28 June 2018
EMA/474026/2018
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Duzallo

International non-proprietary name: allopurinol / lesinurad

Procedure No. EMEA/H/C/004412/0000

Note

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

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

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List of abbreviations

BCS Biopharmaceutics Classification System

BSE Bovine Spongiform Encephalopathies

CEP Certificate of Suitability of the EP

CPP(s) critical process parameter(s)

CQA(s) Critical quality attribute(s)

DoE design of experiments

DSC differential scanning calorimetry

EDQM European Directorate for the Quality of Medicines

FDC fixed dose combination

FT-IR Fourrier Transform Infrared Spectroscopy

GC Gas Chromatography

HPLC High performance liquid chromatography

ICH International Conference on Harmonisation

IPC In-process control

IR Infrared

LDPE low density polyethylene

LESU Lesinurad

MAA Marketing Authorisation Application

MACE Major Adverse Cardiovascular Event

MSU Mono sodium urate

N Number of subjects

NDA New Drug Application

NMT no more than

NOEL No effect level

NSAID Non-steroidal anti-inflammatory drug

OLE Open label extension

PBO Placebo

PD Pharmacodynamic(s)

Ph. Eur. European Pharmacopoeia

PK Pharmacokinetic(s)

PKPD Pharmacokinetic-pharmacodynamic

PRAC Pharmacovigilance Risk assessment Committee

PRO Patient reported outcome

PSUR Periodic Safety Update Report

PT Preferred Term

pUA Plasma uric acid (also referred to as plasma urate)

PV Pharmacovigilance

PVA Polyvinyl alcohol

PVC polyvinyl chloride

PVDC polyvinylidene chloride

PYE Person years of exposure

QbD Quality by design

QD Once daily

RH Relative Humidity

RMP Risk Management Plan

SAE Serious adverse event

sCr Serum creatinine

SMs Starting materials

SmPC Summary of Product Characteristics

SOC System Organ Class

sUA Serum uric acid (also referred to as serum urate)

SURI Selective UA reabsorption inhibitor

TEAE Treatment emergent adverse event

TTC Threshold of Toxicological Concern

UA Uric acid

ULT Urate-lowering therapy

URAT1 Uric acid transporter 1

US United States

USP United States Pharmacopoeia

UV Ultraviolet

XOI Xanthine oxidase inhibitor

XRPD X-ray powder diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Grünenthal GmbH submitted on 23 June 2017 an application for marketing authorisation to the European Medicines Agency (EMA) for Duzallo, 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 25 February 2016. The applicant applied for the following indication

"Duzallo is indicated in adults for the treatment of hyperuricaemia in gout patients who have not achieved target serum uric acid levels with an adequate dose of allopurinol alone".

The legal basis for this application refers to:

Article 10(b) of Directive 2001/83/EC – relating to applications for fixed combination products.

The application submitted is a fixed combination medicinal product.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0239/2016 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.

Scientific advice

The applicant received Scientific advice from the CHMP on 23 June 2016 (EMA/H/SA/3339/1/2016/III). The Scientific advice pertained to quality and clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Kristina Dunder Co-Rapporteur: Tomas Boran

The application was received by the EMA on	23 June 2017
The procedure started on	13 July 2017
The Rapporteur's first Assessment Report was circulated to all CHMP members on	2 October 2017
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	28 September 2017
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	11 October 2017
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	9 November 2017
The applicant submitted the responses to the CHMP consolidated List of Questions on	21 February 2018
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	3 April 2018
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	12 April 2018
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	26 April 2018
The applicant submitted the responses to the CHMP List of Outstanding Issues on	24 May 2018
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	14 June 2018
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 Duzallo on	28 June 2018

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Duzallo (allopurinol/lesinurad 300mg/200 mg and 200mg/200mg Fixed Dose Combination (FDC film-coated tablets) application has been submitted with an indication in the treatment of hyperuricaemia in gout patients who have not achieved target serum uric acid levels with an adequate dose of allopurinol alone, as taken QD in adults.

2.1.2. Epidemiology

Gout is the most common type of inflammatory arthritis. 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 tophaceous arthritis at a young age. Women who develop gout are in general elderly using diuretics.

2.1.3. Aetiology and pathogenesis

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.

2.1.4. Clinical presentation, diagnosis

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.

2.1.5. Management

Several urate lowering therapies (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 Serum uric acid (sUA, also referred to as serum urate), may trigger an inflammatory

reaction. According to clinical treatment guidelines, 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 EU 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.

About the product

Duzallo, a fixed dose combination (FDC) of allopurinol and lesinurad, targets both excretion and production of uric acid, thus providing a dual-mechanism approach to lower sUA levels. Lesinurad is a selective uric acid reabsorption inhibitor (SURI) that inhibits the uric acid transporter 1 (URAT1) in the proximal tubule of the kidney. 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 (Handler 2010). Allopurinol is a purine analogue that inhibits xanthine oxidase (XO) and reduces the production of uric acid.

Lesinurad was authorized via a centralised procedure for Zurampic (EMEA/H/C/003932) on 18.02.2016.

Allopurinol has been authorised for over 50 years at national level.

The FDC Duzallo is submitted as a substitution therapy to free combination of the already approved lesinurad and allopurinol.

The 300/200 strength combines the approved dose of lesinurad (200 mg) with the most commonly prescribed XOI (allopurinol) at the most commonly prescribed daily dose (300 mg). The 200/200 strength provides a lower allopurinol dose option (200mg) e.g. for patients with moderate renal impairment.

2.2. Quality aspects

2.2.1. Introduction

The finished product is a fixed dose combination presented as film-coated tablets containing 200 mg /200 mg or 200 mg/ 300 mg of allopurinol and lesinurad as active substances, respectively.

Other ingredients in the tablet core are hydroxypropylcellulose, microcrystalline cellulose, lactose monohydrate, crospovidone and magnesium stearate. Other ingredients in the tablet coat are: hypromellose, titanium dioxide (E171), triacetin, iron oxide yellow (E172) and iron oxide red (E172).

The product is available in opaque PVC/PVdC/Aluminium blister, as described in section 6.5 of the SmPC.

2.2.2. Active Substance

General information

<u>Lesinurad</u>

General information

The chemical name of lesinurad is 2-((5-bromo-4-(4-cyclopropylnaphthalen-1-yl)-4H-1,2,4-triazol-3-yl)thio)acetic acid corresponding to the molecular formula $C_{17}H_{14}BrN_3O_2S$. It has a molecular mass 404.28 g/mol and the following structure (Figure 1):

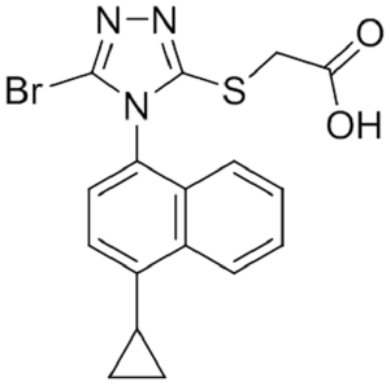


Figure 1. Structure of lesinurad

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.

Lesinurad appears as a white to off-white, not hygroscopic powder. Sufficient information on the solubility in aqueous and organic solvents has been provided. Regarding aqueous solvents, solubility increases with increasing pH. Lesinurad does not contain any chiral centres but is provided as racemic mixture of 2 atropisomers (ratio of 50:50) in which sufficient information has been provided and which are separable by chiral chromatography. Investigation of the kinetics of atropisomer interconversion revealed that the atropisomers are locked into a configuration and do not readily interconvert. Because it is a racemic mixture, lesinurad does not exhibit optical rotation. There are two known non-solvated crystal forms (free acid polymorphs), Form 1 (metastable) and Form 2 (thermodynamically stable). Form 2 was selected for development, is consistently manufactured and does not change upon storage.

Manufacture, characterisation and process controls

Lesinurad active substance is manufactured by two active substance manufacturers from well-defined starting materials. Lesinurad is synthesized in 3 synthetic steps. The step 1 of the synthesis can be are performed by two separate processes. This active substance is the same that has been previously assessed for the centrally authorised product Zurampic.

Lesinurad is synthesized in 3 synthetic steps: the first step of the synthesis leading to an intermediate.

The commercial manufacturing process for the synthesis of the active substance was sufficiently detailed including quantities and operating conditions. Batches may be reprocessed to attain the requisite standard, by repetition of all or part of the processes. Analysis of lesinurad batches manufactured using both routes of step 1 shows that both processes provide material of adequate and comparable quality (based on batch analysis of the intermediate and lesinurad) suitable to be used in the final steps of the synthesis leading to the crystalline drug substance.

The development of the control strategy for the manufacture of lesinurad followed a science and risk-based approach. Critical quality attributes (CQA) have been discussed and are adequately justified and critical process parameters (CPP) have been determined and described sufficiently.

Thorough discussion of impurities (including genotoxic) comprising several spike and purge studies show absence of or sufficient 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. All impurities or potential impurities that tested positive or equivocal (i.e., not a clear negative result) in the Ames assay or are known carcinogens will be controlled based on the Threshold of Toxicological Concern (TTC) approach. The TTC approach indicates that the level for genotoxic compounds is set to 1.5 µg/day according to guideline EMEA/CHMP/QWP/251344/2006. Considering a maximum daily dose of 200 mg of lesinurad, the acceptable level for genotoxic compounds in the active substance is determined to be 7.5 ppm for Ames positive and known carcinogenic compounds. The active substance batches manufactured by the commercial process and used in Phase 3 clinical studies have all been tested using validated methodologies, and it was shown that the potential genotoxic/carcinogenic impurities were either not detected or present at a level less than 30% of the TTC (less than 2.25 ppm) in all tested lots. All genotoxic / mutagenic impurities except for one (formylhydrazine) are controlled in either the starting material or intermediate. This is in line with Option 3 of the ICH M7. Formylhydrazine is not controlled as such, in line with Option 4, which is acceptable, based on the provided purge studies and the purge factor for clearance of the impurity by the process. All impurities tested in the Ames assay that were negative are considered as standard impurities and will be controlled as recommended in ICH Guideline Q3A(R2) Impurities in New Drug Substances and ICH Guideline Q3B(R2) Impurities in New Drug Products. There are no elemental impurities used in the commercial manufacturing process for lesinurad active substance.

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: appearance, identity (FTIR, HPLC), related substances (HPLC), residual solvents (GC), water content (Ph. Eur.), sulfated ash (Ph. Eur.), assay (HPLC), particle size (laser diffraction) and chirality (chiral HPLC).The limits of the specified impurities are above the qualification threshold and have been sufficiently toxicologically qualified. The limit for individual unspecified impurity is in line with ICH guidance and is acceptable. Other impurities are not specified and controlled upstream. Residual solvent limits comply with ICH Q3C.

A number of lesinurad attributes were analysed during development, but have not been included in the proposed commercial specification. Polymorphic form is not included because the synthetic process produces exclusively Form 2 and identity testing by FTIR confirms the form as part of release testing. All development batches and production scale batches of lesinurad have been analyzed using X-ray powder diffraction (XRPD) and differential scanning calorimetry (DSC) to demonstrate that Form 2 has been produced. There are no elemental impurities used in the commercial manufacturing process for lesinurad active substance. The controls in place during the manufacture of lesinurad are adequate to control elemental impurities and it has been justified that a specification for elemental impurities is not necessary. Microbial testing is not included on the lesinurad specification based on the low risk of contamination during manufacturing and on the fact that lesinurad does not support microbial growth.

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data from 8 commercial scale batches manufactured with both commercial process from the two manufacturers (8 from one manufacturer and three batches from the second) were provided. The results are within the specifications and consistent from batch to batch and demonstrated the equivalence of the two processes.

Stability

Stability data on three pilot scale batches of lesinurad stored in the intended commercial packaging from the first manufacturer and three commercial scale batches from the second manufacturer were provided. In addition data from two pilot batches from the first manufacturer using process II were also provided as supportive data. Results for up to 36 months under long term conditions (25.0 ± 2.0 °C / 60.0 % RH ± 5.0 %) and for up to 6 months under accelerated conditions (40.0 ± 2.0 °C / 75.0 % RH ± 5.0 %) were provided according to the ICH guidelines.

Samples were tested for appearance, assay, organic impurities, water content, physical form by XRPD, thermal analysis by DSC and particle size distribution. The test methods are stability indicating. All tested parameters consistently meet the specifications under both accelerated and long-term conditions. No significant changes to any of the measured parameters were observed under long term and accelerated conditions.

Photostability studies on one batch from each manufacturer according to ICH Q1B showed no degradation.

Forced degradation studies

Samples of lesinurad active substance were subjected to stress conditions to confirm the stability indicating power of the HPLC method for assay and impurities, to assess stability, and to identify potential degradation products. Solid or solution/suspension samples of the drug substance were exposed to acid, base, hydrogen peroxide, heat and light, followed by HPLC analysis of assay and organic impurities. Results of these studies demonstrated that lesinurad is stable under photolytic and aqueous basic and acidic conditions, at room temperature, with little or no degradation occurring. Under harsh oxidative conditions degradation was observed with a corresponding increase in impurity 594-T. Under milder oxidative conditions, no degradation was observed. The thermal conditions of 70 °C/75% RH for 1 month led to formation of one identified. The stability results support the proposed retest period of 36 months in the proposed container and stored below 30 °C.

Allopurinol

General information

The chemical name of allopurinol is 1,5-dihydro-4*H*-pyrazolo[3,4-*d*]pyrimidin-4-one corresponding to the molecular formula $C_5H_4N_4O$. It has a molecular mass of 136.11 g/mol and the following structure (Figure 3):

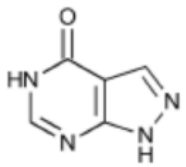


Figure 2. Structure of allopurinol

Allopurinol appears as a fluffy white to off-white non-hygroscopic powder. It is very slightly soluble in water and in alcohol, soluble in solutions of potassium and sodium hydroxides; practically insoluble in chloroform and in ether. Allopurinol does not exhibit stereoisomerism. There is only one known crystal form; it has been demonstrated that all tested batches are isomorphous.

Allopurinol is described in the Ph. Eur. The applicant uses the CEP procedure and a copy of the CEP has been provided. The relevant information has been assessed by the EDQM before issuing the Certificate of Suitability.

Manufacture, characterisation and process controls

Information regarding the manufacture, characterisation and in-process controls of allopurinol is covered by the CEP.

Specification

The active substance specification includes tests and limits for: appearance (visual), identification (Ph. Eur.), related substances (Ph. Eur.), impurities D, E and F (Ph. Eur.), loss on drying (Ph. Eur.), sulfated ash (Ph. Eur.) and assay (Ph. Eur.).

The specification complies with the requirements of the European Pharmacopeia monograph for allopurinol and the tests presented in the CEP are considered justified. All used reference standards are sourced from Ph. Eur.

Stability

Reference is made to the Certificate of Suitability. The re-test period of the active substance is 48 months if stored in double polyethylene (LDPE) transparent bags inside either HDPE opaque blue drum or in light brown carton drums.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

The finished product is oblong shaped, fixed dose combination (FDC), immediate release film-coated tablets available in two strengths containing 200 mg /200 mg or 200 mg/ 300 mg of alopurinol and lesinurad respectively.

The 200 mg/200 mg tablets are pale pink, debossed with “LES200” above“ALO200” on one side and blank on the other measuring 7.14 x 17.15 mm.

The 200 mg/300 mg tablets are orange, slightly brownish, debossed with “LES200” above “ALO300” on one side and blank on the other measuring 7.82 x 18.67 mm.

The finished product is presented as film-coated tablets containing either allopurinol 200 mg/lesinurad 200 mg or allopurinol 300 mg/lesinurad 200 mg as active substances. Other ingredients are lactose monohydrate, microcrystalline cellulose, crospovidone, hydroxypropyl cellulose and magnesium stearate for the tablet core and hypromellose, titanium dioxide, triacetin, iron oxide yellow and iron oxide red for the tablet coat.

The two dose strengths of the FDC have been developed using identical formulation principles (e.g. same qualitative composition, same in-vitro dissolution behaviour) as well as identical manufacturing principles (same manufacturing operations, in-process controls etc.).

Allopurinol/lesinurad film-coated tablets have been developed based on Zurampic (lesinurad) 200 mg film-coated tablets, which were authorized via the centralized procedure (marketing authorization number EU/1/15/1080).

According to the applicant, lesinurad is considered a BCS class II molecule and BCS classification of allopurinol is BCS class IV.

Increase in allopurinol particle size has an impact on dissolution behaviour. Therefore, the specification limit for allopurinol particle size has been proposed and allopurinol specification has been updated. The micronization step is performed by the allopurinol active substance manufacturer.

All excipients are compendial and well-known in oral solid dosage form manufacturing. The excipients used for the coating of the film-coated tablets are used as a commercially available ready-to-use material. All ingredients of the coating formulation are compendial and the iron oxide pigments comply with the regulation (EU) 231/2012. Excipient compatibility was assessed by measuring the chemical stability of the active substances in binary mixtures with selected excipients at 40°C/75% RH for 2-3 months. The active substances compatibility (allopurinol-lesinurad) was also evaluated. In general, most of the excipients studied had no significant impact on the stability of the active substances and the results have been confirmed by the results of stability studies.

There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.2.1. of this report.

The excipients used in Duzallo are standard for this type of formulation. Their choice and levels have been satisfactorily justified based on experiments on the product characteristics, performance, stability and manufacturing processability.

The applicant has applied QbD principles in the development of the finished product and its manufacturing process. However, no design space was claimed for the manufacturing process of the finished product. Proven acceptable ranges for key process parameters are proposed and adequate control strategies for the manufacturing steps are presented.

The manufacturing process consists of dry mixing, wet granulation, wet milling, drying, milling, blending, tableting and coating.

The dry mixing operation combines lesinurad and allopurinol ASs with lactose monohydrate and portions of the microcrystalline cellulose (MCC), crospovidone and hydroxypropyl cellulose (HPC).

A design of experiments (DoE) incorporating both tablet strengths in order to optimise the granulation process has been performed. The objectives were to evaluate the effect of granulation process parameters on compression and dissolution of lesinurad and allopurinol. Results from the DoE study were used to select the wet granulation process parameters (commercial scale). Two batches of lesinurad, one from each supplier, and two batches of allopurinol were used in the DoE study. Elements of the overall control strategy associated with wet granulation were defined and presented.

All DoE batches showed acceptable flow, compressibility and dissolution. Hydroxypropyl cellulose concentration and spray time were identified as having the greatest impact on granulation particle size while the milled and final blend particle size correlated with lesinurad dissolution. Drying and milling studies were performed and proposed proven acceptable ranges parameters were established. Blend uniformity issues are not expected due to drug loading, greater than 20% lesinurad and allopurinol.

The tableting unit operation has the potential to impact the appearance, assay, uniformity of dosage units, and dissolution. Overall stratified core content uniformity data indicate that there is little variability between or within lots and no segregation is observed during compression. The impact of

compression on allopurinol and lesinurad release was evaluated across low and high compression forces. It was shown that there is no impact of compression force on dissolution over the range tested.

The film-coated tablets are coated with a non-functional, aesthetic film coat. The tablets are coated in a pan coater until the tablets are uniformly coated with to a defined approximate weight gain.

The respective elements of the control strategy associated with the steps of drying and milling, blending, tableting and coating were also defined and presented.

The process understanding gained during development has led to the definition of process parameters for the other steps of the process as well. The primary stability and commercial scale batches produced were manufactured with process parameters within the proven acceptable ranges making them representative of the commercial process. The wet granulation process and process parameters are critical to downstream processes, mainly compression (tablet hardness), film coating (appearance) and finished product (dissolution).

The manufacturing process was transferred to the commercial manufacturing site where it was concluded that adaptation of process parameters was required in regard of granulation, blending and coating operations due to different size of otherwise similar equipment. Two batches of each strength were manufactured at the proposed commercial batch size. Process parameters ranges and target values for each process step were compared and adapted if required. The four batches complied with the specifications and content uniformity data showed a very good level of distribution of the active substance. The single assay values fully complied with Ph. Eur. uniformity of dosage units requirements. The *in vitro* dissolution test results were in line with the expected profile, reaching the acceptance limit at 45 min for lesinurad and 30 minutes for allopurinol. The manufacturing process is considered successfully transferred to the commercial manufacturing site.

The dissolution parameters of the individual lesinurad 200 mg film-coated tablet approved method and the allopurinol tablet USP method were considered as starting points for the development of the dissolution method.

Comparison of dissolution profiles of tablet containing one active substance lesinurad (Zurampic) and/or allopurinol (Zyloprim) with proposed finished products containing fixed combination of both active substances have been provided in chosen dissolution conditions. It was concluded that dissolution profiles are similar.

The discriminating ability of the proposed method was challenged by evaluating various method and product attributes and their impact on the dissolution rate of the FDC tablets. This included evaluation by comparing the dissolution profile of the coated tablets, tablet cores, and the related blend, as well as the impact of particle size of both active substances and meaningful variation to the granulation process. The proposed method has been demonstrated to be discriminatory and is therefore considered acceptable for both active substances, allopurinol and lesinurad.

Bioequivalence studies (study 501-fasted, study 503 -fed) was performed between the individual mono-component products (ZURAMPIC (lesinurad) and Zyloprim (allopurinol)) dosed in combination and against both strengths of Duzallo film coated tablets. For the assessment of the bioequivalence studies reference is made to 2.4.2 part of this report. The clinical batches are manufactured in commercial scale and identical to the final formulation except for the PVA-based coating which was changed to HPMC-based coating. Dissolution profiles are provided showing that release of lesinurad and allopurinol is comparable between PVA-based and HPMC-based coating.

Duzallo film coated tablets are packed in a polyvinyl chloride (PVC)/polyvinylidene chloride (PVDC) - aluminium blister material consisting of an opaque PVC film laminated with PVDC and an aluminium

sealing foil. The aluminium foil is coated with heat-seal lacquer. The blister complies with EU Regulation 10/2011/EC as amended and with Ph. Eur. chapter 3.1.3 and 3.1.11.

Manufacture of the product and process controls

The manufacturing process comprises the following main steps: dry mixing, wet granulation, wet milling, drying, milling, blending, tableting and coating. A flow chart of the manufacturing process, identifying the in-process controls, was presented.

The manufacturing process of Duzallo film-coated tablets is a standard process, widely used in the pharmaceutical industry. A criticality assessment has been performed to identify potential critical manufacturing process steps. Critical steps were identified as wet granulation, drying, mixing (lubrication), tabletting (compression) and coating; and adequate IPCs have been established. Based on risk evaluation and mitigation plans, all process steps were deemed appropriately controllable through current GMP manufacturing and batch record controls. The proposed proven acceptable ranges applied for the steps of wet granulation, drying, milling (sieving) blending(mixing) at the commercial manufacturing site are satisfactory as is the proposed control strategy.

The intermediates: granulate, blend, cores and finished product in bulk can be stored prior to undergoing further manufacturing step. Holding time study for finished product in bulk has been completed up to 6 months. Further holding times studies is planned for granulate, blend, and cores.

The batch sizes and manufacturing process has been acceptably described. Because the manufacturing process is considered standard, the proposal to validate the manufacturing process before the product is placed on the market can be accepted. The provided process validation scheme based on prospective validation of three batches of each strength for batch size 1 and concurrent validation of three batches of each strength for batch-size 2 can be accepted based on the standard process and that batch-size 2 is manufactured with 4 granulations and coatings of batch-size 1.

Product specification

The release and shelf-life specifications for the finished products include appropriate tests and limits for: appearance (visual), identification of lesinurad and allopurinol (HPLC, UV), uniformity of dosage units (mass variation-Ph. Eur.), degradation products of lesinurad and allopurinol (HPLC), assay of lesinurad and allopurinol (HPLC), dissolution (Ph. Eur.-HPLC) and microbial contamination (Ph. Eur.).

The specifications for the finished product are prepared in line with ICH guidelines as well as with the requirements set in the current Ph. Eur. and are considered suitable for this type of product.

The parameters water content, residual solvents, elemental impurities have been considered but are not included in the specification; the justifications were based on batch data and were acceptable. Evaluation of elemental impurities according to ICH Q3D has been provided.

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for testing has been presented.

Batch results for nine batches of each strength, most of which at commercial scale, demonstrated compliance with the proposed specifications and consistency in manufacture.

The finished product is released on the market based on the above release specifications, through traditional final product release testing.

Stability of the product

Stability data was provided for four commercial scale batches per strength under long term conditions (25°C ± 2 °C/60 % ± 5 %RH and 30 °C ± 2 °C/75 % ± 5 % RH) for up to 24 months and under accelerated conditions (40 °C ± 2 °C/75 % ± 5 % RH) for 6 months stored in the packaging intended for marketing according to the ICH guidelines.

Stability results of three commercial scale batches per strength coated with the PVA-based film-coating for 18 months' long-term stability studies and 6 months accelerated stability study was also provided as supportive data. The results of the tablets coated with PVA-based film-coating (composition clinical batches) are similar to those of the tablets coated with HPMC-based film-coating (commercial batches).

Tests performed were: description assay degradation products and dissolution. The methods were identical to those used for release and were shown to be stability indicating. All results complied with the specifications and no significant changes or trends were observed.

A photostability study according to the ICH Guideline Q1B was performed on one commercial scale batch per strength. No significant change was observed for any of the tested attributes indicating that the product is not light sensitive.

Based on the presented stability data the proposed shelf life of 36 months without special storage conditions, as stated in the SmPC (sections 6.3) is accepted.

Adventitious agents

The lactose used in Duzallo is certified by the suppliers as produced from milk that is sourced from healthy animals in the same conditions as milk collected for human consumption. The lactose has been prepared without the use of ruminant material other than calf rennet, according to the description given in EMEA/CPMP/571/02 "Lactose Prepared Using Calf Rennet: Risk Assessment in Relationship to Bovine Spongiform Encephalopathies (BSE)", which is based on EMEA/CPMP/BWP/337/02 "Risk and Regulatory Assessment of Lactose and Other Products Prepared Using Calf Rennet". In cases where calf rennet is used in the production of the lactose, the suppliers have further certified that the rennet has been manufactured as required by EMA/410/01 Rev. 3, March 2011

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 defined in the SmPC. 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. Recommendation for future quality development

None.

2.3. Non-clinical aspects

2.3.1. Introduction

For lesinurad, the 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 as part of lesinurad initial MAA. Inspections 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.

Allopurinol belongs to the gold standard maintenance therapy of hyperuricaemia in gout patients. It is well known drug substance with broad clinical experience that has been nationally authorised for more than 50 years. Non-clinical studies in line with the current standards are not available for allopurinol. However, considering the long standing experience with allopurinol for more that 50 years, this is considered acceptable to the CHMP.

The Applicant presented the results of a toxicology study conducted in accordance with GLP with lesinurad and allopurinol mono-components in rats.

In addition, the applicant has provided a number of relevant publically available literature references.

Overall, the CHMP was reassured by the non-clinical package submitted in support of the proposed FDC.

2.3.2. Pharmacology

Primary pharmacodynamic studies

Lesinurad was investigated in vitro, using cellular systems expressing human or rodent URAT1 or human BCRP and NPT1 transporters. The metabolites M2, M3, M4, and M6 were also studied for their effect on URAT1 and OAT4. The effect of lesinurad on xanthine oxidase and purine nucleoside phosphorylase (PNP) was studied. In vivo, the effect on serum uric acid was studied in Cebus monkeys, but uricase activity in Cebus monkeys likely prevented effects of lesinurad on serum uric acid. Based on the obtained data the proposed mechanism of action is inhibition of URAT1 and OAT4.

Allopurinol is a xanthine oxidase (XO) inhibitor. Allopurinol and its main metabolite oxypurinol lower the level of uric acid in plasma and urine by inhibition of xanthine oxidase, the enzyme catalyzing the oxidation of hypoxanthine to xanthine and xanthine to uric acid.

The combination of lesinurad and allopurinol targets both excretion and production of uric acid, providing a dual-mechanism approach to effectively lower sUA levels.

Secondary pharmacodynamic studies

Lesinurad was tested in a series of studies to investigate potential secondary pharmacodynamics effects. The studies included binding to other targets; functional interaction with prostanoid thromboxane or endothelin receptors, neuropeptide Y receptors and metabolic disease-related nuclear receptors; anti-HIV activity, mitochondrial toxicity in HepG2 cells; muscle cell toxicity; and the effect on urate crystal-induced inflammation in Sprague Dawley rats.

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 two monosodium urate (MSU)-dependent rodent acute gout flare models lesinurad was efficacious in reducing inflammation from injected MSU crystals.

In addition to the inhibition of purine catabolism in some but not all hyperuricaemic patients, allopurinol depresses de novo purine biosynthesis via feedback inhibition of hypoxanthine-guanine phosphoribosyltransferase. Other metabolites of allopurinol include allopurinol-riboside and oxypurinol-7-riboside.

Safety pharmacology programme

Lesinurad was evaluated in the core battery of safety pharmacology studies (CNS effect study in rats, a CV telemetry and respiratory study in monkeys, and an in vitro hERG assay), and in additional studies were conducted to assess the effect of lesinurad on GI motility function and renal function in rats. No important safety pharmacology effects on parameters of the CNS, cardiovascular system, respiratory system, gastrointestinal tract and renal/urinary system were observed.

The safety profile of allopurinol data is well characterised since the active substance has been widely used for many years.

