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An open-label, 6-month study of allopurinol safety in gout: The LASSO study

Michael A. Becker, MD[a,*], David Fitz-Patrick, MD[b], Hyon K. Choi, MD, PhD[c,d], Nicola Dalbeth, MD, FRACP[e], Chris Storgard, MD[f], Matt Cravets, MA, MBA[g], Scott Baumgartner, MD[h]

[a] Department of Medicine, University of Chicago Medicine, MC0930, 5841 S Maryland Ave, Chicago, IL 60637
[b] East-West Medical Research Institute, Honolulu, HI
[c] Harvard Medical School, Boston, MA
[d] Gout and Crystal Arthropathy Center, Massachusetts General Hospital, Boston, MA
[e] Department of Medicine, University of Auckland, Auckland, New Zealand
[f] Clinical Research and Development, Ardea Biosciences Inc., San Diego, CA
[g] Biostatistics, Ardea Biosciences, Inc., San Diego, CA, USA
[h] Medical Affairs, Ardea Biosciences, Inc., San Diego, CA, USA

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ABSTRACT

Objectives: Allopurinol is the most widely prescribed serum uric acid-lowering therapy (ULT) in gout. To achieve serum uric acid (sUA) concentrations associated with clinical benefit, allopurinol is serially uptitrated with sUA monitoring. Suboptimal dosing is a key contributor to poor clinical outcomes, but few data are available on the safety and efficacy of dose-titrated allopurinol, particularly at doses > 300 mg/d. The objective of this open-label study was to investigate the safety and efficacy of allopurinol under conditions where investigators were encouraged to titrate to optimal, medically appropriate doses.

Methods: Long-term Allopurinol Safety Study Evaluating Outcomes in Gout Patients (LASSO) was a large, 6-month, multicenter study of allopurinol (NCT01391325). Adults meeting American Rheumatism Association Criteria for Classification of Acute Arthritis of Primary Gout and ≥ 2 gout flares in the previous year were eligible. Investigators were encouraged (but not required) to titrate allopurinol doses to achieve target sUA < 6.0 mg/dL. The primary objective was evaluation of the safety of dose-titrated allopurinol by clinical and laboratory examinations at monthly visits. Secondary objectives included sUA-lowering efficacy and gout flare frequency.

Results: Of 1735 patients enrolled, 1732 received ≥ 1 allopurinol doses. The maximal daily allopurinol dose during study was < 300 mg in 14.4%, 300 mg in 65.4%, and > 300 mg in 20.2% of patients; dosing duration was 115.5, 152.0, and 159.7 days, respectively. Overall, baseline demographic characteristics and comorbidity rates were similar across these three categories, but patients receiving > 300-mg maximal dose had more severe gout. Treatment-emergent adverse events possibly related to allopurinol occurred in 15.2%, 9.5%, and 11.4% of patients in the < 300-, 300-, and > 300-mg categories, respectively. Rash incidence was low (1.5%) and allopurinol hypersensitivity syndrome was not reported. No clinically meaningful changes occurred in laboratory values. sUA < 6.0 mg/dL at month 6 was achieved by 35.9% of patients overall: 22.4%, 35.0%, and 48.3% in dosing categories < 300, 300, and > 300 mg, respectively.

Conclusions: This large multicenter study found that the allopurinol dose-titration strategy was well tolerated, without new safety signals emerging over 6 months. However, despite encouragement to treat to target, significant proportions of patients did not achieve target sUA.

Introduction

The incidence and prevalence of gout are increasing worldwide, with over 8 million individuals affected in the USA alone [1]. This increase appears due in part to changes in demographics and diet and to increased incidences of comorbidities associated with hyperuricemia or gout, including hypertension, obesity, metabolic syndrome, and chronic kidney disease [2,3].

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* Corresponding author.
E-mail address: mbecker@medicine.bsd.uchicago.edu (M.A. Becker).

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Gout is a chronic arthritic disease characterized by hyperuricemia [i.e., serum uric acid concentrations (sUA) exceeding 6.8 mg/dL, the limit of urate solubility] and by symptoms and signs resulting from inflammatory responses to monosodium urate crystals deposited in joints and associated connective tissues from extracellular fluids saturated for uric acid. Although hyperuricemia is necessary (but not alone sufficient) for clinical onset of gout, it is the major risk factor for disease expression and progression [3]. Accordingly, guidelines produced by the European League against Rheumatism (EULAR) [4,5] and the American College of Rheumatology (ACR) [6] recommend achieving and maintaining a target sUA < 6 mg/dL (< 360 μmol/L) for disease control in most gout patients.

Allopurinol is the most widely prescribed first-line sUA-lowering agent in gout [7–10]. Guidelines for allopurinol dosing recommend a starting dose not exceeding 100 mg/d to reduce risk of allopurinol hypersensitivity syndrome (AHS). AHS is associated with the potential for severe morbidity (including rash, fever, eosinophilia, hepatic abnormalities, and acute renal failure) and a mortality rate of 20–25% [6]. Subsequent dose titration in increments of 100 mg/d every 2–4 weeks with sUA monitoring is recommended to guide achievement and maintenance of a target sUA, usually < 6 mg/dL [6]. Allopurinol is approved for use in doses as high as 800 mg (USA) or 900 mg (EU) daily [11], but in practice few patients receive daily doses above 300 mg [12].

Although used in gout treatment for nearly 50 years, there are limited data on the safety and efficacy of dose-titrated allopurinol, particularly for doses exceeding 300 mg/d. Long-term Allopurinol Safety Study Evaluating Outcomes in Gout Patients (LASSO) was an open-label, 6-month study of the safety and sUA-lowering efficacy of allopurinol in adults with gout (NCT01391325), where investigators were encouraged (but not required) to titrate allopurinol to effect—that is, a dose achieving sUA < 6 mg/dL.

Methods

Patients

Adults aged 18–85 years with a diagnosis of gout by American Rheumatism Association Criteria for the Classification of Acute Arthritis of Primary Gout and at least two gout flares in the previous year were eligible for study participation. For patients not receiving sUA-lowering pharmacotherapy (ULT) at screening, the required screening sUA was ≥ 8.0 mg/dL; for those receiving ULT at screening, an sUA of ≥ 6.5 mg/dL was required. The choice of the sUA threshold ≥ 8.0 mg/dL in patients not receiving ULT at screening is consistent with that of earlier trials of febuxostat, which used an sUA threshold ≥ 8.0 mg/dL after washout [13,14]. Since LASSO was primarily a safety trial, patients on concomitant allopurinol (or other ULT) at screening were permitted to remain/be initiated on allopurinol and to be uptitrated to goal as needed, and so they were allowed to be at the lower sUA level of ≥ 6.5 mg/dL at screening. Only patients receiving a ULT other than allopurinol at screening had to complete a washout of ≥ 7 days.

