Lesinurad Combined With Allopurinol

A Randomized, Double-Blind, Placebo-Controlled Study in Gout Patients With an Inadequate Response to Standard-of-Care Allopurinol (a US-Based Study)

Kenneth G. Saag,1 David Fitz-Patrick,2 Jeff Kopicko,3 Maple Fung,3 Nihar Bhakta,3 Scott Adler,4 Chris Storgard,3 Scott Baumgartner,3 and Michael A. Becker5

Objective. Lesinurad is a selective uric acid re-absorption inhibitor used for the treatment of gout in combination with a xanthine oxidase inhibitor. The Combining Lesinurad with Allopurinol Standard of Care in Inadequate Responders (CLEAR 1) study, a 12-month, multi-center, randomized, double-blind, placebo-controlled phase III trial, was conducted to investigate daily lesinurad (200 mg or 400 mg orally) added to allopurinol versus placebo plus allopurinol in patients with serum urate (UA) levels above a target of <6.0 mg/dl.

Methods. Patients receiving ≥300 mg of allopurinol (≥200 mg in those with moderate renal impairment) who had serum UA levels ≥6.5 mg/dl at screening and ≥2 gout flares during the previous year were studied. The primary end point was the proportion of patients achieving a serum UA level of <6.0 mg/dl at month 6. Key secondary end points were the mean gout flare rate requiring treatment (months 7–12) and the proportions of patients with complete resolution of ≥1 target tophus (month 12). Safety assessments included adverse events and laboratory

Conclusion. Lesinurad added to allopurinol provided benefit as compared with allopurinol alone in reducing serum UA levels and represents a new treatment option for patients needing additional urate-lowering therapy.

Current guidelines for the long-term management of gout recommend a combination of lifestyle management and/or pharmacotherapy to lower serum urate (UA) levels to <6.0 mg/dl in most patients or <5.0 mg/dl in patients with more severe disease (1). Allopurinol is the most widely used xanthine oxidase inhibitor and is recommended in treatment guidelines as a first-line urate-lowering therapy in patients with gout, with a maximum daily dose of 800 mg based on the highest approved dose in the
As an inhibitor of xanthine oxidase, allopurinol reduces uric acid production and lowers serum UA levels. However, many patients—more than 50% in clinical trials—do not achieve the serum UA target of < 6.0 mg/dl at the most commonly used allopurinol dosage of 300 mg/day (3–6). In cases where the serum UA target cannot be achieved with allopurinol alone at an appropriate dosage, treatment guidelines recommend substitution therapy (e.g., with febuxostat or a uricosuric agent) or combination therapy that includes allopurinol with a uricosuric agent (1,7,8). The current US-based study is 1 of 2 replicate randomized controlled trials where this recommendation is formally investigated for the first time.

Lesinurad (RDEA594) is a novel selective uric acid reabsorption inhibitor for the treatment of gout in combination with a xanthine oxidase inhibitor. Lesinurad inhibits the uric acid transporter URAT1, which is responsible for reabsorption of urate from the renal tubular lumen (9). By inhibiting URAT1, lesinurad increases the excretion of uric acid in the kidney and lowers serum UA levels (10,11). Lesinurad in combination with allopurinol therefore provides a dual mechanism of action for managing the hyperuricemia of gout: increased urinary excretion of uric acid and reduced urate production.

Lesinurad in combination with allopurinol has demonstrated greater reductions in serum UA than allopurinol alone in phase I and II studies (12–14). The current phase III study, Combining Lesinurad with Allopurinol Standard of Care in Inadequate Responders (CLEAR 1), is 1 of 2 replicate, randomized, double-blind, placebo-controlled, multicenter studies to investigate lesinurad (200 mg or 400 mg orally, once daily) in combination with allopurinol (at the investigator-determined appropriate dosage) in patients with gout (ClinicalTrials.gov Identifier: NCT01510158).

PATIENTS AND METHODS

Study participants. Men and women (ages 18–85 years; body mass index < 45 kg/m²) with a diagnosis of gout were eligible for study inclusion if they had an inadequate response to standard-of-care allopurinol (defined below). The diagnosis of gout was based on the American College of Rheumatology (ACR) criteria for the classification of acute arthritis of primary gout (15). Inclusion criteria were receipt of a stable dosage of allopurinol (judged by the treating physician to be medically appropriate) from 300 mg/day (or at least 200 mg/day in patients with moderate renal impairment [estimated creatinine clearance of 30–59 ml/minute]) up to 800 mg/day (16) as the sole urate-lowering therapy for ≥8 weeks prior to screening. A serum UA level of ≥ 6.5 mg/dl at screening and ≥ 6.0 mg/dl ≤ 7 days prior to the start of treatment on day 1 was required. Patients must also have reported ≥ 2 gout flares during the previous 12 months.

