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Efficacy and safety of epaminurad, a potent hURAT1 inhibitor, in patients with gout: a randomized, placebo-controlled, dose-finding study

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Abstract

Background Gout is the most common inflammatory arthritis. Current urate-lowering therapies have limitations, such as adverse drug reactions or limited efficacy. Epaminurad is a novel selective human urate transporter 1 (hURAT1) inhibitor that has been shown to reduce serum urate (sUA) levels in healthy volunteers and patients with gout. The aims of the current study were to evaluate the urate-lowering efficacy and safety of epaminurad compared with placebo in patients with gout, and to determine the optimal dose.

Methods This multicenter, randomized, double-blind, placebo-controlled, dose-finding phase 2b clinical trial, which incorporated a standard-treatment reference arm, enrolled patients aged 19–70 years with gout and sUA level ≥ 0.42 mmol/L. Participants received gout prophylaxis and followed therapeutic lifestyle changes, and were randomized to receive epaminurad 3 mg, 6 mg or 9 mg, or febuxostat 80 mg, or matching placebo, once daily for 12 weeks. The primary efficacy endpoint was the proportion of patients with sUA level < 0.36 mmol/L at week 4 after initiation of study treatment. Statistical comparisons were performed between the epaminurad and placebo groups.

Results Overall, 169 patients received study medication (99.40% male, mean ± SD age 48.26 ± 13.15 years, sUA level 0.53 ± 0.09 mmol/L). Mean adherence to treatment was > 90% in all groups. The proportion of patients with sUA < 0.36 mmol/L at week 4 was significantly higher in each epaminurad group (9 mg, 88.89%; 6 mg, 71.79%; 3 mg, 54.05%) compared with placebo (0.00%) (all $p < 0.0001$). The response rate in the febuxostat group was 84.21%. The proportion of patients who achieved sUA < 0.30 mmol/L, and mean percent and absolute change in sUA, were also significantly greater in all epaminurad groups versus placebo at week 4. Outcomes were consistent at weeks 8 and 12. The adverse event rate did not differ between epaminurad groups and placebo, and most events were mild. There were no significant differences in mean serum creatinine levels or liver function parameters between the epaminurad groups and placebo.

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Conclusions Epaminurad was effective at reducing sUA levels in patients with gout. The study also confirmed the safety and tolerability profile during 12 weeks of treatment.

Trial registration ClinicalTrials.gov NCT04804111 (registered on 15 November 2020).

Keywords Epaminurad, Gout, Human urate transport 1, hURAT1 inhibitor, Hyperuricemia, URC102

Background

Gout, characterized by deposition of urate crystals within joints, is the most common inflammatory arthritis in developed countries, with a prevalence of 1–4% [1]. It is caused by sustained hyperuricemia, which is most commonly due to reduced renal excretion of urate [2]. Acute gout flares cause severe joint pain, with swelling, tenderness and erythema, while chronic gout with tophi formation leads to chronic joint pain, stiffness and joint damage, on which acute flares are superimposed [3]. Comorbidities are common, particularly cardiovascular disease and renal disease [1], and gout impairs patient's quality of life [4].

Urate-lowering therapy (ULT) is recommended for patients with frequent flares, tophi, or joint damage [5, 6]. The main options are xanthine oxidase inhibitors (XOIs; allopurinol and febuxostat) and uricosuric drugs (e.g. probenecid, benzbromarone). However, although these treatments are effective to some extent, there are areas where improvements are still needed with current ULTs; for example, allopurinol can cause allergic reactions, febuxostat may be associated with cardiovascular risk, and probenecid can be associated with nephrolithiasis and drug-drug interactions [2]. Consequently, new therapeutic options are needed.

Human urate transporter 1 (hURAT1), found in the kidneys, is a member of the organic anion transporter (OAT) family that is involved in regulating serum urate (sUA) levels through reabsorption in the proximal tubule [7]. Uricosuric agents are known to promote urate excretion by inhibiting hURAT1 [8]. However, probenecid is less effective than other ULTs and is associated with multiple drug-drug interactions, while benzbromarone can be associated with hepatotoxicity and is no longer available in many countries [9]. Of note, urate excretion is influenced not only by hURAT1, which increases urate reabsorption, but also by other OATs, some of which increase urate excretion [2]. Uricosuric drugs inhibit both hURAT1 (leading to reduced reabsorption) and OAT1 and OAT3 (leading to reduced excretion), which overall limits the urate-lowering effect of the drugs. In vitro and in vivo studies have shown that epaminurad is a novel and potent hURAT1 inhibitor that has more selective inhibitory activity for hURAT1 than for OAT1 and OAT3 compared with benzbromarone, resulting in an increased urate-lowering effect [10]. Epaminurad also demonstrates lower in vitro potential for mechanisms (e.g. mitochondrial toxicity and reactive metabolite formation) that are proposed to cause benzbromarone-associated hepatoxicity [10]. Oral epaminurad was shown to reduce sUA levels safely and effectively in healthy volunteers [11]. The effect was dose-dependent, and was evident for more than 24 h, making it suitable for once daily administration. A dose-dependent reduction in sUA level was also seen in patients with gout in two phase 2a studies (NCT02290210 and NCT02557126), and the incidence of adverse events was similar in the epaminurad group and the placebo group.

The aims of the current study were to further evaluate the urate-lowering efficacy and safety of epaminurad compared with placebo in patients with gout, and to determine the optimal dose.

Methods

This was a multicenter, randomized, double-blind, placebo-controlled, dose-finding phase 2b clinical trial, which also included a standard-treatment reference arm. The trial was conducted at 18 centers in Korea. Approval was obtained from the Health Authority and each institution's Institutional Review Board, and the trial was conducted in accordance with Korean Good Clinical Practice, International Council for Harmonisation-Good Clinical Practice and the principles of the Declaration of Helsinki. All participants provided written informed consent.

Patients

The study enrolled adults aged 19–70 years diagnosed with gout according to the American College of Rheumatology criteria [12], who had an sUA level ≥ 0.42 mmol/L (≥ 7 mg/dL) at the final screening visit. Patients had to be willing and able to participate in the therapeutic lifestyle changes recommended as part of the study procedures.

Patents were not eligible for the study if they met any of the following exclusion criteria: urolithiasis, clinically important hypersensitivity disorder, uncontrolled diabetes mellitus or hypertension or dyslipidemia or thyroid function, aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥ 2 × upper limit of normal (ULN) or total bilirubin ≥ 1.5 × ULN, estimated glomerular filtration rate < 60 mL/min/1.73m^2, hypersensitivity to any component of the study medications, and the presence of any other clinically significant medical conditions that could potentially preclude participation in this study.

Patients were also excluded if they had received an XOI or uricosuric agent within 3 weeks prior to study treatment, diuretics or drugs acting on hURAT1 within 2 weeks prior to study treatment (except for stable doses of thiazide diuretics or antihypertensive agents for hypertension, fenofibrate or atorvastatin for hyperlipidemia, or aspirin), or mercaptopurine or azathioprine or theophylline within 1 week (or 5 × half-life, if longer) prior to screening.