Exclusion criteria at screening included a history of allopurinol intolerance, estimated creatinine clearance (CrCl) < 30 mL/min, hemoglobin < 10 g/dL (males) or < 9 g/dL (females), > 14 drinks of alcohol per week, and a history of xanthinuria, active liver disease, or hepatic dysfunction. Complete study inclusion and exclusion criteria are included in Table 1.

LASSO was conducted in accordance with the Declaration of Helsinki and consistent with the International Conference on Harmonization/Good Clinical Practice and was approved by appropriate institutional review boards. All patients provided written informed consent. Where appropriate, LASSO complied with the Health Insurance Portability and Accountability Act of 1996. The study was performed between June 2011 and January 2013.

Table 1
Inclusion and exclusion criteria in LASSO

Inclusion criteria
1. 18–85 years of age
2. Male or female; females of childbearing potential who were sexually active must have agreed to use adequate contraception (as determined by the Investigator) and could neither be pregnant nor lactating from screening throughout the duration of the study
3. Patient met the diagnosis of gout according to the American Rheumatism Association (ARA) Criteria for the Classification of Acute Arthritis of Primary Gout
4. Patients not on a ULT must have had an sUA $\geq$ 8.0 mg/dL at screening
5. Patients on concomitant ULT must have had an sUA $\geq$ 6.5 mg/dL at screening
6. Patient must have had at least 2 gout flares in the past year
7. Patient was willing and able to give informed consent and adhere to visit/protocol schedules

Exclusion criteria
1. Baseline sUA $<$ 6.5 mg/dL
2. More than 14 drinks of alcohol per week [e.g., 1 drink = 5 oz (150 mL) of wine, 12 oz (360 mL) of beer, or 1.5 oz (45 mL) of hard liquor]
3. History or suspicion of drug abuse
4. History of myositis or rhabdomyolysis
5. History of autoimmune disease requiring systemic treatment
6. Known or suspected human immunodeficiency virus (HIV), hepatitis C antibody (HCV), or hepatitis B antibody (HBsAg) infection
7. History of malignancy within the previous 5 years (with the exception of nonmelanoma skin cancer that has been treated with no evidence of recurrence, treated cervical dysplasia, or treated in situ Grade 1 cervical cancer)
8. Myocardial infarction, unstable angina, New York Heart Association (NYHA) class III or IV heart failure, or stroke within the last 12 months
9. Uncontrolled hypertension (systolic pressure above 160 mmHg or diastolic pressure above 95 mmHg)
10. Estimated creatinine clearance at screening $<$ 30 mL/min by Cockcroft–Gault formula
11. Kidney or other organ transplant
12. Hemoglobin $<$ 10 g/dL (males) or $<$ 9 g/dL (females)
13. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) $>$ 2 $\times$ upper limit of normal (ULN)
14. Gamma-glutamyl transferase (GGT) $>$ 3 $\times$ upper limit of normal (ULN)
15. Active peptic ulcer disease requiring treatment
16. History of xanthinuria, active liver disease, or hepatic dysfunction
17. Requires therapy with any other sUA-lowering medication, other than allopurinol
18. Unable to take gout flare prophylaxis of either colchicine or NSAID due to contraindication (e.g., toxicity, renal function, and use of contraindicated medications)
19. Received an investigational medication within 8 weeks or 5 half-lives (whichever is longer) prior to the screening visit for this study
20. Previously participated in a clinical study involving lesinurad (RDEA594) or RDEA806
21. Previously received pegloticase
22. Known hypersensitivity or allergy to allopurinol
23. Any other medical or psychological condition that, in the opinion of the Investigator and/or Medical Monitor, might create undue risk to the patient or interfere with the patient's ability to comply with the protocol requirements, or to complete the study

Study design

The study included a screening and pretreatment period of 21 days (including, where appropriate, washout) and initiation, re-initiation, or continuation at day 1 of allopurinol treatment for up to 6 months (Fig. 1). Dose initiation and titration recommendations in the study protocol were to increase the allopurinol dose to reach a target sUA of <6 mg/dL at monthly or more frequent assessments. However, dose adjustments were at the discretion of investigators in accordance with local prescribing guidelines to provide a dose of at least 200 mg daily. Allopurinol dose titration was not specifically adjusted in patients with mild renal impairment (i.e., CrCl, 30–60 mL/min). At completion of study participation, each patient was categorized for safety and efficacy analyses into one of three prespecified allopurinol dosing categories (category one, <300 mg; category two, 300 mg; and category three, >300 mg) according to the maximum total daily allopurinol dose at any time during study. These dosing categories were selected to provide adequate patient numbers for analysis. Patients in each dosing category may thus have received different allopurinol exposures during the study.

Patients received colchicine (0.5 or 0.6 mg daily) or a non-steroidal anti-inflammatory drug (NSAID, dosed according to local guidelines) as prophylaxis for gout flares. Patients who developed intolerance or toxicity to their initial prophylactic regimen could switch to another medication or discontinue. Patients experiencing a gout flare during screening had their baseline (qualifying) visits postponed until the flare resolved.

Patients were assessed for allopurinol safety and efficacy at baseline and monthly visits during study treatment. End-of-study assessments were recorded when patients completed 6 months of dosing or discontinued the study prematurely for any reason. The date and reasons for discontinuation were recorded. Patients with an inadequate response to allopurinol after at least 8 weeks or unable to tolerate allopurinol were eligible for participation in studies of lesinurad, a selective uric acid reabsorption inhibitor (SURI) in development for treatment of gout [15].

Study end points

Primary end point

The primary study end point was the incidence of treatment-emergent adverse events (TEAEs) reported during titrated doses of allopurinol. AEs with a new onset after allopurinol initiation or with increased intensity or severity during study were considered treatment-emergent. TEAEs were coded using the *Medical Dictionary for Regulatory Activities* (*MedDRA*) version 14.0 or higher. Additional safety evaluations included physical examination, vital signs, electrocardiogram, clinical chemistry, hematology, and urinalysis. An independent cardiovascular (CV) events adjudication committee assessed TEAEs by prospectively defined criteria for major adverse cardiovascular events (MACE) and non-MACE CV end points [16].

Secondary end points

Secondary study end points included measurements of sUA-lowering efficacy and the frequency of gout flares requiring treatment; sUA-lowering efficacy was assessed by the proportion of patients with sUA <6 mg/dL at the month 6 visit, the proportions with sUA <6, <5, and <4 mg/dL at each monthly visit, and the absolute and percent reductions in sUA from baseline at monthly intervals; sUA was measured by a central laboratory.

