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EXTENDED REPORT

Lesinurad in combination with allopurinol: a randomised, double-blind, placebo-controlled study in patients with gout with inadequate response to standard of care (the multinational CLEAR 2 study)

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ABSTRACT

Objectives Determine the efficacy and safety of daily lesinurad (200 or 400 mg orally) added to allopurinol in patients with serum uric acid (sUA) above target in a 12-month, randomised, phase III trial.

Methods Patients on allopurinol ≥ 300 mg (≥ 200 mg in moderate renal impairment) had sUA level of ≥ 6.5 mg/dL (≥ 387 $\mu\text{mol/L}$) at screening and two or more gout flares in the prior year. Primary end point was the proportion of patients achieving sUA level of < 6.0 mg/dL (< 357 $\mu\text{mol/L}$) (month 6). Key secondary end points were mean gout flare rate requiring treatment (months 7 through 12) and proportions of patients with complete resolution of one or more target tophi (month 12). Safety assessments included adverse events and laboratory data.

Results Patients (n=610) were predominantly male, with mean (\pm SD) age 51.2 ± 10.90 years, gout duration 11.5 ± 9.26 years and baseline sUA of 6.9 ± 1.2 mg/dL (410 ± 71 $\mu\text{mol/L}$). Lesinurad at 200 and 400 mg doses, added to allopurinol, significantly increased proportions of patients achieving sUA target versus allopurinol-alone therapy by month 6 (55.4%, 66.5% and 23.3%, respectively, $p < 0.0001$ both lesinurad+allopurinol groups). In key secondary end points, there were no statistically significant treatment-group differences favouring lesinurad. Lesinurad was generally well tolerated; the 200 mg dose had a safety profile comparable with allopurinol-alone therapy. Renal-related adverse events occurred in 5.9% of lesinurad 200 mg +allopurinol, 15.0% of lesinurad 400 mg+allopurinol and 4.9% of allopurinol-alone groups, with serum creatinine elevation of $\geq 1.5 \times$ baseline in 5.9%, 15.0% and 3.4%, respectively. Serious treatment-emergent adverse events occurred in 4.4% of lesinurad 200 mg +allopurinol, in 9.5% of lesinurad 400 mg+allopurinol and in 3.9% of allopurinol-alone groups, respectively.

Conclusion Lesinurad added to allopurinol demonstrated superior sUA lowering versus allopurinol-alone therapy and lesinurad 200 mg was generally well tolerated in patients with gout warranting additional therapy.

Trial registration number NCT01493531.

INTRODUCTION

Gout is an inflammatory arthritis characterised by the deposition of monosodium urate (MSU) crystals in the joints, tendons and other connective tissues.

Crystal deposition secondary to long-standing hyperuricemia can be reversed by lowering the concentration of serum uric acid (sUA) below the MSU saturation point—leading, in the long term, to the potential disappearance of signs and symptoms of gout. As a result, current management guidelines recommend maintenance of sUA to < 6.0 mg/dL (< 357 $\mu\text{mol/L}$) in patients with gout.^{1–3}

Allopurinol is recommended as a first-line urate-lowering therapy (ULT).^{2–4} However, clinical trials have demonstrated that $> 50\%$ of patients do not achieve sustained reductions in sUA at the most commonly used allopurinol dose of 300 mg.^{5–8} Lesinurad (RDEA594) is a novel, selective uric acid reabsorption inhibitor (SURI) for treatment of gout in combination with xanthine oxidase inhibitors. Lesinurad inhibits URAT1, a uric acid transporter responsible for the reabsorption of uric acid from the renal tubular lumen.^{9–11} Lesinurad in combination with allopurinol therefore provides a dual mechanism for sUA lowering—an increase in excretion of uric acid and a reduction in urate production.

Clinical studies have demonstrated that lesinurad in combination with allopurinol reduces mean sUA concentrations and increases proportions of patients who achieve sUA targets.^{12–14} The current phase III study—Combining Lesinurad with Allopurinol Standard of Care in Inadequate Responders (CLEAR 2)—is one of two replicate, randomised, double-blind, placebo-controlled, multicentre studies to investigate lesinurad in combination with allopurinol in patients with gout. CLEAR 1 was performed within the USA, included 603 patients with gout and provided outcomes similar to the CLEAR 2 study.¹⁵

METHODS

Study design

CLEAR 2 was an international, phase III trial to investigate the efficacy and safety of two lesinurad doses (200 or 400 mg oral, once daily) in combination with allopurinol, versus allopurinol combined with placebo (the control arm), in patients demonstrating inadequate response to standard-of-care allopurinol (ClinicalTrials.gov Identifier: NCT01493531). The study was conducted in 12 countries in Europe, North America, South Africa, Australia and New Zealand between December 2011 and July 2014.

CLEAR 2 included a screening period of approximately 28 days, including a run-in of approximately 14 days on gout flare prophylaxis and 12-month double-blind treatment (figure 1). 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.

Patients

Male or female patients aged 18–85 years with a diagnosis of gout, body mass index <45 kg/m², inadequate hypouricaemic response to standard-of-care allopurinol and two or more gout flares in the previous 12 months were eligible for study inclusion. Patients were included if they met the 1977 American Rheumatism Association preliminary classification criteria for gout.¹⁶ Patients were required to have received allopurinol as the sole ULT for ≥8 weeks prior to screening at a dose assessed medically appropriate by the treating physician (minimum 300 mg/day (200 mg in moderate renal impairment)¹⁷ up to 800 or 900 mg, depending on locally approved dose). sUA was required to be ≥6.5 mg/dL (≥387 μmol/L) at screening and ≥6.0 mg/dL (≥357 μmol/L) approximately 7 days prior to start of treatment on day 1.

