -0.061 at pH 9			not B
	BCF	not required			
Persistence	ready biodegradability	not readily biodegradable			
	DegT50	$DT_{50, water}$ = 57/53 d (p/c) $DT_{50, sediment}$ = 51/47 d (p/c) $DT_{50, system}$ = 53/99 d (p/c)			p =pond; c =creek; DT_{50} corrected to 12°C. Conclusion: P
Toxicity	NOEC algae NOEC crustacea NOEC fish	30 mg/L 10 mg/L 2 mg/L			not T
	CMR	not investigated			potentially T
PBT-statement :	lesinurad is considered not PBT, nor vPvB				
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
$PEC_{surfacewater}$, default refined	1.0 1.4	µg/L µg/L			> 0.01 threshold (Y)
Other concerns (e.g. chemical class)	not investigated				
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OECD 106	K_{oc} = 364 L/kg (soil) 448 L/kg (soil) 332 L/kg (sediment) 79.1 L/kg (sediment)			Natural water was used for the sediments instead of 0.01 M $CaCl_2$
Ready Biodegradability Test	OECD 301B	Not ready biodergradable			
Aerobic and Anaerobic Transformation in Aquatic Sediment Systems	OECD 308, parent	$DT_{50, water}$ = 27/25 d (p/c) $DT_{50, sediment}$ = 24/27 d (p/c) $DT_{50, system}$ = 25/47 d (p/c) Sediment shifting: >10%			p =pond; c =creek DT_{50} at 20°C; Forms two persistent metabolites (dp1, dp2).
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/ *Pseudokirchneriella subcapitata*	OECD 201	NOEC	30	mg/ L	Yield, growth rate
Daphnia sp. Reproduction Test	OECD 211	NOEC	10	mg/ L	Reproduction, length, survival
Fish, Early Life Stage Toxicity Test/	OECD 210	NOEC	2	µg/L	hatching, survival, length, weight
Activated Sludge, Respiration	OECD 209	NOEC	200	mg/	respiration

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Inhibition Test				L	
Phase IIb Studies					
Sediment dwelling organism/ *Chironomus riparius*	OECD 218	NOEC	4522	mg/ kg	normalised to 10% o.c.

Lesinurad is considered not to be PBT, nor vPvB.

Considering the above data and the environmental risk assessment, lesinurad is not expected to pose a risk to the surface water compartment, groundwater compartment, the sewage treatment plant, and the sediment compartment.

2.3.6. Discussion on non-clinical aspects

Pivotal non-clinical studies were claimed to be performed in accordance with GLP. However the repeated dose toxicology studies were performed in laboratories that were not part of a GLP monitoring program of a Country that is an adherent to the OECD MAD (Mutual acceptance of Data; in this case China). Therefore the CHMP requested a GLP inspection to verify the GLP compliance of those sites. Inspections were conducted in July and September 2015 (INS/GLP/2015/084) and did not reveal any critical findings. The CHMP therefore concluded that the data from the non-clinical studies inspected could be used for the evaluation of the concerned application.

Lesinurad is a urate-lowering therapy being developed for the chronic treatment of gout. It is a SURI that inhibits uric acid transporters in the renal proximal tubules. URAT1 inhibitors such as lesinurad lower sUA by reducing reabsorption of uric acid. Although no animal models are available to test its uric acid lowering efficacy *in vivo*, lesinurad demonstrated inhibition of URAT1 in *in vitro* transporter assays at clinically relevant concentrations. In addition to URAT1, lesinurad inhibits OAT4, another transporter located in the apical membrane of the renal proximal tubules.

Pharmacodynamic drug interaction studies were not submitted and this was considered acceptable by the CHMP as there are no appropriate animal pharmacodynamic models to evaluate the intended effect in humans, due to the fact that animals unlike humans possess the uricase enzyme which converts uric acid to allantoin.

No local tolerance studies were submitted as lesinurad is administered orally and thus local tolerance in the GI tract was evaluated in the repeated-dose toxicity studies.

Data on other targets did not show significant activity at clinically relevant concentrations.

A study on muscle cell toxicity did not reveal muscle toxicity potential of lesinurad in Rat L6 cells *in vitro* at a concentration of 10 µM.

Lesinurad did not exhibit any clinically significant antiviral activity against HIV, but in 2 MSU dependent rodent acute gout flare models, lesinurad was efficacious in reducing inflammation from injected MSU crystals.

No important safety pharmacology effects on parameters of the CNS, cardiovascular system, respiratory system, gastrointestinal tract and renal/urinary system were observed.

The PK properties of lesinurad were studied *in vitro* using animal and human tissues and expressed proteins, and in vivo in the species and strains used in the safety evaluation. Exposures to lesinurad were generally at least dose-proportional in rats and monkeys, and generated large multiples of the human exposure at the MRHD. Following repeated dosing of lesinurad, toxicokinetics revealed evidence of slight auto-induction in rats at ≥ 100 mg/kg and moderate auto-induction in monkeys at ≥ 30 mg/kg.

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Lesinurad was highly protein bound. The free fraction of lesinurad in plasma is low with a fu of 2.3 % in rat, 5% in mouse and 1.7% in human, dog and monkey. Distribution to other tissues except for liver and kidney is limited. In all species, including humans, the major circulating component was unchanged lesinurad, except for monkeys where towards the end of the chronic study the dealkylated M6 metabolite was predominant.

Metabolism is a mixture of oxidation, debromination and glucuronidation, but in monkeys S-dealkylation (M6) and cysteine conjugation (M9) are important as well. All metabolites in humans were identified in the nonclinical toxicology species, with only M4 considered to be a human disproportionate urinary metabolite. M4 is formed via an epoxide intermediate (M3c) that was not detected in animals or humans. The Applicant suggested that *in vivo* M3c is rapidly hydrolyzed by microsomal epoxide hydrolase (mEH) into M4 (major metabolite in human urine) or M9 (major metabolite in monkey bile) and the documentation provided to support this hypothesis was considered sufficient by the CHMP.

The CYP P450 system and mEH are both known to be located in the smooth endoplasmatic reticulum. Further, Nishimura et al (2003) showed that CYP2A9 mRNA is highly expressed in human liver, whereas Enayetallah et al (2004) showed by blot analyses that CYP2C9 is expressed in human bile duct and kidney and Lakehal (1999) using immunohistochemistry showed that mEH is expressed in human bile duct and kidney. The colocalization of mEH and CYP2C9 in liver and kidney enables the M3c formed by CYP2C9 to be readily hydrolyzed, which will limit exposure to M3c.

On the other hand, literature data indicate that certain well-characterized genetic polymorphisms in human mEH exist (Fretland et al., 2000; Pinarbasi et al., 2010). This mEH polymorphism implies that there may be patient populations with an increased risk of adverse effect in liver and kidney as a result of a higher M3c exposure.

The CHMP therefore considered that use of lesinurad in patients with epoxide hydrolase polymorphism should be included in the Risk Management Plan (RMP) as missing information with close surveillance of post-marketing reports for any evidence of hepatotoxicity. In addition, the CHMP recommended that the Applicant should provide the results of a study on metabolite profiling, including metabolite M4 formed by epoxide hydrolase, over 24 hours and this study is also included in the RMP.

Kidney was the main target organ in rats, where severe kidney toxicity was the cause of early deaths in the high dose group in the 14-day study. It appears that toxicity is only evident after short term treatment of up to 3 weeks, after which the effects are resolved. This was evidenced by kidney toxicity (tubular degeneration) at all doses in the 14-day study, at the high dose only after 14 days in the 28-day study, with marginal non- significant increases in sCr levels, and tubular injury resulting in death after 3 weeks dosing in the 6-month study. Despite these findings the CHMP considered that lesinurad is not a classic nephrotoxicant, and possibly the observed effects were species specific, as similar lesions were not observed in monkeys, and there was no classic dose response.

A mechanism of action for the kidney toxicity observed in humans has been proposed, related to the pathological condition of the patient, and more specifically the increased uric acid levels. It appears likely that due to this increased plasma and urine uric acid levels, crystallization occurs, leading to kidney damage. This is further substantiated by the fact that patients receiving concomitant allopurinol to reduce uric acid levels, showed decreased renal toxicity. A similar mechanism of action is not mimicked in animals since uric acid levels are much lower in animals.

Other target organs in the rat were the liver and the thyroid with hepatocellular hypertrophy occurring at 100 mg/kg/day in the 6-month study, and hypertrophy of the follicular epithelium in the thyroid.Limited toxicity was seen in monkeys, with some effects on the gastro-intestinal tract in the form of inflammation. Bilirubin was consistently reduced, and after 12 months of dosing bile duct hyperplasia occurred as well as increased kidney weight. The bile duct hyperplasia might be the result

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of accumulation of metabolite M6 which is excreted via bile, which does not occur in humans. Due to the bile duct hyperplasia, the NOAEL in the 12-month study is 100 mg/kg/day, which is around 3-fold the human exposure. In clinical trials, hepatobiliary disorders including acute cholecystitis was observed at a somewhat greater incidence in the lesinurad arm as compared to placebo. However, in the long-term extension study, no trend of cholestasis in humans was observed after 24 months of follow-up. No relevant cytotoxicity was shown in HeLa-JC53 and human HepG2 cells and in contrast to benzbromarone, no mitochondrial toxicity in HepG2 cells was observed. Yet, it should also be considered that HeLa and HepG2 cells have only limited metabolic activity and therefore insufficiently cover any potential role of metabolites. Only mitochondrial toxicity was considered by the Applicant as a potential cause for DILI.

Dose-related GI toxicity was observed in all tested species and resulted in mortality at high doses in rats and monkeys. In addition, decreased intestinal motility (17%) after an acute dose was seen in rats in the GI safety pharmacology study. However, in the secondary pharmacology screen, lesinurad did not have an effect on the cholinergic pharmacology at 100 µM. Thus, the mechanism underlying the GI toxicity in animals is not known. The applicant proposed that it could be a local direct toxic effect or an off-target toxicity at the supra-physiological concentrations in the GI tract, since most of the GI toxicity occurred at a dose exceeding the MTD. The safety margins, based on systemic exposures, at the NOAEL in rats and monkeys are 4 and 12 times the human exposure at MHD. Clinical data do not point to evidence of significant GI tract safety issues. and Gastro-oesophageal reflux disease (GERD) is included as an adverse effect in section 4.8 of the SmPC. Based on the available data, the CHMP concluded that GI tract toxicity in association with lesinurad use does not appear to be a significant clinical concern .

Lesinurad was shown not to have a genotoxic potential.

Lesinurad was not carcinogenic in the 2-year rat study, with exposures over 50-fold the human exposure or in the 6 month study in the TgrasH2 mouse model, with exposures of over 30 (females) and 60 (males) the human exposure.

The results of the 13-week rat combination study are sufficient to support the treatment of gout patients with lesinurad in combination with allopurinol.

The combination toxicology studies with lesinurad and allopurinol or febuxostat showed no additive, synergistic, overlapping, or new toxicity when the agents were coadministered, supporting combination dosing of lesinurad with either XO inhibitor.

There was no effect on male or female fertility due to treatment with lesinurad. There were no effects on the offspring of rats treated with up to 300 mg/kg/day lesinurad, resulting in 46-fold the human exposure. In rabbits, treatment with lesinurad caused severe maternal toxicity resulting in a reduction in viable foetuses due to increased resorptions. Even though maternal toxicity is still evident at the low dose, no effects on foetuses were observed at this dose, providing a safety margin of 4. No increase in malformations of variations was seen in any of the groups. As noted by the applicant, the number of litters available for analysis was reduced in the mid dose group, and no litters were available in the high dose group due to maternal toxicity. The applicant referred to a scientific advice provided by the CHMP, which stated that no further studies were necessary.

In the pre- and postnatal study in rats, lesinurad was maternally toxic at all doses, resulting in reduced body weight gain at the low dose from GD17 and severe toxicity and death in the mid and high dose groups. Reduced viable foetuses, reduced pup body weight and mortalities were observed in groups treated with 200 mg/kg/day or higher. No such effects were seen at the low dose of 100 mg/kg/day, resulting in and exposure 14-fold the human exposure. Surviving pups did not show any effects on behaviour or reproduction performance at any dose group, up to 40-fold the human exposure.

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2.3.7. Conclusion on the non-clinical aspects

Lesinurad has been well characterised in non-clinical pharmacology, pharmacokinetic and toxicology studies. However, the Applicant will further characterise the metabolite profiling of lesinurad as detailed in the RMP.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Study	Study description	Treatment
Mass balance and bioavailability		
112	Absorption, metabolism, and excretion	LESU: 600 mg, [^{14}C]LESU: 500 µCi
131	Single oral and IV doses, absolute BA	LESU: 400 mg; [^{14}C]LESU: 100 µg
Biopharmaceutical studies		
101	Single ascending dose in fed and fasted healthy subjects	LESU: 5, 25, 100, and 200 mg (fasted); 100, 400, and 600 mg (fed)
103	Single dose in fed and fasted healthy subjects	LESU: 50 and 200 mg (fasted and fed)
107	Single dose of 2 IR formulations in fasted and fed healthy subjects	LESU: 200 mg IR tablet (fasted and fed) LESU: 200 mg IR capsule (fed)
109	Single dose of FA and sodium salt IR formulation in fasted and fed healthy subjects	LESU: 200 mg (fasted), 400 mg (fasted and fed) and 600 mg (fasted and fed)
117	Supratherapeutic dose evaluation in healthy subjects	Moxifloxacin: 400 mg Segment A LESU: 400,800, 1200, 1600 mg
129	Single dose study in fasted and fed healthy volunteers	LESU: 400 mg (tablets manufactured at two different sites)
132	Single dose study in fasted and fed healthy volunteers	LESU: 400 mg (tablets manufactured at two different sites)
Studies performed in patients		
202 main	Multiple doses in subjects with gout	LESU: 200, 400, and 600 mg; Colchicine: 0.5 to 0.6 mg
202 open-label EXT	Multiple doses in subjects with gout	LESU: 200 to 600 mg; Colchicine: 0.6 mg
203 main	Multiple doses in subjects with gout	LESU: 200, 400, 600 mg; Allopurinol: 200 to 600 mg

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		Colchicine: 0.5 to 0.6 mg
203 double-blind EXT	Multiple doses in subjects with gout	LESU: 200, 400, 600 mg; Allopurinol: 200 to 600 mg Colchicine: 0.6 mg
203 open-label EXT	Multiple doses in subjects with gout	LESU: 200, 400, 600 mg; Allopurinol: 200 to 600 mg Colchicine: 0.6 mg
204	Multiple doses in subjects with gout and renal impairment	LESU: 100 and 200 mg; Allopurinol: 100 to 200 mg; Colchicine: 0.5 mg
301	Multiple doses in subjects with gout	LESU: 200, 400 mg Allopurinol: 200 to 800 mg
302	Multiple doses in subjects with gout	LESU: 200, 400 mg Allopurinol: 200 to 900 mg
303	Multiple doses in subjects with gout	LESU: 400 mg
304	Multiple doses in subjects with gout	LESU: 200, 400 mg Febuxostat: 80 mg
305	Multiple doses in subjects with gout	LESU 400 mg
306	Multiple doses in subjects with gout	LESU 200, 400 mg Allopurinol: 200 to 800 mg
307	Multiple doses in subjects with gout	LESU 200, 400 mg Febuxostat: 80 mg
Studies in special populations		
118	Single dose, PK and PD in subjects with hepatic impairment (intrinsic factor)	LESU: 400 mg
104	Single dose in subjects with various degrees of renal insufficiency (intrinsic factor)	LESU: 200 mg
120	Single dose, PK and PD in subjects with renal impairment (intrinsic factor)	LESU: 400 mg
125	Single and multiple ascending doses study in healthy Japanese subjects (intrinsic factor)	LESU: 50, 100, 200, 400, and 600 mg
DDI studies		
105	Multiple doses, DDI with febuxostat (extrinsic factor)	LESU: 200 and 400 mg, Febuxostat: 40 mg
108	Multiple doses, DDI with sildenafil (extrinsic factor)	LESU: 200, 400, 600 mg, Sildenafil: 50 mg
110	Multiple doses, DDI with allopurinol or colchicine in subjects with gout (intrinsic and extrinsic factor)	LESU: 400 and 600 mg, Allopurinol: 300 mg, Colchicine: 0.6 mg
111	Multiple doses, DDI with febuxostat or colchicine in subjects with gout (intrinsic and extrinsic factor)	LESU: 400 and 600 mg, Febuxostat: 40 and 80 mg, Colchicine: 0.6 mg
113	Single or multiple doses, DDI with atorvastatin (extrinsic factor)	LESU: 200 and 400 mg, Atorvastatin: 40 mg
114	Multiple doses, DDI with amlodipine (extrinsic factor)	LESU: 400 mg Amlodipine: 5 mg
115	Single or multiple doses, DDI with	LESU: 400 mg,

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	tolbutamide (extrinsic factor)	Tolbutamide: 500 mg
116	Multiple doses, DDI with repaglinide (extrinsic factor)	LESU: 400 mg, Repaglinide: 0.5 mg
121	Single dose, food and antacid effect BE	LESU: 400 mg; Tums: 3000 mg calcium carbonate; MINTOX: 1600 mg magnesium/ 1600 mg aluminium hydroxide/ 160 mg simethicone
122	Single dose, DDI with fluconazole and rifampin (extrinsic factor)	LESU: 400 mg; Fluconazole: 200 and 400 mg; Rifampin: 600 mg
123	Multiple doses, DDI with warfarin (extrinsic factor)	LESU: 400 mg; Warfarin: 25 mg
126	Two-way PK interaction between lesinurad and naproxen and between lesinurad and indomethacin (extrinsic factor)	LESU: 400 mg, Naproxen: 250 mg, Indomethacin: 25 mg
127	Multiple doses, DDI with ranitidine (extrinsic factor)	LESU: 400 mg, Ranitidine: 150 mg
128	Multiple doses, DDI with metformin or furosemide (extrinsic factor)	LESU: 400 mg; Metformin: 850 mg; Furosemide: 40 mg
130	Multiple doses, DDI with antacids (extrinsic factor)	LESU: 400 mg; Tums: 1250 mg calcium carbonate; MINTOX: 80 mg magnesium/800 mg aluminium hydroxide/80 mg simethicone

2.4.2. Pharmacokinetics

Absorption

The pharmacokinetic properties of lesinurad were evaluated with a number of different formulations including, solutions, immediate-release (IR) capsules and tablets. Lesinurad was present as sodium salt or free acid in the different formulations.

Absorption of lesinurad in healthy subjects after a single dose of lesinurad (5 to 600 mg) using different formulations under fasted conditions was rapid and the C_{max} occurred after ≤3 hours. T_{max} was ~2.0 hours for the immediate release tablet of the free acid.

Bioavailability

The absolute bioavailability of a single oral dose of lesinurad was determined in 10 healthy adult male subjects in study 131. The subjects received a non-radiolabeled oral dose of 400 mg lesinurad tablet under fasted conditions and a 15-minute IV infusion of 100 µg [^{14}C]lesinurad microtracer dose commencing at 1.75 hours post oral dose to coincide with the expected mean oral T_{max}. By comparing dose-normalized $AUC_{0-\infty}$ of lesinurad from oral and IV dosing, the absolute oral bioavailability for lesinurad was determined to be 101% (90% CI: 95.4% to 106%).

Comparison of trial formulations with finished product

In studies 129 and 132, the effect of 2 different manufacturing sites on the bioavailability of commercial lesinurad 400 mg FA tablets was investigated in healthy, adult male subjects under fasted

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and fed conditions. One batch (ELAD) was manufactured at the proposed commercial site (AstraZeneca AB) and compared to batch (12A015) manufactured at the Phase III manufacturing site (Metrics, Inc.). In study 129, 72 subjects were divided over 4 cohorts (2 sequences with 9 subjects per sequence). In study 132, 54 subjects were divided over 2 groups (n=27 per group) who received either lesinurad manufactured at the commercial site or manufactured at the Phase III production site under fasting conditions with a 3 day wash out period. Subjects were separated into 2 dosing subgroups due to limited capacity at the clinical research unit. In both studies, the batch produced at the proposed commercial site was bioequivalent to the batch manufactured at the Phase III site (**Table 10**).

Table 10. Geometric mean ratio (90% CI) of lesinurad plasma pharmacokinetic parameters for 400 mg lesinurad FA tablets manufactured at commercial site relative to Phase II-III manufacturing site in healthy adult male subjects under fasting and fed conditions (studies 129 and 132)

treatment	reference	feeding status	geometric mean ratio (%)		
			C_{max}	AUC	study
tablet (ELAD)	Metrics	fasted	100 (85.0-118)	99.8 (90.0-111)	129
tablet (ELAD)	Metrics	fed	101 (86.1-119)	91.3 (84.0-101)	129
Tablet (ELAD)	Metrics	fasted	96.8 (90.4-103.6)	99.4 (94.9-104.1)	132

Influence of food

The effect of food on the pharmacokinetics of lesinurad was investigated in studies 103, 107, 109, 121, 125 and 129. The effect of low, moderate and high fat breakfast on the bioavailability was studied. The pharmacokinetic parameters for lesinurad under fed and fasted conditions are summarized in **Table 11.**

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Table 11. PK parameters of lesinurad after single oral dose in humans under fasted and fed conditions

dose (mg)	formulation	gender (N)	food status	C_{max} (µg/mL)	C_{max} ratio (%)	T_{max} (h)	AUC_{0-24} (µg×h/mL)	AUC ratio (%)	$AUC_{0-\infty}$ (µg×h/mL)	$t_{½}$ (h)	study
50	IR capsule (sodium salt)	male (9)	fasted	1.98 (1.28-3.05)	ND	1.0 (0.5-3.0)	7.01 (5.59-8.78)	ND	7.07 (5.63-8.88)	6.1 (4.3-8.5)	103
			fed (high-fat breakfast)	1.63 (1.22-2.17)		2.0 (1.0-5.0)	6.47 (4.75-8.80)		6.56 (4.80-8.96)	5.6 (4.6-6.9)	
50	IR tablet (FA)	male (6)	fasted	1.90 (1.09-3.29)	76.8 (51.8-114)	2.0 (1.0-4.0)	7.47 (5.46-10.2)	82.1 (71.4-94.3)	7.51 (5.48-10.3)	3.1 (2.1-4.4)	125
			fed (moderate-fat breakfast)	1.53 (1.08-2.16)		2.0 (1.0-5.0)	6.66 (5.71-7.77)		6.76 (5.83-7.84)	3.9 (2.8-5.4)	
100	IR tablet (FA)	male (6)	fasted	6.41 (5.22-7.86)	47.9 (37.7-60.7)	1.75 (1.5-4.0)	21.3 (17.5-26.0)	74.0 (63.8-85.9)	21.5 (17.7-26.2)	4.4 (4.2-4.6)	125
			fed (moderate-fat breakfast)	3.07 (2.19-4.29)		2.25 (1.0-5.0)	15.8 (13.3-18.7)		15.9 (13.4-18.9)	3.6 (3.1-4.2)	
200	IR tablet (sodium salt)	male (8)	fasted	8.86 (CV=54.2%)	85.2 (29.2-151)	0.75 (0.5-3.0)	29.3 (CV=28.9%)	81.5 (64.8-98.3)	30.2 (CV=28.8)	15.8 (CV=51.6)	107
			fed (low-fat breakfast)	5.98 (CV=18.5)		3.0 (1.0-5.0)	23.1 (CV=14.4)		23.7 (CV=14.6)	13.7 (CV=60.8)	
200	IR tablet (FA)	male (6)	fasted	12.6 (11.6-13.7)	64.9 (53.4-78.8)	2.0 (0.5-4.0)	33.7 (28.7-39.5)	88.8 (80.7-97.9)	34.0 (28.9-40.1)	5.3 (3.7-7.5)	125
			fed (moderate-fat breakfast)	8.17 (6.19-10.8)		3.0 (1.0-4.0)	30.0 (26.6-33.8)		30.4 (26.6-34.7)	4.3 (3.8-4.9)	
400	IR capsule (sodium salt)	male (24)	fasted	17.8 (13.2-24.0)	76.3 (65.2-89.3)	1.5 (1.0-4.0)	56.7 (44.6-72.1)	92.8 (85.1-101)	57.3 (45.0-72.9)	5.7 (5.0-6.5)	109
			fed (low-fat breakfast)	11.7 (9.23-14.8)		3.0 (2.0-4.0)	46.4 (38.4-56.0)		47.1 (38.9-56.9)	9.0 (5.8-14.1)	

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400	IR tablet (FA)	male (16)	fasted	20.1 (17.0-23.8)	81.6 (66.6-99.8)	1.5 (1.0-4.0)	69.3 (57.2-84.1)	92.1 (83.6-102)	69.6 (57.4-84.5)	16.9 (11.2-25.5)	121
			fed (high fat breakfast)	16.3 (12.9-20.4)		2.0 (1.0-4.0)	61.7 (51.6-73.6)		63.[illegible] (52.7-75.4)	17.7 (12.1-26.0)	
400	IR tablet (FA)	male (6)	fasted	24.6 (18.7-32.3)	81.5 (62.6-106)	1.5 (1.0-5.0)	102 (82.1-126)	83.8 (70.3-99.8)	103 (83.2-129)	14.1 (7.0-28.7)	125
			fed (moderate-fat breakfast)	20.0 (13.1-30.7)		1.75 (1.0-5.0)	85.2 (66.4-109)		86.2 (66.8-111)	3.6 (3.0-4.2)	
400	IR tablet (FA) (12A015)	male (9)	fasted	18.6 (16.2-21.5)	ND	1.7 (0.67-4.5)	57.6 (51.4-64.6)	ND	58.8 (52.4-66.1)	10.8 (8.4-13.7)	129
			fed (high-fat breakfast)	12.5 (10.2-15.3)		3.3 (1.3-8.0)	60.0 (51.4-71.3)		62.0 (51.8-74.2)	11.9 (8.1-17.6)	
400	IR tablet (FA)	male (9)	fasted	20.4 (17.5-23.9)	ND	1.7 (0.67-3.3)	59.5 (49.8-71.1)	ND	60.9 (50.8-73.0)	17.5 (12.1-25.3)	129
			fed (high-fat breakfast)	13.9 (11.8-16.4)		3.0 (1.3-5.5)	53.6 (48.8-58.8)		54.8 (50.0-60.0)	14.1 (9.6-20.6)	
400	IR tablet (FA)	male (9)	fasted	20.5 (18.1-23.2)	ND	1.7 (1.0-4.5)	59.1 (50.9-68.7)	ND	60.4 (51.8-70.4)	13.9 (10.2-19.0)	129
			fed (high-fat breakfast)	14.1 (11.8-16.8)		2.7 (1.0-10.0)	51.1 (46.6-56.1)		52.2 (47.5-57.4)	14.6 (9.7-21.9)	
600	IR tablet (FA)	male (24)	fasted	32.4 (25.5-41.1)	54.6 (40.6-73.4)	2.0 (1.0-3.0)	117 (92-148)	68.6 (54.7-86.1)	119 (94-151)	8.7 (6.3-12.0)	109
			fed (low-fat breakfast)	17.7 (13.3-23.5)		3.5 (1.5-5.0)	80.2 (66.7-96.5)		81.7 (67.7-98.5)	8.7 (7.0-10.8)	

ND = not determined; FA = free acid

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Distribution

Plasma protein binding

The *in vitro* binding of lesinurad to human plasma proteins was evaluated using radiolabeled lesinurad at concentrations of 1, 10, and 50 µM in all species using equilibrium dialysis (study SR08-045). Mean plasma protein binding of lesinurad was equal to or greater than 97% over the investigated concentration range (98.5 ± 0.06% at 1 µM; 98.4 ± 0.02% at 10 µM and 97.9 ± 0.17% at 50 µM). The binding was primarily due to interaction with albumin with minimal contribution from α-1-acid glycoprotein.

Plasma protein binding of lesinurad was unchanged in subjects with mild hepatic impairment (99.0% bound) and moderate hepatic impairment (98.8% bound) compared with subjects with normal hepatic function (99.0% bound) (study 118).

Plasma protein binding of lesinurad ranged from 98.7% to 99.0% across the different renal function categories (study 120). Plasma protein binding decreased slightly in subjects with moderate (98.7% ± 0.207%) and severe renal impairment (98.7% ± 0.174%) compared with subjects with normal renal function (99.0% ± 0.142%).

Blood-to-plasma ratio

The blood-to-plasma ratio was determined *in vivo* (study 112). Following a single oral dose of 600 mg [^{14}C]-lesinurad to healthy male volunteers, the mean whole blood to plasma ratios of AUC and C_{max} ranged between 0.54 and 0.55.

Volume of distribution

Following a single IV dose of 100 µg [^{14}C]-lesinurad, the volume of distribution at steady state was 20.3 L (study 131).

Elimination

The elimination half-life ranged from 2.7 to 17.5 hours. The half-life for the immediate release capsule of the free acid ranged from 3.1 to 5.1 hours.

Excretion

The mass balance was evaluated in 6 healthy male volunteers receiving a single 600 mg dose of [^{14}C]-lesinurad (sodium salt) oral solution (Absorption, metabolism and excretion Study 112). Renal clearance is 25.6 mL/min (CV=36%). In total, 63% of the radioactivity was recovered in urine and 32% in feces after a period of 0 to 144 hours (**Figure 5**). The majority of the administered dose was excreted within the first 24 hours (~60% via urine).

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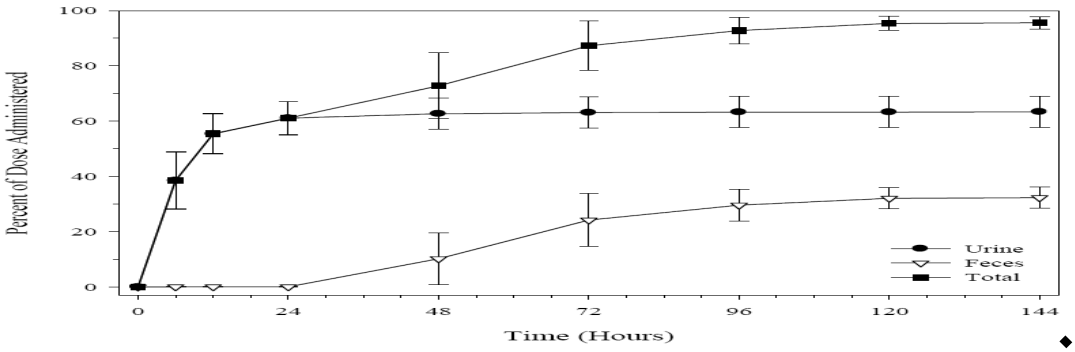
Figure 5. Mean cumulative percent excretion of total radioactivity in urine and faeces (study 112)



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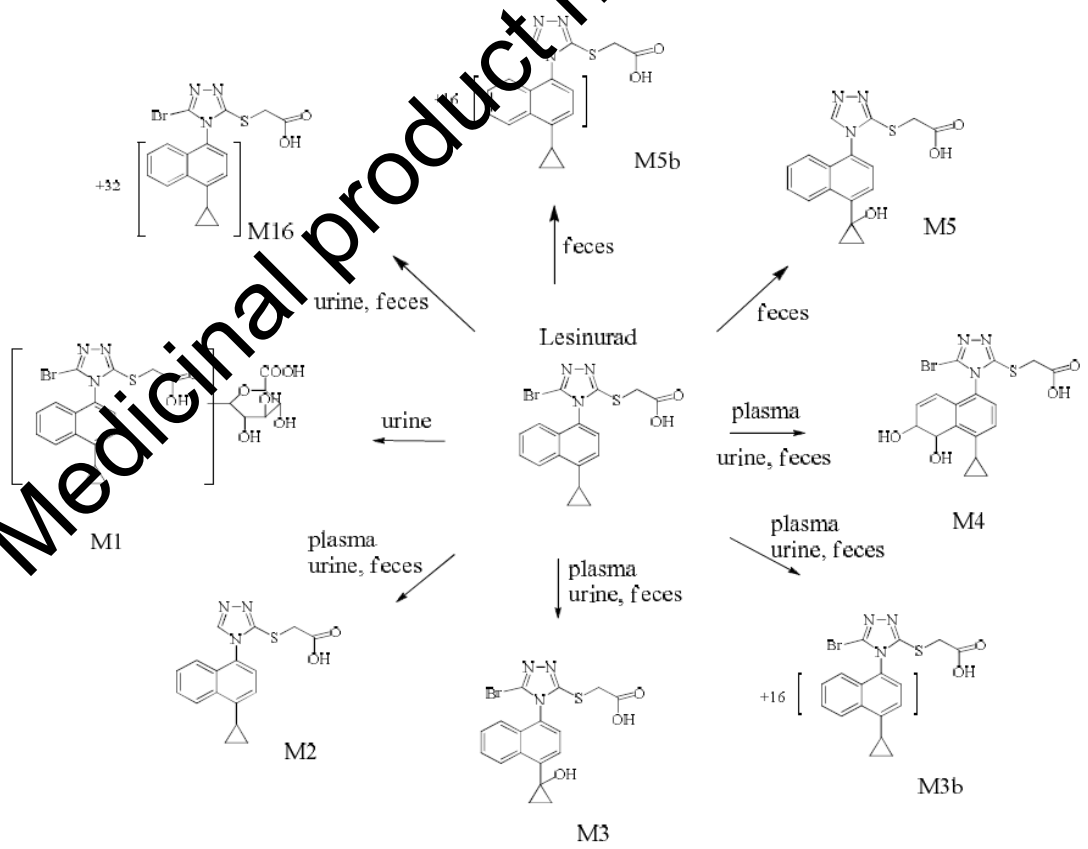
Metabolism

From *in vitro* studies (presented in Section 2.3 of this report), the metabolism of lesinurad in humans was found to be mediated mainly by CYP2C9 with minimal contributions from CYP1A1, CYP2C19, and CYP3A. CYP2C9 is considered to play a major role in the formation of oxidative metabolites (M3, M3b, M4, M5, M5b). CYP2C9 metabolizes lesinurad to form an epoxide intermediate M3c, which is rapidly hydrolyzed to the M4 metabolite by microsomal epoxide hydrolase (mEH). Formation of M5 is mediated through the combination of CYP2C9 and gastrointestinal microflora. The formation of M6 is catalysed by CYP3A4, but the elimination of lesinurad through this pathway is negligible in humans in vivo. Based on the data from study 112 (AME study), the applicant proposed the following metabolic pathway of lesinurad:

Figure 6. Major metabolic pathways of lesinurad in humans



Lesinurad is a racemic mixture (50:50) of 2 atropisomers. Quality tests have shown that the atropisomers do not readily interconvert even under extreme conditions. Lesinurad atropisomers were investigated individually to assess potential metabolism differences in human and monkey liver microsomes and recombinant CYPs. The formation of lesinurad metabolite M3c was primarily from atropisomer 1, the M3 and M4 metabolites were formed from both atropisomers with higher levels by atropisomer 1. M6 was also formed from both atropisomers with greater preference from atropisomer 2.

The ratios of atropisomer 1 and atropisomer 2 were determined in study 126 Cohort 2 and were 43:57 at $C_{max,ss}$ and 20:80 at $C_{min,ss}$. The half-live is 3.8 h for atropisomer 1 and 6.2 h for atropisomer 2. The urinary atropisomer 1/atropisomer 2 ratio was 0.648 for the amount excreted unchanged from 0 to 24 hours (Ae_{0-24}) and 0.836 for renal clearance from 0 to 24 hours (CL_{R0-24}). No atropisomer ratios are warranted for faeces since the majority of the radioactivity is excreted via urine and not faeces.

Atropisomer 1 is *in vitro* extensively metabolised by CYP2C9 to M3 and M3c. M3c is further metabolised to M4 by microsomal epoxide hydrolase. Atropisomer 2 is metabolised to M6 by CYP3A4, but to a more limited extent. The in vitro metabolism studies are consistent with the observed in vivo plasma concentrations of atropisomer 1 and 2 and the shorter t½ observed for atropisomer 1 compared to atropisomer 2.

All metabolites observed in vivo in humans were identified in the non-clinical toxicology species, although the relative contributions to the metabolic profile were different between species. Major metabolites detected in animals were M3 and M5 (rat) and M6 (monkey), and the predominant metabolites detected in humans were M3 and M4.

Median Tmax of the lesinurad metabolite M4 was observed at 2.25 hours post-dose in plasma, compared to 0.5 hours for lesinurad. The mean half-life of M4 was 5.73 hours. The mean M4-to-radioactivity and M4-to-lesinurad ratios of Cmax and AUCinf were less than 4%.

A mean total of 27.7% of the lesinurad dose was excreted unchanged in urine, which is around 44% of the total radioactivity recovered in the urine. The renal clearance of lesinurad was 25 mL/min (1.5 L/hr).

Based on metabolic profiling using pooled 0-24 hour urine, 24.8% of the radioactivity recovered in the urine was attributable to the M4 metabolite, and 18.9% to M3, equivalent to 15.7% and 12.0% of the dose respectively. The clearance of M4 ranged from 280 mL/min to 370 mL/min.

In urine, lesinurad was the major excreted component. The 2 most abundant metabolites, M3 and M4, both oxidative metabolites, accounted for a further 27.7% of the dose. In faeces, the majority of the radioactivity was attributed to metabolites.

Transporters

From *in vitro* studies lesinurad was found to be a substrate of OATP1B1, OCT1, OAT1 and OAT3. Further limited increased uptake could be detected *in vitro* in BCRP and OATP1B3 expressing cells (<30% increase). Lesinurad was not a substrate of P-glycoprotein, MRP2, MRP4 and OCT2.

Consequences of possible genetic polymorphism

The applicant submitted a cross-study analysis of the effect of CYP2C9 polymorphism on lesinurad pharmacokinetics in humans. This was based on data from studies 109 (relative BA study), 110 (DDI study of allopurinol and colchicine), 111 (DDI study of febuxostat and colchicine), 202 and 203 (dose finding). CYP2C9 genotype information was collected in 8 healthy subjects and 110 gout patients.

The effect of CYP2C9 polymorphism on lesinurad PK was evaluated by calculating differences in PK parameters between *1/*1 subjects and other CYP2C9 polymorphisms (**Table 12**).

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Table 12. Frequency of CYP2C9 Genotypes in 118 Subjects from five lesinurad clinical studies

Population[a]	CYP2C9 Genotype; Frequency (%) (n[b])						
	*1/*1	*1/*2	*2/*2	*1/*3	*2/*3	*3/*3	Total
All subjects (n=118)	72.9% (86)	10.2% (12)	2.54% (3)	10.2% (12)	2.54% (3)	1.69% (2)	100%

Of the 118 subjects genotyped, 67 subjects provided PK data (**Table 13**).