Pharmacodynamic drug interactions

No lesinurad or allopurinol pharmacodynamic drug interaction studies were submitted in support of this application. The absence of pharmacodynamics studies was considered acceptable as there are no appropriate animal pharmacodynamics models to evaluate the intended effect in humans due to the fact that animlas unlike humans possesses the uricase enzyme which converts uric acid to allantoin.

2.3.3. Pharmacokinetics

In the pharmacokinetic studies provided, pharmacokinetics of lesinurad after single and repeated administration was investigated in rats, dogs, and monkeys. The toxicokinetics of lesinurad were investigated in mice, rats, rabbits and monkeys.

The Applicant did not discuss the pharmacokinetic profile of allopurinol separately. In the pharmacokinetic studies provided, selected aspects of the pharmacokinetics of allopurinol alone or in combination with lesinurad after single and repeated administration were investigated in rats and monkeys.

Absorption

Single dose PK studies with lesinurad showed a low volume of distribution and clearance (CL) in rats, dogs and monkeys at 10 or 20 mg/kg intravenous (i.v.) dosing. Lesinurad was rapidly absorbed in rats, dogs, and monkeys; bioavailability ranged from highest in dogs (100%), followed by rats (71% - 75%), and monkeys (41%). Exposure, as measured by AUC0-24 and Cmax, increased in a dose-dependent manner in rats and monkeys in toxicokinetics (TK) evaluations. In general, there was no apparent sex difference in plasma exposure in either rats or monkeys. However, the relative importance of renal excretion and metabolic profiles in urine is different between male and female rats, where female rats have higher renal excretion of parent compound and less oxidized metabolite. There was evidence of mild auto-induction in rats at ≥100 mg/kg dosing and moderate auto-induction in monkeys at ≥30 mg/kg dosing.

In pharmacokinetic studies provided, selected aspects of the pharmacokinetics of allopurinol were investigated. Following a single dose of combination of allopurinol and lesinurad, Cmax and AUC

exposures of allopurinol appeared to be slightly lower compared to the single agent formulation, while AUC exposure of oxypurinol, the main human metabolite of allopurinol, appeared higher with combination treatment. Following a single dose of combination of allopurinol and lesinurad, contradictory results regarding AUC exposures of allopurinol/oxypurinol between male and female rats were observed.

Distribution

Lesinurad was highly protein bound (~98%) in rat, dog, monkey and human plasma at 1, 10, and 50 µM, and binding was primarily to albumin. Slightly lower plasma protein binding (≥94%) was observed in mouse plasma. There was no indication of preferred distribution of [14C]lesinurad-derived radioactivity into red blood cells in rats or monkeys. There was no evidence of [14C]lesinurad-derived radioactivity binding to pigmented tissues following oral dosing in pigmented rats, and no preferential uptake into brain.

Allopurinol's distribution profile is well characterised since the active substance has been widely used for many years.

Metabolism

Lesinurad showed low turnover following in vitro incubations in rat, dog, monkey and human microsomes or hepatocytes. In rats, lesinurad was the major component in circulation following single or multiple dosing, and the oxidized metabolite M3 is the major metabolite in urine. In monkeys, lesinurad was the major component in circulation following single dosing, but the amounts of metabolite M6, the S-dealkylated metabolite, reached levels of 2- to 6-fold of lesinurad at Months 6, 9, and 12 in the chronic monkey toxicology study. Qualitative analysis showed increasing levels of 3 isomeric glucuronide conjugates of metabolite M6 (designated as M8) at the same time. Clearance of lesinurad following absorption was through renal excretion, hepatic metabolism, biliary excretion, and gastrointestinal (GI) microflora.

In human in vitro evaluations, biotransformation of lesinurad was primarily mediated through cytochrome P450 (CYP) 2C9 with minimal contribution from CYP1A1, CYP2C19, and CYP3A4. 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.

Formation of metabolite M6 was catalyzed by CYP3A in rats (CYP3A1/2), monkeys (CYP3A8), and humans (CYP3A4) in the in vitro evaluations. M6 is a major metabolite in monkeys following chronic dosing. Elimination of metabolite M6 is primarily through glucuronidation of M6 to M8 and subsequent excretion in bile and urine. Both metabolites M6 and M8 were either not detected or detected only at negligible levels in humans following chronic dosing. Therefore, the finding of increasing metabolite M6 exposures in monkeys is not considered relevant to humans.

Lesinurad is a racemic mixture (50:50) of 2 atropisomers. Lesinurad atropisomers were investigated individually to assess potential metabolism differences in rat, monkey and human liver microsomes and recombinant CYPs. The metabolism of lesinurad atropisomers was stereoselective in all species. In human liver microsomes, the formation of M3c in human liver microsomes mediated by CYP2C9 was significantly greater from atropisomer 1 than from atropisomer 2. Similarly, formation of M3 and M4 was greater from atropisomer 1 than from atropisomer 2. In contrast, CYP3A4-mediated formation of M6 was preferentially from atropisomer 2 than from atropisomer 1. Metabolism studies with

recombinant CYP2C9, CYP2C75, and CYP2C11 (male rat) confirmed the formation of M3c metabolite from atropisomer 1. In addition, formation of M4 in liver microsomes of human and monkey preferred atropisomer 1, while male and female rats preferred atropisomer 2. These results provide qualitative support that animal species formed same metabolites as those observed in humans despite differences in the extent of metabolite formation. Any potential impact of varying preferential metabolism of either atropisomer among species is not considered to be significant.

Lesinurad exhibited covalent binding in rat and human liver microsomes and human hepatocytes. The covalent binding of lesinurad was reduced in the presence of GSH.

In vitro, glucuronidation of lesinurad was mediated via uridine 5'-diphospho-glucuronosyl-transferase (UGT) isozymes UGT1A1 and UGT2B7 as a minor metabolic pathway. The glucuronide of lesinurad (M1) was detected in rat and monkey bile at much higher levels than in urine. This is consistent with the findings in a clinical human absorption, metabolism, and excretion (ADME) study, where only trace levels of glucuronide of lesinurad were detected in urine.

Based on the similar in vitro metabolic profiles between humans and monkeys and the lack of M4 metabolite in dogs, monkey was selected as the non-rodent species for toxicology evaluation. More metabolites were identified in animals used for toxicological evaluation than in humans and all metabolites identified in humans were also observed in animals, although the relative contributions to the metabolic profiles were different among species in vivo.

The main human metabolite of allopurinol is oxypurinol. Other metabolites of allopurinol include allopurinol-riboside and oxypurinol-7-riboside. Oxypurinol is also a main allopurinol metabolite in rats and monkeys.

Excretion

Excretion of lesinurad parent and metabolites into urine is in the range of 10% to 50% of dose in rats and monkeys. The majority of the radioactivity excreted into urine is in the form of parent, suggesting renal excretion is an important elimination pathway following dosing of lesinurad. In a human ADME study, approximately 63% of dose was recovered in urine, and 31.3% of dose was excreted as unchanged drug.

Allopurinol's excretion profile is well characterised since the active substance has been widely used for many years.

Pharmacokinetic drug interactions

Please refer to section 2.4.2.

2.3.4. Toxicology

Single dose toxicity

The ICH Guidance on Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals M3(R2)states: "*Historically, acute toxicity information has been obtained from single-dose toxicity studies in two mammalian species using both the clinical and a parenteral route of administration. However, such information can be obtained from appropriately conducted dose-escalation studies or short duration dose-ranging studies that define an Maximum Tolerated Dose (MTD) in the general toxicity test species (1, 2). When this acute toxicity information is available from any study, separate single-dose studies are not recommended. Studies providing acute toxicity information can be limited to the clinical route only and such data can be obtained from non-*

GLP studies if clinical administration is supported by appropriate GLP repeated-dose toxicity studies. Lethality should not be an intended endpoint in studies assessing acute toxicity." All the toxicity studies submitted with the present application included observation of clinical signs on Day 1 of the dosing phase. Except study SR-08-015, all above mentioned studies included toxicokinetics on Day 1 of the dosing phase. Toxicokinetic data after a single administration of lesinurad in Sprague-Dawley rats were obtained in a 28-day oral toxicity and toxicokinetic study on Day 1 of the dosing phase. Overall, the Applicant considered that the data on toxicity and toxicokinetics after a single administration of lesinurad, allopurinol or the combination of both are available and that there was no need for the conduct of additional single dose studies.

The CHMP accepted this justification for not submitting single dose toxicity studies.

Repeat dose toxicity

Lesinurad repeat-dose studies were conducted in mice and rats up to 6 months duration and up to 12 months duration in monkeys. Allopurinol repeat-dose studies (non-GLP considering that it has been nationally authorized for more than 50 years, it is considered acceptable to the CHMP) were conducted in male rats up to 3 months duration. Lesinurad and allopurinol combination studies (GLP) were conducted in rats up to 3 months duration.

Lesinurad

In lesinurad studies, the target organs of toxicity were GI tract (mice, rats, monkeys), kidney (mice and rats), liver (mice, rats, and monkeys) and thyroid (rats).

GI tract

Dose-related GI toxicity was observed in all tested species and resulted in mortality at high doses in rats and monkeys. In all tested species, GI tract toxicity was associated with decreased food consumption, low or no faecal output, and reductions in body weight. Emesis and diarrhoea were observed in monkeys. Gross observations in rats and monkeys found dead included multifocal discoloration of the GI tract, primarily in small intestines. Single-cell necrosis of the epithelium was the most common histological observation in rats. Gastrointestinal microscopic findings observed in monkeys included neutrophilic inflammations and erosions in intestines at high doses associated with diarrhoea. Microscopic findings were also present in the glandular region of the stomachs in female TgrasH2 mice given ≥30 mg/kg/day for 6 months. 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 exposure margins, based on systemic AUC exposures, at the No-Observed-Adverse-Effect Level (NOAEL) in rats and monkeys are 4 and 12 times the maximum recommended human dose (MR HD).

Kidney

In rats, severe kidney toxicity was the cause of early deaths in the high dose group in a 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 creatinine levels, and tubular injury resulting in death after 3 weeks dosing in the 6-month study. The CHMP considered that lesinurad is not a classical nephrotoxicant, and the observed effects were possibly species-specific, as similar lesions were not observed in monkeys, and there was no classic dose-response relationship.

Liver and thyroid gland

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.

In monkeys, 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. 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 AUC 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.

Allopurinol

In allopurinol rat studies, the main target organ of toxicity was the kidney. In the first 4-week study (non-GLP), renal tubular nephropathy characterized by renal tubular epithelial basophilia and tubular dilation of minimal to mild severity was noted in males given ≥12.5 mg/kg/day and females given ≥25 mg/kg/day. A NOAEL was set to 50 mg/kg/day, corresponding to AUC exposures 11- and <1-fold the clinical AUC for allopurinol and the main metabolite oxypurinol, respectively.

In the second 13-week study (non-GLP), dose levels of 200 and 300 mg/kg/day to male rats caused severe toxicity and mortality leading the early termination of all animals at these dose levels. Gross findings were evident mainly in kidney but also in liver. A dose of 100 mg/kg/day was tolerated in male rats and associated with decreased body weight gain and changes in clinical chemistry parameters. Chronic interstitial nephritis with tubular dilatation, regeneration and cast formation was observed in all rats given allopurinol, the distribution and severity of which increased with increasing doses. A NOAEL was not established in this study, and is therefore <100 mg/kg/day.

Combination allopurinol and lesinurad

The results of the 13-week combination rat study with lesinurad and allopurinol show that there was no synergistic, additive, or new toxicity when lesinurad and allopurinol were administered together. In rats at the high doses, exposure to lesinurad was ≥38 times the human exposure at the lesinurad MRHD and exposure to allopurinol was ≥20 times the human exposure of allopurinol. It was noted that systemic exposure for oxypurinol in rats, the active metabolite of allopurinol and the main circulating entity in humans, was lower than the human exposure in the clinical study at the most commonly used dose of 300 mg/day. The dose selected for the combination study was however the maximal tolerated as demonstrated in non-GLP 13-week study with allopurinol.

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 was concluded not to have a genotoxic potential.

The results of in-vitro mutagenicity studies of allopurinol from the US National Library of Medicine database TOXNET in the Chemical Carcinogenesis Research Information System (CCRIS) were all negative. The data was generated within the scope of the Short-Term Test Program sponsored by the Division of Cancer Biology, National Cancer Institute. The tests comprise:

- Ames tests in Salmonella typhimurium strains TA98, TA100, TA1535, TA1537, and TA1538 with arochlor-induced rat liver S9 mix
- Ames tests in Salmonella typhimurium strains TA98, TA100, TA1535, TA1537, and TA1538 with arochlor-induced hamster liver S9 mix
- Ames tests in Salmonella typhimurium strains TA98, TA100, TA1535, TA1537, and TA1538 without S9 mix
- Mouse lymphoma assays in L5178Y (TK+/TK-) cells with arochlor-induced rat liver S9 mix
- Mouse lymphoma assays in L5178Y (TK+/TK-) cells without S9 mix

On the TOXNET Hazardous Substances Data Bank (HSDB), the following results are available regarding the genotoxicity of allopurinol: “Allopurinol administered intravenously to rats (50 mg/kg) was not incorporated into rapidly replicating intestinal DNA. No evidence of clastogenicity was observed in an in vivo micronucleus test in rats, or in lymphocytes taken from patients treated with allopurinol (mean duration of treatment 40 months), or in an in vitro assay with human lymphocytes.”

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.

In transgenic (TgrasH2) mice, administration of lesinurad for 26 weeks resulted in no significant effect on survival and no microscopic evidence of increased neoplastic lesions. The NOEL for neoplasia in transgenic mice for lesinurad is 125 mg/kg/day for males and 250 mg/kg/day for females, the highest doses tested. The maximum exposures at the neoplastic NOELs were 16.9 (males) and 26.9 (females) times the human exposure at the MRHD at Day 181 of dosing.

In Sprague Dawley rats, administration of lesinurad for up to 97 or 100 weeks in males and females, respectively, did not have effect on survival and did not cause an increase in neoplasms. The AUC0-24h established in Week 78 at the 200 mg/kg/day was 909 µg·h/mL and 1040 µg·h/mL in males and females, respectively. This corresponds to 32.5 times and 37.1 times the human exposure at the MRHD in males and females, respectively.

Allopurinol was administered at doses up to 20 mg/kg/day to mice and rats for the majority of their life span. No evidence of carcinogenicity was seen in either mice or rats. (US National Library of Medicine database TOXNET in the Hazardous Substances Data Bank (HSDB)) Brambilla et al (2012) collected data on carcinogenicity studies in animals and humans and reported allopurinol as negative in a long-term carcinogenicity in mice at doses up to 20 mg/kg/day. The data are supported by DRUGBANK in silico generated with ADMET, using admetSAR: the probability of allopurinol being non-carcinogenic is 0.921.

Reproduction Toxicity

Fertility and early embryonic development

There was no effect on male or female fertility or early embryonic development due to treatment with lesinurad. No toxicokinetics were performed in this study, but based on other study data, the exposure

at the NOAEL was likely around 40-fold and 50-fold the human exposure in females and males, respectively.

Developmental or Reproductive Toxicity/ Reproduction studies with allopurinol in rats and rabbits using dosages up to 20 times the usual human dosage have not revealed evidence of impaired fertility (TOXNET Hazardous Substances Data Bank (HSDB).

Embryo-fœtal development

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 the scientific advice provided by the CHMP, which stated that no further studies were necessary. This was endorsed by the CHMP.

Single intraperitoneal doses of 50 or 100 mg/kg of allopurinol on gestation days 10 or 13 produced significant increases in foetal deaths and teratogenic effects (cleft palate, harelip, and digital defects). It is uncertain whether these findings represented a fetal effect or an effect secondary to maternal toxicity. There was no evidence of fetotoxicity or teratogenicity in rats or rabbits treated during the period of organogenesis with oral allopurinol at doses up to 200 mg/kg/day and up to 100 mg/kg/day, respectively.

Prenatal and postnatal development, including maternal function

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 an 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.

Allopurinol and its metabolite oxypurinol are excreted in human breast milk. Hence, Duzallo is not recommended during breastfeeding as indicated in Section 4.6 of the SmPC.

Juvenile toxicity

No juvenile studies have been conducted. This is acceptable for the CHMP as the intended patient population for Duzallo is adult patients.

Local Tolerance

The oral route of administration was adequately evaluated in the repeat-dose studies. No dedicated local studies have been conducted with lesinurad, allopurinol or the combination. This is acceptable for the CHMP.

In lesinurad studies, dose-related GI toxicity was observed in all tested species and resulted in mortality at high doses in rats and monkeys. The effect is likely 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.

Other toxicity studies

Metabolites

Metabolism of lesinurad in humans was mediated mainly by CYP2C9 with minimal contributions from CYP1A1, 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.

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 human plasma, the major component at 0-24 hours was unchanged lesinurad with 74% of total radioactivity, M3 was the most abundant metabolite observed which amounted to 3% of total radioactivity. In addition, 7 other metabolites were observed to a minor extent.

For lesinurad, the epoxide intermediate M3c only detected in vitro has been adequately 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.

The absence of specific studies on allopurinol or the FDC is justified as allopurinol's profile is well characterised since the active substance has been widely used for many years. This was considered acceptable by the CHMP.

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, or a concentration of 7.5 ppm in the 200 mg tablet (once daily) of lesinurad.

The specification of allopurinol complies with European Pharmacopoeia (please refer to Section 2.2).

Phototoxicity

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

The absence of specific studies on allopurinol or the FDC is justified as Allopurinol's profile is well characterised since the active substance has been widely used for many years. This was considered acceptable by the CHMP.

2.3.5. Ecotoxicity / environmental risk assessment

Lesinurad

The Applicant has submitted an environmental risk assessment (ERA) for lesinurad. The ERA and the included study reports are identical to those submitted in the Zurampic MAA. This ERA is considered valid to support the present application as the maximum recommended dose levels, duration of dosing and patient population remain the same as for Zurampic. Therefore, the lack of new studies is acceptable and the previous conclusions are considered as valid. A summary of the properties of lesinurad based on information provided in the EPAR is included below.

Table 1 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) $DT_{50,sediment}$=51/57 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 µg/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 $PEC_{surfacewater}$, 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 biodegradable			
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 Inhibition Test	OECD 209	EC	200	mg/L	respiration
Phase IIb Studies					
Sediment dwelling organism/ *Chironomus riparius*	OECD 218	NOEC	4522	mg/kg	normalised to 10% o.c.

In conclusion, 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.

Allopurinol

No environmental risk assessment for allopurinol has been submitted. The Applicant argues that compared to the global consumption of allopurinol, no additional adverse environmental impacts are foreseen with the use and/or disposal of the fixed dose combination allopurinol/lesinurad. The product is to be given to patients that were already treated with allopurinol but are insufficient responders; hence, in practice it is not expected to lead to a significant increase in the environmental exposure for allopurinol. The justification by the Applicant for not providing an ERA for allopurinol is therefore considered acceptable by the CHMP.

2.3.6. Discussion on non-clinical aspects

Lesinurad is a selective uric acid reabsorption inhibitor that inhibits uric acid transporter URAT1. Allopurinol is a xanthine-oxidase inhibitor. Allopurinol and its main metabolite oxypurinol lower the level of uric acid in plasma and urine by inhibition of xanthine oxidase, the enzyme catalyzing the oxidation of hypoxanthine to xanthine and xanthine to uric acid.

Lesinurad, when combined with a xanthine oxidase inhibitor, increases uric acid excretion and decreases uric acid production resulting in greater sUA lowering.

In the toxicity study conducted with lesinurad in rats, kidney was the main target organ for toxicity. The tubular degeneration was however only transient in nature as no toxicity was observed in longer studies with corresponding doses. The same effect was observed in the 13-week combination study. Similar lesions or dose-related renal toxicities were not observed in other species in monkeys. Kidney toxicity is also seen in the clinical situation, and appears related to increased plasma and urine uric acid levels, leading to crystallization and then kidney damage. This is further supported 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. Renal impairment is included as an Important Identified Risk in the RMP and warnings and recommendations are included in SmPC sections 4.4 and 4.8.

The Applicant submitted two non-pivotal repeat-dose toxicity studies with allopurinol with toxicokinetic analysis in rats for 4 and 13 weeks. Studies were in general used to determine the dose of allopurinol in 13-week study combination study with lesinurad. In 13-week study, oral repeated doses of ≥200 mg/kg/day allopurinol caused severe toxicity and mortality. Lesions observed in kidney and

alternations in BUN and creatinine were indicative of renal toxicity. The MTD for allopurinol in male rats in this study was 100 mg/kg/day and the NOAEL was not determined, and is therefore <100 mg/kg/day.

Repeat-dose combination studies with lesinurad and allopurinol revealed no synergistic, additive, or new toxicity. Aggravation of nephrotoxicity due to combination with lesinurad was not observed in the study in rats for 13 weeks. Precaution measures as defined in SmPC (renal function evaluated prior to initiation of therapy and monitored periodically thereafter e. g. 4 times per year) and the RMP are considered as sufficient.

Lesinurad has no genotoxic or carcinogenic potential based on standard battery of tests. Reproductive and developmental toxicity studies in rats and rabbits showed no adverse effects at safety margins sufficiently exceeding clinical exposures. Lesinurad does not present a photosafety concern.

In vitro and in vivo studies conducted to date showed no evidence of mutagenic or carcinogenic potential. One study in mice receiving intraperitoneal doses of 50 or 100 mg/kg on days 10 or 13 of gestation resulted in foetal abnormalities, however in a similar study in rats at 100 mg/kg on day 12 of gestation no abnormalities were observed. Extensive studies of high oral doses of allopurinol in mice up to 100 mg/kg/day, rats up to 200 mg/kg/day and rabbits up to 150 mg/kg/day during days 8 to 16 of gestation produced no teratogenic effects.

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.

Allopurinol is already used in existing marketed products and no significant increase in environmental exposure is anticipated.

2.3.7. Conclusion on the non-clinical aspects

The FDC of allopurinol/lesinurad is considered approvable from a non-clinical perspective.

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

Table 2 - Dose response study

Study	Study description	Treatment
203 main	Multiple doses in subjects with gout	LESU: 200, 400, 600 mg; Allopurinol: 200 to 600 mg Colchicine: 0.5 to 0.6 mg
203 double-	Multiple doses in subjects with gout	LESU: 200, 400, 600 mg;

blind EXT		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

Table 3 - Phase 3 efficacy and safety studies of lesinurad in combination with allopurinol in inadequate responders to allopurinol

2 pivotal Core Studies (RDEA594-301 and RDEA594-302)
12-month DB Core Study 301: LESU 200 mg + ALLO (N = 201), LESU 400 mg + ALLO (N = 201), or PBO + ALLO (N = 201). LESU doses were QD. ALLO dose was 200 mg to 800 mg daily.
12-month DB Core Study 302: LESU 200 mg + ALLO (N = 204), LESU 400 mg + ALLO (N = 200), or PBO + ALLO (N = 206). LESU doses were QD. ALLO dose was 200 mg to 900 mg daily.
1 Extension Study (RDEA594-306)
Up to 16 months of exposure in the OLE period (First Interim CSR): LESU 200 mg + ALLO (N = 361) mean (SD) exposure 176.0 (122.59) days; LESU 400 mg + ALLO (N = 353) 174.8 (121.18) days.
Up to 26 months of exposure in the OLE period (Second Interim CSR): LESU 200 mg + ALLO (N = 362) mean (SD) exposure 431.1 (189.19) days; LESU 400 mg + ALLO (N = 354) 430.9 (188.61) days.
Up to 40 months of exposure in the OLE period (Final Synopsis CSR): LESU 200 mg + ALLO (N = 362) mean (SD) duration of exposure 685.3 (331.03) days; LESU 400 mg + ALLO (N = 354) 685.3 (330.38) days.

LESU = lesinurad; N = number of subjects who n-label (extension); PBO = placebo; QD = once daily; SD = standard deviation.

The following studies were conducted with lesinurad and febuxostat. These data are not discussed in the efficacy assessment; however, reference to these studies is made in the Safety assessment.

Table 4 Phase 3 efficacy and safety studies of lesinurad in combination with febuxostat 80mg/daily

	objective	**Study posology**
Study 304 (also referred as RDEA594-304) Rand, PC, DB, Para 3-arm	Superiority	Placebo LESU 200 mg LESU 400 mg
Study 307 (also referred as RDEA594-307) OLE Study 304	Efficacy and safety in combination with FBX in subjects with tophaceous gout	LESU 200 mg LESU 400 mg

DB=double blind, Para=parallel, PC=placebo-controlled OLE=open-label extension

2.4.2. Pharmacokinetics

Study RDEA594-501 (fasting) and -503 (fed), comparing the new FDC tablet with the free combination of lesinurad and allopurinol are thus pivotal for the current application.

Table 5 Clinical studies in the FDC clinical development program

Protocol number	Title	Objectives
RDEA594-501	A Phase 1, Randomized, Open-Label, Crossover Study to Assess the Relative BA of Allopurinol/lesinurad FDC Tablets and co-administered Lesinurad and Allopurinol Tablets and the Effect of Food on the PK of Allopurinol/lesinurad FDC Tablets in Healthy Adult Subjects	To assess the BA of allopurinol/lesinurad 300/200 FDC tablets and allopurinol/lesinurad 200/200 FDC tablets relative to co-administered lesinurad and allopurinol tablets in healthy adult subjects. To assess the effect of a high-fat/high-calorie meal on the PK of allopurinol/lesinurad 300/200 FDC tablets in healthy adult subjects. To assess the safety and tolerability of allopurinol/lesinurad 300/200 FDC tablets, allopurinol/lesinurad 200/200 FDC tablets, and lesinurad co-administered with allopurinol in healthy adult subjects.
RDEA594-503	A Phase 1, Randomized, Open-Label, Replicate, Crossover Study to Assess the Bioequivalence of Allopurinol/lesinurad Fixed-Dose Combination Tablets and Coadministered Lesinurad and Allopurinol Tablets in Fed Healthy Adult Subjects	To assess the BE between allopurinol/lesinurad 300/200 FDC tablets and co-administered lesinurad and allopurinol tablets in the fed state based on the PK evaluation of healthy adult subjects. To assess the safety and tolerability of allopurinol/lesinurad 300/200 FDC tablets and lesinurad co-administered with allopurinol in healthy adult subjects.
ALLO-101 In Vitro-In Vivo Relationship	In Vitro-In Vivo Relationship Study to Assess the Impact of the In Vitro Dissolution Profile of Allopurinol on the PK Parameters Used to Establish BE	1. To determine whether defined and limited changes in in vitro dissolution impact the in vivo PK and relative BA of allopurinol and the active metabolite oxypurinol. 2. To provide additional safety information on allopurinol in healthy subjects.

BA = bioavailability; BE = bioequivalence; FDC = fixed-dose combination; PK = pharmacokinetics

In an open-label, sequential-dose, 4-period design, Study ALLO-101 in healthy subjects assessed the impact of the in vitro dissolution profile of allopurinol on its PK parameters. This study utilized a flexible protocol design using the concept of design space to alter manufacturing variables (e.g., tablet hardness or granulation parameters) that would result in variations in in vitro dissolution to allow decision making in response to interim PK observations.

Absorption

The absolute bioavailability of lesinurad is approximately 100%. Lesinurad is rapidly absorbed after oral administration. In clinical trials, lesinurad was administered with food, because the serum uric acid lowering was improved under fed conditions.

Allopurinol is rapidly absorbed from the gastrointestinal tract and is reported to have a plasma half-life of about one hour.

- **Relative bioavailability / bioequivalence**

Two pivotal single-dose relative bioavailability/bioequivalence studies have been conducted comparing the FDC tablet with the free combination of lesinurad and allopurinol.

Study RDEA594-501 (also referred as 501): randomized, open-label, single-dose, crossover study to assess the bioavailability of allopurinol/lesinurad 300/200 and 200/200 FDC tablets relative to that of co-administered lesinurad and allopurinol tablets, and the effect of a high-fat/high-calorie meal on the PK of allopurinol/lesinurad FDC tablets in healthy adult subjects.

Table 6 Lesinurad pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range), n=35. Test: FDC 300/200 mg, Ref: allopurinol 300 mg+ lesinurad 200 mg (Study 501).

Treatment	AUC_{0-t} µg*h/ml	AUC_{inf} µg*h/ml	C_{max} µg/ml	t_{max} h
Test	32.3 ± 11.0	32.6 ± 11.0	10.9 ± 3.14	2.05 0.67-5.00
Reference	33.0 ± 11.9	33.3 ± 11.9	9.84 ± 3.19	2.00 0.67-4.50
***Ratio (90% CI)**	**0.9895 (0.9501-1.0306)**	**0.9889 (0.9494-1.0299)**	**1.1026 (1.0056-1.2090)**	**-**

AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
AUC_{inf} area under the plasma concentration-time curve from time zero to infinity
C_{max} maximum plasma concentration
t_{max} time for maximum plasma concentration
*calculated based on ln-transformed data

Table 7 Allopurinol pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range), n=35. Test: FDC 300/200 mg, Ref: allopurinol 300 mg+ lesinurad 200 mg (Study 501).