Complete exclusion criteria are shown in Supplementary Table 1 (available on the Arthritis & Rheumatology web site at http://onlinelibrary.wiley.com/doi/10.1002/art.39840/abstract). A history of kidney stones was not a criterion for study exclusion.

Trial design. Treatment procedures. CLEAR 1 was a 12-month, multicenter, randomized, double-blind, placebo-controlled, US-based phase III trial investigating the efficacy and safety of lesinurad (200 mg or 400 mg orally, once a day) in combination with allopurinol versus allopurinol in combination with placebo (control arm). The study included a screening period of ~28 days, which included a run-in period of ~14 days during which gout flare prophylaxis was initiated, and a 12-month double-blind treatment period (Figure 1).

Eligible patients were randomized in a double-blind manner to receive lesinurad 200 mg, lesinurad 400 mg, or placebo in a 1:1:1 ratio, added to continued treatment with allopurinol at the same prestudy dosage (permitted range 300–800 mg/day; 200 mg allowed in those with moderate renal impairment). 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 1 cup of water. Patients were encouraged to drink 2 liters of fluid a day and remain well hydrated, according to the ACR guidelines (1). Compliance with study medication was determined by assessment of dispensing records and verification of returned medication packaging. Concomitant medication use was also recorded at each study visit.

Gout flare prophylaxis was initiated at the same time as sponsor-provided allopurinol (day −14) and consisted of colchicine (0.5 mg or 0.6 mg once a day, per protocol and as locally available) or a nonsteroidal antiinflammatory drug (NSAID) if patients were intolerant of, or had contraindications for, colchicine. Gout flare prophylaxis was continued through month 5 unless the patient became intolerant or developed toxicity to the drug.

The study was conducted in accordance with Independent Ethics Committee E6 Good Clinical Practice, the Declaration of Helsinki (October 2008), and applicable local regulatory requirements (including Institutional Review Board approval and Health Insurance Portability and Accountability Act assurances). Patients were permitted to withdraw from the medication or the study at any time. The study was conducted between February 8, 2012 and July 1, 2014.

Evaluations. The primary efficacy end point was the proportion of patients with a serum UA level of < 6.0 mg/dl by month 6 in each treatment group. There were 2 key secondary end points. First was a mean rate of gout flares requiring treatment for the 6-month period from the end of month 6 to the end of month 12. Permitted gout flare treatments included colchicine, analgesics, and/or antiinflammatory medications, including oral and intraarticular corticosteroids. Gout flares were reported in a daily electronic diary. Second was the proportion of patients with target tophi at baseline who experienced complete resolution of ≥1 tophus by month 12. Target tophi (up to 5 per patient) were those measuring ≥ 5 mm and ≤ 20 mm in the longest diameter located on the hands/wrists and/or feet/ankles. Tophi were measured with digital Vernier calipers every 3 months.

Other secondary efficacy end points included the proportion of patients with serum UA levels of < 6.0 mg/dl, < 5.0 mg/dl, and < 4.0 mg/dl at each monthly visit, as well as the mean absolute change and the mean percentage change from baseline in serum UA levels at each visit. Patients were assessed at baseline (day 1) and from month 1 through month 12 for serum UA levels and were assessed daily by diary for gout flare data.

Safety assessments included treatment-emergent adverse events (TEAEs; coded according to the Medical Dictionary for Regulatory Activities [MedDRA], version 14.0), clinical laboratory
data, physical examination findings, electrocardiogram findings, and vital signs. Adverse events of special interest included assessments of renal and cardiovascular (CV) safety. Renal safety assessments were included because renal impairment is a common comorbid condition in patients with gout (7). Renal safety is also a topic of special interest because of the uricuresis that is caused by lesinurad (12). Increases in the excretion of urinary uric acid have the potential to induce microcrystallization in the renal tubules and/or urinary system, which could manifest as acute uric acid nephropathy or kidney stones. Assessments of renal safety included renal-related and kidney stone TEAEs (Supplementary Table 2, available at http://onlinelibrary.wiley.com/doi/10.1002/art.39840/abstract) and clinical laboratory data, including serum creatinine, creatine kinase, urinary protein-to-creatinine ratio, and estimated creatinine clearance levels.