Table 13. Percent Differences (%) in Geometric Mean Lesinurad Pharmacokinetic Parameters at Various Lesinurad Dose Levels

Lesinurad dose (mg)	n; PK parameter	CYP2C9 Genotype; Difference in PK Parameter Compared to *1/*1 Metabolizers (%)				
		*1/*1	*1/*2	*2/*2	*1/*3	*3/*3
200	n	12	0	0	1	0
	AUC_{0-24}	NA	NA	NA	68.9↑	NA
	C_{max}	NA	NA	NA	11.3 ↓	NA
	Ae_{0-24}	NA	NA	NA	83.[illegible]	NA
400	n	55	6	1	7	1
	AUC_{0-24}	NA	3.55 ↑	81.2 ↑	22.1 ↑	111 ↑
	C_{max}	NA	10.0 ↓	24.5 ↓	2.97 ↑	75.2 ↑
	Ae_{0-24}	NA	6.21 ↑	68.8	65.2 ↑	271 ↑
600	n	39	3	3	0	1
	AUC_{0-24}	NA	3.40 ↓	57.8 ↑	NA	79.1 ↑
	C_{max}	NA	18.9 ↓	33.2 ↓	NA	70.0 ↑
	Ae_{0-24}	NA	30.2	41.1 ↓	NA	124 ↑

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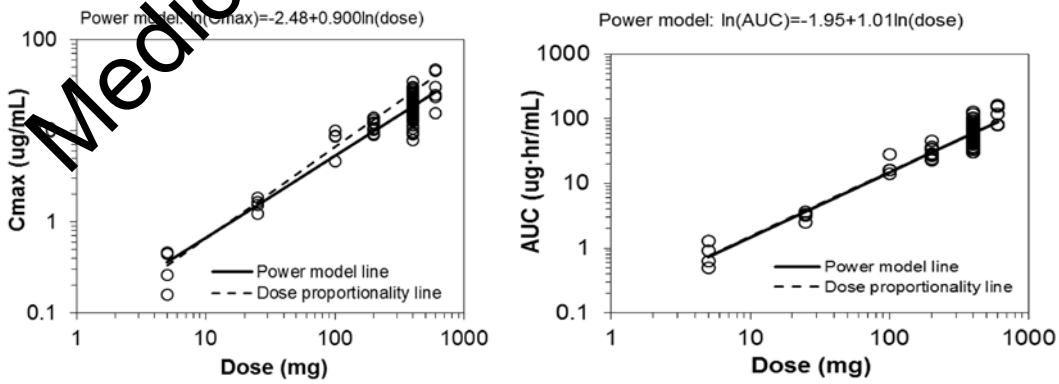
Dose proportionality and time dependencies

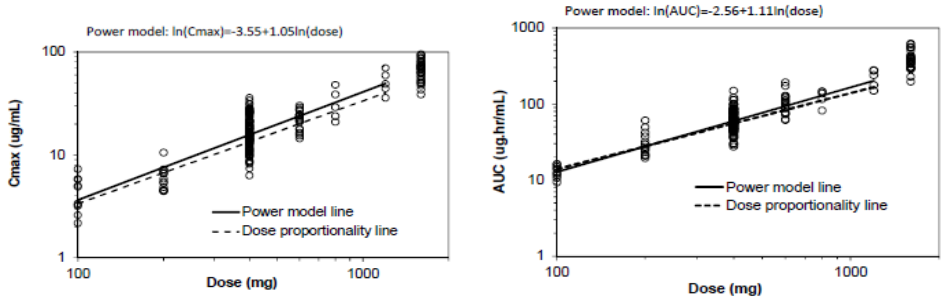
The dose proportionality of lesinurad under the fasted (5 to 600 mg) and fed (100 to 1600 mg) conditions under fasted conditions was assessed separately in pooled PK parameters from healthy volunteers receiving lesinurad alone. Proportionality analysis was performed using the power model (Peng 2004). Data were pooled from studies involving lesinurad solutions, sodium salt and free acid capsules and tablets for the dose-proportionality assessment. Results from the pooled PK parameters confirmed that both Cmax and AUC values for lesinurad increased proportionally between 5 mg to 600 mg under fasted conditions (**Figure 7**).

Figure 7. Dose proportionality: lesinurad C_{max} (A) and AUC (B) versus dose under fasted conditions (5 mg to 600 mg)



Under fed conditions, Cmax increased proportionally with dose (**Figure 8**). The AUC increased slightly greater than proportional (slope 1.23; 95% CI: 1.17 to 1.29).

Figure 8. Dose proportionality: lesinurad C_{max} (A) and AUC (B) versus dose under fed conditions (100 mg to 1200 mg)



Time dependency

Multiple-dose PK of lesinurad was studied in:

- healthy male volunteers following once daily dosing of lesinurad immediate-release (IR) capsules for 10 days under fasted and fed conditions (study 102);
- following once daily dosing of lesinurad IR capsule for 7 days under fed conditions (study 106);
- following once daily dosing of lesinurad FA IR tablets for 7 days under fed conditions (study Days 6 to 12) in healthy Japanese male volunteers (study 125).

The pharmacokinetics were predictable and no unexpected accumulation of lesinurad following once daily sing with 50 mg, 100 mg, 200 mg, or 400 mg was observed, both under fasted and fed conditions.

Pharmacokinetics in target population

Lesinurad PK was assessed in subjects with gout by means of rich PK sampling after multiple dosing in study 110 (allopurinol DDI study) and study 203 (dose finding study). The PK substudy of study 203 included 54 subjects. On day 13 of dosing, plasma PK samples were collected at predose and 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 6.0, 8.0 and 24.0 hours postdose. PK parameters at steady state were compared with those from healthy adult subjects derived from Study 105 (febuxostat DDI study).

Table 14. Summary (Geometric Mean, 95% CI) of Lesinurad Pharmacokinetic Parameters Following Once Daily Multiple Oral Doses of Lesinurad Immediate-Release Capsules in Subjects With Gout or Normal Healthy Subjects

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

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

[a] Presented as median (range).

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

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

In Study 202 (dose-finding study), 3 patients on 600 mg qd were enrolled in a PK sub-study and provided additional serial post-dose blood samples (1, 2, 4 and 8 hours). Concentrations of plasma lesinurad and its metabolites (M4 and M6) were measured. Molar ratios of metabolites (M4 and M6) to lesinurad in blood were low, with median molar ratios for Cmax and AUC less than 4% for M4 and less than 0.3% for M6.

Population PK analysis

A population PK analysis was conducted using lesinurad plasma concentrations from studies 118 (hepatic impairment), 120 (moderate and severe renal impairment), 121 (food effect study), 122, 126 and 127 (DDI study), 301 302, 303 and 304 (Phase 3). The selected Phase 1 studies used the Phase 3 formulation (lesinurad free acid tablet).

A total of 9936 plasma concentrations of lesinurad from 1109 individuals (11% of the subjects were in Phase 1 and 89% in Phase 3) was included in the population PK analysis. Concentration data comprised rich single-dose profiles (3949 samples) from 120 individuals without gout (healthy subjects and subjects with renal or hepatic impairment) from six Phase 1 studies, as well as sparsely collected 5987 plasma samples from 989 out of 1128 (approximately 88%) subjects with gout who received lesinurad in four Phase 3 studies.

Individuals in the population PK data set had a mean age of 51 years (range: 18 to 81 years; 88% was <65 years of age), mean body weight of 104 kg (range: 47 to 239 kg), a mean BMI of 33.1 (range: 14-84), and mean creatinine Clearance of 88 mL/min (range: 17 to 191 mL/min). The majority of individuals were male (95.4%).

The population PK model of lesinurad consisted of a 2-compartment model with first-order absorption rate and lag time for absorption. Based on an exploratory analysis, age, sex, weight, creatinine clearance, markers of liver function (AST and ALT) and baseline sUA were selected for the formal covariate analysis.

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Table 15. Population PK Parameters from lesinurad - Phase 1 and 3 Studies

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

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

Typical CL/F value in Phase 3 subjects was approximately 18% lower than that observed in subjects without gout, assuming the same CrCl levels.

Based on the model, the typical CL/F of lesinurad in subjects in Phase 3 studies with normal renal function (CrCl=105 mL/min), as well as mild (CrCl=75 mL/min), moderate (CrCl=45 mL/min) and severe renal impairment (CrCl= 22 mL/min) would be 6.09, 5.46, 4.64, and 3.68 L/h, respectively. Based on these decreases in CL/F, the estimated increases in lesinurad exposure would be approximately 12%, 31% and 65% in patients with mild, moderate, and severe renal impairment, respectively, compared with patients with normal renal function.

The most important covariate describing the variability was the effect of weight on Vc/F of lesinurad. This would range from 19.6 to 45.1 L based on the body weight range in Phase 3 (46.7 to 239 kg). Age, sex, and race/ethnicity were not found to be statistically significant covariates affecting PK parameters of lesinurad.

Special populations

Impaired renal function

Two studies were conducted in otherwise healthy subjects with renal-impaired (studies 104 and 120). In addition, one study was performed in renal-impaired gout patients (studies 203 main).

In study 104, the pharmacokinetics of lesinurad were evaluated following a single oral dose of 200 mg (2 x 100 mg capsule) in adult volunteers with normal, mild, moderate or severe renal impairment. In study 120, the pharmacokinetics of lesinurad were evaluated following a single oral dose of 400 mg (one FA tablet) in adult volunteers with normal, mild, moderate or severe renal impairment.

In both studies, lesinurad exposure was found to increase with the level of renal impairment (**Table 16**).

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Table 16. Summary plasma pharmacokinetics of lesinurad following a single oral dose to subjects with various degrees of renal function

	C_{max} (µg/mL)	$AUC_{0-\infty}$ (µg×h/mL)	$t_{½}$ (h)	CL/F (L/h)
Study 104 (200 mg)				
normal (n=5)	8.55 (CV=29.6%)	32.6 (CV=36.9%)	10.0 (CV=49.7%)	7.0 (CV=43.3%)
mild (n=10)	10.9 (CV=24.9%)	41.6 (CV=22.0%)	31.6 (CV=71.2%)	5.02 (CV=22.1%)
moderate (n=7)	10.8 (39.4%)	68.8 (CV=37.1%)	16.4 (47.9%)	3.4 (CV=48.2%)
severe (n=2)	9.2 (8.8-9.5)	34.2 (32.5-36.0)	33.8 (27.2-40.3)	5.96 (5.56-6.15)
Study 120 (400 mg)				
normal (n=6)	17.0 (CV=15.5%)	58.2 (CV=31.8%)	28.9 (CV=96.9%)	7.43 (CV=28.6%)
mild (n=2)	12.4 (9.7-15.1)	84.8 (65.3-104)	6.5 (6.3-6.6)	4.98 (3.84-6.13)
moderate (n=5)	18.3 (CV=34.8%)	81.0 (CV=24.9%)	21.9 (CV=54.2%)	5.21 (CV=26.8%)
severe (n=5)	17.0 (CV=29.6%)	132 (CV=36.0%)	16.7 (CV=36.7%)	3.44 (CV=41.5%)

In the Phase 2 study 203 main, lesinurad was administered once daily with a dose of 200 mg, 400 mg or 600 mg (all started with 200 mg and increased if relevant every 7 days with 200 mg to the final dose) to gout patients with normal, mild and moderate renal function. Trough plasma concentrations were determined at Day 7, 13, 14, 21 and 28 were variable and the range of values showed much overlap between dose levels and renal function categories (data not shown).

The full PK analysis was performed on Day 13 and the study results are summarised in **Table 17**.

Table 17. Summary plasma pharmacokinetics of lesinurad following a single oral dose to subjects with various degrees of renal function (study 203 main)

	T_{max}	C_{max} (µg/mL)	$AUC_{0-\infty}$ (µg×h/mL)	$t_{½}$ (h)
200 mg				
normal	4.0 (2.5-6.0)	3.59 (2.63-8.65)	21.2 (18.9-40.4)	3.9 (3.2-4.1)
mild	3.5 (3.0-6.0)	5.34 (2.89-7.18)	37.6 (21.9-42.9)	3.4 (3.4-3.9)
moderate	3.0	7.70	55.3	4.42
400 mg				

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normal	2.5 (0.0-4.0)	8.88 (0.13-20.2)	54.4 (0.39-72.9)	3.7 (3.1-25.2)
mild	2.0 (1.0-6.0)	16.3 (8.2-25.6)	78.7 (40.9-212)	3.4 (2.6-4.0)

Impaired hepatic function

The effect of hepatic impairment on the metabolism of lesinurad was explored in subjects with mild and moderate impairment following a 400 mg dose of lesinurad in study 118. The results are shown in **Table 18**.

Table 18. Summary of plasma pharmacokinetics of lesinurad following a single oral dose of lesinurad 400 mg to subjects with various degrees of hepatic function (study 118)

	C_{max} (µg/mL)	$AUC_{0-\infty}$ (µg×h/mL)	$t_{½}$ (h)	CL/F (L/h)
normal (n=8)	18.4 (16.0-21.2)	62.0 (54.5-70.5)	11.3 (7.6-16.9)	6.45 (5.67-7.34)
mild (n=8)	20.4 (16.1-25.8)	66.5 (48.9-90.3)	20.3 (11.3-36.3)	6.02 (4.43-8.18)
moderate (n=8)	19.9 (13.2-29.9)	82.6 (52.6-130)	15.0 (9.9-22.9)	4.84 (3.08-7.60)

Elderly

All clinical studies used in the population PK analysis and their subject categorisation according to age groups of 65 to 74, 75 to 84, and > 85 years are presented in **Table 19**.

Table 19. Age group breakdown in studies used in the population PK analyses

PK Studies	Age Group 65 to 74 Years (Number of Older Subjects / Total Number of Subjects)	Age Group 75 to 84 Years (Number of Older Subjects / Total Number of Subjects)	Age Group 85+ Years (Number of Older Subjects / Total Number of Subjects)
Study 301	0/363	6/363	0/363
Study 302	30/365	7/365	0/365
Study 303	14/93	5/93	0/93
Study 304	24/193	6/193	0/193
Study 118	0/24	0/24	0/24
Study 120	2/18	0/18	0/18
Study 121	0/16	0/16	0/16
Study 122	0/27	0/27	0/27
Study 126	0/21	0/21	0/21
Study 127	0/16	0/16	0/16
Total	116/1136	24/1136	0/1136

The mean observed lesinurad concentrations as well as average model-predicted lesinurad concentrations (Caverage, determined as AUC / 24 hours) across treatments in the Phase 3 studies were plotted against the 3 age groups (i.e., < 65, 65 to 75, and 75 to 85 years) and are shown in **Figure 9** and **Figure 10**, respectively.

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Figure 9. Box plot of mean observed lesinurad concentration in Phase 3 studies by age groups of < 65, 65 to 75, and 75 to 85 years in the 200 mg (Left) and 400 mg (Right) dose groups

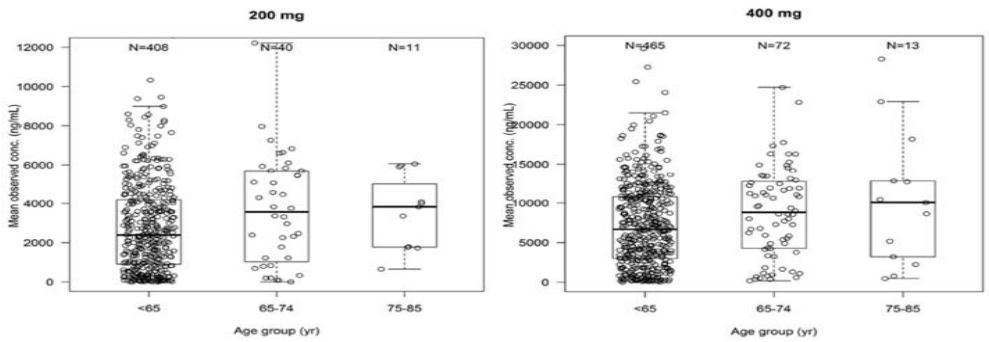
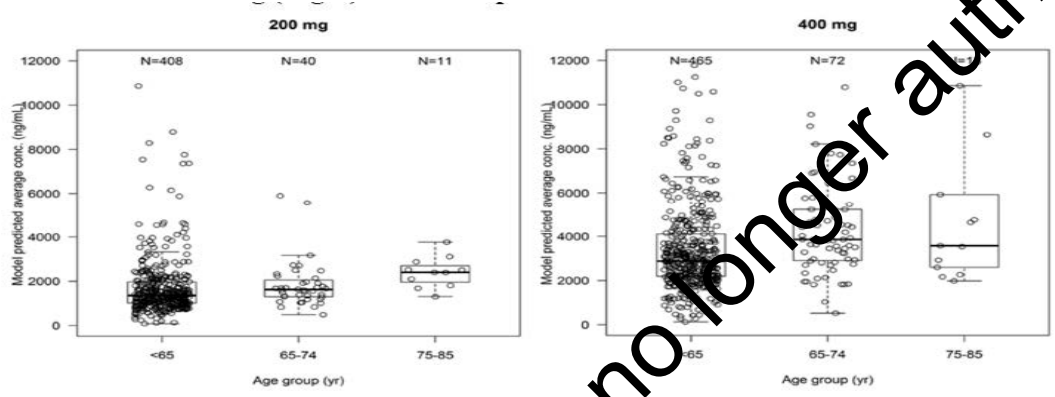


Figure 10. Box plot of average model-predicted lesinurad concentration in Phase 3 studies by age groups of < 65, 65 to 75, and 75 to 85 years in the 200 mg (Left) and 400 mg (Right) dose groups



Pharmacokinetic interaction studies

Effect of other drugs on lesinurad pharmacokinetics

The applicant submitted a number of drug-drug-interaction (DDI) studies to investigate the potential of other drugs to alter the PK of lesinurad. These drugs included other gout therapies, drugs that induce or inhibit CYP2C9, and acid-lowering therapies. The effect of other drugs on lesinurad PK is summarised in **Table 20** and **Figure 11**.

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Table 20. Effects of Co-administered Drugs on Systemic Exposure of Lesinurad

Coadministered Drug	Dose of Coadministered Drug[a]	Dose of Lesinurad[a]	Geometric Mean Ratio (90% CI)[b]	
			AUC	C_{max}
Gout treatments				
Febuxostat (Study 105)	40 mg qd x 7 d	200 mg qd x 7 d 400 mg qd x 7 d	98.3 (95.6-101)[c] 105 (99.2-111)[c]	95.9 (88.1-104) 102 (90.6-115)
Allopurinol (Study 110)	300 mg qd x 7 d	400 mg qd x 7 d 600 mg qd x 7 d	107 (95.9-119)[c] 106 (98.2-115)[c]	117 (105-131) 104 (89.9-120)
Naproxen (Study 126)	250 mg bid x 6d	400 mg	85.5 (79.7-91.8)[c]	72.9 (57.6-92.2)
Indomethacin (Study 126)	25 mg bid x 6d	400 mg	110 (103-119)[c]	118 (103-136)
Antacids				
Calcium carbonate, fasting (Study 121)	3000 mg	400 mg	61.8 (53.5-71.3)[d]	46.0 (39.7-53.2)
Calcium carbonate, fed (Study 130)	1250 mg	400 mg	89.1 (83.9-94.5)[d]	89.9 (77.6-104)
$Al(OH)_3/Mg(OH)_2$, fasting (Study 121)	1600 mg/1600 mg	400 mg	69.4 (66.1-72.9)	63.6 (56.4-71.7)
$Al(OH)_3/Mg(OH)_2$, fed (Study 130)	800 mg/800 mg	400 mg	90.6 (81.8-100)[d]	84.9 (68.0-106)
Ranitidine (Study 127)	150 mg bid x 2.5d	400 mg	109 (103-116)[d]	120 (101-143)
CYP2C9 Modulators				
Fluconazole (inhibitor) (Study 122)	400 mg qd x 1d, then 200 mg qd x 2d	400 mg	156 (141-173)[d]	138 (120-158)
Rifampin (inducer) (Study 122)	600 mg qd x 14d	400 mg	62.4 (57.8-67.2)[d]	76.1 (69.6-83.3)

Abbreviations: AUC, area under the concentration-time curve; bid, twice daily; CI, confidence interval; C_{max}, maximum observed concentration; d, day; qd, once daily.

[a] Single dose unless otherwise noted.

[b] Ratio with/without coadministered drug.

[c] AUC_{0-24} presented.

[d] AUC_{∞} presented.

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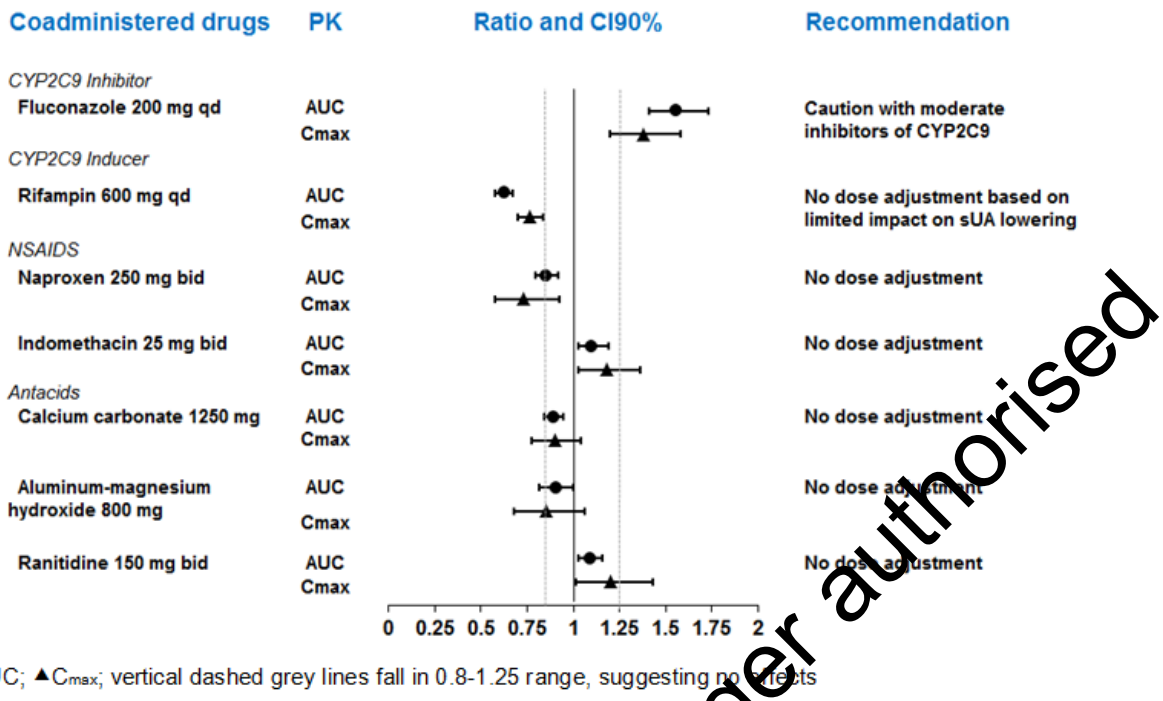
Figure 11. Effect of Co-Administered Drugs on Pharmacokinetics of lesinurad



● AUC; ▲C_{max}; vertical dashed grey lines fall in 0.8-1.25 range, suggesting no effects

Effect of lesinurad on the Pharmacokinetics of Co-Administered Drugs

Based on *in-vitro* results, the predicted induction potential of lesinurad follows the rank order of CYP3A > CYP2C8 > CYP2C9 > CYP2C19 > CYP2B6. The applicant investigated the *in vivo* induction potential using probes for activity of CYP3A4, CYP2C8 and CYP2C9.

In vitro, lesinurad exhibited inhibitory potential on CYP enzymes (CYP3A, CYP2C8, CYP2C9, CYP2C19, and CYP2B6) and OATP1B1, OATP1B3, OAT1, and OAT3 transporters. Although mEH is involved in the biotransformation of lesinurad, lesinurad exerted no inhibitory effect on mEH activity *in vitro*.

Potential interactions with drugs frequently used in the gout population were also investigated. The effect of lesinurad on the PK of CYP and transporter substrates is summarised in **Table 21**.

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Table 21. Effect of lesinurad on systemic exposures of co-administered CYP and transporter substrates

Co-Administered Drug	Dose of Co-Administered Drug	Dose of Lesinurad	Analyte	Geometric Mean Ratio[a] (90% CI)	
				AUC	C_{max}
CYP3A					
Sildenafil (Study 108)	50 mg single dose	200 mg qd x 9d[b] 400 mg qd x 9d[b]	Sildenafil Sildenafil	66.4 (55.9-78.8) 49.6 (34.2-72.0)	66.1 (45.3-96.5) 65.5 (39.7-108)
		400 mg qd x 10d[c]	Sildenafil	38.6 (30.8-48.3)	42.2 (31.0-57.3)
		600 mg qd x 10d[c]	Sildenafil	27.4 (21.2-35.5)	35.7 (26.2-48.7)
Atorvastatin (Study 113)	40 mg single dose	200 mg single dose	Atorvastatin total atorva[d]	96.2 (89.8-103) 107 (98.0-117)	91.9 (80.3-105) 101 (87.9-116)
		200 mg qd x 11d	Atorvastatin total atorva[d]	84.2 (74.2-95.6) 92.2 (82.9-103)	114 (92.6-141) 115 (91.7-144)
		400 mg single dose	Atorvastatin total atorva[d]	101 (91.3-111) 108 (100-118)	117 (94.0-146) 126 (105-150)
		400 mg qd x 11d	Atorvastatin total atorva[d]	72.7 (64.9-81.5) 86.1 (77.3-95.8)	99.5 (80.4-123) 117 (98.0-139)
Amlodipine (Study 114)	5 mg qd x 28d	400 mg qd x 14d	Amlodipine	57.5 (52.1-63.1)	60.4 (55.3-66.0)
CYP2C9					
Tolbutamide (Study 115)	500 mg single dose	400 mg single dose	Tolbutamide OH-tolbutamide	111 (107-115) 114 (111-118)	107 (104-110) 140 (129-151)
		400 mg qd x 13d	Tolbutamide OH-tolbutamide	106 (102-111) 111 (106-116)	102 (95.8-108) 124 (115-134)
Warfarin (Study 123)	25 mg single dose	400 mg qd x 21d	*S*-warfarin *R*-warfarin[e]	104 (99.6-109) 81.2 (77.3-85.3)	102 (97.0-108) 99.6 (94.5-105)
CYP2C8					
Repaglinide (Study 116)	0.5 mg single dose	400 mg single dose	Repaglinide	131 (124-139)	127 (108-148)
		400 mg qd x 12d	Repaglinide	111 (103-120)	101 (91.4-111)
OCT1					
Metformin (Study 128)	850 mg single dose	400 mg single dose	Metformin	103 (91.1-115)	106 (100-113)
OAT1/3					
Furosemide (Study 128)	40 mg single dose	400 mg single dose	Furosemide	69.3 (56.7-84.7)	48.9 (38.7-61.8)

Abbreviations: atorva, atorvastatin; AUC, area under the concentration-time curve; CI, confidence interval; C_{max}, maximum observed concentration; CYP, cytochrome P450; OAT, organic anion transporter; OCT, organic cation transporter; qd, once daily.

[a] Ratio with/without coadministered lesinurad.

[b] Sildenafil dose was administered in the morning together with lesinurad and allopurinol (300 mg).

[c] Sildenafil dose administered in the afternoon following morning dosing of lesinurad.

[d] Sum of atorvastatin and its 2 OH and 4-OH metabolites.

[e] *R*-warfarin metabolized by multiple enzymes including CYP3A4.

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The effect of lesinurad on the pharmacokinetics of other gout drugs was also investigated (**Table 22**).

Table 22. Effect of lesinurad on systemic exposures of co-administered gout drugs

Co-Administered Drug	Dose of Co-Administered Drug	Dose of Lesinurad	Analyte	Geometric Mean Ratio (90% CI)[a]	
				AUC	C_{max}
Febuxostat (Study 105)	40 mg qd x 7d	200 mg qd x 7d	Febuxostat	112 (109-115)	108 (94.9-122)
	40 mg qd x 7d	400 mg qd x 7d	Febuxostat	131 (124-139)	127 (104-155)
Febuxostat (Study 111)	40 mg qd x 7d	400 mg qd x 7d	Febuxostat	108 (98.9-117)	109 (83.2-143)
	40 mg qd x 7d	600 mg qd x 7d	Febuxostat	120 (109-132)	129 (109-154)
	80 mg qd x 7d	400 mg qd x 7d	Febuxostat	119 (112-126)	113 (104-123)
	80 mg qd x 7d	600 mg qd x 7d	Febuxostat	121 (107-137)	118 (93.4-148)
Allopurinol (Study 110)	300 mg qd x 7d	400 mg qd x 7d	Allopurinol Oxypurinol	90.5 (82.6-99.2) 74.2 (65.1-84.7)	78.8 (61.0-102) 79.4 (68.[illegible]3)
	300 mg qd x 7d	600 mg qd x 7d	Allopurinol Oxypurinol	93.7 (83.8-105) 64.7 (61.3-68.3)	[illegible] (82.9-121) [illegible] (67.8-75.7)
Colchicine (Study 110)	0.6 mg qd x 7d	400 mg qd x 7d	Colchicine	74.8 (67.4-83.0)	[illegible].3 (73.0-92.7)
	0.6 mg qd x 7d	600 mg qd x 7d	Colchicine	67.0 (57.5-78.[illegible])	75.6 (63.9-89.5)
Colchicine (Study 111)	0.6 mg qd x 7d	400 mg qd x 7d[b]	Colchicine	78.3 ([illegible]-86.3)	88.6 (78.2-100)
	0.6 mg qd x 7d	600 mg qd x 7d[b]	Colchicine	[illegible]-70.7)	80.4 (69.5-93.0)
	0.6 mg qd x 7d	400 mg qd x 7d[c]	Colchicine	[illegible]4.9-99.2)	91.3 (78.0-107)
	0.6 mg qd x 7d	600 mg qd x 7d[c]	Colchicine	73.0 (58.7-90.7)	84.5 (67.3-106)
Naproxen (Study 126)	250 mg bid x 6d	400 mg	Naproxen	108 (107-109)	104 (99.4-109)
	250 mg bid x 13d	400 mg qd x 8d	Naproxen	101 (98.5-104)	102 (98.5-105)
Indomethacin (Study 126)	25 mg bid x 6d	400 mg	Indomethacin	135 (127-144)	118 (97.7-142)
	25 mg bid x 13d	400 mg qd x 8d	Indomethacin	131 (122-141)	120 (103-140)

Abbreviations: AUC, area under the concentration-time curve; bid, twice daily; CI, confidence interval; C_{max}, maximum observed concentration; d, day; qd, once daily.

[a] Ratio with/without coadministered lesinurad

[b] Coadministered with febuxostat 40 mg

[c] Coadministered with febuxostat 80 mg

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2.4.3. Pharmacodynamics

Pharmacodynamic action of lesinurad was evaluated by measuring the change of sUA levels from baseline, in healthy volunteers, gout patients and renally impaired patients in gout and non-gout patients.

PD interaction-studies with XO-inhibitors were also submitted: Furthermore, a QT study was performed in healthy volunteers using super-therapeutic doses (Study 117).

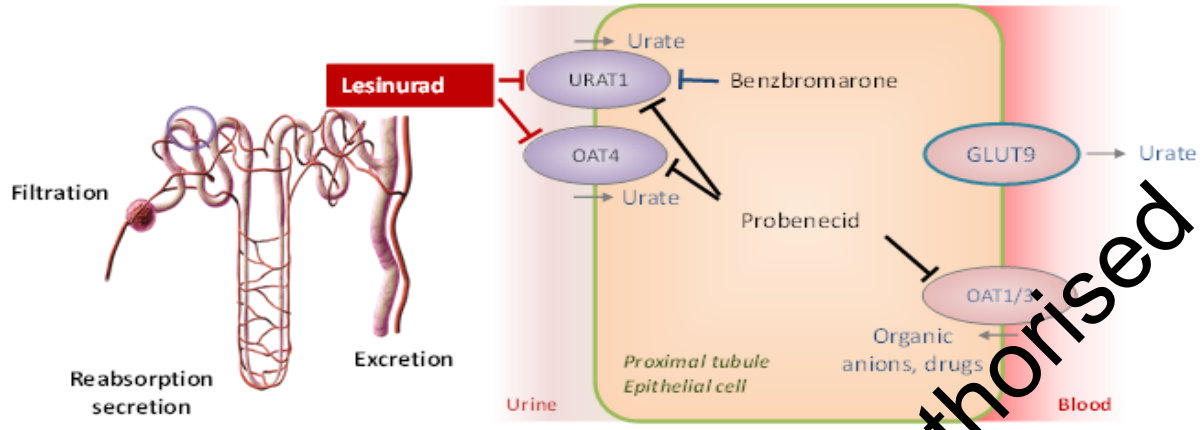
Mechanism of action

Lesinurad was tested in multiple human transporter assays involved in uric acid regulation including URAT1, OATs, and other transporters and enzymes. Lesinurad showed inhibitory activity on both URAT1 and OAT4 (IC50 = 7.3 µM and 3.7 µM, respectively).

URAT1 is considered to be responsible for the majority of the reabsorption of filtered uric acid from the renal tubular lumen. By inhibiting URAT1, lesinurad increases uric acid excretion and thereby lowers sUA. Lesinurad also inhibits OAT4, a uric acid transporter which is thought to be involved in diuretic-

induced hyperuricemia. The schematic proposed mechanism of action of lesinurad is depicted in **Figure 12.**

Figure 12. Mechanism of Action of Lesinurad



Abbreviations: GLUT9, glucose transporter 9; OAT, organic anion transporter; URAT1, uric acid transporter 1.

Primary and Secondary pharmacology

Heathy volunteers: reduction of serum uric acid from baseline

In Study 102, multiple doses of lesinurad 100/200/400 mg or matched placebo were given for 7-10 days to 32 normal healthy volunteers, with a baseline sUA values > 5 mg/dL. Steady-state of the PD effect was achieved at Day 6. The mean reduction from baseline serum Uric Acid (sUA) was ~30-40% for the 200-400 mg dose (**Table 23**) decreases in sUA concentrations were similar in male and female subjects.

Table 23. Serum reduction from baseline by lesinurad in healthy volunteers

Study drug	Fed/fasted	n	sUA reduction from baseline at tmax (LS mean) $	Difference versus placebo (95% CI)
Study 102 monotherapy , healthy volunteers				
LESU 100 mg	fed	6	-17.6%	(-24.4,-10.5)
LESU 200 mg	fasted	6	-31.3%	(-38.0,-24.1)
LESU 200 mg	fed	6	-40.5%	(-47.3,-33.3)
LESU 400 mg	fasted	6	-32.8%	(-39.6,-25.7)
Study 117 monotherapy , healthy volunteers				
LESU 800 mg	fed	9	-57.2	(-65.2, -49.3)
LESU 1200 mg	fed	10	-63.6	(-68.6, -58.6)
LESU 1600 mg	fed	10	-65.1	(-68.2, -62.0)

$: no standard deviations were reported for the 'mean changes from baseline' outcomes

The observed effects were considerable higher under fed conditions. With the 100 mg dose, the sUA effect after a single dose in the morning was attenuated within 12 hrs, whereas a more sustained effect was shown for the 200-400 mg doses. After cessation of the study drugs on Day 10, mean sUA for all lesinurad-treated groups gradually returned to baseline in about 48 hrs. There was no rebound effect.

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Exploratory PD study in gout patients

The proof of concept of lesinurad was explored in gout patients in Study 201, a 2-weeks study in gout patients, with a randomised, double-blind, placebo- and active-controlled design. In Cohort 1, 21 subjects were randomized in a 2:1:1 ratio to lesinurad 400 mg qd, matching placebo or allopurinol 300 mg qd (open-label). In a second cohort, 7 patients were randomised to combination therapy of lesinurad + allopurinol and allopurinol + placebo (5:1 ratio). All patients received colchicine to protect them against ULT-induced flares. Only gout patients were eligible with obvious hyperuricaemia (sUA > 8 mg/dL), who did not received any ULT in the 3 months before the study.

The effects of lesinurad on uric acid serum levels are presented in **Table 24.**

Table 24. Effect of lesinurad versus allopurinol on serum uric acid (Study201, exploratory trial in gout patients)

Treatment	n	Mean sUA change from baseline (Emax)	sUA< 6 mg/dL (% responder rates)	sUA< 5 mg/dL (% responder rates)
Placebo	5	-4%	0	0
LESU 400 mg	11	-34%	45.5%	9.1%
ALLO 300 mg	5	-45%	100%	40.0%
LESU 400 mg + ALLO 300 mg	6	-54%	100%	66.0.%

** p < 0.05 when compared against the placebo treatment group (Fisher's exact test), a One subject had no post-baseline predose assessment and was excluded. RDEA594=study code of lesinurad*

Table 25. Effect of renal impairment on Emax (maximal change from baseline of sUA levels) in Studies 104 and 120

Study	Lesinurad Dose	Renal Function Group	LS Mean $E_{max, CB}$ (%)	N	Difference of LS Means (95% CI)[a]
120	400 mg	Mild impairment	-28.67	2	-2.14 (-23.04, 18.76)
		Moderate impairment	-18.37	5	8.15 (-9.53, 25.83)
		Severe Impairment	-14.55	5	11.98 (-5.24, 29.19)
		Normal	-26.52	6	NA
104	200 mg	Mild impairment	-21.92	10	2.27 (-6.61, 11.14)
		Moderate impairment	-10.66	7	13.53 (2.15, 24.91)
		Severe Impairment	-9.75	2	14.44 (0.18, 28.69)
		Normal	-24.19	5	NA

Abbreviations: CI, confidence interval; $E_{max, CB}$, maximum observed percentage change from baseline in serum urate concentrations; LS, least squares; N, number of subjects; NA, not applicable

[a] Impaired minus normal

QTc study

A blinded, randomised, placebo-controlled thorough QT study in healthy volunteers, with moxifloxacin as positive control, demonstrated no relevant effect following single doses of lesinurad 400 mg or a supra-therapeutic dose of 1600 mg on QTc intervals or other electrocardiogram (ECG) parameters in 89 healthy volunteers (Study 117). There was no relevant effect on heart rate, atrioventricular conduction or cardiac depolarization as measured by PR and QRS interval durations (data not shown).

Pharmacodynamic interactions with other medicinal products or substances

Xanthine-oxidase inhibitors

Interaction with xanthine-oxidase inhibitors (XOI) allopurinol and febuxostat was evaluated in two open-label 3 weeks cross-over PK-PD interaction studies in gout patients, where combinations of lesinurad 400-600 mg + allopurinol 300 mg or lesunirad 400-600 mg + febuxostat 40-80 mg was

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compared to monotherapy of these products. The results from these studies are summarised in **Table 26.**

Table 26. Summary of XOI-lesinurad PD interaction studies

Study drug	n	sUA reduction from baseline at tmax (LS mean)
Study 110 allopurinol interaction (gout patients)		
LESU 400 mg	10	-25.7%
LESU 600 mg	10	-39.4%
ALLO 300 mg	20	-28.4%
LESU 400 mg + ALLO 300 mg	10	-44.7%
LESU 600 mg + ALLO 300 mg	10	-54.7%
Study 111 febuxostat interaction (gout patients)		
FEBU 40 mg	12	-34.8%
LESU 400 mg + FEBU 40 mg	12	-55.5%
LESU 600 mg + FEBU 40 mg	11	-61.2%
FEBU 80 mg	9	-46.6%
LESU 400 mg + FEBU 80 mg	9	-65.4%
LESU 600 mg + FEBU 80 mg	9	-72.9%

NA=not available, NR=not reported $: no standard deviations were reported for the 'mean changes from baseline' outcomes

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2.4.4. Discussion on clinical pharmacology

Pharmacokinetics

The pharmacokinetics of lesinurad are relatively simple, as absorption occurs in a dose proportional manner and there is no accumulation after repeated dosing. The absolute bioavailability of lesinurad is approximately 100%. Lesinurad is rapidly absorbed after oral administration. Following administration of a single oral dose of lesinurad in either the fed or fasted state, maximum plasma concentrations (Cmax) were attained within 1 to 4 hours. Cmax and AUC exposures of lesinurad increased proportionally with single doses of lesinurad from 5 to 1,200 mg. In the fed state, after a single dose of lesinurad 200 mg, geometric mean lesinurad Cmax and AUC were 6 µg/mL and 29 µg/hr/mL, respectively. There was no apparent influence of the fat content in the meal on the pharmacokinetics of lesinurad. In clinical trials, lesinurad was administered with food, because the serum uric acid lowering was improved under fed conditions.

Lesinurad is a racemic mixture and pharmacokinetic studies of the two atropisomers revealed that atropisomer 1 has a slightly lower plasma exposure than atropisomer 2 due to extensive metabolism of the former by CYP2C9 whereas atropisomer 2 is slightly metabolised by CYP2C9 and CYP3A4.

