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Original article

Lesinurad monotherapy in gout patients intolerant to a xanthine oxidase inhibitor: a 6 month phase 3 clinical trial and extension study

Anne-Kathrin Tausche[1], Rieke Alten[2], Nicola Dalbeth[3], Jeff Kopicko[4], Maple Fung[4], Scott Adler[5], Nihar Bhakta[4], Chris Storgard[4], Scott Baumgartner[4] and Kenneth Saag[6]

Abstract

Objective. To investigate the efficacy and safety of lesinurad, a selective uric acid reabsorption inhibitor, in a 6 month, phase 3 clinical trial and extension study.

Methods. Patients with gout who cannot take a xanthine oxidase inhibitor (XOI) and have serum uric acid (sUA) $\geqslant$6.5 mg/dl were randomized to receive oral lesinurad (400 mg daily) or placebo. The primary endpoint was the proportion of patients with sUA $<$6.0 mg/dl at month 6. Safety assessments included treatment-emergent adverse events (TEAEs) and laboratory data. Patients who completed the study were eligible for an open-label, uncontrolled extension study of lesinurad 400 mg monotherapy.

Results. Patients ($n = 214$) were primarily white males (mean age 54.4 years; gout duration 11.2 years). Significantly more patients achieved the primary endpoint with lesinurad than placebo (29.9 *vs* 1.9%; $P < 0.0001$). Overall TEAE rates were higher with lesinurad (77.6 *vs* 65.4%); renal-related TEAEs (17.8%), renal-related serious TEAEs (4.7%) and serum creatinine elevations (1.5 times baseline, 24.3%) occurred only with lesinurad. A total of 143 patients (65 lesinurad, 78 placebo) enrolled in the extension study. Treatment with lesinurad 400 mg resulted in rapid and sustained sUA lowering that persisted for up to 18 months before the study was terminated prematurely. No new safety findings were observed in the extension.

Conclusion. In patients with gout and intolerance/contraindication to XOIs, lesinurad 400 mg monotherapy demonstrated superior sUA lowering compared with placebo, with sustained effects for up to 18 months. Due to a high incidence of serum creatinine elevations and renal-related adverse events, including serious adverse events with lesinurad 400 mg, lesinurad should not be used as monotherapy.

Trial registration: ClinicalTrials.gov (http://clinincaltrials.gov), NCT01508702

Key words: gout, lesinurad, phase 3 trial, serum urate

CLINICAL SCIENCE

Rheumatology key messages

- Lesinurad 400 mg significantly lowered serum uric acid compared with placebo in patients with gout.
- Renal-related treatment-emergent adverse and serious adverse events and serum creatinine elevations occurred only with lesinurad.
- Lesinurad should not be used as monotherapy in patients with gout due to renal complications.

[1]Department of Rheumatology, Technical University Dresden, Dresden, [2]Department of Internal Medicine II, University Medicine Berlin, Berlin, Germany, [3]Department of Medicine, University of Auckland, Auckland, New Zealand, [4]Global Medicines Development, Cardiovascular and Metabolic Diseases Clinical Development Unit, AstraZeneca Pharmaceuticals, Gaithersburg, MD, [5]Clinical Research and Development, Ardea Biosciences, Inc., San Diego, CA and [6]Department of Medicine, University of Alabama at Birmingham, Birmingham, AL, USA

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Correspondence to: Anne-Kathrin Tausche, Technical University Dresden, Fetscherstrasse 74, 01307 Dresden, Germany.
E-mail: Anne-Kathrin.Tausche@uniklinikum-dresden.de

Introduction

Current guidelines for the chronic management of gout recommend maintenance of serum uric acid (sUA) levels <6.0 mg/dl or <5.0 mg/dl in cases of greater disease severity [1]. The first-line therapies recommended for patients with gout are allopurinol and febuxostat, xanthine oxidase inhibitors (XOIs) that block uric acid production [2]. If patients have an intolerance/contraindication to an XOI, treatment guidelines recommend substitution therapy with a uricosuric [1, 3]. Until recently, the only uricosuric available in the USA was probenecid, while only probenecid and benzbromarone were available in the European Union.

Lesinurad is a selective uric acid reabsorption inhibitor approved in the USA and the European Union at a 200 mg dose for use in combination with an XOI for the chronic treatment of hyperuricaemia associated with gout in patients who have not achieved target sUA levels with an XOI alone. Lesinurad inhibits the uric acid transporter URAT1, which is responsible for much of the uric acid reabsorbed from the renal tubular lumen [4]. By inhibiting URAT1, lesinurad increases uric acid excretion and lowers sUA [5, 6]. Therefore lesinurad in combination with an XOI provides a dual mechanism to lower sUA by increasing renal excretion of uric acid and reducing urate production.