Patients completed an ethics committee-approved diary to provide information on the incidence and duration of gout flares requiring treatment. Administration of treatment for flares was confirmed by review of concomitant medication use.

Statistical analysis

The primary objective of the LASSO study was to provide estimates on the frequencies of TEAEs in patients treated with allopurinol.

Continuous data were summarized by descriptive statistics including mean, standard deviation (SD), minimum, and maximum. Categorical data were summarized by the number and percentage of patients and by response rates (proportion of patients who met serum uric acid targets). Selected assessments included 95% confidence intervals (CIs). As this was an open-label study of allopurinol with no control arm, no formal statistical analyses were conducted for any assessment, as these would lack appropriate statistical validity.

All patients who received at least one dose of allopurinol were included in both safety and efficacy analyses.

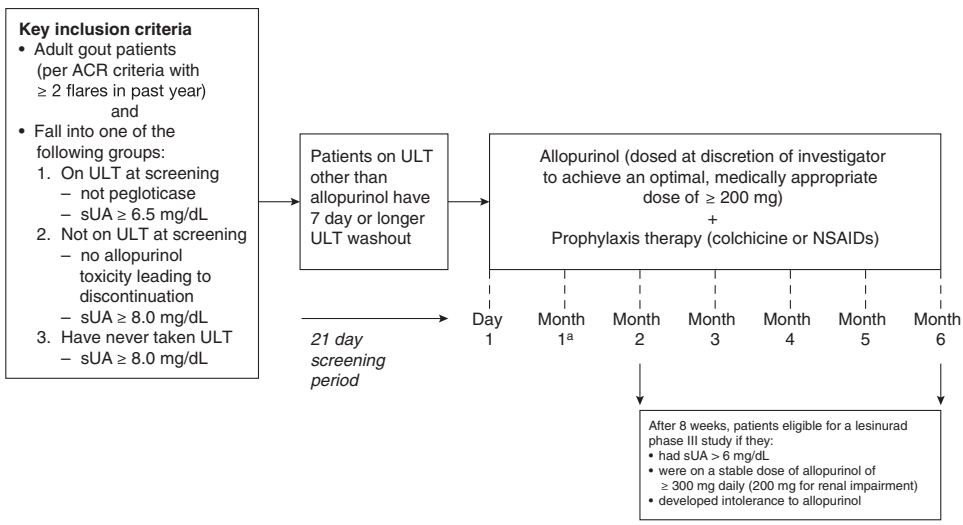

Fig. 1. Open-label design of the LASSO study. [a]Investigators may require more visits for titration or monitoring. ACR, American College of Rheumatology; ULT, uric acid-lowering therapy.

Results

Patient baseline characteristics

Patients were enrolled at 169 study sites in seven countries: Australia (11 sites), Belgium (1), Canada (6), Germany (2), New Zealand (7), South Africa (18), and the United States (124). Of 1735 patients enrolled, 1732 received ≥1 dose of allopurinol. The 6-month study period was completed by 1238 patients (71.5%) (Fig. 2).

Baseline demographic and gout characteristics are shown in Table 2. Most patients were male and white. Mean age and body mass index were 51.4 years and 34.41 kg/m^2, respectively. Baseline comorbidities (in >10% of patients) included hypertension (52.5%), hypercholesterolemia (35.7%), obesity based on medical history records (29.3%), hypertriglyceridemia (16.1%), and diabetes mellitus (13.1%). More than half of the patients had mild or moderately impaired renal function, assessed by CrCl at baseline.

The mean (SD) duration of gout diagnosis was 10.22 (9.2) years, and tophi were present in 17% of patients. The mean (SD) baseline sUA was 8.8 (1.7) mg/dL and was ≥6 mg/dL in 96.0% of patients. Prior use of any ULT was reported by 62.0% of patients. At screening, 32.0% of patients were receiving allopurinol and 1.7% an alternative ULT.

The mean (SD) daily allopurinol dose during study was 269.5 (111.7) mg over a mean (SD) duration of 148.3 (50.0) days. Only 1.1% of patients received a maximum dose ≥700 mg/d and 0.2% of patients received 900 to <1000 mg/d.

Allopurinol dose titration

Details of allopurinol dose titration are provided in Table 3, which displays shifts in allopurinol daily dosing. Of 986 patients who received an initial allopurinol dose <200 mg/d, 722 (73%) were receiving at least 200 mg allopurinol daily at the last sUA determination, but only 152 (15%) were receiving allopurinol at >300 mg daily. As also shown in Table 3, of 746 patients who started the study at allopurinol doses of 200 mg or greater, only 125 (17%) were receiving a higher dose at final sUA determination. Overall, of 1732 patients initiating the study, 937 (54.1%) completed the study on a higher allopurinol daily dose than at baseline.

The maximum daily allopurinol dose at any time during study was <300 mg in 250 patients (14.4%), 300 mg in 1132 patients (65.4%), and >300 mg in 350 patients (20.2%). Mean (SD) total days of dosing were similar in the >300- and 300-mg categories [159.7 (35.7) and 152.0 (46.1) days, respectively] and were lower in the <300-mg category [115.5 (67.7) days]. Patients who received a maximum dose >300 mg/d during study had more severe disease at baseline (i.e., longer gout duration, greater incidence of tophi, and more gout flares in the prior year; Table 2). The proportion of patients with baseline CrCl < 60 mL/min was greater in the <300-mg category (29.2%) than 300-mg (13.8%) and >300-mg categories (9.7%). Other baseline characteristics and rates of comorbidities were similar across dosing categories. Rates of patient-reported adherence with allopurinol were high and similar in each dosing category (97.8%, <300-mg; 96.6%, 300-mg; and