Study procedures

Potential participants underwent a screening period of up to 4 weeks during which they started therapeutic lifestyle changes, underwent a washout period of ≥ 2 weeks for prior XOIs or uricosuric agents, started gout prophylactic therapy (colchicine or, if colchicine was contraindicated, low-dose non-steroidal anti-inflammatory drugs [NSAIDs]) and, at 1 week prior to randomization, had their sUA level checked.

Therapeutic lifestyle changes included dietary measures (minimal alcohol consumption; adequate water intake, i.e. at least 2L/day; avoidance of organs high in purines and drink/foods containing high-fructose corn syrup; limited intake of red meat, high-purine seafood, sugar, gravy and salt) and exercise therapy (regular exercise; weight loss to achieve a body mass index of 18.5–22.9 kg/m^2).

Eligible patients were randomized to receive epaminurad at a dose of 3 mg, 6 mg or 9 mg, or febuxostat 80 mg (standard-treatment reference arm), or matching placebo, in a double-blind manner. All study medications were administered orally once daily for 12 weeks. Patients randomized to epaminurad 6 or 9 mg underwent forced titration during the first 2 weeks to reach the planned dose, starting from a dose of 3 mg. Treatment was assigned using block randomization in a ratio of 2:2:2:2:1 (with the smaller group being the febuxostat reference arm) and an interactive web response system.

During the study, rescue treatment for gout flares comprised continuation of colchicine plus the addition of NSAIDs for up to 2 weeks. Intra-articular corticosteroids could also be used.

Assessments during the study included medical history, physical examination, 12-lead electrocardiogram, laboratory tests (biochemistry, hematology, coagulation, urinalysis) and adverse events.

Outcomes

The primary efficacy endpoint was the proportion of patients with sUA level < 0.36 mmol/L (< 6.0 mg/dL) at week 4 after initiation of study treatment.

Secondary endpoints included the proportion of patients with sUA < 0.30 mmol/L (< 5.0 mg/dL) at week 4; percent and absolute changes in sUA from baseline to week 4; gout flare incidence rate at week 4; proportion of patients with sUA < 0.36 mmol/L and < 0.30 mmol/L at week 8 and week 12; percent and absolute changes in sUA from baseline to week 8 and week 12; and gout flare incidence rate at week 8 and week 12. The definition of a gout flare was based on the characteristics of symptomatic episodes specified in the 2015 ACR/EULAR gout classification criteria [13], and was defined as the occurrence of two or more of the following three symptoms, as determined by the investigator: erythema overlying affected joint (patient-reported or physician-observed), patient cannot bear touch or pressure to affected joint, and great difficulty with walking or inability to use the affected joint.

Safety endpoints included adverse events and changes in laboratory parameters. Adverse events of special interest included abnormal liver function tests (AST or ALT > 3 × ULN, total bilirubin > 2 × ULN), and an increase in serum creatinine to ≥ 1.5 × baseline (with clinical symptoms) or to ≥ 2 × baseline level (regardless of clinical symptoms).

Epaminurad treatment was to be stopped immediately and appropriate treatment performed in any patient with: AST or ALT > 8 × ULN; AST or ALT > 5 × ULN for ≥ 2 weeks; AST or ALT > 3 × ULN and total bilirubin > 2 × ULN, requiring treatment; AST or ALT > 3 × ULN and clinical manifestation of jaundice, requiring treatment; an increase in serum creatinine to ≥ 1.5 × baseline or by ≥ 0.3 mg/dL from baseline with clinical symptoms (e.g. decreased urine output, anuria, transient polyuria, rash, edema, malaise); an increase in serum creatinine level to > 2 × baseline, regardless of clinical symptoms.

Statistical analysis

The primary efficacy analysis was performed on the full analysis set (subjects who received at least one dose of study medication and had efficacy endpoints measured at least once after randomization, with no missing values). Safety was evaluated in the safety set (all subjects who received at least one dose of study medication).

Descriptive statistics were presented for all treatment groups. For continuous variables, the number of subjects, mean, standard deviation (SD) were presented. For categorical variables, frequency and percentage were presented. A two-sided 95% confidence interval (CI) for the incidence was presented, where appropriate.

Between-group comparisons were tested between each epaminurad group and the placebo group. No statistical comparisons were performed versus the febuxostat group. For continuous variables, between-group analyses used the two-sample t-test or Wilcoxon rank sum test, and within-group analyses used the paired t-test or Wilcoxon signed rank test. For categorical variables, the Chi-square test of Fisher's exact test was used. For analysis

of covariance (ANCOVA), adjusted mean and standard error (SE) were presented.

The primary efficacy endpoint was tested using the Fixed Sequence test. If the between-group difference in the primary endpoint was significant for epaminurad 9 mg versus placebo, then 6 mg versus placebo was tested; if that was also significant, then 3 mg versus placebo was tested.

Results

Between April 2019 and October 2020, a total of 171 patients were randomized; however, two did not take any study medication (Fig. 1). Therefore, the safety analysis set included 169 patients. One patient was missing data for the primary endpoint and therefore the full analysis set included 168 patients. Overall, 152 patients completed the 12-week study period; the most common reason for non-completion was withdrawal of consent ($n=7$), followed by use of prohibited medication ($n=5$) and adverse events ($n=4$).

Baseline characteristics

All but one of the participants were male (99.40%). At baseline, the mean ± SD age of the study population was 48.26 ± 13.15 years, the mean ± SD body mass index was 27.25 ± 3.73 kg/m^2, 36.90% of participants were smokers and 77.98% were alcohol drinkers (Table 1). There were no significant differences between any of the epaminurad groups and the placebo group. The characteristics of patients in the febuxostat group were generally consistent with those of other groups.

At baseline, the mean ± SD duration of gout was 6.88 ± 7.13 years, mean ± SD sUA level was 0.53 ± 0.09 mmol/L, and 17.86% of participants had tophi (Table 2). At the time of initial screening, 43.45% of patients were receiving XOIs or uricosuric agents, most commonly febuxostat (29.76% of all patients) and allopurinol (13.69%). Gout characteristics in the febuxostat group were generally consistent with other groups.