Patients with estimated creatinine clearance (eCrCl) <30 mL/min were excluded from study. Patients with a history of kidney stones were permitted. Complete exclusion criteria are included in the online supplementary material 1.

Study medications

Eligible patients were randomised by double-blind method to one of three treatment groups (lesinurad 200 mg, lesinurad 400 mg or placebo) in 1:1:1 ratio, added to continued treatment with allopurinol at pre-study dose. Randomisation at study sites

used a centralised Interactive Voice Response System/Interactive Web Response System.

Doses of lesinurad or matching placebo were taken once daily in the morning with food and one cup of water. Compliance was assessed from dispensing records and verification of returned medication packaging. Concomitant medication use was recorded at each study visit.

Gout flare prophylaxis was initiated at day –14, that is, the same time as sponsor-provided allopurinol. Prophylaxis consisted of colchicine (0.5 or 0.6 mg/day, as locally available) or a non-steroidal anti-inflammatory drug (NSAID, dosed according to local prescribing practice, with or without proton-pump inhibitor) for patients who were intolerant to or had contraindications to colchicine. Gout flare prophylaxis was continued through month 5, unless patients became intolerant or developed toxicity to prophylaxis.

Patients were encouraged to drink 2 L of fluid a day and remain well hydrated, following American College of Rheumatology guidelines for management of gout.²

Assessments

Efficacy assessments

The primary efficacy end point was the proportion of patients in each treatment group with sUA <6.0 mg/dL (<357 μmol/L) by month 6. Other sUA-related end points included proportions of patients with sUA <6.0 mg/dL (<357 μmol/L), <5.0 mg/dL (<297 μmol/L) and <4.0 mg/dL (<238 μmol/L) and mean absolute and mean percentage changes from baseline in sUA at each visit.

Two key secondary end points included: (1) mean rate of gout flares requiring treatment for the 6-month period from end of month 6 to end of month 12, reported on a daily electronic patient diary. This key secondary end point included only

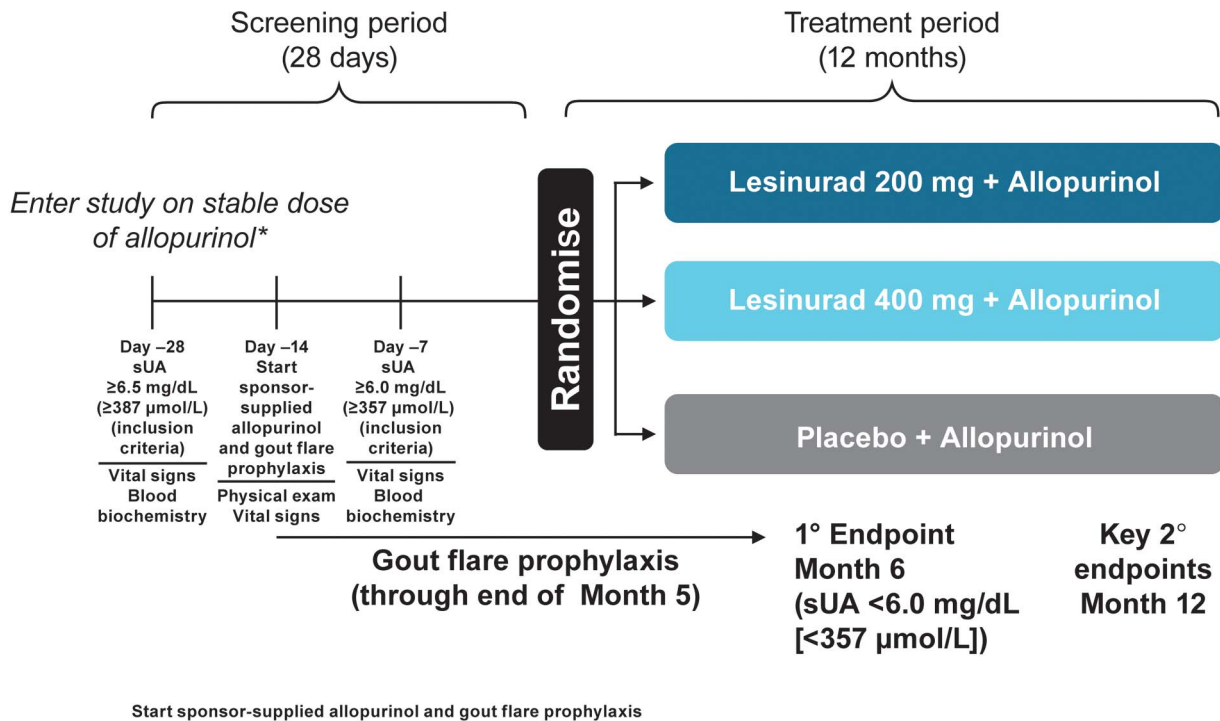


Figure 1 CLEAR 2 trial design is shown. *200 mg permitted for renally impaired. Maximum allopurinol dose: 800 or 900 mg, according to local label. Randomisation was stratified at day –7 by renal function (ie, estimated eCrCl ≥60 vs <60 mL/min, calculated by the Cockcroft-Gault formula using ideal body weight) and by tophus status during screening (ie, one or more tophus versus no tophi). eCrCl, estimated creatinine clearance; sUA, serum uric acid.

clinically relevant gout flares, which were those requiring either an increase in current medication or new medication and (2) proportion of patients with target tophi at baseline who experienced complete resolution of one or more target tophi by month 12, that is, 100% decrease in tophus area. Target tophi (up to five per patient) were tophi on the hands/wrists and/or feet/ankles measured by digital Vernier callipers at ≥ 5 and ≤ 20 mm in longest diameter.¹⁸ Permitted treatments for gout flares were colchicine, analgesics and/or anti-inflammatory medications, including oral and intra-articular corticosteroids.