Age, gender and race did not have an effect on the pharmacokinetics of lesinurad, but weight had an effect on the volume of distribution of lesinurad, but not on the exposure. The pharmacokinetics of lesinurad are similar in gout patients compared to healthy subjects at the clinical dose of 200 mg. Lesinurad is extensively bound to proteins in plasma (greater than 98%), mainly to albumin. Plasma protein binding is not meaningfully altered in patients with renal or hepatic impairment. The mean steady state volume of distribution of lesinurad was approximately 20 L following intravenous dosing. Mean plasma-to-blood ratios of lesinurad AUC and Cmax were approximately 1.8, indicating that radioactivity was largely contained in the plasma space and did not penetrate or partition extensively into red blood cells. Excretion is for ~60% via urine as lesinurad (half of the radioactivity in urine) and metabolites. Around 40% is excreted via faeces and almost completely as metabolite. The metabolite

profile of lesinurad in plasma was determined 3 hours after dose administration which is ~1 hour after Cmax.

Lesinurad is highly protein bound and renal clearance is high (as compared to typical human glomerular filtration rate), indicating that active secretion plays an important role in the renal excretion of lesinurad. Within 7 days following single dosing of radiolabeled lesinurad, 63% of administered radioactive dose was recovered in urine and 32% of administered radioactive dose was recovered in faeces. Most of the radioactivity recovered in urine (>60% of dose) occurred in the first 24 hours. Unchanged lesinurad in urine accounted for approximately 30% of the dose. The elimination half-life (t½) of lesinurad was approximately 5 hours following a single dose. Lesinurad does not accumulate following multiple doses.

Lesinurad undergoes oxidative metabolism mainly via cytochrome P450 (CYP) 2C9 to intermediate metabolite M3c (not detected in vivo) and is subsequently metabolised by mEH to metabolite M4; there is minimal contribution from CYP1A1, CYP2C19, and CYP3A to the metabolism of lesinurad. Metabolites are not known to contribute to the uric acid lowering effects of lesinurad. Lesinurad is mainly metabolised by CYP2C9 and mEH, and to a lesser extent by CYP1A1, CYP2C19 and CYP3A. In vitro, lesinurad is an inhibitor of CYP2C8, but not of CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP3A4 and mEH. In addition, lesinurad is an in vitro inducer of CYP2B6 and CYP3A via CAR/PXR. In vivo, lesinurad is neither an inhibitor nor an inducer of CYP2C9 and 2C8, but a mild to moderate inducer of CYP3A. CYP2B6 has not been studied in vivo.

Lesinurad is a substrate of OATP1B1, OAT1, OAT3 and OCT1. In vitro, lesinurad is an inhibitor of OATP1B1, OAT1, OAT3, OAT4 and OCT1 at clinically relevant plasma concentrations. However, the in vivo activity of OATP1B1, OAT1, OAT3 and OCT1 was not affected by lesinurad

Only one strength (200 mg) was developed which limits the possibility of dose adjustments in special populations. Lesinurad exposure is significantly increased in subjects with moderate and severe renal impairment, but not in subjects with mild renal impairment. As will be discussed later in the Clinical Efficacy and Safety sections, efficacy and renal safety in subjects with mild-moderate renal impairment at baseline was not different from subjects with normal renal function. Therefore, no dosing adjustment is required in subjects with mild to moderate renal impairment. However, a contra-indication has been made for patients with severe renal impairment, as lesinurad may be less effective in this group, as it has to be excreted in the urine to establish a PD effect on the URAT-1 receptors.

No studies were performed in subject with severe hepatic impairment. Therefore, no dose recommendation could be made for this special population. However, use of lesinurad in patients with severe hepatic impairment is included in the RMP as missing information in order to collect further data in this sub-population of patients through signal detection and review of this topic in aggregate safety reports.

The effect of CYP2C9 genotype on the pharmacokinetics of lesinurad was studied in 8 healthy subjects and 55 patients with gout following daily dosing of lesinurad ranging from 200 mg to 600 mg in the absence or presence of a xanthine oxidase inhibitor. At the 400 mg dose, when compared with extensive CYP2C9 metabolisers (CYP2C9 *1/*1) increased lesinurad exposures were observed in intermediate CYP2C9 metabolisers (CYP2C9 *1/*3,) and in poor CYP2C9 metabolisers (CYP2C9 *3/*3), accompanied with higher lesinurad renal excretion. However, individual values were well within the range observed in the extensive metaboliser subjects. Therefore the CHMP recommended that patients who are known or suspected to be CYP2C9 poor metabolisers based on previous history or experience with other CYP2C9 substrates should use lesinurad with caution.

The population pharmacokinetic analysis of clinical data in gout patients treated for up to 12 months estimated increases in lesinurad exposure of approximately 12%, 31% and 65% in patients with mild,

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moderate, and severe renal impairment, respectively, compared with patients with normal renal function.

Following administration of a single dose of Zurampic to individuals with renal impairment compared to those with normal renal function lesinurad Cmax and AUC, respectively, were 36% and 30% higher (200 mg) in patients with mild renal impairment (eCrCL 60 to 89 mL/min), 20% and 73% higher (200 mg) and 3% and 50% higher (400 mg) in patients with moderate renal impairment (eCrCL 30 to 59 mL/min), and 13% higher and 113% higher (400 mg) in patients with severe renal impairment (eCrCL <30 mL/min).

Pharmacokinetic drug interactions demonstrated that lesinurad is an *in vitro* inducer of CYP3A4. The clinical data also indicate that it is a mild to moderate inducer of CYP3A. Lesinurad is also an *in vitro* inducer of CYP2B6, but no relevant in vivo DDI studies were performed. Therefore, it is recommended in the SmPC that patients are monitored for reduced efficacy of CYP2B6 substrates (such as bupropion, efavirenz) when co-administered with lesinurad.

In addition, no *in vitro* studies were performed to exclude that lesinurad acts as an inhibitor of the transporter BSEP (inhibition can be involved in clinically relevant *in vivo* drug interactions excreted via BSEP). The CHMP therefore requested that the Applicant further investigates the potential of lesinurad to inhibit BSEP and this missing information and details of the corresponding study is included in the RMP.

Pharmacodynamics

The proof of concept of lesinurad has been adequately demonstrated. Lesinurad doses of 400-600 mg qd showed a similar rate of sUA reduction from baseline as allopurinol 300 mg or a low dose of febuxostat 40 mg, in gout patients.

The data indicate that the combination with allopurinol or febuxostat at therapeutic doses, significantly reduced systemic and urinary uric acid load. This dual mechanism may thus improve clinical response and safety of lesinurad. No data are available of lower doses of allopurinol background treatment than 300 mg. Therefore, the CHMP recommended that patients are treated with a minimum allopurinol dose of 300 mg as stipulated in Section 4.2 of the SmPC.

Although the plasma levels of lesinurad increase significantly at renal impairment, because lesinurad is cleared by the renal pathway, the overall capacity to excrete UA and the effect of lesinurad was reduced in patients with moderate-severe renal impairment. The impact of mild-moderate renal impairment at chronic use has been further studied in the clinical trial program of lesinurad and described in detail in Section 2.5 of this report.

2.4.5. Conclusions on clinical pharmacology

The pharmacokinetics of lesinurad were thoroughly investigated. However, as detailed in the non-clinical section, additional information regarding metabolite profiling but also on the potential inhibitory effect of lesinurad on the transporter BSEP will be further investigated with two studies which are included in the RMP.

The pharmacodynamic effect of lesinurad in lowering serum uric acid has been convincingly demonstrated. The combination with a XOI is considered as a useful addition to the currently available treatment options in this area. The effect of renal impairment on PK-PD was explored in single dose studies. From these studies it is difficult to tell what would be the net clinical effect at multiple doses. However, based on the main clinical trial data (presented and discussed in Section 2.5 of this report) in subjects with a mild-moderate renal impairment at baseline but also the PK-PD modelling results

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submitted, the CHMP concluded that no dose adjustments of the standard 200 mg dose are required for mild-moderate renal impaired patients.

For patients with severe renal impairment, it is anticipated that lesinurad will be poorly excreted in the renal tubule where it should act, and the aimed PD effects of stimulated UA excretion will be low. The CHMP therefore considered that a contra-indication is required for this vulnerable group and this has been included in the SmPC.

2.5. Clinical efficacy

The main clinical studies submitted in support of this application are summarised in **Table 27**.

Table 27. Overview Main Efficacy and Safety trials

Study ID	Design	Region (total number of sites)	Study Posology	Subjects by arm entered / completed	Study objective	Duration of blind phase	Gender Median Age	Diagnosis Inclusion criteria	Primary Endpoint
COMBINATION STUDIES, add-on to XOI									
Pivotal Confirmatory trials: add-on to allopurinol									
301	Rand, PC, DB, Para 3-arm	US (181)	Placebo LESU 200 mg LESU 400 mg	202/149 202/140 203/141	Superiori-ty	12 M	94% male 52.0 y	insufficient responder to ALLO ≥300 mg #	sUA < 6.0 at Month 6
302	Idem 301	US, EU, CND,SA AU, NZ (185)	Idem 301	206/154 204/162 200/145	Idem 301	Idem 301	96.2% male 52.0y	Idem 301	Idem 301
Pivotal Confirmatory trial: add-on to febuxostat 80 mg daily									
304	Rand, PC, DB, Para 3-arm	US, EU, SA, AU, NZ (152)	Placebo LESU 200 mg LESU 400 mg	109/83 106/76 109/76	Superior-ity	12 M	95.4% male, 54.0 y	Tophaceous gout	sUA <5 .0 at Month 6
Exploratory trial: add-on to allopurinol									
203	Rand, PC, DB, Para 4-arm	EU,US, CND (38)	Placebo LESU 200 mg LESU 400 mg LESU 600 mg	72/66 46/41 42/40 48/42	Dose-finding	4 W	93-100% males, 48-60 y	Gout, hyperuricaemia > 8 mg/dL	sUA < 6.0 at Month 6
203 ext.	Rand, PC, DB, Para 2-arm	EU,US, CND (38)	Placebo LESU 200-600 mg titration	48/35 78/41	Dose titration	44 W	idem	Ext from study 203	sUA < 6.0
MONOTHERAPY STUDIES (supportive)									
202	Rand, PC, DB, Para 4-arm	EU, CND, US	Placebo LESU 200 mg LESU 400 mg LESU 600 mg	27/23 31/28 33/27 32/30	Exploratory dose finding	4W	97-100% males, 48-54.5 y	Gout, hyperuricaemia > 8 mg/dL	sUA < 6.0 at 4W
303	Rand, PC, DB, Para 2-arm	US, EU, CND, AU, NZ SA (103)	Placebo LESU 400 mg	107/90 107/72	Superior-ity	6M	91.1% males, 53 y	Intolerant to XOI	sUA < 6.0 at M6

AU=Australia, CND=Canada, DB=double blind, ext=extension phase, FEBU: febuxostat, M=months, NZ=New Zealand, SA=South Africa, Para=parallel, PC=placebo-controlled, W=weeks, XOI=xanthine-oxidase inhibitor, y=years, #minimal ALLO dose 200 mg in renal patients.

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Long-term open-label extension studies

Patients from phase II and III studies could continue treatment with lesinurad 200 or 400 mg in the open-label extension phase up to 30 months (**Table 28**). Subjects from the allopurinol combination studies (Studies 301, 302 and 203) who continued treatment in the OL extension phase, were pooled

in Study 306. In Study 307, subjects were included from Study 304, the febuxostat combination study. These studies are still ongoing, and interim safety data are included in the dossier. Study 305, the open-label extension study of the Phase III monotherapy Study 303, was terminated prematurely because of an increased incidence of acute renal complications like nephrolithiasis and serum creatinine elevations. However, use of lesinurad as monotherapy was not claimed by the Applicant but only in combination use with either allopurinol or febuxostat. Data form this study and the other monotherapy studies were submitted only as supportive evidence for the claimed indication.

Table 28. Long-term extension studies for lesinurad

	objective	**Numbers**	**status**
Study 306 OLE Study 301 + 302	Efficacy and safety in combination with ALLO in inadequate responders to ALLO	LESU 200 mg: 361 LESU 400 mg: 353	Ongoing. Interim safety data provided.
Study 307 OLE Study 304	Efficacy and safety in combination with FBX in subjects with tophaceous gout	LESU 200 mg:97 LESU 400 mg: 99	Ongoing. Interim safety data provided.
Study 305 OLE Study 303	Efficacy and safety as monotherapy in subjects with an intolerance or contraindication to a XOI	LESU 400 mg: 143	Terminated prematurely because of renal SAE

OLE=open-label extension, SAE=serious Adverse Events, XOI=xanthine-oxidase inhibitor

2.5.1. Dose response study

Lesinurad 200/400/600mg doses were explored in Study 303, a randomised, placebo-controlled, multicentre study, as add on therapy to allopurinol in gout patients.

This Study consisted of two phases: a 4-weeks core study with sequential cohorts of the 200/400/600 mg lesinurad dosing groups, followed by an extended blinded placebo-controlled phase up to 44 weeks. To enter the extension phase, subjects were re-randomised to either lesinurad 200 mg or placebo –disregarding their dose in the prior study phase-. The lesinurad dose and the placebo equivalent could be individually up-titrated to maximal 600 mg, guided by treatment target sUA level and safety. Once the maximal dose of 600 mg was achieved and the treatment sUA target level was still not achieved, the background allopurinol dose could be up-titrated as rescue medication. Subjects received colchicine for gout flare prophylaxis through Week 20 of the Extension Period.

The primary objective of the study was to assess the % reduction from baseline in sUA levels following 4 weeks of continuous treatment with lesinurad in combination with allopurinol compared to allopurinol alone in gout patients with documented inadequate hypouricaemic response to standard doses of allopurinol.

Results

The primary efficacy endpoint was the % reduction from baseline in sUA following 4 weeks of treatment. Statistically significant decreases in sUA were achieved favoring lesinurad versus placebo for the primary efficacy endpoint, which was the percent reduction from Baseline in sUA following 4 weeks of treatment. At Day 27 in the ITT population, as assessed by absolute values, change from Baseline, and percent change from Baseline, there were statistically significant reductions in all lesinurad treatment groups compared to the placebo group ($p < 0.0001$ for all comparisons, **Figure 13**).

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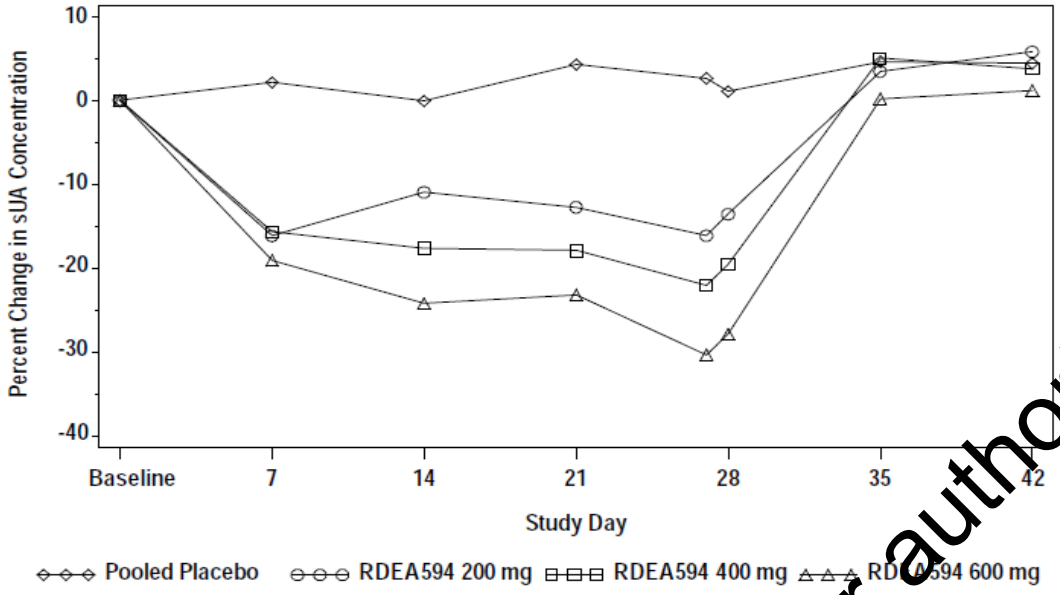
Figure 13. Mean % change from baseline in sUA concentration by study visit (ITT population, Study 203)



At day 27, the mean % reduction from baseline sUA was 16.1%, 22.1% and 30.4% for the 200 mg, 400 mg and 600 mg groups respectively. There was an increase of 2.6% for pooled placebo. The reduction compared to placebo was statistically significant in all cohorts ($p<0.0001$). At day 27, sUA < 6.0 mg/dL was achieved by 72.5%, 77.5%, 92.7% and 27.3% for 200 mg, 400 mg, 600 mg and placebo groups respectively (ITT analysis). The respective reductions were 63.0%, 73.8%, and 79.2% for the non-responder imputation analysis. The percent increase in urine urate excretion from baseline to Day 28 was 22.3%, 33.5%, and 38.3% in the 200 mg, 400 mg, and 600 mg groups, respectively, compared to 6.7% in the placebo group. A similar pattern was apparent for urate clearance and fractional excretion of uric acid (FEUA). During the double-blind treatment and follow-up periods, gout flare was reported by 21.7%, 31.0%, and 31.3% of subjects in the 200 mg, 400 mg, and 600 mg groups, respectively, and 20.8% of subjects in the placebo group.

2.5.2. Main studies

Study 301: A phase 3 randomized, double-blind, multicentre, placebo-controlled, combination study to evaluate the efficacy and safety of lesinurad and allopurinol compared to allopurinol alone in subjects with gout who have had an inadequate hypouricaemic response to standard of care allopurinol.

Methods

The design of the study is depicted in **Figure 14**.

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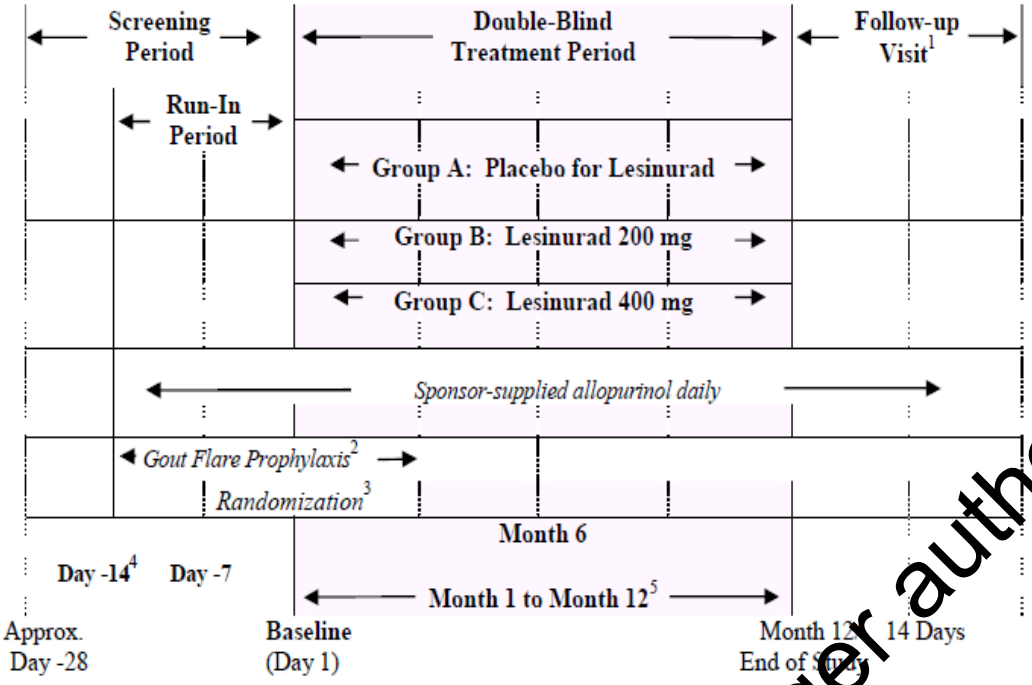
Figure 14. Design of Study 301



[1] Subjects who do not enter an extension study will be required to attend a Follow-up Visit within approximately 14 days of completing the Double-Blind Treatment Period.

[2] Prophylactic treatment for gout flare will consist of Colchicine 0.5 mg to 0.6 mg qd or NSAID ± PPI through Month 5.

[3] Subjects whose sUA is ≥ 6.5 mg/dL (387 µmol/L) at the Screening Visit and ≥ 6.0 mg/dL (357 µmol/L) at the Day -7 Visit will be randomized and will continue to receive Sponsor-supplied allopurinol for the duration of the study.

[4] Subjects will come into the study receiving prescription allopurinol at least 300 mg daily (at least 200 mg daily for subjects with moderate renal impairment) as the sole ULT indicated for the treatment of gout for at least 8 weeks prior to the beginning of the Screening Period until eligibility is confirmed and then will be provided Sponsor-supplied allopurinol beginning on Day -14.

[5] Study visits at Week 2 and monthly beginning at Month 1 through Month 12 (or early termination).

Study Participants

Main inclusion criteria:

- Subject is ≥ 18 years and ≤ 85 years of age;
- Subject is male or female; female of childbearing potential who agrees to use non-hormonal contraception;
- Subject meets the diagnosis of gout as per the American Rheumatism Association Criteria for the Classification of Acute Arthritis of Primary Gout
- Subject has been taking allopurinol as the sole urate-lowering therapy indicated for the treatment of gout for at least 8 weeks prior to the Screening Visit at a stable, medically appropriate dose, as determined by the Investigator, of at least 300 mg per day (at least 200 mg for subjects with moderate renal impairment);
- Subject must be able to take gout flare prophylaxis with colchicine or an NSAID (including Cox-2 selective NSAID) ± PPI;
- Subject has an sUA level ≥ 6.5 mg/dL (387 µmol/L) at the Screening Visit an d ≥ 6.0 mg/dL (357 µmol/L) at the Day -7 Visit;

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- Subject has reported at least 2 gout flares in the prior 12 months.

The American Rheumatism Association Criteria for the Classification of Acute Arthritis of Primary Gout are:

- The presence of characteristic urate crystals in the joint fluid and/or
- A tophus proved to contain urate crystals by chemical or polarized light microscopic means, and/or
- The presence of 6 of the 13 clinical, laboratory, and X-ray phenomena listed below.

1. More than one attack of acute arthritis
11. Maximum inflammation developed within 1 day
12. Monoarthritis attack
13. Redness observed over joints
14. First metatarsophalangeal joint painful or swollen
15. Unilateral first metatarsophalangeal joint attack
16. Unilateral tarsal joint attack
17. Tophus (proven or suspected)
18. Hyperuricemia
19. Asymmetric swelling within a joint on x-ray*
20. Subcortical cysts without erosions on x-ray
21. Monosodium urate monohydrate microcrystals in joint fluid during attack
22. Joint fluid culture negative for organisms during attack

* This criterion could logically be found on examination as well as on x ray.

Main exclusion criteria:

- Subject with an acute gout flare that has not resolved at least 7 days before the Baseline Visit (Day 1);
- Subject with known hypersensitivity or allergy to allopurinol;
- Subject who is taking any other approved urate-lowering medication that is indicated for the treatment of gout other than allopurinol (eg, another xanthine oxidase inhibitor (XOI) or uricosuric agent) within 8 weeks of the Screening Visit;
- Subject who previously received pegloticase;
- Subject who previously participated in a clinical study involving lesinurad (RDEA594) or RDEA806 and received active treatment or placebo;
- Subject who is pregnant or breastfeeding;
- Subject with an estimated creatinine clearance < 30 mL/min calculated by the Cockcroft-Gault formula using ideal body weight.

A total of 181 study sites screened subjects in the US.

Treatments

Subjects were randomised 1:1:1 and assigned to the following treatments:

Group A: placebo + allopurinol (PBO + ALLO group);

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Group B: lesinurad 200 mg + allopurinol (LESU 200 mg + ALLO group);

Group C: lesinurad 400 mg + allopurinol (LESU 400 mg + ALLO group).

All doses of lesinurad/placebo and allopurinol were taken in the morning with food and 240 mL of water. Subjects were instructed to drink 2 L of water per day. If the dose of allopurinol was interrupted, the subject was not to take their dose of lesinurad/placebo until allopurinol was resumed

Objectives

The primary objective was to determine the efficacy of lesinurad by Month 6 when used in combination with allopurinol compared to allopurinol monotherapy.

Secondary objectives included:

- To determine the efficacy of lesinurad by Month 12 when used in combination with allopurinol compared to allopurinol monotherapy;
- To determine the safety of lesinurad over 6 months and 12 months when used in combination with allopurinol;
- To determine the effect of lesinurad when used in combination with allopurinol on Health Related Quality of Life and physical function

Outcomes/endpoints

Primary endpoint:

- The proportion of subjects with a sUA level that is < 6.0 mg/dL at the Month 6 visit. Subjects with missing values at Month 6 for any reason were considered non-responders.

Key secondary endpoints:

- Mean rate of gout flares requiring treatment for the 6-month period from the end of Month 6 to the end of Month 12.
- Proportion of subjects with ≥ 1 target tophus at Baseline who experience complete resolution (CR) of at least 1 target tophus by Month 12 (i.e. last on-study visit).

Secondary endpoints related to sUA were also included:

- Proportion of subjects whose sUA level is < 6.0 mg/dL, < 5.0 mg/dL and < 4.0 mg/dL at each visit.
- Absolute and percent change from Baseline in sUA levels at each visit.

Other tophus related secondary endpoints included:

- Mean percent change from Baseline in the sum of the areas for all target tophi at each visit.

<u>Patient reported outcomes (PROs)</u>

The following secondary endpoints were included:

- Proportion of subjects with an improvement from Baseline in the Health Assessment Questionnaire - Disability Index (HAQ-DI) of at least 0.25 at Month 12.
- Mean change from Baseline to Month 12 in the physical component scale of the Short Form-36.
- Total Treatment Satisfaction Question for Medication Score.
- Mean change from Baseline in the Sheehan Disability Scale.

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- Mean change from Baseline in Patient Global Assessment of Disease Activity.

PRO assessment was conducted at baseline, and at Months 3, 6, 9 and 12.

Sample size

Rather than on the primary endpoint, the sample size of 600 subjects (200 per study arm) was based on the key secondary endpoint of mean rate of gout flares. Based on a clinically meaningful 50% reduction in the rate of flares, and a coefficient of variation of 2.0 or less, a sample size of 200 subjects per treatment group provides greater than 80% power to detect this difference in gout flare rates using a Wilcoxon Rank-Sum test at alpha = 0.025 (two-sided).

A Phase 2b study showed response rates of 70% for lesinurad in combination with allopurinol versus 30% for the allopurinol alone group. This sample size of 600 subjects provides greater than 90% power to detect a difference in response rates if the lesinurad plus allopurinol treatment groups have response rates as low as 48% versus 30% response rate and using Fisher's exact test adjusting for multiplicity with alpha = 0.025 (two-sided) for each test.

Randomisation

Randomisation took place across all study sites using a centralized interactive voice response system / interactive web response system (IVRS/IWRS). Randomisation was stratified by the following factors:

- Renal function at Day -7: eCrCl $\geq$ 60 mL/min vs. < 60 mL/min (Cockcroft-Gault formula, ideal body weight)
- Tophus status: presence of $\geq$ 1 tophus vs. absence

Blinding (masking)

This was a double-blind study.

Statistical methods

All randomized subjects who received at least 1 dose of randomized study medication were included in the ITT Population. This population was used as the primary population for all efficacy analyses. The PP (per protocol) population was used for sensitivity analyses.

Primary analysis:

The difference in sUA response rates between the placebo and each lesinurad treatment group was tested using Cochran-Mantel Haenszel methodology, using the randomisation stratification factors. Results were summarised by treatment group and expressed as proportions, corresponding adjusted 95% confidence intervals (CIs) of the difference between response rates, and p-values.

The primary method for imputing missing data was non-responder imputation (NRI); subjects who were missing their Month 6 sUA result were analysed as non-responders. In addition, the Last observation carried forward (LOCF) method was also used to impute missing data. Sensitivity analyses were performed to examine the robustness of the primary efficacy results. First, an LOCF analysis was performed for response rates at each sUA target for each visit by treatment group. To be included in the LOCF analysis, a subject had to have at least 1 post-Baseline sUA result, as only post-Baseline sUA results can be carried forward. Secondly, an observed cases analysis was conducted for response rates at each level for each visit by treatment group. Third, the proportion of subjects with an sUA < 6.0 mg/dL at all 3 of Months 4, 5, and 6 was computed. Any subject missing any 1 of the Months 4, 5, or 6 sUA levels was considered a non-responder for this analysis.

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Analysis of gout flares

Only disease flares that required the use of colchicine, analgesics, and/or anti-inflammatory medication, were included in the analyses of the key secondary outcome.

The rate of gout flares requiring treatment in each of the 2 lesinurad treatment groups were compared with the placebo group using a negative binomial model. The model included the randomisation stratification factors and the logarithm of the subject's corresponding time on-study in the interval was used as an offset variable in the model to adjust for subjects having different exposure times during which the events occurred.

Analysis of tophi

Tophus measurements for subjects with ≥ 1 target tophus at Baseline were categorized based upon the best response among all measured target tophi at each visit as follows:

- Complete resolution (CR; disappearance of ≥ 1 target tophus);
- Partial resolution (PR; ≥ 50% decrease in the area of ≥ 1 target tophus);
- Stable disease (neither ≥ 50% decrease nor ≥ 25% increase in the area of a target tophus);
- Progressive disease (≥25% increase in the area of a target tophus).

If any single measured target tophus showed progression at a visit, the best tophus response for that subject at that visit was progressive disease, regardless of the response of any other target tophi at that visit.

Subjects with ≥ 1 target tophus at Baseline with a best response of CR of≥ 1 target tophus by Month 12 (analysed using last on-study visit), at their Month 12 Visit, and at each visit were summarized by treatment group. The primary analysis of this endpoint was based on the best response of CR of≥ 1 target tophus by Month 12. Subjects who had progressive disease at their last on-study visit and those who did not achieve a CR at their last on-study visit were considered non-responders. The difference in tophus resolution rates on the subset of subjects with measurable tophi at Baseline between placebo and each lesinurad group was tested using the CMH test statistic, stratifying by Day -7 renal function (randomized values).

Results

Participant flow

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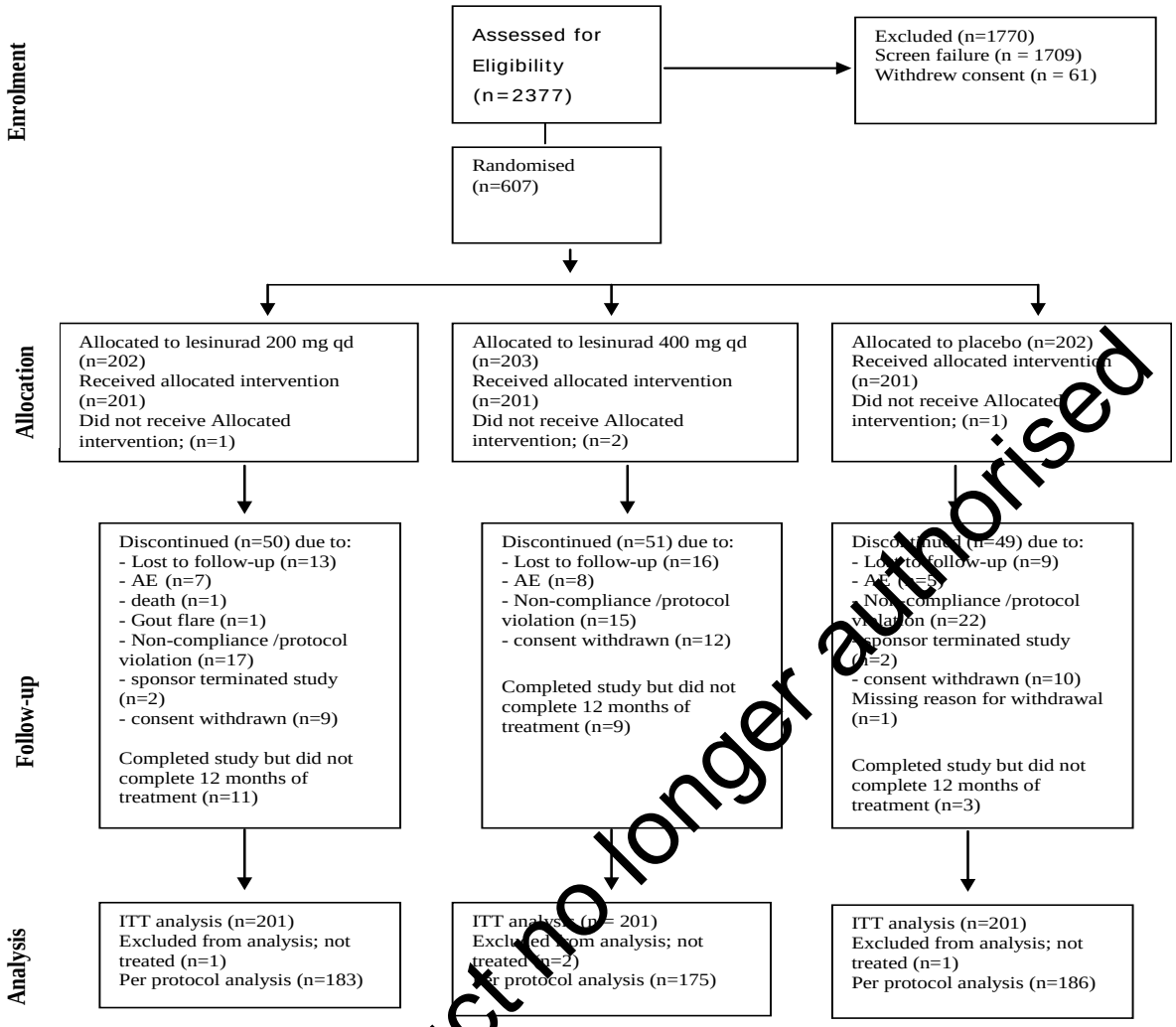

Recruitment

Study initiation date: 08 February 2012 (first subject first visit)

Study completion date: 20 November 2014 (last subject last visit)

Conduct of the study

There were 3 substantial protocol amendments during the study but before breaking the blind.

The first amendment reduced the sUA threshold for eligibility at day -7 (final baseline value) from ≥ 6.5 mg/dL to ≥6.0 mg/dL, following feedback from the FDA. The gout flare secondary endpoint was also modified including an increase in the period of observation, which resulted in a reduced sample size. 177 randomised subjects were screened prior to this amendment.

The second amendment expanded guidance on subject hydration and guidance for investigators in case of raised sCr or kidney stone, and added an independent Renal Events Adjudication Committee (REAC).

The last substantial amendment was triggered by the results of the lesinurad monotherapy study 303 in which SAEs of acute renal failure were reported in subjects receiving lesinurad. The amendment included a requirement to take allopurinol at the same time as lesinurad, to withdraw any subject developing a kidney stone, to increase monitoring of renal function and to tighten withdrawal criteria based on renal function.

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The most common protocol violation and deviation (PDV) was randomised study medication non-compliance, affecting 7.5%, 7.5% and 4.0% of the lesinurad 200 mg, lesinurad 400 mg, and placebo groups, respectively. The next most common PDV was allopurinol dose < 300 mg qd (< 200 mg qd if moderate renal impairment at time of randomisation), affecting 0%, 3.0% and 2.0% of the lesinurad 200 mg, lesinurad 400 mg, and placebo groups, respectively. In addition, 2 subjects received the wrong randomised study kit at one study visit.

Baseline data

The study population was predominantly male and white, with a median age of 52 years. Less than 2% were over 75 years of age. Mean body mass index was 34.8 kg/m^2.

The mean duration since gout diagnosis was around 12 years. At least one target tophi was present at baseline for 9% of subjects, of which the majority had only one. The mean number of gout flares reported in the past 12 months was 4.8. Moderate renal impairment (eCrCl < 60 mL/min) was present at baseline for 20.9%. Those with more severe renal impairment are slightly over-represented in the placebo arm. Mean sUA at baseline was 6.9 mg/dL. Around 90% of subjects were on an allopurinol dose of 300 mg daily at baseline. Demographic characteristics, baseline disease and treatment characteristics are summarised in **Tables 29** and **30** respectively.

Table 29. Demographic characteristics (ITT population, Study 305)

Variable	PBO + ALLO (N=201)	LESU 200 mg + ALLO (N=201)	LESU 400 mg + ALLO (N=201)	TOTAL (N=603)
Sex [n (%)]				
Female	12 (6.0)	9 (4.5)	15 (7.5)	36 (6.0)
Male	189 (94.0)	192 (95.5)	186 (92.5)	567 (94.0)
Race [n (%)]				
American Indian or Alaska Native	1 (0.5)	2 (1.0)	0	3 (0.5)
Asian	10 (5.0)	9 (4.5)	7 (3.5)	26 (4.3)
Black or African American	29 (14.4)	31 (15.4)	30 (14.9)	90 (14.9)
Maori	0	0	0	0
Native Hawaiian or other Pacific Islander	5 (2.5)	4 (2.0)	5 (2.5)	14 (2.3)
White	153 (76.1)	151 (75.1)	156 (77.6)	460 (76.3)
Other	3 (1.5)	4 (2.0)	3 (1.5)	10 (1.7)
Ethnicity [n (%)]				
Hispanic or Latino	19 (9.5)	27 (13.4)	31 (15.4)	77 (12.8)
Not Hispanic or Latino	182 (90.5)	174 (86.6)	170 (84.6)	526 (87.2)
Age (years)				
n	201	201	201	603
Mean (SD)	51.7 (11.70)	51.6 (10.69)	52.3 (11.47)	51.9 (11.28)
Median	52.0	52.0	53.0	52.0
Min, Max	22, 81	25, 77	23, 77	22, 81
Age group (years) [n (%)]				
< 65	169 (84.1)	181 (90.0)	168 (83.6)	518 (85.9)
≥ 65	32 (15.9)	20 (10.0)	33 (16.4)	85 (14.1)
65 - 74	28 (13.9)	16 (8.0)	31 (15.4)	75 (12.4)
≥ 75	4 (2.0)	4 (2.0)	2 (1.0)	10 (1.7)

Abbreviations: ALLO, allopurinol; ITT, Intent-to-treat; LESU, lesinurad; Max, maximum; Min, minimum; PBO, placebo; SD, standard deviation.