An earlier 4-week, phase 2 clinical trial of lesinurad monotherapy demonstrated that lesinurad reduced sUA levels and increased the proportion of patients achieving target sUA levels compared with placebo [7]. This 6 month, phase 3 clinical trial and subsequent extension study investigated the efficacy and safety of lesinurad monotherapy at 400 mg daily in patients with gout who had an intolerance or contraindication to an XOI. Renal safety assessments were included since renal impairment is a common comorbidity in patients with gout [8]. Renal safety was also of special interest due to the increased uric acid excretion (uricuresis) that lesinurad causes. Uricuresis has the potential to induce microcrystallization of uric acid in renal tubules and/or the urinary system, which could manifest clinically as kidney stones and/or changes in kidney function [9].

Methods

Patients

Male and female patients between 18 and 85 years of age with a BMI <45 kg/m^2 and a diagnosis of gout [10] were eligible. Patients had to have a history of intolerance or contraindication to allopurinol or febuxostat. sUA was required to be ⩾6.5 mg/dl at the screening visit and at ~7 days prior to the start of treatment on day 1. Patients with a documented history or suspicion of kidney stones were excluded, as recommended by treatment guidelines [1, 3]. The complete inclusion and exclusion criteria are provided in supplementary Table S1, available at *Rheumatology* Online.

Trial design

The Lesinurad Monotherapy in Gout Subjects Intolerant to Xanthine Oxidase Inhibitors (LIGHT) study was a phase 3, randomized, double-blind, multicentre, placebo-controlled study to evaluate the efficacy and safety of lesinurad 400 mg daily compared with placebo (ClinicalTrials.gov identifier NCT01508702). The study, conducted in North America, Europe, Australia, South Africa and New Zealand, included an approximate 28 day screening period (screening visit to day 1), a 6 month double-blind treatment period and a 14 day safety follow-up period if the patients were not enrolling in the extension study.

Eligible patients were randomized 1:1 in a double-blind fashion to either placebo or oral lesinurad 400 mg once daily. Randomization was stratified by day 7 renal function [estimated creatinine clearance (eCrCl) ⩾60 ml/min *vs* <60 ml/min calculated by the Cockcroft–Gault formula using ideal body weight) and tophus status during screening (presence of one or more tophi *vs* absence of tophi). Randomization at study sites used a centralized interactive voice response system/interactive web response system. Doses of lesinurad or matching placebo were taken once daily in the morning with food and a cup of water. Patients were encouraged to drink 2 l of fluid a day and to remain well hydrated, in agreement with ACR guidelines [1]. Compliance with study medication was assessed by maintenance of dispensing records and verification of the returned medication packaging. Concomitant medication use was recorded at each study visit.

Gout flare prophylaxis was initiated on day 14 and consisted of colchicine (0.5 or 0.6 mg once daily, as available) or an NSAID, including cyclooxygenase 2 selective inhibitors, if patients were intolerant of or had a contraindication to colchicine. Gastroprotection with a proton pump inhibitor could be used in subjects who were receiving an NSAID, if indicated per local treatment guidelines. Gout flare prophylaxis was continued through month 5 unless patients became intolerant of prophylaxis.

The study was conducted in accordance with Independent Ethics Committee E6 Good Clinical Practice, the Declaration of Helsinki (October 2008) and all applicable local regulatory requirements. The study protocol, amendments and informed consent form were reviewed and approved by ethics committees before subjects were screened for entry into the study. Each patient provided written informed consent before the first trial-related activity. The study was conducted between 3 February 2012 and 23 October 2013.

Evaluations

The primary endpoint was the proportion of patients with sUA <6.0 mg/dl at month 6. Secondary efficacy endpoints included the proportion of patients whose sUA level was <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 and the proportion of patients with gout flares requiring treatment (GFRT) during month 6. Gout flares

were reported on a daily electronic patient diary (e-diary) that elicited the duration and extent of pain; presence of warmth, swelling or tenderness and any change in medication to treat the flare. Patients were assessed at baseline (day 1) and monthly from month 1 through month 6 for sUA data. Gout flares were assessed daily.

Safety assessments included treatment-emergent adverse events (TEAEs, coded by MedDRA version 14.0), clinical laboratory data, physical examination, ECG and vital signs. Adverse events (AEs) of special interest included renal and cardiovascular (CV) safety. Assessments of renal safety included renal-related and kidney stone TEAEs (supplementary Table S2, available at *Rheumatology* Online) and clinical laboratory data including serum creatinine (sCr), eCrCl and urine protein:creatinine ratio.