Safety assessments

Safety assessments included treatment-emergent adverse events (TEAEs; coded by Medical Dictionary for Regulatory Activities (V14.0)), clinical laboratory data, physical examination, ECG and vital signs. Adverse events (AEs) of special interest included renal and cardiovascular (CV) safety assessments.

Assessments of renal safety included renal-related and kidney stone TEAEs (see online supplementary material 2) and clinical laboratory data, including serum creatinine (sCr), creatine kinase, urine protein-to-creatinine ratio and eCrCl levels. CV safety was of special interest because of the known high rates of CV risk factors in patients with gout.^{19–20} An independent Cardiovascular Events Adjudication Committee (CEAC) routinely assessed AEs for potential CV relationship, with categorisation into major adverse CV events (MACEs) and non-MACE end points (see online supplementary material 3).²¹

Statistical analyses

Comparisons of response proportions based on sUA level between each lesinurad plus allopurinol group and the allopurinol-alone group were performed using the Cochran-Mantel-Haenszel (CMH) test statistic, stratified by day -7 renal function and tophus status during screening. A Bonferroni correction was used for the primary end point for each of the two treatment comparisons with allopurinol-alone therapy at an α level of 0.025. Testing of the key secondary end points hierarchically at an α level of 0.05 was gated on both dose contrasts being statistically significant for the primary end point. If only one of the primary end point dose contrasts was significant, then $\alpha=0.025$ for each key secondary end point within the surviving dose. All other efficacy end points were evaluated at $\alpha=0.05$ (nominal *p* value), two-sided, without multiplicity adjustment. Results for the primary end point of sUA response are expressed as proportions and *p* values. Patients with missing values at month 6 or month 12 for any reason were considered non-responders (non-responder imputation, NRI).²² Key secondary end points were analysed using negative binomial regression (gout flares) or CMH test (tophus response). Mean rates of gout flares were adjusted for day -7 renal function, tophus status at screening and length of exposure to randomised study medication. The time points and analytical methods used in the study were agreed with multiple regulatory agencies.

Safety data are listed by treatment arm and are not subjected to statistical testing. TEAEs are coded by system organ class and preferred term and are listed according to incidence, severity, relation to study medication and relation to discontinuation. To better identify potential clinically relevant changes in sCr related to lesinurad by minimising discrepancies due to intra-subject variability, baseline sCr was defined as the highest value within 14 days prior to first dose of study medication. Relative increase in sCr (ie, $\geq 1.5\times$ and $\geq 2.0\times$ the baseline level at any time) was selected as the most clinically relevant sCr

assessment.^{23–24} Resolution of sCr elevation was defined as an sCr value returned to $\leq 1.2\times$ baseline.

A sample size of approximately 600 patients was planned to be recruited, for an allocation of approximately 200 patients to each treatment arm. This sample size was calculated to provide greater than 90% power to detect a difference in response rate between treatment groups if the allopurinol-alone group had a 30% response rate and the lesinurad groups had response rates as low as 48% using Fisher's exact test, adjusting for multiplicity with $\alpha=0.025$, two-sided, for each test.

All randomised patients who received at least one dose of study medication were included in the intent-to-treat (ITT) population, which was the primary population for efficacy and safety assessments.

RESULTS

Patient disposition

Of the 2199 patients screened, 611 were randomised at 152 sites. Of the 611 randomised patients, 610 received at least one dose of study medication (figure 2).

Demographic characteristics and clinical history

Demographics and baseline disease characteristics were similar between treatment groups (table 1). Patients generally had long-standing symptomatic gout (mean (\pm SD) time since diagnosis 11.5 ± 9.3 years) and elevated baseline sUA (mean 6.9 ± 1.2 mg/dL (410 ± 71 μ mol/L)), with high rates of one or more predefined comorbidities (ie, CV risk factors or kidney stones) at 79.2%.

Most patients (84.1%) received allopurinol at a daily dose of 300 mg, with 6.6% receiving <300 mg and 9.3% receiving >300 mg; the overall dose range was 200–900 mg.

Study medications

Proportions of patients exhibiting $\geq 80\%$ compliance with study medication were 97.6%, 94.1% and 94.5% in the allopurinol-alone, lesinurad 200 mg+allopurinol and lesinurad 400 mg+allopurinol groups, respectively.

Efficacy assessments

Primary end point of sUA response and secondary sUA end points

Proportions of patients achieving sUA level of <6.0 mg/dL (<357 μ mol/L) by month 6 (the primary end point) were 23.3%, 55.4% and 66.5% in the allopurinol-alone, lesinurad 200 mg+allopurinol and lesinurad 400 mg+allopurinol groups, respectively, using NRI—significant differences were identified for both lesinurad+allopurinol groups versus allopurinol-alone ($p<0.0001$; CMH test) (figure 3).

Subgroup analyses based on age, sex, race, baseline sUA, comorbidities, renal function and thiazide diuretic use provided results consistent with primary analysis of the ITT population (see online supplementary material 4 for renal function and diuretic analyses).