Treatment	AUC_{0-t} µg*h/ml	AUC_{inf} µg*h/ml	C_{max} µg/ml	t_{max} h
Test	3.65 ± 1.01	3.75 ± 1 02	1.34 ± 0.502	1.50 0.67-5.00
Reference	3.64 ± 1.06	3.73 ± 1.05	1.21 ± 0.343	2.00 0.33-4.50
***Ratio (90% CI)**	**1.0045 (0.9675-1.0428)**	**1.0054 (0.9683-1.0440)**	**1.0758 (0.9837-1.1766)**	**-**

AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
AUC_{inf} area under the plasma concentration-time curve from time zero to infinity
C_{max} maximum plasma concentration
t_{max} time for maximum plasma concentration
*calculated based on ln-transformed data

Table 8 Oxypurinol pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range), n=35. Test: FDC 300/200 mg, Ref: allopurinol 300 mg+ lesinurad 200 mg (Study 501).

Treatment	AUC_{0-t} µg*h/ml	AUC_{inf} µg*h/ml	C_{max} µg/ml	t_{max} h
Test	182 ± 31.6	203 ± 42.4	5.27 ± 0.901	3.00 0.67-12.00
Reference	183 ± 32.8	203 ± 42.2	5.31 ± 0.586	3.50 1.00-6.05
***Ratio (90% CI)**	**0.9967 (0.9771-1.0168)**	**1.0022 (0.9804-1.0245)**	**0.9914 (0.9653-1.0183)**	**-**

AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
AUC_{inf} area under the plasma concentration-time curve from time zero to infinity
C_{max} maximum plasma concentration
t_{max} time for maximum plasma concentration

*calculated based on ln-transformed data

Under fasting conditions the 300/200 mg FDC tablet was bioequivalent to the co-administrated mono-components since the 90% CI for the test/reference ratios for lesinurad, allopurinol and oxypurinol were within the conventional bioequivalence limits of 0.80-1.25.

Table 9 Lesinurad pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range), n=53. Test: FDC 200/200 mg, Ref: allopurinol 200 mg+ lesinurad 200 mg (Study 501).

Treatment	AUC_{0-t} µg*h/ml	AUC_{inf} µg*h/ml	C_{max} µg/ml	t_{max} h
Test	33.7 ± 11.9	34.0 ± 11.9	10.9 ± 3.27	2.00 0.43-5.00
Reference	34,0 ± 9.99	34.3 ± 9.9	11.0 ± 2.73	2.50 0.67-4.63
***Ratio (90% CI)**	**0.9816 (0.9439-1.0208)**	**0.9825 (0.9452-1.0214)**	**0.9881 (0.9248-1.0558)**	**-**

AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
AUC_{inf} area under the plasma concentration-time curve from time zero to infinity
C_{max} maximum plasma concentration
t_{max} time for maximum plasma concentration

*calculated based on ln-transformed data

Table 10 Allopurinol pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, tmax median, range), n=53. Test: FDC 200/200 mg, Ref: allopurinol 200 mg+ lesinurad 200 mg (Study 501).

Treatment	AUC_{0-t} µg*h/ml	AUC_{inf} µg*h/ml	C_{max} µg/ml	t_{max} h
Test	2.25 ± 0.647	2.34 ± 0.664	0.928 ± 0.316	1.15 0.33-5.00
Reference	2.07 ± 0.599	2.17 ± 0.601	0.796 ± 0.293	1.50 0.33-4.63
***Ratio (90% CI)**	**1.0914 (1.0520-1.1324)**	**1.0760 (1.0387-1.1147)**	**1.1823 (1.0905-1.2817)**	**-**

AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
AUC_{inf} area under the plasma concentration-time curve from time zero to infinity
C_{max} maximum plasma concentration
t_{max} time for maximum plasma concentration

*calculated based on ln-transformed data

Table 11 Oxypurinol pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, tmax median, range), n=53. Test: FDC 200/200 mg, Ref: lesinurad 200 mg+allopurinol 200 mg (Study 501).

Treatment	AUC_{0-t} µg*h/ml	AUC_{inf} µg*h/ml	C_{max} µg/ml	t_{max} h
Test	119 ± 20.5	132 ± 28.1	3.68 ± 0.733	3.00 0.67-8.00
Reference	118 ± 19.3	130 ± 26.3	3.59 ± 0.712	3.50 1.00-8.00
***Ratio (90% CI)**	**1.0155 (0.9980-1.0333)**	**1.0149 (0.9960-1.0342)**	**1.0253 (1.0034-1.0476)**	**-**

AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
AUC_{inf} area under the plasma concentration-time curve from time zero to infinity
C_{max} maximum plasma concentration
t_{max} time for maximum plasma concentration

*calculated based on ln-transformed data

Following administration of the 200/200 FDC tablet in the fasted state, the conventional bioequivalence criteria were met with respect to AUC and Cmax for all three analytes, with the exception of allopurinol Cmax. Allopurinol Cmax was 18% higher after administration of the FDC compared to the reference mono-components and the upper limit of the 90% CI of 1.28 was slightly above the BE limit of 1.25.

Study RDEA594-503 (fed) (also referred as 503): randomized, open-label, 2-treatment, 4-sequence, 4-period, single-dose, replicate crossover study to assess the bioequivalence of allopurinol/lesinurad 300/200 FDC tablets relative to that of co-administered lesinurad and allopurinol tablets at the same dose level in fed healthy adult subjects.

Table 12 Lesinurad pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, tmax median, range), n=27. Test: FDC 300/200 mg, Ref: allopurinol 300 mg+ lesinurad 200 mg (Study 503).

Treatment	AUC_{0-t} µg*h/ml	AUC_{inf} µg*h/ml	C_{max} µg/ml	t_{max} h
Test	34.4 ± 8.58	34.3 ± 8.30	7.55 ± 2.76	4.26 1.50-8.25
Reference	38.9 ± 7.61	34.2 ± 7.53	7.93 ± 3.21	3.50 1.50-7.76
Intra-subject CV (%) Reference	8.5	7.8	27.0	-
***Ratio (90% CI)**	**1.0036 (0.9764-1.0316)**	**0.9982 (0.9726-1.0243)**	**0.9628 (0.8834-1.0494)**	**-**

AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
AUC_{inf} area under the plasma concentration-time curve from time zero to infinity
C_{max} maximum plasma concentration
t_{max} time for maximum plasma concentration

*calculated based on ln-transformed data

Table 13 Allopurinol pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, tmax median, range), n=27. Test: FDC 300/200 mg, Ref: allopurinol 300 mg+ lesinurad 200 mg (Study 503).

Treatment	AUC_{0-t} µg*h/ml	AUC_{inf} µg*h/ml	C_{max} µg/ml	t_{max} h
Test	3.68 ± 1.07	3.71 ± 1.07	1.41 ± 0.581	2.51 1.08-5.50
Reference	3.58 ± 0.925	3.74 ± 1.02	1.22 ± 0.449	3.00 1.50-5.55
Intra-subject CV (%) Reference	12.4	14.7	30.4	-
***Ratio (90% CI)**	**1.0251 (0.9847-1.0671)**	**0.9941 (0.9478-1.0426)**	**1.1546 (1.0479-1.2721)**	**-**

AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
AUC_{inf} area under the plasma concentration-time curve from time zero to infinity
C_{max} maximum plasma concentration
t_{max} time for maximum plasma concentration

*calculated based on ln-transformed data

Table 14 Oxypurinol pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, tmax median, range), n=27. Test: FDC 300/200 mg, Ref: allopurinol 300 mg+ lesinurad 200 mg (Study 503).

Treatment	AUC_{0-t} µg*h/ml	AUC_{inf} µg*h/ml	C_{max} µg/ml	t_{max} h
Test	166 ± 29.9	180 ± 35.9	5.31 ± 0.897	5.01 2.00-7.50
Reference	168 ± 27.9	183 ± 33.4	5.17 ± 0.824	5.00 2.00-9.75
Intra-subject CV (%) Reference	5.2	5.6	4.0	-
***Ratio (90% CI)**	**0.9790 (0.9628-0.9956)**	**0.9775 (0.9599-0.9954)**	**1.0257 (1.0090-1.0426)**	**-**

AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
AUC_{inf} area under the plasma concentration-time curve from time zero to infinity
C_{max} maximum plasma concentration
t_{max} time for maximum plasma concentration

*calculated based on ln-transformed data

Following administration of the 300/200 FDC tablet under fed conditions, the conventional bioequivalence criteria were met with respect to AUC and Cmax for all three analytes, with the exception of allopurinol Cmax. Allopurinol Cmax was 15% higher after administration of the FDC compared to the reference mono-components and the upper limit of the 90% CI of 1.2721 was slightly above the scaled BE limit of 1.2533.

- **Influence of food**

Following administration of Duzallo FDC under fed conditions (high-fat, high calorie meal), lesinurad and allopurinol Cmax were reduced by 46% and 18%, respectively, and median Tmax was increased from 3.00 to 4.50 hours for lesinurad and from 1.25 to 3.00 hours for allopurinol. The effect on AUC was minor and bioequivalence was demonstrated for all analytes.

A post-hoc supportive PD analysis demonstrated that there was no reduction of the plasma urate lowering effect under fed compared to fasting conditions.

The effect of food on lesinurad in the FDC tablet was within the range of data from earlier studies conducted during the lesinurad single agent development program. In these studies, concomitant food intake resulted in reductions of Cmax within the range 18-58% and within 7-30% for AUC.

Distribution

Mean plasma protein binding of lesinurad was equal to or greater than 97% over the investigated concentration range (1-50 µM). The binding was primarily due to interaction with albumin with minimal contribution from α-1-acid glycoprotein. Following a single IV dose of 100 µg [14C]-lesinurad, the volume of distribution at steady state was 20.3 L. 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.

Allopurinol is negligibly bound by plasma proteins. The apparent volume of distribution of allopurinol is approximately 1.6 litre/kg which suggests relatively extensive uptake by tissues. Tissue concentrations of allopurinol have not been reported in humans, but it is likely that allopurinol and oxypurinol will be present in the highest concentrations in the liver and intestinal mucosa where xanthine oxidase activity is high.

Elimination

- **Excretion**

In the mass balance study, 63% of the radioactivity was recovered in urine and 32% in feces after a period of 0 to 144 hours. The majority of the administered dose was excreted within the first 24 hours (~60% via urine). 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. 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. In urine, lesinurad was the major excreted component. The two 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. Renal clearance is 25.6 mL/min (CV=56%). The elimination half-life ranged from 2.7 to 17.5 hours and was approximately 5 hours following a single dose.

Approximately 20% of the ingested allopurinol is excreted in the faeces. Elimination of allopurinol is mainly by metabolic conversion to oxypurinol by xanthine oxidase and aldehyde oxidase, with less than 10% of the unchanged drug excreted in the urine. Allopurinol has a plasma half-life of about 0.5 to 1.5 hours.

- **Metabolism**

From *in vitro* studies, 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.

The main metabolite of allopurinol is oxypurinol. Other metabolites of allopurinol include allopurinol-riboside and oxypurinol-7-riboside.

- **Inter-conversion**

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 43:57 at Cmax,ss and 20:80 at Cmin,ss. The half-life 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 (Ae0-24) and 0.836 for renal clearance from 0 to 24 hours (CLR0-24). 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.

Allopurinol has no chiral centres.

- **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.

- **Pharmacokinetics of metabolites**

Metabolites are not known to contribute to the uric acid lowering effects of lesinurad. 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%.

Oxypurinol is a less potent inhibitor of xanthine oxidase than allopurinol, but the plasma half-life of oxypurinol is far more prolonged. Estimates range from 13 to 30 hours in man. Therefore effective inhibition of xanthine oxidase is maintained over a 24 hour period with a single daily dose of allopurinol. Patients with normal renal function will gradually accumulate oxypurinol until a steady-state plasma oxypurinol concentration is reached. Such patients, taking 300 mg of allopurinol per day will generally have plasma oxypurinol concentrations of 5-10 mg/litre.

Oxypurinol is eliminated unchanged in the urine but has a long elimination half-life because it undergoes tubular reabsorption. Reported values for the elimination half-life range from 13.6 hours to 29 hours. The large discrepancies in these values may be accounted for by variations in study design and/or creatinine clearance in the patients.

- **Consequences of genetic polymorphism**

Approximately half of an oral dose of lesinurad is cleared via CYP2C9 metabolism. When compared with extensive CYP2C9 metabolisers (CYP2C9 *1/*1 [N=41]), increased lesinurad exposures were observed in intermediate CYP2C9 metabolisers (CYP2C9 *1/*3 [N=4], approximately 22% increase in AUC) and in poor CYP2C9 metabolisers (CYP2C9 *3/*3 [N=1], approximately 111% increase in AUC) accompanied with higher lesinurad renal excretion. However, individual values were well within the range observed in the extensive metaboliser subjects. Therefore, patients known to be poor metabolisers of CYP2C9 should be treated with caution as the risk of lesinurad renal-related adverse reactions may be increased.

Dose proportionality and time dependencies

- **Dose proportionality**

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

Dose-linearity of allopurinol after administration of Duzallo FDC tablet was assessed based on data from Study 501 and 503. There were no signs of non-linearity when the allopurinol dose was increased from 200 mg (FDC 200/200 mg) to 300 mg (FDC 300/200 mg).

- **Time dependency**

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

Special populations

- **Impaired renal function**

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

Following administration of a single dose of lesinurad to individuals with renal impairment compared to those with normal renal function lesinurad Cmax and AUC, respectively, were 36% and 30% higher 14 (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).

Allopurinol and oxypurinol clearance is greatly reduced in patients with poor renal function resulting in higher plasma levels in chronic therapy. Patients with renal impairment, where creatinine clearance values were between 10 and 20 ml/min, showed plasma oxypurinol concentrations of approximately 30 mg/litre after prolonged treatment with 300 mg allopurinol per day. This is approximately the concentration which would be achieved by doses of 600 mg/day in those with normal renal function.

- **Impaired hepatic function**

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

There is no evidence to derive a recommendation regarding a reduction of the daily allopurinol dose to less than 300 mg in patients with hepatic impairment.

- **Gender**

The effect of gender was evaluated by the analysis of PK parameters following a single dose of 400 mg or 1600 mg lesinurad FA tablets in 54 healthy volunteers (28 males and 26 females). No gender effect is observed if corrected for differences in body weight.

- **Race**

No effect of race on the pharmacokinetics of lesinurad when corrected for differences in body weight was observed between Japanese and Caucasian volunteers. Race and ethnicity were evaluated as a covariate in a population PK analysis and were found not to be significant covariates.

- **Weight**

Weight (as BMI) was evaluated as a covariate in the population PK model (range: 47 to 239 kg). The apparent volume of distribution increased less than proportionally with increasing body weight (eg for a 50% increase in body weight apparent volume of distribution increased by 23%). No effect of weight was observed on the AUC and C_{max}.

- **Elderly**

Age (n=974 for <65 years of age, n=135 for >65 years of age and n=24 for >75-84 years of age, n=0 for >85 years of age) was evaluated as a covariate in the population PK model and was found not to be a significant covariate.

The kinetics of allopurinol are not likely to be altered other than due to deterioration in renal function.

Pharmacokinetic interaction studies

- **In vitro**

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 androstane receptor (CAR)/pregnane X receptor (PXR).

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. Lesinurad is not an in vitro inhibitor of P-glycoprotein, BCRP, OATP1B3, MRP2, MRP4, OCT2, MATE1, MATE2-K and BSEP.

- **In vivo**

Lesinurad+allopurinol

Based on interaction studies in healthy subjects or gout patients, lesinurad does not have clinically significant interactions with allopurinol. Lesinurad slightly decreased exposure of oxypurinol (a URAT1 substrate), the major metabolite of allopurinol; however, the uric acid-lowering effect of the combination with allopurinol was significantly greater than for either substance alone.

Lesinurad

Effect of lesinurad on other medicinal products

Several in vivo DDI studies have been performed with substrates for CYP2C8, 2C9 and 3A4 to investigate the clinical relevance of the observed in vitro inhibition and induction. Overall, the clinical data indicate that lesinurad is not an inhibitor or inducer of CYP2C9 and 2C8, but a weak inducer of CYP3A. The in vivo activity of OATP1B1, OAT1, OAT3 and OCT1 was not affected by lesinurad.

- *CYP3A substrates:* Mild to moderate induction of CYP3A by lesinurad may reduce plasma exposures of co-administered medicines that are sensitive substrates of CYP3A. In interaction studies conducted in healthy subjects with lesinurad and CYP3A substrates, lesinurad reduced the plasma concentrations of sildenafil and amlodipine. HMG-CoA reductase inhibitors that are sensitive CYP3A substrates may interact with lesinurad. The possibility of reduced efficacy of concomitant medicinal products that are CYP3A substrates should be considered and their efficacy (e.g. blood pressure and cholesterol levels) should be monitored.
- *Warfarin:* In an interaction study conducted in healthy subjects with multiple doses of lesinurad 400 mg and single dose warfarin (25 mg), lesinurad led to a decrease in exposure of R-warfarin (the less active enantiomer) and had no effect on the exposure of S-warfarin (the more active enantiomer). Additionally, lesinurad led to a 6-8% decrease in International Normalised Ratio (INR) and Prothrombin Time (PT).
- *Hormonal contraceptives:* Lesinurad is a mild to moderate inducer of CYP3A and therefore may lower plasma concentrations of some hormonal contraceptives, thereby decreasing contraceptive effectiveness. Female patients of childbearing age should therefore practise additional methods of contraception when taking Duzallo.
- *CYP2B6 substrates:* Based on in vitro data, lesinurad may be a mild inducer of CYP2B6 but this interaction has not been studied in vivo. The possibility of reduced efficacy of co-administered CYP2B6 substrates (e.g. bupropion, efavirenz) should therefore be considered.
- *Other drugs:* Based on interaction studies in healthy subjects or gout patients, lesinurad does not have clinically significant interactions with NSAIDs (naproxen and indomethacin), colchicine, repaglinide, tolbutamide, or febuxostat.

Effect of other medicinal products on lesinurad

- *CYP2C9 inhibitors and inducers:* Lesinurad exposure is increased when it is co-administered with inhibitors of CYP2C9. Fluconazole, a moderate CYP2C9 inhibitor, increased lesinurad AUC (56%) and Cmax (38%), as well as the amount of lesinurad excreted unchanged in urine. Duzallo should therefore be used with caution in patients taking moderated inhibitors of CYP2C9. Lesinurad exposure is expected to decrease when it is co-administered with inducers of CYP2C9 (e.g. carbamazepine, a moderate CYP2C9 inducer). When Duzallo is co-administered with a CYP2C9 inducer, monitoring for decreased efficacy should be done.
- *Rifampin:* Rifampin, an inhibitor of OATPs and an inducer of CYP2C9, decreased lesinurad exposure and slightly reduced the amount of lesinurad excreted unchanged in urine with no clinically relevant effect. The lack of an observed interaction could be due to the combination of the induction of CYP2C9 and inhibition of OATP1B1 and 1B3.
- *Epoxide hydrolase inhibitors:* Inhibitors of microsomal Epoxide Hydrolase (mEH) (e.g. valproic acid, valpromide) may interfere with the metabolism of lesinurad. Duzallo should not be administered with inhibitors of mEH.

Allopurinol

Effect of allopurinol on other medicinal products

- *Vidarabine (Adenine Arabinoside):* Evidence suggests that the plasma half-life of vidarabine is increased in the presence of allopurinol. Hence, as indicated in the SmPC, when these two active substances are administered concomitantly, extra vigilance is required to recognize enhanced toxic effects.

- *Phenytoin:* Allopurinol may inhibit hepatic oxidation of phenytoin but the clinical significance of this effect has not been demonstrated.
- *Theophylline:* Inhibition of the metabolism of theophylline has been reported. The mechanism of the interaction may be explained by xanthine oxidase being involved in the biotransformation of theophylline in man. Theopylline levels should be monitored in patients undergoing Duzallo therapy.
- *Ciclosporin:* Reports suggest that the plasma concentration of ciclosporin may be increased during concomitant treatment with allopurinol. However, the clinical relevance is not known when taking Duzallo owing to the mild to moderate CYP3A inducing properties of lesinurad. In transplant patients frequent measurement of ciclosporin levels and, if necessary, ciclosporin dosage ad-justment is required, particularly during the introduction or withdrawal of Duzallo.
- *Didanosine*: In healthy volunteers and HIV patients receiving didanosine, plasma didanosine Cmax and AUC values were approximately doubled with concomitant allopurinol treatment (300 mg daily) without affecting terminal half-life. Co-administration is generally not recommended.

Effect of other medicinal products on allopurinol

- *Salicylates and uricosuric agents*: Oxypurinol, the major metabolite of allopurinol and itself therapeutically active, is excreted by the kidney in a similar way to urate. Hence, drugs with uricosuric activity such as probenecid or large doses of salicylate may accelerate the excretion of oxypurinol. The efficacy of Duzallo may be decreased.
- *Chlorpropamide:* If allopurinol is given concomitantly with chlorpropamide when renal function is poor, there may be an increased risk of prolonged hypoglycaemic activity because allopurinol and chlorpropamide may compete for excretion in the renal tubule.
- *Diuretics:* An increased risk of hypersensitivity has been reported when allopurinol is given with diuretics, in particular thiazides, especially in renal impairment..
- *Aluminium hydroxide*: If aluminium hydroxide is taken concomitantly, allopurinol-containing medicinal products may have an attenuated effect. There should be an interval of at least 3 hours between the concomitant use of those medicinal products.
- *6-mercaptopurine and azathioprine*: Serum concentrations of 6-mercaptopurine and azathioprine can reach toxic levels unless dose reduction is undertaken. Patients taking Duzallo which contains the active substance component allopurinol and 6-mercaptopurine or azathioprine must reduce their dose to 25 % of the intended dose of 6-mercaptopurine or azathioprine. Patients should be closely monitored for therapeutic response and the appearance of toxicity.

2.4.3. Pharmacodynamics

Mechanism of action

Lesinurad is a selective uric acid reabsorption inhibitor that inhibits uric acid transporter URAT1. Allopurinol is a xanthine-oxidase inhibitor. Allopurinol and its main metabolite oxypurinol lower the level of uric acid in plasma and urine by inhibition of xanthine oxidase, the enzyme catalyzing the oxidation of hypoxanthine to xanthine and xanthine to uric acid.

Primary and Secondary pharmacology

Changes in pUA concentrations, following single oral doses of allopurinol/lesinurad 300/200 FDC tablets or co-administered allopurinol 300 mg + lesinurad 200 mg tablets, were evaluated in healthy subjects in the fed state (Study 503). The effect on plasma urate concentrations were comparable after administration of Duzallo FDC compared to co-administration of lesinurad and allopurinol tablets.

Also, a post-hoc analysis of pUA levels from Study 501 comparing the fed and fasted results were provided. The lowering effect on plasma urate concentrations were prolonged when Duzallo was administered under fed conditions. These data support the proposed SmPC-recommendation that Duzallo should be administered with food.

2.4.4. Discussion on clinical pharmacology

Study 501 (fasting 200/200 and 300/200) and study 503 (fed 300/200) are pivotal in the bridging between Duzallo fixed dose combination tablet and the concomitant administration of lesinurad and allopurinol mono-components.

Study design

Duzallo 200/200 mg and 300/200 mg are not proportional in composition. Thus, the general conditions for biowaiver for additional strength are not fulfilled and therefore comparative bioavailability studies with both strengths should be conducted.

According to the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1) bioequivalence studies should generally be conducted under fed conditions for products where the SmPC recommends intake of the reference medicinal product only in fed state. Both lesinurad and allopurinol are recommended to be administered with or after a meal according to their respective SmPC. Given the guideline recommendation, the CHMP stated in the scientific advice that bioequivalence should be demonstrated under fed conditions.

In the current application, bioequivalence under fed conditions was only evaluated with the highest strength of 300/200 mg. This is considered acceptable for the following reasons: both strengths were studied in study 501 under fasting conditions, which is generally the most sensitive conditions to detect formulation related differences. Also, the recommendations to administer the reference drugs with food are not due to pharmacokinetic reasons. For lesinurad, the serum Uric Acid (sUA) lowering effect of lesinurad was improved under fed conditions. For this reason, lesinurad was administered with food in the clinical trials. Allopurinol should be administered with food to avoid gastrointestinal adverse events. The effect of food on lesinurad and allopurinol PK was small to moderate in studies with the mono-components and also for Duzallo FDC 300/200 mg. The value of an additional bioequivalence study under fed conditions with the FDC 200/200 strength was therefore considered to be minor by the CHMP. In addition, similar in vitro dissolution profiles of the 200/200 and the 300/200 mg strength have been demonstrated.

In conclusion, the number of studies was considered sufficient to support the application of the FDC tablet by the CHMP. The overall design of the studies was considered to be adequate by the CHMP.

Results

Bioequivalence between Duzallo 300/200 and the co-administered mono-components was demonstrated for lesinurad, allopurinol and oxypurinol under fasting conditions. Under fed conditions the conventional bioequivalence criteria were met with respect to AUC and Cmax for all three analytes, with the exception of allopurinol Cmax. Allopurinol Cmax was 15% higher after administration of the

FDC compared to the reference mono-components and the upper limit of the 90% CI of 1.2721 was slightly above the scaled BE limit of 1.2533. Although strict BE for allopurinol Cmax could not be demonstrated under fed conditions, the results were largely in line with the results from the fasting BE study with allopurinol Cmax T/R ratio of 1.15 and 1.07 under fed and fasting conditions respectively. All other parameters were bioequivalent in both studies.

With Duzallo 200/200, under fasting conditions the conventional bioequivalence criteria were met with respect to AUC and Cmax for all three analytes, with the exception of allopurinol Cmax. Allopurinol Cmax was 18% higher after administration of the FDC compared to the reference mono-components and the upper limit of the 90% CI of 1.28 was slightly above the BE limit of 1.25.

At the CHMP request, the Applicant has discussed the above mentioned issues of higher allopurinol Cmax from a pharmacokinetic, efficacy and safety point of view. The main point was the safety of the FDC: adverse reactions in association with allopurinol exposure are rare and AE due to allopurinol treatment mostly relates to oxypurinol exposure. This is due to the fact that half-life of allopurinol is short comparing with oxypurinol and exposure to oxypurinol is much higher. From a safety perspective it is therefore reassuring that bioequivalence was satisfactorily demonstrated for oxypurinol in both studies. Regarding efficacy, the Applicant presented data indicating that the small increase in Cmax should not have any influence on PD effect, which is agreed. Overall, the CHMP concluded that the minor increase in allopurinol Cmax is not clinically relevant; therefore, equivalent efficacy and safety profile of FDC comparing with the reference mono-products can be concluded.

For lesinurad, the serum Uric Acid (sUA) lowering effect of lesinurad is improved under fed conditions. Allopurinol should be administered with food to avoid gastrointestinal adverse events. Also, a post-hoc analysis of pUA levels from Study 501 comparing the fed and fasted results were provided. The lowering effect on plasma urate concentrations were prolonged when Duzallo was administered under fed conditions. These data support the SmPC-recommendation that Duzallo should be administered with food.

Allopurinol and oxypurinol clearance is greatly reduced in patients with poor renal function resulting in higher plasma levels in chronic therapy. A reduction in the dose of allopurinol is therefore required in patients with renal impairment.

Patients who are known or suspected to be CYP2C9 poor metabolisers based on previous history or experience with other CYP2C9 substrates should use Duzallo with caution as the potential risk of lesinurad renal-related adverse reactions may be increased.

Lesinurad is a mild to moderate inducer of CYP3A. As indicated in the SmPC, additional monitoring of lipids and blood pressure is recommended in patients using sensitive CYP3A substrate lipid lowering medicinal products (such as lovastatin or simvastatin) or antihypertensive medicinal products (such as amlodipine, felodipine or nisoldipine), since their efficacy may be reduced. Hormonal contraceptives, including oral, injectable, transdermal, and implantable forms, may not be reliable when Duzallo is co-administered. Female patients of childbearing age should practice additional methods of contraception and not rely on hormonal contraception alone when taking Duzallo.

Considering the potential drug drug interactions, the following medicines are not recommended to be used with Duzallo: salicylates and non-selective uricosuric active substances such as probenecid, ampicillin/amoxicillin, didanosine, epoxide hydrolase inhibitors (e.g. valproic acid, valpromide).

2.4.5. Conclusions on clinical pharmacology

The FDC of allopurinol/lesinurad is considered approvable from a clinical pharmacology perspective. Appropriate statements have been included in the SmPC.

2.5. Clinical efficacy

2.5.1. Dose response study(ies)

Lesinurad 200/400/600mg doses were explored in Study 203, 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 of < 5 mg/dL 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 cf figure below).

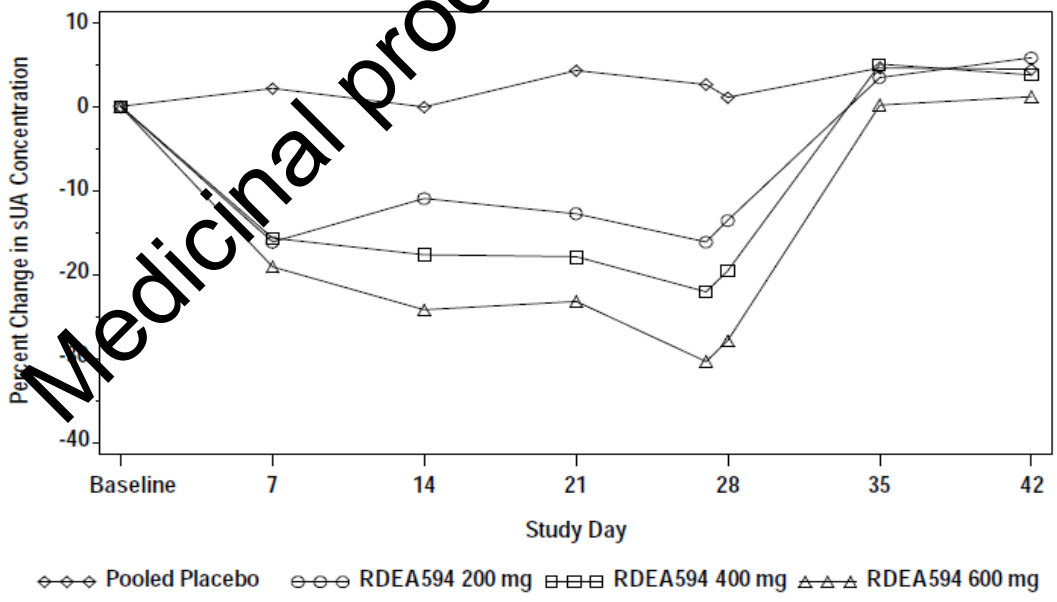


Figure 3 - Mean % change from baseline in sUA concentration by study visit (ITT population, Study 203)

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.