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Table 30. Baseline Disease and Treatment Characteristics (ITT Population, Study 301)

Variable	PBO + ALLO (N=201)	LESU 200 mg +ALLO (N=201)	LESU 400 mg +ALLO (N=201)	TOTAL (N=603)
American Rheumatism Association diagnostic criteria [n (%)]	200 (99.5)	200 (99.5)	201 (100)	601 (99.7)
Duration since gout diagnosis (years)				
n	201	201	201	603
Mean (SD)	11.59 (8.75)	12.76 (10.04)	11.16 (9.23)	11.84 (9.37)
Median	10.40	10.40	8.90	10.20
Min, Max	0.2, 40.4	0.2, 45.2	0.0, 43.0	0.0, 45.2
Presence of tophi at Screening[a] [n (%)]				
Yes	27 (13.4)	30 (14.9)	29 (14.4)	86 (14.3)
No	174 (86.6)	171 (85.1)	172 (85.6)	517 (85.7)
Presence of ≥ 1 target tophus at Baseline [n (%)]				
Yes	17 (8.5)	18 (9.0)	19 (9.5)	54 (9.0)
No	184 (91.5)	183 (91.0)	182 (90.5)	549 (91.0)
Number of target tophi at Baseline				
n	17	18	19	54
Mean (SD)	1.8 (1.47)	1.8 (1.06)	1.1 (1.45)	1.9 (1.32)
Median	1.0	1.5	1.0	1.0
Min, Max	1, 5	1, 5	1, 5	1, 5
Number of target tophi at Baseline [n (%)]				
0	184 (91.5)	183 (91.0)	182 (90.5)	549 (91.0)
1	12 (6.0)	9 (4.5)	10 (5.0)	31 (5.1)
2	1 (0.5)	6 (3.0)	3 (1.5)	10 (1.7)
3	1 (0.5)	2 (1.0)	2 (1.0)	5 (0.8)
4	1 (0.5)	0	2 (1.0)	3 (0.5)
5	2 (1.0)	1 (0.5)	2 (1.0)	5 (0.8)
Total area of target tophi at Baseline (mm^2)				
n	17	18	19	54
Mean (SD)	321.85 (281.49)	334.95 (207.27)	254.19 (165.19)	302.41 (219.73)
Median	273.48	282.70	230.55	259.51
Min, Max	60.60, 1162.37	75.65, 852.68	56.25, 632.56	56.25, 1162.37
Number of gout flares in the past 12 months				
n	201	201	201	603
Mean (SD)	4.8 (4.09)	4.8 (3.16)	4.9 (3.49)	4.8 (3.60)
Median	3.0	4.0	4.0	4.0
Min, Max	2, 36	2, 20	2, 20	2, 36

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Variable	PBO + ALLO (N=201)	LESU 200 mg +ALLO (N=201)	LESU 400 mg +ALLO (N=201)	TOTAL (N=603)
Number of gout flares in the past 12 months [n (%)]				
2	48 (23.9)	48 (23.9)	57 (28.4)	153 (25.4)
3	59 (29.4)	52 (25.9)	34 (16.9)	145 (24.0)
4	25 (12.4)	24 (11.9)	30 (14.9)	79 (13.1)
≥ 5	69 (34.3)	77 (38.3)	80 (39.8)	226 (37.5)
Renal function at Day -7[a] (mL/min) [n (%)]				
eCrCl ≥ 60	165 (82.1)	165 (82.1)	164 (81.6)	494 (81.9)
eCrCl < 60	36 (17.9)	36 (17.9)	37 (18.4)	109 (18.1)
Renal function at Baseline (mL/min) [n (%)]				
eCrCl ≥ 90	77 (38.3)	83 (41.3)	76 (37.8)	236 (39.1)
eCrCl < 90	123 (61.2)	117 (58.2)	124 (61.7)	364 (60.4)
eCrCl ≥ 60	160 (79.6)	155 (77.1)	159 (79.1)	474 (78.6)
eCrCl < 60	40 (19.9)	45 (22.4)	41 (20.4)	126 (20.9)
eCrCl ≥ 45	180 (89.6)	188 (93.5)	185 (92.0)	553 (91.7)
eCrCl < 45	20 (10.0)	12 (6.0)	15 (7.5)	[illegible]
eCrCl 60 - < 90	83 (41.3)	72 (35.8)	83 (41.3)	238 (39.5)
eCrCl 30 - < 60	39 (19.4)	44 (21.9)	41 (20.4)	124 (20.6)
eCrCl 45 - < 60	20 (10.0)	33 (16.4)	26 (12.9)	79 (13.1)
eCrCl 30 - < 45	19 (9.5)	11 (5.5)	15 (7.5)	45 (7.5)
eCrCl < 30	1 (0.5)	1 (0.5)	0	2 (0.3)
Missing	1 (0.5)	1 (0.5)	1 (0.5)	3 (0.5)
sUA level at Baseline (mg/dL)				
n	201	201	201	603
Mean (SD)	6.99 (1.25)	7.01 (1.62)	6.83 (1.24)	6.94 (1.27)
Median	6.70	6.[illegible]	6.70	6.80
Min, Max	3.8, 12.2	3.8, 13.3	3.6, 12.2	3.6, 13.3
sUA category at Baseline[b] (mg/dL) [n (%)]				
< 6.0	31 (15.4)	36 (17.9)	45 (22.4)	112 (18.6)
6.0 - < 7.0	82 (40.8)	76 (37.8)	72 (35.8)	230 (38.1)
7.0 - < 8.0	52 (25.9)	52 (25.9)	52 (25.9)	156 (25.9)
8.0 - < 10.0	32 (15.9)	31 (15.4)	28 (13.9)	91 (15.1)
≥ 10.0	4 (2.0)	6 (3.0)	4 (2.0)	14 (2.3)
Prior ULT[c] [n (%)]				
Allopurinol	4 (2.0)	8 (4.0)	4 (2.0)	16 (2.7)
Febuxostat	5 (2.5)	3 (1.5)	5 (2.5)	13 (2.2)
Probenecid	3 (1.5)	2 (1.0)	2 (1.0)	7 (1.2)
Other	1 (0.5)	0	2 (1.0)	3 (0.5)
Type of gout flare prophylaxis at Baseline [n (%)]				
Colchicine	166 (82.6)	170 (84.6)	168 (83.6)	504 (83.6)
NSAID	34 (16.9)	28 (13.9)	33 (16.4)	95 (15.8)
Both	1 (0.5)	2 (1.0)	3 (1.5)	6 (1.0)
Other or Missing	2 (1.0)	5 (2.5)	3 (1.5)	10 (1.7)
Allopurinol dose at Baseline (mg/day)				
n	201	201	201	603
Mean (SD)	310.0 (70.00)	309.5 (59.67)	300.2 (46.50)	306.6 (59.58)
Median	300.0	300.0	300.0	300.0
Allopurinol dose at Baseline (mg/day) [n (%)]				
< 300	12 (6.0)	5 (2.5)	12 (6.0)	29 (4.8)
= 300	176 (87.6)	187 (93.0)	183 (91.0)	546 (90.5)
> 300	13 (6.5)	9 (4.5)	6 (3.0)	28 (4.6)
200 - < 300	12 (6.0)	5 (2.5)	12 (6.0)	29 (4.8)
300 - < 400	176 (87.6)	187 (93.0)	183 (91.0)	546 (90.5)
400 - < 500	3 (1.5)	1 (0.5)	3 (1.5)	7 (1.2)
500 - < 600	1 (0.5)	1 (0.5)	0	2 (0.3)
≥ 600	9 (4.5)	7 (3.5)	3 (1.5)	19 (3.2)

Abbreviations: ALLO , allopurinol; eCrCl, estimated creatinine clearance; ITT, Intent-to-treat; LESU, lesinurad; Max, maximum; Min, minimum; PBO, placebo; SD, standard deviation; sUA, serum urate; ULT, urate-lowering therapy.

[a] Actual stratification factor values.

[b] Subjects had received a medically appropriate stable dose of allopurinol for at least 10 weeks before their Baseline Visit.

[c] More than one response can apply; percentages can sum to > 100%.

Note: Baseline eCrCl is calculated using the highest serum creatinine value recorded ≤ 14 days prior to the first dose of randomized study medication. Fourteen subjects were mis-stratifed (Listing 16.1.1.2).

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Numbers analysed

The primary analysis was based on the ITT population (subjects randomised who received at least one dose of study medication).

Outcomes and estimation

Primary efficacy endpoint analysis

The results of the primary efficacy endpoint are presented in **Table 31**. Patients with missing data at month 6 were included as non-responders.

Table 31. Primary Endpoint: Proportion of Subjects with an sUA Level < 6.0 mg/dL by Month 6 – Non-Responder Imputation (ITT Population, Study 301)

	PBO + ALLO (N=201) n (%)	LESU 200 mg + ALLO (N=201) n (%)	LESU 400 mg + ALLO (N=201) n (%)
Proportion with sUA < 6.0 mg/dL by Month 6	56 (27.9)	109 (54.2)	139 (69.2)
Difference in proportions vs. PBO + ALLO (95% CI)		0.26 (0.17, 0.36)	0.41 (0.22, 0.41)
p-value[a]		<0.0001	<0.0001

Abbreviations: ALLO, allopurinol; CI, confidence interval; ITT, intent-to-treat; LESU, lesinurad; PBO placebo; sUA, serum urate.
[a] Cochran-Mantel Haenszel test stratified by Day -7 renal function (eCrCl ≥ 60 mL/min versus < 60 mL/min) and tophus status during Screening (presence versus absence), randomized stratification values.
Note: Subjects missing the Month 6 sUA result are treated as non-responders.

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Sensitivity analyses

Using the last observation carried forward (LOCF) imputation method, the proportion of subjects who achieved the target of sUA < 6.0 mg/dL at Month 6 was 61.7% and 67.5% versus 32.3% for lesinurad 200 mg qd, lesinurad 400 mg qd, and placebo arms respectively (p < 0.0001 for both comparisons).

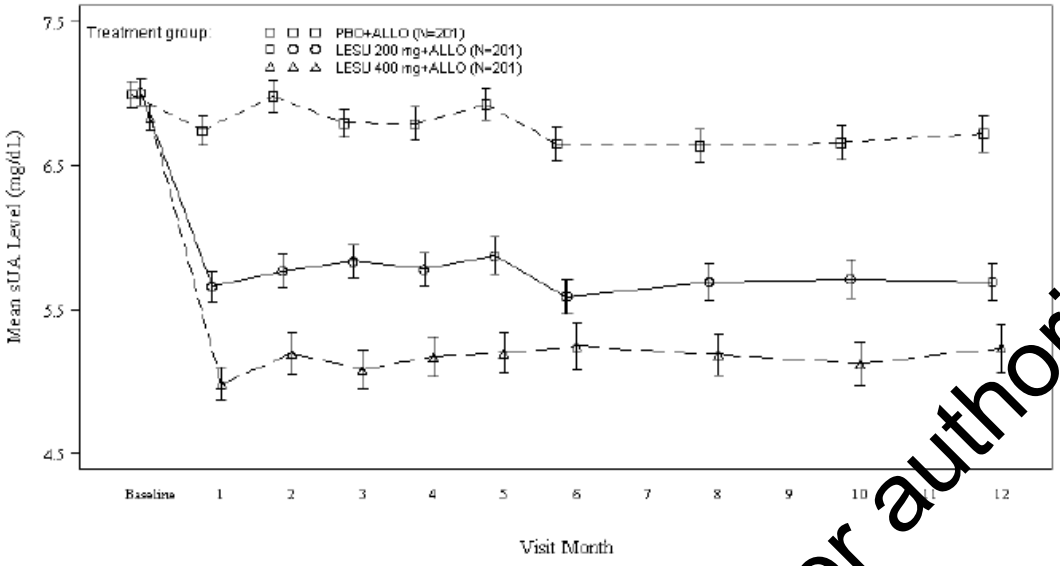
The proportion of subjects with sUA < 6.0 mg/dL at 3 consecutive study visits (Months 4, 5, and 6) using NRI for lesinurad 200 mg, lesinurad 400 mg and placebo were 35.3%, 49.3% and 10.4% (p < 0.0001 for both comparisons).

The results in the per protocol (PP) population confirmed those of the primary analysis. In the PP population, significantly more subjects in the lesinurad 200 mg and lesinurad 400 mg groups achieved the target goal of sUA < 6.0 mg/dL at Month 6 compared with the placebo group: 57.9% versus 28.5% (p < 0.0001) and 62.9% versus 28.5% (p < 0.0001), respectively.

sUA secondary endpoint analyses

The mean absolute and mean percentage changes for both doses of lesinurad + allopurinol were significantly greater than those for placebo + allopurinol at all time-points (p < 0.0001 for all comparisons, **Figure 15**).

Figure 15. Mean Serum Urate Levels by Visit- Observed Cases (ITT Population, Study 301)



Abbreviations: ALLO, allopurinol; ITT, intent-to-treat; LESU, lesinurad; PBO, placebo; sUA, serum urate.
Note: End of Study/Early Termination data are included in the appropriate visit month if no scheduled visit occurred during that visit month. Error bars represent standard error of the mean. Months 7, 9, and 11 data are excluded because the timing of the last protocol amendment (Protocol Amendment 4), which added sUA assessments at these timepoints, resulted in minimal data collection at these timepoints for NRI analysis. At each post-Baseline visit (ie, Months 1 through 12), the adjusted differences in the mean change from Baseline in sUA levels for the LESU 200 mg + ALLO and LESU 400 mg + ALLO groups versus the PBO + ALLO group were statistically significant: $p < 0.0001$ for all comparisons.

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Other secondary efficacy endpoint analyses

Gout flares

The rates of gout flares per subject that required treatment over the 6-month period from end of Month 6 to end of Month 12 were 0.57, 0.51 and 0.58 for the lesinurad 200 mg, lesinurad 400 mg and placebo groups respectively. The rates for the lesinurad groups were not significantly different from the placebo group.

The proportion of subjects requiring treatment for a gout flare between the end of Month 6 and the end of Month 12 was 28.8%, 20.4% and 27.9% for the lesinurad 200 mg, lesinurad 400 mg and placebo groups respectively.

Analyses of subject diary entries for gout flares requiring treatment demonstrated no clear patterns of differences for duration of gout flare, pain scores, associated gout flare symptoms and gout flare treatment.

Tophus resolution

The proportions of subjects with $\geq$ 1 target tophus at baseline who achieved a complete response by Month 12 were 0/18 (0%) and 4/19 (21.1%) versus 5/17 (29.4%) for the lesinurad 200 mg, lesinurad 400 mg and placebo groups respectively.

There was no significant difference between treatment groups in the mean % change for baseline in the sum of the areas for all target tophi at any visit.

Study 302: A phase 3 randomized, double-blind, multicentre, placebo-controlled, combination study to evaluate the efficacy and safety of lesinurad and allopurinol compared to allopurinol alone in subjects with gout who have had an inadequate hypouricaemic response to standard of care allopurinol.

Methods

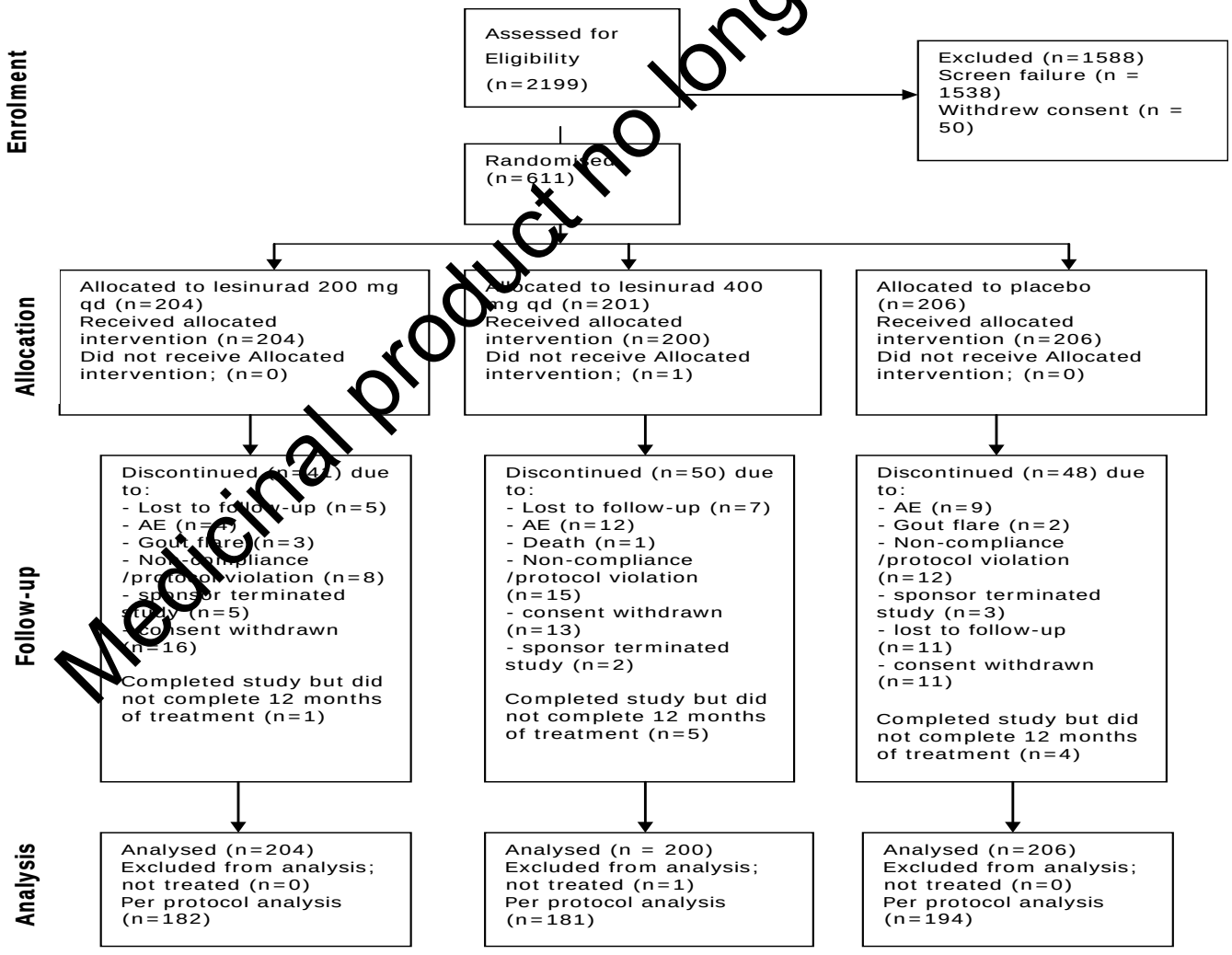
This study was identical in design to study 301.

Study participants

Subjects were screened at 185 study sites in 12 countries: US, Canada, Spain, France, Belgium, Germany, Poland, Switzerland, Ukraine, South Africa, Australia, and New Zealand. Approximately 600 subjects were planned. Subjects were randomised at 142 sites in 4 regions: North America (54.7% of total), Europe (21.9%), South Africa (16.2%) and Australia /New Zealand (7.2%).

Results

Participant flow



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Recruitment

Study initiation date: 16 December 2011 (first subject first visit)

Study completion date: 03July 2014 (last subject last visit)

Conduct of the study

In addition to the protocol amendments described for Study 301, on 20 December 2013, the BfArM required restriction of recruitment of subjects in Germany to those who had failed to respond to all other established alternative therapies as given in national and international treatment guidelines. The Sponsor discontinued all subjects in Germany, and all German sites were closed. This affected 7 randomised subjects, who are included in the participant flow diagram (above) as discontinued (sponsor terminated study).

The most common PDV was randomised study medication non-compliance, affecting 3.9%, 5.5% and 2.4% of the lesinurad 200 mg, lesinurad 400 mg, and placebo groups, respectively. The next most common PDV was allopurinol dose < 300 mg qd (< 200 mg qd if moderate renal impairment at time of randomisation), affecting 2.5% to 2.9% across the treatment groups.

Baseline data

The study population was predominantly male and white, with a median age of 52 years. Less than 2% were over 75 years of age. Mean body mass index was 34.1 kg/m^2. Demographic characteristics were balanced between the groups. Demographic characteristics, baseline disease are summarised in **Table 32.**

Table 32. Demographic Characteristics (ITT Population)

Variable	PBO + ALLO (N=206)	LESU 200 mg + ALLO (N=204)	LESU 400 mg + ALLO (N=200)	TOTAL (N=610)
Sex [n (%)]				
Female	10 (4.9)	7 (3.4)	6 (3.0)	23 (3.8)
Male	196 (95.1)	197 (96.6)	194 (97.0)	587 (96.2)
Race [n (%)]				
American Indian or Alaska Native	1 (0.5)	1 (0.5)	0	2 (0.3)
Asian	14 (6.8)	10 (4.9)	9 (4.5)	33 (5.4)
Black or African American	22 (10.7)	15 (7.4)	21 (10.5)	58 (9.5)
Maori	1 (0.5)	4 (2.0)	1 (0.5)	6 (1.0)
Native Hawaiian or other Pacific Islander	5 (2.4)	3 (1.5)	2 (1.0)	10 (1.6)
White	155 (75.2)	167 (81.9)	160 (80.0)	482 (79.0)
Other	8 (3.9)	4 (2.0)	6 (3.0)	18 (3.0)
Missing	0	0	1 (0.5)	1 (0.2)
Ethnicity [n (%)]				
Hispanic or Latino	7 (3.4)	10 (4.9)	7 (3.5)	24 (3.9)
Not Hispanic or Latino	199 (96.6)	194 (95.1)	193 (96.5)	586 (96.1)
Age (years)				
n	206	204	200	610
Mean (SD)	51.4 (10.56)	51.0 (11.11)	51.3 (11.08)	51.2 (10.90)
Median	52.0	51.0	52.0	52.0
Min, Max	21, 80	21, 82	18, 80	18, 82
Age group (years) [n (%)]				
< 65	185 (89.8)	184 (90.2)	175 (87.5)	544 (89.2)
≥ 65	21 (10.2)	20 (9.8)	25 (12.5)	66 (10.8)
65 - 74	19 (9.2)	16 (7.8)	22 (11.0)	57 (9.3)
≥ 75	2 (1.0)	4 (2.0)	3 (1.5)	9 (1.5)

Abbreviations: ALLO, allopurinol; ITT, Intent-to-treat; LESU, lesinurad; Max, maximum; Min, minimum; PBO, placebo; SD, standard deviation.

The mean duration since gout diagnosis was around 12 years. At least one target tophi was present at baseline for 16% of subjects, of which the majority had only one. The mean number of gout flares reported in the past 12 months was 6.2. Moderate renal impairment (eCrCl < 60 mL/min) was present

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at baseline for 16.1%, and slightly over-represented in the placebo arm. Mean sUA at baseline was 6.9 mg/dL. Around 84% of subjects were on an allopurinol dose of 300 mg daily at baseline. Baseline disease and treatment characteristics are summarised in **Table 33.**

Table 33. Baseline disease and treatment characteristics

Variable	PBO + ALLO (N=206)	LESU 200 mg +ALLO (N=204)	LESU 400 mg +ALLO (N=200)	TOTAL (N=610)
American Rheumatism Association diagnostic criteria [n (%)]	205 (99.5)	204 (100)	200 (100)	609 (99.8)
Duration since gout diagnosis (years)				
n	206	204	200	610
Mean (SD)	11.31 (9.38)	12.25 (9.76)	11.02 (8.59)	11.53 (9.36)
Median	9.40	10.30	9.05	9.80
Min, Max	0.2, 53.0	0.5, 45.0	0.0, 47.4	0.0, 53.0
Presence of tophi at Screening[a] [n (%)]				
Yes	48 (23.3)	49 (24.0)	47 (23.5)	144 (23.6)
No	158 (76.7)	155 (76.0)	153 (76.5)	466 (76.4)
Presence of ≥ 1 target tophus at Baseline [n (%)]				
Yes	33 (16.0)	35 (17.2)	29 (14.5)	97 (15.9)
No	173 (84.0)	169 (82.8)	171 (85.5)	513 (84.1)
Number of target tophi at Baseline				
n	33	35	29	97
Mean (SD)	2.2 (1.36)	2.0 (1.34)	2.5 (1.53)	2.2 (1.40)
Median	2.0	2.0	2.0	2.0
Min, Max	1, 5	1, 5	1, 5	1, 5
Number of target tophi at Baseline [n (%)]				
0	173 (84.0)	169 (82.8)	171 (85.5)	513 (84.1)
1	14 (6.8)	18 (8.8)	12 (6.0)	44 (7.2)
2	7 (3.4)	6 (2.9)	4 (2.0)	17 (2.8)
3	7 (3.4)	7 (3.4)	4 (2.0)	18 (3.0)
4	1 (0.5)	0	5 (2.5)	6 (1.0)
5	4 (1.9)	4 (2.0)	4 (2.0)	12 (2.0)
Total area of target tophi at Baseline (mm^2)				
n	33	35	29	97
Mean (SD)	373.04 (378.95)	346.63 (335.78)	559.69 (715.27)	419.31 (495.62)
Median	294.84	246.03	351.42	289.00
Min, Max	23.92, 1795.66	31.62, 1643.15	54.00, 3365.82	23.92, 3365.82
Number of gout flares in the past 12 months				
n	206	204	200	610
Mean (SD)	5.8 (4.92)	6.7 (7.01)	6.1 (5.65)	6.2 (5.93)
Median	4.0	4.0	4.0	4.0
Min, Max	2, 30	2, 50	2, 48	2, 50
Number of gout flares in the past 12 months [n (%)]				
2	49 (23.8)	47 (23.0)	43 (21.5)	139 (22.8)
3	40 (19.4)	36 (17.6)	38 (19.0)	114 (18.7)
	31 (15.0)	24 (11.8)	32 (16.0)	87 (14.3)
≥	86 (41.7)	97 (47.5)	87 (43.5)	270 (44.3)

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Variable	PBO + ALLO (N=206)	LESU 200 mg +ALLO (N=204)	LESU 400 mg +ALLO (N=200)	TOTAL (N=610)
Renal function at Day -7[a] (mL/min) [n (%)]				
eCrCl ≥ 60	174 (84.5)	174 (85.3)	171 (85.5)	519 (85.1)
eCrCl < 60	32 (15.5)	30 (14.7)	29 (14.5)	91 (14.9)
Renal function at Baseline (mL/min) [n (%)]				
eCrCl ≥ 90	72 (35.0)	80 (39.2)	85 (42.5)	237 (38.9)
eCrCl < 90	133 (64.6)	124 (60.8)	114 (57.0)	371 (60.8)
eCrCl ≥ 60	165 (80.1)	175 (85.8)	170 (85.0)	510 (83.6)
eCrCl < 60	40 (19.4)	29 (14.2)	29 (14.5)	98 (16.1)
eCrCl ≥ 45	195 (94.7)	198 (97.1)	193 (96.5)	586 (96.1)
eCrCl < 45	10 (4.9)	6 (2.9)	6 (3.0)	22 (3.6)
eCrCl 60 - < 90	93 (45.1)	95 (46.6)	85 (42.5)	273 (44.8)
eCrCl 30 - < 60	39 (18.9)	29 (14.2)	29 (14.5)	97 (15.9)
eCrCl 45 - < 60	30 (14.6)	23 (11.3)	23 (11.5)	76 (12.5)
eCrCl 30 - < 45	9 (4.4)	6 (2.9)	6 (3.0)	21 (3.4)
eCrCl < 30	1 (0.5)	0	0	1 (0.2)
Missing	1 (0.5)	0	1 (0.5)	2 (.3)
sUA level at Baseline[b] (mg/dL)				
n	206	204	200	610
Mean (SD)	6.99 (1.26)	6.84 (1.11)	6.86 (1.19)	6.90 (1.19)
Median	6.80	6.75	6.80	6.80
Min, Max	3.4, 11.3	4.0, 11.3	3.8, 1	3.4, 11.3
sUA category at Baseline (mg/dL) [n (%)]				
< 6.0	38 (18.4)	39 (19.1)	9.5)	116 (19.0)
6.0 - < 7.0	80 (38.8)	88 (43.1)	0(40.0)	248 (40.7)
7.0 - < 8.0	44 (21.4)	50 (24.5)	45 (22.5)	139 (22.8)
8.0 - < 10.0	39 (18.9)	22 (10.8)	32 (16.0)	93 (15.2)
≥ 10.0	5 (2.4)	5 (2.5)	4 (2.0)	14 (2.3)
Prior ULT[c] [n (%)]				
Allopurinol	23 (11.2)	9 (8.8)	28 (14.0)	69 (11.3)
Febuxostat	5 (2.4)	4 (2.0)	1 (0.5)	10 (1.6)
Benzbromarone	2 (1.0)	0	2 (1.0)	4 (0.7)
Probenecid	0	2 (1.0)	3 (1.5)	5 (0.8)
Other	4 (9)	1 (0.5)	1 (0.5)	6 (1.0)
Type of gout flare prophylaxis at Baseline [n (%)]				
Colchicine	159 (77.2)	181 (88.7)	167 (83.5)	507 (83.1)
NSAID	51 (24.8)	23 (11.3)	36 (18.0)	110 (18.0)
Both	8 (3.9)	4 (2.0)	3 (1.5)	15 (2.5)
Other or Missing	4 (1.9)	4 (2.0)	0	8 (1.3)
Allopurinol dose at Baseline (mg/day)				
n	206	204	200	610
Mean (SD)	308.7 (69.29)	313.5 (78.33)	314.8 (77.62)	312.3 (75.08)
Median	300.0	300.0	300.0	300.0
Min, Max	200, 600	200, 900	200, 900	200, 900
Allopurinol dose at Baseline (mg/day) [n (%)]				
< 300	15 (7.3)	14 (6.9)	11 (5.5)	40 (6.6)
= 300	176 (85.4)	168 (82.4)	169 (84.5)	513 (84.1)
> 300	15 (7.3)	22 (10.8)	20 (10.0)	57 (9.3)
200 - < 400	15 (7.3)	14 (6.9)	11 (5.5)	40 (6.6)
300 - 400	176 (85.4)	168 (82.4)	169 (84.5)	513 (84.1)
[illegible] - 500	5 (2.4)	13 (6.4)	10 (5.0)	28 (4.6)
500 - 600	2 (1.0)	3 (1.5)	3 (1.5)	8 (1.3)
≥ 600	8 (3.9)	6 (2.9)	7 (3.5)	21 (3.4)

Abbreviations: ALLO, allopurinol; eCrCl, estimated creatinine clearance; ITT, Intent-to-treat; LESU, lesinurad; Max, maximum; Min, minimum; PBO, placebo; SD, standard deviation; sUA, serum urate; ULT, urate-lowering therapy.
Note: Baseline eCrCl was calculated using the highest serum creatinine value recorded ≤ 14 days prior to the first dose of randomized study medication. Twenty-one subjects were mis-stratifed (Listing 16.1.1.2).
[a] Actual stratification factor values.
[b] Subjects had received a medically appropriate stable dose of allopurinol for at least 10 weeks before their Baseline Visit.
[c] More than one response can apply; percentages can sum to > 100%.

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Outcomes and estimation

Primary efficacy endpoint analysis

The proportion of subjects who achieved the target of sUA < 6.0 mg/dL at Month 6 was 55.4% and 66.5% versus 23.3% for lesinurad 200 mg qd, lesinurad 400 mg qd, and placebo arms respectively (p < 0.0001 for both comparisons). Patients with missing data at month 6 were included as non-responders.

Table 34. Primary Endpoint: Proportion of Subjects with an sUA Level < 6.0 mg/dL by Month 6 – Non-Responder Imputation (ITT Population, Study 302)

	PBO + ALLO (N=206) n (%)	LESU 200 mg + ALLO (N=204) n (%)	LESU 400 mg + ALLO (N=200) n (%)
Proportion with sUA < 6.0 mg/dL by Month 6	48 (23.3)	113 (55.4)	133 (66.5)
Difference in proportions vs. PBO + ALLO (95% CI)		0.32 (0.23, 0.41)	0.43 (0.34, 0.52)
p-value[a]		<0.0001	<0.0001

Abbreviations: ALLO, allopurinol; ITT, Intent-to-treat; LESU, lesinurad; PBO, placebo; sUA, serum urate.
[a] Cochran-Mantel Haenszel test stratified by Day -7 renal function (eCrCl ≥ 60 mL/min versus < 60 mL/min) and tophus status during Screening (presence versus absence), randomized values.
Note: sUA, serum urate. Subjects missing the Month 6 sUA result are treated as non-responders.

Sensitivity analyses

Using the LOCF imputation method, the proportion of subjects who achieved the target of sUA < 6.0 mg/dL at Month 6 was 62.8% and 71.1% versus 25.5% for lesinurad 200 mg qd, lesinurad 400 mg qd, and placebo arms respectively (p < 0.0001 for both comparisons).

The proportion of subjects with sUA < 6.0 mg/dL at 3 consecutive study visits (Months 4, 5, and 6) using nonresponder imputation for lesinurad 200 mg, lesinurad 400 mg and placebo were 41.2% and 48.5% vs. 13.1% (p < 0.0001 for both comparisons).

The results in the Per Protocol Population confirmed those of the primary analysis. In the Per Protocol Population, significantly more subjects in the lesinurad 200 mg and lesinurad 400 mg groups achieved the target goal of sUA < 6.0 mg/dL at Month 6 compared with the placebo group: 57.7% and 69.6% vs. 24.2% respectively (p < 0.0001 for both comparisons).

sUA secondary endpoint analyses

The mean absolute and mean percentage changes for both doses of lesinurad in combination with allopurinol were significantly greater than those for placebo +allopurinol at all time-points (p < 0.0001 for all comparisons, **Figure 16**).

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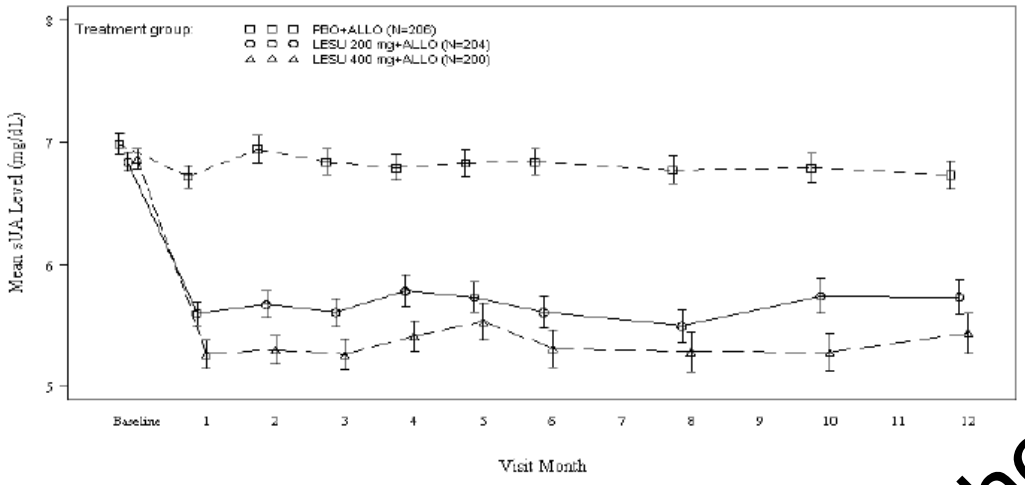
Figure 16. Mean Serum Urate Levels by Visit- Observed Cases (ITT Population, Study 302)



Abbreviations: ALLO, allopurinol; ITT, Intent-to-treat; LESU, lesinurad; PBO, placebo; sUA, serum urate.
Note: End of study/early termination data are included in the appropriate visit month if no scheduled visit occurred during that visit month. Error bars represent standard error of the mean. Months 7, 9, and 11 data are excluded because the timing of the last protocol amendment (Protocol Amendment 6), which added sUA assessments at these timepoints, resulted in minimal data collection at these timepoints for NRI analysis.
At each post-Baseline visit (ie, Months 1 through 12), the adjusted differences in the mean change from Baseline in sUA levels for the LESU 200 mg + ALLO and LESU 400 mg + ALLO groups versus PBO + ALLO groups had $p < 0.0001$.

Other secondary efficacy endpoint analyses

Gout flares

The rates of gout flares per subject that required treatment over the 6-month period from end of Month 6 to end of Month 12 were 0.73, 0.77 and 0.83 for the lesinurad 200 mg, lesinurad 400 mg and placebo groups respectively. The rates for the lesinurad groups were not significantly different from the placebo group.

The proportion of subjects requiring treatment for a gout flare between the end of Month 6 and the end of Month 12 was 31.3%, 30.5% and 32.2% for the lesinurad 200 mg, lesinurad 400 mg and placebo groups respectively.

Analyses of subject diary entries for gout flares requiring treatment demonstrated no clear patterns of differences for duration of gout flare, pain scores, associated gout flare symptoms and gout flare treatment.

Tophus resolution

The proportions of subjects with > 1 target tophus at baseline who achieved a complete response by Month 12 were 11/35 (31.4%) and 8/29 (27.6%) versus 11/33 (33.3%) for the lesinurad 200 mg, lesinurad 400 mg and placebo groups respectively

There was no significant difference between treatment groups in the mean % change from baseline in the sum of the areas for all target tophi at Month 12.

Study 304: A phase 3 randomized, double-blind, multicentre, placebo-controlled, combination study to evaluate the efficacy and safety of lesinurad and febuxostat compared to febuxostat alone at lowering serum uric acid and resolving tophi in subjects with tophaceous gout.

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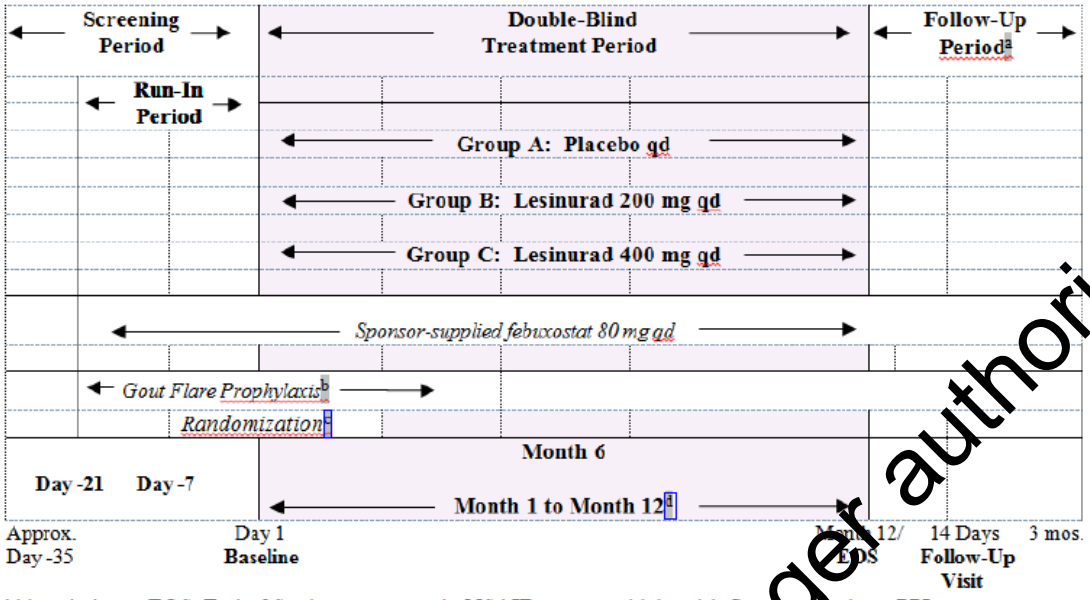
Methods
The design of the study is depicted in **Figure 17**.

Figure 17. Design of Study 304



Abbreviations: EOS, End of Study; mos., month; NSAID, nonsteroidal anti-inflammatory drug; PPI, proton pump inhibitor; qd, once daily.

[a] Subjects who did not enter an extension study were required to attend a Follow-Up Visit within approximately 14 days of completing the Double-Blind Treatment Period. Subjects who completed the study and did not continue into an extension study, or who withdrew from the study for any reason other than consent withdrawn and had a serum creatinine (sCr) value > 0.1 mg/dL above their Baseline value were followed until their sCr value was ≤ 0.1 mg/dL of their Baseline value or until 3 monthly assessments after their Follow-Up Visit took place, whichever came first.

[b] Prophylactic treatment for gout flare consisted of colchicine 0.5 to 0.6 mg qd or NSAID ± PPI through Month 5.

[c] Subjects who qualified for the study were randomized in a double-blind fashion to 1 of 3 treatment groups in a 1:1:1 ratio: Groups A, B, or C.

[d] Study visits at Week 2 and monthly from Month 1 through Month 12 (or early termination).

Study participants

Main inclusion criteria:

- Subject is ≥ 18 years and ≤ 85 years of age;
- Subject is male or female; female of childbearing potential who agrees to use non-hormonal contraception;
- Subject meets the diagnosis of gout as per the American Rheumatism Association Criteria for the Classification of Acute Arthritis of Primary Gout;
- Subject meets one of the following criteria:
    - subjects who are not currently taking an approved ULT must have an sUA value ≥8 mg/dL (476 µmol/L);
    - subjects entering the study on a medically appropriate dose of febuxostat or allopurinol must have an sUA value ≥ 6.0 mg/dL (357 µmol/L);
- Subject must be able to take gout flare prophylaxis with colchicine or an NSAID (including Cox-2 selective NSAID) ± PPI;
- Subject with at least 1 measurable tophus on the hands/wrists and/or feet/ankles ≥5 mm and ≤ 20 mm in the longest diameter.

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Main exclusion criteria:

- Subject with an acute gout flare that has not resolved at least 7 days before the Baseline Visit (Day 1);
- Subject with known hypersensitivity or allergy to febuxostat;
- Subject who is taking any other approved urate-lowering medication that is indicated for the treatment of gout other than allopurinol (eg, uricosuric agent) within 8 weeks of the Screening Visit;
- Subject who previously received pegloticase;
- Subject who previously participated in a clinical study involving lesinurad (RDEA594) or RDEA806 and received active treatment or placebo;
- Subject who is pregnant or breastfeeding;
- Subject with an estimated creatinine clearance < 30 mL/min calculated by the Cockcroft-Gault formula using ideal body weight.