The most common type of comorbidity was 'metabolism and nutrition disorders' (33.33%), of which the most common individual disorder was hyperlipidemia (19.05%) (Table 1). Gout flares that occurred between

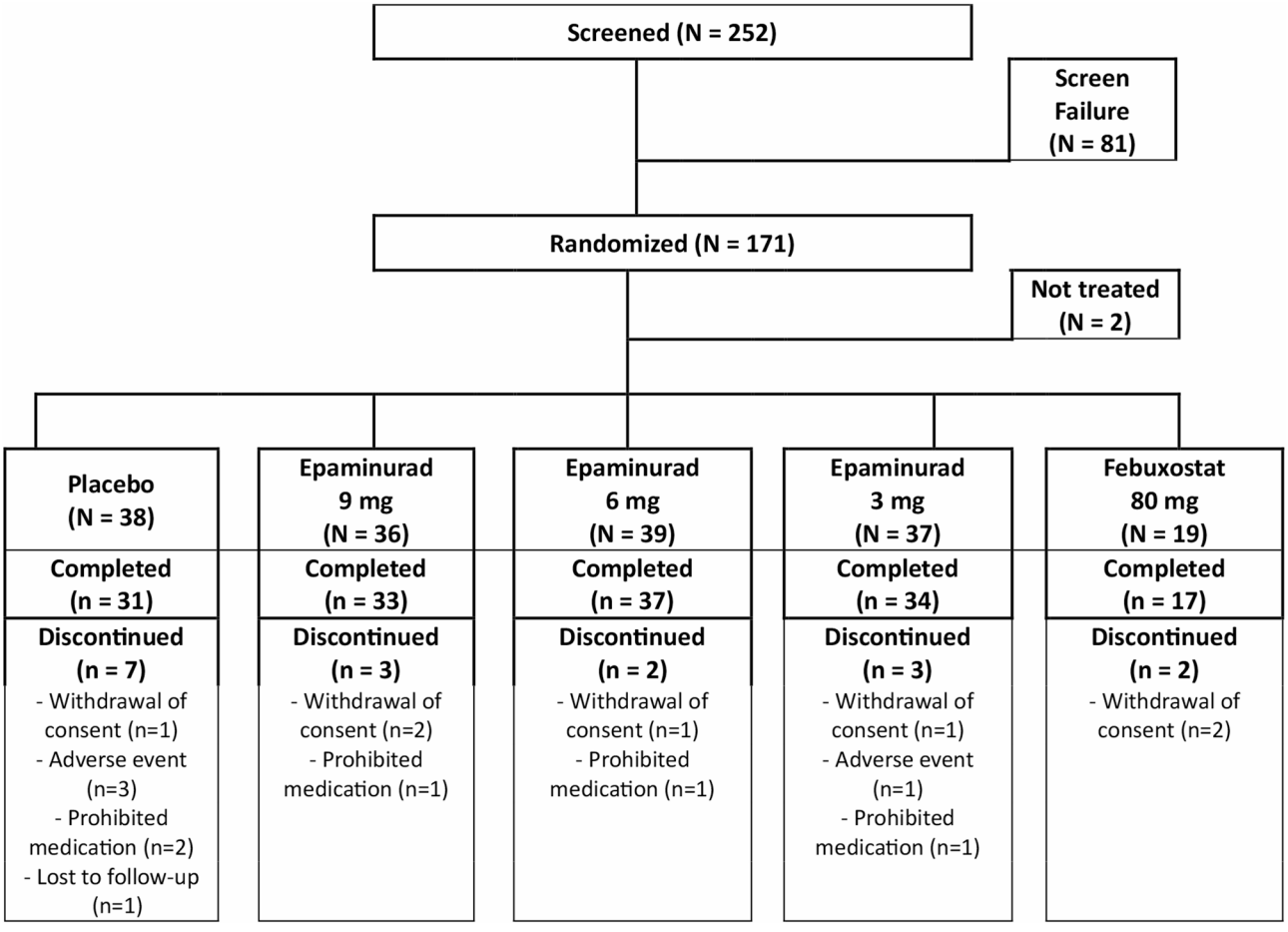


Fig. 1 Patient disposition

Table 1 Demographics and baseline characteristics

	Placebo (*N* = 37)	Epaminurad 9 mg (*N* = 36)	Epaminurad 6 mg (*N* = 39)	Epaminurad 3 mg (*N* = 37)	Febuxostat 80 mg (*N* = 19)	Total (*N* = 168)
Gender						
Male, n (%)	37 (100.00)	36 (100.00)	39 (100.00)	36 (97.30)	19 (100.00)	167 (99.40)
Female, n (%)	0 (0.00)	0 (0.00)	0 (0.00)	1 (2.70)	0 (0.00)	1 (0.60)
p-value		-	-	>.9999[a]		
Age (years)						
Mean ± SD	48.16 ± 13.21	51.33 ± 14.15	47.77 ± 12.68	46.97 ± 12.69	46.11 ± 13.28	48.26 ± 13.15
p-value		0.2842[b]	0.8951[c]	0.6941[c]		
Smoking						
Yes, n (%)	14 (37.84)	8 (22.22)	19 (48.72)	15 (40.54)	6 (31.58)	62 (36.90)
No, n (%)	23 (62.16)	28 (77.78)	20 (51.28)	22 (59.46)	13 (68.42)	106 (63.10)
p-value		0.1460[d]	0.3388[d]	0.8118[d]		
Alcohol						
Yes, n (%)	26 (70.27)	31 (86.11)	30 (76.92)	29 (78.38)	15 (78.95)	131 (77.98)
No, n (%)	11 (29.73)	5 (13.89)	9 (23.08)	8 (21.62)	4 (21.05)	37 (22.02)
p-value		0.1019[d]	0.5103[d]	0.4247[d]		
BMI (kg/m^2)						
Mean ± SD	26.43 ± 3.76	27.50 ± 3.04	27.41 ± 3.87	27.21 ± 3.81	28.08 ± 4.47	27.25 ± 3.73
p-value		0.1867[c]	0.3338[b]	0.3770[c]		
Comorbidity, n (%) [events][‡]	24 (64.86) [43]	27 (75.00) [63]	27 (69.23) [49]	29 (78.38) [54]	15 (78.95) [29]	122 (72.62) [238]
p-value		0.3454[d]	0.6855[d]	0.1973[d]		
Metabolism and nutrition disorders[‡]	10 (27.03) [12]	12 (33.33) [15]	13 (33.33) [14]	16 (43.24) [25]	5 (26.32) [7]	56 (33.33) [73]
Hyperlipidaemia	5 (13.51) [5]	7 (19.44) [7]	10 (25.64) [10]	7 (18.92) [7]	3 (15.79) [3]	32 (19.05) [32]
Gout flare[#‡]	4 (10.81) [4]	2 (5.56) [2]	2 (5.13) [2]	7 (18.92) [10]	2 (10.53) [2]	17 (10.12) [20]
Vascular disorders[‡]	9 (24.32) [9]	13 (36.11) [13]	11 (28.21) [11]	11 (29.73) [11]	7 (36.84) [7]	51 (30.36) [51]
Hypertension	9 (24.32) [9]	13 (36.11) [13]	11 (28.21) [11]	10 (27.03) [10]	7 (36.84) [7]	50 (29.76) [50]

p-value from [a] Fisher's exact test, [b] Wilcoxon rank sum test, [c] t-test, [d] Chi-square test (placebo vs. epaminurad 3 mg, 6 mg, 9 mg)

[‡] System organ class morbidity reported for > 10% of participants overall

[#] Gout flares that occurred between informed consent and randomization were recorded as comorbidity

SD = standard deviation

provision of informed consent and randomization were reported by 10.12% of patients.