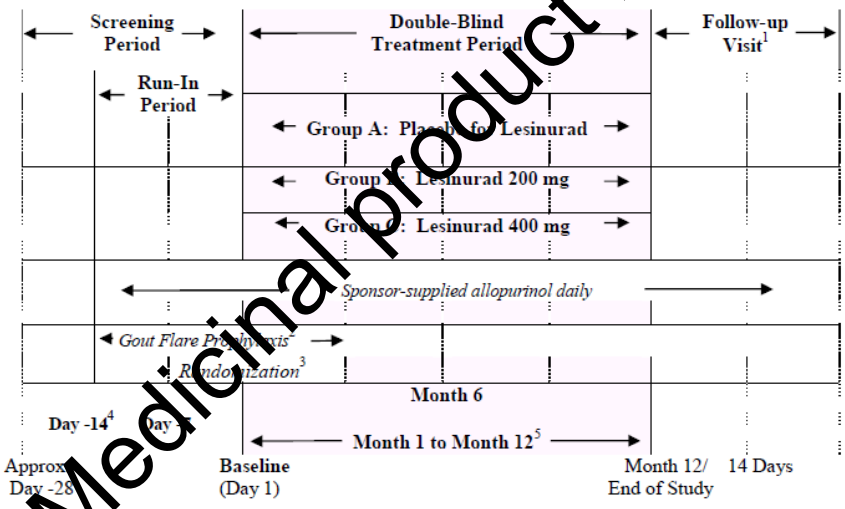
2.5.2. Main studies

The Phase 3 program included both the 200 mg qd and 400 mg qd doses, both as monotherapy, and in combination with allopurinol. However, the applicant has not sought approval for the 400 mg qd dose level, or for a monotherapy indication, due to renal safety considerations and in line with the approved indication for lesinurad.

Study 301 (CLEAR 1): 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

Study design



[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 - 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).

Figure 4 Study design for Study 301

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;
- 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.

Treatments

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

- Group A: placebo + allopurinol (PBO + ALLO group);
- 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 2L 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.

Patient-reported outcomes (PROs)

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 0.22 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.
- 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 > 60 mL/min vs. < 60 mL/min (Cockcroft-Gault formula, ideal body weight)

- Tophus status: presence of > 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.

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

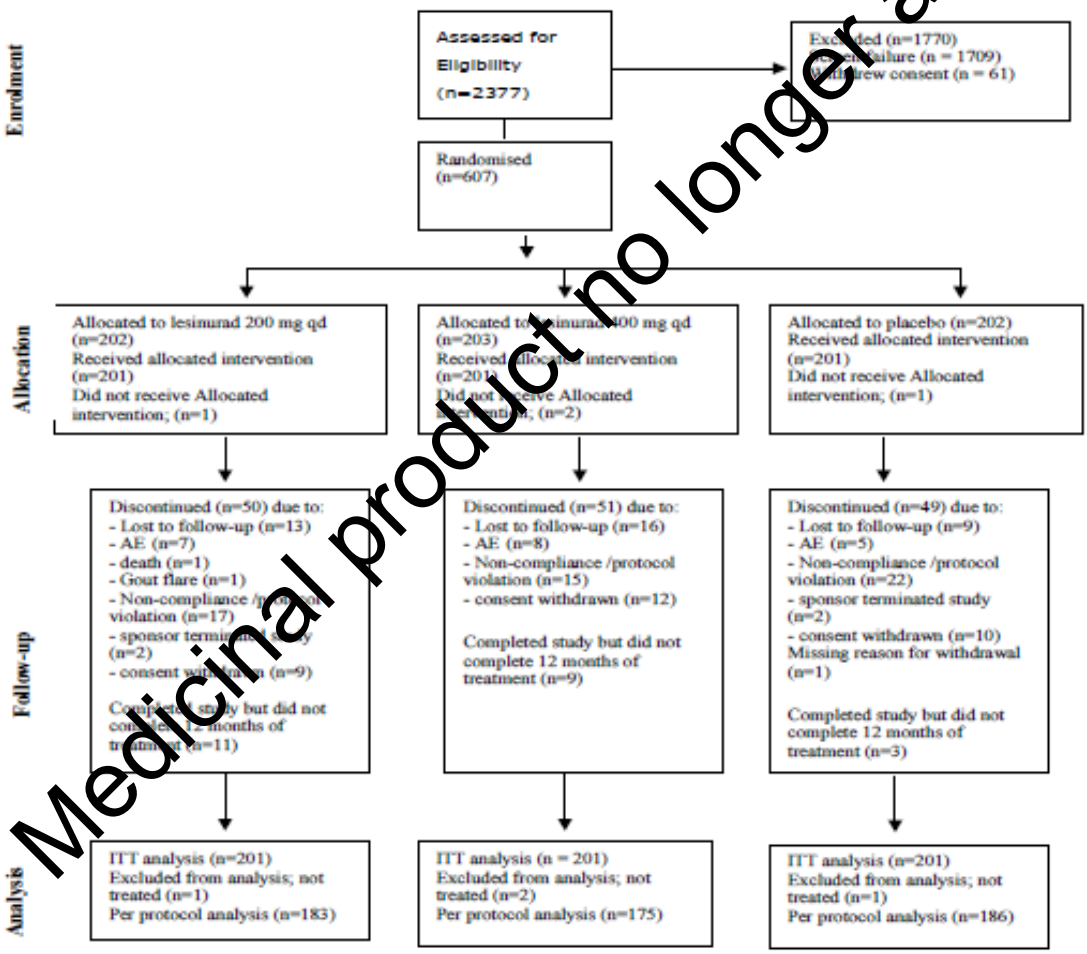


Figure 5 Participant flow study 301

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. One hundred and seventy seven (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.

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 3.0% 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 the table below.

Table 15 Demographic 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)
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 (11.77)	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.

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)	1.9 (1.68)	2.1 (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

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)	47 (7.8)
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 (1.32)	6.83 (1.24)	6.94 (1.27)
Median	6.70	6.80	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).

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 the table below. Patients with missing data at month 6 were included as non-responders.

Table 16 Primary Endpoint: Proportion of Subjects with 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)	119 (59.2)
Difference in proportions vs. PBO + ALLO (95% CI)		0.26 (0.17, 0.36)	0.31 (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.

Sensitivity analyses

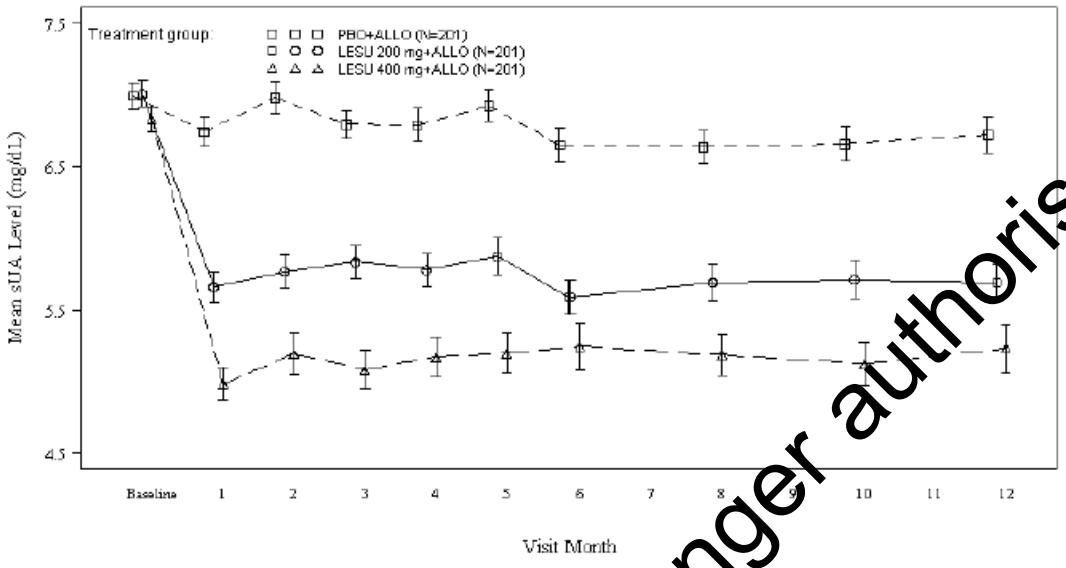
Using the last observation carried forward (LOCF) imputation method, the proportion of subjects who achieved the target of sUA < 6.0 mg/dL at Month 6 was 61.7% and 67.5% versus 32.3% for lesinurad 200 mg qd, lesinurad 400 mg qd, and placebo arms respectively (p < 0.0001 for both comparisons).

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).



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.

Figure 6 Mean Serum Urate Levels by Visit- Observed Cases (ITT Population, Study 301)

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 > 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 (CLEAR 2): 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

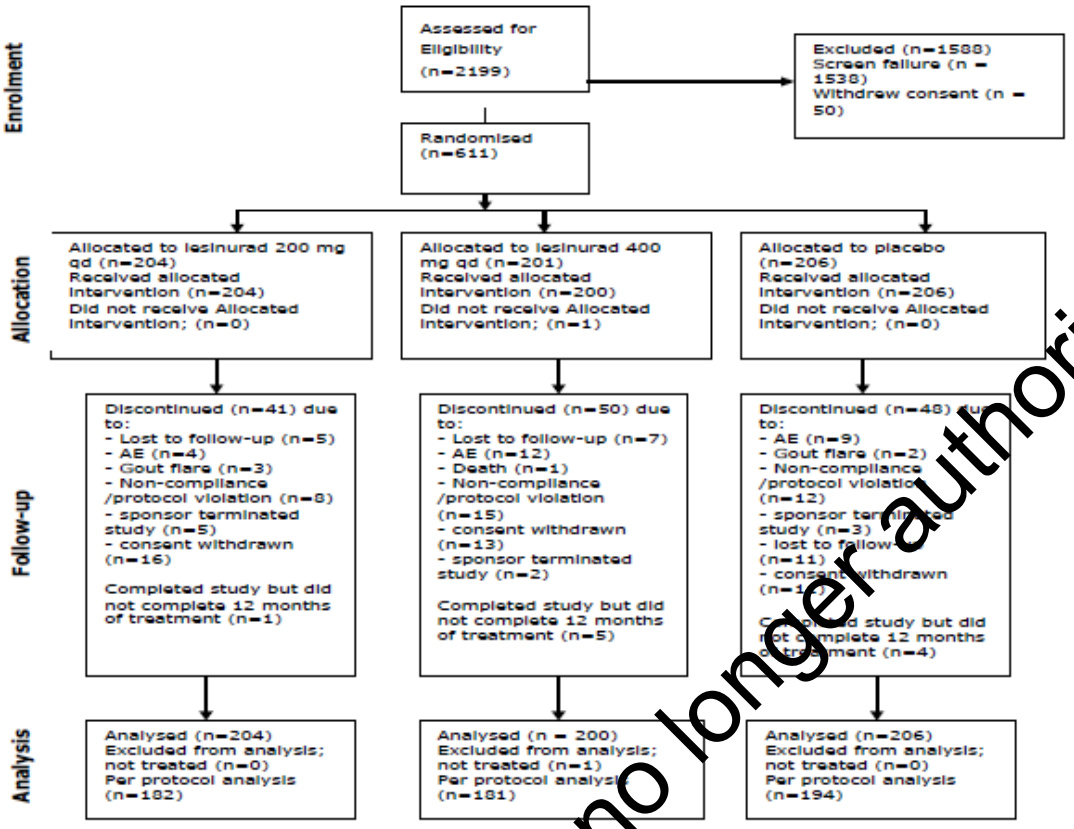


Figure 7 Participant flow in study 301

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 5.9%, 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/m2. Demographic characteristics were balanced between the groups. Demographic characteristics, baseline disease are summarized the table below.

Table 17 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	52.0	52.0	52.0
Min, Max	21, 80	19, 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 at baseline for 16.1% and slightly over-represented in the placebo arm. Mean sUA at baseline was 6.9 mg/dL. Around 24% of subjects were on an allopurinol dose of 300 mg daily at baseline. Baseline disease and treatment characteristics are summarised in the table below.

Table 18 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 (9.26)
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	1.0	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)	373.0 (383.95)	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)
4	31 (15.0)	24 (11.8)	32 (16.0)	87 (14.3)
> 5	86 (41.7)	97 (47.5)	87 (43.5)	270 (44.3)

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 (0.3)
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.[illegible])	6.90 (1.19)
Median	6.80	6.75	6.80	6.80
Min, Max	3.4, 11.3	4.0, 11.3	[illegible], 11.0	3.4, 11.3
sUA category at Baseline (mg/dL) [n (%)]				
< 6.0	38 (18.4)	39 (19.1)	39 (19.5)	116 (19.0)
6.0 - < 7.0	80 (38.8)	88 (43.1)	80 (40.0)	248 (40.7)
7.0 - < 8.0	44 (21.4)	5[illegible] (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)	18 (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 (1.9)	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 - < 300	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)
400 - < 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%.

Outcomes and estimation

Primary efficacy endpoint analysis

The proportion of subjects who achieved the target of sUA < 6.0 mg/dL at Month 6 for lesinurad 200 mg qd, lesinurad 400 mg qd, and placebo arms are summarized in the table below. Patients with missing data at month 6 were included as non-responders.

Table 19 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

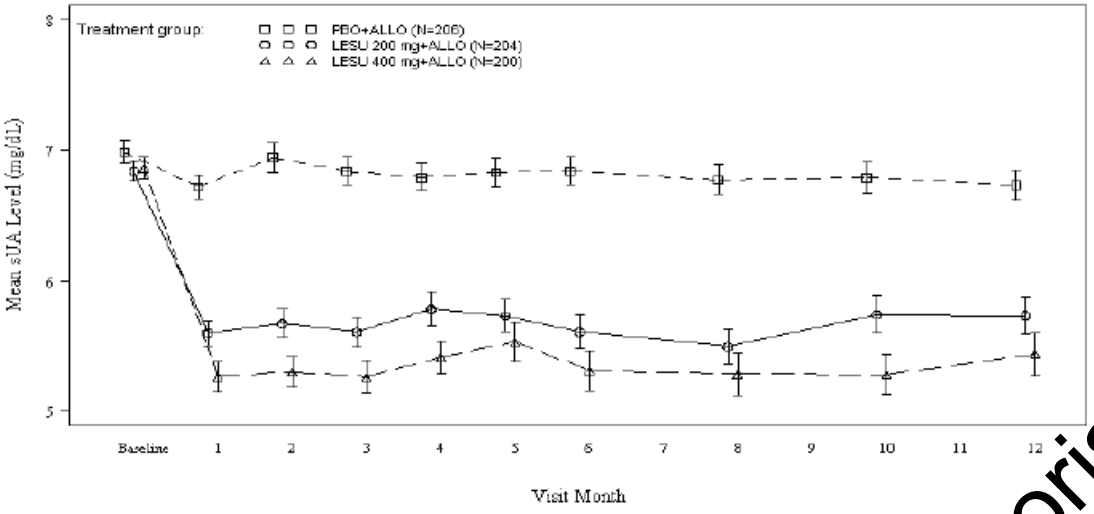
Using the LOCF imputation method, the proportion of subjects who achieved the target of sUA < 6.0 mg/dL at Month 6 was 62.8% and 71.1% versus 25.5% for lesinurad 200 mg qd, lesinurad 400 mg qd, and placebo arms respectively (p < 0.0001 for both comparisons).

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).



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 $p < 0.0001$.

Figure 8 Mean Serum Urate Levels by Visit- Observed Cases (ITT Population, Study 302)

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 0.78, 0.71 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.

Summary of main studies

The following table 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 20 Summary of efficacy for trials 301 and 302

Title: A Phase 3 Randomized, Double-Blind, Multicenter, 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 Hypouricemic Response to Standard of Care Allopurinol			
Study identifier	**Clear 1 (RDEA594-301) and CLEAR 2 (RDEA594-302)**		
Design	Study 301 & 302: Randomized, double-blind, multicenter, parallel, placebo-controlled , add-on to a stable dose of ALLO (at least 300 mg/day for at least 8 weeks [or 200 mg/day for moderate renal impairment]).		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		12 months Days -14 to- 1: Stable ALLO 200-800 mg and initiation of gout flare prophylaxis 18 months (open-label, ongoing)
Hypothesis	Superiority to placebo		
Treatments groups	Group A (Placebo)		Placebo + ALLO, 12 months, numbers randomized: 208 (Study 301); 206 (Study 302)
	Group B (Low Dose)		Lesinurad 200 mg/day + ALLO, 12 months, numbers randomized: 202 (Study 301) 204 (Study 302)
	Group C (High dose)		Lesinurad 400 mg/day+ ALLO, 12 months, numbers randomized: 203 (Study 301); 201 (Study 302)
Endpoints and definitions	Primary endpoint	sUA<6	Proportion of subjects with sUA level < 6.0 mg/dL by Month 6
	Key secondary	Flare rate	Mean rate of gout flares requiring treatment from end of Month 6 to end of Month 12
	Key secondary	Tophi remission	Complete remission of at least 1 target tophus by Month 12
	Secondary	Sustained responders	Proportion sUA<6 at each of Months 4, 5, and 6 Proportion sUA<6 at each of Month 12
Database lock	Study 301: 01Jul2014; Study 302: 03Jul2014		

Results and Analysis

Analysis description	**Primary Analysis (non-responder imputation)**			
Analysis population	ITT, 6 months (primary endpoint) or 12 months (key secondary endpoints)			
Descriptive statistics and estimate variability	**Treatment group**	**A (placebo)**	**B (low dose)**	**C (high dose)**
	Number of subjects ITT	Study 301: 201 Study 302: 206	Study 301: 201 Study 302:204	Study 301: 201 Study 302: 200
	Primary endpoint sUA<6 mg/dL (%)	Study 301: 27.9 Study 302: 23.3	Study 301: 54.2 Study 302: 55.4	Study 301: 59.2 Study 302: 66.5
	variability statistic	NR	NR	NR
	Key secondary endpoint; Flare rates (means)	Study 301: 0.6 Study 302: 0.9	Study 301: 0.6 Study 302: 0.7	Study 301: 0.5 Study 302: 0.8
	SD	Study 301: 1.3 Study 302: 1.8	Study 301: 1.2 Study 302:1.4	Study 301: 1.2 Study 302: 1.7
	Key secondary endpoint; CR tophi, n/N (%)	Study 301: 5/17 (29.4) Study 302: 11/33 (33.3)	Study 301: 0/18 (0) Study 302: 11/35 (31.4)	Study 301: 4/19 (21.1) Study 302: 8/29 (27.6)

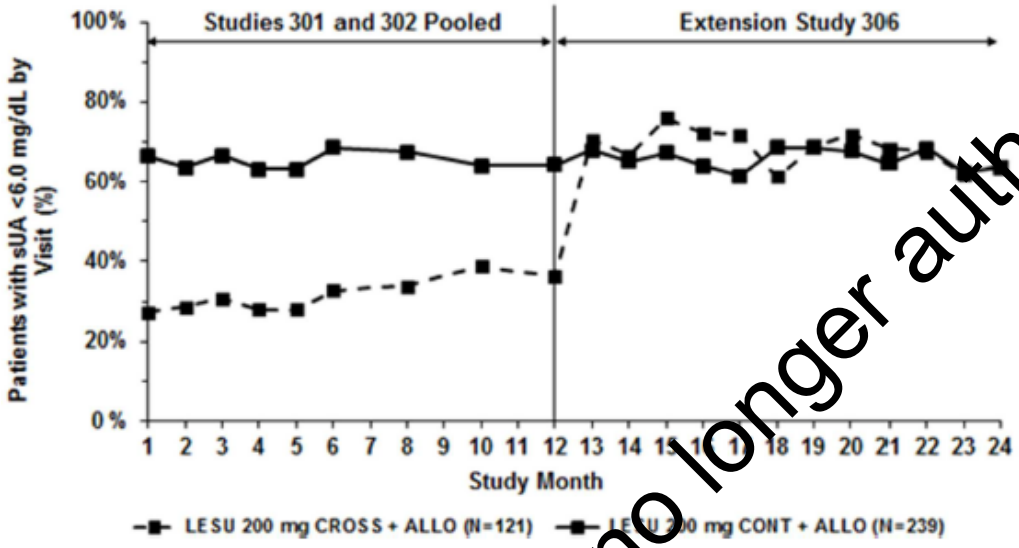
	variability statistic	NR	NR	NR
Effect estimate per comparison	**Primary endpoint** sUA<6	**Comparison groups**	**High Dose vs Placebo**	
		Difference in proportions vs Placebo	Study 301: 0.31 Study 302: 0.43	
		95% CI of the difference	Study 301: 0.22, 0.41 Study 301: 0.34, 0.52	
		p-value	Study 301: <0.0001 Study 302: <0.0001	
		Comparison groups	**Low Dose vs Placebo**	
		Difference in proportions vs Placebo	Study 301: 0.26 Study 302: 0.32	
		95% CI of the difference	Study 301: 0.17, 0.36 Study 302: 0.23, 0.41	
		P-value	Study 301: <0.0001 Study 302: <0.0001	
	Key Secondary endpoint: **flare rates**	**Comparison groups**	**High Dose vs Placebo**	
		Incidence Rate Ratio	Study 301: 0.88 Study 302: 0.93	
		95% CI	Study 301: 0.54-1.43 Study 302: 0.60-1.45	
		p-value	Study 301: 0.6125 Study 302: 0.7454	
		Comparison groups	**Low Dose vs Placebo#**	
		Incidence Rate Ratio	Study 301: 0.99 Study 302: 0.88	
		95% CI	Study 301: 0.61-1.61 Study 302: 0.57-1.37	
		p-value	Study 301: 0.9796 Study 302: 0.5716	
Effect estimate per comparison	Key Secondary endpoint **CR tophus**	**Comparison groups**	**High Dose vs Placebo#**	
		Difference in proportions vs Placebo	Study 301: -0.08 Study 302: -0.06	
		95% CI of the difference	Study 301: -0.37,0.20 Study 302: -0.29,0.17	
		p-value	Study 301: 0.5974 Study 302: 0.6301	
		Comparison groups	**Low Dose vs Placebo#**	
		Difference in proportions vs Placebo	Study 301: -0.29 Study 302: -0.02	
		95% CI of the difference	Study 301: -0.51, 0.08 Study 302: -0.24,0.20	
		P-value	Study 301: 0.0183 Study 302: 0.8466	
Notes	#According to the hierarchical testing schedule in the Statistical Analyses Plan, testing was formally stopped after the first Key secondary endpoint (flares; High Dose) failed to meet its endpoint. Data are included for information purposes.			
Analysis description	**Primary analyses Study 302:** 3 randomised subjects from a site where GCP irregularities were noted were excluded from the primary analyses. Inclusion of these subjects did not lead to significant different outcomes/conclusions. **Secondary analysis: LOCF, ITT, Primary endpoint** (sUA<6 at M6); difference in proportion vs placebo (95% CI), p-value LESU 200 mg: Study 301: 0.29 (0.20,0.39), p<0.0001 LESU 400 mg: Study 301: 0.35 (0.26, 0.44), p<0.0001 LESU 200 mg: Study 302: 0.37 (0.28,0.46), p<0.0001 LESU 400 mg: Study 302: 0.46 (0.37,0.54), p<0.0001 **Robustness: See Table 3.4.5.10**			

Long-term open-label extension study 306

Results

Of the 1213 subjects enrolled and randomized in Study 301 or Study 302, a total of 362 patients were enrolled to study 306 and received up to 40 months of lesinurad 200 mg + allopurinol.

The proportion of patients with sUA <6 g/dl through the 2 years extension period in study 306 remained stable and switching from placebo to lesinurad had increased the proportion of patients with the target sUA from month 12 to 24).



The Study 301/302 data shown (Month 1 through Month 12) are for those subjects who participated in Study 306. Only subjects with a non-missing sUA result at a particular visit were included for that visit. End of study/early termination data were included in the appropriate visit month if no scheduled visit occurred during that visit month. Core Months 7, 9, and 11 data were excluded due to the limited data because of the timing of the last protocol amendment where these measurements were implemented. Due to Protocol amendment, not all subjects had scheduled visits at every month, and data were sparse at Extension Months 3, 5, 7, 8, 10, and 11 (i.e., Months 15, 17, 19, etc. in this figure).

Numbers shown are for Month 1 – Month 12.
Numbers for Month 24: LESU 200 mg CROSS + ALLO (N = 86); LESU 200 mg CONT + ALLO (N = 190).

ALLO = allopurinol; CONT = continuation of lesinurad treatment; CROSS = crossover from placebo to lesinurad; LESU = lesinurad; N = number of subjects; sUA = serum uric acid.

Figure 9 Proportion of Study 306 subjects with serum uric acid < 6 mg/dl-observed case (pivotal studies/302 and extension study 306

Of the 1213 subjects enrolled in studies 301 or 302, 718 subjects (59.2%) were enrolled in the optional extension study 306 and 716 subjects received at least 1 dose of lesinurad. Approximately 40% subjects discontinued the treatment prematurely. A summary of the reasons which led to the subject's withdrawals before completing 12 month of this extension open label study was provided at the CHMP's request. No substantial difference was seen among subjects receiving 200mg or 400mg of lesinurad. The reasons for subjects' withdrawals were comparable to those observed in studies 301 and 302.

Gout flares and tophus reduction / resolution

In both Study 301 and Study 302, the rates of gout flare requiring treatment during the last 6 months of the treatment period (i.e., Study Months 7 through 12, after gout flare prophylaxis was discontinued) were not significantly different between the lesinurad 200 mg + allopurinol and placebo + allopurinol groups. The mean rate of gout flares requiring treatment was low in these 2 studies (0.5 to 0.8 events per subject across treatment groups for the 6- month period). After

adjustment for Day -7 renal function, tophus status at Screening, and length of exposure to randomized study medication, the mean rates of gout flares that required treatment during the 6-month period from the end of Month 6 through Month 12 (when subjects were to be off gout flare prophylaxis) were similar for LESU 200 mg or LESU 400 mg + ALLO when compared with PBO + ALLO, with no statistically significant differences at the $p < 0.05$ level.

Table 21 Mean Rate of gout flares requiring treatment per subject for the 6-month period from the end of month 6 to the end of month 12 in studies 301 and 302 (ITT population)

	Study 301			Study 302		
	PBO + ALLO (N=201)	LESU 200 mg + ALLO (N=201)	LESU 400 mg + ALLO (N=201)	PBO + ALLO (N=206)	LESU 200 mg + ALLO (N=204)	LESU 400 mg + ALLO (N=200)
Mean (SD) rate of gout flares requiring treatment[a] per subject per 6 months (number of flares per subject over the 6-month period)	0.6 (1.3)	0.6 (1.2)	0.5 (1.2)	0.9 (1.8)	0.7 (1.4)	0.8 (1.7)
Median	0.0	0.0	0.0	0.0	0.0	0.0
Min, Max	0, 8	0, 7	0, 8	0, 10	0, 6	0, 11
Adjusted Rate of Gout Flares Requiring Treatment (standard error)b	0.58 (0.10)	0.57 (0.10)	0.51 (0.09)	0.83 (0.13)	0.73 (0.12)	0.77 (0.13)
Incidence Rate Ratio (95% CI) vs. PBO + ALLO[b]		0.99 (0.61, 1.61)	0.88 (0.54, 1.43)		0.88 (0.57, 1.37)	0.93 (0.60, 1.45)
p-value[b]		0.9796	0.6125		0.5716	0.7454

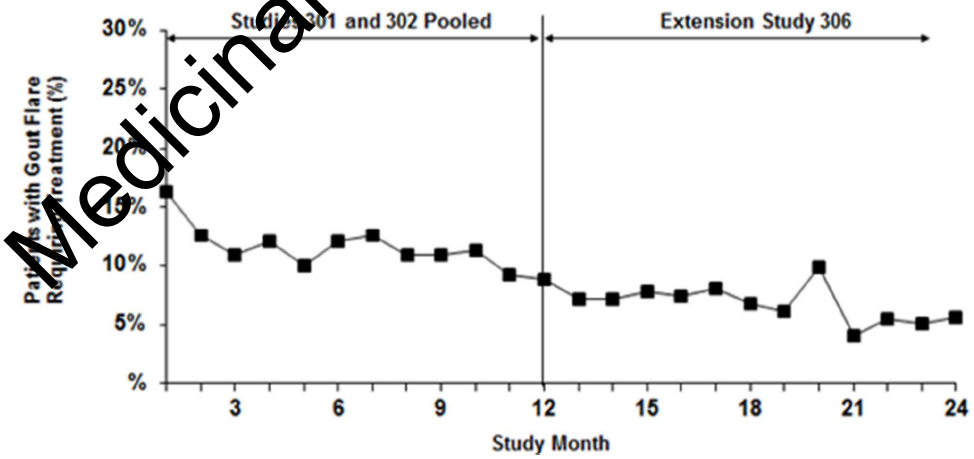
Abbreviations: CI, confidence interval; ALLO, allopurinol; ITT, intent-to-treat; LESU, lesinurad; PBO, placebo; SD, standard deviation.