Assessment of CV safety was included because of the high rates of CV disease and known CV risk factors (hypertension, hyperlipidaemia, diabetes mellitus) in patients with gout [11, 12]. An independent Cardiovascular Events Adjudication Committee routinely assessed AEs for potential CV relationships, with categorization into major adverse CV event (MACE) and non-MACE endpoints (supplementary Table S3, available at *Rheumatology* Online) [13].

Extension study

Patients who completed the double-blind treatment period (core study) were given the option to enrol in an open-label, uncontrolled extension study so that patients assigned to placebo could receive open-label lesinurad 400 mg once daily and those assigned to lesinurad could receive continued treatment with lesinurad 400 mg (ClinicalTrials.gov identifier NCT01650246). All patients were given gout flare prophylaxis for the first 2 months. The primary objective was to determine the long-term efficacy and safety of lesinurad monotherapy. Patients were assessed for sUA levels at baseline and monthly thereafter. Safety was assessed as in the core study.

Statistical analyses

All randomized patients who received at least one dose of randomized study medication were included in the intent-to-treat population, which was the primary population for efficacy and safety assessments. Comparison of response proportions based on sUA levels between the lesinurad 400 mg and placebo groups was performed using the Cochran–Mantel–Haenszel test statistic, stratified by day 7 renal function and tophus status (present/absent) during screening. Results were summarized and expressed as proportions, corresponding adjusted 95% CIs of the difference between response rates, and *P*-values. Patients with missing values for any reason at month 6 were considered non-responders (non-responder imputation).

The mean change and mean percent change from baseline in sUA were analysed by a covariance model with baseline sUA as the covariate and adjusted for day 7 renal function and tophus status during screening. Treatment difference in the mean rate of GFRT from baseline to the end of month 6 was analysed using a Wilcoxon rank-sum test, while the treatment difference in the proportion of patients with GFRT during month 6 was analysed with a Cochran–Mantel–Haenszel model adjusted for day 7 renal function and tophus status during screening.

Safety data were listed by treatment group and were not subjected to statistical hypothesis testing. TEAEs were coded by system organ class and preferred term and listed according to incidence, severity, relation to study medication and relation to discontinuation. Relative increases ($\geqslant$1.5 times and $\geqslant$2.0 times the baseline level) in sCr were assessed [14, 15]. Baseline values were defined as the highest sCr value recorded $\leqslant$14 days prior to the first dose of study medication. Resolution of sCr elevation was defined as sCr $\leqslant$1.2 times the baseline level following elevation.

Approximately 200 patients were planned to be recruited, for an allocation of ~100 to each treatment group. This sample size was calculated to provide ~90% power to detect a difference in response rate between treatment groups if the placebo group had an 8% response rate and the lesinurad group had a response rate of 25% using Fisher's exact test, with a two-sided alpha level of 0.05.

sUA levels during the extension study were analysed using descriptive statistics by the core study treatment group (observed cases). Safety data are reported for the total extension study population.