Gout flare prophylaxis and rescue therapy

All patients received gout flare prophylaxis during the trial, as specified by the study protocol. During the trial, rescue therapy for gout flares was required by 17.86% of patients overall. There were no significant differences in the rate of rescue therapy between any of the epaminurad groups and the placebo group. The rate in the febuxostat group was similar to the rates in the epaminurad groups.

Adherence to study medication

Mean adherence to study medication during the trial was more than 90% in all groups (95.00 ± 9.65% in the placebo group, 96.30 ± 10.13% in the epaminurad 9 mg group, 95.06 ± 11.97% in the 6 mg group, 94.98 ± 9.35% in the 3 mg group, and 98.98 ± 2.65% in the febuxostat group).

Response rate

The proportion of patients with sUA < 0.36 mmol/L at week 4 (primary endpoint) was significantly higher in each of the epaminurad groups (9 mg, 88.89%; 6 mg, 71.79%; 3 mg, 54.05%) compared with placebo (0.00%) ($p < 0.0001$ for all comparisons) (Table 3; Fig. 2). The response rate in the febuxostat group was 84.21%.

In addition, a significantly higher proportion of patients in each of the epaminurad groups achieved sUA < 0.30 mmol/L at week 4 compared with the placebo group ($p < 0.0001$ for 9 and 6 mg, $p = 0.0003$ for 3 mg) (Table 3; Fig. 2).

The effect was consistent at weeks 8 and 12, with a significantly higher proportion of patients in each of the epaminurad groups achieving sUA < 0.36 mmol/L and sUA < 0.30 mmol/L at these timepoints ($p < 0.0001$ for each dose group versus placebo for both target sUA

Table 2 Baseline gout characteristics

	Placebo (*N* = 37)	Epaminurad 9 mg (*N* = 36)	Epaminurad 6 mg (*N* = 39)	Epaminurad 3 mg (*N* = 37)	Febuxostat 80 mg (*N* = 19)	Total (*N* = 168)
Duration of gout (years)						
Mean ± SD	8.59 ± 7.66	5.33 ± 5.09	7.54 ± 7.76	5.76 ± 7.06	7.26 ± 7.87	6.88 ± 7.13
p-value		0.0725[a]	0.5143[a]	0.0584[a]		
Presence of tophus						
Yes, n (%)	7 (18.92)	5 (13.89)	6 (15.38)	8 (21.62)	4 (21.05)	30 (17.86)
No, n (%)	30 (81.08)	31 (86.11)	33 (84.62)	29 (78.38)	15 (78.95)	138 (82.14)
p-value		0.5621[c]	0.6826[c]	0.7725[c]		
sUA (mmol/L)						
Mean ± SD	0.53 ± 0.09	0.52 ± 0.07	0.55 ± 0.10	0.51 ± 0.08	0.53 ± 0.11	0.53 ± 0.09
p-value		0.7064[b]	0.3039[b]	0.3959[a]		
Use of XOIs or uricosuric agents[#]						
Yes, n (%)	14 (37.84)	12 (33.33)	26 (66.67)	13 (35.14)	8 (42.11)	73 (43.45)
No, n (%)	23 (62.16)	24 (66.67)	13 (33.33)	24 (64.86)	11 (57.89)	95 (56.55)
p-value		0.6878[c]	0.0119[c]	0.8092[c]		
Type of XOI or uricosuric agent§						
Allopurinol, n (%)	5 (13.51)	5 (13.89)	6 (15.38)	4 (10.81)	3 (15.79)	23 (13.69)
Febuxostat, n (%)	9 (24.32)	7 (19.44)	20 (51.28)	9 (24.32)	5 (26.32)	50 (29.76)
Benzbromarone, n (%)	0 (0.00)	0 (0.00)	1 (2.56)	0 (0.00)	0 (0.00)	1 (0.60)

p-value from [a] Wilcoxon rank sum test, [b] t-test, [c] Chi-square test (placebo vs. epaminurad 3 mg, 6 mg, 9 mg)

[#] At initial screening visit

§ Multiple counting

levels, except for the 3 mg group at sUA < 0.30 mmol/L, $p = 0.0114$ at week 8 and $p = 0.0251$ at week 12) (Table 3).

Change in sUA level

A significant decrease in sUA level from baseline to week 4 was seen in all active treatment groups but not in the placebo group (Table 4). Both mean percent change and mean absolute change in sUA were significantly greater in each of the epaminurad groups compared with the placebo group.

A consistent effect was seen at weeks 8 and 12, with a significantly greater mean percent change and mean absolute change in sUA seen with each epaminurad dose group compared with placebo at both timepoints ($p < 0.0001$ for all comparisons; Table 4).

Gout flare incidence rate

The incidence rate of gout flares from baseline to week 4 in the epaminurad 9 mg group (5.56%) and 6 mg group (12.82%) did not differ significantly from the rate in the placebo group (2.70%), whereas the incidence rate in the epaminurad 3 mg group was significantly higher (21.62%, $p = 0.0281$) (Table 5). The rate in the febuxostat group was 15.79%.

The pattern was generally consistent at weeks 8 and 12, with a higher rate of gout flares in the URC 3 mg group compared with placebo ($p = 0.0116$ and $p = 0.0176$), but not in the 6 mg and 9 mg groups, except for a higher rate in the 9 mg group at week 8 ($p = 0.0462$) (Table 5).

Safety and tolerability

Overall, 99 patients (58.58%) experienced a total of 211 treatment-emergent adverse events (TEAEs). Thirty-seven patients (21.89%) experienced a total of 61 events considered to be adverse drug reactions (ADRs). There were no significant differences in the incidence of TEAEs or ADRs between any of the epaminurad groups and the placebo group (Table 6). Most TEAEs were mild in severity. No serious adverse events that were related to study medication occurred. TEAEs led to treatment discontinuation in 2 patients in each of the epaminurad 9 mg (5.56%) and 3 mg (5.41%) groups and in 5 patients (13.16%) in the placebo group.

The incidences of TEAEs and ADRs in the febuxostat group were 68.42% and 26.32%, respectively. Most TEAEs in the febuxostat group were mild, there were no serious adverse events, and no patients discontinued treatment.