[a] A gout flare requiring treatment was defined as one with a protocol-specified medication recorded with indication of "Treatment for Gout Flare" beginning within 3 days prior to the start of a gout flare and 3 days after the end of the gout flare.

[b] Estimates obtained from Negative Binomial Regression adjusted for Day -7 renal function (eCrCl ≥ 60 mL/min versus < 60 mL/min) and tophus status during Screening (presence versus absence), randomized values, and log follow-up time as the offset variable.

Note: The gout flare requiring treatment rate was defined as the total number of gout flares requiring treatment during the interval per subject. Summary statistics use observed data (no imputation).

In subjects who received lesinurad 200 mg + allopurinol for up to 24 months (12 months in Study 301 or Study 302 and up to 24 months in the open-label extension Study 306), the proportion of subjects who experienced gout flare requiring treatment each month is shown in the figure below.

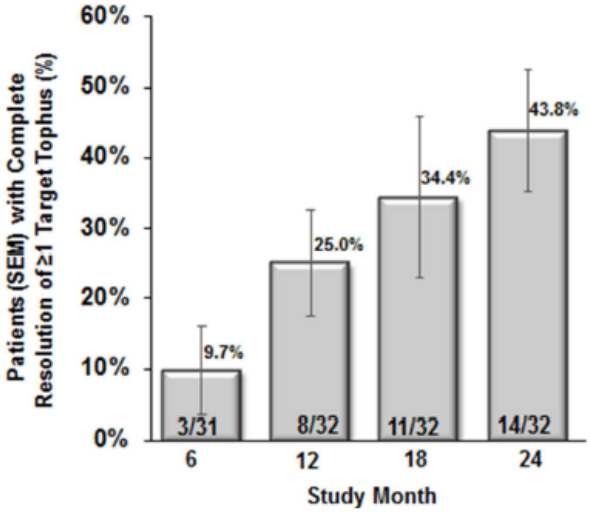


The Study 301/302 data shown (Months 1 through 12) are for those subjects who received LESU 200 mg + ALLO in Study 301 AND Study 306 or Study 302 AND Study 306. Beginning with Studies 301/302 Day 1, monthly intervals were based on actual study days where 28 days represents 1 month.

ALLO = allopurinol; LESU = lesinurad; sUA = serum uric acid.

Figure 10 Proportion of subjects taking lesinurad 200 mg plus allopurinol in Studies 301, 302, and Study 306 who required treatment for a gout flare – observed cases

The proportion of patients with ≥1 target tophus at Baseline who experienced complete resolution (CR) or either CR or partial resolution of ≥1 target tophus in the lesinurad 200 mg + allopurinol group than in the placebo + allopurinol group in studies 301, 302and 306 are shown in the figure below. None of the observed decreases was statistically significant for the core studies.



The Study 301/302 data shown (Month 1 through Month 12) are for those subjects who received LESU 200 mg ALLO in Study 301 AND Study 306 or in Study 302 AND Study 306. Each subject was categorized according to his or her best tophus response over all target tophi at each visit. If any single measured target tophus showed progression at a visit, the best tophus response for that subject at that visit was categorized as progressive disease, regardless of the response of any other target tophi at that visit.

ALLO = allopurinol; LESU = lesinurad; LOCF = last observation carried forward; SEM = standard error of the mean.

Figure 11 Proportion of subjects taking lesinurad 200 mg plus allopurinol in Studies 301, 302 and Study 306 who experienced complete resolution of at least one target tophus – LOCF

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

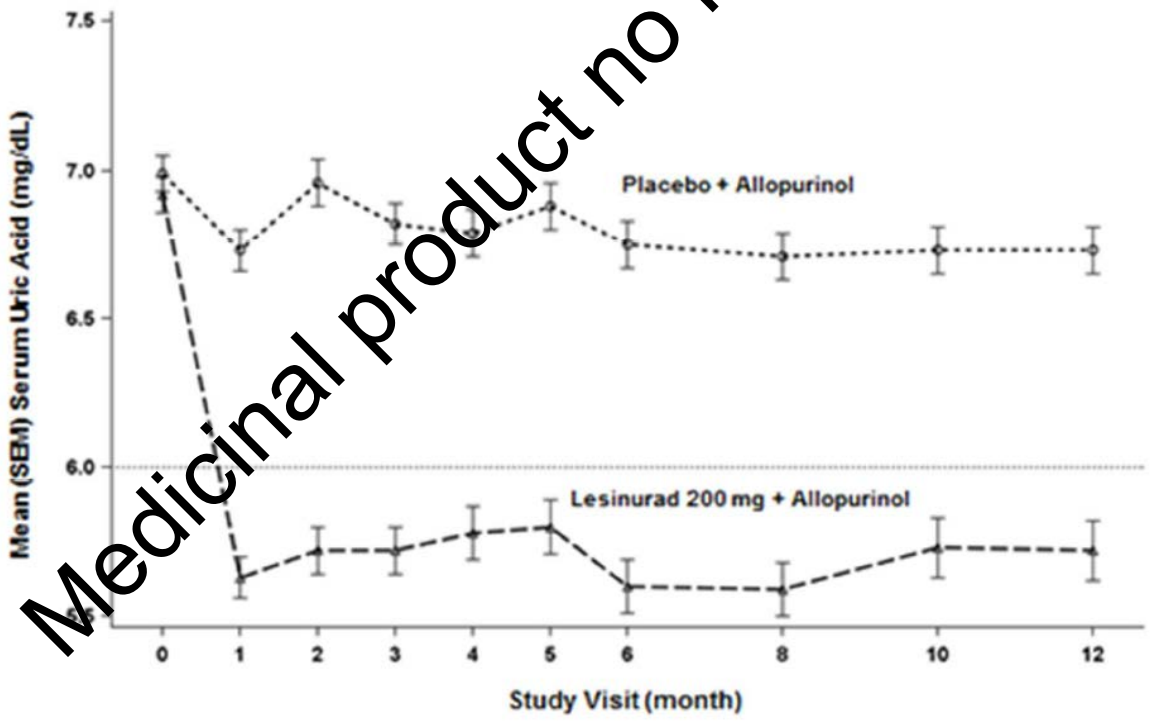
The Applicant provided pooled analyses of studies 301 and 302, as they were identical in design and recruited similar patient numbers. The primary endpoint results and the mean SuA levels by visit are presented in the table below.

Table 22 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.

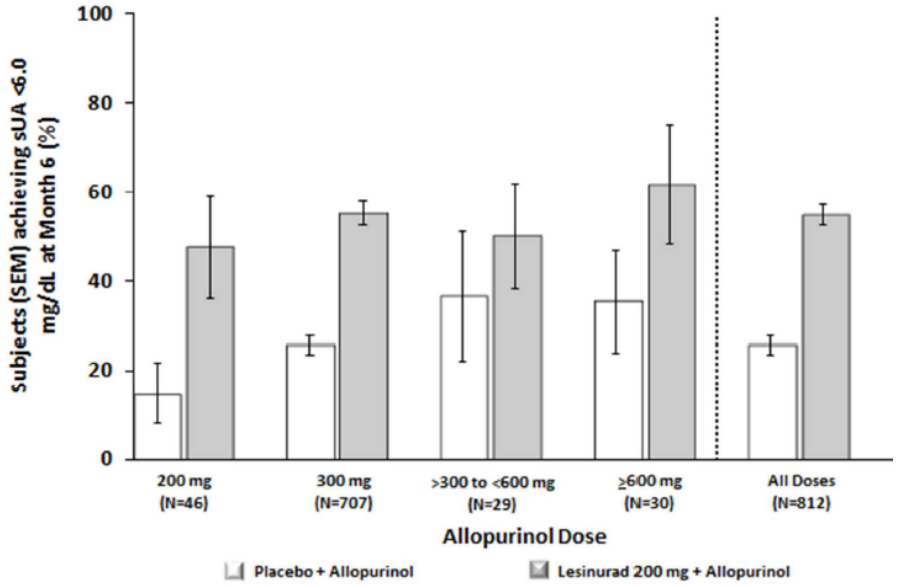
A mean sUA of less than 6 mg/dL was observed for subjects in the lesinurad 200 mg + allopurinol groups at the Month 1 visit and was maintained throughout month 12.



SEM =standard error of the mean.

Figure 12 Mean serum uric acid levels by visit-observed cases (Study 301 and 302 pooled)

The most common prescribed dose for allopurinol was 300 mg in the pivotal studies. Addition of lesinurad in the treatment of patients who have been receiving allopurinol treatment at least 8 weeks increased the proportion of patients achieving the target SUA level in Study 301 and Study 302 with an sUA level <6 mg/dL at Month 6.

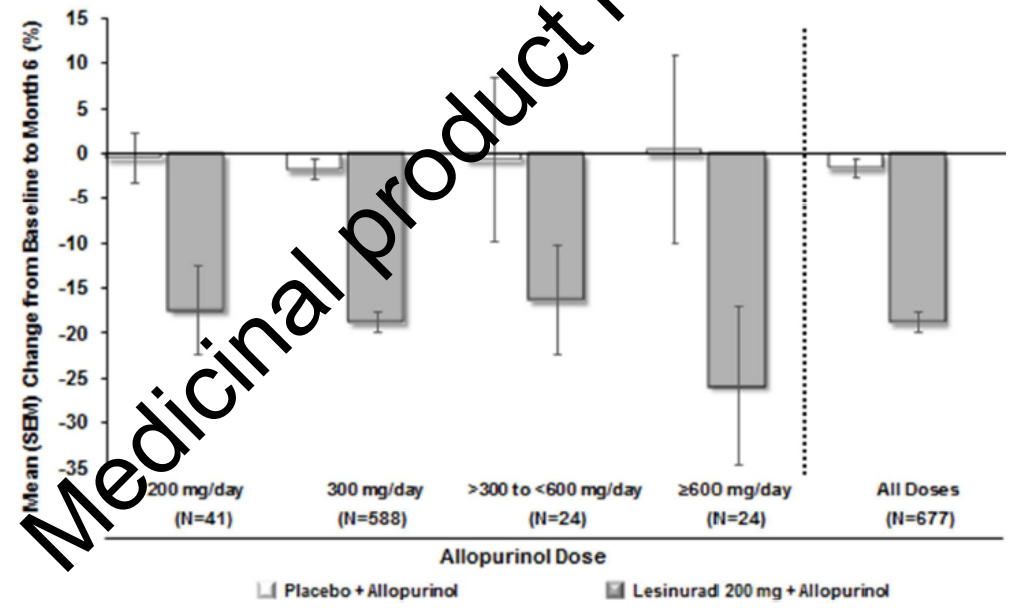


Subjects missing an sUA result at Month 6 were treated as non-responders.

ITT = intent-to-treat; N = number of subjects; NRI = non-responder imputation; SEM = standard error of the mean; sUA = serum uric acid.

Figure 13 Proportion of responders (sUA <6 mg/dL) at Month 6 by allopurinol dose in the core Phase 3 combination studies – NRI (Studies 301 and 302 pooled)

Figure 10 shows pooled data from Study 301 and Study 302 on the percent change in sUA from Baseline for all Baseline allopurinol dose groups at Month 6.



Only subjects with a non-missing sUA result are included in the Observed Cases analysis. Figure depicts arithmetic means; statistical significance is based on difference in least square means.

N = number of subjects; SEM = standard error of the mean; sUA = serum uric acid.

Figure 14 Percent change in sUA levels from baseline to Month 6 by allopurinol dose - observed cases (Studies 301 and 302 pooled)

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.

Clinical studies in special populations

The number of elderly patients (aged 75-84) included in the clinical studies was limited and patients over 85 year were excluded. The proportion of female patients was also low. No studies have been conducted in children as a paediatric waiver has been granted on the grounds of safety. Subjects with renal impairment and with mild (Child-Pugh class A) or moderate (Child-Pugh class B) hepatic impairment were studied during Phase 1 with lesinurad.

Subjects with moderate renal impairment were also included in adequate numbers in the Phase 3 studies. Consistent with the overall population, the proportion of patients with mild to moderate renal impairment (eCrCL 30-89 mL/min) who achieved target serum uric acid levels at Month 6 in the main clinical studies was 56% for lesinurad 200 mg versus 29% for placebo when added to allopurinol at doses ranging from 200 mg to 900 mg.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The demonstration of the efficacy for Duzallo is based on the efficacy data from the Phase 3 pivotal studies (301, 302) and supported by a PK-PD bridge.

Phase 3 pivotal studies (301, 302) investigated lesinurad in combination with allopurinol 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 allopurinol. However, the applicant has not sought approval for the 400 mg qd dose level, or for a monotherapy indication, due to renal safety considerations and in line with the approved indication for lesinurad.

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.

In studies 301 and 302, subjects were required to take allopurinol at a medically-appropriate dose for at least 8 weeks prior to screening. 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. Subjects were eligible if sUA was > 6.5 mg/dL at screening (sUA > 6.0 mg/dL at day -7).

The Applicant justifies the medical rationale for the FDC by the potential convenience with intake and potential increase in compliance to the treatment. As the evidence is based on concomitant use of lesinurad and allopurinol, taken together at the same time point in lesinurad pivotal studies, this is considered relevant for the FDC and no further dedicated clinical trials to the FDC is considered necessary. A PK-PD bridge is provided to support the existing clinical evidence base. Thus, the provided development program and justification for FDC are considered to be in accordance with the CHMP Guideline on clinical development of fixed combination medicinal products (EMA/CHMP/158268/2017).

Efficacy data and additional analyses

Ninety point five per cent (90.5%) of patients in study 301 and 84.1% in study 302 received 300 mg allopurinol.

Of the 405 patients who received lesinurad dose of 200 mg concomitant with allopurinol in these core studies, 362 patients completed up to 40 months of treatment in the open-label extension study (306) with lesinurad 200 mg and allopurinol combination.

The addition of lesinurad on allopurinol treatment in patients who have not achieved target serum uric acid levels with an adequate dose of allopurinol alone has been proven effective in achieving target serum uric acid levels. Indeed, 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. The rates of gout flare requiring treatment were low and comparable to placebo in the last 6 months of the randomised trials (after gout flare prophylaxis was discontinued) with median scores of zero. However, the improvement of flares and tophi reduction compared to placebo after 12 months was not statistically significant. In the long term uncontrolled extension trials, the rates of gout flares requiring treatment further decreased in the 60% of subjects who entered the extension studies and continued treatment with lesinurad 200 mg in combination with allopurinol or febuxostat for up to an additional year of treatment.

The proposed fixed dose allopurinol/lesinurad combinations concern doses of 200/200 mg and 300/200 mg which combines the recommended (and the maximum) dose of lesinurad with the most commonly prescribed dose of allopurinol during the lesinurad phase 3 studies (300 mg) and 200 mg for patients who would need lower doses (e.g., for patients with moderate renal impairment). In clinical practice patients may require higher doses of allopurinol than 300 mg (up to 900 mg). Hence, the Applicant has included a statement in Section 4.2 of the SmPC to state that patients who are currently treated with allopurinol doses higher than 300 mg can be switched to Duzallo and should receive complementary doses of allopurinol to cover the total dose of allopurinol taken before the switch.

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. During the evaluation of Zurampic (lesinurad) 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 combination of lesinurad with allopurinol reduced the sUA below the treatment target level in (tophaceous) gout patients, who were insufficient responders to allopurinol. This effect is of high importance for the target population and the combination is already approved for Zurampic (lesinurad). The importance of the FDC with respect to increasing compliance and convenience has not been documented but can be assumed.

2.6. Clinical safety

Patient exposure

The safety profile of lesinurad in combination with allopurinol was based on data from studies 301 and 302. The Applicant didn't update the Integrated Analysis of Safety (IAS) since the cut-off date for interim data from the phase 3 open-label extension study 306 (17 June 2014) which was applied for the lesinurad application. However, the final CSRs were submitted with the present application.

All subjects who received at least 1 dose of randomized study medication were included in the safety analyses. The phase 3 core + extension integrated datasets are included from studies 301, 302, and 306. Of the 1213 subjects enrolled in core studies 301 or 302, 891 subjects (73.5%) completed 12 months of treatment with randomized study medication, and 718 subjects (59.2%) enrolled in the optional extension study 306 of whom 362 patients received lesinurad 200 mg + placebo up to 40 months. A total of 527 subjects received at least one dose of lesinurad 200 mg in combination with allopurinol**.**

Table 23 Subject disposition

	LESU 200 mg + ALLO			LESU 400 mg + ALLO		
Variable	CROSS (N=122) n (%)	CONT (N=240) n (%)	Total (N=362) n (%)	CROSS (N=122) n (%)	CONT (N=232) n (%)	Total (N=354) n (%)
Completed through Month 6 visit on lesinurad in extension study	107 (87.7)	213 (88.8)	320 (88.4)	99 (81.1)	213 (91.8)	312 (88.1)
Completed through Month 12 visit on lesinurad in extension study	90 (73.8)	194 (80.8)	284 (78.5)	86 (70.5)	193 (83.2)	279 (78.8)
Completed through Month 24 visit on lesinurad in extension study	77 (63.1)	160 (66.7)	237 (65.5)	76 (62.3)	161 (69.4)	237 (66.9)
Study termination (primary reason)	53 (43.4)	93 (38.8)	146 (40.3)	50 (41.0)	88 (37.9)	138 (39.0)
Adverse event	13 (10.7)	21 (8.8)	34 (9.4)	11 (9.0)	30 (12.9)	41 (11.6)
Gout flare	0	0	0	2 (1.6)	0	2 (0.6)
Pregnancy	0	0	0	0	0	0
Requires treatment with protocol prohibited or contraindicated medication	0	5 (2.1)	5 (1.4)	1 (0.8)	1 (0.4)	2 (0.6)
Non-compliance/protocol violation	9 (7.4)	13 (5.4)	22 (6.1)	4 (3.3)	6 (2.6)	13 (3.7)
Sponsor terminated study	3 (2.5)	3 (1.3)	6 (1.7)	2 (1.6)	3 (1.3)	5 (1.4)
Lost to follow up	9 (7.4)	17 (7.1)	26 (7.2)	11 (9.0)	7 (3.0)	18 (5.1)
Consent withdrawn	16 (13.1)	30 (12.5)	46 (12.7)	14 (11.5)	38 (16.4)	52 (14.7)
Death	3 (2.5)	4 (1.7)	7 (1.9)	2 (1.6)	3 (1.3)	5 (1.4)

Abbreviations: ALLO, allopurinol; CONT; continuation of treatment; CROSS; crossover of treatment;
Note: Reasons for study termination are based on the end of study Case Report Form page. Counts and percentages of subjects who completed through Months 6, 12, and 24 refer to the extension study.

Following 12 months in the core studies, 362 patients taking lesinurad 200 mg and allopurinol in the extension study 306 had a mean (SD) duration of exposure of 685.3 (331.03) days. The minimum duration a patient treated with lesinurad 200 mg and allopurinol was 1169 days in the extension study.

The final integrated database with N = 527 subjects revealed a total treatment of 994.5 PYEs. The exposure-adjusted incidence rates, expressed as subjects with events per 100 PYEs, were 72.2 for the initial reporting period (lesinurad MAA), 55.8 through 15 May 2015, and 42.8 per 100 PYE for patients who completed the study with up to a total treatment of up to 52 months.

Demographics

The population was predominantly male (95.1%) and White (78.3%) with a mean age of approximately 52.0 years and a mean BMI of 34.06 kg/m2. Subjects generally had longstanding, symptomatic gout with elevated sUA levels and tophi.

Table 24 Subject demographic characteristics in the pivotal phase 3 studies (12-month studies 301, 302, and 304)

Variable	PBO +XOI (N=516)	LESU 200 mg +XOI (N=511)	LESU 400 mg +XOI (N=510)	TOTAL LESU +XOI (N=1021)
Sex [n (%)]				
Female	24 (4.7)	22 (4.3)	28 (5.5)	50 (4.9)
Male	492 (95.3)	489 (95.7)	482 (94.5)	971 (95.1)
Race [n (%)]				
American Indian or Alaska Native	2 (0.4)	4 (0.8)	0	4 (0.4)
Asian	30 (5.8)	27 (5.3)	22 (4.3)	49 (4.8)
Black or African American	59 (11.4)	60 (11.7)	64 (12.5)	124 (12.1)
Maori	1 (0.2)	4 (0.8)	4 (0.8)	8 (0.8)
Native Hawaiian or other Pacific Islander	10 (1.9)	8 (1.6)	9 (1.8)	17 (1.7)
White	402 (77.9)	398 (77.9)	401 (78.6)	799 (78.3)
Other	12 (2.3)	10 (2.0)	9 (1.8)	19 (1.9)
Missing	0	0	1 (0.2)	1 (0.1)

Variable	PBO +XOI (N=516)	LESU 200 mg +XOI (N=511)	LESU 400 mg +XOI (N=510)	TOTAL LESU +XOI (N=1021)
Race categories [n (%)]				
White	402 (77.9)	398 (77.9)	401 (78.6)	799 (78.3)
Black	59 (11.4)	60 (11.7)	64 (12.5)	124 (12.1)
Other	55 (10.7)	53 (10.4)	44 (8.6)	97 (9.5)
Missing	0	0	1 (0.2)	1 (0.1)
Ethnicity [n (%)]				
Hispanic or Latino	35 (6.8)	44 (8.6)	43 (8.4)	87 (8.5)
Not Hispanic or Latino	481 (93.2)	467 (91.4)	467 (91.6)	934 (91.5)
Age (years)				
N	516	511	510	1021
Mean (SD)	52.2 (11.13)	51.9 (10.88)	52.1 (11.25)	52.0 (11.11)
Median	52.0	53.0	53.0	52.0
Min, Max	21, 81	21, 82	18, 82	18, 82
Age group (years) [n (%)]				
< 65	443 (85.9)	454 (88.8)	433 (84.9)	887 (86.9)
≥ 65	73 (14.1)	57 (11.2)	77 (15.1)	134 (13.1)
≥ 75	9 (1.7)	12 (2.3)	8 (1.6)	20 (2.0)
Height (cm)				
N	514	511	509	1020
Mean (SD)	176.8 (8.12)	177.1 (8.06)	177.1 (8.33)	177.1 (8.19)
Median	177.5	177.8	177.8	177.8
Min, Max	147.0, 198.1	148.9, 198.1	152.0, 203.2	148.9, 203.2
Weight (kg)				
N	513	511	510	1021
Mean (SD)	105.5 (22.32)	108.0 (22.40)	106.2 (23.67)	107.1 (23.05)
Median	102.1	106.2	103.2	104.7
Min, Max	47.6, 183.0	55.5, 204.0	54.0, 238.9	54.0, 238.9
Waist circumference (cm)				
N	510	503	505	1008
Mean (SD)	111.7 (15.92)	113.1 (15.25)	112.1 (16.37)	112.6 (15.82)
Median	109.0	111.8	109.5	110.0
Min, Max	76.0, 177.5	68.6, 202.5	73.0, 188.0	68.6, 202.5
Body mass index (kg/m^2)				
N	513	511	509	1020
Mean (SD)	33.65 (6.21)	34.34 (6.23)	33.78 (6.85)	34.06 (6.55)
Median	32.78	33.52	33.18	33.29
Min, Max	15.91, 56.27	17.79, 59.38	15.77, 83.65	15.77, 83.65
Body mass index categories (kg/m^2) [n (%)]				
< 30	165 (32.0)	132 (25.8)	163 (32.0)	295 (28.9)
≥ 30	348 (67.4)	379 (74.2)	346 (67.8)	725 (71.0)
≥ 40	89 (17.2)	94 (18.4)	84 (16.5)	178 (17.4)
Missing	3 (0.6)	0	1 (0.2)	1 (0.1)

Abbreviations: LESU, lesinurad; PBO, placebo; SD, standard deviation; XOI, xanthine oxidase inhibitor (allopurinol/febuxostat).

Studies were performed during the FDC tablet development

- The phase 1 study ALLO-101 was performed in 22 healthy subjects to assess the impact of the *in vitro* dissolution profile of 4 different allopurinol formulations on the pharmacokinetic parameters used to establish bioequivalence. No lesinurad was given in this study.
- Two phase 1 studies (501 and 503) were performed in healthy subjects exposed to lesinurad 200 mg, allopurinol 200 mg or 300 mg, and the 200/200 or 300/200 FDC tablets (see Section 2.4.2).

Adverse events

In the pooled safety database from studies 301 and 302, most AEs were mild or moderate in severity and reported to be resolved with continuing therapy.

Table 25 Incidence of adverse events by category (studies 301 and 302 pooled)

Adverse event category	PBO + ALLO (N = 407) n (%)	LESU 200 mg + ALLO (N = 405) n (%)
Any AE	284 (69.8)	299 (73.8)
AE with RCTC toxicity Grade 3 or 4	35 (8.6)	41 (10.1)
AE leading to discontinuation of PBO or LESU	19 (4.7)	23 (5.7)
Serious AE	19 (4.7)	18 (4.4)
Deaths	0	1 (0.2)

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

AE = adverse event; ALLO = allopurinol; LESU = lesinurad; N = total number of subjects; n = number of subjects meeting criterion; PBO = placebo; RCTC = Rheumatology Common Toxicity Criteria.

Among the subjects treated in the lesinurad 200 mg + allopurinol group, the most commonly reported TEAEs were upper respiratory tract infection (8.9% incidence in lesinurad 200 mg + allopurinol vs. 7.9% for allopurinol + placebo), nasopharyngitis (8.6% vs. 8.4%, respectively), and back pain (8.1% vs. 8.4%, respectively).

The Group A1A studies in the table consists of two controlled randomized Phase 3 studies (301, 302) and the extension study 306 while Group 1B include the febuxostad study 304 and the extension study 307 provided for comparison of certain AEs as MACE.