Subjects were randomised at 102 sites in 3 regions: North America (80.6%), Europe (10.3%), and Australia/New Zealand (9.1%).

Treatments

At the start of a 21 day run-in period (day -21), subjects discontinued their ULT (if applicable) and began taking 80 mg qd of sponsor-supplied febuxostat. At day 1, subjects were randomised 1:1:1 to:

- Lesinurad 200 mg qd + febuxostat 80 mg qd
- Lesinurad 400 mg qd + febuxostat 80 mg qd
- Placebo + febuxostat 80 mg

All subjects were to receive randomised study medication, in addition to febuxostat, for 12 months.

All doses of lesinurad/placebo were taken in the morning with food and 240 mL water. Subjects were instructed to drink 2L of liquid per day. Febuxostat was taken at the same time as lesinurad/placebo. If febuxostat was interrupted, lesinurad/placebo was also stopped until febuxostat was resumed.

Objectives

Primary objective:

To determine the efficacy of lesinurad by Month 6 when used in combination with febuxostat compared to febuxostat monotherapy.

A secondary objective was to determine efficacy and safety by Month 12.

Outcomes/endpoints

Primary endpoint:

- The proportion of subjects with a sUA level that is < 5.0 mg/dL by Month 6.

Key secondary endpoints:

- Proportion of subjects who experience complete resolution of at least 1 target tophus by Month 12;

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- Proportion of subjects with a best tophus response on at least 1 target tophus of complete or partial resolution by Month 12;
- Proportion of subjects with an improvement from Baseline in HAQ-DI of at least 0.25 at Month 12.

Other sUA related secondary endpoints:

- Proportion of subjects whose sUA level is < 6.0 mg/dL, < 5.0 mg/dL and < 4.0 mg/dL at each visit;
- Absolute and percent change from Baseline in sUA levels at each visit

Other tophus related secondary endpoints:

- Mean percent change from Baseline in the sum of the areas of all target tophi at each visit;
- Proportion of subjects whose sUA level is < 6.0 mg/dL, < 5.0 mg/dL and < 4.0 mg/dL at each visit.

Other gout flares related secondary endpoints:

- Mean rate of gout flares requiring treatment for the 6 month period from the end of Month 6 to the end of Month 12;
- Proportion of subjects requiring treatment for a gout flare at monthly intervals between Month 6 and Month 12.

Sample size

Approximately 315 subjects were to be randomized in this study, of which approximately 105 subjects were to be randomized to each treatment group. Based on previous studies of lesinurad and febuxostat, it was conservatively assumed that the proportion of subjects with sUA < 5.0 mg/dL after 6 months of treatment would be 40% or less in the placebo plus febuxostat group and 65% or higher in the lesinurad plus febuxostat groups. Detecting a significant treatment effect under these assumptions with approximately 90% power and $\alpha = 0.025$ (two-sided) required 105 subjects per treatment group using Fishers exact test.

Randomisation

Subjects were randomised to the 3 treatment groups in the ratio 1:1:1. Randomisation was stratified by:

- Renal function at day -7: eCrCl $\geq$ 60 mL/min vs. < 60 mL/min (calculated by the Cockcroft-Gault formula using IBW)
- sUA at Day -7: $\geq$ 6.0 mg/dL versus < 6.0 mg/dL

Subjects were randomised after the Investigator verified that they were eligible for the study. Randomisation took place across all study sites using a centralized interactive voice response system / interactive web response system.

Blinding (masking)

This was a double-blind study.

Statistical methods

These were similar to those used in Studies 301 and 302.

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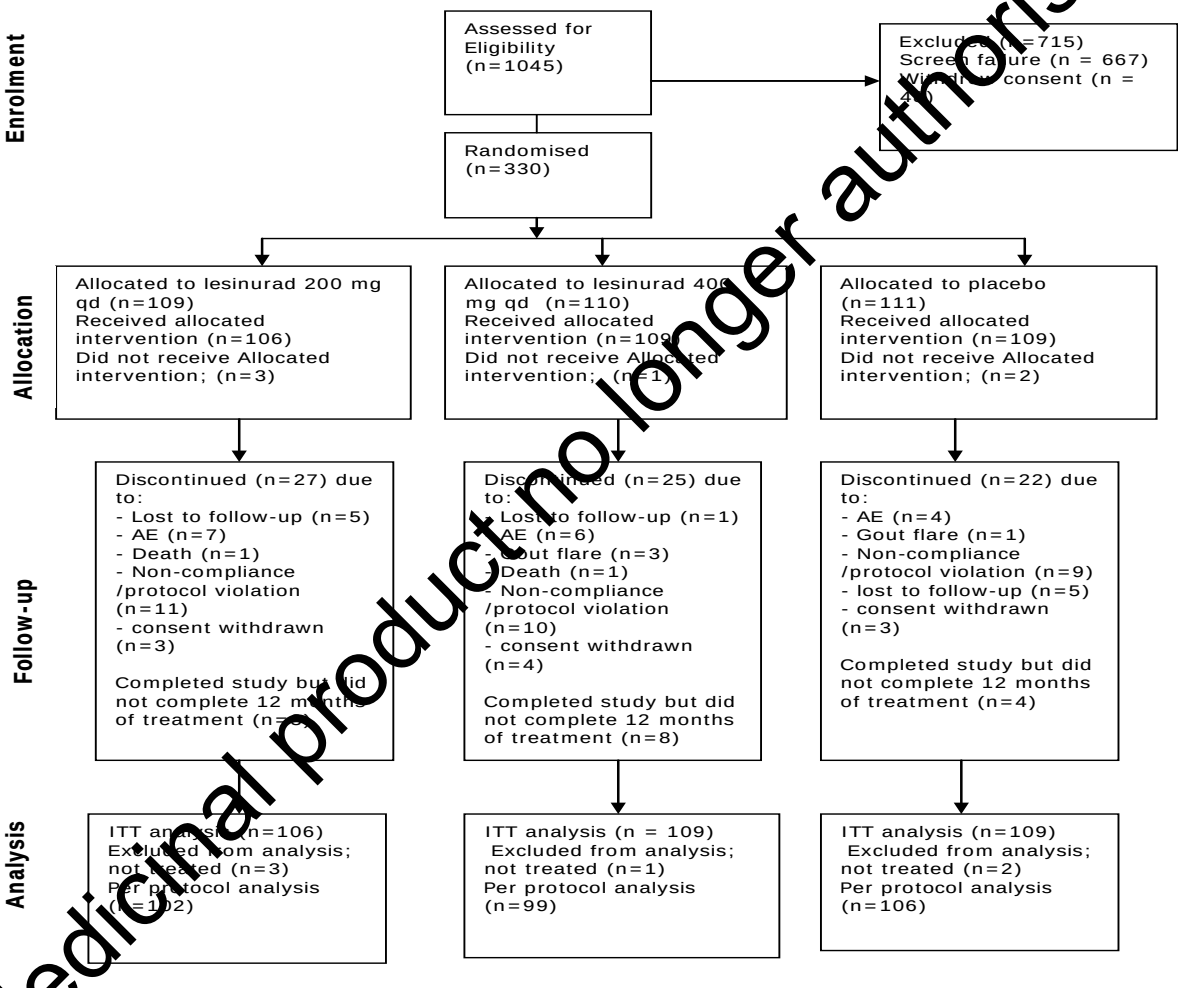
Diverse sensitivity analyses were performed to evaluate the robustness of the primary endpoints.

Subgroup analyses were performed in subjects that did not already achieve the target sUA < 5mg/dL after the 3 weeks open-label lead-in of febuxostat monotherapy. Additional sensitivity analyses were either different approaches of missing data (LOCF, Per-Protocol population, Observed Cases), different cut-off points of sUA (<3,4,6 mg/dL at Month 6), or endpoints reflecting a more sustained effect on sUA levels ((a) sUA < 5 mg/dL at Month 4,5,6 consecutively or on at Month 12, subjects with a median sUA level <5 mg/dL throughout the study), or the immediate effect (< 5 mg/dL at Month 1).

Results

Participant flow



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Recruitment

Study initiation date: 23 February 2012 (first subject first visit)

Study completion date: 17 April 2014 (last subject last visit)

Conduct of the study

There were 4 substantial protocol amendments during the study but before breaking the blind.

The first clarified that a dose reduction of febuxostat to 40 mg qd following interruption due to potential toxicity was not permitted. No subjects were randomised prior to this amendment.

With the second, the sUA inclusion criterion was lowered from ≥ 10 mg/dL to ≥ 8 mg/dL for subjects not taking an approved ULT at screening. The gout flare secondary endpoint was also modified, including an increase in the period of observation. 80 patients were randomised prior to this amendment.

The other two were the same as the ones applied to Studies 301 and 302 regarding expanded guidance on hydration and the tightening of renal function monitoring triggered by the results in Study 303.

The most common PDV was randomised study medication non-compliance, affecting 2.8%, 7.3% and 0.9% of the lesinurad 200 mg, lesinurad 400 mg, and placebo groups, respectively. 5.5% of subjects were excluded from the per protocol population.

Baseline data

The study population was predominantly male and white, with a median age of 54 years. Around 3% were over 75 years of age. Mean body mass index was 32.0 kg/m^2. Demographic characteristics were balanced between the groups and summarised in **Table 35**.

Table 35. Demographic Characteristics (ITT Population, Study 304)

Variable	PBO + FBX 80 mg (N=109)	LESU 200 mg + FBX 80 mg (N=106)	LESU 400 mg + FBX 80 mg (N=109)	TOTAL (N=324)
Sex [n (%)]				
Female	2 (1.8)	6 (5.7)	7 (6.4)	15 (4.6)
Male	107 (98.2)	100 (94.3)	102 (93.6)	309 (95.4)
Race [n (%)]				
American Indian or Alaska Native	0	1 (0.9)	0	1 (0.3)
Asian	6 (5.5)	8 (7.5)	6 (5.5)	20 (6.2)
Black or African American	8 (7.3)	14 (13.2)	13 (11.9)	35 (10.8)
Maori	0	0	3 (2.8)	3 (0.9)
Native Hawaiian or other Pacific Islander	0	1 (0.9)	2 (1.8)	3 (0.9)
White	94 (86.2)	80 (75.5)	85 (78.0)	259 (79.9)
Other	1 (0.9)	2 (1.9)	0	3 (0.9)
Ethnicity [n (%)]				
Hispanic or Latino	9 (8.3)	7 (6.6)	5 (4.6)	21 (6.5)
Not Hispanic or Latino	100 (91.7)	99 (93.4)	104 (95.4)	303 (93.5)
Age (years)				
n	109	106	109	324
Mean (SD)	54.6 (10.87)	54.2 (11.04)	53.3 (11.16)	54.1 (11.00)
Median	54.0	54.0	53.0	54.0
Min, Max	27, 77	28, 80	28, 82	27, 82
Age group (years) [n (%)]				
< 65	89 (81.7)	89 (84.0)	90 (82.6)	268 (82.7)
≥ 65	20 (18.3)	17 (16.0)	19 (17.4)	56 (17.3)
65 - 74	17 (15.6)	13 (12.3)	16 (14.7)	46 (14.2)
≥ 75	3 (2.8)	4 (3.8)	3 (2.8)	10 (3.1)

Abbreviations: FBX, febuxostat; ITT, Intent-to-treat; LESU, lesinurad; Max, maximum; Min, minimum; PBO, placebo; SD, standard deviation.

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The mean duration since gout diagnosis was around 15 years. The mean number of target tophi at baseline was 1.8. The mean number of gout flares reported in the past 12 months was 6.7. Moderate renal impairment (eCrCl < 60 mL/min) was present at baseline for 23.1. Baseline sUA was <5.0 mg/dL for more than 50% of all subjects: 44.3%, 53.2% and 53.2% in the lesinurad 200 mg, lesinurad 400 mg and placebo groups respectively. Baseline Disease and Treatment Characteristics are summarised in **Table 36**.

Table 36. Baseline Disease and Treatment Characteristics (ITT Population, Study 304)

Variable	PBO + FBX 80 mg (N=109)	LESU 200 mg +FBX 80 mg (N=106)	LESU 400 mg +FBX 80 mg (N=109)	TOTAL (N=324)
American Rheumatism Association diagnostic criteria [n (%)]	109 (100)	106 (100)[a]	109 (100)	324 (100)
Duration since gout diagnosis (years)				
n	109	106	109	324
Mean (SD)	15.17 (10.90)	15.82 (11.00)	13.15 (10.64)	14.71 (10.87)
Median	12.20	14.10	10.10	12.80
Min, Max	0.3, 51.0	0.2, 49.2	0.0, 53.1	0.0, 53.1
Number of target tophi at Baseline				
n	109	106	109	324
Mean (SD)	1.9 (1.3)	1.8 (1.3)	1.8 (1.2)	1.8 (1.2)
Median	1.0	1.0	1.0	1.0
Min, Max	1, 5	0, 5	1, 5	0, 5
Number of target tophi at Baseline [n (%)]				
0	0	1 (0.9)	0	1 (0.3)
1	56 (51.4)	62 (58.5)	63 (57.8)	181 (55.9)
2	26 (23.9)	21 (19.8)	26 (23.9)	73 (22.5)
3	14 (12.8)	8 (7.5)	9 (8.3)	31 (9.6)
4	3 (2.8)	6 (5.7)	4 (3.7)	13 (4.0)
5	10 (9.2)	8 (7.5)	7 (6.4)	25 (7.7)
Total area of target tophi at Baseline (mm^2)				
n	109	105	109	323
Mean (SD)	291.08 (246.36)	310.12 (227.85)	280.34 (230.28)	293.64 (234.65)
Median	220.40	241.57	210.60	216.72
Min, Max	11.52, 1352.68	12.10, 1172.85	37.40, 1233.56	11.52, 1352.68
Number of gout flares in the past 12 months				
n	109	106	109	324
Mean (SD)	6.1 (5.1)	6.9 (11.2)	7.0 (7.4)	6.7 (8.2)
Median	4.0	4.0	4.0	4.0
Min, Max	2, 24	0, 104	0, 50	0, 104
Number of gout flares in the past 12 months [n (%)]				
0	0	1 (0.9)	2 (1.8)	3 (0.9)
1	0	4 (3.8)	6 (5.5)	10 (3.1)
2	19 (17.4)	12 (11.3)	12 (11.0)	43 (13.3)
3	26 (23.9)	21 (19.8)	18 (16.5)	65 (20.1)
4	13 (11.9)	20 (18.9)	18 (16.5)	51 (15.7)
≥5	51 (46.8)	48 (45.3)	53 (48.6)	152 (46.9)
Renal function at Day -7[b] (mL/min) [n (%)]				
eCrCl ≥ 60	86 (78.9)	83 (78.3)	88 (80.7)	257 (79.3)
eCrCl < 60	23 (21.1)	23 (21.7)	21 (19.3)	67 (20.7)
Renal function at Baseline (mL/min) [n (%)]				
eCrCl ≥ 90	31 (28.4)	37 (34.9)	42 (38.5)	110 (34.0)
eCrCl < 90	78 (71.6)	69 (65.1)	67 (61.5)	214 (66.0)
eCrCl ≥ 60	84 (77.1)	78 (73.6)	87 (79.8)	249 (76.9)

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Variable	PBO + FBX 80 mg (N=109)	LESU 200 mg +FBX 80 mg (N=106)	LESU 400 mg +FBX 80 mg (N=109)	TOTAL (N=324)
eCrCl < 60	25 (22.9)	28 (26.4)	22 (20.2)	75 (23.1)
eCrCl ≥ 45	105 (96.3)	98 (92.5)	101 (92.7)	304 (93.8)
eCrCl < 45	4 (3.7)	8 (7.5)	8 (7.3)	20 (6.2)
eCrCl 60 - < 90	53 (48.6)	41 (38.7)	45 (41.3)	139 (42.9)
eCrCl 30 - < 60	23 (21.1)	28 (26.4)	22 (20.2)	73 (22.5)
eCrCl 45 - < 60	21 (19.3)	20 (18.9)	14 (12.8)	55 (17.0)
eCrCl 30 - < 45	2 (1.8)	8 (7.5)	8 (7.3)	18 (5.6)
eCrCl < 30	2 (1.8)	0	0	2 (0.6)
sUA level at Screening (mg/dL)				
n	109	106	109	324
Mean (SD)	8.83 (1.53)	8.71 (1.58)	8.57 (1.76)	8.71 (1.62)
Median	8.70	9.00	8.70	8.75
Min, Max	5.5, 12.4	4.8, 13.3	4.5, 13.2	4.5, 13.3
sUA level at Day -7 (mg/dL)				
n	109	106	109	324
Mean (SD)	5.27 (1.34)	5.36 (1.78)	5.19 (1.48)	5.28 (1.54)
Median	5.10	5.10	5.00	5.10
Min, Max	2.4, 9.3	2.2, 12.2	2.0, 10.2	2.0, 12.2
sUA level at Baseline[c] (mg/dL)	109	106	109	324
n	109	106	109	324
Mean (SD)	5.22 (1.53)	5.35 (1.72)	5.23 (1.64)	5.27 (1.63)
Median	4.90	5.10	4.80	4.90
Min, Max	2.2, 9.6	2.0, 11.6	1.4, 10.0	1.4, 11.6
sUA category at Baseline (mg/dL) [n (%)]				
< 5.0	58 (53.2)	47 (44.3)	58 (53.2)	163 (50.3)
5.0 - < 6.0	19 (17.4)	28 (26.4)	23 (21.1)	70 (21.6)
6.0 - < 7.0	16 (14.7)	14 (13.2)	11 (10.1)	41 (12.7)
7.0 - < 8.0	12 (11.0)	9 (8.5)	8 (7.3)	29 (9.0)
8.0 - < 10.0	4 (3.7)	6 (5.7)	8 (7.3)	18 (5.6)
≥ 10.0	0	2 (1.9)	1 (0.9)	3 (0.9)
sUA category at Day -7[b] (mg/dL) [n (%)]				
< 6.0	80 (73.4)	78 (73.6)	81 (74.3)	239 (73.8)
≥ 6.0	29 (26.6)	28 (26.4)	28 (25.7)	85 (26.2)
Prior ULT[d] [n (%)]				
Allopurinol	38 (34.9)	26 (24.5)	28 (25.7)	92 (28.4)
Febuxostat	4 (3.7)	2 (1.9)	6 (5.5)	12 (3.7)
Benzbromarone	1 (0.9)	1 (0.9)	0	2 (0.6)
Probenecid	2 (1.8)	2 (1.9)	1 (0.9)	5 (1.5)
Pegloticase	0	0	0	0
Other	0	0	1 (0.9)	1 (0.3)
Type of gout flare prophylaxis at Baseline [n (%)]				
Colchicine	87 (79.8)	95 (89.6)	94 (86.2)	276 (85.2)
NSAID	26 (23.9)	10 (9.4)	20 (18.3)	56 (17.3)
Both	4 (3.7)	1 (0.9)	5 (4.6)	10 (3.1)

Abbreviations: eCrCl, estimated creatinine clearance; FBX, febuxostat; ITT, Intent-to-treat; LESU, lesinurad; Max, maximum; Min, minimum; NSAID, nonsteroidal anti-inflammatory drug; PBO, placebo; SD, standard deviation; sUA, serum urate; ULT, urate-lowering therapy.

Note: Baseline eCrCl was calculated using the highest serum creatinine value recorded ≤ 14 days prior to the first dose of randomized study medication. One subject in the LESU 400 mg + FBX group was mis-stratifed (Listing 16.1.1.2).

[a] One subject was reported to have a diagnosis of gout per the ARA criteria at the start of the study; however, it was later determined that the diagnosis was not adequately documented and did not meet the criteria (a protocol deviation). See Listing 16.1.2.

[b] Actual stratification factor values.

[c] Subjects had received approximately 21 days of treatment with febuxostat 80 mg qd alone before their Baseline Visit.

[d] More than one response can apply; percentages can sum to > 100%. Prior ULT reflects data captured by sites on the Prior ULT CRF.

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Outcomes and estimation

Primary efficacy endpoint analysis

The results of the primary efficacy endpoint are presented in **Table 37**. Patients with missing data at month 6 were included as non-responders.

The difference between the lesinurad 400 mg qd and placebo groups was statistically significant (p < 0.0001). However for lesinurad 200 mg qd vs. placebo, the difference was not statistically significant.

Table 37. Primary Endpoint: Proportion of Subjects with an sUA Level < 5.0 mg/dL by Month 6 – Non-Responder Imputation (ITT Population, Study 304)

	PBO + FBX 80 mg (N=109) n (%)	LESU 200 mg + FBX 80 mg (N=106) n (%)	LESU 400 mg + FBX 80 mg (N=109) n (%)
Proportion with sUA < 5.0 mg/dL by Month 6	51 (46.8)	60 (56.6)	83 (76.1)
Difference in proportions vs. PBO + FBX 80 mg (95% CI)		0.10 (-0.03, 0.23)	0.29 (0.17, 0.42)
p-value[a]		0.1298	<0.0001*

Abbreviations: CI, confidence interval; FBX, febuxostat; ITT, Intent-to-treat; LESU, lesinurad; PBO, placebo; sUA, serum urate.
[a] Cochran-Mantel Haenszel test stratified by Day -7 renal function (eCrCl ≥ 60 mL/min versus < 60 mL/min) and Day -7 sUA status (sUA ≥ 6.0 mg/dL versus < 6.0 mg/dL), randomized values.
*Statistically significant after adjustment for multiple testing.
Note: Subjects missing the Month 6 sUA result were treated as nonresponders.

Sensitivity analyses

Using the LOCF imputation method, the proportion of subjects who achieved the target of sUA < 5.0 mg/dL at Month 6 was 64.1% for lesinurad 200 mg vs. 50.9% for placebo (p=0.0377). For the lesinurad 400 mg group the proportion was 83.0% (p<0.0001 vs. placebo).

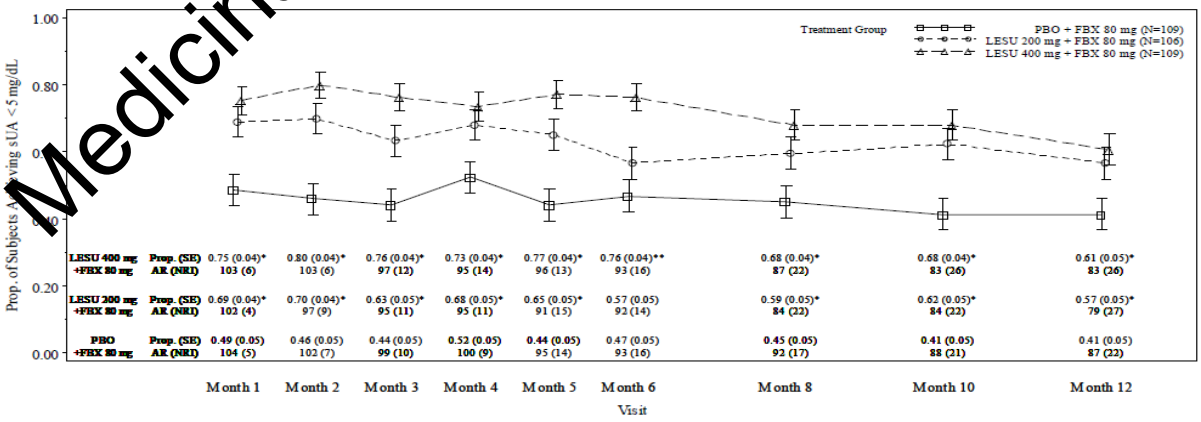
The proportion of subjects with an sUA < 5.0 mg/dL at 3 consecutive study visits (Months 4, 5, and 6) using nonresponder imputation was higher in the lesinurad 200 mg group compared with the placebo group (51.9% versus 33.0%, respectively; p = 0.0034), and in the lesinurad 400 mg group compared with placebo (64.2% versus 33.0%; p < 0.0001).

The results in the Per Protocol Population confirmed those of the primary analysis. In the Per Protocol Population, significantly more subjects in the lesinurad 400 mg group achieved the target goal of sUA < 5.0 mg/dL at Month 6 compared with the placebo group: 80.0% vs. 58.8% (p < 0.0001). The respective proportions for the comparison of lesinurad 200 mg with placebo was 58.8% vs. 48.1% (p = 0.1001).

sUA secondary endpoint analyses

At all time-points other than Month 6 (primary endpoint), the increase in sUA lowering in the lesinurad 200 mg group, compared to placebo, was statistically significant, **Figure 18**.

Figure 18. Proportion of Subjects Achieving sUA Level Target < 5.0 mg/dL by Visit Line Plot Using Non-responder Imputation (ITT Population, Study 304)



Abbreviations: AR, at risk; ITT, Intent-to-treat; LESU, lesinurad; NRI, nonresponder imputation; PBO, placebo; Prop, proportion; SE, standard error; sUA, serum urate.
* Indicates p < 0.05.
** Indicates statistical significance of treatment group vs. placebo at the 0.025 level 2-sided using Cochran-Mantel Haenszel test stratified by Day-7 renal function and Day-7 sUA status (randomized values) after adjustment for multiple comparisons (primary endpoint).
Note: Months 7, 9, and 11 data are excluded because the timing of the last protocol amendment (Protocol Amendment 5), which added sUA assessments at these timepoints, resulted in minimal data collection at these timepoints for NRI analysis.

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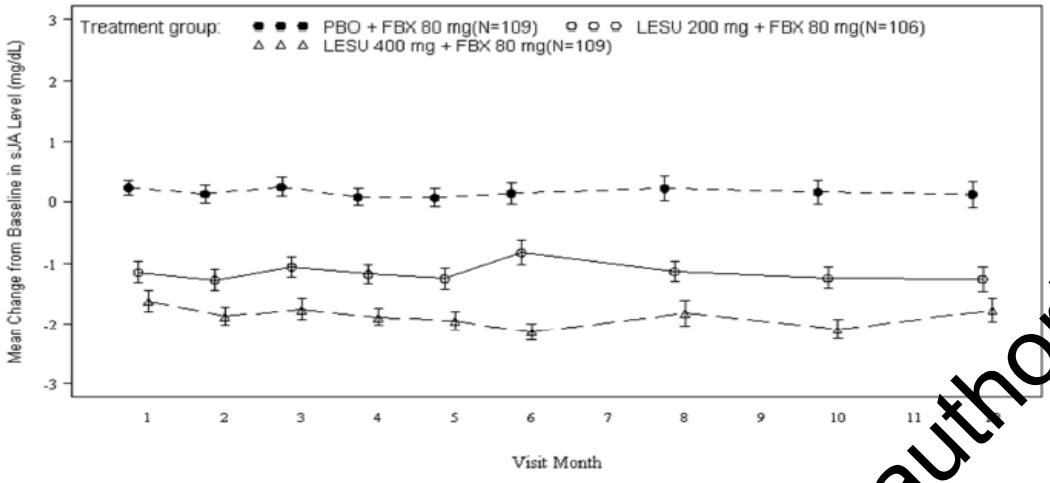
The mean absolute and mean percentage changes for both doses of lesinurad + febuxostat were significantly greater than those for placebo + febuxostat at all time-points (**Figure 19**).

Figure 19. Mean Serum Urate Levels by Visit- Observed Cases (ITT Population, Study 304)



Abbreviations: FBX, febuxostat; ITT, Intent-to-treat; LESU, lesinurad; PBO, placebo; sUA, serum urate.
Note: End of Study/Early Termination data are included in the appropriate visit month if no scheduled visit occurred during that visit month. Error bars represent SE. Months 7, 9, and 11 data are excluded because the timing of the last protocol amendment (Protocol Amendment 5), which added sUA assessments at these timepoints, resulted in minimal data at these timepoints for NRI analysis.

Subgroup analyses were also performed in subjects that had not achieved the target sUA < 5mg/dL after the 3 weeks open-label lead-in of febuxostat monotherapy and are summarised in **Table 38**.

Table 38. Proportion of subjects with an sUA < 5.0 mg/dL by visit- Non responder imputation (ITT population, baseline sUA subgroup ≥5 mg/dl, Study 304)

Visit	PBO + FBX 80 mg (N=51) n (%)	LESU 200 mg + FBX 80 mg (N=59) n (%)	LESU 400 mg + FBX 80 mg (N=51) n (%)
Month 6	12 (23.5)	26 (44.1)	36 (70.6)
Difference in proportions vs. PBO + FBX 80 mg (95% CI)		0.21 (0.03, 0.38)	0.47 (0.30, 0.64)
p-value[a]		0.0243	<0.0001
Month 12	12 (23.5)	27 (45.8)	24 (47.1)
Difference in proportions vs. PBO + FBX 80 mg (95% CI)		0.22 (0.05, 0.39)	0.24 (0.06, 0.42)
p-value		0.0136	0.0137

[a] Cochran-Mantel Haenszel test stratified by Day -7 renal function (eCrCl ≥ 60 mL/min versus < 60 mL/min) as factors, randomized values.
Note: sUA, serum urate; PBO, placebo; FBX, febuxostat; LESU, lesinurad. Subjects missing an sUA result at a visit are treated as non-responders for that visit. End of study/early termination data are included in the appropriate visit month if no scheduled visit occurred during that visit month. Months 7, 9, and 11 data are excluded due to the limited data because of the timing of the last protocol amendment where these measurements were implemented.

In this subgroup, subjects treated with lesinurad were also more likely to have sustained sUA response achieving target sUA < 5.0 mg/dL at 3 consecutive months (between months 4 and 6, **Table 39**).

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Table 39. Proportion of subjects with an sUA < 5.0 mg/dL at each of months 4, 5 and 6- Non responder imputation (ITT population, baseline sUA subgroup ≥5 mg/dl, Study 304)

	PBO + FBX 80 mg (N=51) n (%)	LESU 200 mg + FBX 80 mg (N=59) n (%)	LESU 400 mg + FBX 80 mg (N=51) n (%)
Proportion with sUA < 5.0 mg/dL at each of Months 4, 5, and 6[a]	6/51 (11.8)	23/59 (39.0)	27/51 (52.9)
Difference in proportions vs. PBO + FBX 80 mg (95% CI)		0.27 (0.12, 0.42)	0.41 (0.25, 0.57)
p-value[b]		0.0013	<0.0001

[a] Subjects missing any of the Months 4, 5, or 6 sUA results are treated as non-responders.
[b] Cochran-Mantel Haenszel test stratified by Day -7 renal function (eCrCl ≥ 60 mL/min versus < 60 mL/min), randomized values. Nominal p-value without adjustment for multiplicity.

In the lesinurad 200 mg group, 23/59 (39%), achieved this target compared to and 27/51 (52.9%) and 6/51 (11.8%) of the subjects treated with lesinurad 400mg and placebo respectively. The differences in the proportions were 0.27 (95% CI: 0.12, 0.42), p = 0.0013 for lesinurad 200 + febuxostat and 0.41 (95% CI: 0.25, 0.57), p < 0.0001 for lesinurad 400mg + febuxostat compared to placebo + febuxostat.

The results of a sensitivity analysis of subjects with Baseline sUA ≥7.0 mg/dL in Study 304 is shown in **Table 40**.

Table 40. Proportion of subjects with a baseline serum uric acid ≥7.0 mg/dL who achieved a serum uric acid < 5.0 by month 6-NRI in study (ITT population)

	Study 304		
	PBO + FBX 80 mg (N=16) n (%)	LESU 200 mg + FBX 80 mg (N=17) n (%)	LESU 400 mg + FBX 80 mg (N=17) n (%)
Proportion with sUA < 5.0 mg/dL by Month 6	0	4 (23.5)	10 (58.8)
Difference in proportions vs. PBO + FBX (95% CI)		0.24 (0.03, 0.44)	0.59 (0.35, 082)
p-value[a]		0.0440	0.0003

Abbreviations: CI, confidence interval; eCrCl, estimated creatinine clearance; FBX, febuxostat; ITT, intent-to-treat; LESU, lesinurad; NRI, non-responder imputation; PBO, placebo; sUA, serum uric acid..
Note: Subjects missing the Month 6 sUA result are treated as non-responders.
[a] Cochran-Mantel-Haenszel test stratified by Day -7 renal function (eCrCl ≥ 60 mL/min versus < 60 mL/min) and Day -7 sUA status (sUA ≥ 6.0 mg/dL versus < 6.0 mg/dL), randomized values.

Key secondary outcomes

In accordance with the hierarchical testing schedule, the key secondary endpoints were not formally tested for the 200 mg dose, as the primary endpoint failed. For the 400 mg dose, the formal testing stopped right after the first key secondary tested, as this one failed to meet statistical significance

Other secondary efficacy endpoint analyses

Tophus resolution

The proportions of subjects who achieved a complete response for at least one target tophus by Month 12 were 25.5% and 30.3% versus 21.1% for the lesinurad 200 mg, lesinurad 400 mg and placebo

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groups respectively. The differences were not statistically significant. Results were similar for proportions achieving a complete or partial response (56.6% and 58.7% versus 50.5%, respectively).

By Month 12, reductions in the sum of the areas of all target tophi were observed in all groups. The mean % change from baseline at 12 months was 55.8% and 57.9% vs. 31.3% for lesinurad 200 mg, lesinurad 400 mg and placebo groups respectively (observed cases). The differences between both lesinurad groups and placebo were statistically significant ($p<0.05$).

Gout flares

The rates of gout flares per subject that required treatment over the 6-month period from end of Month 6 to end of Month 12 were 1.4, 0.7 and 1.2 for the lesinurad 200 mg, lesinurad 400 mg and placebo groups respectively. The rate for the lesinurad 400 mg group was statistically significantly lower than placebo ($p<0.05$).

The proportion of subjects requiring treatment for a gout flare between the end of Month 6 and the end of Month 12 was 42.0%, 31.2% and 38.9% for the lesinurad 200 mg, lesinurad 400 mg and placebo groups respectively.

Analyses of subject diary entries for gout flares requiring treatment demonstrated no clear patterns of differences for duration of gout flare, pain scores, associated gout flare symptoms and gout flare treatment.

Summary of main studies

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 41. Summary of Efficacy for Study 301

Title: A phase 3 randomized, double-blind, multicentre, placebo-controlled, combination study to evaluate the efficacy and safety of lesinurad and allopurinol compared to allopurinol alone in subjects with gout who have had an inadequate hypouricaemic response to standard of care allopurinol.			
Study identifier	301		
Design	Randomised, double-blind, placebo-controlled multicentre study		
	Duration of main phase:		48 weeks
	Duration of Run-in phase:		14 days
	Duration of Extension phase:		not applicable
Hypothesis	Superiority		
Treatments groups	Lesinurad 200 mg		Lesinurad 200 mg qd + allopurinol for 48 weeks; randomized n=202
	Lesinurad 400 mg		Lesinurad 400 mg qd + allopurinol for 48 weeks; randomized n=203
	Placebo		Placebo + allopurinol for 48 weeks; randomized n=202
Endpoints and definitions	Primary endpoint	sUA	The proportion of subjects with a sUA level that is < 6.0 mg/dL at the Month 6 visit (NRI analysis)
	Secondary endpoint	Gout flares	Mean rate of gout flares requiring treatment for the 6-month period from the end of Month 6 to the end of Month 12.