Proportions of patients achieving the sUA target of <6.0 mg/dL (<357 μ mol/L) were greater in the lesinurad 200 mg+allopurinol and lesinurad 400 mg+allopurinol versus allopurinol-alone group at all monthly assessments from month 1 to month 12 (nominal $p<0.0001$, all comparisons). Proportions of patients achieving sUA level of <5.0 mg/dL (<297 μ mol/L) and <4.0 mg/dL (<238 μ mol/L) were also greater in both lesinurad+allopurinol groups versus allopurinol-alone group at each monthly visit (sUA <5.0 mg/dL (<297 μ mol/L): nominal $p<0.0001$, both comparisons; sUA <4.0 mg/dL (<238 μ mol/L): nominal $p<0.0001$, both comparisons, except $p<0.01$ at

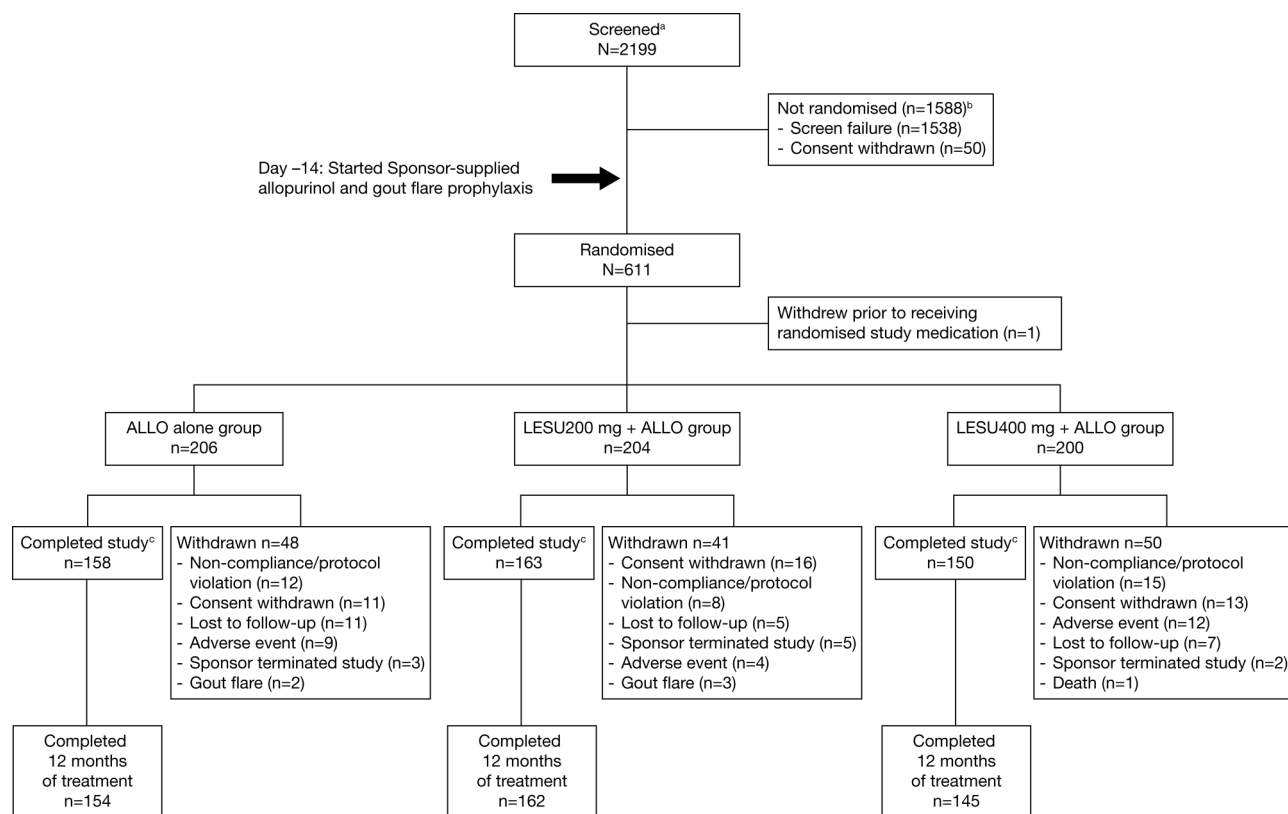


Figure 2 Patient disposition is shown. ^aScreened was defined as signing an informed consent form; ^b2 deaths reported for non-randomised patients during screening and ^ccompleted the study with or without completing randomised study medication. One additional death occurred in the LESU 400 mg+ALLO group. The subject experienced a serious adverse event and withdrew from the study. The primary reason for study withdrawal was reported as 'adverse event'. Of the 1538 screen failures, 1183 were related to inclusion criteria, 252 to exclusion criteria, 94 to both inclusion and exclusion criteria and 9 to other. ALLO, allopurinol; LESU, lesinurad.

month 1, lesinurad 200 mg+allopurinol). **Figure 3** shows proportions of patients at each sUA threshold by months 6 and 12.

Mean sUA levels were lower in both lesinurad+allopurinol groups versus allopurinol-alone group at all time points (nominal $p < 0.001$, both comparisons compared with allopurinol-alone therapy) (**figure 4**).

Secondary end point: gout flares requiring treatment

The gout flare rate and the proportions of patients with gout flares requiring treatment were low and similar in all groups throughout the study. Mean (\pm SE) rates of gout flares requiring treatment from the end of month 6 to end of month 12 were 0.83 ± 0.13 for allopurinol-alone group versus 0.73 ± 0.12 and 0.77 ± 0.13 , respectively, in the lesinurad 200 mg+allopurinol and lesinurad 400 mg+allopurinol groups ($p = 0.57$ and 0.75 vs allopurinol-alone group). Proportions of patients with a gout flare requiring treatment through the study are shown in online supplementary figure S2.

Secondary end point: tophus resolution

The numbers of patients with one or more target tophi at baseline were low: 33, 35 and 29 in the allopurinol-alone, lesinurad 200 mg+allopurinol and lesinurad 400 mg+allopurinol groups, respectively. In these respective groups, 33.3%, 31.4% and 27.6% of patients achieved complete resolution of one or more target tophi by month 12 ($p > 0.05$, both lesinurad+allopurinol groups vs allopurinol-alone group).