Another area of special interest was CV safety, because of the known high rates of CV risk factors (e.g., hypertension, hyperlipidemia, and diabetes mellitus) in patients with gout (17,18). An independent Cardiovascular Events Adjudication Committee (CEAC) routinely assessed adverse events for a potential CV relationship, with categorization into major adverse CV event (MACE) and non-MACE end points (Supplementary Table 3, available at http://onlinelibrary.wiley.com/doi/10.1002/art.39840/abstract) (19).

Patients who completed the double-blind treatment period in the CLEAR 1 trial were eligible to enroll in a separate extension study of lesinurad in combination with allopurinol. Those who did not enter the extension study attended a follow-up visit within 14 days of completing the double-blind treatment.

**Statistical analysis.** The study consisted of a 12-month treatment period, with the primary end point evaluated at month 6 and key secondary end points at month 12. Comparisons of proportions of responders based on serum UA levels between each of the 2 lesinurad plus allopurinol groups and the allopurinol-alone group were performed using the Cochran-Mantel-Haenszel 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 2 treatment comparisons with allopurinol alone at an alpha level of 0.025. Testing of the key secondary end points hierarchically at an alpha level of 0.05 was gated on both dosage contrasts being statistically significant for the primary end point. If only 1 of the primary end point dosage contrasts was significant, then alpha = 0.025 for each key secondary end point within the surviving dosage. All other efficacy end points were evaluated at alpha = 0.05 (nominal P value), 2-sided, without adjustment for multiple comparisons.

Results for the primary end point of serum UA response are expressed as proportions, corresponding adjusted 95% confidence intervals for the difference between proportions, and P values. Patients with missing values for any reason at month 6 were considered nonresponders (nonresponder imputation) (20).

Key secondary end points were analyzed using negative binomial regression (gout flares) or the Cochran-Mantel-Haenszel test (tophus response). Mean rates of gout flares were adjusted for day –7 renal function, tophus status at screening, and duration of exposure to randomized study medication. Safety data are presented by treatment arm and were not subjected to statistical testing. TEAEs are coded by system organ class and preferred term and are listed according to their occurrence, severity, relation to study medication, and relation to discontinuation. In order to better identify potentially clinically relevant changes in serum creatinine levels related to lesinurad by minimizing any discrepancies due to intrasubject variability, the baseline serum creatinine level was defined as the highest value within 14 days prior to the first dose of study medication. Relative increases in serum creatinine levels (i.e., ≥1.5 times and ≥2.0 times the baseline level) were calculated for the primary end point of serum UA response are expressed as proportions, corresponding adjusted 95% confidence intervals for the difference between proportions, and P values. Patients with missing values for any reason at month 6 were considered nonresponders (nonresponder imputation) (20).
Resolution of serum creatinine elevation was defined as a serum creatinine level that returned to \( \leq 1.2 \) times the baseline level.

A sample size of \( \sim 600 \) subjects to be recruited was planned, to yield an allocation of \( \sim 200 \) to each treatment arm. This sample size was calculated to provide \( 90\% \) power to detect a difference in the 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 \( \alpha = 0.025 \), 2-sided, for each test. A previous 4-week, phase IIb study of lesinurad in combination with allopurinol showed response rates (i.e., serum UA <6.0 mg/dl) of \( \sim 30\% \) for the allopurinol-alone arm versus \( \geq 70\% \) for the lesinurad (200 mg, 400 mg, and 600 mg) plus allopurinol arms (13).

All randomized patients who received \( \geq 1 \) dose of randomized study medication were included in the intent-to-treat population, which was the primary population for the efficacy and safety assessments.

RESULTS

Distribution of the study subjects. Of 2,377 patients screened, 607 were randomized at 138 study sites. The remaining 1,770 patients were withdrawn prior to randomization, including 1,709 who failed the screening step and 61 who withdrew their consent. Of the 607 randomized patients, 603 received at least 1 dose of study medication. Four patients withdrew prior to receiving study medication: 2 because they were non-compliant/deviated from the protocol and 2 because they withdrew their consent. A total of 150 patients (24.9%) withdrew during the study, with similar rates in the group taking allopurinol alone (24.4%), lesinurad 200 mg plus allopurinol (24.9%), and lesinurad 400 mg plus allopurinol (25.4%) (Figure 2).