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	Secondary endpoint	Tophus resolution	Proportion of subjects with ≥ 1 target tophus at Baseline who experience complete resolution of at least 1 target tophus by Month 12 (i.e. last on-study visit).
Database lock	Date not given		

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	Intent to treat – all patients randomized and treated			
Descriptive statistics and estimate variability	Treatment group	Lesinurad 200 mg + allopurinol	Lesinurad 400 mg + allopurinol	Placebo + allopurinol
	Number of subjects	201	201	201
	Patients with sUA < 6.0 mg/dL at month 6	109 (54.2%)	119 (59.2%)	56 (27.9%)

Effect estimate per comparison	Proportion with sUA < 6.0 mg/dL at month 6	Comparison groups	Lesinurad 200mg vs. placebo
		Difference in proportions	0.26
		95% CI	(0.17, 0.36)
		P-value	p<0.0001
		Comparison groups	Lesinurad 400mg vs. placebo
		Difference in proportions	0.31
		95% CI	(0.22, 0.41)
		P-value	p<0.0001
Notes	Patients with missing data at month 6 included as non-responders		

Analysis description	**Key Secondary Endpoint**			
Analysis population and time point description	Intent to treat – all patients randomized and treated			
Descriptive statistics and estimate variability	Treatment group	Lesinurad 200 mg + allopurinol	Lesinurad 400 mg + allopurinol	Placebo + allopurinol
	Number of subjects	201	201	201
	Adjusted mean rate of gout flares requiring treatment per subject from the end of month 6 to the end of month 12	0.57	0.51	0.58
	Standard error	0.10	0.09	0.10

Effect estimate per comparison	Adjusted mean rate of gout flares requiring	Comparison groups	Lesinurad 200mg vs. placebo

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	treatment per subject from the end of month 6 to the end of month 12	Incidence rate ratio	0.99
		95% CI	(0.61, 1.61)
		P-value	0.9796
		Comparison groups	Lesinurad 400mg vs. placebo
		Incidence rate ratio	0.88
		95% CI	(0.54, 1.43)
		P-value	0.6125
Notes	Estimates obtained from Negative Binomial Regression adjusted for Day 1 renal function (eCrCl ⩾ 60 mL/min versus < 60 mL/min) and tophus status during Screening (presence versus absence), and log follow-up time as the offset variable. This was the first secondary endpoint in a hierarchical procedure. As the result was negative, no further secondary endpoints can formally be tested.		
Analysis description	Key Secondary Endpoint		
Analysis population and time point description	All patients randomized and treated with at least one tophus at baseline		

Descriptive statistics and estimate variability	Treatment group	Lesinurad 200 mg + allopurinol	Lesinurad 400 mg + allopurinol	Placebo + allopurinol
	Number of subjects	18	19	17
	Subjects who experience complete resolution of at least one target tophus by month 12	0	4 (21.1%)	5 (29.4%)

Effect estimate per comparison	Proportion of subjects who experience complete resolution of at least one target tophus by month 12	Comparison groups	Lesinurad 200mg vs. placebo
		Difference in proportions	-0.29
		95% CI	(-0.51, -0.08)
		P-value	0.0183 (in favour of placebo)
		Comparison groups	Lesinurad 400mg vs. placebo
		Difference in proportions	-0.08
		95% CI	(-0.37, 0.20)
		P-value	0.5974

Table 42. Summary of efficacy for study 302

Title: A phase 3 randomized, double-blind, multicentre, placebo-controlled, combination study to evaluate the efficacy and safety of lesinurad and allopurinol compared to allopurinol alone in subjects with gout who have had an inadequate hypouricaemic response to standard of care allopurinol.		
Study identifier	302	
Design	Randomised, double-blind, placebo-controlled multicentre study	
	Duration of main phase:	48 weeks
	Duration of Run-in phase:	14 days

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	Duration of Extension phase:		not applicable
Hypothesis	Superiority		
Treatments groups	Lesinurad 200 mg		Lesinurad 200 mg qd + allopurinol for 48 weeks; randomized n=202
	Lesinurad 400 mg		Lesinurad 400 mg qd + allopurinol for 48 weeks; randomized n=203
	Placebo		Placebo + allopurinol for 48 weeks; randomized n=202
Endpoints and definitions	Primary endpoint	sUA	The proportion of subjects with a sUA level that is < 6.0 mg/dL at the Month 6 visit (NRI analysis)
	Secondary endpoint	Gout flares	Mean rate of gout flares requiring treatment for the 6-month period from the end of Month 6 to the end of Month 12.
	Secondary endpoint	Tophus resolution	Proportion of subjects with ≥ 1 target tophus at Baseline who experience complete resolution of at least 1 target tophus by Month 12 (i.e. last on-study visit).
Database lock	Date not given		

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	Intent to treat – all patients randomized and treated			
Descriptive statistics and estimate variability	Treatment group	Lesinurad 200 mg + allopurinol	Lesinurad 400 mg + allopurinol	Placebo + allopurinol
	Number of subjects	204	200	206
	Patients with sUA < 6.0 mg/dL at month 6	113 (55.4%)	133 (66.5%)	48 (23.3%)

Effect estimate per comparison	Proportion with sUA < 6.0 mg/dL at month 6	Comparison groups	Lesinurad 200mg vs. placebo
		Difference in proportions	0.32
		95% CI	(0.23, 0.41)
		P-value	p<0.0001
		Comparison groups	Lesinurad 400mg vs. placebo
		Difference in proportions	0.43
		95% CI	(0.34, 0.52)
		P-value	p<0.0001
Notes	Patients with missing data at month 6 included as non-responders		

Analysis description	**Key Secondary Endpoint**			
Analysis population and time point description	Intent to treat – all patients randomized and treated			
Descriptive statistics and estimate variability	Treatment group	Lesinurad 200 mg + allopurinol	Lesinurad 400 mg + allopurinol	Placebo + allopurinol

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	Number of subjects	204	200	206
	Adjusted mean rate of gout flares requiring treatment per subject from the end of month 6 to the end of month 12	0.73	0.77	0.83
	Standard error	0.12	0.13	0.13

Effect estimate per comparison	Adjusted mean rate of gout flares requiring treatment per subject from the end of month 6 to the end of month 12	Comparison groups	Lesinurad 200mg vs. placebo
		Incidence rate ratio	0.88
		95% CI	(0.57, 1.37)
		P-value	0.5716
		Comparison groups	Lesinurad 400mg vs. placebo
		Incidence rate ratio	0.93
		95% CI	(0.60, 1.45)
		P-value	0.7454
Notes	Estimates obtained from Negative Binomial Regression adjusted for Day -7 renal function (eCrCl $\geqslant$ 60 mL/min versus < 60 mL/min) and tophus status during Screening (presence versus absence), and log follow-up time as the offset variable. This was the first secondary endpoint in a hierarchical procedure. As the result was negative, no further secondary endpoints can formally be tested.		
Analysis description	Key Secondary Endpoint		
Analysis population and time point description	All patients randomized and treated with at least one tophus at baseline		

Descriptive statistics and estimate variability	Treatment group	Lesinurad 200 mg + allopurinol	Lesinurad 400 mg + allopurinol	Placebo + allopurinol
	Number of subjects	35	29	33
	Subjects who experience complete resolution of at least one target tophus by month 12	11 (31.4%)	8 (27.6%)	11 (33.3%)

Effect estimate per comparison	Proportion of subjects who experience complete resolution of at least one target tophus by month 12	Comparison groups	Lesinurad 200mg vs. placebo
		Difference in proportions	-0.02
		95% CI	(-0.24, -0.20)
		P-value	0.8466
		Comparison groups	Lesinurad 400mg vs. placebo
		Difference in proportions	-0.06

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		95% CI	(-0.29, 0.17)
		P-value	0.6301

Table 43. Summary of efficacy for study 304

Title: A phase 3 randomized, double-blind, multicenter, placebo-controlled, combination study to evaluate the efficacy and safety of lesinurad and febuxostat compared to febuxostat alone at lowering serum uric acid and resolving tophi in subjects with tophaceous gout.					
Study identifier	304				
Design	Phase 3, randomised, double-blind, multicentre, placebo-controlled, combination study				
	Duration of main phase: 48 weeks Duration of Run-in phase: 21 days Duration of Extension phase: not applicable				
Hypothesis	Superiority				
Treatments groups	Lesinurad 200 mg		Lesinurad 200 mg qd + febuxostat 80 mg qd for 48 weeks; randomized n=109		
	Lesinurad 400 mg		Lesinurad 400 mg qd + febuxostat for 48 weeks; randomized n=110		
	Placebo		Placebo + febuxostat for 48 weeks; randomized n=111		
Endpoints and definitions	Primary endpoint	sUA	The proportion of subjects with a sUA level that is < 5.0 mg/dL by Month 6		
	Secondary endpoint	Tophus resolution	Proportion of subjects who experience complete resolution of at least 1 target tophus by Month 12.		
	Secondary endpoint	Gout flares	Mean rate of gout flares requiring treatment for the 6 month period from the end of Month 6 to the end of Month 12		
Database lock	Date not given				
Results and Analysis					
Analysis description	**Primary Analysis**				
Analysis population and time point description	Intent to treat – all patients randomized and treated				
Descriptive statistics and estimate variability	Treatment group		Lesinurad 200 mg + FBX 80mg	Lesinurad 400 mg + FBX 80mg	Placebo + FBX 80mg
	Number of subjects		106	109	109
	Patients with sUA < 5.0 mg/dL at month 6		60 (56.6%)	83 (76.1%)	51 (46.8%)
Effect estimate per comparison	Proportion with sUA < 5.0 mg/dL at month 6	Comparison groups		Lesinurad 200mg vs. placebo	
		Difference in proportions		0.10	
		95% CI		(-0.03, 0.23)	
		P-value		p=0.1298	

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		Comparison groups	Lesinurad 400mg vs. placebo	
		Difference in proportions	0.29	
		95% CI	(0.17, 0.42)	
		P-value	p<0.0001	
Notes	Patients with missing data at month 6 included as non-responders			
Analysis description	**Key Secondary Endpoint**			
Analysis population and time point description	All patients randomized and treated			
Descriptive statistics and estimate variability	Treatment group	Lesinurad 200 mg + FBX 80mg	Lesinurad 400 mg + FBX 80mg	Placebo + FBX 80mg
	Number of subjects	106	109	109
	Subjects who experience complete resolution of at least one target tophus by month 12	27 (25.5%)	33 (30.3%)	23 (21.1%)
Effect estimate per comparison	Proportion of subjects who experience complete resolution of at least one target tophus by month 12	Comparison groups	Lesinurad 200mg vs. placebo	
		Difference in proportions	0.04	
		95% CI	(-0.07, 0.16)	
		P-value	0.4453	
		Comparison groups	Lesinurad 400mg vs. placebo	
		Difference in proportions	0.09	
		95% CI	(-0.02, 0.21)	
		P-value	0.1149	
Notes	This was the first secondary endpoint in a hierarchical procedure. As the result was negative, no further secondary endpoints can formally be tested.			
Analysis description	**Secondary Endpoint**			
Analysis population and time point description	Intent to treat – all patients randomized and treated			
Descriptive statistics and estimate variability	Treatment group	Lesinurad 200 mg + FBX 80mg	Lesinurad 400 mg + FBX 80mg	Placebo + FBX 80mg
	Number of subjects	106	109	109
	Adjusted mean rate of gout flares requiring treatment per subject from the end of month 6 to the end of month 12	1.5	0.7	1.3

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	Standard error	0.31	0.15	0.25

Effect estimate per comparison	Adjusted mean rate of gout flares requiring treatment per subject from the end of month 6 to the end of month 12	Comparison groups	Lesinurad 200mg vs. placebo
		Incidence rate ratio	1.2
		95% CI	(0.7, 2.1)
		P-value	0.5493
		Comparison groups	Lesinurad 400mg vs. placebo
		Incidence rate ratio	0.5
		95% CI	(0.3, 1.0)
		P-value	0.0401
Notes	Estimates obtained from Negative Binomial Regression adjusted for Day -7 renal function (eCrCl ⩾ 60 mL/min versus < 60 mL/min), and log follow-up time as the offset variable.		

Analysis performed across trials (pooled analyses and meta-analysis)

The Applicant provided pooled analyses of studies 301 and 302, as they were identical in design and recruited similar patient numbers. The primary endpoint results and the mean SuA levels by visit are presented in **Table 47** and **Figure 21** respectively.

Table 44. Primary endpoint: Proportion of Subjects Achieving Serum Urate < 6.0 mg/dL by Month 6 in Studies 301 and 302 - NRI (ITT Population)

	Studies 301/302 pooled		
	Lesinurad 200 mg + allopurinol (n=405)	Lesinurad 400 mg + allopurinol (n=401)	Placebo + allopurinol (n=407)
Proportion of Responders[a] by Month 6, [n (%)]	222 (54.8)	252 (62.8)	104 (25.6)
Difference in proportions vs. placebo (95% CI)	0.29 (0.23, 0.36)	0.37 (0.31, 0.44)	
p-value[b]	<0.0001	<0.0001	

Abbreviations: CI, confidence interval; ITT, intent-to-treat; NRI, nonresponder imputation; [a] Responders were subjects with sUA < 6.0 mg/dL in Studies 301 and 302. [b] Cochran-Mantel Haenszel test stratified by Day -7 renal function (eCrCl ≥ 60 mL/min versus < 60 mL/min) and tophus status during Screening (presence versus absence), randomized values; for pooled Study 301/302, study was also included as a stratification factor. Source: Integrated Analysis of Efficacy (IAE) Ad Hoc Table 2.7.1.1.

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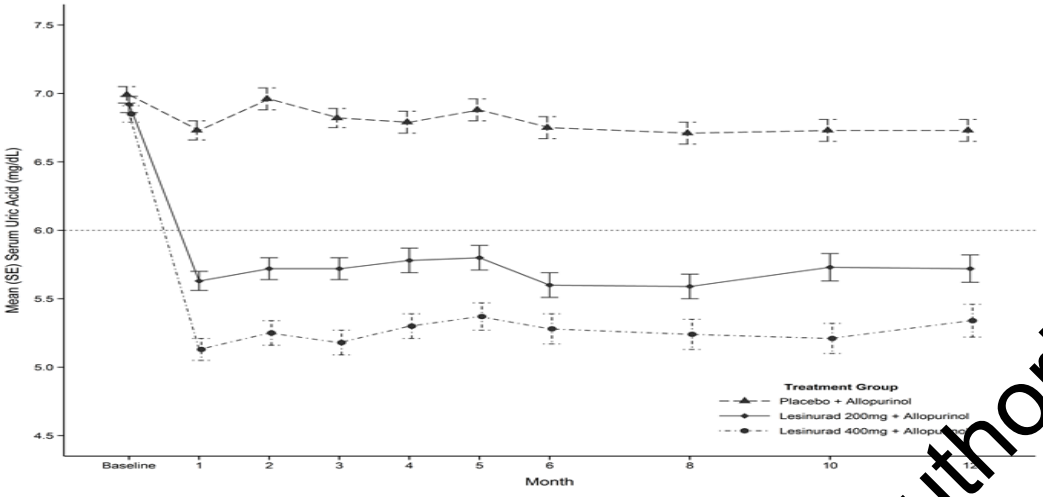
Figure 20. Mean Serum Uric Acid Levels by Visit in Studies 301 and 302 Pooled – Observed Cases (ITT Population)



Abbreviations: ITT, intent-to-treat; SE, standard error.
Dotted line indicates target sUA (< 6.0 mg/dL).

Further analyses were conducted across these trials based on the allopurinol dose they were receiving (**Table 45**).

Table 45. Proportion of subjects with a serum uric acid<6.0 mg/dL by month 6 for baseline allopurinol in studies 301 and 302 pooled-NRI (ITT population)

	Studies 301 and 302		
	PBO + ALLO (N=407) n/N (%)	LESU 200 mg + ALLO mg (N=405) n/N (%)	LESU 400 mg + ALLO (N=401) n/N (%)
Baseline ALLO All Doses			
Proportion with sUA < 6.0 mg/dL by Month 6	104/407 (25.6)	222/405 (54.8)	252/401 (62.8)
Difference in proportions vs. PBO + ALLO (95% CI)		0.29 (0.23, 0.36)	0.37 (0.31, 0.44)
p-value[a]		<0.0001	<0.0001
Baseline ALLO Dose > 300 mg /day Subgroup			
Proportion with sUA < 6.0 mg/dL by Month 6	10/28 (35.7)	17/31 (54.8)	16/26 (61.5)
Difference in proportions vs. PBO + ALLO (95% CI)		0.19 (- 0.06, 0.44)	0.26 (0.00, 0.52)
p-value[a]		0.0891	0.0436
Baseline ALLO > 300 mg/day or Baseline ALLO 300 mg with Moderate Renal Impairment Subgroup			
Proportion with sUA < 6.0 mg/dL by Month 6	22/73 (30.1)	46/81 (56.8)	47/78 (60.3)
Difference in proportions vs. PBO + ALLO (95% CI)		0.27 (0.12, 0.42)	0.30 (0.15, 0.45)
p-value[a]		0.0011	0.0002

Abbreviations: ALLO, allopurinol; CI, confidence interval; ITT, intent-to-treat; LESU, lesinurad; NRI, non-responder imputation; PBO, placebo; sUA, serum uric acid.
[a] Cochran-Mantel Haenszel test stratified by Day -7 renal function and tophus status during Screening (randomized values); study was also included as a stratification factor.
Note: Subjects missing the Month 6 sUA result were treated as non-responders.

Abbreviations: ALLO, allopurinol; CI, confidence interval; ITT, intent-to-treat; LESU, lesinurad; NRI, non-responder imputation; PBO, placebo; sUA, serum uric acid.
[a] Cochran-Mantel Haenszel test stratified by Day -7 renal function and tophus status during Screening (randomized values); study was also included as a stratification factor.
Note: Subjects missing the Month 6 sUA result were treated as non-responders.

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Sensitivity analyses of subjects with Baseline sUA ≥ 8.0 mg/dL in Study 301 and Study 302 is shown in **Table 46.**

Table 46. Proportion of subjects with Baseline sUA ≥ 8.0 mg/dL who achieved a serum uric acid < 6.0 mg/dL by month 6 in Studies 301 and 302 pooled-NRI (ITT population)

	Study 301			Study 302			Studies 301/302 Pooled		
	PBO +ALLO (N=36)	LESU 200 mg +ALLO (N=37)	LESU 400 mg +ALLO (N=32)	PBO +ALLO (N=44)	LESU 200 mg +ALLO (N=27)	LESU 400 mg +ALLO (N=36)	PBO +ALLO (N=80)	LESU 200 mg +ALLO (N=64)	LESU 400 mg +ALLO (N=68)
Proportion with sUA <6 by Month 6, [n (%)]	5 (13.9)	13 (35.1)	10 (31.3)	2 (4.5)	7 (25.9)	17 (47.2)	7 (8.8)	20 (31.3)	27 (39.7)
Difference in proportions vs. PBO + ALLO (95% CI)		0.21 (0.02, 0.40)	0.17 (-0.02, 0.37)		0.21 (0.04, 0.39)	0.43 (0.25, 0.60)		0.23 (0.10, 0.35)	0.31 (0.18, 0.44)
p-value[a]		0.0391	0.0659		0.0036	<0.0001		0.0008	<0.0001

Abbreviations: ALLO, allopurinol; CI, confidence interval; eCrCL, estimated creatinine clearance; ITT, intent-to-treat; LESU, lesinurad; NRI, non-responder imputation; PBO, placebo; sUA, serum uric acid.
Note: Subjects missing the Month 6 sUA result were treated as nonresponders.
[a] Cochran-Mantel Haenszel test stratified by Day -7 renal function (eCrCl ≥ 60 mL/min versus < 60 mL/min) and tophus status during Screening (randomized values); for pooled Study 301/302, study was also included as a stratification factor. Nominal p-values not adjusted for multiplicity.

Clinical studies in special populations

The submitted clinical studies in gout patients included low numbers of elderly (aged 75-84); over 85 year olds were excluded. The proportion of women was also low. No studies have been conducted in children; a paediatric waiver has been granted on the grounds of safety. Subjects with renal impairment and hepatic impairment were studied during Phase 1. Subjects with moderate renal impairment were also included in adequate numbers in Phase 3.

Supportive studies

Long-term extension studies

Study 306 (add-on to allopurinol)

Of the 1213 subjects enrolled and randomized in Study 301 or Study 302, 718 were enrolled in Study 306, representing 59.2%. A total of 244 subjects who had received placebo were re-randomized to lesinurad 200 mg (n = 122) or 400 mg (n = 122). For the interim analyses, 281 subjects in the LESU 200 mg + ALLO group and 275 subjects in the LESU 400 mg + ALLO group completed the full 12 months in the extension study, which was 45.8% of all subjects originally randomized in Studies 301 and 302.

Adding lesinurad to previous placebo nearly doubled the proportion of subjects that achieved the sUA target at all time-points in Study 306 (from 27.3% to 38.8% in placebo period to 61.3% to 75.9% when lesinurad was initiated. The response to prior lesinurad treatment was maintained in in the maintenance phase (**Figure 21**).

Figure 21. Proportion of Subjects With sUA < 6.0 mg/dL in Pivotal Studies 301/302 and Extension Study 306 – Observed Cases

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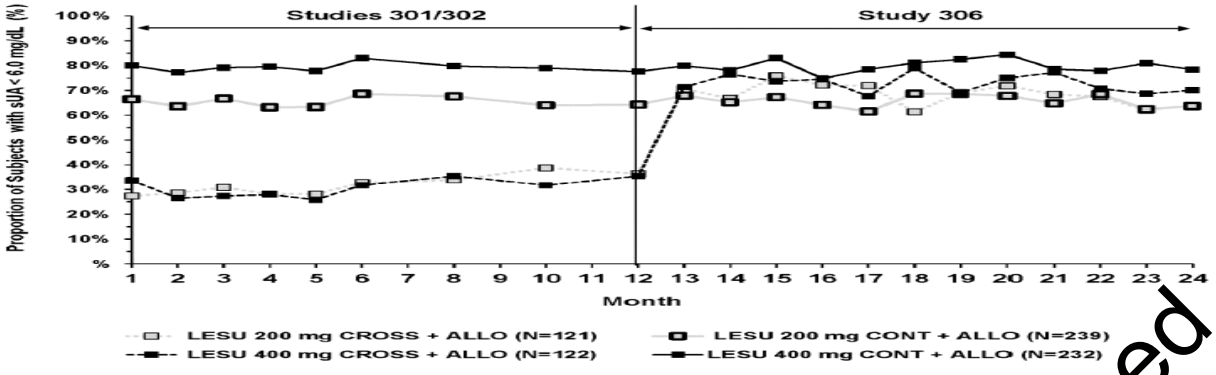


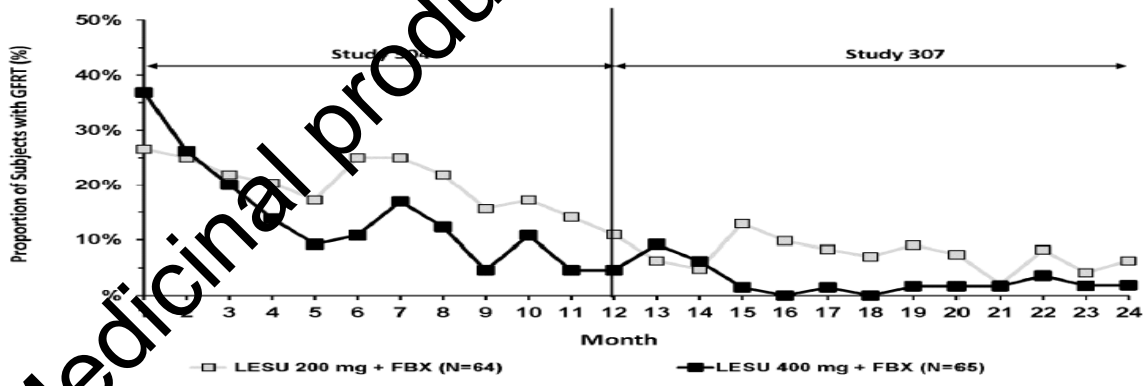
Study 307

Of the 324 subjects enrolled and randomized in Study 304, 235 (72.5%) subjects completed 12 months of treatment with randomized study medication , and 196 subjects (60.5%) were enrolled in Study 307. A total of 67 subjects who had received placebo and febuxostat in Study 304 were randomized to receive either lesinurad 200 mg (n = 33) or 400 mg (n = 34). For the interim analyses, 72 subjects and 80 subjects after lesinurad 200 or 400 mg dose completed the full 1 year in the extension study, representing 46.9% of all subjects originally randomized in the pivotal Study 304.

The percentage of patients with complete resolution increased from Month 12 to 24 from 26.6 to 53.1% for the 200 mg dose, and from 35.4% to 58.5% for the 400 mg dose (ITT population).

The flare rate also continued to decrease to a low level as illustrated in **Figure 22.**

Figure 22. Proportion of Subjects Receiving Lesinurad Combination Therapy With Febuxostat for Greater Than 12 to 24 Months Requiring Treatment for a Gout Flare by Monthly Intervals in Study 304 and Study 307- Observed Cases



Abbreviations: CONT, continuation of treatment; FBX, febuxostat; GFRT, gout flare requiring treatment; ITT, intent-to-treat; LESU, lesinurad.

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Monotherapy Studies

Exploratory monotherapy Study 202

Monotherapy was explored in gout patients in Study 202, a 4 weeks randomised controlled multicentre study, with 4 study arms (lesinurad 200/400/600 mg and placebo). In total 127 subjects were randomised (1:1:1:1 ratio) The proportions of subjects achieving sUA < 6.0 mg/dL at Day 27 were 7.4%, 27.6%, and 44.8% in the LESU 200, 400, and 600 mg groups, respectively, and 0% in the PBO

group (p < 0.01 for the LESU 400 and 600 mg groups when compared with PBO, but the difference for LESU 200 mg was not statistically significant). The incidence of elevated creatinine levels (> 1.5 times x baseline) was approximately two-fold higher in the LESU groups compared with PBO, but remained under 10%. Elevations were usually mild and resolved after discontinuation. No SAEs were reported.

Monotherapy Study 303

Study 303 was a confirmatory randomized, double-blind, multicenter, placebo-controlled study to assess the efficacy and safety of lesinurad monotherapy in gout patients, who were intolerant of or had a contraindication to an XO-inhibitor. A total of 214 subjects were randomized to lesinurad (107 in each study arm), of which 162 (72 on lesinurad and 90 on placebo) completed the 6-month treatment period. Non-responder imputation was applied for missing data.

By Month 6, significantly more subjects in the lesinurad 400 mg group achieved the target goal of sUA < 6.0 mg/dL compared with the Placebo group: 29.9% versus 1.9%, respectively (difference 28%, 95% CI 19-37, p < 0.0001).

In comparison to placebo, the lesinurad group had a higher proportion of subjects with kidney-associated TEAEs (23.4% versus 3.7%), kidney- associated TEAEs leading to discontinuation of randomized study medication (11.2% versus 0.9%), and kidney-associated SAEs (5.6% versus 0%).

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The clinical efficacy was supported by 3 Phase 3 pivotal studies (301, 302 and 304) investigating lesinurad in combination with a xanthine oxidase) inhibitor for the treatment of gout. The Phase 3 program included both the 200 mg qd and 400 mg qd doses, both as monotherapy, and in combination with a xanthine oxidase inhibitor. However the applicant is not seeking approval for the 400 mg qd dose level, or for a monotherapy indication, due to renal safety considerations (see also Section 2.6, Clinical Safety of this Report).

The primary efficacy endpoint for the pivotal studies is considered a surrogate endpoint. During a CHMP scientific advice procedure, it was agreed that sUA lowering could be an acceptable primary endpoint for the pivotal lesinurad studies.

Lesinurad is intended for gout patients with hyperuricaemia despite adequate urate lowering monotherapy. In studies 301 and 302, subjects were required to take allopurinol at a medically-appropriate dose for at least 8 weeks prior to screening. In study 304, subjects were eligible irrespective of the sUA response to 3 weeks of febuxostat 80 mg daily. The CHMP noted that in these, only 7% of subjects were taking more than 300 mg daily of allopurinol at baseline and no patients received febuxostat 120 mg daily at baseline. The Applicant was therefore requested to provide further justification that the patient populations in the clinical trials were representative of the target population.

The Applicant responded that in clinical practice, despite prescribing information allowing for allopurinol daily doses of up to 900 mg for more than 5 decades in Europe, evidence from multiple studies shows that few patients (< 4%) are prescribed allopurinol doses higher than 300 mg daily. Retrospective analyses showed that 2.1% of 7,443 patients in the United Kingdom (UK), and 3.4% of 4006 patients in Germany received > 300 mg/day of allopurinol (Sarawate 2006, Annemans 2008). An electronic medical record-based pharmaco-epidemiologic study of gout patients, known as International Comorbidity and Resource Utilization Study of Gout (ICARUS), was conducted by the Applicant to assess disease control and comorbid conditions, health resource use, and healthcare costs in the US and Europe. The ICARUS study reported that only 3.7% of 19,886 patients with gout in the UK had

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recorded doses of allopurinol > 300 mg, with even lower percentages with recorded daily allopurinol doses > 300 mg in both France (0.3% of 6,293 patients) and Germany (0.5% of 34,963 patients (Ardea Biosciences, data on file, 2015). These studies indicate that across Europe and the US, allopurinol 300 mg is the highest dose used by approximately 95% of patients, and doses of allopurinol > 300 mg are seldom used. In Studies 301 and 302 pooled, 7.1% (86 of 1,213) of subjects were on doses of allopurinol > 300 mg, which is greater than that observed in the studies using electronic medical records.

In Studies 301 and 302, a minimal allopurinol dose of 200 mg was permitted if patients had moderate renal impairment, as dose adjustments are recommended in this group based on potential side effects (Stamp 2012). Across both studies, 7.1% of subjects were receiving > 300 mg of allopurinol, which is nearly twice the proportion of patients in clinical practice receiving allopurinol doses > 300 mg (Sarawate 2006, Jennings 2014). Conservative allopurinol dosing in renal-impaired patients has been recommended, with previous studies showing that approximately 75% of renal-impaired patients take doses < 300 mg/day (Jeyaruban 2015). Across Studies 301 and 302, greater than 60% (147 of 224) of subjects with moderate renal impairment were taking allopurinol 300 mg daily. The plasma exposure levels of allopurinol 300 mg in subjects with moderate renal insufficiency is comparable to 600 mg allopurinol plasma exposures levels observed in patients with normal renal function (Hande 1984). Thus, in effect, 232 patients (19.1%) of subjects across Studies 301 and 302 could be considered as receiving doses > 300 mg allopurinol because they were taking actual doses > 300 mg or had plasma exposures significantly > 300 mg allopurinol due to comorbid moderate renal impairment.

Evidence shows that few patients are prescribed febuxostat in Europe, and when febuxostat is prescribed, it is predominantly at the recommended 80 mg daily dose with limited prescribing of the 120 mg dose. Data from the IMS Midas database, a well-established and widely used data source from IMS Health for global pharmaceutical and prescribing data, show that < 5% of urate lowering therapy prescriptions are for febuxostat. Across Europe in 2014, of those receiving febuxostat, 92% of standard unit sales were for 80 mg tablets versus 8% for 120 mg tablets (IMS Health, MIDAS, MAT 4Q 2014). These results were corroborated by data from the ICARUS pharmaco-epidemiologic study, which shows that few patients in Europe receive febuxostat at any dose (2.2% of all XO inhibitor use) and in these patients on febuxostat, < 10% were prescribed a dose of 120 mg (82 of 893 [9%] in France, 26 of 382 [7%] in Germany, and 1 of 90 [1%] in the UK). Thus, < 1% of all prescriptions for XO inhibitors was for febuxostat 120 mg daily. The CHMP considering this information considered that the patient populations in the lesinurad clinical trials were representative of the target population.

In study 301 and 302, subjects were eligible if sUA was > 6.5 mg/dL at screening (sUA > 6.0 mg/dL at day -7).

In study 304, subjects were eligible irrespective of the sUA response to 3 weeks of febuxostat 80 mg daily. However, a pre-defined subgroup of sUA > 5.0 mg/dL could be considered non-responders to febuxostat, although the febuxostat dose was inadequate. In fact around 50% of subjects in study 304 had sUA > 5.0 mg/dL at baseline. The applicant however provided additional analyses for the subgroup with sUA > 6.0 mg/dL at baseline, in order to allow comparison with the outcomes of studies 301 and 302.

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Efficacy data and additional analyses

Lesinurad in combination with allopurinol

Clinically relevant, as well as statistically significant, sUA lowering was demonstrated for lesinurad 200 mg qd or 400 mg qd in combination with allopurinol, compared to allopurinol alone. The effect was

consistent across sub-groups, including subjects with moderate renal impairment, and subjects receiving more than 300 mg allopurinol daily. The sUA lowering effect of lesinurad, in addition to allopurinol, is maximal by 1 month, and sustained throughout the 12 month study period.

Lesinurad in combination with febuxostat

Although the primary endpoint was not met for the 200 mg qd dose, Month 6 was the only timepoint at which the proportion meeting the sUA target was not significantly different from placebo. The proportions achieving sUA < 5.0 mg/dL were more strongly in favour of lesinurad at Month 12, and at Months 4, 5 and 6 combined. Furthermore, the sub-group of subjects with > 5.0 mg/dL at baseline despite 3 weeks of febuxostat monotherapy would be expected to benefit the most from combination therapy. For this sub-group, the proportions with sUA < 5.0 mg/dL at Month 6 were 44.1% vs. 18.5% ($p<0.05$) for the lesinurad 200 mg group vs placebo respectively.

Therefore, in subjects not responding to monotherapy with febuxostat 80 mg qd, there is evidence that lesinurad 200 mg qd as add-on provides additional sUA lowering that is clinically relevant.

Due to modest baseline sUA levels across all the trials, it was unclear whether lesinurad is sufficiently effective in more resistant patients (e.g. sUA levels >7-8mg/dl). However, the Applicant provided additional analyses to demonstrate that the combination of lesinurad with an XO inhibitor is efficacious in more resistant subjects, including those with higher Baseline sUA levels.

More than twice the proportion of subjects achieved target sUA goals with the addition of lesinurad 200 mg even in the more resistant subjects with higher Baseline sUA. It should be noted that Baseline sUA levels in the pivotal Phase 3 combination therapy studies reflect the effect of treatment with an XO inhibitor. In Studies 301 and 302, Baseline sUA reflects at least 8 weeks of physician determined, medically appropriate dose allopurinol (≥ 300 mg to 600 mg to 900 mg; ≥ 200 mg for moderate renal impairment). In Study 304, the Baseline sUA reflects 3 weeks of Sponsor-supplied febuxostat 80 mg daily. The CHMP concluded that the efficacy of lesinurad in these patients had been adequately demonstrated.

Nevertheless, the CHMP considered that the initially proposed indication by the Applicant for the chronic treatment of hyperuricaemia in combination with allopurinol or febuxostat in gout patients when additional therapy is warranted, did not adequately reflect the intended second line treatment option for lesinurad. To more clearly reflect this the CHMP recommended that lesinurad should be indicated in combination with a xanthine oxidase inhibitor, for the adjunctive treatment of hyperuricaemia in gout patients (with or without tophi) who have not achieved target serum uric acid levels with an adequate dose of a xanthine oxidase inhibitor alone.

2.5.4. Conclusions on the clinical efficacy

In allopurinol non-responders, the additional treatment of lesinurad provided a significant and sustained reduction of sUA levels below the treatment target of < 6.0 mg/dL or lower. The CHMP acknowledged that as this was a surrogate endpoint, the clinical relevance of this effect was not clear as the improvement of flares and tophi reduction compared to placebo after 12 months was not statistically significant. However, the long-term efficacy data after 24 months of treatment, provided sufficient evidence of a clinical effect with continuous decline of the tophi load and flares.

The additional effect of lesinurad 200 mg on top of febuxostat 80 mg was modest. However a relevant effect was shown in a subgroup of non-responders to febuxostat which reflects the intended use of lesinurad as an add-on therapy in patients not achieving target serum uric acid levels with an adequate dose of a xanthine oxidase inhibitor alone.

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2.6. Clinical safety

The clinical safety was supported by clinical studies of lesinurad monotherapy as well as combination therapy, and including doses greater than or equal to 200 mg qd. The Phase 3 core combination studies (301, 302 and 304) were placebo-controlled and provide the pivotal safety data. An updated Safety Report was also submitted to provide updated safety data from Studies 301, 302 and 304 with a data cut-off of 4 November 2014.

Renal safety was a particular focus due to the mechanism of action of lesinurad. Cardiovascular safety was also a particular concern for the gout patient population.

An Independent Data Monitoring Committee (IDMC) was appointed to monitor potential safety signals during the Phase 3 clinical trial program. In addition, two independent and blinded Adjudication Committees were established,, one for review and adjudication of Cardiovascular Endpoints (CEAC), and one other for the adjudication of Renal Events (REAC). The Adjudication Committees classified the seriousness of renal and CV events, and the likelihood whether the case were drug-related.

Patient exposure

The global lesinurad clinical development program included 3010 subjects (healthy volunteers and patients), 2586 of whom received at least 1 dose of lesinurad across all studies. In the Phase 2/3 clinical development program, 1799 patients with gout were exposed to lesinurad at 1 or more doses (948 subjects exposed to 200 mg qd, 1070 subjects exposed to 400 mg qd, and 132 subjects exposed to 600 mg qd). A total of 1224 subjects were exposed (any dose) for approximately 6 months (at least 24 weeks), and 919 were exposed for approximately 1 year (at least 48 weeks). Maximal exposure to lesinurad was approximately 3 years. The total exposure to lesinurad + XOI combination was 1093.8 patient-years.

The primary safety evaluation is based on data from the three pivotal randomised placebo-controlled trials (Studies 301 and 302 and Study 304) evaluating the efficacy and safety of lesinurad 200 mg and 400 mg qd in combination with an XO inhibitor for 12 months.

Additional safety data from the ongoing Phase 3 extension studies (Studies 306 and 307) of these 3 main studies were submitted.

Supportive safety data from the Phase 3 monotherapy program (Studies 303 and its OLE 305) and the Phase 2 studies (Studies 202 and 203) were also submitted.

Demographic characteristics in the primary safety evaluation dataset are summarised in **Table 47.**

Table 47. Demographic characteristics in safety population Group A1

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Variable	LESU 200 mg +XOI (N=511)	LESU 400 mg +XOI (N=510)	TOTAL LESU +XOI (N=1021)	PBO +XOI (N=516)
Sex [n (%)]				
Female	22 (4.3)	28 (5.5)	50 (4.9)	24 (4.7)
Male	489 (95.7)	482 (94.5)	971 (95.1)	492 (95.3)
Race [n (%)]				
American Indian or Alaska Native	4 (0.8)	0	4 (0.4)	2 (0.4)
Asian	27 (5.3)	22 (4.3)	49 (4.8)	30 (5.8)
Black or African American	60 (11.7)	64 (12.5)	124 (12.1)	59 (11.4)
Maori	4 (0.8)	4 (0.8)	8 (0.8)	1 (0.2)
Native Hawaiian or other Pacific Islander	8 (1.6)	9 (1.8)	17 (1.7)	10 (1.9)
White	398 (77.9)	401 (78.6)	799 (78.3)	402 (77.9)
Other	10 (2.0)	9 (1.8)	19 (1.9)	12 ([illegible])
Missing	0	1 (0.2)	1 (0.1)	0
Race categories [n (%)]				
White	398 (77.9)	401 (78.6)	799 (78.3)	[illegible] (77.9)
Black	60 (11.7)	64 (12.5)	124 (12.1)	[illegible] (11.4)
Other	53 (10.4)	44 (8.6)	97 (9.5)	55 (10.7)
Missing	0	1 (0.2)	1 (0.1)	0
Ethnicity [n (%)]				
Hispanic or Latino	44 (8.6)	43 (8.4)	[illegible] ([illegible])	35 (6.8)
Not Hispanic or Latino	467 (91.4)	467 (91.6)	[illegible] ([illegible])	481 (93.2)
Age (years)				
n	511	510	1021	516
Mean (SD)	51.9 (10.98)	52.1 (11.28)	52.0 (11.11)	52.2 (11.13)
Median	52.0	53.0	52.0	52.0
Min, Max	21, 82	18, [illegible]	18, 82	21, 81
Age group (years) [n (%)]				
< 65	454 (88.8)	[illegible] ([illegible])	887 (86.9)	443 (85.9)
≥ 65	57 (11.2)	77 (15.1)	134 (13.1)	73 (14.1)
≥ 75	12 ([illegible])	8 (1.6)	20 (2.0)	9 (1.7)
Height (cm)				
n	511	509	1020	514
Mean (SD)	[illegible] ([illegible])	177.1 (8.33)	177.1 (8.19)	176.8 (8.12)
Median	[illegible]	177.8	177.8	177.5
Min, Max	[illegible], 198.1	152.0, 203.2	148.9, 203.2	147.0, 198.1
Weight (kg)				
n	511	510	1021	513
Mean (SD)	108.0 (22.40)	106.2 (23.67)	107.1 (23.05)	105.5 (22.32)
Median	106.2	103.2	104.7	102.1
Min, Max	55.5, 204.0	54.0, 238.9	54.0, 238.9	47.6, 183.0
Waist circumference (cm)				
n	503	505	1008	510
Mean (SD)	113.1 (15.25)	112.1 (16.37)	112.6 (15.82)	111.7 (15.92)
Median	111.8	109.5	110.0	109.0
Min, Max	68.6, 202.5	73.0, 188.0	68.6, 202.5	76.0, 177.5
Body mass index (kg/m2)				
n	511	509	1020	513
Mean (SD)	34.34 (6.23)	33.78 (6.85)	34.06 (6.55)	33.65 (6.21)
Median	33.52	33.18	33.29	32.78
Min, Max	17.79, 59.38	15.77, 83.65	15.77, 83.65	15.91, 56.27
Body mass index categories (kg/m^2) [n (%)]				
< [illegible]	132 (25.8)	163 (32.0)	295 (28.9)	165 (32.0)
≥ [illegible]	379 (74.2)	346 (67.8)	725 (71.0)	348 (67.4)
[illegible]	94 (18.4)	84 (16.5)	178 (17.4)	89 (17.2)
Missing	0	1 (0.2)	1 (0.1)	3 (0.6)

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Adverse events

Adverse events were more common for the combination of lesinurad + a XO-inhibitor, than placebo + XO-inhibitor (**Table 48**). The overall incidence of Serious Adverse Event (SAE) was similar between the 200mg dose and placebo but higher for the 400 mg dose.

Table 48. Number (%) of Subjects With ≥ 1 Adverse Event by Category in the Pivotal Phase 3 Studies (12-Month Studies 301, 302, and 304)

Adverse Event Category [n (%)]	PBO +XOI (N=516)	LESU 200 mg +XOI (N=511)	LESU 400 mg +XOI (N=510)	TOTAL LESU +XOI (N=1021)
Any TEAE	363 (70.3)	386 (75.5)	407 (79.8)	793 (77.7)
Any TEAE with RCTC toxicity Grade 3 or 4	48 (9.3)	52 (10.2)	67 (13.1)	119 (11.7)
Any TEAE possibly related to randomized study medication	80 (15.5)	98 (19.2)	118 (23.1)	216 (21.2)
Any TEAE possibly related to XOI	52 (10.1)	49 (9.6)	66 (12.9)	115 (11.3)
Any TEAE possibly related to prophylaxis	52 (10.1)	56 (11.0)	61 (12.0)	117 (11.5)
Any serious TEAE	29 (5.6)	24 (4.7)	44 (8.6)	68 (6.7)
Any fatal TEAE	0	2 (0.4)	3 (0.6)	5 (0.5)
Any TEAE leading to randomized study medication discontinuation	28 (5.4)	32 (6.3)	48 (9.4)	80 (7.8)
Any TEAE leading to XOI discontinuation	8 (1.6)	10 (2.0)	20 (3.9)	30 (2.9)
Any TEAE leading to prophylaxis discontinuation	12 (2.3)	21 (4.1)	26 (5.1)	47 (4.6)
Any TEAE leading to study withdrawal	18 (3.5)	20 (3.9)	27 (5.3)	47 (4.6)

Abbreviations: LESU, lesinurad; PBO, placebo; RCTC, Rheumatology Common Toxicity Criteria; TEAE, treatment-emergent adverse event; XOI, xanthine oxidase inhibitor (allopurinol/febuxostat).
Note: Events are treatment-emergent events. For each category, subjects are included only once, even if they experienced multiple events in that category.

