Effect of Intensive Urate Lowering With Combined Verinurad and Febuxostat on Albuminuria in Patients With Type 2 Diabetes: A Randomized Trial

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Rationale & Objective: Hyperuricemia has been implicated in the development and progression of chronic kidney disease. Verinurad is a novel, potent, specific urate reabsorption inhibitor. We evaluated the effects on albuminuria of intensive urate-lowering therapy with verinurad combined with the xanthine oxidase inhibitor febuxostat in patients with hyperuricemia and type 2 diabetes mellitus (T2DM).

Study Design: Phase 2, multicenter, prospective, randomized, double-blind, parallel-group, placebo-controlled trial.

Setting & Participants: Patients 18 years or older with hyperuricemia, albuminuria, and T2DM.

Intervention: Patients randomly assigned 1:1 to verinurad (9 mg) plus febuxostat (80 mg) or matched placebo once daily for 24 weeks.

Outcomes: The primary end point was change in urinary albumin-creatinine ratio (UACR) from baseline after 12 weeks' treatment. Secondary end points included safety and tolerability and effect on glomerular filtration.

Results: 60 patients were enrolled (n = 32, verinurad and febuxostat; n = 28, placebo). UACRs after treatment with verinurad plus febuxostat were lower than after placebo at 1, 12, and 24 weeks: −38.6% (90% CI, −60.9% to −3.6%), −39.4% (90% CI, −61.8% to −3.8%), and −49.3% (90% CI, −68.2% to −19.0%), respectively. Serum urate levels after treatment with verinurad plus febuxostat were 59.6% and 63.7% lower than after placebo at 12 and 24 weeks, respectively. No clinically meaningful changes were observed in estimated glomerular filtration rate or serum creatinine or serum cystatin C concentrations. Verinurad plus febuxostat was well tolerated.

Limitations: Sample size and study duration were insufficient to evaluate definitive effects of verinurad plus febuxostat on UACR and glomerular filtration. Generalizability was limited by exclusion of patients with stages 4 and 5 chronic kidney disease.

Conclusions: Verinurad plus febuxostat reduced albuminuria and lowered serum urate concentrations in patients with T2DM, albuminuria, and hyperuricemia. Definitive assessment of their combined impact on preservation of kidney function awaits larger clinical studies.

Funding: This study was supported by AstraZeneca.

Trial Registration: Registered at ClinicalTrials.gov with study number NCT03118739.

Complete author and article information provided before references.

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Am J Kidney Dis. 77(4):481-489. Published online October 29, 2020.

doi: 10.1053/j.ajkd.2020.09.009

Type 2 diabetes mellitus (T2DM) remains the leading cause of kidney failure,[1] with a global increase in chronic kidney disease (CKD) deaths due to T2DM of 39.5% between 2005 and 2015.[2] Despite advances in clinical care, including increased use of renin-angiotensin system (RAS) inhibitors and implementation of evidence-based guidelines, patients with T2DM continue to have high residual risk for progression to CKD and cardiovascular (CV) events, especially those with albuminuria.[3] Therefore, lowering albuminuria in patients with T2DM remains a major goal to prevent CKD progression and its consequences,[4] with albuminuria emerging as a biomarker for CKD progression and a surrogate end point for longer term kidney disease outcomes.[5,6]

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Hyperuricemia, characterized by elevated serum urate concentrations, is associated with the presence and development of CKD. It is also an independent predictor for the development of moderately increased albuminuria, with risk greatest for those with the highest serum urate concentrations.[7] Furthermore, evidence from clinical trials suggests that lowering serum urate levels through xanthine oxidase inhibition may slow kidney disease progression and reduce major renal and CV events.[8-10] Underpinning these clinical observations are experimental animal models that suggest hyperuricemia induces kidney injury through multiple pathways, including oxidative stress, vascular smooth muscle proliferation, endothelial dysfunction, and RAS dysregulation.[11-13]