Results

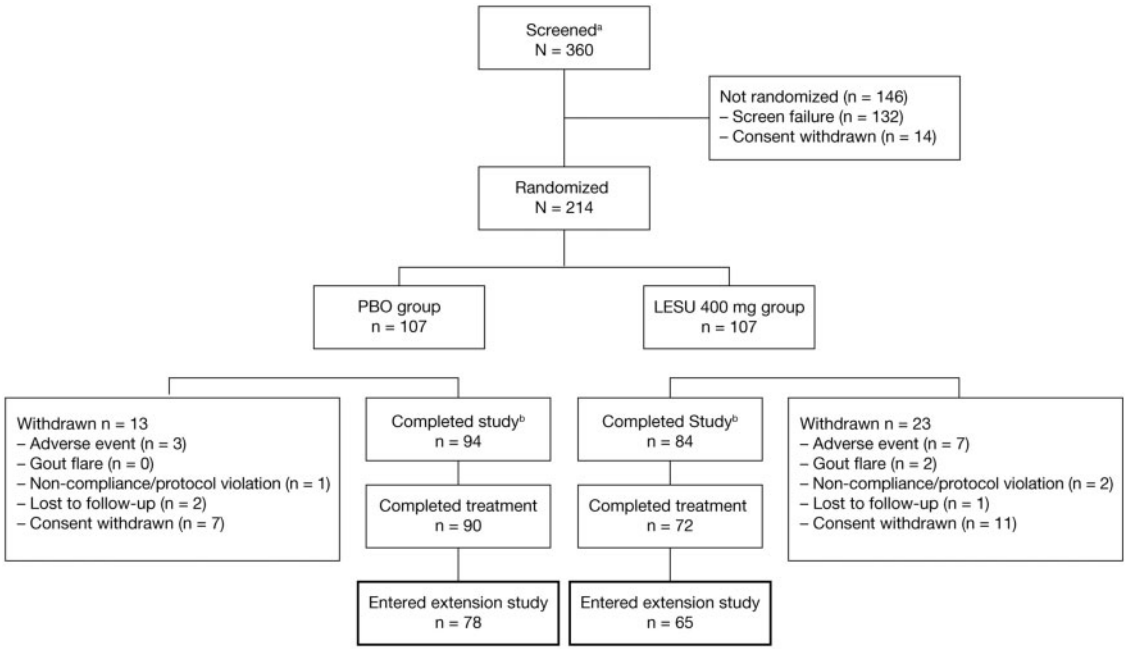
Patient disposition

Of the 360 patients screened (Fig. 1), 214 were randomized at 86 sites in North America, South Africa, Europe and Australasia. The remaining 146 patients were not randomized; 132 were screen failures and 14 withdrew consent. All 214 randomized patients received at least one dose of randomized study medication: 107 in the lesinurad 400 mg group and 107 in the placebo group. A total of 36 of 214 patients (16.8%) withdrew from the study: 23/107 (21.5%) in the lesinurad 400 mg group and 13/107 (12.2%) in the placebo group. The most common reasons for withdrawal were AEs (4.7%) and consent withdrawn (8.4%).

Baseline demographics and clinical history

Demographics and baseline disease characteristics were similar between the treatment groups (Table 1). Patients were predominately male (91.1%) and white (81.8%), with a mean age of 54.4 years (S.D. 12.3) and a BMI of 31.9 kg/m^2 (S.D. 5.4). The mean time since gout diagnosis was 11.2 years (S.D. 8.7) and baseline sUA levels were 9.3 mg/dl (S.D. 1.5). A total of 41.1% of patients had an eCrCl >90 ml/min, 41.1% had an eCrCl >60 and $\leqslant$90 ml/min and 17.8% had an eCrCl <60 ml/min. The majority (69.6%) had a CV comorbidity or risk factor. A total of 25.2% of patients had tophi at screening, 91.1% of patients

Fig. 1 Patient disposition



[a]Screened was defined as signing an informed consent form. [b]Completed the study with or without completing randomized study medication. LESU: lesinurad; PBO: placebo.

had an intolerance and/or a contraindication to allopurinol, 8.9% had an intolerance and/or a contraindication to febuxostat and 4.2% had an intolerance and/or a contraindication to both XOIs. Patients self-reported a mean of 6.2 flares (S.D. 7.3) in the 12 months prior to study entry.

Study medication

The proportion of patients exhibiting $\geqslant$80% compliance with study medications was 92.5% in the lesinurad 400 mg group and 97.2% in the placebo group.

Efficacy assessments

Primary endpoint of sUA response and secondary sUA endpoints

The proportion of patients who achieved sUA $<$6.0 mg/dl at month 6 was 29.9% in the lesinurad group and 1.9% in the placebo group (Fig. 2). Significantly more patients treated with lesinurad achieved the primary endpoint compared with placebo ($P < 0.0001$). A greater proportion of patients treated with lesinurad also achieved sUA levels $<$5.0 mg/dl and $<$4.0 mg/dl at month 6 compared with the placebo group (Fig. 2).

The proportion of patients who achieved sUA $<$6.0 mg/dl was greater with lesinurad starting at month 1 and at each monthly visit through month 6 ($P < 0.0001$) (supplementary Fig. S1, available at *Rheumatology* Online). Mean sUA levels were lower with lesinurad *vs* placebo at all time points ($P < 0.0001$, all comparisons of percent sUA change from baseline) (supplementary Fig. S1, available at *Rheumatology* Online).

Secondary endpoint: gout flares

During month 6 (when patients were no longer receiving gout flare prophylaxis), the proportion of patients requiring treatment for a gout flare was similar for lesinurad and placebo (11.8 *vs* 14.6%; $P = 0.68$). The mean rate of GFRT was low ($\sim$0.25/month) and similar from months 1 to 6 for both groups.