The most common TEAE reported in the epaminurad groups was gout flare (9 mg: $n = 8$, 22.22%; 6 mg: $n = 8$, 20.51%; 3 mg: $n = 11$, 29.73%); The next most common TEAEs in the 9 mg group were blood creatinine increased ($n = 3$; 8.33%), followed by hypertriglyceridemia, high-density lipoprotein decreased, nasopharyngitis, and rash (each $n = 2$; 5.56%). After gout flare, the next most common TEAEs in the 6 mg group were blood

Table 3 Response rate: proportion of patients with sUA < 0.36 Mmol/L or < 0.30 Mmol/L at weeks 4, 8 and 12

	Placebo (*N* = 37)	Epaminurad 9 mg (*N* = 36)	Epaminurad 6 mg (*N* = 39)	Epaminurad 3 mg (*N* = 37)	Febuxostat 80 mg (*N* = 19)
Week 4					
sUA < 0.36 mmol/L					
n (%)	0 (0.00)	32 (88.89)	28 (71.79)	20 (54.05)	16 (84.21)
95% CI*	(0.00, 9.49)	(73.94, 96.89)	(55.13, 85.00)	(36.92, 70.51)	(60.42, 96.62)
p-value		< 0.0001[a]	< 0.0001[a]	< 0.0001[a]	
sUA < 0.30 mmol/L					
n (%)	0 (0.00)	28 (77.78)	18 (46.15)	11 (29.73)	10 (52.63)
95% CI*	(0.00, 9.49)	(60.85, 89.88)	(30.09, 62.82)	(15.87, 46.98)	(28.86, 75.55)
p-value		< 0.0001[a]	< 0.0001[a]	0.0003[a]	
Week 8					
sUA < 0.36 mmol/L					
n (%)	0 (0.00)	32 (88.89)	27 (69.23)	17 (45.95)	17 (89.47)
95% CI*	(0.00, 9.49)	(73.94, 96.89)	(52.43, 82.98)	(29.49, 63.08)	(66.86, 98.70)
p-value		< 0.0001[a]	< 0.0001[a]	< 0.0001[a]	
sUA < 0.30 mmol/L					
n (%)	0 (0.00)	26 (72.22)	18 (46.15)	7 (18.92)	10 (52.63)
95% CI*	(0.00, 9.49)	(54.81, 85.80)	(30.09, 62.82)	(7.96, 35.16)	(28.86, 75.55)
p-value		< 0.0001[a]	< 0.0001[a]	0.0114[b]	
Week 12					
sUA < 0.36 mmol/L					
n (%)	1 (2.70)	27 (75.00)	24 (61.54)	16 (43.24)	12 (63.16)
95% CI*	(0.07, 14.16)	(57.80, 87.88)	(44.62, 76.64)	(27.10, 60.51)	(38.36, 83.71)
p-value		< 0.0001[a]	< 0.0001[a]	< 0.0001[a]	
sUA < 0.30 mmol/L					
n (%)	0 (0.00)	21 (58.33)	16 (41.03)	6 (16.22)	8(42.11)
95% CI*	(0.00, 9.49)	(40.76, 74.49)	(25.57, 57.90)	(6.19, 32.01)	(20.25, 66.50)
p-value		< 0.0001[a]	< 0.0001[a]	0.0251[b]	

The primary endpoint was the proportion of patients with sUA < 0.36 mmol/L at week 4.

*95% Exact confidence interval

p-value from [a] Chi-square test, [b] Fisher's exact test (placebo vs. epaminurad 3 mg, 6 mg, 9 mg)

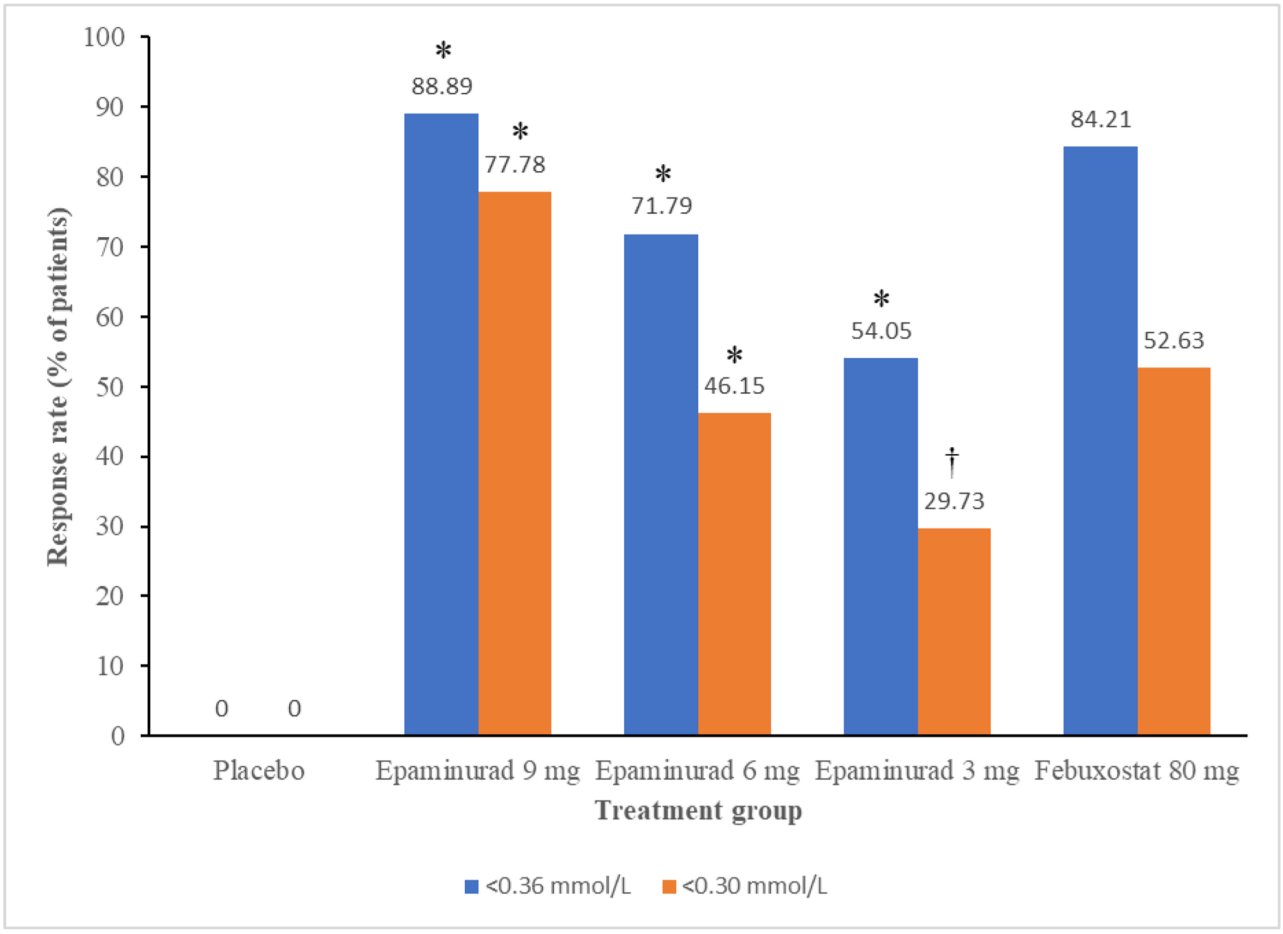
sUA = serum urate. sUA < 0.36 mmol/L (< 6.0 mg/dL), < 0.30 mmol/L (< 5.0 mg/dL)

creatinine increased, arthralgia, back pain, and oropharyngeal pain (each $n = 3$; 7.69%), and in the 3 mg group they were blood creatinine increased, blood creatine phosphokinase increased, gamma-glutamyltransferase increased, myalgia, and abdominal discomfort (each $n = 2$; 5.41%). No TEAEs involving clinically significant abnormalities in urine pH tests or urine sediment tests suggesting crystals were reported.