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For monotherapy with the 400 mg dose, the overall rate of AEs was similar as reported for the combination, although these occurred in a shorter time frame: 77.6% within 6 months for monotherapy versus 79.8% in 12 months for the combination. The incidence of AEs was lower for placebo in the monotherapy study (65.4%), possibly as no background therapy with a XOI was provided. Of note, the rate of withdrawal of the study drugs due to AEs was considerable higher for monotherapy (18.7% versus 5.6% placebo), than the same dose in the XOI-combination studies (9.4% vs 5.4% placebo). Monotherapy with the 200mg dose was not evaluated.

The AEs by System Organ Class (SOC) of the main confirmatory 12-months add-on trials are summarised in **Table 49**.

Table 49. Adverse Events per SOC (outline), Phase III XOI-combination studies (pooled data Study 301.302, 304)

System Organ Class Preferred Term [n (%)]	LESU 200 mg +XOI (N=511)	LESU 400 mg +XOI (N=510)	TOTAL LESU +XOI (N=1021)	PBO +XOI (N=516)
Infections and infestations *	203 (39.7)	207 (40.6)	410 (40.2)	175 (33.9)
Neoplasms benign, malignant and unspecified	9 (1.8)	14 (2.7)	23 (2.3)	12 (2.3)
Blood and lymphatic system disorders	8 (1.6)	8 (1.6)	16 (1.6)	9 (1.7)
Immune system disorders	2 (0.4)	9 (1.8)	11 (1.1)	9 (1.7)
Endocrine disorders	5 (1.0)	6 (1.2)	11 (1.1)	5 (1.0)
Metabolism and nutrition disorders*	45 (8.8)	50 (9.8)	95 (9.3)	36 (7.0)
Psychiatric disorders	23 (4.5)	23 (4.5)	23 (4.5)	23 (4.5)
Nervous system disorders*	72 (14.1)	61 (12.0)	133 (13.0)	56 (10.9)
Eye disorders	19 (3.7)	10 (2.0)	29 (2.8)	19 (3.7)
Ear and labyrinth disorders	7 (1.4)	6 (1.2)	13 (1.3)	9 (1.7)
Cardiac disorders**	17 (3.3)	22 (4.3)	39 (3.8)	20 (3.9)
Vascular disorders *	41 (8.0)	45 (8.8)	86 (8.4)	33 (6.4)
Respiratory, thoracic and mediastinal disorders*	53 (10.4)	54 (10.6)	107 (10.5)	42 (8.1)
Gastrointestinal disorders*	92 (18.0)	103 (20.2)	195 (19.1)	89 (17.2)
Hepatobiliary disorders **	9 (1.8)	6 (1.2)	15 (1.5)	5 (1.0)
Skin and subcutaneous tissue disorders	44 (8.6)	38 (7.5)	82 (8.0)	33 (6.4)
Musculoskeletal and connective tissue disorders*	149 (29.2)	145 (28.4)	294 (28.8)	136 (26.4)
Renal and urinary disorders **	24 (4.7)	39 (7.6)	63 (6.2)	34 (6.6)
Reproductive system and breast disorders	11 (2.2)	16 (3.1)	27 (2.6)	10 (1.9)
Congenital, familial and genetic disorders	0	1 (0.2)	1 (0.1)	0
General disorders and administration site conditions	56 (11.0)	56 (11.0)	56 (11.0)	56 (11.0)
Investigations*	85 (16.6)	119 (23.3)	204 (20.0)	92 (17.8)

Injury, poisoning and procedural complications	95 (18.6)	105 (20.6)	200 (19.6)	100 (19.4)
Social circumstances	0	0	0	1

***SOCs with a higher rate for lesinurad than placebo >2%, **SOCs of Special Interest**

The most common Adverse Events per Preferred Term are summarised in **Table 50**.

Table 50. Adverse Events With Incidence ≥ 5% in Any Dose Group in the Pivotal Phase 3 Studies (12-Month Studies 301, 302, and 304)

Preferred Term [n (%)]	PBO +XOI (N=516)	LESU 200 mg +XOI (N=511)	LESU 400 mg +XOI (N=510)	TOTAL LESU +XOI (N=1021)
Upper respiratory tract infection	44 (8.5)	46 (9.0)	57 (11.2)	103 (10.1)
Nasopharyngitis	43 (8.3)	45 (8.8)	47 (9.2)	92 (9.0)
Arthralgia	41 (7.9)	42 (8.2)	32 (6.3)	74 (7.2)
Back pain	39 (7.6)	41 (8.0)	29 (5.7)	70 (6.9)
Hypertension	25 (4.8)	31 (6.1)	35 (6.9)	66 (6.5)
Blood creatinine increased	12 (2.3)	22 (4.3)	40 (7.8)	62 (6.1)
Headache	21 (4.1)	27 (5.3)	30 (5.9)	57 (5.6)
Blood creatine phosphokinase increased	25 (4.8)	23 (4.5)	30 (5.9)	53 (5.2)
Diarrhoea	23 (4.5)	23 (4.5)	27 (5.3)	50 (4.9)
Influenza	14 (2.7)	26 (5.1)	16 (3.1)	42 (4.1)

Abbreviations: LESU, lesinurad; PBO, placebo; XOI, xanthine oxidase inhibitor (allopurinol/febuxostat).
Note: Adverse events are treatment-emergent events and coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 14.0. For each preferred term (PT), subjects are included only once, even if they experienced multiple events in that PT.

Adverse Drug Reactions were identified from the core, placebo controlled periods of Studies 301, 302 and 304, based on the comparative incidence of TEAEs. More specifically ADRs were considered those which were observed at incidences >2% for subjects in the lesinurad 200 mg + XOI group and >1% higher compared to the PBO + XOI group (**Table 51**).

Table 51. Adverse Events Occurring in ≥ 2% of Lesinurad 200 mg Treated Patients and at Least 1% Greater Than Seen in Patients Receiving Placebo in Controlled Studies in Combination With an XO Inhibitor

Adverse Event	Placebo + XO Inhibitor (N=516)	Lesinurad 200 mg + XO Inhibitor (N=511)
Hypertension	4.8%	6.1%
Headache	4.1%	5.3%
Influenza	2.7%	5.1%
Blood creatinine increased	2.3%	4.3%
Gastrooesophageal reflux disease	0.8%	2.7%

In addition, the Applicant considered Renal Failure, Renal Impairment and Nephrolithiasis as potential adverse events, because of the mode of action of lesinurad, which could cause local renal toxicity and uric acid crystals due to hyper-saturation of uric acid in the nephron. Analysis of these events is described in detail in under the Renal and Urinary Disorders SOC.

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Adverse events in Phase 3 monotherapy studies

For the Phase 3 monotherapy study (303), the incidence of any TEAE was 77.6% and 65.4% in the lesinurad 400 mg and placebo groups respectively. For any Grade 3 or 4 TEAE, the respective rates were 16.8% and 3.7%. For 'at least possibly related TEAEs', the respective rates were 29.9% and 10.3%.

In contrast to the pooled combination data, there were increased rates of TEAEs for lesinurad 400 mg compared to placebo in the *Gastrointestinal disorders* SOC overall (77.5% vs 35.2%), mainly driven by

diarrhoea, nausea and constipation. There were increased rates of TEAEs for lesinurad 400 mg compared to placebo in the *Renal and urinary disorders* SOC overall, and particularly for renal impairment and renal failure. This was also reflected in the *Investigations* SOC (see Section 4.5).

When the Phase 3 monotherapy extension data is considered (study 305), the pattern of TEAEs is in line with that observed in the core phase. Regarding the SOC *Renal and urinary disorders*, there were 5 new reports of renal impairment, 4 new reports of renal failure and 6 new reports of PTs related to renal calculus.

When considering Grade 3 or 4 toxicities reported for the Phase 3 monotherapy study (303), the exposure-adjusted incidences were 41.2 events per 100 PY vs. 8.8 events per 100 PY in the placebo group. This difference was explained mainly by increased rates of renal failure, renal failure acute and blood creatinine raised. A similar pattern was observed when extension data (study 305) was included.

System Organ Classes (SOCs) of special interest are discussed below in detail.

SOC Renal and Urinary Disorders

REAC-adjudicated events

The Renal Events Adjudication Committee (REAC) reviewed pre-defined renal events (AEs in the SMQ for acute renal failure that were serious or led to discontinuation of randomised study medication) as well as all increases in sCr > 1.5 x baseline. Review and adjudication were blinded to treatment allocation. For the Phase 3 core combination studies, the proportion of subjects with any adjudicated event was 6.5%, 14.9% and 3.3% in the lesinurad 200 mg, lesinurad 400 mg and placebo groups respectively. Of the events adjudicated, the proportion with at least one confounding factor with a moderate of high level of contribution were 36.1%, 39.3% and 44.4% for the lesinurad 200 mg, lesinurad 400 mg and placebo groups.

Resolution of a sCr elevation was defined as a value ≤ 1.2 x Baseline following an elevation. This was based on the intra-subject variability of baseline sCr values of approximately 22%. Estimated creatinine clearance (eCrCl) was calculated with the Cockcroft-Gault formula, using baseline age and ideal body weight. Other routine measurements were serum electrolytes. Urine was routinely monitored for glucose, ketones, occult blood, and protein. Protein-creatinine ratios were provided for subjects with sCR elevations.

Renal events

The rate of renal events increased with the dose, and was considerably higher in lesinurad monotherapy versus XOI-combination therapy. Most frequently reported adverse event was Blood Creatinine Increased, followed by renal impairment (**Table 52**).

Table 52. Renal events at lesinurad-XOI combination therapy and monotherapy

	Combination XOI (pooled Phase 3 data Study 301/302/304)			**Monotherapy (study 303)**	
	Plac	LESU 200 mg	LESU 400 mg	LESU 400 mg	placebo
Any renal TEAE	**4.5%**	**5.7%**	**11.8%**	**17.8%**	**0**
Renal SAEs	0.4%	0	1.0%	4.7%	0
Discontinuation due to renal AEs	1.0%	1.2%	3.3%	8.4%	0.9%
Renal impairment	0	0.2%	1.0%	3.7%	0
Acute Renal failure	0.4%	0	0.8%	2,8%	0
lithiasis	1.7%	0.6%	2.5%	0.9%	0
Elevations in Serum					

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Creatinine					
sCr elevated ≥ 1.5 fold	2.3%	4.3%	7.8%	24.3%	0
sCr elevations ≥ 2-fold	0	1.8%	6.7%	8.4%	0

The incidence of renal events was generally higher in elderly subjects, in those with lower Baseline renal function (eCrCl < 60), and in those with tophi at Screening.

In the pivotal XOI-combination trials, two-fold sCR elevations were reported in nine (1.8%), and 34 subjects (6.7%) in lesinurad 200 and 400 mg treatment groups, respectively, versus 0 in the Placebo arm. At lesinurad 200 mg dose, 88.9% (8/9) elevations were reported to be resolved, 66.7% (6/9) without interruption of lesinurad. The 400 mg dose, 80.0% (32/40) of these elevations were reported to be resolved, and 57.5% (23/40) without interruption of lesinurad. In the 200 mg dose arm, about 50% of the two-fold sCr elevation was resolved within 14 days, however, time to recovery was significantly longer for the 400 mg dose (**Table 53**).

Creatinine clearance

In the pivotal XOI-combination trials, the 400 mg dose was associated with a decline of eCrCl of -2.4% in Month 1 that remained stable to Month 12. No declining trend was observed for the 200 mg dose or placebo.

There were 2 subjects who had shifts in Protein-Creatinine ratio exceeding >1.0 mg/mg together with sCr elevations, indicating tubular dysfunction (incomplete tubular reabsorption of proteins). Both cases occurred at the 400 mg dose. No trends of abnormalities were observed for electrolytes or urinary parameters like proteinuria.

Table 53. Incidences of sCr elevations and time to resolution in the main XOI-combination studies (Study 301, 302, 304, 12 months follow-up)

Variable [n (%)]	LESU 200 mg +XOI (N=504)	LESU 400 mg +XOI (N=510)	TOTAL LESU +XOI (N=1021)	PBO +XOI (N=516)
Serum Creatinine Elevation Category				
sCr ≥ 1.5 x Baseline	29 (5.7)	73 (14.3)	102 (10.0)	12 (2.3)
sCr ≥ 2.0 x Baseline	9 (1.8)	34 (6.7)	43 (4.2)	0
sCr ≥ 3.0 x Baseline	4 (0.8)	12 (2.4)	16 (1.6)	0
Maximum time to resolution for subjects with sCr ≥ 2.0 x Baseline (days)	N=9	N=34	N=43	N=0
1 - 14	5 (55.6)	7 (20.6)	12 (27.9)	0
> 14 - 28	0	7 (20.6)	7 (16.3)	0
> 28 - 56	1 (11.1)	8 (23.5)	9 (20.9)	0
> 56 - 84	0	5 (14.7)	5 (11.6)	0
> 84	2 (22.2)	2 (5.9)	4 (9.3)	0

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Long-term renal safety (24 months follow-up)

Lesinurad was more frequently associated with renal events than placebo by baseline renal function, in a dose dependent manner (**Table 54**). Lesinurad was also associated with an increased incidence of serum creatinine elevations 1.5 times baseline, most of which gradually resolved after treatment withdrawal. The incidence rate of renal events slightly increased at longer-term follow-up for the 200 mg dose (see **Table 55** below). However, this was not the case for the 400 mg dose.

Table 54. Exposure adjusted incidence rates (per 100 PYE) for renal-related adverse events by baseline renal function: Core studies (301, 302 and 304) + Extension Studies (301, 302, 304, 306 and 307), data cut-off: 04 November 2014.

	PBO + XOI			LESU 200 mg + XOI					LESU 400 mg + XOI				
Baseline eCrCl category (mL/min)	N	Core PYE	Core n (rate)	N	Core PYE	Core n (rate)	Core + Extension PYE	Core + Extension n (rate)[a]	N	Core PYE	Core n (rate)	Core + Extension PYE	Core + Extension n (rate)[a]
All subjects	516	408.5	23 (5.6)	511	396.3	29 (7.3)	763.6	54 (8.4)	510	390.5	60 (15.4)	754.5	89 (14.0)
≥ 90	180	139.6	1 (0.7)	200	159.2	8 (5.0)	312.9	14 (5.4)	203	155.3	18 (11.6)	304.2	29 (11.3)
≥ 60 to < 90	229	185.7	8 (4.3)	208	156.5	8 (5.1)	307.4	15 (5.9)	213	163.1	26 (15.9)	321.3	35 (13.1)
< 60	105	82.3	14 (17.0)	102	79.6	13 (16.3)	141.0	25 (20.3)	92	70.3	15 (21.3)	125.5	24 (22.1)
≥ 45 to < 60	71	57.8	8 (13.9)	76	61.3	7 (11.4)	103.5	13 (14.0)	63	46.7	9 (19.3)	83.6	15 (20.6)
< 45	34	24.5	6 (24.5)	26	18.3	6 (32.8)	37.5	12 (39.6)	29	23.6	6 (25.4)	41.9	9 (25.2)

Abbreviations: 4MSU, 4-Month Safety Report; eCrCl, estimated creatinine clearance; IAS, Integrated Analysis of Safety; LESU, lesinurad; PBO, placebo; PYE, person-years of exposure to lesinurad/placebo; XOI, xanthine oxidase inhibitor (allopurinol/febuxostat).

[a] In order to focus on the effects of exposure beyond 12 months, the core plus extension data shown here include data for only those subjects who received lesinurad in a core study; ie, not the placebo rollovers.

Note: Baseline is defined as the highest sCr value recorded ≤ 14 days prior to the first dose of randomized study medication.

For each category, subjects are included only once, even if they experienced multiple events in that category.

Table 55. Exposure adjusted incidence rates (per 100 PYE) for for serum creatinine elevations by baseline renal function: Core studies (301, 302 and 304) + Extension Studies (301, 302, 304, 306 and 307), data cut-off: 04 November 2014.

	PBO + XOI			LESU 200 mg + XOI					LESU 400 mg + XOI				
Baseline eCrCl category (mL/min)	N	Core PYE	Core n (rate)	N	Core PYE	Core n (rate)	Core + Extension PYE	Core + Extension n (rate)[a]	N	Core PYE	Core n (rate)	Core + Extension PYE	Core + Extension n (rate)[a]
sCr elevation ≥ 1.5 x Baseline													
All subjects	516	408.5	12 (2.9)	511	396.3	29 (7.3)	763.6	54 (8.4)	510	390.5	73 (18.7)	754.5	109 (17.1)
≥ 90	180	139.6	7 (5.0)	200	159.2	11 (6.9)	312.9	24 (9.2)	203	155.3	25 (16.1)	304.2	41 (15.9)
≥ 60 to < 90	229	185.7	3 (1.6)	208	156.5	13 (8.3)	307.4	21 (8.2)	213	163.1	38 (23.3)	321.3	51 (19.1)
< 60	105	82.3	2 (2.4)	102	79.6	5 (6.3)	141.0	9 (7.3)	92	70.3	10 (14.2)	125.5	17 (15.7)
≥ 45 to < 60	71	57.8	2 (3.5)	76	61.3	4 (6.5)	103.5	8 (8.6)	63	46.7	5 (10.7)	83.6	9 (12.4)
< 45	34	24.5	0	26	18.3	1 (5.5)	37.5	1 (3.3)	29	23.6	5 (21.2)	41.9	8 (22.4)
sCr elevation ≥ 2.0 x Baseline													
All subjects	516	408.5	0	511	396.3	9 (2.3)	763.6	16 (2.5)	510	390.5	34 (8.7)	754.5	41 (6.4)
≥ 90	180	139.6	0	200	159.2	7 (4.4)	312.9	11 (4.2)	203	155.3	12 (7.7)	304.2	17 (6.6)
≥ 60 to < 90	229	185.7	0	208	156.5	2 (1.3)	307.4	4 (1.6)	213	163.1	18 (11.0)	321.3	19 (7.1)
< 60	105	82.3	0	102	79.6	0	141.0	1 (0.8)	92	70.3	4 (5.7)	125.5	5 (4.6)
≥ 45 to < 60	71	57.8	0	76	61.3	0	103.5	1 (1.1)	63	46.7	3 (6.4)	83.6	4 (5.5)
< 45	34	24.5	0	26	18.3	0	37.5	0	29	23.6	1 (4.2)	41.9	1 (2.8)

Abbreviations: 4MSU, 4-Month Safety Report; eCrCl, estimated creatinine clearance; IAS, Integrated Analysis of Safety; LESU, lesinurad; N, number of subjects in subgroup / treatment group, n, number of subjects with events; PBO, placebo; PYE, person-years of exposure to lesinurad/placebo; sCr, serum creatinine; XOI, xanthine oxidase inhibitor (allopurinol/febuxostat).

[a] In order to focus on the effects of exposure beyond 12 months, the core + extension data shown here include data for only those subjects who received lesinurad in a core study; ie, not the placebo rollovers.

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Mean CrCL remained stable over 24months follow-up from baseline for the 200 mg dose. However, the mean CrCL slightly decreased with -2.77 ml/min from baseline for the 400 mg dose.

SOC Cardiac Disorders

Case reports of CV adverts were sent to the Cardiovascular Endpoints Adjudication Committee (CEAC), to adjudicate their CV origin. Deaths, non-fatal myocardial infarction (MI) and non-fatal stroke were classified as MACE (Major Adverse Cardiovascular Events). Non-MACE categories were pre-defined as Unstable angina with urgent coronary revascularization, Urgent cerebral revascularization (non-elective), Congestive heart failure with hospitalization, Arrhythmia not associated with ischemia,

Venous and peripheral arterial thromboembolic event, Transient ischemic attack, and remainder category 'Other CV events'.

Baseline CV risk factors in the study population

According to the protocols, patients with hypertension and a history of cardiac disorder were eligible, provided that the disease and symptoms were adequately controlled, and the patient was in a reasonable physical condition (NYHA criteria I-II). Over 75% of the subjects had ≥ 1 CV comorbidity or CV risk factor at Baseline (**Table 56**).

In addition the majority of subjects had a BMI ≥ 30 kg/m^2 (67.4% and 71.0% in the placebo and total lesinurad groups, respectively). About 17% of the total study population had a BMI ≥ 40 kg/m^2, with similar distribution over the treatment arms.

Overall, the rates of subjects with adverse cardiac events were reported to be similar for Placebo and lesinurad (3.3% (n=17) and 4.3% (n=22) for lesinurad 200 and 400 mg, versus 3.9% (n=20) Placebo). However, about 60 % of these cases were reported to be severe for lesinurad (12/17 and 14/22 for the 200 mg and 400 mg dose, respectively), versus 10% in placebo (2/20).

Table 56. Cardiovascular co-morbidities at baseline in the main studies (Study 301,302, 304)

Comorbidity [n (%)]	PBO +XOI (N=516)	LESU 200 mg +XOI (N=511)	LESU 400 mg +XOI (N=510)	TOTAL LESU +XOI (N=1021)	TOTAL SUBJECTS (N=1537)
Any CV comorbidity or CV disease history (combined)	401 (77.7)	398 (77.9)	400 (78.4)	798 (78.2)	1199 (78.0)
Hyperlipidemia	221 (42.8)	230 (45.0)	241 (47.3)	471 (46.1)	692 (45.0)
Hypercholesterolemia	200 (38.8)	203 (39.7)	209 (41.0)	412 (40.4)	612 (39.8)
Hypertriglyceridemia	82 (15.9)	101 (19.8)	101 (19.8)	202 (19.8)	284 (18.5)
Diabetes mellitus	80 (15.5)	96 (18.8)	78 (15.3)	174 (17.0)	254 (16.5)
Myocardial infarction	19 (3.7)	26 (5.1)	22 (4.3)	48 (4.7)	67 (4.4)
Angina pectoris	17 (3.3)	13 (2.5)	19 (3.7)	32 (3.1)	49 (3.2)
Stroke	7 (1.4)	4 (0.8)	6 (1.2)	10 (1.0)	17 (1.1)
Transient ischemic attack	6 (1.2)	7 (1.4)	5 (1.0)	12 (1.2)	18 (1.2)
Hypertension	340 (65.9)	330 (64.6)	325 (63.7)	655 (64.2)	995 (64.7)
Peripheral vascular disease	7 (1.4)	9 (1.8)	4 (0.8)	13 (1.3)	20 (1.3)
Heart failure	12 (2.3)	20 (3.9)	21 (4.1)	41 (4.0)	53 (3.4)

Analyses by the CEC adjudication committee

The Cardiovascular cases assigned by the Cardiovascular Endpoints Adjudication Committee are summarised in **Table 57**.

Table 57. Cardiovascular cases assigned by the Cardiovascular Endpoints Adjudication Committee (Study 301,302, 304)

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	PBO +XOI (N=516) n (%) [no. events]	LESU 200 mg +XOI (N=511) n (%) [no. events]	LESU 400 mg +XOI (N=510) n (%) [no. events]	TOTAL LESU +XOI (N=1021) n (%) [no. events]
Subjects with events sent for adjudication	28 (5.4) [38]	32 (6.3) [44]	28 (5.5) [47]	60 (5.9) [91]
Number of subjects with adjudicated events classified as CV event	15 (2.9) [17]	18 (3.5) [21]	15 (2.9) [24]	33 (3.2) [45]
Other CV event	2 (0.4) [2]	8 (1.6) [9]	6 (1.2) [10]	14 (1.4) [19]
Congestive heart failure with hospitalization	1 (0.2) [1]	1 (0.2) [1]	3 (0.6) [4]	4 (0.4) [5]
Venous and peripheral arterial thromboembolic event	1 (0.2) [1]	2 (0.4) [2]	0	2 (0.2) [2]
Arrhythmia not associated with ischemia	7 (1.4) [7]	4 (0.8) [5]	1 (0.2) [1]	5 (0.5) [6]
Cardiovascular death	0	2 (0.4)	2 (0.4)	4 (0.4)
Non-fatal myocardial infarction	1 (0.2) [1]]	2 (0.4) [2]	7 (1.4) [7]	9 (0.9) [9]
Non-fatal stroke	3 (0.6) [3]	0	0	0
Transient ischemic attack	1 (0.2) [2]	0	0	0
Unstable angina with urgent coronary revascularization	0	0	0	0
Urgent cerebral revascularization (non-elective)	0	0	0	0
Number of subjects with MACE[a] events	3 (0.6) [4]	4 (0.8) [4]	8 (1.6) [9]	12 (1.2) [13]

Fifteen (1.0%) subjects from the pivotal trials were identified as MACE cases (**Table 58**), including three (0.6%) subjects with 4 events (3 nonfatal strokes, 1 nonfatal MI) in the placebo group, four (0.8%) subjects with 4 events (2 nonfatal MIs, 2 CV deaths) in the lesinurad 200 mg group, and eight (1.6%) subjects with 9 events (7 nonfatal MIs, 2 CV deaths) in the lesinurad 400 mg group.

Table 58. Exposure-Adjusted Incidence Rate of Major Adverse Cardiovascular Events in the Core Phase 3 Studies (12-Month Studies 301, 302, and 304)

	PBO + XOI (N=516)[1] (421.1 PY)[2]	LESU 200 mg + XOI (N=511)[1] (414.6 PY)[2]	LESU 400 mg + XOI (N=510)[1] (413 PY)[2]	Total LESU + XOI (N=1021)[1] (827.5 PY)[2]
Number of Subjects with MACE Events	3	4	8	12
Incidence Rate[3] (95% CI)[4]	0.71 (0.23, 2.21)	0.96 (0.36, 2.57)	1.94 (0.97, 3.87)	1.45 (0.82, 2.55)
Number of MACE Events	4	4	9	13
Incidence Rate[5] (95% CI)[4]	0.95 (0.36, 2.53)	0.96 (0.36, 2.57)	2.18 (1.13, 4.19)	1.57 (0.91, 2.71)
CV death	0	2, 0.48 (0.12, 1.93)	2, 0.48 (0.12, 1.94)	4, 0.48 (0.18, 1.29)
Non-fatal myocardial infarction	1, 0.24 (0.03, 1.69)	2, 0.48 (0.12, 1.93)	7, 1.70 (0.81, 3.56)	9, 1.09 (0.57, 2.09)
Non-fatal stroke	3, 0.71 (0.23, 2.21)	0	0	0

Additional univariate analyses revealed pre-existing cardiovascular disease, moderate renal impairment, and age ≥65 years to be highly significant predictors of MACE irrespective of treatment (**Table 59**).

Table 59. Univariate analyses of Major Adverse Cardiovascular Event covariates based in Cox proportional hazards model in the Pivotal Phase 3 Studies (12-Month Studies 301, 302, and 304)

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Variable	Ratio Description	Hazard Ratio	95% CI Lower Limit[a]	95% CI Upper Limit[b]	p-value[c]
Risk Classes	High Risk/ Low-Mod Risk	13.045	4.643	36.650	<.0001
Age Group 1	>=65 years old / <65 years old	7.769	2.817	21.427	<.0001
Renal Function on Day -7	eCrCl <60 mL/min / >=60 mL/min	9.489	3.243	27.761	<.0001
CYP3A4 Lipid Lowering Medicine at Core Baseline	Yes / No	3.199	1.139	8.987	0.0274

Abbreviations: CI, confidence interval; eCrCl, estimated creatinine clearance; MACE, major adverse cardiovascular event; MI, myocardial infarction; sUA, serum uric acid; TIA, transient ischemic attack.

[a]Based on Cox Proportional Hazard's Model

[b]Wald confidence limits

[c]Chi square test

Note: Responder is defined as sUA< 6mg/dL in Study 301 and Study 302 and < 5mg/dL in Study 304. Subjects missing an sUA result at a visit are treated as a non-responder for that visit. No females were recorded as experiencing a MACE event. High risk defined by the presence of one or more of the following baseline comorbidities: TIA, angina pectoris, heart failure, MI, peripheral vascular disease, or stroke.

Combined analysis were scheduled of parameters that had both a $p < 0.1$ difference in distribution in the 3 treatment groups (e.g. placebo, lesinurad 200 mg or lesinurad 400 mg) and a $p < 0.3$ association with MACE events. However, a combined analysis was not performed because there were no baseline parameters that met these pre-specified p-value criteria.

Exploratory univariate analyses per treatment allocation indicated that patients with a history of CV disorders, the risk of MACE was higher in lesinurad groups (7.0-7.6%) than in the placebo group (1.9%, **Table 60**).

Table 60. Exploratory analysis of potential MACE covariates, Safety population –XOI combination Phase 3 Studies

Variable	Comorbidity Group	PBO N=516 n^a/n^b(%)	LESU 200 N=511 n^a/n^b(%)	LESU 400 N=510 n^a/n^b(%)
Risk Classes	High Risk	1/ 52 (1.92)	4/ 53 (7.55)	4/ 57 (7.02)
	Low to Moderate Risk	2/ 464 (0.43)	0/ 458 (0.00)	4/ 453 (0.88)
Age Group	<65 years old	1/ 443 (0.23)	2/ 454 (0.44)	4/ 433 (0.92)
	>=65 years old	2/ 73 (2.74)	2/ 57 (3.51)	4/ 77 (5.19)
Renal Function on Day -7	Missing	0/ 3 (0.00)	0/ 4 (0.00)	0/ 3 (0.00)
	<60 mL/min	2/ 89 (2.25)	4/ 90 (4.44)	4/ 86 (4.65)
	>=60 mL/mi	1/ 424 (0.24)	0/ 417 (0.00)	4/ 421 (0.95)

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Furthermore, the observed cardiovascular mortality rate in lesinurad-treated subjects (0.48/100 PYE;) in the pivotal Phase 3 combination therapy studies was in the expected range based on data obtained in an analysis of gout patients in the UK (matched for age, gender, and other key entry criteria), which was performed by an independent epidemiologist. Results of this analysis indicated a predicted total mortality and ischemic heart disease event rates of 1.17/100 PYE and 1.2/100 PYE, respectively.

SOC Hepatobiliary disorders

Hepatobiliary safety was considered of special interest, as DILI (drug induced hepatotoxicity) has been reported for benzbromarone, another uricosuric drug with the same mode of action as lesinurad.

At routine monitoring, there were no notable differences in liver enzymes increments in the lesinurad treatment arms versus placebo. In addition, no cases of DILI (meeting Hy's law) were observed for lesinurad in the total safety database.

AEs of the Hepatobiliary disorders domain were slightly more frequently reported for lesinurad (2.3% for the 200mg dose, 1.5% for the 400mg dose and 1.2% for Placebo), with hepatic steatosis and biliary events (including cholecystitis, cholelithiasis , bile duct stone, cholecystitis) as the most common reported events in this category. Moreover, three hepatobiliary events including acute cholecystitis and bile duct stone were classified as Serious Adverse Events for lesinurad, but none for placebo. However, at long-term follow-up for 24 months, no increasing trend of hepatobiliary disorders or signals of bile duct hyperplasia-was observed.

SOC Metabolism and nutrition disorders The overall incidence of this SOC was 8.3% for 200 mg dose, 9.8% for 400 mg dose, and 7% for placebo. This difference was mainly attributed to a higher incidence of the PT Type 2 Diabetes (10 subjects (2.0%) & 8 subjects (1.8%) for lesinurad 200 and 400 mg, versus 3 subjects (0.6%) for placebo), and the PT Diabetes Mellitus (7 subjects (1.4 %) & 3 subjects (0.6%) for lesinurad 200 and 400 mg, versus 2 subjects (0.4%) for placebo).

Notably, dehydration was also reported more frequently for active treatment (4 cases (0.8%) and 5 cases (1.0%) versus 2 cases (0.4%) for placebo). Moreover, two dehydration cases for active treatment were considered serious, versus none for Placebo.

SOC Gastrointestinal disorders: GI disorders were commonly reported (18% 200 mg dose, 20.2% high 400 mg dose, and 17.2% for placebo). Gastro-intestinal intolerability was common in the preclinical studies at high doses. Except for Gastro-oesophagal Reflux (2.7%, 1.4% versus 0.8%) and Abdominal Discomfort (2.7%, 1.4% versus 0.8%), no obvious trends of GI intolerability were observed in the Phase III studies (diarrhoea 4.5%, 5.3% versus 4.5%; nausea 4.5%, 5.3% versus 4.5%; Constipation 2.2%, 2.0% versus 1.7%, for Low Dose (200 mg), High Dose (400 mg) versus Placebo).

SOC Investigations: Overall, the rate of positive investigations was higher for the 400 mg dose (23.3%), versus the lower lesinurad 200 mg dose (16.6%) and placebo (17.8%). This was mainly caused by over-reporting of blood creatinine increments for the High lesinurad dose (7.8%), versus 4.3% for the low dose, and 2.3% for placebo.

Serious adverse events and deaths

The overall incidence of SAEs was lower for the 200 mg group than for the placebo group in the pivotal randomised trials, but increased in the 400 mg group (**Table 61**).

Table 61 Incidence of Serious Adverse Events by System Organ Class in the Pivotal Phase 3 Studies (12-Month Studies 301, 302, and 304)

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System Organ Class [n (%)]	PBO +XOI (N=516)	LESU 200 mg +XOI (N=511)	LESU 400 mg +XOI (N=510)	TOTAL LESU +XOI (N=1021)
Any SAE	29 (5.6)	24 (4.7)	44 (8.6)	68 (6.7)
Infections and infestations	6 (1.2)	4 (0.8)	6 (1.2)	10 (1.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3 (0.6)	2 (0.4)	5 (1.0)	7 (0.7)
Metabolism and nutrition disorders	0	2 (0.4)	5 (1.0)	7 (0.7)
Psychiatric disorders	1 (0.2)	1 (0.2)	1 (0.2)	2 (0.2)
Nervous system disorders	6 (1.2)	0	0	0
Ear and labyrinth disorders	1 (0.2)	0	1 (0.2)	1 (0.1)
Cardiac disorders	2 (0.4)	10 (2.0)	14 (2.7)	24 (2.4)
Vascular disorders	0	0	1 (0.2)	1 (0.1)
Respiratory, thoracic and mediastinal disorders	1 (0.2)	0	1 (0.2)	1 (0.1)
Gastrointestinal disorders	2 (0.4)	2 (0.4)	2 (0.4)	4 (0.4)
Hepatobiliary disorders	0	2 (0.4)	1 (0.2)	3 (0.3)
Musculoskeletal and connective tissue disorders	2 (0.4)	3 (0.6)	4 (0.8)	7 (0.7)
Renal and urinary disorders	4 (0.8)	0	8 (1.6)	8 (0.8)
General disorders and administration site conditions	2 (0.4)	2 (0.4)	1 (0.2)	3 (0.3)
Injury, poisoning and procedural complications	3 (0.6)	3 (0.6)	1 (0.2)	4 (0.4)

The incidence of renal SAE was twice as high at 400 mg dose as compared to placebo (1.6% versus 0.8%), whereas none occurred at the recommended 200 g dose. The renal SAEs included renal failure and nephrolithiasis.

The causes of SAE were quite heterogeneous in the placebo arm. However, for lesinurad 200 and 400 mg, the far most common SAE was a cardiac disorder, in contrast to placebo (2.0% (10 subjects) and 2.7% (14 subjects), versus 0.4% (2 subjects) for placebo). Myocardial infarction, coronary disorders and congestive heart failure were the most common reported SAE's for lesinurad.

Deaths

In total, 13 deaths were reported. Eleven deaths were adjudicated by the independent assignment committee CEAC as a MACE (Major Adverse Cardiovascular Event). The remaining 2 deaths were due to non-cardiovascular causes (suicide and gastric cancer). All the deaths occurred in male subjects, with the youngest being 37 years old (pulmonary thromboembolism) and the oldest being 78 years old (pulseless electrical activity). None of the deaths were considered to be treatment-related by the CEAC.

Notably, all fatal MACE cases occurred on active treatment with lesinurad, and none on placebo. Six fatal MACE cases (five on combination therapy, one on monotherapy) occurred in the 6-12 months placebo-controlled period in the randomised studies, versus 0 in the corresponding placebo arms (pooled Study 203, 301, 302, 303, 304). Another three fatal MACE cases occurred shortly (7-48 days) after the patients switched from prior 12 months of placebo to active treatment. The two remaining fatal CV cases occurred on continued use of lesinurad in the open-label extension period after the 12 months blind-phase.

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Laboratory findings

Haematology screening

The following haematology parameters were routinely monitored: Haematocrit, Haemoglobin, mean corpuscular hemoglobin, mean corpuscular haemoglobin concentration, mean corpuscular volume, platelet count, erythrocyte count, and White Blood Cell count (differential). Overall, the post-Baseline shifts to abnormal values was low and similar between treatment arms (<2%), and the mean levels of these parameters remained stable over the observed treatment period.

Clinical chemistry screening

Routine screening was performed of ALT, AST, bilirubin, direct bilirubin, sodium, chloride, potassium, bicarbonate, glucose, CK, and lipids (cholesterol, and triglycerides). No notably difference was observed.

Enhanced creatinine phosphokinase (CK) levels were reported frequently, but were equally distributed over treatment arms (4.5, 5.9 and 4.8% for the 200/400 mg lesinurad and placebo groups respectively).

Vital signs

No notable differences were reported for blood pressure and heart rate at routine monitoring. The changes from baseline were reported at a similar rate among lesinurad and placebo (data not shown).

No other meaningful signals of abnormal investigations were observed. E.g. liver enzyme increments were rarely reported, at an equal rate for active treatment or placebo.

Safety in special populations

Renal patients

For the subgroup of subjects with moderate renal impairment at baseline (CrCl < 60 mL/min), a higher rate of TEAEs compared to the rates observed in the overall population was observed, not in favour of lesinurad (**Table 62**).

Table 62. Incidence of TEAEs in renal impaired subjects (Study 301, 302 and 304)

Total Subjects with ≥ 1 TEAE	PBO + XOI		LESU 200 mg + XOI		LESU 400 mg + XOI		TOTAL LESU + XOI	
	N	n (%)	N	n (%)	N	n (%)	N	n (%)
CrCl								
≥ 90 mL/min	180	124 (68.9)	200	153 (76.5)	203	162 (79.8)	403	315 (78.2)
< 90 mL/min	334	239 (71.6)	312	232 (74.8)	305	244 (80.0)	615	476 (77.4)
≥ 60 mL/min	409	284 (69.4)	408	296 (72.5)	416	331 (79.6)	824	627 (76.1)
< 60 mL/min	105	79 (75.2)	102	89 (87.3)	92	75 (81.5)	194	164 (84.5)

No trend of increased renal risk was observed for lesinurad in patients with moderate renal impairment (10.5% in the placebo group versus 7.8% in the lesinurad 200 mg and 7.6% in the 400 mg lesinurad group) in the 12 months placebo-controlled phase of the studies. This was also confirmed by longer-term follow up data till 24 months.

At prolonged treatment till 24 months in the extension phase, there were mean increases of CrCL from baseline at the lesinurad 200 mg dose level.

Three case reports of renal failure requiring dialysis emerged in the open-label extension phase for the 200 mg dose. These were not considered treatment-related, and occurred long-term after discontinuation of lesinurad. One case was described as a complication of acute cardiac failure.

The incidence of cardiac disorders was 8.6% in the placebo group, 9.8% in the lesinurad 200 mg group, and 9.8% in the lesinurad 400mg group.

Elderly

In the pivotal XOI-combination studies, 14.1% and 13.1% of subjects in the placebo and total lesinurad groups were ≥ 65 years of age, and 1.7% and 2.0% were ≥ 75 years of age, respectively. Subjects ≥ 65 years of age had a higher incidence of Cardiac Disorders compared to subjects < 65 years of age across all treatment groups including placebo (8.8%-11.7% (lesinurad 200-400 mg) vs 12.3% placebo in elderly, and 2.6-3.0% versus 2.5% in placebo group, in subjects < 65 year). There

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were no signals of enhanced risk of renal events with increasing age. The subgroup ≥ 75 years of age was too small to draw final conclusions.

Safety related to drug-drug interactions and other interactions

Lesinurad has been shown to be a weak to moderate inducer of CYP3A4 based on *in vitro* data and clinical DDI studies. To investigate implications for safety, the applicant submitted a pre-planned analysis of the impact of lesinurad on concomitant CYP3A4 substrates during Phase 3, specifically anti-cholesterol (**Table 63**) and anti-hypertensive medications (**Table 64**).