Safety assessments

AEs

TEAEs were reported in 77.6% of patients in the lesinurad group and 65.4% in the placebo group (Table 2). The majority of patients in both treatment groups had TEAEs with a maximum severity of grade 1 or 2 based on Rheumatology Common Toxicity Criteria [16]. The most common TEAEs in the lesinurad *vs* placebo groups were blood creatinine increased (8.4 *vs* 0%), constipation (5.6 *vs* 0%), renal impairment (4.7 *vs* 0%), diarrhoea (9.3 *vs* 5.6%) and nausea (6.5 *vs* 4.7%).

In the lesinurad *vs* placebo groups, the percentage of patients with TEAEs possibly related to randomized study medication was 29.9 *vs* 10.3%; with TEAEs leading to discontinuation of randomized study medication, 18.7 *vs* 5.6%; and with TEAEs leading to withdrawal from the study, 7.5 *vs* 2.8%.

Serious TEAEs were reported in 8.4% of patients in the lesinurad group and 3.7% in the placebo group. The only serious TEAEs that occurred in more than one patient in any treatment group were renal failure and renal failure acute ($n = 2$ patients each) in the lesinurad group. One patient died of unknown causes 100 days after his

Table 1 Demographic and baseline characteristics of patients in the core study intent-to-treat population

Characteristics	PBO ($n = 107$)	LESU400 ($n = 107$)	Total ($N = 214$)
Age, mean (S.D.), years	55.3 (12.0)	53.6 (12.5)	54.4 (12.3)
Male, *n* (%)	97 (97.3)	98 (91.6)	195 (91.1)
Race, *n* (%)			
Asian	3 (2.8)	4 (3.7)	7 (3.3)
Black/African American	11 (10.3)	9 (8.4)	20 (9.3)
White	87 (81.3)	88 (82.2)	175 (81.8)
Other	6 (5.6)	6 (5.6)	12 (5.6)
Ethnicity, *n* (%)			
Hispanic/Latino	11 (10.3)	12 (11.2)	23 (10.7)
Not Hispanic/Latino	96 (89.7)	95 (88.8)	191 (89.3)
Body weight, mean (S.D.), kg	98.9 (17.8)	99.6 (21.0)	99.2 (19.4)
BMI, mean (S.D.), kg/m^2	31.6 (4.6)	32.1 (6.2)	31.9 (5.4)
Duration since gout diagnosis, mean (S.D.), years	10.9 (8.6)	11.5 (8.8)	11.2 (8.7)
Presence of tophi at screening, *n* (%)	26 (24.3)	28 (26.2)	54 (25.2)
Number of gout flares in the past 12 months, mean (S.D.)	6.2 (8.4)	6.2 (6.2)	6.2 (7.3)
Gout flare prophylaxis at baseline, *n* (%)			
Colchicine	91 (85.0)	88 (82.2)	179 (83.6)
NSAID	16 (15.0)	19 (17.8)	35 (16.4)
Prior XOI intolerance, *n* (%)			
Allopurinol	90 (84.1)	90 (84.1)	180 (84.1)
Febuxostat	7 (6.5)	3 (2.8)	10 (4.7)
Both	3 (2.8)	6 (5.6)	9 (4.2)
Neither	6 (5.6)	6 (5.6)	12 (5.6)
XOI contraindication, *n* (%)			
Allopurinol	4 (3.7)	2 (1.9)	6 (2.8)
Febuxostat	0	0	0
Both	0	0	0
Neither	33 (30.8)	42 (39.3)	75 (35.0)
Renal function at baseline, *n* (%)			
eCrCl $\geqslant$90 ml/min	44 (41.1)	44 (41.1)	88 (41.1)
eCrCl 60–$<$90 ml/min	46 (43.0)	42 (39.3)	88 (41.1)
eCrCl $<$60 ml/min	17 (15.9)	21 (19.6)	38 (17.8)
sUA at baseline, mean (S.D.), mg/dl	9.18 (1.51)	9.48 (1.50)	9.33 (1.51)
CV comorbidity or CV risk factor (combined), *n* (%)	74 (69.2)	75 (70.1)	149 (69.9)
Hypertension, *n* (%)	61 (57.0)	60 (56.1)	121 (56.5)
Hyperlipidaemia, *n* (%)			
Hypercholesterolaemia	40 (37.4)	48 (44.9)	88 (41.1)
Hypertriglyceridaemia	16 (15.0)	16 (15.0)	32 (15.0)
Diabetes mellitus, *n* (%)	15 (14.0)	20 (18.7)	35 (16.4)
Myocardial infarction, *n* (%)	2 (1.9)	5 (4.7)	7 (3.3)

LESU: lesinurad; PBO: placebo; ULT: urate-lowering therapy; sUA: serum uric acid; eCrCl: estimated creatinine clearance; XOI: xanthine oxidase inhibitor.

last 40 day supply of lesinurad was dispensed. All serious TEAEs that were not renal related were comparable between groups.