Intensive lowering of serum urate levels may improve kidney protection above and beyond existing renal protection strategies by reducing albuminuria and risk for CKD progression. Verinurad is a novel, highly potent, specific urate transporter 1 (URAT1) inhibitor that reduces serum urate levels in patients with gout.[14,15] By combining verinurad with febuxostat, a competitive xanthine oxidase inhibitor commonly used to treat hyperuricemia in

PLAIN-LANGUAGE SUMMARY

People with chronic kidney disease and type 2 diabetes are at risk for deteriorating kidney function and progressive chronic kidney disease. Loss of albumin into the urine is an early marker of kidney damage and is associated with further deterioration. In this study, the combination of verinurad and febuxostat, drugs that reduce uric acid levels using different mechanisms, led to greater reductions in the amount of albumin in the urine and uric acid in the blood than did placebo. The treatment was generally well tolerated, with nausea and dizziness the most common adverse events seen after verinurad and febuxostat treatment. Although verinurad and febuxostat may help protect the kidneys against further decline in people with chronic kidney disease and type 2 diabetes, definitive assessment of their impact on preservation of kidney function awaits larger clinical studies.

patients with gout,[16] an intensive urate-lowering effect may be achieved, potentially leading to greater kidney protection. Preliminary studies in healthy volunteers have shown that the novel combination of verinurad plus febuxostat provides greater reductions in serum urate levels than either drug alone,[17] with dose-dependent reductions in serum urate levels of up to 80% in patients with gout and little change in urinary urate levels from baseline.[18,19]

We hypothesized that an intensive urate-lowering strategy with a combination of verinurad plus febuxostat would reduce serum urate concentrations and lead to measurable benefits on kidney function. The aim of this trial was to evaluate the impact of this combination on albuminuria in hyperuricemic patients with T2DM, assess any additional effects on kidney function, and examine the safety profile of this novel combination.

Methods

Study Design

This was a multicenter, prospective, randomized, double-blind, parallel-group, placebo-controlled trial in hyperuricemic patients with T2DM and albuminuria receiving standard-of-care treatment (ClinicalTrials.gov identifier NCT03118739). The primary objective was to assess the effect of verinurad plus febuxostat on albuminuria. Secondary objectives included evaluation of kidney function, CV health, and assessment of metabolic effects. The trial was designed and conducted in accordance with the ethical principles originating in the Declaration of Helsinki and in compliance with the International Council for Harmonisation and Good Clinical Practice. Ethical review and approval of the study protocol were provided by the Advarra Institutional Review Board.

Patients were randomly assigned 1:1 to once-daily oral verinurad (9 mg) and febuxostat (80 mg) or matched placebo. Randomization codes were assigned by the investigator sequentially using the AstraZeneca randomization system (AZRand). Patients received treatment for 24 weeks and were evaluated at multiple predefined time points for changes in outcome parameters. Patients were followed up for 4 weeks after treatment had ended to assess the effects of treatment discontinuation.

Because previous studies have reported transient elevations in serum creatinine levels with URAT1 inhibitors,[20,21] strict discontinuation criteria were applied in the event of creatinine level elevations at any time during the study. This included serum creatinine level elevation of 3.0 or more times baseline, absolute serum creatinine value ≥ 4.0 mg/dL, or estimated creatinine clearance (CL_{cr}) < 25 mL/min.

Study Participants

Adults 18 years or older with T2DM, serum urate concentration ≥ 6.0 mg/dL, estimated glomerular filtration rate (eGFR) ≥ 30 mL/min/1.73 m^2, and urinary albumin-creatinine ratio (UACR) of 30 to 3,500 mg/g were eligible for participation. Patients were required to be receiving a stable dose of an RAS inhibitor (unless contraindicated, not tolerated, unavailable, or considered unsuitable by the investigator) for 1 month or longer before randomization.