The most common TEAEs in the placebo group were gout flare, low-density lipoprotein increased, pain in extremity (each $n = 3$; 7.89%), blood creatine phosphokinase increased, arthralgia, diarrhea, nasopharyngitis, and headache (each $n = 2$; 5.26%). The most common TEAE in the febuxostat group was gout flare ($n = 5$; 26.32%), followed by arthralgia, diarrhea, and headache (each $n = 2$; 10.53%).

There were no significant increases in mean levels of AST, ALT or total bilirubin in any of the epaminurad groups or in the febuxostat group over time (Table 7). The only significant differences versus the placebo group were due to decreases in AST and ALT in the epaminurad 6 mg at week 4. ALT increased to > 3 × ULN in 2 (5.56%) patients in the epaminurad 9 mg group and 1 (2.63%) patient in the placebo group; the increase in one patient in the epaminurad 9 mg group was considered a mild adverse event, but resolved without discontinuing treatment. AST increased to > 3 × ULN in 1 (2.78%) patient in the epaminurad 9 mg group; it was recorded as a mild adverse event but was not considered to be related to epaminurad. No patients experienced total bilirubin levels > 2 × ULN.

There were no significant increases in mean serum creatinine level over time in any of the epaminurad groups or in the febuxostat group, and there were no significant differences between the epaminurad groups versus placebo (Table 7). Some patients experienced serum creatinine elevations ≥ 1.5 × and > 2 × baseline (Table 7). Serum creatinine increased by ≥ 1.5 × baseline in 10 recipients



* p<0.0001 † p=0.0003 for epaminurad versus placebo. Statistical comparison was not performed for febuxostat.

Fig. 2 Response rate: proportion of patients with serum urate level < 0.36 mmol/L (primary endpoint) or < 0.30 mmol/L at week 4

of epaminurad, including 3 (8.33%) in the 9 mg group, 4 (10.26%) in the 6 mg group, and 3 (8.11%) in the 3 mg group, versus 1 patient (2.63%) in the placebo group and 1 patient (5.26%) in the febuxostat group. Epaminurad 3 mg was discontinued in one patient for 22 days, after which it was restarted with no other increase in serum creatinine seen. Serum creatinine levels returned to normal during the study period in 9 of the 10 epaminurad recipients and in the placebo and febuxostat recipients. Although the level had not returned to normal within the study period for 1 epaminurad recipient, no additional follow-up was deemed necessary by the investigator. Serum creatinine increased by > 2 × baseline in 1 (2.56%) patient in the epaminurad 6 mg group and 1 (2.70%) in the 3 mg group versus 1 (2.63%) in the placebo group. Serum creatinine levels returned to normal during the study period in 2 of these 3 patients. Although the level had not returned to normal within the study period for the patient in the 6 mg group, no additional follow-up was deemed necessary by the investigator and the level returned to normal by 6 days after study end. Based on evaluation of all 14 patients with an increase in serum creatinine ≥ 1.5 × and > 2 × baseline or reported as an AE, there was no evidence of a correlation between poor adherence and a rise in creatinine level: 12 (85.71%) patients (83.33% on epaminurad) had adherence of > 90% prior to the creatinine increase.

Discussion

In patients with gout and hyperuricemia, epaminurad reduced sUA levels and increased sUA response rates (< 0.36 mmol/L and < 0.30 mmol/L) significantly compared with placebo. The effect was dose-dependent and was maintained for 12 weeks. Epaminurad also appeared to be generally safe and well tolerated.

hURAT1 plays a key role in the renal reabsorption of urate, and uricosuric drugs such as probenecid and benzbromarone promote urate excretion by inhibiting hURAT1 [7, 8]. However, both probenecid and benzbromarone are non-selective and also inhibit other

Table 4 Percent and absolute change in serum urate (sUA) level at weeks 4, 8 and 12

	Placebo (*N* = 37)	Epaminurad 9 mg (*N* = 36)	Epaminurad 6 mg (*N* = 39)	Epaminurad 3 mg (*N* = 37)	Febuxostat 80 mg (*N* = 19)
Baseline					
Mean ± SD (mmol/L)	0.53 ± 0.09	0.52 ± 0.07	0.55 ± 0.10	0.51 ± 0.08	0.53 ± 0.11
Week 4					
Mean ± SD (mmol/L)	0.54 ± 0.09	0.26 ± 0.10	0.31 ± 0.09	0.39 ± 0.13	0.29 ± 0.09
Change from baseline					
Mean ± SD (mmol/L)	0.01 ± 0.06	-0.25 ± 0.11	-0.23 ± 0.09	-0.13 ± 0.11	-0.25 ± 0.12
p-value (within arm)	0.3224[a]	< 0.0001[b]	< 0.0001[a]	< 0.0001[a]	< 0.0001[a]
p-value (ANCOVA)		< 0.0001	< 0.0001	< 0.0001	
% Change from baseline					
Mean ± SD	3.04 ± 13.58	-48.86 ± 19.36	-42.58 ± 14.73	-25.24 ± 21.03	-45.41 ± 16.04
p-value (within arm)	0.1825[a]	< 0.0001[b]	< 0.0001[b]	< 0.0001[a]	< 0.0001[a]
p-value (ANCOVA)		< 0.0001	< 0.0001	< 0.0001	
Week 8					
Mean ± SD (mmol/L)	0.54 ± 0.09	0.25 ± 0.11	0.32 ± 0.12	0.39 ± 0.12	0.29 ± 0.09
Change from baseline					
Mean ± SD (mmol/L)	0.01 ± 0.07	-0.26 ± 0.11	-0.23 ± 0.11	-0.12 ± 0.11	-0.24 ± 0.11
p-value (within arm)	0.2041[a]	< 0.0001[b]	< 0.0001[a]	< 0.0001[a]	< 0.0001[a]
p-value (ANCOVA)		< 0.0001	< 0.0001	< 0.0001	
% Change from baseline					
Mean ± SD	3.88 ± 14.81	-50.95 ± 20.28	-41.79 ± 18.81	-22.80 ± 21.48	-43.94 ± 15.73
p-value (within arm)	0.0991[b]	< 0.0001[b]	< 0.0001[b]	< 0.0001[b]	< 0.0001[a]
p-value (ANCOVA)		< 0.0001	< 0.0001	< 0.0001	
Week 12					
Mean ± SD (mmol/L)	0.54 ± 0.10	0.30 ± 0.14	0.35 ± 0.12	0.41 ± 0.13	0.33 ± 0.11
Change from baseline					
Mean ± SD (mmol/L)	0.02 ± 0.08	-0.21 ± 0.15	-0.20 ± 0.13	-0.11 ± 0.11	-0.20 ± 0.11
p-value (within arm)	0.2571[a]	< 0.0001[a]	< 0.0001[a]	< 0.0001[a]	< 0.0001[a]
p-value (ANCOVA)		< 0.0001	< 0.0001	< 0.0001	
% Change from baseline					
Mean ± SD	4.35 ± 19.67	-40.51 ± 27.11	-35.53 ± 20.58	-21.29 ± 22.22	-37.61 ± 17.62
p-value (within arm)	0.2603[b]	< 0.0001[b]	< 0.0001[a]	< 0.0001[a]	< 0.0001[a]
p-value (ANCOVA)		< 0.0001	< 0.0001	< 0.0001	

%change = (sUA at week 4 or 8 or 12–baseline sUA)/baseline sUA*100. ANCOVA with baseline sUA as a covariate. Within arm p-value from [a] Paired t-test, [b] Wilcoxon signed rank test. ANCOVA = analysis of covariance, CI = confidence interval, SD = standard deviation

anion transporters, such as OAT1 and OAT3 which are involved in urate secretion [2, 14]. Selective urate reabsorption inhibitors specifically targeting hURAT1 have also been developed, including lesinurad which is no longer available, and more recently dotinurad, which has been approved in Japan and is under development in the USA [2, 14].