Renal safety analysis

Renal-related TEAEs occurred in 17.8% of patients in the lesinurad group and none in the placebo group. Five (4.7%) patients experienced a renal-related SAE: two with renal failure, two with acute renal failure and one with renal impairment. Kidney stones were reported in one patient in the lesinurad group and none of the placebo group.

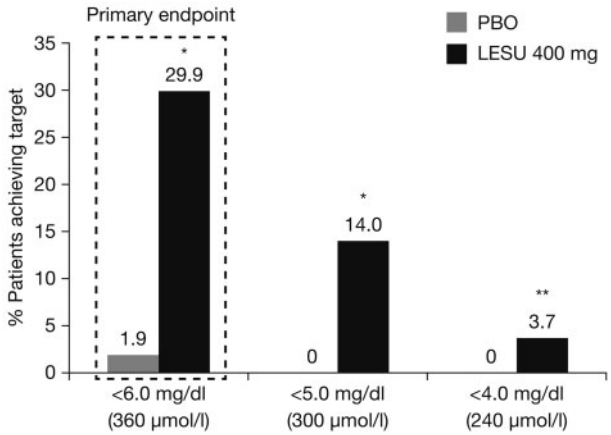
sCr elevation $\geqslant$1.5 times baseline and $\geqslant$2.0 times baseline occurred in 24.3 and 8.4% of patients in the lesinurad group, respectively, and none in the placebo group. Resolution of sCr elevations $\geqslant$1.5 times and $\geqslant$2.0 times occurred by the last study assessment in 14/26 (53.9%) cases and 6/9 (66.7%) cases, respectively, with 12 cases and 3 cases unresolved at the last assessment in the core study.

The change in mean sCr value between baseline and month 6 was 0.23 mg/dl (S.D. 0.33) in the lesinurad group and 0.01 mg/dl (S.D. 0.10) in the placebo group. The change in mean eCrCl was −12.90 ml/min (S.D. 16.96) and −1.17 ml/min (S.D. 8.70) in the lesinurad and placebo groups, respectively, and the change in mean urine protein:creatinine ratio was 0.00 (S.D. 0.05) and −0.02 (S.D. 0.14).

CV safety analyses

One TEAE classified as a CV event was reported in each group. There was one death from unknown causes

FIG. 2 Percent of patients achieving serum uric acid targets by month 6 in the core study



Non-responder imputation (intention-to-treat population). *$P < 0.0001$ *vs* PBO; **$P = 0.0422$ *vs* PBO. LESU: lesinurad; PBO: placebo.

TABLE 2 Overall summary of treatment-emergent adverse events in the core study and extension (safety population)

Adverse event category	Core study		Extension
	PBO ($n = 107$), *n* (%)	LESU400 ($n = 107$), *n* (%)	LESU400 ($n = 143$), *n* (%)
Any TEAE	70 (65.4)	83 (77.6)	105 (73.4)
Any TEAE with RCTC toxicity grade 3 or 4	4 (3.7)	18 (16.8)	14 (9.8)
Any serious TEAE	4 (3.7)	9 (8.4)	15 (10.5)
Any fatal TEAE	0	1 (0.9)	1 (0.7)
Renal-related AEs			
Patients with renal-related AEs	0 (0.0)	19 (17.8)	24 (16.8)
Patients with serious renal-related AEs	0 (0.0)	5 (4.7)	2 (1.4)
Patients with kidney stones	0 (0.0)	1 (0.9)	6 (4.2)
sCr elevation $\geqslant$1.5 times baseline[a]			
Patients with $\geqslant$1.5 times increase in sCr	0 (0.0)	26 (24.3)	44 (30.8)
Cases of sCr elevation unresolved[b] at last study assessment	0	12	9
sCr elevation $\geqslant$2.0 times baseline			
Patients with $\geqslant$2.0 times increase in sCr	0 (0.0)	9 (8.4)	9 (6.3)
Cases of sCr elevation unresolved[b] at last study assessment	0	3	4

[a]All $\geqslant$2 times elevations captured within $\geqslant$1.5 times elevations. [b]sCr resolution defined as an sCr elevation returning to $\leqslant$ 1.2 times baseline. LESU: lesinurad; PBO: placebo; RCTC: Rheumatology Common Toxicity Criteria; AE: adverse events; TEAE: treatment-emergent adverse event; sCr: serum creatinine.