Demographic characteristics and clinical history. The study patients were predominantly male (94.0%) and white (76.3%), with a mean \( \pm \) SD age of 51.90 \( \pm \) 11.28 years and a mean \( \pm \) SD body mass index of 34.77 \( \pm \) 6.66 kg/m\(^2\) (Table 1). The study population had, in general, longstanding symptomatic gout, with a mean \( \pm \) SD time since diagnosis of 11.84 \( \pm \) 9.37 years. The mean \( \pm \) SD baseline serum UA level was 6.94 \( \pm \) 1.27 mg/dl. Only 86 patients (14.3%) had tophi at screening, and 54 (9.0%) had \( \geq 1 \) target tophus (i.e., measurable on hands/wrists or
feet/ankles) at baseline; the mean ± SD number of target tophi in these patients was 1.9 ± 1.32. The study patients self-reported a mean ± SD of 4.8 ± 3.60 flares in the 12 months prior to study entry. Demographic and disease characteristics at baseline were similar between treatment groups (Table 1).
The dosage range of allopurinol administered at baseline was from 200 mg/day (permitted only for those with moderate renal impairment) to 600 mg/day, compared with the maximum permitted dosage of 800 mg/day. Most patients (90.5%) received allopurinol at a daily dose of 300 mg, consistent with general clinical practice (23); another 4.8% received a daily dose of 200 mg to <300 mg and 4.6% took >300 mg/day. One or more pre-defined comorbid conditions (i.e., CV risk factors or kidney stones) were recorded in 82.1% of patients.

**Study medications.** The overall proportions of patients exhibiting ≥80% compliance with study medications were 95.0%, 93.5%, and 93.0%, respectively, in the groups taking allopurinol alone, lesinurad 200 mg plus allopurinol, and lesinurad 400 mg plus allopurinol.

**Efficacy assessments.** *Primary endpoint of serum UA response and secondary serum UA end points.* The proportions of patients achieving a serum UA level of <6.0 mg/dl by month 6 (the primary end point) were 27.9%, 54.2%, and 59.2% in the groups taking allopurinol alone, lesinurad 200 mg plus allopurinol, and lesinurad 400 mg plus allopurinol, respectively. This represents a significant difference for each of the groups taking lesinurad plus allopurinol as compared with allopurinol alone (P < 0.0001 for each comparison; nonresponder imputation) (Figure 3).

Subgroup analyses based on age, sex, race, baseline serum UA levels, comorbid conditions, renal function, and thiazide diuretic use provided results consistent with those from the primary analysis in the intent-to-treat population. For the renal function and thiazide diuretic analyses, see Supplementary Figure 1 (available at http://onlinelibrary.wiley.com/doi/10.1002/art.39840/abstract).

The proportion of patients achieving a serum UA target level of <6.0 mg/dl was greater in both the lesinurad 200 mg plus allopurinol and the lesinurad 400 mg plus allopurinol groups than in the allopurinol-alone group at all monthly assessments from month 1 to month 12 (P < 0.0001 for each comparison; nonresponder imputation). The proportion of patients who achieved serum UA levels of <5.0 mg/dl and <4.0 mg/dl was also greater in both groups taking lesinurad plus allopurinol as compared with the group taking allopurinol alone, starting at month 1 and at each monthly visit through month 12 (serum UA target <5.0 mg/dl, P < 0.0001 for each comparison; serum UA target <4.0 mg/dl, P < 0.01 for lesinurad 200 mg plus allopurinol and P < 0.0001 for lesinurad 400 mg plus allopurinol). The proportions of patients at each serum UA threshold by months 6 and 12 are shown in Figure 3.

Mean serum UA levels were lower in both groups taking lesinurad plus allopurinol as compared with allopurinol alone at all time points assessed (P < 0.0001 for each comparison of the percentage change in serum UA levels from baseline) (Figure 4).

**Secondary end point: gout flare rate.** The gout flare rate and the proportion of patients with gout flares requiring treatment were low and were similar in all groups throughout the study. The mean ± SEM rates of gout flares requiring treatment from the end of month 6 to the end of month 12 were 0.58 ± 0.10 for the group taking allopurinol alone compared with 0.57 ± 0.10 and 0.51 ± 0.09 in the groups taking lesinurad 200 mg plus allopurinol and lesinurad 400 mg plus allopurinol (P = 0.98 and P = 0.61), respectively.