Epaminurad is a novel potent, selective hURAT1 inhibitor [11]. The results of the current study suggest that it shows urate-lowering efficacy without any serious safety concerns. The incidence of TEAEs in the epaminurad groups did not differ from that in the placebo group, most events were mild in severity, and no serious adverse events related to epaminurad occurred. Gout flare (reported as an adverse event) was the most common TEAE in the epaminurad, febuxostat and placebo groups.

Amongst available uricosuric agents, benzbromarone is more efficacious than probenecid [15]; however, it can be associated with rare but potentially fatal hepatotoxicity [9]. Liver function abnormalities have also been reported in clinical trials of other ULTs, such as allopurinol and febuxostat [16]. In the current study, there were no significant increases in mean levels of AST, ALT and total bilirubin in any of the epaminurad groups over time or compared with placebo. ALT or AST levels increased to > 3 × ULN in 3 patients in the epaminurad 9 mg group and 1 patient in the placebo group; the increase was considered clinically significant in two cases (both epaminurad 9 mg), one of which was considered possibly related to epaminurad but resolved without discontinuation of the drug, while the other was not considered related to study medication. These findings provide further support to the in vitro differences observed between epaminurad

Table 5 Gout flare incidence rate at weeks 4, 8 and 12

	Placebo (*N* = 37)	Epaminurad 9 mg (*N* = 36)	Epaminurad 6 mg (*N* = 39)	Epaminurad 3 mg (*N* = 37)	Febuxostat 80 mg (*N* = 19)
Week 4					
n (%)	1 (2.70)	2 (5.56)	5 (12.82)	8 (21.62)	3 (15.79)
95% CI*	(0.07, 14.16)	(0.68, 18.66)	(4.30, 27.43)	(9.83, 38.21)	(3.38, 39.58)
p-value		0.6145[b]	0.2008[b]	0.0281[b]	
Week 8					
n (%)	2 (5.41)	8 (22.22)	6 (15.38)	10 (27.03)	5 (26.32)
95% CI*	(0.66, 18.19)	(10.12, 39.15)	(5.86, 30.53)	(13.79, 44.12)	(9.15, 51.20)
p-value		0.0462[b]	0.2634[b]	0.0116[a]	
Week 12					
n (%)	3 (8.11)	8 (22.22)	8 (20.51)	11 (29.73)	5 (26.32)
95% CI*	(1.70, 21.91)	(10.12, 39.15)	(9.30, 36.46)	(15.87, 46.98)	(9.15, 51.20)
p-value		0.0919[a]	0.1245[a]	0.0176[a]	

Incidence rate of gout flares at each visit was confirmed by using the difference between baseline visit and onset date

*95% Exact confidence interval

p-value from [a] Chi-square test or [b] Fisher's exact test (placebo vs. epaminurad 3 mg, 6 mg, 9 mg)

Table 6 Adverse events

	Placebo (*N* = 38)	Epaminurad 9 mg (*N* = 36)	Epaminurad 6 mg (*N* = 39)	Epaminurad 3 mg (*N* = 37)	Febuxostat 80 mg (*N* = 19)	Total (*N* = 169)
TEAEs, n (%), [events]	20 (52.63), [41]	19 (52.78), [44]	24 (61.54), [44]	23 (62.16), [47]	13 (68.42), [35]	99 (58.58), [211]
p-value		0.9900[a]	0.4298[a]	0.4041[a]		
ADRs, n (%), [events]	9 (23.68), [17]	9 (25.00), [9]	8 (20.51), [11]	6 (16.22), [13]	5 (26.32), [11]	37 (21.89), [61]
p-value		0.8951[a]	0.7373[a]	0.4189[a]		
SAEs, n (%), [events]	0	0	0	1 (2.70), [1]	0	1 (0.59), [1]
p-value		-	-	0.4933[b]		
SAEs related to study drug, n (%), [events]	0	0	0	0	0	0
TEAEs leading to interruption or discontinuation, n (%), [events]	5 (13.16) [8]	2 (5.56) [2]	0	2 (5.41) [6]	0	9 (5.33) [16]
ADRs leading to interruption or discontinuation, n (%), [events]	5 (13.16) [8]	2 (5.56) [2]	0	2 (5.41) [6]	0	9 (5.33) [16]

p-value from [a] Chi-square test, [b] Fisher's exact test (placebo vs. epaminurad 3 mg, 6 mg, 9 mg)

ADR = adverse drug reaction, SAE = serious adverse event, TEAE = treatment-emergent adverse event

and benzbromarone, with epaminurad showing lower in vitro potential for mechanisms proposed to cause the hepatotoxicity induced by benzbromarone [10].

Lesinurad was associated with a high incidence of elevated serum creatinine levels, most of which resolved [17, 18]. The underlying mechanism was not clear, but it may have been due to microcrystallization of urate in the renal tubules [18]. In contrast, significant changes in serum creatinine levels and renal adverse events were not reported in phase 3 clinical trials of dotinurad [19, 20]. In the current study, there was no significant increase in mean serum creatinine level in any of the epaminurad groups over time or versus the placebo group. An increase in serum creatinine of > 2 × baseline occurred in 2 patients treated with epaminurad, while another 10 patients had elevations of ≥ 1.5 × baseline. Blood creatinine increased was reported as a TEAE for 8 recipients of epaminurad, including 3 (8.33%) in the 9 mg group, 3 (7.69%) in the 6 mg group and 2 (5.41%) in the 3 mg group. There was no evidence of a common time of onset for the increase or of a correlation with poor adherence, and levels generally recovered to normal within a short period of time despite continued administration of epaminurad. Additional data from a larger number of patients will be needed to clarify whether or not epaminurad has an effect on serum creatinine levels or renal function.