Table 26 Adverse event with incidence > 1% in either lesinurad group by preferred term during core study safety population-XOI combination phase 3 studies

Preferred Term [n (%)]	LESU 200 mg +ALLO (N=405)	LESU 400 mg +ALLO (N=401)	TOTAL LESU +ALLO (N=806)	PBO +ALLO (N=407)	LESU 200 mg +FBX (N=106)	LESU 400 mg +FBX (N=109)	TOTAL LESU +FBX (N=215)	PBO +FBX (N=109)
Upper respiratory tract infection	36 (8.9)	48 (12.0)	84 (10.4)	32 (7.9)	10 (9.4)	9 (8.3)	19 (8.8)	12 (11.0)
Nasopharyngitis	35 (8.6)	32 (8.0)	67 (8.3)	34 (8.4)	10 (9.4)	15 (13.8)	25 (11.6)	9 (8.3)
Back pain	33 (8.1)	23 (5.7)	56 (6.9)	34 (8.4)	8 (7.5)	6 (5.5)	14 (6.5)	5 (4.6)
Arthralgia	32 (7.9)	22 (5.5)	54 (6.7)	28 (6.9)	10 (9.4)	10 (9.2)	20 (9.3)	13 (11.9)
Hypertension	25 (6.2)	23 (5.7)	48 (6.0)	17 (4.2)	6 (5.7)	12 (11.0)	18 (8.4)	8 (7.3)
Blood creatinine increased	15 (3.7)	32 (8.0)	47 (5.8)	9 (2.2)	7 (6.6)	8 (7.3)	15 (7.0)	3 (2.8)
Blood creatine phosphokinase increased	17 (4.2)	26 (6.5)	43 (5.3)	22 (5.4)	6 (5.7)	4 (3.7)	10 (4.7)	3 (2.8)
Headache	17 (4.2)	24 (6.0)	41 (5.1)	13 (3.2)	10 (9.4)	6 (5.5)	16 (7.4)	8 (7.3)
Diarrhoea	18 (4.4)	22 (5.5)	40 (5.0)	15 (3.7)	5 (4.7)	5 (4.6)	10 (4.7)	8 (7.3)
Sinusitis	15 (3.7)	20 (5.0)	35 (4.3)	9 (2.2)	2 (1.9)	0	2 (0.9)	4 (3.7)
Influenza	20 (4.9)	14 (3.5)	34 (4.2)	12 (2.9)	6 (5.7)	2 (1.8)	8 (3.7)	2 (1.8)
Muscle strain	12 (3.0)	17 (4.2)	29 (3.6)	14 (3.4)	2 (1.9)	4 (3.7)	6 (2.8)	3 (2.8)
Bronchitis	12 (3.0)	11 (2.7)	23 (2.9)	5 (1.2)	2 (1.9)	5 (4.6)	7 (3.3)	8 (7.3)
Nausea	9 (2.2)	13 (3.2)	22 (2.7)	16 (3.9)	4 (3.8)	6 (5.5)	10 (4.7)	6 (5.5)
Myalgia	8 (2.0)	13 (3.2)	21 (2.6)	8 (2.0)	5 (4.7)	4 (3.7)	9 (4.2)	3 (2.8)
Pain in extremity	14 (3.5)	7 (1.7)	21 (2.6)	13 (3.2)	6 (5.7)	9 (8.3)	15 (7.0)	4 (3.7)
Fall	12 (3.0)	8 (2.0)	20 (2.5)	13 (3.2)	0	1 (0.9)	1 (0.5)	2 (1.8)
Fatigue	10 (2.5)	10 (2.5)	20 (2.5)	6 (1.5)	3 (2.8)	2 (1.8)	5 (2.3)	2 (1.8)
Gastrooesophageal reflux disease	13 (3.2)	7 (1.7)	20 (2.5)	2 (0.5)	1 (0.9)	0	1 (0.5)	2 (1.8)
Urinary tract infection	6 (1.5)	14 (3.5)	20 (2.5)	10 (2.5)	5 (4.7)	4 (3.7)	9 (4.2)	4 (3.7)
Contusion	10 (2.5)	9 (2.2)	19 (2.4)	15 (3.7)	2 (1.9)	7 (6.4)	9 (4.2)	3 (2.8)
Vomiting	10 (2.5)	9 (2.2)	19 (2.4)	9 (2.2)	2 (1.9)	1 (0.9)	3 (1.4)	1 (0.9)
Constipation	9 (2.2)	9 (2.2)	18 (2.2)	9 (2.2)	2 (1.9)	1 (0.9)	3 (1.4)	0
Cough	10 (2.5)	8 (2.0)	18 (2.2)	12 (2.9)	4 (3.8)	9 (8.3)	13 (6.0)	3 (2.8)
Dizziness	5 (1.2)	13 (3.2)	18 (2.2)	6 (1.5)	3 (2.8)	1 (0.9)	4 (1.9)	1 (0.9)
Muscle spasms	10 (2.5)	8 (2.0)	18 (2.2)	10 (2.5)	2 (1.9)	1 (0.9)	3 (1.4)	1 (0.9)
Rash	9 (2.2)	8 (2.0)	17 (2.1)	9 (2.2)	1 (0.9)	3 (2.8)	4 (1.9)	1 (0.9)
Gastroenteritis	10 (2.5)	6 (1.5)	16 (2.0)	11 (2.7)	2 (1.9)	3 (2.8)	5 (2.3)	2 (1.8)
Pyrexia	8 (2.0)	8 (2.0)	16 (2.0)	12 (2.9)	1 (0.9)	7 (6.4)	8 (3.7)	4 (3.7)
Joint sprain	10 (2.5)	5 (1.2)	15 (1.9)	7 (1.7)	4 (3.8)	6 (5.5)	10 (4.7)	2 (1.8)
Oedema peripheral	8 (2.0)	7 (1.7)	15 (1.9)	8 (2.0)	4 (3.8)	4 (3.7)	7 (3.3)	3 (2.8)
Hypertriglyceridaemia	9 (2.2)	5 (1.2)	14 (1.7)	4 (1.0)	1 (0.9)	2 (1.8)	3 (1.4)	2 (1.8)
Tendonitis	8 (2.0)	6 (1.5)	14 (1.7)	8 (2.0)	2 (1.9)	0	2 (0.9)	2 (1.8)
Abdominal pain upper	6 (1.5)	7 (1.7)	13 (1.6)	3 (0.7)	1 (0.9)	1 (0.9)	2 (0.9)	5 (4.6)
Bursitis	6 (1.5)	7 (1.7)	13 (1.6)	2 (0.5)	0	1 (0.9)	1 (0.5)	2 (1.8)
Oropharyngeal pain	7 (1.7)	6 (1.5)	13 (1.6)	3 (0.7)	2 (1.9)	1 (0.9)	3 (1.4)	2 (1.8)
Type 2 diabetes mellitus	6 (1.5)	7 (1.7)	13 (1.6)	2 (0.5)	4 (3.8)	1 (0.9)	5 (2.3)	1 (0.9)
Blood glucose increased	6 (1.5)	6 (1.5)	12 (1.5)	5 (1.2)	3 (2.8)	3 (2.8)	6 (2.8)	1 (0.9)
Blood triglycerides increased	3 (0.7)	9 (2.2)	12 (1.5)	11 (2.7)	2 (1.9)	3 (2.8)	5 (2.3)	4 (3.7)
Blood urea increased	6 (1.5)	6 (1.5)	12 (1.5)	2 (0.5)	1 (0.9)	1 (0.9)	2 (0.9)	1 (0.9)
Musculoskeletal pain	6 (1.5)	6 (1.5)	12 (1.5)	15 (3.7)	3 (2.8)	1 (0.9)	4 (1.9)	3 (2.8)
Flank pain	7 (1.7)	4 (1.0)	11 (1.4)	5 (1.2)	0	0	0	1 (0.9)
Haematuria	6 (1.5)	5 (1.2)	11 (1.4)	2 (0.5)	1 (0.9)	0	1 (0.5)	3 (2.8)
Insomnia	8 (2.0)	3 (0.7)	11 (1.4)	7 (1.7)	2 (1.9)	3 (2.8)	5 (2.3)	2 (1.8)
Nephrolithiasis	2 (0.5)	9 (2.2)	11 (1.4)	5 (1.2)	1 (0.9)	2 (1.8)	3 (1.4)	4 (3.7)
Non-cardiac chest pain	9 (2.2)	2 (0.5)	11 (1.4)	6 (1.5)	1 (0.9)	3 (2.8)	4 (1.9)	1 (0.9)
Osteoarthritis	4 (1.0)	7 (1.7)	11 (1.4)	5 (1.2)	4 (3.8)	3 (2.8)	7 (3.3)	5 (4.6)
Gamma-glutamyltransferase increased	5 (1.2)	5 (1.2)	10 (1.2)	7 (1.7)	2 (1.9)	1 (0.9)	3 (1.4)	3 (2.8)
Gastroenteritis viral	5 (1.2)	5 (1.2)	10 (1.2)	5 (1.2)	2 (1.9)	1 (0.9)	3 (1.4)	0
Joint injury	3 (0.7)	6 (1.5)	9 (1.1)	3 (0.7)	0	0	0	2 (1.8)
Pruritus	6 (1.5)	3 (0.7)	9 (1.1)	0	1 (0.9)	0	1 (0.5)	0
Renal failure	3 (0.7)	6 (1.5)	9 (1.1)	4 (1.0)	1 (0.9)	0	1 (0.5)	2 (1.8)
Sinus congestion	5 (1.2)	4 (1.0)	9 (1.1)	5 (1.2)	4 (3.8)	0	4 (1.9)	0
Tooth abscess	4 (1.0)	5 (1.2)	9 (1.1)	4 (1.0)	0	0	0	0
Anxiety	5 (1.2)	3 (0.7)	8 (1.0)	3 (0.7)	2 (1.9)	2 (1.8)	4 (1.9)	0
Blood bicarbonate decreased	3 (0.7)	5 (1.2)	8 (1.0)	3 (0.7)	0	1 (0.9)	1 (0.5)	1 (0.9)
Dyspepsia	3 (0.7)	5 (1.2)	8 (1.0)	5 (1.2)	0	1 (0.9)	1 (0.5)	0
Erectile dysfunction	2 (0.5)	6 (1.5)	8 (1.0)	2 (0.5)	2 (1.9)	0	2 (0.9)	0
Joint swelling	3 (0.7)	5 (1.2)	8 (1.0)	0	1 (0.9)	0	1 (0.5)	3 (2.8)
Abdominal discomfort	3 (0.7)	4 (1.0)	7 (0.9)	1 (0.2)	1 (0.9)	2 (1.8)	3 (1.4)	0
Arthropod bite	2 (0.5)	5 (1.2)	7 (0.9)	4 (1.0)	0	1 (0.9)	1 (0.5)	2 (1.8)
Chills	2 (0.5)	5 (1.2)	7 (0.9)	7 (1.7)	0	2 (1.8)	2 (0.9)	1 (0.9)
Dehydration	4 (1.0)	3 (0.7)	7 (0.9)	1 (0.2)	0	2 (1.8)	2 (0.9)	1 (0.9)
Diabetes mellitus	5 (1.2)	2 (0.5)	7 (0.9)	1 (0.2)	2 (1.9)	1 (0.9)	3 (1.4)	1 (0.9)
Dyspnoea	5 (1.2)	2 (0.5)	7 (0.9)	6 (1.5)	0	1 (0.9)	1 (0.5)	2 (1.8)
Epistaxis	1 (0.2)	6 (1.5)	7 (0.9)	1 (0.2)	0	1 (0.9)	1 (0.5)	0
Excoriation	5 (1.2)	2 (0.5)	7 (0.9)	3 (0.7)	3 (2.8)	2 (1.8)	5 (2.3)	0
Laceration	2 (0.5)	5 (1.2)	7 (0.9)	4 (1.0)	4 (3.8)	8 (7.3)	12 (5.6)	4 (3.7)

Preferred Term [n (%)]	LESU 200 mg +ALLO (N=405)	LESU 400 mg +ALLO (N=401)	TOTAL LESU +ALLO (N=806)	PBO +ALLO (N=407)	LESU 200 mg +FBX (N=106)	LESU 400 mg +FBX (N=109)	TOTAL LESU +FBX (N=215)	PBO +FBX (N=109)
Nasal congestion	3 (0.7)	4 (1.0)	7 (0.9)	2 (0.5)	3 (2.8)	1 (0.9)	4 (1.9)	1 (0.9)
Angina pectoris	3 (0.7)	3 (0.7)	6 (0.7)	2 (0.5)	1 (0.9)	3 (2.8)	4 (1.9)	0
Arthritis	2 (0.5)	4 (1.0)	6 (0.7)	1 (0.2)	2 (1.9)	3 (2.8)	5 (2.3)	1 (0.9)
Cellulitis	1 (0.2)	5 (1.2)	6 (0.7)	6 (1.5)	0	3 (2.8)	3 (1.4)	1 (0.9)
Depression	3 (0.7)	3 (0.7)	6 (0.7)	3 (0.7)	3 (2.8)	2 (1.8)	5 (2.3)	1 (0.9)
Limb injury	5 (1.2)	1 (0.2)	6 (0.7)	3 (0.7)	1 (0.9)	3 (2.8)	4 (1.9)	1 (0.9)
Alanine aminotransferase increased	3 (0.7)	2 (0.5)	5 (0.6)	4 (1.0)	4 (3.8)	2 (1.8)	6 (2.8)	4 (3.7)
Aspartate aminotransferase increased	4 (1.0)	1 (0.2)	5 (0.6)	3 (0.7)	3 (2.8)	0	3 (1.4)	5 (4.6)
Blood amylase increased	4 (1.0)	1 (0.2)	5 (0.6)	3 (0.7)	1 (0.9)	2 (1.8)	3 (1.4)	1 (0.9)
Dental caries	1 (0.2)	4 (1.0)	5 (0.6)	4 (1.0)	0	3 (2.8)	3 (1.4)	0
Herpes zoster	3 (0.7)	2 (0.5)	5 (0.6)	1 (0.2)	2 (1.9)	0	2 (0.9)	0
Pneumonia	2 (0.5)	3 (0.7)	5 (0.6)	4 (1.0)	1 (0.9)	2 (1.8)	3 (1.4)	1 (0.9)
Tooth infection	2 (0.5)	3 (0.7)	5 (0.6)	4 (1.0)	0	3 (2.8)	3 (1.4)	1 (0.9)
Vision blurred	3 (0.7)	2 (0.5)	5 (0.6)	1 (0.2)	2 (1.9)	1 (0.9)	3 (1.4)	0
Hepatic steatosis	3 (0.7)	1 (0.2)	4 (0.5)	2 (0.5)	2 (1.9)	0	2 (0.9)	0
Vertigo	2 (0.5)	2 (0.5)	4 (0.5)	1 (0.2)	0	2 (1.8)	2 (0.9)	2 (1.8)
Dry mouth	2 (0.5)	1 (0.2)	3 (0.4)	4 (1.0)	1 (0.9)	2 (1.8)	3 (1.4)	0
Furuncle	1 (0.2)	2 (0.5)	3 (0.4)	0	0	2 (1.8)	2 (0.9)	0
Paraesthesia	2 (0.5)	1 (0.2)	3 (0.4)	0	3 (2.8)	1 (0.9)	4 (1.9)	2 (1.8)
Procedural pain	2 (0.5)	1 (0.2)	3 (0.4)	3 (0.7)	2 (1.9)	2 (1.8)	4 (1.9)	1 (0.9)
Seasonal allergy	0	3 (0.7)	3 (0.4)	5 (1.2)	2 (1.9)	1 (0.9)	3 (1.4)	2 (1.8)
Toothache	2 (0.5)	1 (0.2)	3 (0.4)	4 (1.0)	1 (0.9)	3 (2.8)	4 (1.9)	0
Viral upper respiratory tract infection	2 (0.5)	1 (0.2)	3 (0.4)	2 (0.5)	2 (1.9)	0	2 (0.9)	0
Cataract	1 (0.2)	1 (0.2)	2 (0.2)	1 (0.2)	2 (1.9)	0	2 (0.9)	1 (0.9)
Flatulence	1 (0.2)	1 (0.2)	2 (0.2)	0	0	2 (1.8)	2 (0.9)	0
Hyperlipidaemia	0	2 (0.5)	2 (0.2)	2 (0.5)	2 (1.9)	0	2 (0.9)	2 (1.8)
Influenza like illness	2 (0.5)	0	2 (0.2)	3 (0.7)	0	2 (1.8)	2 (0.9)	4 (3.7)
Local swelling	1 (0.2)	1 (0.2)	2 (0.2)	2 (0.5)	2 (1.9)	0	2 (0.9)	0
Localised infection	2 (0.5)	0	2 (0.2)	0	2 (1.9)	0	2 (0.9)	1 (0.9)
Otitis media	0	2 (0.5)	2 (0.2)	0	2 (1.9)	0	2 (0.9)	0
Plantar fasciitis	2 (0.5)	0	2 (0.2)	0	1 (0.9)	2 (1.8)	3 (1.4)	0
Sciatica	1 (0.2)	1 (0.2)	2 (0.2)	5 (1.2)	2 (1.9)	1 (0.9)	3 (1.4)	2 (1.8)
Tinnitus	1 (0.2)	1 (0.2)	2 (0.2)	2 (0.5)	2 (1.9)	0	2 (0.9)	0
Dermatitis allergic	0	1 (0.2)	1 (0.1)	1 (0.2)	1 (0.9)	2 (1.8)	3 (1.4)	1 (0.9)
Leukocytosis	1 (0.2)	0	1 (0.1)	3 (0.7)	2 (1.9)	0	2 (0.9)	1 (0.9)
Liver function test abnormal	1 (0.2)	0	1 (0.1)	4 (1.0)	1 (0.9)	2 (1.8)	3 (1.4)	2 (1.8)
Scratch	1 (0.2)	0	1 (0.1)	0	2 (1.9)	0	2 (0.9)	0
Tendon pain	1 (0.2)	0	1 (0.1)	1 (0.2)	0	2 (1.8)	2 (0.9)	1 (0.9)
Thermal burn	0	1 (0.2)	1 (0.1)	0	0	2 (1.8)	2 (0.9)	1 (0.9)
C-reactive protein increased	0	0	0	1 (0.2)	2 (1.9)	1 (0.9)	3 (1.4)	0
Dyslipidaemia	0	0	0	0	0	3 (2.8)	3 (1.4)	1 (0.9)
Exostosis	0	0	0	0	0	2 (1.8)	2 (0.9)	0
Hyperkalaemia	0	0	0	3 (0.7)	1 (0.9)	2 (1.8)	3 (1.4)	1 (0.9)
Muscle atrophy	0	0	0	0	0	2 (1.8)	2 (0.9)	0

Note: XOI, xanthine oxidase inhibitor (allopurinol/febuxostat); LESU, lesinurad; ALLO, allopurinol; FBX, febuxostat; PBO, placebo. Analysis Group A1A and A1B: Studies RDEA594-301, RDEA594-302 and RDEA594-304. Adverse events are treatment-emergent events and coded using MedDRA version 14.0. For each system organ class (SOC) and preferred term (PT), subjects are included only once, even if they experienced multiple events in that SOC or PT.

Adverse events by allopurinol dose

The table below summarizes the incidence of AEs for the overall study population in study 301 and 302 and for 2 allopurinol dose subgroups. The subgroup of subjects who received allopurinol >300 mg and the subgroup of subjects with renal function-adjusted high-dose allopurinol are defined in the table footnotes. In both subgroups, the incidence of any AE in the lesinurad 200 mg + allopurinol group was comparable to the placebo + allopurinol group: 87.1% versus 89.3% for subjects with a Baseline allopurinol dose >300 mg and 85.2% versus 79.5% for subjects with renal function adjusted high-dose allopurinol. In these subgroups, the incidences of Infections and Infestations AEs and of Gastrointestinal Disorders AEs were higher in the lesinurad 200 mg + allopurinol group than in the placebo + allopurinol group; however, interpretation is limited due to the small sample size.

Table 27 Treatment-emergent adverse events by System Organ Class and allopurinol dose subgroup (Studies 301 and 302 pooled)

System Organ Class	Subject Population	PBO +ALLO n (%)	LESU 200 mg + ALLO n (%)
Sample size	Overall ALLO Population	407	405
	Baseline ALLO >300 mg	28	31
	Renal Function Adjusted High Dose ALLO [a]	73	81
Any adverse event	Overall ALLO Population	284 (69.8)	299 (73.8)
	Baseline ALLO >300 mg	25 (89.3)	27 (87.1)
	Renal Function Adjusted High Dose ALLO [a]	58 (79.5)	69 (85.2)
Blood and lymphatic system disorders	Overall ALLO Population	8 (2.0)	5 (1.2)
	Baseline ALLO >300 mg	0	0
	Renal Function Adjusted High Dose ALLO [a]	2 (2.7)	2 (2.5)
Cardiac disorders	Overall ALLO Population	16 (3.9)	12 (3.0)
	Baseline ALLO >300 mg	2 (7.1)	1 (3.2)
	Renal Function Adjusted High Dose ALLO [a]	6 (8.2)	7 (8.6)
Gastrointestinal disorders	Overall ALLO Population	65 (16.0)	75 (18.5)
	Baseline ALLO >300 mg	7 (25.0)	12 (38.7)
	Renal Function Adjusted High Dose ALLO [a]	15 (20.5)	23 (28.4)
Infections and infestations	Overall ALLO Population	137 (33.7)	159 (39.3)
	Baseline ALLO >300 mg	11 (39.3)	18 (58.1)
	Renal Function Adjusted High Dose ALLO [a]	26 (35.6)	40 (49.4)
Investigations	Overall ALLO Population	66 (16.2)	59 (14.6)
	Baseline ALLO >300 mg	5 (17.9)	4 (12.9)
	Renal Function Adjusted High Dose ALLO [a]	14 (19.2)	13 (16.0)
Hepatobiliary disorders	Overall ALLO Population	4 (1.0)	6 (1.5)
	Baseline ALLO >300 mg	0	0
	Renal Function Adjusted High Dose ALLO [a]	0	0
Renal and urinary disorders	Overall ALLO Population	2[illegible] (4.9)	16 (4.0)
	Baseline ALLO >300 mg	3 (10.7)	1 (3.2)
	Renal Function Adjusted High Dose ALLO [a]	(8.2)	5 (6.2)
Vascular disorders	Overall ALLO Population	23 (5.7)	32 (7.9)
	Baseline ALLO >300 mg	2 (7.1)	1 (3.2)
	Renal Function Adjusted High Dose ALLO [a]	9 (12.3)	5 (6.2)

Adverse events are treatment-emergent and coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 14.0. For each SOC within each subgroup population, subjects are included only once, even if they experienced multiple events in that SOC.

a) Subjects with a high renal function adjusted Baseline allopurinol dose are defined as subjects with Baseline allopurinol dose >300 mg for Day -7 estimated creatinine clearance (eCrCl) ≥60 mL/min or Baseline allopurinol dose >200 mg for Day -7 eCrCl <60 mL/min.

ALLO = allopurinol; LESU = lesinurad; n = number of subjects, PBO = placebo; SOC = System Organ Class.

AEs in in Phase 1 FDC studies

Study 501

No deaths or other serious adverse events (SAEs) were reported. Three subjects were withdrawn from the study due to adverse events (AEs; 1 due to erythema, 1 due to neutropenia, and 1 due to diabetes mellitus).

Study 503

No deaths, other SAEs, AEs leading to withdrawal, or other significant AEs of interest were reported during the study.

ALLO-101

There were no deaths or other SAEs reported and no AEs related to allopurinol reported. One AE (clavicle fracture) that led to withdrawal of study medication and study discontinuation was reported.

Renal safety

The incidence of renal events (i.e., sCr elevations and renal-related AEs) in patient groups treated with lesinurad 200 mg in combination with allopurinol and placebo + allopurinol are summarized in the table below.

Table 28 Incidence of renal safety events by category (Studies 301 and 302 pooled)

Event Category [n (%)]	PBO + ALLO (N = 407) n (%)	LESU 200 mg + ALLO (N = 405) n (%)
Any renal-related AE	17 (4.2)	20 (4.9)
Renal-related AE leading to discontinuation of PBO or LESU	4 (1.0)	4 (1.0)
Renal-related SAE	1 (0.2)	0
Any kidney stone AE	5 (1.2)	2 (0.5)
Kidney stone AE leading to discontinuation of PBO or LESU	1 (0.2)	1 (0.2)
Kidney stone SAE	0	0
sCr elevation ≥1.5 to <2.0 × Baseline	9 (2.2)	18 (4.4)
Fraction resolved [a] by end of study	6/9 (66.7)	16/18 (88.9)
sCr elevation ≥2.0 × Baseline	0	6 (1.5)
Fraction resolved [a] by end of study	N/A	6/6 (100.0)

Adverse events were classified as renal-related or kidney stone Aes as prespecified by the sponsor. Baseline sCr was defined as the highest sCr value recorded ≤14 days prior to first dose of randomized study medication.

a) Returned to ≤1.2 × Baseline.

AE = adverse event; ALLO = allopurinol; LESU = lesinurad; N = total number of subjects; n = number of subjects meeting criterion; N/A = not applicable; PBO = placebo; SAE = serious adverse event; sCr = serum creatinine.

The most common renal-related preferred term (PT) was blood creatinine increased, with a 2.2% incidence in the placebo + allopurinol group and 3.7% in the lesinurad 200 mg + allopurinol group.

Long-term renal safety

Safety information from extension Study 306 revealed no new findings with respect to renal safety. Incidences of renal-related TEAEs are shown in the table below. The incidence of renal-related TEAEs was 13.0% in the total lesinurad 200 mg + allopurinol group. Blood creatinine increased was the most frequently reported renal-related TEAE.

Table 29 Incidence of treatment-emergent Renal-related Adverse Events by preferred term

Preferred Term	LESU 200 mg + ALLO CROSS (N=122) n (%)	LESU 200 mg + ALLO CONT (N=240) n (%)	LESU 200 mg + ALLO Total (N=362) n (%)	LESU 400 mg + ALLO CROSS (N=122) n (%)	LESU 400 mg + ALLO CONT (N=232) n (%)	LESU 400 mg + ALLO Total (N=354) n (%)
Any renal-related TEAE	15 (12.3)	32 (13.3)	47 (13.0)	22 (18.0)	39 (16.8)	61 (17.2)
Blood creatinine increased	13 (10.7)	24 (10.0)	37 (10.2)	14 (11.5)	29 (12.5)	43 (12.1)
Renal failure acute	1 (0.8)	3 (1.3)	4 (1.1)	5 (4.1)	4 (1.7)	9 (2.5)
Blood urea increased	2 (1.6)	2 (0.8)	4 (1.1)	1 (0.8)	6 (2.6)	7 (2.0)
Creatinine renal clearance decreased	0	4 (1.7)	4 (1.1)	1 (0.8)	3 (1.3)	4 (1.1)
Renal failure	0	1 (0.4)	1 (0.3)	1 (0.8)	2 (0.9)	3 (0.8)
Renal impairment	0	0	0	2 (1.6)	1 (0.4)	3 (0.8)
Renal failure chronic	1 (0.8)	0	1 (0.3)	0	1 (0.4)	1 (0.3)
Glomerular filtration rate decreased	0	1 (0.4)	1 (0.3)	0	0	0
Nephropathy	0	0	0	0	1 (0.4)	1 (0.3)
Oliguria	0	0	0	1 (0.8)	0	1 (0.3)
Any renal-related SAE	0	3 (1.3)	3 (0.8)	4 (3.3)	2 (0.9)	6 (1.7)
Renal failure acute	0	3 (1.3)	3 (0.8)	4 (3.3)	2 (0.9)	6 (1.7)
Nephropathy	0	0	0	0	1 (0.4)	1 (0.3)
Any renal-related TEAE leading to study withdrawal	1 (0.8)	6 (2.5)	7 (1.9)	3 (2.5)	8 (3.4)	11 (3.1)
Blood creatinine increased	0	4 (1.7)	4 (1.1)	1 (0.8)	6 (2.6)	7 (2.0)
Renal failure acute	0	1 (0.4)	1 (0.3)	2 (1.6)	1 (0.4)	3 (0.8)
Blood urea increased	0	0	0	0	1 (0.4)	1 (0.3)
Creatinine renal clearance decreased	0	1 (0.4)	1 (0.3)	0	1 (0.4)	1 (0.3)
Glomerular filtration rate decreased	0	1 (0.4)	1 (0.3)	0	0	0

Abbreviations: ALLO, allopurinol; CONT, continuation of treatment; CROSS, crossover treatment; LESU, lesinurad; SAE, serious adverse event; TEAE, treatment-emergent-adverse event.
Note: Treatment-emergent adverse events are those that started on or after the first lesinurad dose date in extension study, or those that started prior to the first lesinurad dose date but worsened during the extension study 306. Adverse events are coded using Medical Dictionary for Regulatory Activities Version 14.0. For each renal term category and preferred term (PT), subjects are included only once, even if they experienced multiple events in that category or PT. Renal-related adverse event preferred terms were pre-specified and listed in the

Final exposure-adjusted incidence rates for renal events as well as core + extension data through 15 May 2015 (interim analysis) are compared to data with data cut-off 04 November 2015 in the table below.

Table 30 Exposure-adjusted incidence rates for renal events: Lesinurad MAA cutoff, 2015 updated analysis, and final data (Studies 301, 302 and 306)

Category	LESU 200 mg + ALLO Lesinurad MAA (N = 526; PYE = 495.6) n (Rate)	LESU 200 mg + ALLO 2015 Interim Analysis (N = 527; PYE = 742.5) n (Rate)	LESU 200 mg + ALLO Final Analysis (N = 527; PYE = 994.5) n (Rate)
Renal-related adverse event [a]	35 (7.1)	60 (8.1)	70 (7.0)
Kidney stone adverse event [a]	4 (0.8)	5 (0.7)	8 (0.8)
Serum creatinine elevation [b]			
≥1.5 × Baseline	39 (7.9)	60 (8.1)	71 (7.1)
≥2.0 × Baseline	10 (2.0)	19 (2.6)	23 (2.3)
≥3.0 × Baseline	5 (1.0)	7 (0.9)	8 (0.8)

For each event, subjects are included only once, even if they experienced multiple events in that category. Exposure-adjusted incidence rates are expressed as subjects with events per 100 person-years of exposure.

a) Comprehensive custom renal-related and kidney stone preferred term lists were pre-specified for use in the lesinurad Phase 3 studies.

b) Elevation categories are nested; i.e., the ≥1.5 × Baseline category includes all elevations ≥1.5, ≥2.0, or ≥3.0 × Baseline, and the ≥2.0 × Baseline category includes all elevations ≥2.0 or ≥3.0 × Baseline. Baseline is defined as the highest serum creatinine value recorded ≥14 days prior to the first dose of lesinurad, whether in the Core Study or the Extension Study.

ALLO = allopurinol; LESU = lesinurad; MAA = Marketing Authorisation Application; N = total number of subjects; n = number of subjects meeting criterion; PYE = person-years of exposure.

The resolution rates for SCr elevations are summarized in the table below. A resolution was defined in the protocol as a sCr value ≤ 1.2 × lesinurad baseline following an elevation.