(adjudicated as a MACE event) in the lesinurad group 199 days after the first dose of lesinurad. The death was considered unexpected and was considered by the investigator and sponsor to be not related to lesinurad. One patient had a non-serious TEAE of angina pectoris in the placebo group. Both patients had one or more baseline CV comorbidities.

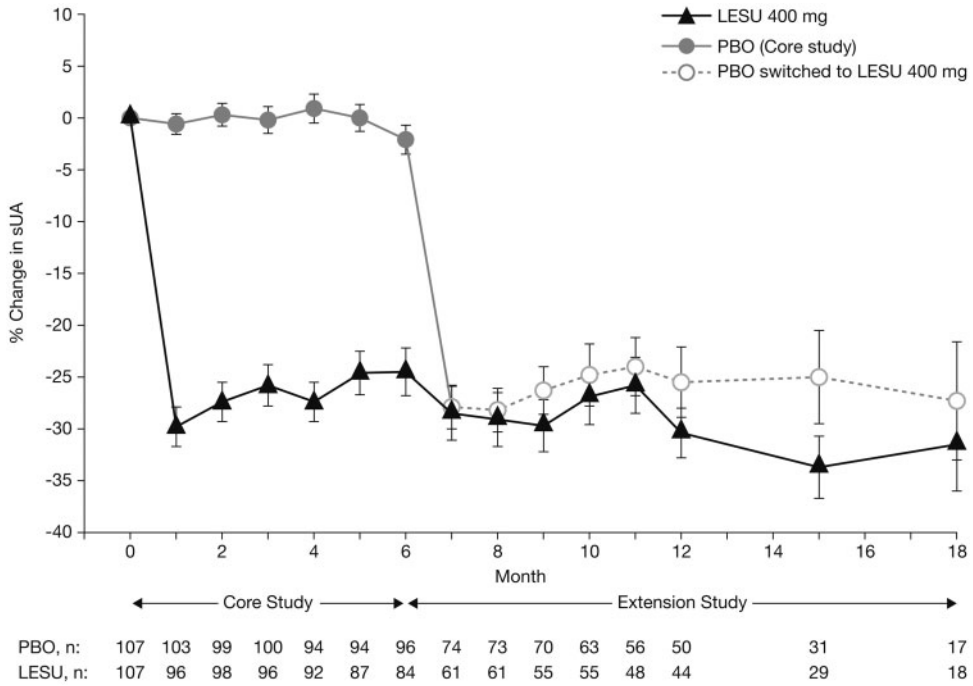
Other clinical laboratory tests and vital signs

Clinical laboratory test results, including haematology, serum chemistry parameters (excluding the renal laboratory results reported above) and urinalysis, were comparable between the treatment groups during the study. There were no notable changes from baseline during the study in vital signs in either group.

Extension study

All subjects in the extension study were to take lesinurad 400 mg once daily for ~24 months. Following the availability of the unblinded renal safety data from the core study and subsequent interactions with regulatory authorities in Germany and Canada and with the US Institutional Review Board, subjects in Germany, Canada and the USA were removed from the study. Only 11 of 143 patients were potentially eligible to continue on treatment in

Fig. 3 Mean (s.e.) percent change in serum uric acid during the core and extension studies



Observed cases (intention-to-treat population). LESU: lesinurad; PBO: placebo; sUA: serum uric acid.

other countries, therefore the study was terminated prematurely because of the limited scientific value.

A total of 143 of 162 patients (88.3%) who completed the core study enrolled in the open-label extension study: 65/72 (90.3%) from the lesinurad group and 78/90 (86.7%) from the placebo group. This population was generally representative of the entire core study population. In total, 84 patients [84/143 (58.7%)] completed 6 months in the extension study and 35 (24.5%) completed 12 months prior to study closure. The mean treatment compliance was 94.8% (s.d. 12.7).

Figure 3 shows the mean (s.e.) percent change in sUA during both the core and extension studies. For patients from the core study who were on placebo previously, the mean change from baseline in sUA after 1 month on lesinurad in the extension study was −27.9% (s.e. 2.1) and sUA levels remained stable over the next 11 months, with the mean change from baseline ranging from −24.0 to −29.2%. For patients from the core study on lesinurad 400 mg, the change from baseline after 6 months in the core study was −28.5% (s.e. 2.6). sUA levels remained stable over the next 12 months of the extension study, with the mean change from baseline ranging from −25.8 to −33.7%. The proportion of patients with sUA <6.0 mg/dl at any extension study visit was 67.9% for patients from the core study placebo group and 58.5% for those from the core study lesinurad group; 41.0 and 40.0%, respectively, had sUA <5.0 mg/dl and 15.4 and 7.7%, respectively, had sUA <4.0 mg/dl at any extension visit.