Safety assessments

Adverse events

TEAEs were reported in 70.9%, 74.5% and 80.5% of the allopurinol-alone, lesinurad 200 mg+allopurinol and lesinurad 400 mg+allopurinol groups, respectively (**table 2**). The majority of TEAEs in each group had a maximum severity of grade 1 or grade 2, based on Rheumatology Common Toxicity Criteria.²⁵ The most common individual TEAEs—reported for allopurinol-alone, lesinurad 200 mg+allopurinol and lesinurad 400 mg+allopurinol groups, respectively—were upper respiratory tract infection (10.2%, 6.9%, 15.0%), hypertension (4.9%, 8.3%, 8.0%), arthralgia (4.4%, 11.8%, 3.0%), increased blood creatinine (3.4%, 3.9%, 9.5%) and diarrhoea (3.4%, 4.9%, 7.0%). The most common grade 3 or grade 4 TEAEs in these respective groups were increased blood creatine kinase (1.5%, 0.5%, 1.5%) and myocardial infarction (MI) (0%, 0%, 1.5%).

Serious TEAEs were reported in 3.9%, 4.4% and 9.5% of patients, respectively (**table 2**). Two deaths occurred in the lesinurad 400 mg+allopurinol group (pulmonary oedema and gastric cancer, respectively). TEAEs led to study-medication discontinuation in 5.3%, 3.4% and 9.5% of the allopurinol-alone, lesinurad 200 mg+allopurinol and lesinurad 400 mg+allopurinol groups, respectively; the most common TEAE leading to discontinuation was increased blood creatinine (1.0%, 0% and 2.5%, respectively).

Renal safety analyses

Renal-related TEAEs occurred in 4.9%, 5.9% and 15.0%, of allopurinol-alone, lesinurad 200 mg+allopurinol and lesinurad

Table 1 Demographic and baseline disease characteristics (intent-to-treat population)

	ALLO alone (n=206)	Lesinurad 200 mg+ALLO (n=204)	Lesinurad 400 mg+ALLO (n=200)	Total (n=610)
Sex (n (%))				
Male	196 (95.1)	197 (96.6)	194 (97.0)	587 (96.2)
Female	10 (4.9)	7 (3.4)	6 (3.0)	23 (3.8)
Race (n (%))				
White	155 (75.2)	167 (81.9)	160 (80.0)	482 (79.0)
Black or African-American	22 (10.7)	15 (7.4)	21 (10.5)	58 (9.5)
Asian	14 (6.8)	10 (4.9)	9 (4.5)	33 (5.4)
Native Hawaiian or other Pacific Islander	5 (2.4)	3 (1.5)	2 (1.0)	10 (1.6)
American-Indian or Alaska Native	1 (0.5)	1 (0.5)	0	2 (0.3)
Other	8 (3.9)	4 (2.0)	6 (3.0)	18 (3.0)
Missing	0	0	1 (0.5)	1 (0.2)
Age (years)				
Mean (SD)	51.4 (10.56)	51.0 (11.11)	51.3 (11.08)	51.2 (10.90)
Min, max	21, 80	21, 82	18, 80	18, 82
BMI (kg/m²)				
Mean (SD)	33.87 (6.19)	34.67 (6.43)	33.81 (6.68)	34.12 (6.44)
Min, max	21.91, 56.27	22.55, 55.63	22.76, 69.36	21.91, 69.36
Duration since gout diagnosis (years)				
Mean (SD)	11.31 (9.38)	12.25 (9.75)	11.02 (8.59)	11.53 (9.26)
Min, max	0.2, 53.0	0.5, 45.0	0.0, 47.4	0.0, 53.0
Presence of tophi at screening (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)
No. 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)
Min, max	1, 5	1, 5	1, 5	1, 5
No. of gout flares in the past 12 months				
Mean (SD)	5.8 (4.92)	6.7 (7.01)	6.1 (5.65)	6.2 (5.93)
Min, max	2, 30	2, 50	2, 48	2, 50
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)
CV risk factors (n (%))				
Hypertension	141 (68.4)	131 (64.2)	121 (60.5)	393 (64.4)
Hyperlipidaemia	76 (36.9)	86 (42.2)	93 (46.5)	255 (41.8)
Type 2 diabetes	28 (13.6)	31 (15.2)	26 (13.0)	85 (13.9)
History of kidney stones (n (%))				
28 (13.6)	23 (11.3)	18 (9.0)	69 (11.3)	
Baseline thiazide/thiazide-like diuretic use (n (%))				
37 (18.0)	43 (21.1)	35 (17.5)	115 (18.9)	
sUA at baseline (mg/dL) (μmol/L)				
Mean (SD)	7.0 (1.3) (416 (75))	6.8 (1.1) (407 (66))	6.9 (1.2) (410 (71))	6.9 (1.2) (410 (71))
Min, max	3.4, 11.3 (202, 672)	4.0, 11.3 (238, 672)	3.8, 11.0 (226, 654)	3.4, 11.3 (202, 672)
sUA category at baseline (n (%))				
<8.0 mg/dL (<476 μmol/L)	162 (78.6)	177 (86.8)	164 (82.0)	503 (82.5)
≥8.0 mg/dL (≥476 μmol/L)	44 (21.4)	27 (13.2)	36 (18.0)	107 (17.5)

Continued

Table 1 Continued

	ALLO alone (n=206)	Lesinurad 200 mg+ALLO (n=204)	Lesinurad 400 mg+ALLO (n=200)	Total (n=610)
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)				
Mean (SD)	308.7 (69.29)	313.5 (78.33)	314.8 (77.62)	312.3 (75.08)
Min, max	200, 600	200, 900	200, 900	200, 900

ALLO, allopurinol; BMI, body mass index; CV, cardiovascular; eCrCl, estimated creatinine clearance; NSAID, non-steroidal anti-inflammatory drug; sUA, serum uric acid.