**Secondary end point: tophus resolution.** The numbers of patients with ≥1 target tophus at baseline were low: 17 (8.5%), 18 (9.0%), and 19 (9.5%), respectively, in the groups taking allopurinol alone, versus lesinurad 200 mg plus allopurinol, and lesinurad 400 mg plus allopurinol. Of these patients, 5 (29.4%), 0 (0%), and 4 (21.1%), respectively, achieved complete resolution of a target tophus by month 12 (P = 0.02 for allopurinol alone versus lesinurad 200 mg plus allopurinol and P = 0.60 for allopurinol alone versus lesinurad 400 mg plus allopurinol).
Safety assessments. Adverse events. TEAEs were reported in 68.7%, 73.1%, and 77.6% of those taking allopurinol alone, lesinurad 200 mg plus allopurinol, and lesinurad 400 mg plus allopurinol, respectively (Table 2). The majority of TEAEs in each group had a maximum severity of grade 1 or 2, based on Rheumatology Common Toxicity Criteria (RCTC) (24). Grade 3 or 4 TEAEs occurred in 6.0%, 10.9%, and 14.4% of patients in the 3 groups, respectively. TEAEs led to discontinuation of study medication in 4.0%, 8.0%, and 7.0% of patients in the respective groups. The most common individual TEAEs in the groups taking allopurinol alone, lesinurad 200 mg plus allopurinol, and lesinurad 400 mg plus allopurinol, respectively, were upper respiratory tract infection (5.5%, 10.9%, and 9.0%), increased blood creatine phosphokinase levels (2.5%, 4.5%, and 8.0%), sinusitis (2.0%, 4.5%, and 6.0%), increased blood creatinine levels (1.0%, 3.5%, and 7.0%), and headache (2.5%, 3.5%, and 6.0%). The most common grade 3 or 4 TEAEs in the respective groups were influenza (0%, 1.5%, and 1.0%) and acute myocardial infarction (0%, 0.5%, and 1.5%).

Serious TEAEs were reported in 5.5%, 4.5%, and 8.0% of the patients, respectively. Serious TEAEs occurring in more than 1 patient in any treatment group included cerebrovascular accident (2 patients) in those taking allopurinol alone, coronary artery disease (2 patients) in those taking lesinurad 200 mg plus allopurinol, and acute myocardial infarction (3 patients) and congestive heart failure (2 patients) in those taking lesinurad 400 mg plus allopurinol. One death due to cardiac arrest was reported in the lesinurad 200 mg plus allopurinol group.

Renal safety analyses. Renal-related TEAEs occurred in 3.5%, 4.0%, and 10.0% of the allopurinol-alone, lesinurad 200 mg plus allopurinol, and lesinurad 400 mg plus allopurinol groups, respectively. The most common renal-related TEAEs in these respective groups were increased blood creatinine levels (1.0%, 3.5%, and 7.0%), increased blood urea nitrogen levels (1.0%, 1.0%, and 1.5%), and renal failure (1.5%, 0.5%, and 1.5%). One serious renal-related TEAE (renal failure) was reported in 1 patient (0.5%) in the lesinurad 400 mg plus allopurinol group. Kidney stone TEAEs were reported in 2.0%, 1.0%, and 2.5% of patients, respectively.

Serum creatinine elevations ≥1.5 times the baseline levels occurred in 1.0% (n = 2), 6.0% (n = 12), and 15.9% (n = 32) of patients in the groups taking allopurinol alone, lesinurad 200 mg plus allopurinol, and lesinurad 400 mg plus allopurinol, respectively. Such elevations were transient and reversible in most cases during the study, and the majority had resolved by the time of the next assessment.

Table 2. Overall summary of treatment-emergent adverse events (safety population)*

| Adverse event                                             | Allopurinol alone (n = 201) | Lesinurad 200 mg plus allopurinol (n = 201) | Lesinurad 400 mg plus allopurinol (n = 201) |
|-----------------------------------------------------------|----------------------------|---------------------------------------------|---------------------------------------------|
| Any TEAE                                                  | 138 (68.7)                 | 147 (73.1)                                  | 156 (77.6)                                  |
| Any TEAE with RCTC toxicity grade 3 or 4                 | 12 (6.0)                   | 22 (10.9)                                   | 29 (14.4)                                   |
| Any TEAE possibly related to randomized study medication  | 19 (9.5)                   | 35 (16.4)                                   | 41 (20.4)                                   |
| Any serious TEAE                                          | 11 (5.5)                   | 9 (4.5)                                     | 16 (8.0)                                    |
| Any fatal TEAE                                           | 0                          | 1 (0.5)                                     | 0                                           |
| Any TEAE leading to discontinuation of randomized study medication | 8 (4.0)                   | 16 (8.0)                                   | 14 (7.0)                                    |
| Any TEAE leading to study withdrawal                      | 7 (3.5)                    | 9 (4.5)                                     | 8 (4.0)                                     |

* Values are the number (%). TEAE = treatment-emergent adverse event; RCTC = Rheumatology Common Toxicity Criteria.
There were 2 unresolved serum creatinine elevations in the lesinurad 200 mg plus allopurinol group and 9 unresolved elevations in the lesinurad 400 mg plus allopurinol group at the last study visit. Serum creatinine elevations ≥2.0 times the baseline levels were reported in 0%, 1.0% (n = 2), and 6.0% (n = 12) of patients in the respective groups. Again, most cases were transient and reversible. No serum creatinine elevations ≥2.0 times baseline levels were unresolved at the last study visit in the lesinurad 200 mg plus allopurinol group and 2 cases were unresolved in the lesinurad 400 mg plus allopurinol group. In approximately two-thirds of the cases, resolution of elevated serum creatinine levels occurred without interruption of the study medication.