Table 63. Incidence of Post-Baseline Total Cholesterol Increase and New Lipid Lowering Medication in Subjects With Comorbidity of Hyperlipidemia by CYP3A Medication at Baseline in the Pivotal Phase 3 Studies (12-Month Studies 301, 302, and 304)

Variable Criterion [n (%)]	PBO +XOI (N=516)	LESU 200 mg +XOI (N=511)	LESU 400 mg +XOI (N=510)	TOTAL LESU +XOI (N=1021)
Subjects with a CYP3A substrate lipid lowering Baseline medication (n)	99	89	78	167
Increase from baseline ≥ 20%	37 (37.4)	45 (50.6)	44 (56.4)	89 (53.3)
Subjects with a new lipid lowering post Baseline (n)	6 (6.1)	12 (13.5)	11 (14.1)	23 (13.8)
Subjects without a CYP3A substrate lipid lowering Baseline medication (n)	417	422	432	854
Increase from baseline ≥ 20%	102 (24.5)	104 (24.6)	150 (34.7)	254 (29.7)
Subjects with a new lipid lowering post Baseline (n)	22 (5.3)	20 (4.7)	20 (4.6)	40 (4.7)

Abbreviations: CYP3A, Cytochrome P450 3A; LESU, lesinurad; PBO, placebo; XOI, xanthine oxidase inhibitor (allopurinol/febuxostat).

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Table 64. New Anti-Hypertensive Medication in Subjects With Comorbidity of Hypertension by CYP3A Medication at Baseline in the Pivotal Phase 3 Studies (12-Month Studies 301, 302, and 304)

Variable Criterion [n (%)]	PBO +XOI (N=516)	LESU 200 mg +XOI (N=511)	LESU 400 mg +XOI (N=510)	TOTAL LESU +XOI (N=1021)
Subjects with a CYP3A substrate anti-hypertensive Baseline medication (n)	119	107	135	242
Increase from Baseline of SBP >10 mmHg	68 (57.1)	60 (56.1)	89 (65.9)	149 (61.6)
Increase from Baseline of DBP >7 mmHg	76 (63.9)	57 (53.3)	81 (60.0)	138 (57.0)
Increase in either above	89 (74.8)	76 (71.0)	107 (79.3)	183 (75.6)
Subjects with a new anti-hypertensive post-Baseline (n)	13 (10.9)	20 (18.7)	27 (20.0)	47 (19.4)
Subjects without a CYP3A substrate anti-hypertensive Baseline medication (n)	397	404	375	779
Increase from Baseline of SBP >10 mmHg	227 (57.2)	245 (60.6)	220 (58.7)	465 (59.7)
Increase from Baseline of DBP >7 mmHg	221 (55.7)	207 (51.2)	189 (50.4)	396 (50.8)
Increase in either above	286 (72.0)	291 (72.0)	266 (70.9)	557 (71.5)
Subjects with a new anti-hypertensive post-Baseline (n)	18 (4.5)	17 (4.2)	19 (5.1)	36 (4.6)

Abbreviations: CYP3A, Cytochrome P450 3A; DBP, diastolic blood pressure; LESU, lesinurad; PBO, placebo; SBP, systolic blood pressure; XOI, xanthine oxidase inhibitor (allopurinol/febuxostat).

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Discontinuation due to adverse events

Core phase 3 combination studies (301, 302 and 304)

During the core Phase 3 combination studies, the rates of randomised study medication discontinuation due to an AE were 6.3%, 9.4% and 5.4% in the lesinurad 200 mg, lesinurad 400 mg and placebo groups respectively.

Table 65. Incidence of Adverse Events Leading to Discontinuation of Randomized Study Medication by System Organ Class in the Pivotal Phase 3 Studies (12-Month Studies 301, 302, and 304)

System Organ Class [n (%)]	PBO +XOI (N=516)	LESU 200 mg +XOI (N=511)	LESU 400 mg +XOI (N=510)	TOTAL LESU +XOI (N=1021)
Any adverse event	28 (5.4)	32 (6.3)	48 (9.4)	80 (7.8)
Investigations	9 (1.7)	7 (1.4)	11 (2.2)	18 (1.8)
Musculoskeletal and connective tissue disorders	2 (0.4)	3 (0.6)	9 (1.8)	12 (1.2)
Renal and urinary disorders	5 (1.0)	3 (0.6)	9 (1.8)	12 (1.2)
Nervous system disorders	4 (0.8)	3 (0.6)	5 (1.0)	8 (0.8)
Gastrointestinal disorders	2 (0.4)	4 (0.8)	4 (0.8)	8 (0.8)
General disorders and administration site conditions	1 (0.2)	3 (0.6)	4 (0.8)	7 (0.7)
Cardiac disorders	2 (0.4)	3 (0.6)	3 (0.6)	6 (0.6)
Metabolism and nutrition disorders	0	1 (0.2)	3 (0.6)	4 (0.4)
Skin and subcutaneous tissue disorders	1 (0.2)	3 (0.6)	1 (0.2)	4 (0.4)
Neoplasms benign, malignant and unspecified	1 (0.2)	0	2 (0.4)	2 (0.2)
Hepatobiliary disorders	0	1 (0.2)	1 (0.2)	2 (0.2)
Infections and infestations	0	1 (0.2)	0	1 (0.1)
Blood and lymphatic system disorders	1 (0.2)	1 (0.2)	0	1 (0.1)
Psychiatric disorders	0	0	1 (0.2)	1 (0.1)
Eye disorders	1 (0.2)	0	1 (0.2)	1 (0.1)
Ear and labyrinth disorders	1 (0.2)	0	1 (0.2)	1 (0.1)
Vascular disorders	0	0	1 (0.2)	1 (0.1)
Respiratory, thoracic and mediastinal disorders	2 (0.4)	0	1 (0.2)	1 (0.1)
Reproductive system and breast disorders	0	1 (0.2)	0	1 (0.1)
Injury, poisoning and procedural complications	2 (0.4)	0	0	0

Abbreviations: LESU, lesinurad; PBO, placebo; XOI, xanthine oxidase inhibitor (allopurinol/febuxostat).
Note: System organ class (SOCs) sorted by descending rate in the TOTAL LESU + XOI group. Adverse events are treatment-emergent events and coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 14.0. For each SOC and preferred term (PT), subjects are included only once, even if they experienced multiple events in that SOC or PT.

Phase 3 combination extension studies (306 and 307)

Overall, there was no change in the pattern of exposure-adjusted rates of discontinuation compared to the core studies. For the *Renal and urinary disorders* SOC there were additional TEAEs leading to

discontinuations during the extension phase: 5 in the lesinurad 200 mg group and 4 in the lesinurad 400 mg group.

Monotherapy studies

The exposure-adjusted rates of discontinuation of randomised study medication were significantly higher for the lesinurad 400 mg group compared to placebo during the core monotherapy study (303): 48.5 per 100 PY vs. 13.2 per 100 PY. This was predominantly due to a higher rate of discontinuations for lesinurad in the *Renal and urinary disorders* SOC, including PTs for renal failure, renal impairment and calculus. During the extension study (305), there were a further 7 TEAEs in the *Renal and urinary disorders* SOC, in addition to the 9 reported in the lesinurad 400 mg group during the core study. There were also an additional 5 reports of *Blood creatinine increased* which led to discontinuation in the extension phase, in addition to the 2 reports in the lesinurad 400 mg group of the core study. During the extension study, there was a new TEAE of hypersensitivity leading to discontinuation of lesinurad. During the Phase 2 monotherapy study (202), there were 2 AEs leading to discontinuation, including a report of *Blood creatinine increased* in the lesinurad 400 mg group. During the extension phase of study 202, a further 6 AEs leading to discontinuation were reported, including 4 reports of *Blood creatinine increased.*

2.6.1. Discussion on clinical safety

Patient exposure

The safety population was sufficiently large to draw conclusions regarding the presence of common adverse events. The CHMP noted that the over 75s were relatively under-represented in the clinical safety database and this is reflected in the SmPC which states that therapeutic experience in patients 75 years and older is limited. Caution should be used when treating these patients.

Renal safety

Because of lesinurad's mode of action which causes an increase in renal uric acid excretion, and may lead to transient increases in serum creatinine, renal-related adverse reactions and kidney stones renal function and signals of renal damage were routinely monitored throughout the study program. In general, the incidence of renal AEs in the main XOI-combination studies increased with the dose (i.e. 5.7% at the 200 mg dose and 11.8% for 400 mg dose, versus 4.5% at placebo), and further increased in lesinurad monotherapy (17.8% for the 400 mg dose). Furthermore, the renal adverse events were more severe in the 400 mg dose group and in monotherapy, with higher frequencies of renal SAE (1-4.7%, respectively) when compared to the 200 mg dose. No renal SAE were reported for the 200 mg dosing regimen and the renal cases consist primarily of laboratory abnormalities without clinical evident symptoms, which resolved without treatment discontinuation.

In three 12-month placebo-controlled trials of lesinurad in combination with a xanthine oxidase inhibitor versus placebo, serum creatinine elevations between 1.5-fold and 2-fold over baseline occurred in 3.9% of patients on lesinurad 200 mg, 10.0% of patients on lesinurad 400 mg and 2.3% on placebo; serum creatinine elevations 2-fold or greater over baseline occurred in 1.8% of patients on lesinurad 200 mg, 6.7% of patients on lesinurad 400 mg and 0% on placebo. These serum creatinine elevations generally resolved, most without treatment interruption. Renal-related adverse reactions were reported in patients treated with lesinurad 200 mg (5.7%) and lesinurad 400 mg (11.8%) compared to placebo (4.5%), resulting in discontinuation of treatment in 1.2%, 3.3% and 1%, respectively. The most frequent renal-related adverse reaction was blood creatinine increased (4.3% with lesinurad 200 mg and 7.8% with lesinurad 400 mg compared to 2.3% with placebo).

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The CHMP therefore recommended that the dose is limited to 200 mg, and that lesinurad must be co-administered at the same time as the morning dose of a xanthine oxidase inhibitor, i.e. allopurinol or febuxostat, as a precautionary measure to prevent urinary uric acid overload. Lesinurad dosing must be interrupted if treatment with the xanthine oxidase inhibitor is interrupted.

To further minimise the potential for renal adverse events the CHMP recommended that renal function should be evaluated prior to initiation of lesinurad and monitored periodically thereafter, e.g. 4 times per year, based on clinical considerations, such as baseline renal function, volume depletion, concurrent illness or concomitant medications. Patients with serum creatinine elevations to greater than 1.5 times the baseline value should be closely monitored. Lesinurad treatment should be interrupted if serum creatinine is elevated to greater than 2 times the pre-treatment value or in case of an absolute serum creatinine value greater than 4.0 mg/dL. Treatment should also be interrupted in patients who report symptoms that may indicate acute uric acid nephropathy including flank pain, nausea or vomiting, and measure serum creatinine promptly. Finally, lesinurad should not be restarted if another explanation for the serum creatinine abnormalities cannot be deducted. The CHMP recommendations are reflected in the SmPC.

Renal safety of lesinurad use in patients with a history of moderate or severe renal impairment

In patients with moderate renal impairment, the incidence of renal-related adverse reactions was similar across all treatment groups: lesinurad 200 mg (12.7%), lesinurad 400 mg (16.3%) and placebo (13.3%). Serious renal-related adverse reactions, e.g. acute renal failure and renal impairment, were reported in patients treated with lesinurad 400 mg (1%) and placebo (0.4%) but not in patients on lesinurad 200 mg. Including the combination long-term extension studies, the incidences of serious renal-related adverse reactions (including acute renal failure) per 100 patient-years of exposure were 0.4 and 1.4 for lesinurad 200 mg and lesinurad 400 mg in combination with a xanthine oxidase inhibitor, respectively. Data from the long-term open-label Phase 3 extension studies revealed a renal safety profile consistent with that observed in the pivotal placebo-controlled studies.

The totality of the long-term safety dataset does not suggest that treatment with the low dose of lesinurad would induce severe renal damage at the long term. Although there was a slight increment of the incidence rates of the 200 mg dose at longer term follow-up till 2-3 years, this was not observed for the 400 mg dose. Most AEs consisted of mild and temporary increments of serum creatinine. Neither a signal of deterioration of the mean creatinine clearance, nor a signal of proteinuria was observed in the 200 mg dose group after 2 years' of follow-up. More importantly, no significant deterioration of renal function was noted in patients with mild-moderate renal impairment at baseline.

However, given that experience with lesinurad in patients with an estimated CrCL less than 45 mL/min is limited, the CHMP recommended that lesinurad should not be used in patients with severe renal impairment (CrCL less than 30 mL/min), end stage renal disease, kidney transplant recipients or patients on dialysis and used with caution in patients with a CrCL from 30 mL/min to less than 45 mL/min.

In addition, the CHMP requested that the safety and efficacy of lesinurad in patients with moderate renal impairment with CrCl 30-45 mL/min should be further investigated and the Applicant has included a study in the RMP in order to address this request.

Cardiovascular safety

Cardiovascular co-morbidities are common in gout patients, and this was also reflected by the study population, which had a high prevalence of hypertension, obesity and diabetes.

The overall cardiac events reporting rates were similar among placebo and the lesinurad treatment arms. However, cardiac events were 5-7 times more frequently reported as a SAE for the lesinurad

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treatment, in comparison with placebo. Not only the severity, but also the nature of the cardiac events was different, with more cases of myocardial infarction and cardiac fatalities for lesinurad, and primarily arrhythmia cases in the placebo arm. In the randomised, double-blind, placebo-controlled combination therapy clinical studies, the incidences of patients with adjudicated Major Adverse Cardiovascular Events (CV death, non-fatal myocardial infarction or non-fatal stroke) per 100 patient-years of exposure were: 0.71 (95% CI 0.23, 2.21) for placebo, 0.96 (95% CI 0.36, 2.57) for lesinurad 200 mg, and 1.94 (95% CI 0.97, 3.87) for lesinurad 400 mg, when used in combination with a xanthine oxidase inhibitor. However, the CHMP considered that a causal relationship with lesinurad and these events was not established, especially as all patients with a Major Adverse Cardiovascular Event treated with lesinurad 200 mg had a history of heart failure, stroke or myocardial infarction.

Furthermore, the observed cardiovascular mortality rate in lesinurad-treated subjects in the pivotal Phase 3 combination therapy studies was in the expected range based on data obtained in an analysis of gout patients in the UK (matched for age, gender, and other key entry criteria), which was performed by an independent epidemiologist. Results of this analysis indicated a predicted total mortality and ischemic heart disease event rates of 1.17/100 PYE and 1.2/100 PYE, respectively in these patients. These rates are similar to the observed rates in lesinurad-treated subjects in the pivotal Phase 3 combination therapy studies.

Nevertheless, CHMP noted that lesinurad has not been studied in patients with unstable angina, New York Heart Association (NYHA) class III or IV heart failure, uncontrolled hypertension or with a recent event of myocardial infarction, stroke, or deep venous thrombosis within the last 12 months and therefore considered that lesinurad treatment is not recommended in these patients. For cardiovascular patients in a stable condition, the benefit/risk balance should be assessed for each individual patient on an ongoing basis, taking into account the benefits of lowering urate levels versus a potential increase in cardiac risk.

In addition, to further characterise the cardiovascular risks associated with lesinurad use, especially in patients at high risk, such as those with a history of cardiovascular events, the CHMP recommended that the Applicant should conduct an observational study post-authorisation and that this study should be a condition of the marketing authorisation.

Hypertension was the most frequently cardiovascular reported adverse event in the lesinurad cores studies, with a higher incidence in the 200 mg and 400 mg groups compared to the placebo group (6.1% and 6.9% versus 4.8%, respectively). However the CHMP noted that in the more informative "Hypertension Standardised MedDRA Query (SMQ)", which includes terms such as blood pressure increased and blood pressure systolic increased the difference in the incidence of these events was greatly reduced with very small differences between the recommend 200mg dose and the placebo groups (6.5% and 6.2%, respectively). The CHMP therefore recommended that hypertension should not be considered an ADR and therefore is not included in the product's SmPC.

Other Adverse Events

The following TEAEs were reported with an incidence > 1%, and more commonly for lesinurad 200 mg and lesinurad 400 mg compared to placebo: influenza, headache, hypertension, gastro-oesophageal reflux and blood creatinine increased. The incidence of serious infections requiring hospitalisation was similar between lesinurad and placebo. No viral infections like herpes zoster were reported, indicating that the immune system was not compromised. Overall, the CHMP considered that these safety issues were sufficiently addressed by listing influenza, headache, hypertension, gastro-oesophageal reflux and blood creatinine increased in the ADR table of section 4.8, and that no additional warnings were required in this respect.

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Other potential adverse events that the CHMP noted was dehydration, which was reported as serious AEs for lesinurad only, and three cases of chronic pyelo-nephritis in the 400 mg dose arm. Considering the mode of action of lesinurad, causality could not be excluded for this adverse event and the CHMP recommended that dehydration should be listed in Section 4.8 of the SmPC. Furthermore, the SmPC states that patients should be instructed to stay well hydrated (e.g. 2 litres of liquid per day) whilst on lesinurad treatment.

In preclinical models, drug-induced bile duct hyperplasia was observed. A small number of cases of hepatobiliary events were reported for lesinurad. However, there was no increasing trend of hepatobilary after 24 months follow-up.

Enhanced creatinine phosphokinase (CK) levels were reported frequently, but were equally distributed over treatment arms (4.5, 5.9 and 4.8% for the 200/400 mg lesinurad and placebo groups, respectively). The CHMP considered that this could be explained by the co-medication colchicine, which was administered to about 85% of the study population to prevent ULT-induced flares, and which is known to induce CK.

Patients with severe hepatic impairment

As there are no data in patients with severe hepatic impairment, the CHMP noted that no dose recommendations can be made for these patients. However, the CHMP also considered that there is currently no urgent need for additional PK studies in this population as severe hepatic impairment is rare in gout patients, and the PK studies in moderate hepatic impairment did not indicate a significant effect.

Drug-drug Interactions

Based on available in vitro and clinical data the CHMP concluded that mild induction of CYP3A by lesinurad may reduce plasma exposures of co-administered medicines that are sensitive substrates of CYP3A. In the pivotal clinical trials, a greater proportion of patients using lipid lowering or anti-hypertensive medications that were CYP3A substrates required concomitant medication change when treated with lesinurad 200 mg in combination with a xanthine oxidase inhibitor, compared with patients treated with placebo in combination with a xanthine oxidase inhibitor (35% versus 28%, respectively). In Section 4.5 of the SmPC stipulates that the possibility of reduced efficacy of concomitant medications that are CYP3A substrates should be considered and their efficacy (e.g. blood pressure and cholesterol levels) should be monitored.

2.6.2. Conclusions on the clinical safety

The use of lesinurad is associated with the risk of hyper-saturation of uric acid in the urine, which may be damaging to the renal tissue. However, it has been shown that this risk can be largely attenuated by precautionary measures, such as a limitation of the lesinurad dose to 200 mg, and the concurrent use of XO inhibitors. In addition, routine monitoring of the renal function is proposed in the SmPC.

Available data also point towards an increased risk of severe cardiac events including myocardial infarction and fatalities in patients with a prior history of CV events. Since cardiovascular co-morbidity is common in the intended target population, the CHMP considered that that any potential increase in cardiovascular risk could have a significant impact on the benefit-risk balance of lesinurad. The CHMP therefore recommended that the risk of CV events in association with lesinurad use should be further evaluated through a post-authorisation safety study which should be a condition of the authorisation.

Meanwhile, adequate warnings have been included in the SmPC to use lesinurad with caution in stable CV compromised patients –and not to use lesinurad in patients with unstable and recent CV disorders, as there is no experience in this group.

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Other adverse drug drugs associated with lesinurad used were headache, influenza, increased blood creatinine and gastric reflux. These events were in general mild and did not lead to treatment withdrawal and are considered manageable with routine risk minimisation measures, and are reflected in the SmPC.

The CHMP considers the following measures necessary to address issues related to safety:

In order to investigate the cardiovascular risk in association with lesinurad exposure, mainly in patients with a history of cardiovascular disorders, the Applicant shall conduct and submit the results of an observational prospective study according to an agreed protocol.

2.7. Risk Management Plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the Risk Management Plan version 4.0 could be acceptable if the applicant implements the changes to the RMP as described in the PRAC endorsed PRAC Rapporteur assessment report.

The CHMP endorsed this advice without changes.

The applicant implemented the changes in the Risk Management Plan as requested by PRAC.

The CHMP endorsed the Risk Management Plan version 6.0 with the following content:

Safety concerns

Table 66. Summary of safety concerns

Summary of safety concerns	
Important identified risks	Renal impairment
Important potential risks	Major Adverse Cardiovascular Events (MACE) (mainly in patients with history of cardiovascular disorders)
Missing information	• Use in children • Use in pregnant or lactating women • Use in pre-existing hepatic impairment • Use in subjects ≥ 75 years of age • Use in patients with moderate renal impairment with CrCl 30-45 mL/min) • Bile salt export pump inhibition and use in patients with epoxide hydrolase polymorphism

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Pharmacovigilance plan

Table 67. On-Going and Planned Additional PhV Studies/Activities in the Pharmacovigilance Plan

Activity/Study title (type of activity, study title category 1-3)*	Objectives	Safety concerns addressed	Status Planned, started,	Date for submission of interim or final reports
Prospective postmarketing observational cohort study, Lesinurad observational post-authorization safety study Category 1	A well-defined large observational database study will be used as a signal detection tool to evaluate CV safety with focus on MACE events. Proposal: prospective observational cohort database study which the MAH believes will meet those objectives with valid and rapid accumulation of data and thus can provide timely information to inform the question of CV risk.	MACE (mainly in patients with a history of cardiovascular events)	Proposed	Final report planned 2nd quarter 2019
A Phase 4, Randomized, Double-Blind, Multicenter, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Lesinurad 200 mg in Combination with a Xanthine Oxidase Inhibitor (XOI), Compared with an XOI Alone, in Subjects with Gout and Creatinine Clearance 30 to 45 mL/min Who Have Not Achieved Target Serum Uric Acid Levels on an XOI Alone Category 3	Study in gout patients to assess the efficacy of lesinurad in the population of patients with creatinine clearance (CrCl) levels of 30-45 mL/min. This study will also provide some additional safety data in this population.	Patients with creatinine clearance of 30-45mL/min	Proposed	Date to be provided with final protocol 2nd quarter 2016

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In vitro study, study title not available Category 3	To conduct an in vitro BSEP inhibition assessment with lesinurad and lesinurad atropisomers.	BSEP inhibition with potential to induce hepatobiliary adverse effects	Proposed	2nd quarter 2016.
Retrospective analysis of clinical samples, study title not available Category 3	To further characterize the metabolic profile, including metabolite M4	Potential accumulation of metabolites over 24 hours	Ongoing	1st quarter 2016

*Category 1 are imposed activities considered key to the benefit risk of the product.
Category 2 are specific obligations
Category 3 are required additional PhV activity (to address specific safety concerns or to measure effectiveness of risk minimisation measures)

Risk minimisation measures

Table 68. Summary Table of Risk Minimisation Measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important identified risks		
Renal impairment	Statements within Sections 4.2 (Posology and method of administration), 4.4 (Special warnings and precautions for use), and 4.8 (Undesirable Effects) of the SPC	None
Important potential risks		
Major Adverse Cardiovascular Events (MACE) (mainly in patients with a history of cardiovascular disorders)	Statements within Sections 4.4 (Special warnings and precautions for use), and 4.8 (Undesirable Effects)	None
Missing Information		
Use in children	Statement within Sections 4.2 (Posology and method of administration) and 5.2 (Pharmacokinetic properties) of the SPC	None
Use in pregnant or lactating women	Statement within Section 4.6 (Fertility, pregnancy and lactation) of the SPC	None
Pre-existing hepatic impairment	Statement within Sections 4.2 (Posology and method of administration) and 5.2 (Pharmacokinetic properties) of	None

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	the SPC	
Use in Patients ≥ 75 Years of Age	Statement within Section 4.2 (Posology and method of administration)	None
Use in patients with moderate renal impairment with CrCl 30-45 mL/min	Statement within Section 4.2 (Posology and method of administration) and 4.8 (Undesirable effects)	None
Bile salt export pump inhibition and use in in patients with epoxide hydrolase polymorphism	None proposed	None

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Zurampic (LESINURAD) is included in the additional monitoring list as:

- It contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU;
- It has a PASS imposed either at the time of authorisation

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

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3. Benefit-Risk Balance

Benefits

Beneficial effects

Lesinurad as an add-on therapy to allopurinol or febuxostat, has shown a robust an sustainable sUA lowering effect in patients with insufficient response to allopurinol or febuxostat alone, at the aimed lesinurad 200 mg daily dose.

In two identically designed randomised trials in patients who did not receive their sUA treatment target level after 10 weeks of allopurinol 300 mg or more, 54.8% in the lesinurad 200 mg group and 25.6%

in the placebo group achieved the primary endpoint of sUA < 6 mg/dL in Month 6 (difference versus placebo: 29% (95% CI: 23-36), pooled data Study 301+302). The sUA lowering effect below the target of 6 mg/dL was sustainable, as shown by higher percentage of subjects that achieved a sUA level < 6 mg/dL in Month 4,5,6 –the primary endpoint for other ULT product approved by the CHMP- and in Month 12, in favour of lesinurad (see benefits-risks table below). In those subjects who continued treatment for 24 months (about 45% of the randomised population), the percentage of subjects experiencing flare rates decreased to approximately 0-5% at Month 12, without the help of colchicine prophylaxis.

Furthermore, in a randomised trial in gout patients with visible tophi at baseline (Study 304), the addition of lesinurad 200 mg to febuxostat 80 mg lead to a significant increment of responder rates of sUA < 5 mg/dL in month 6, in a subgroup of patients who did not already achieve this sUA target level after 3 weeks lead-in treatment of febuxostat 80 mg monotherapy (44.1% versus 23.5%, difference 21% (95% CI 3, 38). In long-term extension Study 307, the total tophi area continued to decline from baseline till 24 months by -70%. The percentage of patients with complete resolution of tophi steadily increased from 26.6% at Month 12, to 53.1% at Month 24 for lesinurad 200 mg + febuxostat.

Uncertainty in the knowledge about the beneficial effects

Although the primary endpoint of lowering sUA below the target level was met for lesinurad , the clinical relevance of this surrogate outcome was not supported by some secondary endpoints regarding gout flares, tophi resolution, which were not statistically different from placebo at Month 12.

Only the 200 mg dose is proposed in the labelling, because of renal safety reasons. A higher response was noted for the 400 mg dose regarding the primary endpoints, i.e. the proportion of patients achieving the target sUA level at Month 6. However, the long-term efficacy data after 24 months of treatment, provided sufficient evidence of a clinical effect with continuous decline of the tophi load and flares.

The additional effect of lesinurad 200 mg on top of febuxostat 80 mg was modest. However a relevant effect was shown in a subgroup of non-responders to febuxostat which reflects the granted indication of lesinurad as an add-on therapy in patients not achieving target serum uric acid levels with an adequate dose of a xanthine oxidase inhibitor alone.

Risks

Unfavourable effects
Renal

Due to the uricosuric mechanism of action of lesinurad, there is a potential risk of hyper-saturation of uric acid in the urine (i.e. hyperuricosuria) associated with its use, which could lead to renal toxicity events. The trials submitted in support of this application, demonstrated that limiting the lesinurad dose to 200 mg and administering in combination with a XOI the risk of renal events can be greatly reduced. Most renal related adverse events consisted of sCr elevations, which often resolved without treatment interruption.

Serious events like e.g. acute renal failure and nephrolithiasis rarely occurred (lesinurad 200 mg + XOI 0% versus 0.4% XOI + Placebo); nephrolithiasis (0.6% vs 1.7%). Furthermore, the long-term follow-up database of 24 months indicate that renal function (mean CrCL) remained stable from baseline for the 200 mg dose treatment group, whereas a small decline was noted for the 400 mg dose arm. Only 1.2% left the study prematurely, because of renal adverse events in the low dose group. Moreover, recovery was delayed at the higher dose. At lesinurad 200 mg dose, 50% of the sCr elevations were reported to be resolved within two weeks, often without treatment interruption of lesinurad. In contrast, about 60% of the sCr increment cases did not recover within a month for the 400 mg dose.

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Renal adverse events could occur at any time during lesinurad treatment. In the SmPC, it is recommended that renal function will be monitored 4 times a year, based on clinical considerations, such as prior renal function of the patient, volume depletion, concurrent illness or concomitant medications. Patients with serum creatinine elevations to greater than 1.5 times the pre-treatment value should be closely monitored.

Cardiovascular

Although the overall rates of cardiac AEs were similar between study treatment arms, an imbalance was noted regarding cardiac Serious AEs in a dose dependent way (lesinurad 200 mg 2.0%, lesinurad 400 mg 2.7%, Placebo 0.4%). The incidence of MACE (Major Adverse Cardiovascular Events, including CV death, non-fatal myocardial infarction or non-fatal stroke) increased with the dose: (0.71 (95% CI 0.23, 2.21) per 100 patient- years for placebo, 0.96 (95% CI 0.36, 2.57) for lesinurad 200 mg, and 1.94 (95% CI 0.97, 3.87) for lesinurad 400 mg, when used in combination with a xanthine oxidase inhibitor.

Special populations

Renal impaired patients

Renal impairment is common in gout. About 20% of the study population had moderate renal impairment (< 60 ml/min) at baseline. Notably, no trend of increased renal risk was observed for lesinurad as compared to placebo in patients with moderate renal impairment at baseline (10.5% in the PBO + XOI group versus 7.8% in the LESU 200 mg + XOI group and 7.6% in the LESU 400 mg + XOI group). Long-term safety has been established as well, considering that a small trend of improvement of CrCl (+1.99 ml/min, SD 8.9) was observed in the subgroup with moderate renal impairment at baseline, after two year continued treatment with lesinurad 200 mg.

Cardiovascular patients

Post-hoc analyses in a subgroup of 162 cardiovascular compromised patients at baseline, showed that the incidence of MACE was 7.6% (4/53) for lesinurad 200 mg compared to 1.9% (1/52) for placebo. A warning has been included in the SmPC that lesinurad should be used with caution in stable cardiovascular compromised patients and should not be used at unstable CV conditions.

Elderly

In the pivotal XOI-combination studies, about 14% of the subjects were ≥ 65 years of age. Elderly had a higher incidence of cardiac disorders compared to subjects < 65 years of age across all treatment groups including placebo (8.8%-11.7% (lesinurad 200-400 mg) vs 12.3% placebo in elderly, and 2.6-3.0% versus 2.5% in placebo group, in subjects < 65 year). There were no signals of enhanced renal risks in elderly.

Uncertainty in the knowledge about the unfavourable effects

Special populations

The clinical data from patients in the *low range* of moderate renal impairment (i.e. CrCl 30-45 ml/min) were sparse (26 were randomised to lesinurad 200 mg, and 29 to the 400 mg dose). Clinical data in patients with severe renal impairment (GFR <30 ml/min) are lacking. A contra-indication regarding the use of lesinurad in patients with severe renal impairment has been included in the SmPC. In addition, the safety and efficacy of lesinurad in these patients will be further evaluated in a phase 4-randomised double-blind, placebo controlled study as described in the RMP.

There is also no experience in patients with severe hepatic impairment. This has been adequately addressed in the RMP where further information in these patients will be collected post-marketing.

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Patients with unstable or severe CV patients (e.g. NYHA class III-IV), were excluded from the trials and therefore there is no experience about the magnitude of risks in these patients. Therefore, a strict warning has been included in the SmPC that lesinurad treatment is not recommended in these patients. Moreover, a post-authorisation study will be performed to further evaluate CV risks. Due to the high rates of CV co-morbidities in this population any increase in the CV risk could have a significant impact on the benefit-risk balance of Zurampic and therefore the CHMP considered that this study should be a condition of the authorisation.

There was limited experience in very elderly. Only 34 subjects were older than 74 years of age. This is included as missing information in the RMP and appropriate warnings in the SmPC about the limited experience with lesinurad treatment in this population.

Effects table

Table 69. Effects Table for Zurampic for the adjunctive treatment of hyperuricaemia in gout patients (with or without tophi) who have not achieved target serum uric acid levels with an adequate dose of a xanthine oxidase inhibitor alone

Effect	Description	Unit	LESU 200 mg	Placebo	Uncertainties / Strength of evidence
Favourable effects					
Add-on to allopurinol (Study 301+ 302)					
sUA	< 6 mg/dL at M6	%	54.8	25.6	Pooled 301+ 302: difference vs Placebo: 29 (95% CI 23, 36) A sustained sUA response was shown: (sUA < 6 Months 4,5,6: diff vs Plac: 26 (11, 38), Month 12: diff vs Plac: 24 (25, 50)
Add-on to febuxostat (Study 304):					
sUA	< 5 mg/dL at M6 in FEBU IR	%	44.1	23.5	
Tophi	Complete remission at M12	%	26.6	21.1	The percentage of patients with complete resolution of tophi steadily increased to 53.1% at Month 24 for LESU 200 mg + febuxostat
Unfavourable Effects (pooled data Study 301, 302, 304)					
Renal	All AEs SAEs 2 x sCR>	%	6.7 0 1.7	4.5 0.4 0	Uncertainty: risk increased with dose and at monotherapy: LESU400 mg + XOI: renal AEs: 11.8% (monotherapy 17.8%), SAE: 1% (monotherapy 4.7%), 2xsCR>:6.7% (monotherapy 8.4%)
Cardiac	All AEs SAEs	%	3.3 2.0	3.9 0.4	Uncertainty: Risk increased with dose: LESU 400 mg: 2.7%,
MACE	Overall Phase III study population	100 PY	0.96 (95% CI 0.36, 2.57)	0.71 (95% CI 0.23, 2.21)	Uncertainty: Dose dependent effect was shown: LESU 400 mg: 1.94 (95% CI 0.97, 3.87)
	Subgroup analysis in 101 patients with prior history of CV events at baseline		7.6% (4/53)	1.9% (1/52)	Uncertainty: The target population may contain patients at higher baseline CV risk than the selected study population.

Abbreviations: AE=adverse event, BL=baseline, CR=complete resolution of tophi, FEBU=febuxostat, , IR=irresponsive, LESU=lesinurad, MACE= major adverse cardiac event, PE=primary endpoint, Plac=placebo, PY= patients years, RR=responder rates, SAE: serious adverse event, 2 x sCR>: more than two-fold increment of serum creatinine from baseline, vs=versus, XOI=xanthine oxidase inhibitors,

Notes: ^flares requiring pharmacological treatment,

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Balance

Importance of favourable and unfavourable effects

Lesinurad in combination with a XOI, promptly and robustly reduced the sUA below the treatment target level in (tophaceous) gout patients, who were insufficient responders to allopurinol or febuxostat. Efficacy of lesinurad has been confirmed in patients with a limited uricosuric capacity at baseline, secondary to moderate renal impairment or the use of thiazide diuretics.

The size of the tophi and the flare rates continued to decrease at treatment prolongation till 24 months. In those subjects who continued treatment for 24 months, the percentage of patients with flares decreased to nearly zero, without the help of colchicine prophylaxis.

Due to its mode of action, lesinurad may cause hyper-saturation of uric acid in the urinary tract and as a consequence renal damage.

A small signal of serious cardiovascular complications was noted for lesinurad in a dose-related way. Post-hoc subgroup analyses in cardiovascular compromised patients at baseline showed that the incidence of MACE was numerically higher for lesinurad than placebo.

Benefit-risk balance

Discussion on the benefit-risk balance

Benefits

Lesinurad 200 mg in combination with a XOI effectively reduced the sUA levels in gout patients who did not achieve their sUA treatment targets with allopurinol or febuxostat alone. The sUA lowering effect of lesinurad was prompt and robust. The responder rates of patients achieving their target sUA level (<5-6 mg/dL) were double those compared to placebo. No apparent tolerance to its pharmacodynamic effects on the URAT-1 receptor occurred, since efficacy was maintained throughout the 12 months placebo-controlled period and thereafter.

Clinical relevance of the treatment effect

Although lesinurad significantly reduce sUA levels, no clear clinical benefits were shown regarding the reduction of flares and tophi at Month 6 and 12. This may be due to the fact that the introduction of urate lowering therapies like lesinurad, initially increase the flare rates. It is thought that a sudden reduction of the sUA levels causes dissolution of the uric acid crystals, which may trigger an inflammatory host response. Another reason may be carry–over effect of colchicine, an anti-inflammatory drug, which was given as a flare prophylaxis for 5 months in the trials. This may have limited the difference between lesinurad and placebo at the 12-months endpoint.

Furthermore, the percentage of patients with complete resolution of tophi steadily increased from 26.6% at Month 12, to 53.1% at Month 24. A lower tophus burden is expected to lead to a reduced number of flares. The mean percentage of patients who experienced a flare decreased to nearly zero, at longer term treatment till 24 months, without the help of colchicine prophylaxis. This could be considered as a clinically relevant reduction.

Risks

Renal safety

Because of its mode of action to promote the urinary excretion of UA, hyperuricosuria may occur. High level of UA in the urinary system may cause local damage and nephrotoxicity. It was noted in the Phase III program that lesinurad monotherapy and at the high 400 mg dose, were more commonly associated with an increased risk of renal related events, than at the use of the low 200 mg dose in

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combination with a XOI. Concurrent use of XOIs, which act by reducing the endogenous production of UA, diminish the urinary UA load and consecutively the occurrence of high peak UA levels and renal toxic events. Based on these findings, the lesinurad dose was limited to 200 mg, and lesinurad have to be taken together with a XOI. In addition, routine monitoring of the renal function should be applied throughout treatment.

The use of lesinurad in renal impaired patients

Thus far, there is limited experience in patients with moderate renal impairment CKD Stage 3b (eCrCl 30 to 45 mL/min)). A warning regarding the limited experience in patients with a CrCl 30-45 ml/min is reflected in the SmPC which states that lesinurad should be used with caution in this group. However, considering the complicated PK-PD relationship of lesinurad in renal impairment and the observed heterogenicity in PK-PD, safety and efficacy will be further established in this special group in the post-marketing setting.

Patients with severe renal impairment (CrCL < 30/min) were excluded from the trials and the use of lesinurad in this special population is contra-indicated in the SmPC.

Cardiac safety

A signal of increased CV events like myocardial infarction in a dose dependent fashion was observed in association with lesinurad use. It is noted that gout patients are a population at risk of CV events, and more than 60% of the study population had one or more risk factors like obesity, or were treated for hypertension, hyperlipidaemia or diabetes at baseline. However, the background risk could not fully explain the occurrence of MACE in the lesinurad trials, since known risk-factors like a prior history of CV events, renal impairment and high age, were equally distributed over the study arms. Moreover, post-hoc analyses showed that the risk of MACE was higher for lesinurad than placebo in patients with a prior history of CV events at baseline.

Overall, the number of MACE cases in the trials was considered low to draw definitive conclusions regarding the exact magnitude of CV risk with lesinurad, and another study in a larger population will be performed in post-authorisation setting to address this concern.

In addition, the potential cardiovascular risks have been adequately addressed by limiting the maximum recommend dose to 200 mg and warnings in the SmPC against the use of lesinurad in CV compromised patients.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Zurmapic in adults for the adjunctive treatment of hyperuricaemia in gout patients (with or without tophi) who have not achieved target serum uric acid levels with an adequate dose of a xanthine oxidase inhibitor alone is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

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The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Obligation to complete post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	**Due date**
Non-interventional post-authorisation safety study (PASS): In order to investigate the cardiovascular risk in association with lesinurad exposure, mainly in patients with a history of cardiovascular disorders, the MAH shall conduct and submit the results of an observational prospective study according to an agreed protocol.	2Q 2019

New Active Substance Status

Based on the CHMP review of data on the quality properties of the active substance, the CHMP considers that lesinurad is qualified as a new active substance.

Medicinal product no longer authorised