TEAEs occurred in the extension in a majority of patients (73.4%; Table 2) and were similar in patients from the core study placebo (75.6%) and lesinurad groups (70.8%). The most common TEAEs were blood creatinine increased (11.2%), upper respiratory tract infection (9.8%) and hypertension (7.0%). TEAEs possibly related to study medication occurred in 25.2% of patients, those that led to discontinuation of study medication in 16.8% and those that led to study withdrawal in 16.1%.

Renal-related TEAEs occurred in 16.8% of patients, with more events occurring in patients from the core study placebo group (19.2%) than the core study lesinurad group (13.8%). The most common renal-related TEAE was blood creatinine increased (11.2%), with more events occurring in patients from the core study placebo group (14.1%) than the core study lesinurad group (7.7%). Renal-related serious TEAEs occurred in two patients from the core study placebo group (renal failure and renal impairment). Kidney stone TEAEs occurred in 4.2% of patients, with more in patients from the core study placebo group (5.1%) than the core study lesinurad group (3.1%). A total of 30.8 and 6.3% of patients had sCr elevation $\geqslant$1.5 times and $\geqslant$2.0 times baseline, respectively. Resolution of sCr elevation $\geqslant$1.5 times and $\geqslant$2.0 times baseline occurred in 38/47 (80.9%) and 6/10 (60%) cases, respectively, with 9 cases and 4 cases unresolved at the last study assessment. Two MACE events (one death from an unknown cause and one non-fatal myocardial infarction) occurred during the extension study.

Discussion

LIGHT investigated the efficacy and safety of lesinurad monotherapy at 400 mg daily in patients with relatively

severe gout (most had tophi present) who had elevated sUA levels and intolerance or contraindication to an XOI. Lesinurad 400 mg significantly increased the proportion of patients achieving the sUA target of <6.0 mg/dl at 6 months (29.9 *vs* 1.9% with placebo). The onset of sUA reduction achieved by lesinurad was rapid (by month 1). The reduction in sUA levels was maintained in the lesinurad group over the 6 month core study and throughout the ~12 months of the extension study. These results are consistent with the phase 2 monotherapy study, where a significantly greater proportion of patients receiving lesinurad 400 mg compared with placebo achieved sUA <6.0 mg/dl after 4 weeks of dosing [7].

The mean rate of GFRT was low initially due to co-administrated gout flare prophylaxis, and lesinurad 400 mg had no significant effect on the rate over the 6 month treatment period. Gout flares were not evaluated in the extension study.

Patients receiving lesinurad 400 mg had a higher incidence of TEAEs, grade 3 or 4 TEAEs, serious TEAEs and TEAEs that led to randomized study medication discontinuation compared with placebo. Renal-related TEAEs leading to discontinuation of randomized study medication and renal-related serious TEAEs were only observed in the lesinurad group, as were sCr elevations ⩾1.5 times or ⩾2.0 times baseline, and a number of elevations were unresolved at the last core study visit.

The mechanism of the sCr elevation associated with lesinurad is believed to be due to increased urinary excretion of uric acid, which has the potential to induce uric acid microcrystallization in the renal tubules that could manifest clinically as transient and reversible elevation in sCr. Although there is an absence of large, well-done clinical trials with either probenecid or benzbromarone (which is only available in certain markets), renal findings are believed to be more limited to renal stones; however, cases of acute renal failure have been reported to health authorities (i.e. US Food and Drug Administration MedWatch). With lesinurad, lower overall rates of sCr elevations and renal-related AEs have been observed in phase 3 trials when added in combination with an XOI [17–19]. Patients on an XOI produce less uric acid, thereby excreting less uric acid and reducing the risk of microcrystallization when lesinurad is added.

Limitations to LIGHT include the short study duration, especially to assess gout flares as well as the longer-term safety and efficacy of lesinurad monotherapy. Other limitations include the use of just a single dosage level and the limited number of female patients and patients with moderate renal impairment.

In conclusion, nearly one-third of patients treated with lesinurad monotherapy at 400 mg once daily achieved an sUA <6.0 mg/dl at 6 months in this multinational study of patients with gout and intolerance or contraindication to an XOI. Sustained sUA lowering was maintained for up to 18 months. Due to the high incidence of serum creatinine elevations and renal-related AEs, including SAEs, observed in this study, an indication for the use of lesinurad 400 mg in patients with gout was not pursued for regulatory approval as either monotherapy or in combination with an XOI. The lesinurad 200 mg dose was approved for use in combination with an XOI.

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Supplementary data

Supplementary data are available at *Rheumatology* Online.

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