In subgroups categorized according to baseline renal function (estimated creatinine clearance <60, <90, and ≥90 ml/minute), treatment-group differences in TEAE and serum creatinine elevation rates were consistent with those in the overall study population (data not shown).

Renal function remained stable over the study across the treatment groups. Mean ± SD changes in estimated creatinine clearance in the allopurinol-alone, lesinurad 200 mg plus allopurinol, and lesinurad 400 mg plus allopurinol groups, respectively, were 3.07 ± 10.54, −0.53 ± 10.98, and −3.56 ± 12.14 ml/minute from baseline to the last visit on treatment and were 2.15 ± 8.34, 3.26 ± 10.69, and 2.32 ± 10.12 ml/minute from baseline to the last visit off treatment. Mean changes in the urinary protein-to-creatinine ratio in the 3 study groups were 0.05 ± 0.39, 0.03 ± 0.14, and 0.05 ± 0.40, respectively.

Cardiovascular safety analyses. TEAEs were adjudicated as CV events in 3.5% (n = 7), 4.5% (n = 9), and 4.0% (n = 8), respectively, of those taking allopurinol alone, lesinurad 200 mg plus allopurinol, and lesinurad 400 mg plus allopurinol. CEAC-adjudicated criteria for MACE were met by 2 patients (3 events) in the allopurinol-alone, 2 patients (2 events) in the lesinurad 200 mg plus allopurinol, and 3 patients (3 events) in the lesinurad 400 mg plus allopurinol groups. Non-MACE CV end points were reported in 4 patients (5 events), 2 patients (2 events), and 3 patients (4 events) in the respective groups.

Other clinical laboratory tests and vital signs. Clinical laboratory test results, including hematologic analyses, liver function tests, other serum chemistry parameters (excluding renal laboratory results reported above), and urinalysis, demonstrated no notable differences between the treatment groups over time. Elevations in creatine kinase levels >5 times the upper limit of normal occurred in 3.5%, 5.5%, and 3.0%, respectively, in those taking allopurinol alone, lesinurad 200 mg plus allopurinol, and lesinurad 400 mg plus allopurinol. There were no notable changes in vital signs from baseline in any group during the study.

DISCUSSION

In the CLEAR 1 trial, we investigated the efficacy and safety of lesinurad (200 mg and 400 mg) in combination with allopurinol in patients who had a suboptimal response to standard-of-care allopurinol. Consistent with treatment patterns currently seen in clinical practice, the mean allopurinol dosage was 306.6 mg/day (range 200–600) (25,26). Lesinurad at a dosage of 200 mg/day is now approved by the US Food and Drug Administration and European Medicines Agency for the treatment of hyperuricemia associated with gout in combination with a xanthine oxidase inhibitor in patients who have not achieved target serum UA levels with a xanthine oxidase inhibitor alone.

Lesinurad at both doses (200 or 400 mg) in combination with allopurinol significantly increased the proportions of patients achieving a serum UA target level of <6.0 mg/dl by month 6 (the primary end point) (P < 0.0001 for each comparison), with approximately twice as many patients in the lesinurad 200 mg group reaching target levels when compared with allopurinol alone. The onset of serum UA reduction achieved with lesinurad plus allopurinol therapy was rapid, with significant differences from the levels achieved with allopurinol alone by the first serum UA assessment at month 1. The significant increase in the proportion of patients who achieved the serum UA target in both lesinurad plus allopurinol groups versus the allopurinol alone group was sustained over the 12-month study.

For the key secondary end points, including rates of gout flare requiring treatment and complete resolution of tophi, there were no statistically significant treatment differences favoring the lesinurad treatment groups. The mean rate of gout flares requiring treatment was low initially and declined in all groups during the study, favoring lesinurad but without significant between-group differences during the 6-month period from the end of month 6 to the end of month 12. Notably, discontinuation of prophylaxis at month 5 was not followed by an increase in the rate of gout flares requiring treatment in the lesinurad groups compared with the allopurinol-alone group. In the assessment of complete resolution of tophi, the proportion of evaluable patients with target tophi was low at baseline (9.0%), which affected the interpretation of this secondary end point. In relation to both gout flare rates and tophus resolution, a treatment duration of >12 months may be required for the full effects to be observed (25).