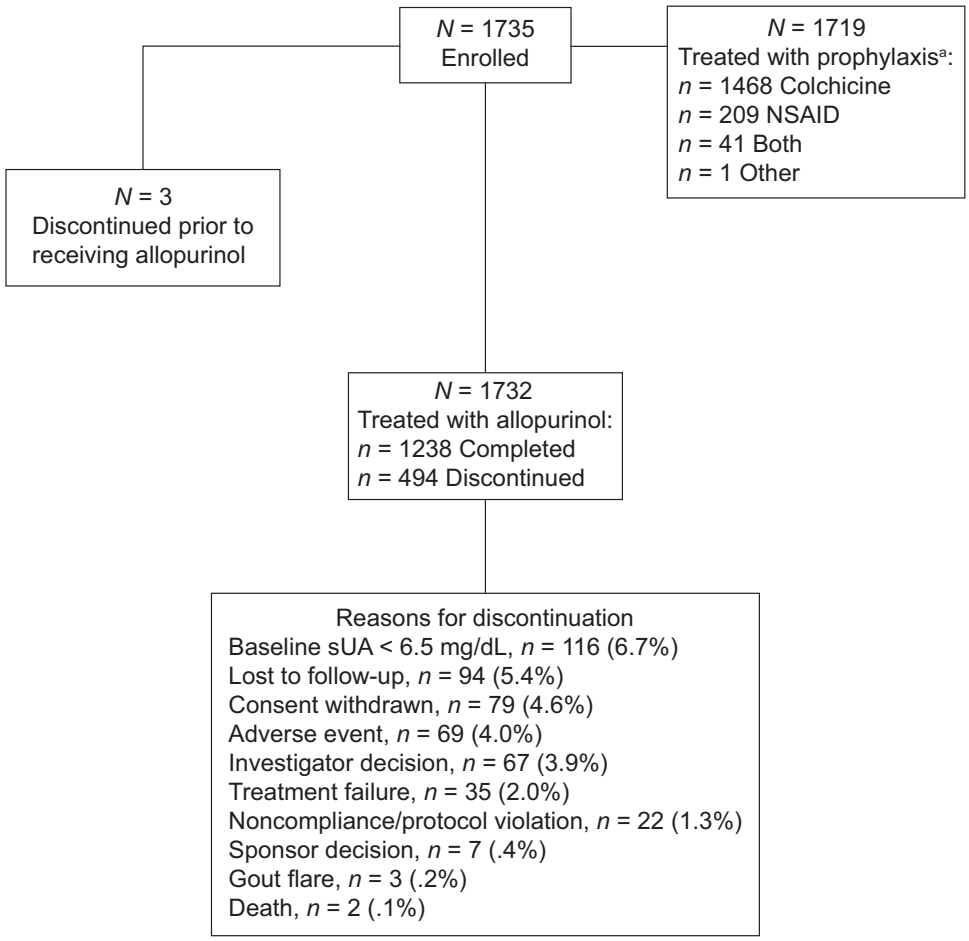

Fig. 2. Study flow. [a]Subjects who received both colchicine and NSAIDs are not counted in the individual counts for colchicine and NSAIDs. Data represents enrolled population. NSAIDs, nonsteroidal anti-inflammatory drugs.

Table 2
Baseline demographic and gout characteristics of the study population categorized by maximum daily allopurinol dose and overall

Variable	Maximum allopurinol daily dose			
	< 300 mg (n = 250)	300 mg (n = 1132)	> 300 mg (n = 350)	Total (N = 1732)
Sex [n (%)]				
Female	39 (15.6)	69 (6.1)	10 (2.9)	118 (6.8)
Male	211 (84.4)	1063 (93.9)	340 (97.1)	1614 (93.2)
Race [n (%)]				
American Indian or Alaska Native	1 (0.4)	11 (1.0)	0	12 (0.7)
Asian	16 (6.4)	58 (5.1)	21 (6.0)	95 (5.5)
Black or African American	28 (11.2)	109 (9.6)	30 (8.6)	167 (9.6)
Native Hawaiian or other Pacific Islander	9 (3.6)	35 (3.1)	11 (3.1)	55 (3.2)
White	186 (74.4)	841 (74.3)	266 (76.0)	1293 (74.7)
Other	10 (4.0)	78 (6.9)	22 (6.3)	110 (6.4)
Age (years)				
n	250	1132	350	1732
Mean (SD)	55.7 (12.9)	51.2 (11.8)	48.9 (11.2)	51.4 (11.9)
Body mass index (kg/m^2)				
n	249	1131	347	1727
Mean (SD)	33.04 (6.8)	34.39 (7.5)	35.45 (8.1)	34.41 (7.7)
sUA (mg/dL)				
n	250	1132	350	1732
Mean (SD)	8.4 (1.7)	8.8 (1.7)	8.9 (1.6)	8.8 (1.7)
Duration of gout diagnosis (years)				
n	250	1132	350	1732
Mean (SD)	8.89 (8.3)	9.92 (9.0)	12.14 (10.0)	10.22 (9.2)
Presence of tophi at baseline [n (%)]				
Yes	36 (14.4)	167 (14.8)	90 (25.7)	293 (16.9)
No	214 (85.6)	965 (85.2)	260 (74.3)	1439 (83.1)
Number of gout flares requiring treatment in prior year [n (%)]				
0	22 (8.8)	71 (6.3)	10 (2.9)	103 (5.9)
1	13 (5.2)	95 (8.4)	15 (4.3)	123 (7.1)
2	60 (24.0)	222 (19.6)	48 (13.7)	330 (19.1)
3	56 (22.4)	211 (18.6)	71 (20.3)	338 (19.5)
4	27 (10.8)	148 (13.1)	42 (12.0)	217 (12.5)
≥ 5	72 (28.8)	385 (34.0)	164 (46.9)	621 (35.9)
Renal function at baseline (estimated CrCl in mL/min)				
≥ 90	83 (33.2)	533 (47.1)	197 (56.3)	813 (46.9)
60 to < 90	94 (37.6)	442 (39.0)	118 (33.7)	654 (37.8)
30 to < 60	70 (28.0)	154 (13.6)	33 (9.4)	257 (14.8)
< 30[a]	3 (1.2)	2 (0.2)	1 (0.3)	6 (0.3)
Missing	0	1 (0.1)	1 (0.3)	2 (0.1)

CrCl, creatinine clearance; sUA, serum uric acid.

[a] An estimated CrCl < 30 mL/min at screening was an exclusion criterion. In subjects with moderate renal impairment, creatinine clearance may have dropped below 30 mL/min when measured at baseline.

97.3%, > 300-mg category). Discontinuation rates were higher in the < 300-mg category (49.6%) than 300-mg (26.7%) or > 300-mg (19.4%) categories. Reasons for discontinuation are reported in Figure 2.

Prophylaxis for gout flares was taken by 1719 (99.2%) patients (Fig. 2); the most common was colchicine (n = 1468), followed by an NSAID (n = 209), both colchicine and NSAID (n = 41), or another (n = 1). Concomitant medication use was high (99.9%);

Table 3
Number (%) of patients at final daily allopurinol dose categorized by baseline dose