400 mg+allopurinol groups, respectively. The most common renal-related TEAEs in these respective groups were increased blood creatinine (3.4%, 3.9%, 9.5%), increased blood urea (0%, 2.0%, 1.5%) and renal failure (0.5%, 1.0%, 1.5%). One patient (0.5%) in the allopurinol-alone group experienced a serious renal-related TEAE, versus no patients in the lesinurad 200 mg+allopurinol and two patients (1.0%) in the lesinurad 400 mg+allopurinol group. Kidney stone TEAEs were reported in 0.5%, 0% and 3.0%, respectively.

sCr elevation $\geq 1.5 \times$ baseline occurred in 3.4% (n=7), 5.9% (n=12) and 15.0% (n=30) of allopurinol-alone, lesinurad 200 mg+allopurinol and lesinurad 400 mg+allopurinol groups, respectively. sCr elevation $\geq 1.5 \times$ was transient and reversible in most cases and the majority of sCr elevations resolved by the time of the next assessment; there were three unresolved sCr elevations in the allopurinol-alone group at last visit versus none in the lesinurad 200 mg+allopurinol and seven in the lesinurad 400 mg+allopurinol group (see online supplementary table S1). sCr elevation $\geq 2.0 \times$ baseline occurred in 0%, 2.0% (n=4) and 8.0% (n=16) of patients, respectively. Again, most elevations $\geq 2.0 \times$ baseline were transient and reversible; no sCr elevations $\geq 2.0 \times$ were unresolved at last visit in the lesinurad 200 mg+allopurinol group and five cases were unresolved in the lesinurad 400 mg+allopurinol group. In approximately two-thirds of sCr elevations, resolution occurred while patients continued on study medication.

In all treatment groups, proportions of patients with an sCr elevation $\geq 1.5 \times$ baseline tended to be higher for patients (1) who were taking an NSAID than colchicine; (2) who did not achieve target sUA at month 6 versus responders and (3) who had one or more tophi at screening versus those without tophi, although small subgroup sizes render interpretation difficult (see online supplementary table S2). There was no apparent association between sCr elevation and baseline renal function or other concomitant medications.

Renal function remained stable across the treatment groups, as measured by mean (SD) changes in eCrCl, from baseline to last value. Mean (\pm SD) changes in eCrCl in the allopurinol-alone, lesinurad 200 mg+allopurinol and lesinurad 400 mg+allopurinol groups were 3.0 ± 9.7 , -0.5 ± 11.5 and -5.7 ± 13.9 mg/dL, respectively, from baseline to last value on treatment and were 1.8 ± 11.7 , 2.7 ± 10.0 and 1.1 ± 24.2 mg/dL from baseline to last value off treatment at follow-up (in patients not entering a separate extension study, n=133).

CV safety analyses

TEAEs were adjudicated as CV events in 5.3% (n=11 patients), 3.9% (n=8 patients) and 3.0% (n=6 patients) of allopurinol-alone, lesinurad 200 mg+allopurinol and lesinurad 400 mg+allopurinol groups, respectively. CEAC-adjudicated criteria for MACE were met by three patients (four events, including three MIs and one death due to pulmonary oedema), all in

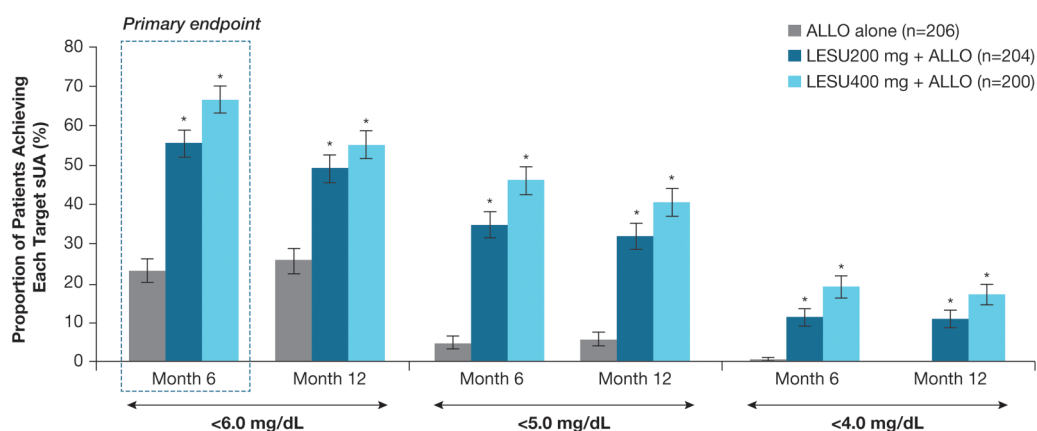
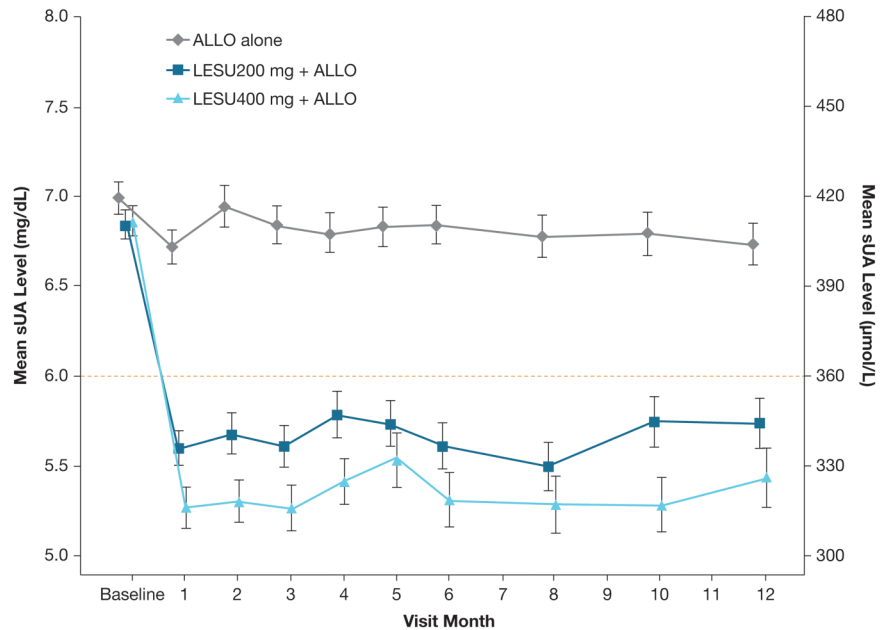