Lesinurad was generally well tolerated, particularly at the 200-mg dose, where the AE profile was comparable to that of allopurinol alone. The majority of TEAEs were grade 1 or 2, and the proportions of patients with serious adverse events and TEAEs leading to study withdrawal were comparable across treatment groups.
In renal safety analyses, the incidence of renal-related TEAEs was comparable in the lesinurad 200 mg plus allopurinol and allopurinol-alone groups, with higher rates for lesinurad 400 mg plus allopurinol.

Laboratory assessments revealed that serum creatinine elevations occurred at higher rates in the lesinurad plus allopurinol groups (particularly the 400-mg dose) versus allopurinol alone. In the majority of cases, elevated serum creatinine levels resolved during the study, without interruption of the study medications and without adverse effects on renal function over the course of the study. The mechanism of the serum creatinine elevation associated with lesinurad is believed to be due to increased excretion of urinary uric acid, which has the potential to induce uric acid microcrystallization in the renal tubules, which could manifest clinically as transient and reversible elevations in serum creatinine levels. There was no evidence that patients with impaired renal function at baseline were at increased risk of serum creatinine elevations during the study.

There was also no apparent association between serum creatinine elevations and either of the gout flare prophylaxis medications (colchicine or NSAID) (data not shown). The urinary protein-to-creatinine ratios and urinalysis results did not change during the study, suggesting that serum creatinine elevations were not associated with renal parenchymal sequelae.

Of note, the US prescribing information for lesinurad recommends assessing renal function prior to the initiation of lesinurad therapy and periodically thereafter, particularly in patients with creatinine clearance values between 30 ml/minute and <45 ml/minute. Lesinurad treatment should be discontinued in patients with creatinine clearance values persistently <30 ml/minute and is contraindicated in patients with end-stage renal disease, kidney transplant recipients, and patients undergoing dialysis.

Few kidney stone TEAEs were reported during the study, and the incidence did not differ significantly between treatment groups. Other therapies that inhibit URAT1 have been associated with the development of kidney stones (26,27). The lack of increase in kidney stone events during lesinurad therapy is possibly explained by the fact that by decreasing the production of uric acid, allopurinol reduced the amount of uric acid excreted by the kidneys, as reported previously for xanthine oxidase inhibitors (28,29). The timing of lesinurad administration may also have contributed to the low rate of nephrolithiasis, as once-daily dosing in the morning increases urinary uric acid levels during the period when urine volume and urine pH are highest and the potential for uric acid precipitation is therefore lowest (30,31).

In CV safety analyses, CV comorbidities and risk factors were present in 80% of patients at baseline, reflecting the high rates of CV disease in gout patients. The proportions of patients with TEAEs classified as CV events during the study were low and were similar in the treatment groups (range 3.5–4.5%), and all except 1 of these patients had at least 1 baseline CV comorbid condition or a history of CV disease. Incidences of MACE events were also similarly low and comparable across the 3 treatment groups. Low rates of MACE events in association with gout treatment have also been reported in the recent open-label Long-Term Allopurinol Safety Study Evaluating Outcomes in Gout Patients (LASSO) study, which provided an event rate of 0.58% for MACE over 6 months (incidence rate 1.42 per 100 patient-years) during allopurinol treatment (4), and in the double-blind CONFIRMS study, which reported a 0.4% rate of MACE with allopurinol (32).

Limitations of the CLEAR 1 trial include the limited data on allopurinol doses >300 mg, the exclusion of allopurinol dosage adjustments during the study, the low number of patients with evaluable tophi, and the relatively short follow-up period that limits the ability to adequately study tophi. Lesinurad was developed as an add-on treatment for patients in whom serum UA target levels were not achieved with allopurinol alone. The majority of patients in the CLEAR 1 study were receiving allopurinol 300 mg. It is thus unclear whether further up-titration of allopurinol, as recommended by treatment guidelines (1), would have been an effective option for these patients. A post hoc pooled analysis of both replicate studies on lesinurad in combination with allopurinol demonstrated similar serum UA–lowering and response rates regardless of the allopurinol dose (33).

In conclusion, lesinurad is a novel selective uric acid reabsorption inhibitor for the treatment of gout in combination with xanthine oxidase inhibitors. Combination therapy with lesinurad and allopurinol may represent a treatment option for patients with gout in whom target levels of serum UA cannot be achieved with a xanthine oxidase inhibitor alone and additional therapy is warranted.

**AUTHOR CONTRIBUTIONS**

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Saag had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Study conception and design.** Saag, Fitz-Patrick, Kopicko, Fung, Bhakta, Adler, Storgard, Baumgartner, Becker.