Table 31 Resolution rates for SCr elevations in Studies 301, 302 and 306

	Core Treatment Group			Core Treatment Group			Core Treatment Group		
Variable	LESU 200 mg +ALLO (N=405)	PBO +ALLO (N=122)	TOTAL LESU 200 mg +ALLO (N=527)	LESU 400 mg +ALLO (N=401)	PBO +ALLO (N=122)	TOTAL LESU 400 mg +ALLO (N=523)	LESU +ALLO (N=806)	PBO +ALLO (N=244)	TOTAL LESU +ALLO (N=1050)
Number of subjects with									
No elevation	358 (88.4)	109 (89.3)	467 (88.6)	300 (74.8)	91 (74.6)	391 (74.8)	658 (81.6)	200 (82.0)	858 (81.7)
At least one elevation	47 (11.6)	13 (10.7)	60 (11.4)	101 (25.2)	31 (25.4)	132 (25.2)	148 (18.4)	44 (18.0)	192 (18.3)
1 elevation	37 (9.1)	10 (8.2)	47 (8.9)	67 (16.7)	26 (21.3)	93 (17.8)	104 (12.9)	36 (14.8)	140 (13.3)
2 elevations	7 (1.7)	3 (2.5)	10 (1.9)	26 (6.5)	4 (3.3)	30 (5.7)	33 (4.1)	7 (2.9)	40 (3.8)
>2 elevations	3 (0.7)	0	3 (0.6)	8 (2.0)	1 (0.8)	9 (1.7)	11 (1.4)	1 (0.4)	12 (1.1)
Total number of elevations	60	16	76	147	37	184	207	53	260
Total number and peroent of resolutions[a]	55/60 (91.7)	13/16 (81.3)	68/76 (89.5)	129/147 (87.8)	30/37 (81.1)	159/184 (86.4)	184/207 (88.9)	43/53 (81.1)	227/260 (87.3)
Number (%) of resolutions after an interruption of randomized study medication	15/60 (25.0)	4/16 (25.0)	19/76 (25.0)	29/147 (19.7)	11/37 (29.7)	40/184 (21.7)	44/207 (21.3)	15/53 (28.3)	59/260 (22.7)
Number (%) of resolutions without an interruption of randomized study medication	40/60 (66.7)	9/16 (56.3)	49/76 (64.5)	100/147 (68.0)	19/37 (51.4)	119/184 (64.7)	140/207 (67.6)	28/53 (52.8)	168/260 (64.6)
Time to resolution (days)	N=60	N=16	N=76	N=147	N=37	N=184	N=207	N=53	N=260
1 - 14	15 (25.0)	1 (6.3)	16 (21.1)	29 (19.7)	7 (18.9)	36 (19.6)	44 (21.3)	8 (15.1)	52 (20.0)
> 14 - 28	10 (16.7)	2 (12.5)	12 (15.8)	29 (19.7)	10 (27.0)	39 (21.2)	39 (18.8)	12 (22.6)	51 (19.6)
> 28 - 56	17 (28.3)	5 (31.3)	22 (28.9)	34 (23.1)	5 (13.5)	39 (21.2)	51 (24.6)	10 (18.9)	61 (23.5)
> 56 - 84	5 (8.3)	1 (6.3)	6 (7.9)	17 (11.6)	3 (8.1)	20 (10.9)	22 (10.6)	4 (7.5)	26 (10.0)
> 84	8 (13.3)	4 (25.0)	12 (15.8)	20 (13.6)	5 (13.5)	25 (13.6)	28 (13.5)	9 (17.0)	37 (14.2)
Unresolved at last study assessment	5 (8.3)	3 (18.8)	8 (10.5)	18 (12.2)	7 (18.9)	25 (13.6)	23 (11.1)	10 (18.9)	33 (12.7)

Note: XOI, xanthine oxidase inhibitor (allopurinol/febuxostat); ALLO, allopurinol; LESU, lesinurad; PBO, placebo; sCr, serum creatinine. Analysis Group A1A: Studies RDEA594-301, RDEA594-302 with Extension Study RDEA594-306. [a] Resolution is defined as a serum creatinine value that is ≤ 1.2 x Baseline following an elevation. A subject remains elevated until a resolution is observed. Denominators are the total number of elevations in each group. Baseline is defined as the highest serum creatinine value recorded ≤ 14 days prior to the first dose of lesinurad in either the Core period/study or the Extension Period/study.

Cardiovascular safety

An independent, external Cardiovascular Endpoints Adjudication Committee (CEAC), blinded to study treatment, assessed whether potential cardiovascular events met criteria for a MACE (i.e., cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke) or a non-MACE cardiovascular AE (e.g., arrhythmias, hospitalization for heart failure, or unstable angina). The incidence and exposure-adjusted incidence of adjudicated MACE in the placebo + allopurinol and lesinurad 200 mg + allopurinol groups are summarized in the table below.

Table 32 Exposure-adjusted incidence of adjudicated MACE (Studies 301 and 302 pooled)

Event category	PBO + ALLO (N = 407; PYE = 332.3) n (rate)	LESU 200 mg + ALLO (N = 405; PYE = 329.6) n (rate)
Any CEAC-adjudicated MACE	2 (0.60)	2 (0.61)
Cardiovascular death	0	1 (0.30)
Nonfatal myocardial infarction	1 (0.30)	1 (0.30)
Nonfatal stroke	2 (0.60)	0

ALLO = allopurinol; CEAC = Cardiovascular Endpoints Adjudication Committee; LESU = lesinurad; MACE = Major Adverse Cardiovascular Event; N = number of subjects; n = number of subjects with events; PBO = placebo; PYE = person-years of exposure.

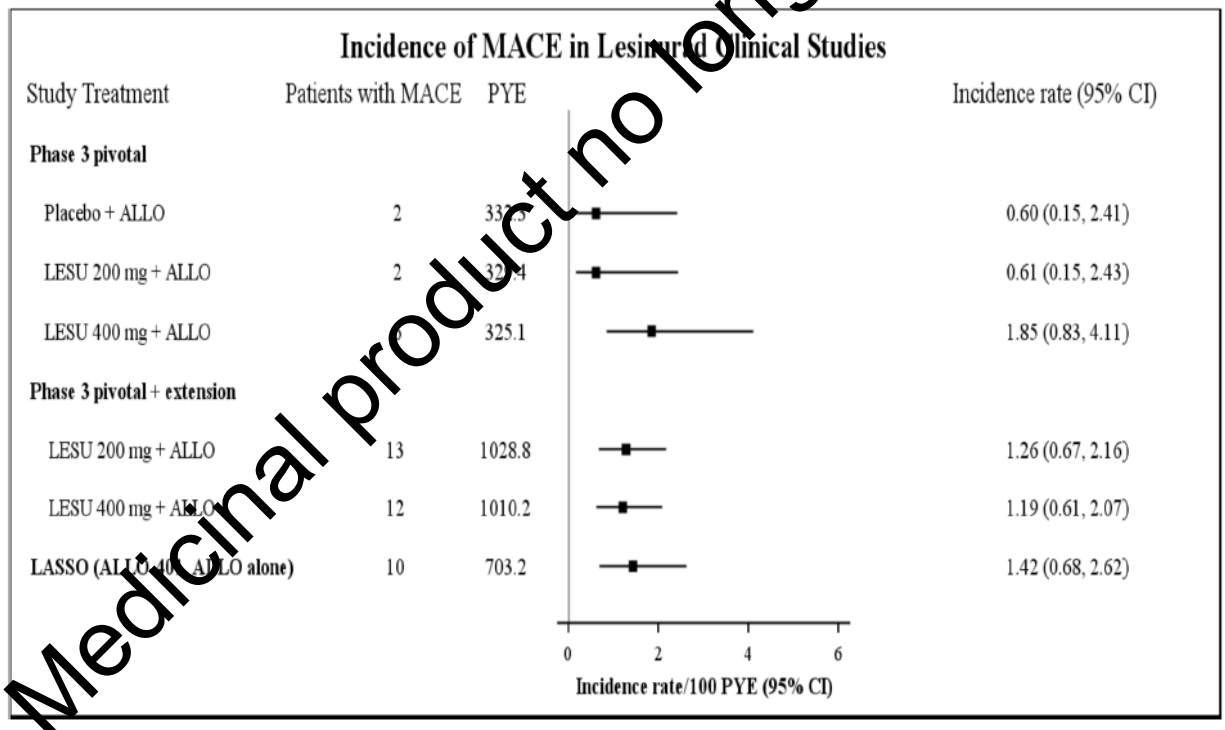
In studies 301, 302 and 304 pooled, the incidence of MACE was 3 (0.6%), 4 (0.8%), and 8 (1.6%) in the placebo + XOI, lesinurad 200 mg + XOI, and lesinurad 400 mg + XOI groups, respectively. The incidences of patients with adjudicated MACE per 100 PYE were 0.71 (95% CI 0.23, 2.21) for placebo,

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 an XOI.

A causal relationship with lesinurad has not been established. All patients with a MACE treated with lesinurad 200 mg had a history of heart failure, stroke, or myocardial infarction. Post-hoc analyses in a subgroup of patients with high cardiovascular risk at baseline (as defined by transient ischemic attack, angina pectoris, heart failure, myocardial infarction, peripheral vascular disease and/or stroke) showed that the incidence of MACE was 1/52 for placebo and 4/53 for lesinurad 200 mg, when used in combination with an XOI.

Long-term cardiovascular safety

Safety information from extension Study 306 revealed no new findings with respect to cardiovascular safety, including exposure-adjusted MACE rates. In the figure below, core + extension study data through completion of the study are compared to data from pivotal Studies 301 and 302, and to data from 1732 allopurinol-treated patients who were followed for 6 months in the open-label prospective LASSO study (ALLO-401; published by Becker et al. 2015), which had similar entry criteria and utilized prospective adjudication of MACE by the same CEAC that was used in the lesinurad phase 3 program. In ALLO-401, allopurinol was dosed at the discretion of the investigator, according to the local product label, to achieve an optimal, medically-appropriate dose of at least 200 mg daily for each subject. Investigators were encouraged to increase the dose of allopurinol to reach a target sUA of <6 mg/dL.



Pivotal + Extension results include data from Studies 301, 302, 306 (final data).

The CIs for the Phase 3 pivotal study data were calculated using Poisson regression. The CIs for the Phase 3 Pivotal + Extension data were calculated using the Poisson Exact method.

CI = confidence interval; LASSO = Study ALLO-401; LESU = lesinurad; MACE = major adverse cardiovascular event; PYE = person-years of exposure.

Figure 15 Exposure-adjusted MACE rates (Studies 301, 302, 306 and LASSO study)

Serious adverse event / deaths / other significant events

Among the subjects treated with lesinurad 200 mg + allopurinol group in the core studies, the most commonly reported SAEs were pneumonia (0.5% [2 subjects] in LESU 200mg + allopurinol vs. 0.2% [1 subject] in allopurinol+ placebo, respectively), coronary artery disease (0.5% incidence vs. 0% for allopurinol + placebo), and non-cardiac chest pain (0.5% vs. 0.2%, respectively).

In the study 306, 161 SAEs were reported in 93 of 716 subjects.

Table 33 SAEs in > 1% of subjects in either total treatment group by System Organ Class and preferred term

	LESU 200 mg + ALLO			LESU 400 mg + ALLO			All Extension Subjects (N= 716) n (%)
System Organ Class Preferred Term	CROSS (N=122) n (%)	CONT (N= 240) n (%)	Total (N= 362) n (%)	CROSS (N= 122) n (%)	CONT (N= 232) n (%)	Total (N= 354) n (%)	
Any serious treatment-emergent adverse event	19 (15.6)	29 (12.1)	48 (13.3)	19 (15.6)	26 (11.2)	45 (12.7)	93 (13.0)
Infections and infestations	3 (2.5)	10 (4.2)	13 (3.6)	1 (0.8)	3 (1.3)	4 (1.1)	17 (2.4)
Pneumonia	1 (0.8)	4 (1.7)	5 (1.4)	0	0		5 (0.7)
Renal and urinary disorders	2 (1.6)	3 (1.3)	5 (1.4)	5 (4.1)	3 (1.3)	8 (2.3)	13 (1.8)
Renal failure acute	0	3 (1.3)	3 (0.8)	5 (4.1)	3 (1.3)	8 (2.3)	11 (1.5)

Moreover a few SAEs within the SOC of Cardiac disorders have been reported including myocardial infarction and cardiac failure.

Table 34 SAEs within the SOC of Cardiac disorders

	LESU 200 mg + ALLO Extension Subjects by Therapy in Core Study			LESU 400 mg + ALLO Extension Subjects by Therapy in Core Study			
System Organ Class Preferred Term	PBO + ALLO (N=122) n (%)	LESU 400 mg + ALLO (N=240) n (%)	Total (N=362) n (%)	PBO + ALLO (N=122) n (%)	LESU 400 mg + ALLO (N=232) n (%)	Total (N=354) n (%)	All Extension Subjects (N=716) n (%)
Cardiac disorders	5 (4.1)	8 (3.3)	13 (3.6)	3 (2.5)	4 (1.7)	7 (2.0)	20 (2.8)
Acute myocardial infarction	1 (0.8)	1 (0.4)	2 (0.6)	0	2 (0.9)	2 (0.6)	4 (0.6)
Cardiac failure congestive	0	2 (0.8)	2 (0.6)	2 (1.6)	0	2 (0.6)	4 (0.6)
Coronary artery disease	0	1 (0.4)	1 (0.3)	1 (0.8)	2 (0.9)	3 (0.8)	4 (0.6)
Atrial fibrillation	1 (0.8)	1 (0.4)	2 (0.6)	0	1 (0.4)	1 (0.3)	3 (0.4)
Myocardial infarction	0	2 (0.8)	2 (0.6)	0	0	0	2 (0.3)
Angina pectoris	0	1 (0.4)	1 (0.3)	0	0	0	1 (0.1)
Angina unstable	0	1 (0.4)	1 (0.3)	0	0	0	1 (0.1)
Aortic valve stenosis	0	0	0	1 (0.8)	0	1 (0.3)	1 (0.1)
Atrial flutter	1 (0.8)	0	1 (0.3)	0	0	0	1 (0.1)
Hypertensive heart disease	1 (0.8)	0	1 (0.3)	0	0	0	1 (0.1)
Ischaemic cardiomyopathy	1 (0.8)	0	1 (0.3)	0	0	0	1 (0.1)
Myocardial ischaemia	1 (0.8)	0	1 (0.3)	0	0	0	1 (0.1)
Myocarditis	0	1 (0.4)	1 (0.3)	0	0	0	1 (0.1)

Note: ALLO = allopurinol, LESU = lesinurad, PBO = placebo. Treatment-emergent adverse events are those that started on or after the first lesinurad dose date in the core study, or those that started prior to the first lesinurad dose date but worsened during the extension study 306. Gout flares were captured via an electronic diary and recorded as an adverse event only if it met the definition of a serious adverse event. Adverse events are coded using MedDRA version 20.0. For each system organ class (SOC) and preferred term (PT), subjects are included only once, even if they experienced multiple events in that SOC or PT.

Deaths

Across all Phase 3 studies in the program, the deaths (n=13) were primarily cardiovascular-related (n=11), however, none were considered to be treatment related by the CEAC. All fatal MACE cases were on active treatment, 6 during the Phase 3 placebo-controlled studies, 5 during the Phase 3 uncontrolled extension studies, and 2 in Phase 1/2 studies. The remaining 2 deaths were due to suicide (one subject following participation in a Phase 1 study) and gastric cancer (one subject in Study 306).

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 by the Investigator or the Sponsor to be related to treatment with lesinurad and allopurinol.

In study 306, 4 deaths reported since the data cutoff date for the second interim CSR (15 May 2015) and included sudden death due to cardiac arrest (n=1), haemorrhagic stroke (n=1), myocardial infarction (n=2). All of these cases were white males, aged between 51 to 73 years. No deaths were considered by the Investigator to be related to lesinurad and allopurinol.

Laboratory findings

No clinically relevant changes from baseline were reported for lesinurad 200 mg in combination with allopurinol with respect to any vital signs, haematology, clinical chemistry parameters, with the exception of renal parameters.

Based upon the known hepatic toxicities associated with XOIs, extensive evaluations of hepatic function were performed in the lesinurad clinical development program; these evaluations showed no evidence of hepatic toxicity associated with the use of lesinurad alone or in combination with an XOI.

In the extension Study 306, no new laboratory findings were observed with longer exposure. Clinical safety laboratory values (hematology, serum chemistries including liver function tests, and urinalysis) over time were generally similar across treatment groups. No notable mean or median changes from lesinurad baseline in the laboratory values were observed across the groups. No subject met the Hy's law definition of hepatic toxicity.

There were no safety concerns for any of the serum chemistry, hematology, urinalysis, or coagulation parameters that were assessed in studies ALLO-101, 501 or 503.

Vital signs

In the pooled core studies, no notable differences were reported for blood pressure and heart rate at routine monitoring. In study 306, following long-term treatment with lesinurad, the mean changes from baseline to last value for all vital signs evaluated (systolic and diastolic blood pressure, pulse rate, respiratory rate, and temperature) were small and comparable across treatment groups (data not shown). Among the small subset of subjects with ECG interval data, there were no clinically significant findings for heart rate, PR interval, QRS duration, or QT/QTcF.

No clinically significant findings in any vital signs or physical examinations were reported in studies ALLO-101, 501 or 503.

Safety in special populations

For the subgroup of subjects with moderate renal impairment at baseline (CrCl < 60 mL/min), a higher rate of TEAEs compared to the rates were observed in the overall population for studies 301, 302 and 304.

Table 35 Incidence of TEAEs in basline renal function groups (Studies 301, 302 and 304 pooled)

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)	310	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)

Similarly, in study 306 in subjects with eCrCl < 60 ml/min and <45 ml /min the incidence of TEAEs, SAEs and withdrawals were higher in patients continued lesinurad 200 mg + allopurinol treatment compared to patients who crossed over from placebo + allopurinol to lesinurad 200 mg + allopurinol arm.

Table 36 Summary of treatment-emergent adverse event by lesinurad baseline renal function subgroups and overall population

	Creatinine Clearance Category	LESU 200 mg + ALLO			LESU 400 mg + ALLO		
		CROSS n/N(%)	CONT n/N (%)	TOTAL n/N (%)	CROSS n/N(%)	CONT n/N (%)	TOTAL n/N (%)
TEAE							
	Overall	86/122 (70.5)	175/240 (72.9)	261/362 (72.1)	87/122 (71.3)	175/232 (75.4)	262/354 (74.0)
	< 90 mL/min	48/70 (68.6)	99/136 (72.8)	147/206 (71.4)	49/74 (66.2)	98/129 (76.0)	147/203 (72.4)
	< 60 mL/min	12/18 (66.7)	30/40 (75.0)	42/58 (72.4)	16/21 (76.2)	29/36 (80.6)	45/57 (78.9)
	< 45 mL/min	4/6 (66.7)	10/11 (90.9)	14/17 (82.4)	6/8 (75.0)	11/12 (91.7)	17/20 (85.0)
SAE							
	Overall	14/122 (11.5)	21/240 (8.8)	35/362 (9.7)	17/122 (13.9)	17/232 (7.3)	34/354 (9.6)
	< 90 mL/min	8/70 (11.4)	16/136 (11.8)	24/206 (11.7)	13/74 (17.6)	7/129 (5.4)	20/203 (9.9)
	< 60 mL/min	2/18 (11.1)	6/40 (15.0)	8/58 (13.8)	8/21 (38.1)	5/36 (13.9)	13/57 (22.8)
	< 45 mL/min	0/6	2/11 (18.2)	2/17 (11.8)	4/8 (50.0)	1/12 (8.3)	5/20 (25.0)
AE Leading to Withdrawal							
	Overall	9/122 (7.4)	15/240 (6.3)	24/362 (6.6)	10/122 (8.2)	17/232 (7.3)	27/354 (7.6)
	< 90 mL/min	3/70 (4.3)	14/136 (10.3)	17/206 (8.3)	6/74 (8.1)	8/129 (6.2)	14/203 (6.9)
	< 60 mL/min	0/18	7/40 (17.5)	7/58 (12.1)	2/21 (9.5)	4/36 (11.1)	6/57 (10.5)
	< 45 mL/min	0/6	4/11 (36.4)	4/17 (23.5)	1/8 (12.5)	1/12 (8.3)	2/20 (10.0)

Abbreviations: AE, adverse event; ALLO, allopurinol; CONT, continuation of treatment; CROSS, crossover of treatment; LESU, lesinurad, SAE, serious adverse event; TEAE, treatment-emergent adverse event.
Note: TEAEs are those that started on or after the first lesinurad dose date in extension study, or those that started prior to the first lesinurad dose date but worsened during the extension study 306. Gout flares were captured via an electronic diary and recorded as an adverse event only if each met the definition of a SAE. For each category, subjects are included only once, even if they experienced multiple events in that category. Lesinurad Baseline eCrCl is calculated using the highest serum creatinine value recorded ≤ 10 days prior to the first dose of lesinurad. Subjects who discontinued lesinurad were required to discontinue the study.

The incidence of renal-related AEs in baseline renal function subgroups in core studies 302, 302 and 304 and in subjects with mild to moderate baseline renal impairment in study 306 are summarized in the tables below:

Table 37 Incidence of renal-related treatment-emergent adverse events in the pivotal phase 3 studies by subgroup (12-month studies 301, 302 and 304)

Category	PBO +XOI		LESU 200 mg +XOI		LESU 400 mg +XOI		TOTAL LESU +XOI	
	n/N	(%)	n/N	(%)	n/N	(%)	n/N	(%)
All subjects	23/516	(4.5%)	29/511	(5.7%)	60/510	(11.8%)	89/1021	(8.7%)
Age								
< 65	15/443	(3.4%)	23/454	(5.1%)	50/433	(11.5%)	73/887	(8.2%)
≥ 65	8/73	(11.0%)	6/57	(10.5%)	10/77	(13.0%)	16/134	(11.9%)
Sex								
Male	23/492	(4.7%)	28/489	(5.7%)	55/482	(11.4%)	83/971	(8.5%)
Female	0/24	-	1/22	(4.5%)	5/28	(17.9%)	6/50	(12.0%)
Baseline eCrCl category								
≥ 90 mL/min	1/180	(0.6%)	8/200	(4.0%)	18/203	(8.9%)	26/403	(6.5%)
< 90 mL/min	22/334	(6.6%)	21/310	(6.8%)	41/305	(13.4%)	62/615	(10.1%)
≥ 60 mL/min	9/409	(2.2%)	16/408	(3.9%)	44/416	(10.6%)	60/824	(7.3%)
< 60 mL/min	14/105	(13.3%)	13/102	(12.7%)	15/92	(16.3%)	28/194	(14.4%)
Tophus status at Screening								
Present	11/183	(6.0%)	15/184	(8.2%)	23/185	(12.4%)	38/369	(10.3%)
Absent	12/333	(3.6%)	14/327	(4.3%)	37/325	(11.4%)	51/652	(7.8%)

Abbreviations: ALLO, allopurinol; eCrCl, estimated creatinine clearance; LESU, lesinurad; PBO, placebo; sCr, serum creatinine; XOI, xanthine oxidase inhibitor (allopurinol/febuxostat).
[a] Baseline is defined as the highest sCr value recorded ≤ 14 days prior to the first dose of randomized study medication

Table 38 Incidence of renal-related AEs in subjects with mild to moderate baseline renal impairment in study 306

Renal Function at Baseline: eCrCl < 60 mL/min						
	LESU 200 mg + ALLO			LESU 400 mg + ALLO		
	Extension Subjects by Therapy in Core Study			Extension Subjects by Therapy in Core Study		
System Organ Class Preferred Term	PBO + ALLO (N=18) n(%)	LESU 200 mg + ALLO (N=40) n (%)	Total (N=58) n (%)	PBO + ALLO (N=21) n (%)	LESU 400 mg + ALLO (N=36) n (%)	Total (N=57) n (%)
Musculoskeletal and connective tissue disorders (cont'd)						
Renal osteodystrophy	0	1 (2.5)	1 (1.7)	0	0	0
Renal and urinary disorders	2 (11.1)	5 (12.5)	7 (12.1)	6 (28.6)	4 (11.1)	10 (17.5)
Renal failure acute	1 (5.6)	3 (7.5)	4 (6.9)	4 (19.0)	1 (2.8)	5 (8.8)
Haematuria	0	1 (2.5)	1 (1.7)	1 (4.8)	1 (2.8)	2 (3.5)
Renal impairment	0	0	0	1 (4.8)	1 (2.8)	2 (3.5)
Hypertonic bladder	0	0	0	0	1 (2.8)	1 (1.8)
Nephropathy	0	0	0	0	1 (2.8)	1 (1.8)
Oliguria	0	0	0	1 (4.8)	0	1 (1.8)
Pollakiuria	0	0	0	1 (4.8)	0	1 (1.8)
Renal failure	0	0	0	1 (4.8)	0	1 (1.8)
Renal failure chronic	0	0	0	0	1 (2.8)	1 (1.8)
Urinary incontinence	0	1 (2.5)	1 (1.7)	1 (4.8)	0	1 (1.8)
Urinary retention	0	0	0	0	1 (2.8)	1 (1.8)
Urine flow decreased	0	0	0	1 (4.8)	0	1 (1.8)
Renal and urinary disorders (cont'd)						
Dysuria	1 (5.6)	1 (2.5)	2 (3.4)	0	0	0
Proteinuria	1 (5.6)	1 (2.5)	2 (3.4)	0	0	0
Pyuria	0	1 (2.5)	1 (1.7)	0	0	0
Renal cyst	0	1 (2.5)	1 (1.7)	0	0	0
Reproductive system and breast disorders	1 (5.6)	2 (5.0)	3 (5.2)	2 (9.5)	1 (2.8)	3 (5.3)
Benign prostatic hyperplasia	0	1 (2.5)	1 (1.7)	2 (9.5)	0	2 (3.5)
Prostatism	0	0	0	0	1 (2.8)	1 (1.8)
Genital rash	0	1 (2.5)	1 (1.7)	0	0	0
Gynaecomastia	0	1 (2.5)	1 (1.7)	0	0	0
Nipple pain	1 (5.6)	0	1 (1.7)	0	0	0

Renal Function at Baseline: eCrCl ≥ 45 mL/min

System Organ Class Preferred Term	LESU 200 mg + ALLO Extension Subjects by Therapy in Core Study PBO + ALLO (N=114) n (%)	LESU 200 mg + ALLO Extension Subjects by Therapy in Core Study LESU 200 mg + ALLO (N=228) n (%)	LESU 200 mg + ALLO Total (N=342) n (%)	LESU 400 mg + ALLO Extension Subjects by Therapy in Core Study PBO + ALLO (N=113) n (%)	LESU 400 mg + ALLO Extension Subjects by Therapy in Core Study LESU 400 mg + ALLO (N=218) n (%)	LESU 400 mg + ALLO Total (N=331) n (%)
Renal and urinary disorders	10 (8.8)	11 (4.8)	21 (6.1)	11 (9.7)	15 (6.9)	26 (7.9)
Renal failure acute	1 (0.9)	1 (0.4)	2 (0.6)	4 (3.5)	4 (1.8)	8 (2.4)
Haematuria	3 (2.6)	3 (1.3)	6 (1.8)	3 (2.7)	4 (1.8)	7 (2.1)
Renal failure	0	1 (0.4)	1 (0.3)	1 (0.9)	2 (0.9)	3 (0.9)
Hypertonic bladder	0	1 (0.4)	1 (0.3)	1 (0.9)	1 (0.5)	2 (0.6)
Nephrolithiasis	1 (0.9)	1 (0.4)	2 (0.6)	1 (0.9)	1 (0.5)	2 (0.6)
Pollakiuria	0	0	0	1 (0.9)	1 (0.5)	2 (0.6)
Proteinuria	2 (1.8)	2 (0.9)	4 (1.2)	1 (0.9)	1 (0.5)	2 (0.6)
Pyuria	0	1 (0.4)	1 (0.3)	1 (0.9)	1 (0.5)	2 (0.6)
Renal impairment	0	0	0	1 (0.9)	1 (0.5)	2 (0.6)
Urinary incontinence	0	1 (0.4)	1 (0.3)	2 (1.8)	0	2 (0.6)
Nephropathy	0	0	0	0	1 (0.5)	1 (0.3)
Oliguria	0	0	0	1 (0.9)	0	1 (0.3)
Renal failure chronic	1 (0.9)	0	1 (0.3)	0	1 (0.5)	1 (0.3)
Urinary retention	0	0	0	0	1 (0.5)	1 (0.3)
Renal and urinary disorders (cont'd)						
Urine flow decreased	0	0	0	1 (0.9)	0	1 (0.3)
Bladder spasm	0	1 (0.4)	1 (0.3)	0	0	0
Calculus ureteric	1 (0.9)	0	1 (0.3)	0	0	0
Dysuria	1 (0.9)	2 (0.9)	3 (0.9)	0	0	0
Micturition urgency	0	1 (0.4)	1 (0.3)	0	0	0
Renal colic	1 (0.9)	0	1 (0.3)	0	0	0
Renal cyst	0	1 (0.4)	1 (0.3)	0	0	0
Urethral haemorrhage	0	1 (0.4)	1 (0.3)	0	0	0

Renal Function at Baseline: eCrCl < 45 mL/min

System Organ Class Preferred Term	LESU 200 mg + ALLO Extension Subjects by Therapy in Core Study PBO + ALLO (N=6) n (%)	LESU 200 mg + ALLO Extension Subjects by Therapy in Core Study LESU 200 mg + ALLO (N=11) n (%)	LESU 200 mg + ALLO Total (N=17) n (%)	LESU 400 mg + ALLO Extension Subjects by Therapy in Core Study PBO + ALLO (N=8) n (%)	LESU 400 mg + ALLO Extension Subjects by Therapy in Core Study LESU 400 mg + ALLO (N=12) n (%)	LESU 400 mg + ALLO Total (N=20) n (%)
Renal and urinary disorders	0	2 (18.2)	2 (11.8)	2 (25.0)	0	2 (10.0)
Renal failure acute	0	2 (18.2)	2 (11.8)	1 (12.5)	0	1 (5.0)
Renal impairment	0	0	0	1 (12.5)	0	1 (5.0)
Reproductive system and breast disorders	(16.7)	0	1 (5.9)	0	0	0
Nipple pain	(16.7)	0	1 (5.9)	0	0	0
General disorders and administration site conditions		2 (18.2)	2 (11.8)	0	2 (16.7)	2 (10.0)
Non-cardiac chest pain	0	0	0	0	1 (8.3)	1 (5.0)
Oedema peripheral	0	2 (18.2)	2 (11.8)	0	1 (8.3)	1 (5.0)

Note: ALLO = allopurinol, LESU = lesinurad, PBO = placebo. Treatment-emergent adverse events are those that started on or after the first lesinurad dose date in extension study, or those that started prior to the first lesinurad dose date but worsened during the extension study 306. Gout flares were captured via an electronic diary and recorded as an adverse event only if it met the definition of a serious adverse event. Adverse events are coded using MedDRA version 14.0. For each system organ class (SOC) and preferred term (PT), subjects are included only once, even if they experienced multiple events in that SOC or PT. Lesinurad Baseline eCrCl is calculated using the highest serum creatinine value recorded ≤ 14 days prior to the first dose of lesinurad.