Allopurinol is generally recommended as preferred first-line ULT [5, 6]. However, it can be associated with allopurinol hypersensitivity syndrome, which is more

Table 7 Liver function and renal function test results

		Placebo (*N* = 38)	Epaminurad 9 mg (*N* = 36)	Epaminurad 6 mg (*N* = 39)	Epaminurad 3 mg (*N* = 37)	Febuxostat 80 mg (*N* = 19)
AST (IU/L)						
Baseline	Mean ± SD	25.92 ± 10.13	31.25 ± 23.17	30.92 ± 12.75	27.57 ± 10.68	29.63 ± 14.41
Week 4	Mean ± SD	27.83 ± 10.86	27.06 ± 8.44	27.92 ± 10.14	27.77 ± 12.73	30.94 ± 17.26
	p-value (within)	0.1507[a]	0.8981[b]	0.0388[b]	0.4744[b]	0.4737[b]
	p-value (between)		0.4066[d]	0.0217[d]	0.0945[d]	
Week 12	Mean ± SD	29.19 ± 11.26	28.36 ± 15.04	28.33 ± 9.25	29.49 ± 13.66	28.58 ± 10.34
	p-value (within)	0.1116[a]	0.5328[b]	0.2909[b]	0.2688[b]	0.6286[b]
	p-value (between)		0.4564[d]	0.1185[d]	0.5178[d]	
ALT (IU/L)						
Baseline	Mean ± SD	29.92 ± 17.97	33.78 ± 16.06	40.15 ± 27.20	34.92 ± 17.30	31.53 ± 14.82
Week 4	Mean ± SD	33.94 ± 22.11	34.03 ± 15.93	32.76 ± 17.61	36.49 ± 19.66	31.89 ± 13.81
	p-value (within)	0.2250[b]	0.9133[b]	0.0674[b]	0.8802[b]	0.9521[a]
	p-value (between)		0.2921[d]	0.0354[d]	0.2867[d]	
Week 12	Mean ± SD	31.81 ± 17.72	35.61 ± 26.96	35.00 ± 18.36	37.70 ± 21.54	30.74 ± 13.51
	p-value (within)	0.5626[b]	0.7759[b]	0.3675[b]	0.4650[b]	0.7585[a]
	p-value (between)		0.4533[d]	0.2651[d]	0.9692[d]	
Total bilirubin (μmol/L)						
Baseline	Mean ± SD	10.95 ± 4.45	11.63 ± 5.99	10.60 ± 3.42	9.58 ± 4.10	10.26 ± 4.96
Week 4	Mean ± SD	11.46 ± 3.76	11.63 ± 6.16	10.43 ± 3.76	10.60 ± 3.93	11.63 ± 4.96
	p-value (within)	0.8272[a]	0.9903[a]	0.8367[a]	0.1938[a]	0.2507[a]
	p-value (between)		0.8959[c]	0.7628[c]	0.4076[c]	
Week 12	Mean ± SD	10.43 ± 4.28	11.12 ± 6.33	10.43 ± 4.62	10.78 ± 7.53	11.12 ± 3.25
	p-value (within)	0.2554[a]	0.5475[b]	0.8173[a]	0.8838[b]	0.4535[a]
	p-value (between)		0.6976[d]	0.5305[c]	0.3774[d]	
sCR (μmol/L)						
Baseline	Mean ± SD	90.17 ± 10.61	88.40 ± 12.38	91.05 ± 13.26	88.40 ± 13.26	83.98 ± 15.03
Week 4	Mean ± SD	88.40 ± 7.07	86.63 ± 13.26	93.70 ± 17.68	90.17 ± 15.03	87.52 ± 13.26
	p-value (within)	0.3497[a]	0.1116[a]	0.7002[b]	0.5666[a]	0.5155[b]
	p-value (between)		0.7134[c]	0.8085[d]	0.2917[c]	
Week 12	Mean ± SD	92.82 ± 22.98	91.05 ± 15.91	93.70 ± 23.87	90.17 ± 15.03	83.10 ± 9.72
	p-value (within)	0.4005[b]	0.9043[b]	0.7274[b]	0.4124[b]	0.8606[a]
	p-value (between)		0.4990[d]	0.8072[d]	0.3892[d]	
sCR ≥ 1.5 × baseline	n (%)	1 (2.63)	3 (8.33)	4 (10.26)	3 (8.11)	1 (5.26)
sCR > 2× baseline	n (%)	1 (2.63)	0	1 (2.56)	1 (2.70)	0

P values for change from baseline. Within arm p-value from [a] Paired T-test, [b] Wilcoxon signed rank test. Between arm p-value from [c] T-test, [d] Wilcoxon rank sum test (placebo vs. epaminurad 3 mg, 6 mg, 9 mg). ALT = alanine aminotransferase; AST = aspartate aminotransferase; sCR = serum creatinine

common in people carrying the HLA-B*5801 allele, such as those of Southeast Asian or African-American descent [21, 22]. In some countries with populations at increased risk of allopurinol hypersensitivity syndrome, such as Korea, febuxostat is considered an alternative first-line option [23]. However, there are concerns about a possible increased risk of cardiovascular-related deaths with febuxostat, although conflicting data have been reported [23].

In the current study, febuxostat was included as a reference arm. Although statistical comparison between epaminurad and febuxostat was not performed, the sUA response rate (< 0.36 mmol/L) in the epaminurad 9 mg dose group (88.89%) was similar to that in the febuxostat 80 mg group (84.21%), and the sUA response rate (< 0.30 mmol/L) was higher in the epaminurad 9 mg group (77.78%) than in the febuxostat group (52.63%). The febuxostat response rates from the current study are consistent with those from previous clinical trials of febuxostat 80 mg (response rate < 0.36 mmol/L: 74–76%; <0.30 mmol/L: 40.5–47%) [24–26].

In our study, the incidence rate of gout flare in the epaminurad 3 mg group was significantly higher than that in the placebo group. The incidence rates in the epaminurad 6 mg and 9 mg groups also tended to be higher than that in the placebo group. It is known that an increased rate of gout flare can occur early during ULT [27], so the ACR guideline recommends that gout flare prophylaxis is performed before or at the start of ULT [5]. Considering that dose dependence was not observed, and similar rates and

trends were observed in the febuxostat 80 mg group, this increase is also considered to be a phenomenon due to its function as an ULT.

The main limitation of the study is the lack of statistical comparison with an active comparator. However, the inclusion of a febuxostat group provided some preliminary evidence that the efficacy of epaminurad appears to be consistent with that of an approved drug. A larger trial formally comparing epaminurad with existing ULTs will be necessary to confirm the clinical usefulness of epaminurad, and longer-term studies will be needed to confirm the safety profile of epaminurad.

Conclusion

Epaminurad at doses of 3, 6 and 9 mg, was effective at reducing sUA levels in patients with gout, in a dose-dependent manner. The study also confirmed the safety and tolerability profile during 12 weeks of treatment. The results suggest that epaminurad has potential as a treatment for patients with gout.

Abbreviations

ADR	adverse drug reaction
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
CI	confidence interval
hURAT1	human urate transporter 1
NSAID	non-steroidal anti-inflammatory drug
SD	standard deviation
TEAE	treatment-emergent adverse event
sUA	serum urate
ULN	upper limit of normal
ULT	urate-lowering therapy

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Data availability

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

Approval was obtained from the relevant Institutional Review Board for each of the 18 participating centers.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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