	Final allopurinol dose (mg/d)								
Baseline dose (mg/d)	0	> 0–50	> 50–100	> 100–200	> 200–300	> 300–400	> 400–500	> 500–600	> 600
≤ 50 (n = 25)	0 (0)	**1 (4)**	*0 (0)*	*2 (8.0)*	*17 (68.0)*	*4 (16.0)*	*0 (0)*	*1 (4.0)*	*0 (0)*
> 50–100 (n = 566)	0 (0)	1 (0.2)	**38 (6.7)**	*88 (15.5)*	*344 (60.8)*	*72 (12.7)*	*11 (1.9)*	*11 (1.9)*	*1 (0.2)*
> 100–200 (n = 395)	1 (0.3)	0 (0)	4 (1.0)	**129 (32.7)**	*209 (52.9)*	*31 (7.8)*	*14 (3.5)*	*5 (1.3)*	*2 (0.5)*
> 200–300 (n = 662)	0 (0)	0 (0)	1 (0.2)	8 (1.2)	**557 (84.1)**	*55 (8.3)*	*19 (2.9)*	*14 (2.1)*	*8 (1.2)*
> 300–400 (n = 62)	0 (0)	0 (0)	0 (0)	0 (0)	2 (3.2)	**34 (54.8)**	*17 (27.4)*	*7 (11.3)*	*2 (3.2)*
> 400–500 (n = 11)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (9.1)	**8 (72.7)**	*0 (0)*	*2 (18.2)*
> 500–600 (n = 8)	0 (0)	0 (0)	0 (0)	0 (0)	2 (25.0)	0 (0)	0 (0)	**5 (62.5)**	*1 (12.5)*
600 (n = 3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	**3 (100)**

Bold values= percentage of patients in same category in last visit as at baseline. Those above the diagonal (italics) were at a higher dose level, and those below the diagonal (non-italics) were at a lower dose level than at baseline.

concomitant medications, besides colchicine and NSAID, taken by >10% of patients included lisinopril (16.7%), acetylsalicylic acid (16.2%), and simvastatin (10.9%).

Primary end point

Treatment-emergent adverse events

In total, 955 patients (55.1%) experienced a TEAE, including 185 patients (10.7%) with a TEAE reported possibly related to allopurinol and 183 (10.6%) with a TEAE possibly related to flare prophylaxis (Table 4). The most common TEAEs in the total population were upper respiratory tract infection, diarrhea, and arthralgia. There was an apparent positive dose relationship for TEAEs of upper respiratory tract infection, back pain, and headache. Nephrolithiasis was reported in 7 (0.4%) patients, all in the 300-mg allopurinol category. Rash incidence was low overall (1.5%) and AHS was not reported (Table 4).

The incidence of TEAEs possibly related to allopurinol was the highest in the <300-mg (15.2%) and the lowest in the 300-mg category (9.5%). The most common TEAEs possibly related to allopurinol (in <300-, 300-, and >300-mg categories, respectively) were alanine aminotransferase increase (2.0%, 1.1%, and 2.0%), diarrhea (1.2%, 1.1%, and 2.0%), and rash (2.0%, 0.8%, and 0.3%). TEAEs possibly related to allopurinol occurred at a lower incidence in patients receiving allopurinol at screening (7.6%) than in those not receiving ULT (12.1%). TEAEs possibly related to allopurinol occurred at similar incidences in categories divided by baseline renal function.

Serious AEs (SAEs) occurred in 51 (2.9%) patients, including three patients with pneumonia, three with acute myocardial infarction, and two patients each with cellulitis, diverticulitis, prostate cancer, gout, acute coronary syndrome, atrial fibrillation, atrial flutter, supraventricular tachycardia, and small intestinal obstruction. One patient in the <300-mg category and two patients in the 300-mg category had an SAE with outcome of death, categorized respectively as sudden death, pulmonary embolism, and death due to natural causes. No SAEs were considered possibly related to allopurinol or flare prophylaxis.

The incidence of TEAEs leading to allopurinol withdrawal or study discontinuation was 4.3% overall, with the highest rate in the <300-mg category (10.8%), followed by 300-mg (3.6%) and >300-mg categories (1.7%). The most common TEAEs associated with allopurinol withdrawal or study discontinuation were rash (10 patients) and diarrhea, alanine aminotransferase increase, and gamma-glutamyl transferase increase (six patients each). TEAEs leading to withdrawal of flare prophylaxis or switch occurred at an incidence of 5.4% overall, with the highest frequency in the <300-mg category (10.8%), followed by 300-mg (4.9%) and >300-mg categories (3.1%).

There were no consistent clinically meaningful changes in laboratory values during the study, including liver function parameters (alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase, and bilirubin). Modest but consistent decreases from baseline were observed in mean values for platelets, leukocytes, neutrophils, and percent neutrophils/leukocytes. Mean decreases in these parameters were greater in patients who received colchicine than NSAIDs for flare prophylaxis. No clinically meaningful changes were reported for urinalysis results or vital signs.

The CV adjudication committee reported a high rate of concordance with events reported by the study-site investigators. The overall incidence of MACE (CV death, nonfatal myocardial infarction, and nonfatal stroke) was 0.58%, with an incidence rate

Table 4
TEAEs and TEAEs possibly related to allopurinol experienced by ≥1% in any dosing category of the study population

Category	Maximum allopurinol daily dose			
	<300 mg (n = 250), n (%)	300 mg (n = 1132), n (%)	>300 mg (n = 350), n (%)	Total (N = 1732), n (%)
Any TEAE	124 (49.6)	623 (55.0)	208 (59.4)	955 (55.1)
TEAE with Rheumatology Common Toxicity Criteria Grade 3 or 4	14 (5.6)	60 (5.3)	21 (6.0)	95 (5.5)
TEAE possibly related to allopurinol	38 (15.2)	107 (9.5)	40 (11.4)	185 (10.7)
TEAE possibly related to prophylaxis	32 (12.8)	110 (9.7)	41 (11.7)	183 (10.6)
Serious TEAE	8 (3.2)	34 (3.0)	9 (2.6)	51 (2.9)
TEAE with outcome of death	1 (0.4)	2 (0.2)	0	3 (0.2)
TEAE leading to allopurinol withdrawal or study discontinuation	27 (10.8)	41 (3.6)	6 (1.7)	74 (4.3)
TEAE leading to prophylaxis switch or withdrawal	27 (10.8)	56 (4.9)	11 (3.1)	94 (5.4)
Most frequent TEAEs (incidence >1.0% of total subjects)				
Upper respiratory tract infection	4 (1.6)	65 (5.7)	31 (8.9)	100 (5.8)
Diarrhea	10 (4.0)	49 (4.3)	18 (5.1)	77 (4.4)
Arthralgia	4 (1.6)	39 (3.4)	12 (3.4)	55 (3.2)
Nasopharyngitis	8 (3.2)	32 (2.8)	13 (3.7)	53 (3.1)
Blood creatine phosphokinase increased	9 (3.6)	24 (2.1)	15 (4.3)	48 (2.8)
Back pain	2 (0.8)	28 (2.5)	15 (4.3)	45 (2.6)
Pain in extremity	10 (4.0)	26 (2.3)	8 (2.3)	44 (2.5)
Hypertension	6 (2.4)	28 (2.5)	9 (2.6)	43 (2.5)
Headache	4 (1.6)	24 (2.1)	13 (3.7)	41 (2.4)
Alanine aminotransferase increased	5 (2.0)	21 (1.9)	12 (3.4)	38 (2.2)
Bronchitis	3 (1.2)	18 (1.6)	8 (2.3)	29 (1.7)
Influenza	1 (0.4)	16 (1.4)	9 (2.6)	26 (1.5)
Rash	6 (2.4)	16 (1.4)	4 (1.1)	26 (1.5)
Muscle strain	2 (0.8)	19 (1.7)	4 (1.1)	25 (1.4)
Nausea	4 (1.6)	15 (1.3)	5 (1.4)	24 (1.4)
Aspartate aminotransferase increased	4 (1.6)	14 (1.2)	5 (1.4)	23 (1.3)
Nasal congestion	2 (0.8)	14 (1.2)	6 (1.7)	22 (1.3)
Musculoskeletal pain	1 (0.4)	8 (0.7)	11 (3.1)	20 (1.2)
Urinary tract infection	3 (1.2)	15 (1.3)	2 (0.6)	20 (1.2)
Liver function test abnormal	3 (1.2)	14 (1.2)	2 (0.6)	19 (1.1)