Patients with impaired renal function who require a dose reduction of allopurinol are advised to take the allopurinol/lesinurad FDC 200/200. The allopurinol/lesinurad FDC is contraindicated in patients with severe renal impairment (CrCl less than 30 mL/min), end-stage renal disease, kidney transplant recipients or patients on dialysis (see Section 4.2 and Section 4.3 of the SmPC).

Lesinurad has not been studied in patients with severe hepatic impairment. Therefore, no dose recommendation can be given for the FDC. However, no dose adjustment is necessary in patients with mild or moderate hepatic impairment (Child-Pugh classes A and B).

Pregnancy and lactation

No adequate and well-controlled studies of lesinurad or allopurinol use during pregnancy or lactation have been conducted in humans. A review of the literature revealed rare reports of congenital anomalies in infants exposed to allopurinol in utero in the first trimester; the expected incidence of these anomalies is consistent with the rate in the general population. No notable new safety findings were identified with respect to lactation.

However, allopurinol and its metabolite oxypurinol are excreted in human breast milk. Hence, Duzallo is not recommended during breastfeeding.

Elderly

The number of patients above 75 years evaluated during the lesinurad development program was very limited as only 34 subjects were older than 74 years of age and patients over 85 years were excluded from studies. In the pivotal 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 of ≥ 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 years).

There 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. In the pivotal clinical trials, a greater proportion of patients using lipid lowering or anti-hypertensive medicinal products that were CYP3A substrates required concomitant medicinal product 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). The possibility of reduced efficacy of concomitant medicinal products that are CYP3A substrates should be considered and their efficacy (e.g. blood pressure and cholesterol levels) should be monitored. This is adequately reflected in the SmPC.

Immunological events

Hypersensitivity reactions associated with allopurinol treatment including maculopapular exanthema, hypersensitivity syndrome (also known as DRESS), and SJS/TEN are well known risks.

The HLA-B*5801 allele has been shown to be associated with the risk of developing allopurinol related hypersensitivity syndrome and SJS/TEN. The frequency of the HLA-B*5801 allele varies widely between ethnic populations: up to 20% in Han Chinese population, 8-15% in the Thai, about 12% in the Korean population and 1-2% in individuals of Japanese or European origin. Screening for HLA-B*5801 should be considered before starting treatment with allopurinol in patient subgroups where the prevalence of this allele is known to be high. Chronic kidney disease may increase the risk in these patients additionally. If no HLA-B*5801 genotyping is available for patients with Han Chinese, Thai or Korean descent, the benefits should be thoroughly assessed and considered to outweigh the possible higher risks before starting therapy. The use of genotyping has not been established in other patient populations. If the patient is a known carrier of HLA-B*5801, especially in those who are of Han Chinese, Thai or Korean descent, allopurinol should not be started unless there are no other reasonable therapeutic options and the benefits are thought to exceed risks. Extra vigilance for signs of hypersensitivity syndrome or SJS/TEN is required and the patient should be informed of the need to stop treatment immediately at the first appearance of symptoms.

SJS/TEN can still occur in patients who are found to be negative for HLA-B*5801 irrespective of their ethnic origin.

Discontinuation due to adverse events

In the pooled 301 and 302 studies, AEs leading to discontinuation have been reported with the incidence of 4.7% (n=19) in patients treated with allopurinol + placebo compared to 5.7% (n=23) in LESU 200 mg + allopurinol group. These were most frequently within investigations (blood creatinine increased, abnormal liver function, increased blood CPK) and renal disorders (mainly renal failure and nephrolithiasis) were of similar incidence between groups.

In the study 306, a total of 83 patients were reported to have AEs leading to discontinuation of study medication most frequently within the SOC of investigations, renal and urinary disorders.

Table 39 Treatment-emergent adverse events leading to stidy withdrawal in > 1 subject in treatment groups

	LESU 200 mg + ALLO			LESU 400 mg + ALLO			All Extension Subjects
System Organ Class Preferred Term	CROSS (N=122) n (%)	CONT (N= 240) n (%)	Total (N= 362) n (%)	CROSS (N= 122) n (%)	CONT (N= 232) n (%)	Total (N= 354) n (%)	(N= 716) n (%)
Any adverse event leading to study withdrawal	13 (10.7)	24 (10.0)	37 (10.2)	13 (10.7)	31 (13.4)	44 (12.4)	81 (11.3)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.8)	1 (0.4)	2 (0.6)	1 (0.8)	2 (0.9)	3 (0.8)	5 (0.7)
Renal cell carcinoma	0	0	0	1 (0.8)	1 (0.4)	2 (0.6)	2 (0.3)
Respiratory, thoracic and mediastinal disorders	2 (1.6)	0	2 (0.6)	1 (0.8)	2 (0.9)	3 (0.8)	5 (0.7)
Pulmonary embolism	0	0	0	1 (0.8)	1 (0.4)	2 (0.6)	2 (0.3)
Musculoskeletal and connective tissue disorders	1 (0.8)	1 (0.4)	2 (0.6)	3 (2.5)	2 (0.9)	5 (1.4)	7 (1.0)
Flank pain	0	0	0	2 (1.6)	0	2 (0.6)	2 (0.3)
Renal and urinary disorders	5 (4.1)	2 (0.8)	7 (1.9)	3 (2.5)	3 (1.3)	6 (1.7)	13 (1.8)
Renal failure acute	0	1 (0.4)	1 (0.3)	2 (1.6)	2 (0.9)	4 (1.1)	5 (0.7)
Nephrolithiasis	2 (1.6)	1 (0.4)	3 (0.8)	0	1 (0.4)	1 (0.3)	4 (0.6)
Investigations	0	10 (4.2)	10 (2.8)	3 (2.5)	13 (5.6)	16 (4.5)	26 (3.6)
Blood creatinine increased	0	7 (2.9)	7 (1.9)	3 (2.5)	6 (2.6)	9 (2.5)	16 (2.2)
Creatinine renal clearance decreased	0	1 (0.4)	1 (0.3)	0	3 (1.3)	3 (0.8)	4 (0.6)
Gamma-glutamyltransferase increased	0	0	0	0	2 (0.9)	2 (0.6)	2 (0.3)

Abbreviations: ALLO, allopurinol; CONT, continuation of treatment; CROSS, crossover of treatment; LESU, lesinurad; PT, preferred term; SOC, system organ class.
Note: Gout flares were captured via an electronic diary and recorded as an adverse event only if it met the definition of a serious adverse event. Adverse events were coded using Medical Dictionary for Regulatory Activities version 14.0. For each SOC and PT, subjects are included only once, even if they experienced multiple events in that SOC or PT.

2.6.1. Discussion on clinical safety

No update of the Integrated Analysis of Safety was performed to cover the long-term extension periods of the phase 3 studies beyond the cut-off date which was applied for the lesinurad EU submission. However, final CSRs are provided. This was considered acceptable by CHMP.

The size of the safety population and duration of exposure to concomitant treatment of 200 mg lesinurad and allopurinol 200 mg and 300 mg are considered sufficient for the proposed indication and posology.

Based on the mechanism of action, due to increased renal excretion of uric acid, a high risk for renal adverse events including increases in serum creatinine, kidney stones and other signals of renal damage has been identified for lesinurad and is pertinent for Duzallo as well. The overall incidence of renal adverse events was 4.2% in allopurinol + placebo while 4.9% in lesinurad 200 mg + allopurinol in the pivotal studies (301 and 302) and was 13% in the long-term open-label extension study 306. The rate of discontinuations due to renal-events was 1% in the core studies both in the placebo + allopurinol and lesinurad 200 mg + allopurinol groups while it was 1.9% in the extension study 306.

The most common renal-related AE was blood creatinine increased, with a 2.2% incidence in the placebo + allopurinol group and 3.7% in the lesinurad 200 mg + allopurinol group in the core studies (301 and 302) and 10.2% in the extension study 306. Up to 66.7% of the events resolved without interruption of the treatment, while 8.3% was reported as unresolved at last study assessment of study 306. As reflected in the product information, evaluation of renal function is required prior to and periodically after initiation of allopurinol/lesinurad FDC (e. g. 4 times per year). Patients with serum creatinine elevations to greater than 1.5 times the baseline value should be closely monitored. The 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, Duzallo should not be restarted if another explanation for the serum creatinine abnormalities cannot be deducted.

For the subgroup of subjects with mild to moderate renal impairment at baseline (CrCl < 60 mL/min and <45 min/ml), a higher rate of AEs compared to the rates were reported in the phase 3 pivotal trials 301,302 and 304 in lesinurad group 200 mg with a XOI compared to patients who received placebo+ XOI (87% vs 72.5% in patients with baseline CrCl < 60 mL/min and 60 or more, respectively). Similarly, in the extension study 306, the incidence of AEs were higher in patients with decreased creatinine clearance when patients who continued on the lesinurad 200 mg + allopurinol treatment were compared to those who were crossed overed from placebo + allopurinol to the active arm (75% vs 66.7% for CrCl < 60 ml/min and 90.9% vs 66.7% for CrCl < 45 ml /min). Moreover, the incidence of SAEs and AEs leading to study withdrawal were also reported with higher frequencies in these groups. However, no trend of increased risk for renal related AEs was reported in these patients. Following the first round of assessment, the Applicant provided a summary and discussion of safety data from the long-term extension periods of the phase 3 studies beyond the cut-off date which was applied for the lesinurad (Zurampic) EU submission with special focus on the patients with decreased creatinine clearance at baseline. There were no signs of increasing rates of nephrolithiasis or elevated creatinine levels in the long term studies. This conclusion was however based on a pooled analysis with data from the two extension studies RDEA594-306 (lesinurad 200 mg combined with 300 mg allopurinol) and RDEA594-307 (lesinurad 200 mg combined with febuxostat). The exposure adjusted incidence of MACE is somewhat higher in the extension studies than in the core studies. However, numbers are too small to draw firm conclusions.

In line with the SmPC for Zurampic, allopurinol/lesinurad FDC is contraindicated in patients with severe renal impairment (CrCl less than 30 mL/min), end-stage renal disease, kidney transplant recipients, or patients on dialysis. Indeed, based on its mechanism of action, lesinurad may not be effective in these patients. Renal impairment is listed as an important identified risk in the RMP for the FDC with routine risk minimisation measures. An additional pharmacovigilance activity was requested by the CHMP to further investigate the safety and efficacy of lesinurad (Zurampic) in patients with moderate renal impairment with CrCl 30-45 mL/min in a category 3 study.

At this point it is considered sufficient to further characterise renal impairment via routine pharmacovigilance activities as the applicant is already conducting a study with the monocomponent lesinurad alone. These results are expected to inform on the safety profile for Duzallo; however, depending on the results further activities may be requested.

Lesinurad has not been studied in patients with severe hepatic impairment. Therefore, no dose recommendation can be given for the FDC. This is adequately reflected in the SmPC and included as missing information with routine PhV activity in the RMP.

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. In the randomised, double-blind, placebo-controlled combination therapy clinical studies, the exposure-adjusted incidences rate for adjudicated Major Adverse Cardiovascular Events (CV death, non-fatal myocardial infarction or non-fatal stroke) were 0.60 (0.15, 2.41) in placebo + allopurinol group (1 nonfatal myocardial infarction and 2 nonfatal stroke), 0.61 (0.60, 2.23) for lesinurad 200 mg and allopurinol group (1 cardiovascular death, 1 non-fatal myocardial infarction). When data from studies 301, 302 and 306 combined, the exposure adjusted incidence rate for MACE were 1.26 (0.67, 2.16, 95%CI) in lesinurad 200 mg + allopurinol group.

No increased incidences for adjudicated Major Adverse Cardiovascular Events (MACE) were observed in the randomised, double-blind, placebo-controlled combination therapy clinical studies. As part of the evaluation of Zurampic MAA, a signal of increased CV events like myocardial infarction in a dose dependent fashion was observed in association with lesinurad use. It was 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. An additional pharmacovigilance activity was requested by the CHMP in order to investigate the cardiovascular risk in association with lesinurad (Zurampic) exposure, mainly in patients with a history of cardiovascular disorders.

At this point it is considered sufficient to further characterise the risk of MACE via routine pharmacovigilance activities as the applicant is already conducting a study with the monocomponent lesinurad alone. These results are expected to inform on the safety profile for Duzallo; however, depending on the results further activities may be requested.

In addition, the potential cardiovascular risks have been adequately addressed in the SmPC as Duzallo is not recommended 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, due to insufficient data with lesinurad. For cardiovascular patients in a stable condition, the benefit/risk balance of a treatment with Duzallo 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.

The HLA-B*5801 allele has been shown to be associated with the risk of developing allopurinol related hypersensitivity syndrome and SJS/TEN. Screening for HLA-B*5801 should be considered before starting treatment with allopurinol in patient subgroups where the prevalence of this allele is known to be high. SJS/TEN can still occur in patients who are found to be negative for HLA-B*5801 irrespective of their ethnic origin. This information is adequately reflected in the SmPC.

The most commonly reported SAEs were pneumonia, coronary artery disease and non-cardiac chest pain in the core and extension studies. Three acute renal failure cases were reported in the lesinurad 200 mg + allopurinol group the open-label extension study 306, of 2 led to discontinuation of the study drug.

Among the other AEs some were reported with a slightly higher frequency in lesinurad 200 mg and allopurinol group compared to placebo + allopurinol group: hypertension, headache, influenza, gastro-oesophageal reflux and blood creatinine increased. This information is adequately reflected in the SmPC.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

2.6.2. Conclusions on the clinical safety

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), which could lead to renal damage. Based on its safety profile, lesinurad dose was limited to 200 mg and administered in combination with a XOI, for a reduced risk of renal events. Most of the renal related adverse events consisted of sCr elevations, which often resolved without treatment interruption.

As reflected in the SmPC, evaluation of renal function is required prior to and periodically after initiation of allopurinol/lesinurad FDC (e. g. 4 times per year).

Available data also point towards an increased risk of severe cardiac events including myocardial infarction and fatalities in patients treated with lesinurad with a prior history of CV events. Adequate warnings have been included in the SmPC to use allopurinol/lesinurad with caution in stable CV compromised patients and not to use allopurinol/lesinurad in patients with unstable and recent CV disorders, as there is no experience in this group.

2.7. Risk Management Plan

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Renal impairment	*Routine risk minimisation measures:* Routine risk communication: – Statements within Sections 4.2, 4.4, and 4.8 of the SmPC – Statements within Sections 2, 3 and 4 of the PL Routine risk minimisation activities recommending specific clinical measures to address the risk: – Recommendations for healthcare professionals regarding renal function monitoring are included in SmPC Section 4.4 – Recommendations for patients to stay well hydrated to reduce the risk of kidney stones are included in in Section 3 of the PL	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: For post-marketing reports involving reported suspected adverse reactions related to renal impairment, a specific renal event questionnaire (follow-up form) will be used
Serious hypersensitivity (allergic) reactions and increased risk for certain serious skin reactions particularly in people of Han Chinese or Thai origin	*Routine risk minimisation measures:* Routine risk communication: – Statements within Sections 4.4 and 4.8 of the SmPC – Statement within Sections 2 and 4 of the PL Routine risk minimisation activities recommending specific clinical measures to address the risk: – Recommendations for healthcare professionals regarding the potential role	Routine pharmacovigilance activities

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	of screening for HLA-B*5801 before starting treatment with allopurinol are included in SmPC Section 4.4	
Major Adverse Cardiovascular Events (MACE) (mainly in patients with history of cardiovascular disorders)	*Routine risk minimisation measures:* Routine risk communication: – Statements within Sections 4.4 and 4.8 of the SmPC – Statement within Section 2 of the PL	Routine pharmacovigilance activities
Concomitant administration of ampicillin/amoxicillin	*Routine risk minimisation measures:* Routine risk communication: – Statements within Section 4.5 of the SmPC – Statement within Section 2 of the PL	Routine pharmacovigilance activities
Use in children	*Routine risk minimisation measures:* Routine risk communication: – Statements within Section 4.2 of the SmPC – Statement within Section 2 of the PL	Routine pharmacovigilance activities
Use in pregnant or lactating women	*Routine risk minimisation measures:* Routine risk communication: – Statements within Section 4.6 of the SmPC – Statement within Section 2 of the PL	Routine pharmacovigilance activities
Use in pre-existing hepatic impairment	*Routine risk minimisation measures:* Routine risk communication: – Statements within Section 4.2 of the SmPC – No specific statement in the PL	Routine pharmacovigilance activities
Use in subjects ≥75 years of age	*Routine risk minimisation measures:* Routine risk communication: Statement within Section 4.2 of the SmPC – No specific statement in the PL	Routine pharmacovigilance activities
Use in patients with moderate renal impairment with CrCl 30-45 ml/min)	*Routine risk minimisation measures:* Routine risk communication: – Statements within Sections 4.2 and 4.4 of the SmPC – Statement within Section 2 of the PL	Routine pharmacovigilance activities

Conclusion

The CHMP and PRAC considered that the risk management plan version 4.2 is acceptable.

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.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 22 December 2015. The new EURD list entry will therefore use the 22 December 2015 to determine the forthcoming Data Lock Points.

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, Duzallo (lesinurad / allopurinol) 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.

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.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Gout is a form of inflammatory arthritis induced by deposition of monosodium urate crystals within joints and other tissues. It is closely associated with hyperuricaemia, caused by ingestion of purines or fructose rich diet, overproduction of urate and primarily by inefficient excretion of uric acid.

The prevalence of gout is around 1-2% in Europe; primarily diagnosed in middle-aged and elderly males. Patients with a genetic predisposition of hyperuricaemia, however, may develop severe gout and chronic tophaceous arthritis at a younger age. Women who develop gout are in general elderly using diuretics.

The aims of treatments for gout are 1) to terminate acute attacks and 2) to prevent recurrent flares and the development of complications 3) to prevent paradoxical flares during initiation of urate lowering therapy and 4) to treat the complications of chronic tophaeous gout.

Instability of the crystal deposits could lead to an inflammatory reaction with arthritis flares or lithiasis. In tophaceous gout, large deposits formed are called tophi, which may lead to chronic arthritis or renal impairment.

3.1.2. Available therapies and unmet medical need

There are two treatment modalities in gout: Urate lowering therapies (ULT), where the treatment goal is a reduction of the UA load -guided by serum uric acid levels below a critical level (sUA of < 6 mg/dL (360 µmol/L)), in order to prevent flares and renal impairment in the long term. In addition, symptomatic treatment of the acute flares with anti-inflammatory drugs is applied.

Xanthine-oxidase inhibitors (XOI), allopurinol and febuxostat, are the mainstay of ULT therapy.

Initiation of ULT may 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, 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 XOIs, and warrant additional treatment to control their disease. Oral uricosuric agents (probenecid, benzbromarone, and sulphinpyrazone) 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. A pegylated recombinant uricase enxzyme, pegloticase, converts uric acid to more soluble allantoin for renal excretion, is also among available therapies for gout.The available treatment options have their limitations regarding safety, and are not overall available in the European countries.

Lesinurad (Zurampic) belongs to the oral uricosuric agents. It selectively inhibits URAT-1, a UA transporter enzyme in the renal tubulus, which mediates the re-absorption of UA from urine. Furthermore, lesinurad inhibits the OAT4 transporter, which is thought to be involved in hyperuricaemia due to thiazide diuretics. Lesinurad, in combination with allopurinol or febuxostat, has been approved as 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.

The current application concerns a fixed dose combination (FDC) of lesinurad and allopurinol in two strengths (allopurinol/lesinurad 200mg/200mg, 300mg/200 mg).

3.1.3. Main clinical studies

The efficacy of the FDC is based on efficacy data from the use of lesinurad in free combination with allopurinol supported with a PK-PD bridge.

The pivotal phase 3 studies (Studies 301 and 302) provided randomized comparison of lesinurad 200 mg in combination with allopurinol against placebo and allopurinol up to 12 months in gout patients who did not achieve target SUA levels despite at least 8 weeks treatment with allopurinol treatment. In these core studies, 90.5% of patients in study 301 and 84.1% in study 302 received 300 mg allopurinol.

Of the 405 patients who received lesinurad dose of 200 mg concomitant with allopurinol in these core studies, 362 patients completed up to 40 months of treatment in the open-label extension study (306) with lesinurad 200 mg and allopurinol combination.

The allopurinol/lesinurad FDC development program included two Phase 1 studies in healthy subjects (studies 501 and 503) which support a PK-PD bridge between the FDC formulation and free combination of mono-components used in the Phase 3 studies.

3.2. Favourable effects

In the pivotal Phase 3 trials (301 and 302), 54.8% in the lesinurad 200 mg + allopurinol group and 25.6% in the placebo + allopurinol group achieved the primary endpoint of sUA < 6 mg/dL at month 6 (difference versus placebo: 29% (95% CI: 23-36)). The sUA lowering effect below the target of 6 mg/dL continued through month 12 with a higher percentage of subjects that achieved a sUA level < 6 mg/dL shown for patients receiving lesinurad 200 mg + allopurinol compared to patients receiving allopurinol + placebo.

In the pharmacokinetic comparison of the FDC tablet and the free combination of lesinurad and allopurinol (studies 501 and 503) bioequivalence was demonstrated for lesinurad AUC and Cmax, for allopurinol AUC and for oxypurinol (active metabolite of allopurinol) AUC and Cmax.

The long-term efficacy data after 24 months of treatment with lesinurad combined with allopurinol provided further evidence of a clinical effect with continuous decline of the tophi load and flares.

3.3. Uncertainties and limitations about favourable effects

The fixed dose combination of lesinurad 200 mg with the most commonly prescribed dose of allopurinol 300 mg and a lower allopurinol dose 200 mg, provided for patients who would require lower doses of allopurinol (e.g. patients with moderated renal impairment), are proposed to be of convenience considering the need of concomitant intake of lesinurad with a XOI and therefore to increase the compliance. However, this claim has not been substantiated by any data.

3.4. Unfavourable effects

The safety data from the long-term extension periods of the phase 3 studies beyond the cut-off date applied for the Zurampic EU submission including data in patients with decreased renal function was provided upon request, and does not raise any new safety concerns.

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), which could lead to renal damage. Based on its safety profile, lesinurad dose was limited to 200 mg and administered in combination with a XOI, for a reduced risk of renal events. Most of the renal related adverse events consisted of sCr elevations, which often resolved without treatment interruption.

Periodical monitoring of the renal function (e. g. 4 times per year) is recommended in the product information based on clinical considerations, such as prior renal function of the patient, volume depletion, concurrent illness or concomitant medications.

No increased incidences for adjudicated Major Adverse Cardiovascular Events (MACE) were observed in the randomised, double-blind, placebo-controlled combination therapy clinical studies. However, due to known increased risk in the target population and limited data available for lesinurad, MACE (mainly in patients with history of cardiovascular events) is listed as an important potential risk in the RMP with routine risk minimization measures. In addition, a warning is included in the SmPC, that allopurinol/lesinurad should be used with caution in stable cardiovascular compromised patients, and should not be used at unstable CV conditions.

3.5. Uncertainties and limitations about unfavourable effects

Clinical data in patients with severe renal impairment (GFR <30 ml/min) are lacking. A contra-indication regarding the use of Duzallo in patients with severe renal impairment is included in the SmPC. Indeed, based on its mechanism of action, lesinurad may not be effective in these patients.

There is also no experience in patients with severe hepatic impairment. This has been adequately addressed in the SmPC and is included as missing information in the RMP.

There was limited experience in elderly with Zurampic EU MAA. Only 34 subjects were older than 74 years of age. This is included as missing information in the RMP and this information is adequately reflected in the product information.

3.6. Effects Table

Table 40 Effects Table for Duzallo

Effect	Description	U-nit	LESU 200 mg + allopurinol	Plac. + allopurinol	Uncertainties (U) / Strength of evidence (SoE)
Favourable effects					
Allopurinol non-responders: add-on to allopurinol (Study 301+ 302)					
sUA	< 6 mg/dL at M6 (PE)	%	54.8	25.6	Pooled 301+ 302: diff vs Plac: 29 (95% CI 23, 36) SoE: A sustained sUA response was shown: (sUA < 6 M4,5,6: diff vs Plac: 26 (1[illegible]38), M12: diff vs Plac: 24 (25, 50)
Flares	Mean rates (per patient), M6-12,	n	0.6 0.7	0.6 0.9	Uncertainity: 301: IRR 0.99 (0.61, 1.61), 302: IRR 0.88 (0.57, 1.37) Strength of evidence: the percentage of flaring patients continued to decrease during 24 months
Unfavourable Effects (Study 301 + 302, 306)					
Renal	301 + 302 pool All AEs SAEs 2 x sCR> Study 306 All AEs SAEs 2 x sCR>	%	4.9 0 1.5 13 0[illegible]	4.2 0.2 0	Uncertainity: The frequency of renal AEs increased in the long-term study in the lesinurad 200 mg + allopurinol group.
Safety in patients with CrCL< 60 and 45 ml /min	Study 306 Patients with CrCl< 60 ml/min Any AEs SAEs AE leading to withdrawal Patients with CrCl< 45 ml /min Any AEs SAEs AE leading to withdrawal	%	CONT 75 15 36.4 90.9 18.2 36.4	CROSS 66.7 11 0 66.7 0 0	Uncertainity: In patients with decreased creatinine clearance (< 60 ml/min and <45 ml/min) the incidence of AEs, SAEs and withdrawals were higher in patients who continued lesinurad 200 mg+ allopurinol comopared to patients who crossed over to active treatment in extension study 306
MACE	301 and 302 306 Subgroup analysis in	100 PY	0.61 (95% CI 0.15, 2.43) 1.26 (95% CI 0.67, 2.16)	0.60(95% CI 0.15, 2.41)	Uncertainity: Higher exposure-adjusted MACE rates in the lesinurad 200 mg + allopurinol group in study 306 compared to core studies

Effect	Description	U-nit	LESU 200 mg + allopurinol	Plac. + allopurinol	Uncertainties (U) / Strength of evidence (SoE)
	101 patients with prior history of CV events at baseline		7.6%	1.9%	Uncertainity: All patients treatd with lesinurad has CV risk history. Thus, the target population may contain patients at higher baseline CV risk than the selected study population.

Abbreviations: =adverse event, BL=baseline, CR=complete resolution of tophi, diff=difference, , 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, CONT: patients who continued lesinurad 200 mg+ allopurinol, CROSS: patients who crossed over to active treatment in extension study 306.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The combination of lesinurad with allopurinol reduced the sUA below the treatment target level in (tophaceous) gout patients, who were insufficient responders to allopurinol. This effect is of high importance for the target population and the combination is already approved for Zurampic (lesinurad). The importance of the FDC with respect to increasing compliance and convenience has not been documented but can be assumed.

Bioequivalence between Duzallo FDC and the co-administered mono-components was demonstrated for lesinurad, allopurinol and oxypurinol under fasting conditions. Under fed conditions the conventional bioequivalence criteria were met with respect to AUC and Cmax for all three analytes, with the exception of allopurinol Cmax. The Applicant has thoroughly discussed this finding from a pharmacokinetic, efficacy and safety point of view. Of most importance is the safety aspect. Adverse reactions in association with allopurinol exposure are rare and AE due to allopurinol treatment mostly relates to oxypurinol exposure. This is particularly due to the fact that half-life of allopurinol is short comparing with oxypurinol and exposure to oxypurinol is much higher. From a safety perspective it is therefore reassuring that bioequivalence was satisfactorily demonstrated for oxypurinol in both studies. Regarding efficacy, the Applicant presented data indicating that the small increase in Cmax should not have any influence on PD effect which is agreed. Overall, the CHMP concluded that the minor increase in allopurinol Cmax is not clinically relevant; therefore, equivalent efficacy and safety profile of FDC comparing with the reference mono-products can be concluded.

Unfavourable effects (eg. potential risk of renal and cardiac adverse events), are the same as for Zurampic (which is only approved in combination with allopurinol) and are adequately covered by the SmPC and the RMP.

3.7.2. Balance of benefits and risks

Lesinurad 200 mg in combination with allopurinol reduced the sUA levels in gout patients who did not achieve their sUA treatment targets with allopurinol or alone. The combination is already approved for Zurampic. The efficacy and safety is not expected to differ with the proposed FDC Duzallo and the presentation is expected facilitate the compliance.

3.7.3. Additional considerations on the benefit-risk balance

The indication for allopurinol/lesinurad is already approved indication for Zurampic. The Applicant has provided some additional data from open label extension studies, which do not raise any specific concerns.

3.8. Conclusions

The overall benefit risk balance of Duzallo is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Duzallo is favourable in the following indication.

"Duzallo is indicated in adults for the treatment of hyperuricaemia in gout patients who have not achieved target serum uric acid levels with an adequate dose of allopurinol alone".

Conditions or restrictions regarding supply and use

Medicinal product subject on medical prescription.

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

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.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.