Figure 3 Proportions of patients achieving sUA target of <6.0 mg/dL (<357 μ mol/L), <5.0 mg/dL (<297 μ mol/L) and <4.0 mg/dL (<238 μ mol/L), by months 6 and 12 (ITT population) are shown. Primary end point: proportion of patients achieving sUA target of <6.0 mg/dL (<357 μ mol/L) by month 6. *p<0.0001. Note: Subjects missing sUA results were treated as non-responders. All comparisons used a two-sided Cochran-Mantel-Haenszel test stratified by day -7 renal function and tophus status during screening (randomised stratification factor values), with non-responder imputation and adjustment for multiple comparisons for the primary end point (Bonferroni correction). ALLO, allopurinol; ITT, intention to treat; LESU, lesinurad; sUA, serum uric acid.

Figure 4 Graph showing the mean (SE) sUA levels by visit (observed cases, intent-to-treat population). Mean change from baseline for each active treatment group was compared with the ALLO-alone group using analysis of covariance, with $p < 0.001$ at each time point. ALLO, allopurinol; LESU, lesinurad; sUA, serum uric acid.



the lesinurad 400 mg+allopurinol group. Non-MACE CV end points were reported in five patients (five events), two patients (two events) and no patients, respectively.

Other clinical laboratory tests and vital signs

Clinical laboratory results (excluding renal laboratory results, reported above) and urinalysis were comparable between treatment groups. Elevations in creatine kinase $>5\times$ upper limit of normal were in 5.3%, 2.0% and 3.0% of allopurinol-alone, lesinurad 200 mg+allopurinol and lesinurad 400 mg+allopurinol groups, respectively. There were no notable changes in vital signs.

DISCUSSION

Allopurinol at the 300 mg dose is frequently unable to achieve target sUA levels.^{5–8} Guidelines recommend increasing the allopurinol dose above 300 mg/day to attain target sUA, but this happens rarely in practice, in part due to physician's concerns over safety of doses >300 mg.^{4 6 25–29} Other management options include switching from allopurinol to febuxostat, or adding a uricosuric to allopurinol, based on evidence from earlier, small trials.^{30–32} CLEAR 2 and the similarly designed CLEAR 1¹⁵ were the initial large studies to validate a combination approach using a URAT1 inhibitor that inhibits uric acid reabsorption (ie, lesinurad) with allopurinol.

In CLEAR 2, lesinurad at both doses (200 or 400 mg) combined with continued allopurinol significantly increased the proportions of patients achieving sUA target of <6.0 mg/dL (<357 $\mu\text{mol/L}$) by month 6 ($p < 0.0001$), with more than twice as many patients reaching goal versus allopurinol-alone therapy. Onset of sUA reduction in the lesinurad groups was rapid, with significant differences from allopurinol-alone group by first assessment at month 1. The significant increase in proportions of patients who achieved sUA target in both lesinurad+allopurinol groups versus allopurinol-alone group was sustained over the 12-month study. Consistent response rates were observed, irrespective of renal function or thiazide diuretic use.

There were no statistically significant differences favouring lesinurad treatment in the rates of gout flare requiring treatment or complete resolution of tophi, which occurred at low incidences at baseline and during study. In relation to these key

secondary end points, treatment may be required for more than 12 months for the full effects to be observed.³³

Lesinurad was generally well tolerated, particularly at the 200 mg dose, where the TEAE and serious TEAE profiles were comparable with the allopurinol-alone group. Higher TEAE incidences were seen in the lesinurad 400 mg+allopurinol group. Renal-related TEAEs occurred at similar incidences in the lesinurad 200 mg+allopurinol and allopurinol-alone groups, with a higher incidence in the lesinurad 400 mg+allopurinol than lesinurad 200 mg+allopurinol group; the lesinurad 400 mg+allopurinol group also showed a higher incidence of sCr elevation. The majority of sCr elevations resolved by the next assessment and in most cases without interruption in study medication. Mean renal function did not differ between the treatment groups both before and after treatment. The mechanism of sCr elevation associated with lesinurad may be via increased excretion of urinary uric acid, which has the potential to induce uric acid microcrystallisation in the renal tubules. Urine protein-to-creatinine ratio and urinalyses did not change during the study, suggesting that sCr elevation was not associated with renal parenchymal sequelae. Patients with unresolved sCr elevations showed no defining characteristics compared with those whose sCr elevation resolved.

Other therapies which inhibit URAT1 have been associated with development of kidney stones.^{34 35} The lack of increase in kidney stone numbers during lesinurad therapy is potentially because of concomitant allopurinol use, which reduces uric acid production.^{36 37} The rate of nephrolithiasis may also have been influenced by timing of lesinurad administration, as once-daily dosing in the morning increases urinary uric acid at a time when urine volume and urine pH are highest and the potential for uric acid precipitation is lowest.^{38 39}

Prescribing information for the approved dose of lesinurad 200 mg recommends assessment of renal function prior to initiation of therapy and periodically thereafter, particularly in patients whose CrCl is 30 – <45 mL/min, with discontinuation recommended if CrCl is persistently <30 mL/min (ie, severe renal impairment). Lesinurad is also contraindicated in subjects with end-stage renal disease, kidney transplant recipients or patients on dialysis.