TEAE, treatment-emergent adverse events.

Table 5
Patients who achieved serum uric acid targets by visit

Visit	Maximum allopurinol daily dose			
Serum uric acid target	< 300 mg (n = 250), n (RESP) [95% CI on RESP]	300 mg (n = 1132), n (RESP) [95% CI on RESP]	> 300 mg (n = 350), n (RESP) [95% CI on RESP]	Total (N = 1732), n (RESP) [95% CI on RESP]
Month 1				
< 6 mg/dL	78 (0.31) [0.26, 0.37]	348 (0.31) [0.28, 0.34]	74 (0.21) [0.17, 0.26]	500 (0.29) [0.27, 0.31]
< 5 mg/dL	18 (0.07) [0.04, 0.11]	105 (0.09) [0.08, 0.11]	19 (0.05) [0.03, 0.08]	142 (0.08) [0.07, 0.10]
< 4 mg/dL	1 (0.004) [0.00, 0.02]	11 (0.01) [0.00, 0.02]	4 (0.01) [0.00, 0.03]	16 (0.01) [0.01, 0.01]
Month 2				
< 6 mg/dL	75 (0.30) [0.24, 0.36]	448 (0.40) [0.37, 0.42]	122 (0.35) [0.30, 0.40]	645 (0.37) [0.35, 0.40]
< 5 mg/dL	23 (0.09) [0.06, 0.13]	129 (0.11) [0.10, 0.13]	41 (0.12) [0.09, 0.16]	193 (0.11) [0.10, 0.13]
< 4 mg/dL	1 (0.004) [0.00, 0.02]	17 (0.02) [0.01, 0.02]	7 (0.02) [0.01, 0.04]	25 (0.01) [0.01, 0.02]
Month 3				
< 6 mg/dL	77 (0.31) [0.25, 0.37]	442 (0.39) [0.36, 0.42]	145 (0.41) [0.36, 0.47]	664 (0.38) [0.36, 0.41]
< 5 mg/dL	16 (0.06) [0.04, 0.10]	139 (0.12) [0.10, 0.14]	41 (0.12) [0.09, 0.16]	196 (0.11) [0.10, 0.13]
< 4 mg/dL	1 (0.004) [0.00, 0.02]	13 (0.01) [0.01, 0.02]	8 (0.02) [0.01, 0.04]	22 (0.01) [0.01, 0.02]
Month 4				
< 6 mg/dL	71 (0.28) [0.23, 0.34]	431 (0.38) [0.35, 0.41]	159 (0.45) [0.40, 0.51]	661 (0.38) [0.36, 0.40]
< 5 mg/dL	18 (0.07) [0.04, 0.11]	145 (0.13) [0.11, 0.15]	52 (0.15) [0.11, 0.19]	215 (0.12) [0.11, 0.14]
< 4 mg/dL	1 (0.004) [0.00, 0.02]	20 (0.02) [0.01, 0.03]	10 (0.03) [0.01, 0.05]	31 (0.02) [0.01, 0.03]
Month 5				
< 6 mg/dL	70 (0.28) [0.23, 0.34]	425 (0.38) [0.35, 0.40]	167 (0.48) [0.42, 0.53]	662 (0.38) [0.36, 0.41]
< 5 mg/dL	18 (0.07) [0.04, 0.11]	135 (0.12) [0.10, 0.14]	68 (0.19) [0.15, 0.24]	221 (0.13) [0.11, 0.14]
< 4 mg/dL	3 (0.01) [0.00, 0.03]	13 (0.01) [0.01, 0.02]	15 (0.04) [0.02, 0.07]	31 (0.02) [0.01, 0.03]
Month 6				
< 6 mg/dL	56 (0.22) [0.17, 0.28]	396 (0.35) [0.32, 0.38]	169 (0.48) [0.43, 0.54]	621 (0.36) [0.34, 0.38]
< 5 mg/dL	20 (0.08) [0.05, 0.12]	129 (0.11) [0.10, 0.13]	67 (0.19) [0.15, 0.24]	216 (0.13) [0.11, 0.14]
< 4 mg/dL	2 (0.01) [0.00, 0.03]	24 (0.02) [0.01, 0.03]	15 (0.04) [0.02, 0.07]	41 (0.02) [0.02, 0.03]

CI, confidence interval; RESP, response rate (proportion of patients who met serum uric acid targets).

of 1.42/100 patient-years (95% CI: 0.68–2.61); the incidence of non-MACE CV end points was 0.75%.

Secondary end points

sUA-lowering efficacy of allopurinol

At month 6, 35.9% of patients had sUA < 6.0 mg/dL. A greater proportion of patients met this target in the > 300-mg category (48.3%) than 300-mg (35.0%) and < 300-mg categories (22.4%) (Table 5). The CIs for response rate in Table 5 demonstrate the wide interpatient variability in each dosing category. Mean (SD) decreases in sUA from baseline to month 6 were 1.5 (1.84), 2.4 (1.97), and 2.7 (2.04) mg/dL in the < 300-, 300-, and > 300-mg categories, respectively, representing decreases of 16.6%, 25.1%, and 28.7%.

sUA targets of < 5 mg/dL and < 4 mg/dL were met by 12.5% and 2.4% of patients, respectively, at month 6 (Table 5); the proportions of patients meeting targets of < 5 and < 4 mg/dL were the highest in the > 300-mg and the lowest in the < 300-mg category.