**Acquisition of data.** Kopicko, Fung, Bhakta, Adler, Storgard, Baumgartner.

**Analysis and interpretation of data.** Saag, Fitz-Patrick, Kopicko, Fung, Bhakta, Adler, Storgard, Baumgartner, Becker.

**ROLE OF THE STUDY SPONSOR**

Ardea Biosciences, Inc., a member of the AstraZeneca group, played a role in the design and conduct of the study, the collection, management, analysis, and interpretation of the data, and the review
and approval of the manuscript. Editorial support for the manuscript was provided by Bill Wolvey (PAREXEL, a contract research organization) and was funded by AstraZeneca.

REFERENCES

1. Khanna D, Fitzgerald JD, Khanna PP, Bae S, Singh MK, Neogi T, et al. 2012 American College of Rheumatology guidelines for management of gout. Part 1. Systematic nonpharmacologic and pharmacologic therapeutic approaches to hyperuricemia. Arthritis Care Res (Hoboken) 2012;64:1431–46.

2. Pacher P, Nivorozhkin A, Szabo C. Therapeutic effects of xanthine oxidase inhibitors: renaissance half a century after the discovery of allopurinol. Pharmacol Rev 2006;58:87–114.

3. Becker MA, Schumacher HR Jr, Wortmann RL, MacDonald PA, Eustace D, Palo WA, et al. Febuxostat compared with allopurinol in patients with hyperuricemia and gout. N Engl J Med 2005;353:2450–61.

4. Becker MA, Fitz-Patrick D, Choi HK, Dalbeth N, Storgard C, Cravets M, et al. An open-label, 6-month study of allopurinol safety in gout: the LASSO study. Semin Arthritis Rheum 2015;45:174–83.

5. Edwards NL. Febuxostat: a new treatment for hyperuricemia in gout. Rheumatology (Oxford) 2009;48 Suppl 2:i15–i19.

6. Schumacher HR Jr, Becker MA, Wortmann RL, MacDonald PA, Hunt B, Streit J, et al. Effects of febuxostat versus allopurinol and placebo in reducing serum urate in subjects with hyperuricemia and gout: a 28-week, phase III, randomized, double-blind, parallel-group trial. Arthritis Rheum 2008;59:1540–8.

7. Richette P, Perez-Ruiz F, Doherty M, Jansen TL, Nuki G, Pascual TF. Preliminary criteria for the classification of the acute arthritis of primary gout. Arthritis Rheum 1977;20:895–900.

10. Fleischmann R, Kerr B, Yeh LT, Suster M, Shen Z, Polvent E, et al. Pharmacodynamic, pharmacokinetic and tolerability evaluation of concomitant administration of lesinurad and febuxostat during uricosuric treatment of hyperuricemia in patients with gout. Part II. Management. Report of a task force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCISt). Ann Rheum Dis 2006;65:1312–24.

11. Bobulescu IA, Moe OW. Renal transport of uric acid: evolving concepts and uncertainties. Adv Chronic Kidney Dis 2012;19:359–71.

12. Fleischmann R, Kerr B, Yeh LT, Suster M, Shen Z, Polvent E, et al. Pharmacodynamic, pharmacokinetic and tolerability evaluation of concomitant administration of lesinurad and febuxostat in gout patients with hyperuricemia. Rheumatology (Oxford) 2014;53:2167–74.

13. Girardet JL, Miner JN. Urate crystal deposition disease and gout: new therapies for an old problem. Annu Rep Med Chem 2014;49:151–64.

14. Perez-Ruiz F, Hingorani V, Welp J. Efficacy and safety of RDEA594, a novel uricosuric agent, as combination therapy with allopurinol in gout patients: randomized, double-blind, placebo-controlled, phase 2 experience. Ann Rheum Dis 2010;69:609.

15. Perez-Ruiz F, Sundy J, Krishnan E. Efficacy and safety of lesinurad (RDEA594), a novel uricosuric agent, as a single agent, given in combination with allopurinol in allopurinol-refractory gout patients: randomized, double-blind, placebo-controlled, phase 2b study. Ann Rheum Dis 2011;70:104.

16. Shen Z, Yeh LT, Kerr B. RDEA594, a novel uricosuric agent, shows significant additive activity in combination with allopurinol in gout patients [poster]. Presented at the American Society for Clinical Pharmacology and Therapeutics; 2011 March 2–5; Dallas, Texas.

17. Wallace SL, Robinson H, Masi AT, Decker JL, McCarty DJ, Yu TF. Preliminary criteria for the classification of the acute arthritis of primary gout. Arthritis Rheum 1977;20:895–900.