Table 2 Overall summary of TEAEs (safety population)

Adverse event category, n (%)	ALLO alone (n=206)	Lesinurad 200 mg+ALLO (n=204)	Lesinurad 400 mg+ALLO (n=200)
Any TEAE	146 (70.9)	152 (74.5)	161 (80.5)
Any TEAE with RCTC toxicity grade 3 or 4	23 (11.2)	19 (9.3)	27 (13.5)
Any TEAE possibly related to randomised study medication	39 (18.9)	40 (19.6)	50 (25.0)
Any serious TEAE	8 (3.9)	9 (4.4)	19 (9.5)
Any fatal TEAE	0	0	2 (1.0)
Any TEAE leading to randomised study medication discontinuation	11 (5.3)	7 (3.4)	19 (9.5)
Any TEAE leading to study withdrawal	7 (3.4)	4 (2.0)	12 (6.0)
Individual serious TEAEs, n (%)			
Infections and infestations			
Pneumonia	0	2 (1.0)	0
Bronchopneumonia	0	0	1 (0.5)
Cellulitis	0	0	1 (0.5)
Empyema	0	1 (0.5)	0
Pyelonephritis chronic	0	0	1 (0.5)
Sinobronchitis	0	1 (0.5)	0
Abscess limb	1 (0.5)	0	0
Appendicitis	1 (0.5)	0	0
Diverticulitis	1 (0.5)	0	0
Neoplasms benign, malignant and unspecified			
Basal cell carcinoma	0	0	1 (0.5)
Gastric cancer	0	0	1 (0.5)*
Ovarian adenoma	0	1 (0.5)	0
Parathyroid tumour benign	0	1 (0.5)	0
Prostate cancer	0	0	1 (0.5)
Pancreatic neuroendocrine tumour	1 (0.5)	0	0
Metabolism and nutrition disorders			
Gout flare	0	0	2 (1.0)
Psychiatric disorders			
Depression	0	1 (0.5)	0
Dissociative disorder	0	0	1 (0.5)
Nervous system disorders			
Subarachnoid haemorrhage	1 (0.5)	0	0
Cardiac disorders			
Myocardial infarction	0	0	3 (1.5%)
Atrial fibrillation	0	1 (0.5)	0
Coronary artery disease	0	0	1 (0.5)
Intracardiac thrombus	0	0	1 (0.5)
Vascular disorders			
Hypertensive crisis	0	0	1 (0.5)
Respiratory, thoracic and mediastinal disorders			
Pulmonary oedema	0	0	1 (0.5)*
Gastrointestinal disorders			
Duodenal ulcer haemorrhage	1 (0.5)	0	1 (0.5)
Gastrointestinal haemorrhage	0	1 (0.5)	0

Continued

Table 2 Continued

Adverse event category, n (%)	ALLO alone (n=206)	Lesinurad 200 mg+ALLO (n=204)	Lesinurad 400 mg+ALLO (n=200)
Musculoskeletal and connective tissue disorders			
Osteoarthritis	0	0	2 (1.0)
Arthralgia	0	1 (0.5)	0
Back pain	0	1 (0.5)	0
Flank pain	0	1 (0.5)	0
Intervertebral disc degeneration	0	0	1 (0.5)
Renal and urinary disorders			
Nephrolithiasis	0	0	2 (1.0)
Renal failure acute	1 (0.5)	0	1 (0.5)
Renal impairment	0	0	1 (0.5)
General disorders and administration site conditions			
Adverse drug reaction	0	1 (0.5)	0
Non-cardiac chest pain	0	1 (0.5)	0
Injury, poisoning and procedural complications			
Multiple drug overdose	0	1 (0.5)	0
Multiple injuries	0	1 (0.5)	0
Femur fracture	1 (0.5)	0	0

*Fatal serious TEAE.
ALLO, allopurinol; RCTC, Rheumatology Common Toxicity Criteria; TEAE, treatment-emergent adverse event.

CV comorbidities and risk factors were present in approximately 80% of patients, reflecting the high rates of CV disease in patients with gout.^{40–42} The proportions of patients with TEAEs classified as CV events during study were low and similar in treatment groups. Incidences of MACE events—that is, serious CV events including CV deaths, non-fatal MI and non-fatal stroke—were similarly low. Three patients experienced MACE in the study, all receiving lesinurad 400 mg. Low rates of MACE events during gout treatment were also reported in the open-label Long-term Allopurinol Safety Study Evaluating Outcomes in Gout Patients (LASSO) study, which reported a rate of 0.58% over 6 months for MACE during allopurinol treatment (incidence rate 1.42/100 patient-years).⁶

Limitations of CLEAR 2 include the limited data on allopurinol doses >300 mg, the relatively low proportion of women enrolled, low number of patients with evaluable tophi and the relatively short-term follow-up period that limits the ability to adequately study flares and tophi. Rates of gout flares and tophus resolution over the longer term are being investigated in an extension study (NCT01808131).

In conclusion, lesinurad (200 and 400 mg), a novel SURI, in combination with allopurinol significantly increased the proportion of patients achieving the target sUA of <6.0 mg/dL (<357 μmol/L) by month 6 and other sUA end points compared with allopurinol-alone therapy. There were no statistically significant treatment-group differences favouring lesinurad for rate of gout flares or complete tophus resolution. The combination therapy was generally well tolerated, particularly at the 200 mg lesinurad dose approved by the US Food and Drug Administration and European Medicines Agency, except for higher incidences of predominantly reversible sCr elevation compared with allopurinol-alone therapy. There were no cases of unresolved sCr elevation ≥1.5× in the lesinurad 200 mg +allopurinol group, versus three unresolved cases in the allopurinol-alone group and seven in the lesinurad 400 mg

+allopurinol group. By using a dual mechanism approach to reduce sUA, combination therapy with lesinurad and allopurinol represents a treatment option for patients with gout inadequately controlled on allopurinol-alone therapy.

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