Monthly sUA assessments showed that the lowest proportion of patients meeting the sUA target of < 6 mg/dL was in month 1 (28.9%), while months 2 – 6 had higher and similar proportions of patients meeting target (range: 35.9–38.3%) (Table 5). The proportions of patients meeting this sUA target were generally similar across subgroups categorized by race, type of gout flare prophylaxis, number of gout flares in the prior year, presence of tophi at baseline, and use of concomitant diuretics at baseline (Table 6). Older patients (≥ 65 years), women, non-users of allopurinol at screening, patients with baseline sUA, 7 to < 8 mg/dL (versus other dose groups), and patients with lower baseline renal function showed higher goal-range sUA-lowering response rates than other subgroups.

Additional efficacy analyses were performed post hoc to determine the proportions of patients who met the sUA target of < 6.0 mg/dL when categorized by final allopurinol dose (rather than the highest dose during study, as described above). At the time of last dose, 43.0% of patients receiving a final dose > 200–300 mg/d and 54.1% of patients receiving a final dose > 300 mg/d met the sUA target (Fig. 3). Safety analyses were not performed on the population categorized by final allopurinol dose.

Incidences of gout flares requiring treatment

Approximately one-third of patients (33.4%) experienced one or more gout flares requiring treatment, with a greater proportion in the > 300-mg (44.3%) than 300-mg (33.7%) or < 300-mg (16.4%) categories. For all three dosing categories, highest incidences of gout flares requiring treatment were in month 1 and declined over subsequent months.

Proportions of patients experiencing gout flares requiring treatment were greater in those with higher baseline sUA, higher baseline CrCl, non-users of allopurinol at screening, and users of NSAID versus colchicine prophylaxis during study (Table 7).

Discussion

Although allopurinol is a first-line ULT in patients with gout [5,6], sUA targets are frequently not achieved, possibly due to perceived intolerability of doses above 300 mg [6,12,13,17–19]. Study data on the safety and efficacy of allopurinol at doses above 300 mg/d are limited [20,21].

LASSO was a large, open-label, 6-month study of allopurinol under conditions where investigators were encouraged to titrate to optimal, medically appropriate doses. The 350 patients treated with > 300 mg daily of allopurinol are, to our knowledge, the largest cohort to date of individuals receiving daily doses at these levels. Mean total days of dosing were similar in the > 300- and 300-mg categories and lower in the < 300-mg category, which

Table 6
Patients who achieved serum uric acid target < 6.0 mg/dL by month 6: categorization by subgroups

Patient subgroup	Patients meeting sUA target, *n/N* (RESP) [95% CI on RESP]
Age	
≥ 65 years	109/249 (0.44) [0.38–0.50]
< 65 years	512/1483 (0.35) [0.32–0.37]
Gender	
Female	49/118 (0.42) [0.33–0.51]
Male	572/1614 (0.35) [0.33–0.38]
Race	
White	476/1293 (0.37) [0.34–0.40]
Non-white	145/439 (0.33) [0.29–0.38]
Type of gout flare prophylaxis	
Colchicine	543/1508 (0.36) [0.34–0.38]
NSAID	87/253 (0.34) [0.29–0.41]
Number of gout flares in prior year	
$n = 2$	112/303 (0.37) [0.32–0.43]
$n > 2$	509/1429 (0.36) [0.33–0.38]
Tophi at baseline	
Yes	104/293 (0.36) [0.30–0.41]
No	517/1439 (0.36) [0.33–0.38]
Allopurinol use at screening	
Yes	173/555 (0.31) [0.27–0.35]
No	448/1177 (0.38) [0.35–0.41]
Concomitant diuretics at baseline	
Yes	101/293 (0.35) [0.29–0.40]
No	520/1439 (0.36) [0.34–0.39]
sUA at baseline	
≥ 10.0 mg/dL	109/388 (0.28) [0.24–0.33]
8.0 to < 10.0 mg/dL	321/828 (0.39) [0.35–0.42]
7.0 to < 8.0 mg/dL	143/288 (0.50) [0.44–0.56]
6.0 to < 7.0 mg/dL	44/159 (0.28) [0.21–0.35]
Renal function at baseline	
CrCl ≥ 90 mL/min	260/813 (0.32) [0.29–0.35]
CrCl: 60 to < 90 mL/min	253/654 (0.39) [0.35–0.43]
CrCl: 30 to < 60 mL/min	105/257 (0.41) [0.35–0.47]

CI, confidence interval; RESP, response rate (proportion of patients who met serum uric acid target); *n/N*, number of subjects achieving target/number of eligible patients in subgroup.

Table 7
Patients who experienced gout flares requiring treatment: categorization by subgroups

Patient subgroup	Patients with 1 or more gout flares *n/N* (RESP) [95% CI on RESP]
sUA at baseline	
≥ 10.0 mg/dL	168/388 (0.43) [0.38–0.48]
8.0 to < 10.0 mg/dL	281/828 (0.34) [0.31–0.37]
7.0 to < 8.0 mg/dL	86/288 (0.30) [0.25–0.36]
6.0 to < 7.0 mg/dL	37/159 (0.23) [0.17–0.31]
Renal function at baseline	
CrCl ≥ 90 mL/min	292/813 (0.36) [0.33–0.39]
CrCl: 60 to < 90 mL/min	214/654 (0.33) [0.29–0.36]
CrCl: 30 to < 60 mL/min	70/257 (0.27) [0.22–0.33]
Allopurinol use at screening	
Yes	154/555 (0.28) [0.24–0.32]
No	424/1177 (0.36) [0.33–0.39]
User of colchicine versus NSAID prophylaxis during study	
Colchicine	494/1508 (0.33) [0.30–0.35]
NSAID	100/250 (0.40) [0.34–0.46]

RESP, response rate (proportion of patients who met serum uric acid target).

can be explained by uptitration of allopurinol doses during the study.

Allopurinol was generally well tolerated during the 6-month study, with low rates of TEAEs possibly related to allopurinol and discontinuation-related TEAEs. The types of TEAEs were consistent with the known profile of allopurinol [20,22], incidences of rash were low, and there were no cases of AHS, which typically has an onset within days to weeks after initiation of allopurinol [23]. The current data suggest that the 6-month rate of serious CV AEs in this study of patients with gout ranged from 1.0% to 1.5% during treatment with allopurinol, representing an overall incidence rate for MACE of 1.42/100 patient-years. These rates of CV events are broadly similar to those reported in other long-term follow-up studies of patients with gout, a population recognized to be at elevated CV risk [13,24].

Incidences of TEAEs possibly related to allopurinol and of discontinuation-related TEAEs were the highest in the < 300-mg category, while the highest dosing category (> 300 mg) had intermediate/lowest incidences. A potential explanation is that patients who developed intolerance early in the study were withdrawn before allopurinol dose uptitration. TEAEs occurred at a lower incidence in patients receiving allopurinol at baseline compared with those not receiving ULT, which likely reflects the demonstration of tolerability to allopurinol in the former group prior to study entry. TEAEs, including upper respiratory tract infection, back pain, and headache, occurred at a higher frequency in the > 300-mg than < 300-mg category. Whether this observation indicates a dose relationship or the effect of longer duration or greater exposure to allopurinol in the higher dosing category

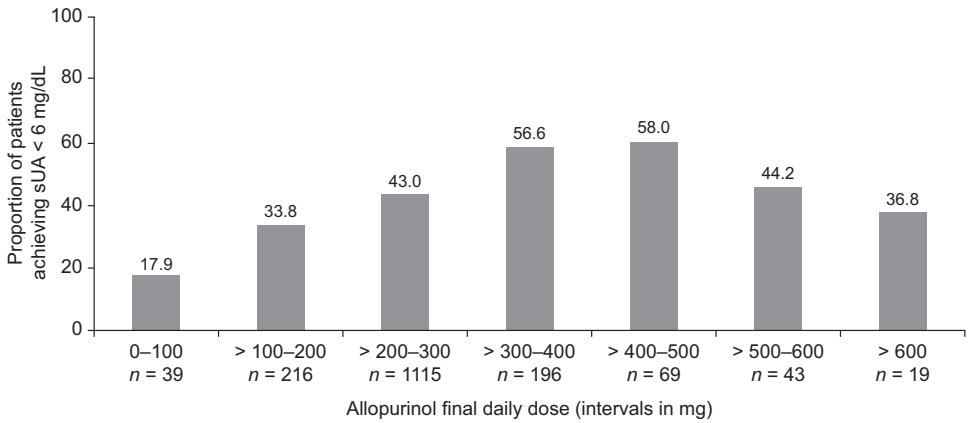

Fig. 3. Proportion of patients with sUA < 6.0 mg/dL categorized by their final daily allopurinol dose.

cannot be determined. Finally, the proportion of patients with baseline CrCl < 60 mL/min was greater in the < 300-mg category than 300-mg and > 300-mg categories. This difference is most likely a reflection of clinical practice, as investigators were less likely to uptitrate allopurinol in patients with lower levels of renal function.

Previous studies have shown that achievement of the target sUA range is associated with gout control [25,26]. In LASSO, only 35.9% of patients met the sUA target of < 6 mg/dL at 6 months, which is consistent with response rates reported previously for allopurinol at a dose of 300 mg [14,17,21]. Studies of allopurinol at higher doses have reported greater rates of achievement of target sUA [21,22]. Although demonstration of a dose–response effect is not possible in LASSO because of the nature of the study with variable dose titration, it is notable that highest response rates (48.3%) were in the > 300-mg category and lowest rates (22.4%) in the < 300-mg category. Even at the highest allopurinol doses, a proportion of patients showed no response, perhaps indicative that some patients do not benefit from increased doses of this xanthine oxidase inhibitor. Finally, while rates of patient self-reported adherence were high in LASSO, oxypurinol levels were not assessed to confirm compliance. This is consistent with usual clinical practice, in which drug concentrations are not routinely monitored.

The success rate for achieving sUA targets in gout is increased if physicians closely follow dose-titration guidelines, and patients are informed of the benefits of continuing treatment [22,27]. Despite the recommendation to titrate allopurinol doses to an sUA target range in LASSO, it is notable that physicians readily titrated allopurinol from low doses to 300 mg daily, but they much less frequently advanced the dose beyond 300 mg.

Two additional issues for comment in the LASSO study are the potential influence of acetylsalicylic acid intake on sUA and the impact of allopurinol on occurrences of back pain. Use of acetylsalicylic acid is known to elevate sUA. Acetylsalicylic acid was taken by 16.2% of patients in LASSO, but in the majority of cases at low dose as an antithrombotic. Acetylsalicylic acid taken at this dose would be expected to have minimal, if any, effect on sUA or flares in a gout population treated with allopurinol and/or a URAT1 inhibitor [6,28–30]. Back pain was reported in 2.6% of patients. It is not possible in LASSO to assess whether kidney stones (reported in 0.4% of patients) or changes in sUA were related to occurrences of back pain. However, as allopurinol does not cause “resaturation” in the kidneys but rather decreases nephrolithiasis [31], it would not be expected that allopurinol treatment contributed to the development of back pain. It is more likely that back pain in this predominantly male, middle-aged population was musculoskeletal in origin.

Limitations of the LASSO study include the open-label study design, lack of information on why subjects were not dose-titrated when not at goal, the different durations of treatment between dosing categories, the exclusion of patients with severely impaired renal function (i.e., CrCl < 30 mL/min), and the use of concomitant medications so that safety and efficacy results cannot be attributed solely to allopurinol. Patients who showed a lack of response to allopurinol after at least 8 weeks, or who were intolerant to allopurinol, were eligible for participation in phase 3 studies of lesinurad; this may have influenced discontinuation rates, limiting assessments of efficacy and safety. Finally, the population comprised both patients already receiving allopurinol and those not on ULT at the time of study entry (including those who had or had not received ULT in the past). A larger number of patients who are confirmed never to have received allopurinol may be needed to detect rare TEAEs such as hypersensitivity reactions. The strengths of the LASSO study are its large patient population, long treatment duration, and use of allopurinol in regimens that reflect clinical practice.

In conclusion, this large multicenter study identified no new safety signals for allopurinol at doses including > 300 mg daily, in agreement with previous studies [20–22]. There were minor differences in the incidence of TEAEs possibly related to allopurinol among the dosing categories (< 300, 300, and > 300 mg daily), while rates of adherence were high for all doses. Despite encouragement to treat to target, 300 mg daily was the most commonly used dose, and significant proportions of patients did not achieve target sUA. The results of LASSO may prove valuable for future trials of allopurinol as monotherapy and in combination with current and emerging therapies in the treatment of gout.

Clinical significance

Before the LASSO study, there were limited data on the safety and efficacy of dose-titrated allopurinol in gout, particularly at doses exceeding 300 mg/d. LASSO was a large open-label, 6-month study in which investigators were encouraged to titrate allopurinol doses to achieve a target serum uric acid concentration (sUA) < 6.0 mg/dL. We observed that the dose-titration strategy was generally well tolerated, including at allopurinol doses > 300 mg daily. A greater proportion of patients met the sUA target in > 300-mg than 300-mg and < 300-mg allopurinol dose categories. However, despite encouragement to treat to target, 300 mg daily was the most commonly used dose and significant proportions of patients did not achieve target sUA.

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Dr Becker (the lead author) 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.

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Appendix A. Supplementary Materials

Supplementary material cited in this article is available online at http://dx.doi.org/10.1016/j.semarthrit.2015.05.005.

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