Key exclusion criteria were prior treatment with any urate-lowering agents in the 6 months before randomization, uncontrolled hypertension (systolic blood pressure > 180 mm Hg), history of gout requiring prophylaxis with nonsteroidal anti-inflammatory drugs or colchicine, diagnosis of heart failure (New York Heart Association functional classification class IV), known hypersensitivity to either study drug, a change in dosage of certain agents that can lower serum urate levels by nonselective mechanisms (losartan, guaifenesin, fenofibrate, or sodium/glucose cotransporter 2 inhibitors) within 2 weeks of randomization or expected dose titration after randomization, and pregnancy, lactation, or plans for pregnancy. A full list can be found in Table S1.

Informed consent was required before study participation. Patients were permitted to withdraw or discontinue from the study for any reason, including patient or physician decision, patients being lost to follow-up, or adverse events (AEs).

Outcomes

The primary end point was change from baseline in UACR within the treatment and placebo arms at 12 weeks, expressed as the ratio of the UACR values. UACR was measured at baseline in both study arms and at successive predefined time points during the study. For UACR determination, 3 first-morning urine void samples were

collected at each visit: 2 days before, 1 day before, and on the day of the study visit.

Several secondary end points were evaluated. The effects of treatment on kidney function were evaluated from measurement of changes in eGFR, serum cystatin C, and serum creatinine values, as were the effects on serum urate levels. To investigate the potential effects of treatment on CV health, markers of CV stress (high-sensitivity troponin I) and inflammation (high-sensitivity C-reactive protein) were measured and compared between arms. Additional analysis explored the impact of treatment on other related biomarkers. Vascular function was assessed by measuring flow-mediated dilatation using a noninvasive device (SmartCuff; Cordex Systems LLC). The effects of treatment on kidney and heart structure and function were also investigated using magnetic resonance imaging. Plasma exposure of verinurad plus febuxostat was assessed from plasma trough concentrations measured approximately 24 hours postdosing.

Safety and tolerability were assessed from reports of AEs, physical examinations, and changes in vital signs and laboratory parameters.

Statistical Analysis

A placebo-corrected reduction in UACR of 30%, corresponding to a ratio of 0.7 (−0.357 on a natural logarithmic scale) was considered to be a clinically meaningful target for this patient population, and a standard deviation (SD) for change in ln(UACR) of 0.8 was assumed based on previous studies.[22] It was determined that 27 patients per arm with available UACR data at baseline and at 12 weeks should ensure with 90% probability that the observed placebo-controlled reduction does not differ from the true unknown reduction with more than this clinically meaningful effect under the assumed SD. It was therefore planned to enroll 30 patients per treatment arm for 1:1 randomization to ensure the availability of 27 evaluable patients per arm.

A mixed-effects model for repeated measures was used to analyze both primary and secondary efficacy variables for the full analysis set, following the intent-to-treat principle. Measurements were taken at baseline; weeks 1, 2, 4, 12, and 24; and at follow-up for all primary and secondary efficacy variables. In this analysis, ln(UACR) was the outcome and change in ln(UACR) was the parameter of interest. For the primary outcome, ln(UACR) was the response variable with randomized treatment and visit as fixed discrete factors and baseline ln(UACR) and patients as random factors. Treatment-visit interactions were included in the mixed-effects model. Geometric least squares mean changes from baseline in ln(UACR) and 95% CIs were calculated by treatment and by visit at the 0.05 significance level, and least squares mean differences between treatment arms were calculated with the same mixed-effects model for repeated measures by visit but presented with 90% CI as prespecified due to the limited sample size.

Standard descriptive statistics were calculated for other variables associated with primary, secondary, and exploratory objectives. Safety data were also presented as standard descriptive statistics by treatment and visit, as well as change from baseline.

Results

Characteristics of Study Participants

In total, 60 patients were enrolled from 19 sites across the United States from May 2017 until January 2018; a total of 32 were randomly assigned to the verinurad plus febuxostat group, and 28, to the placebo group (Fig 1).

Baseline demographic and clinical characteristics were generally balanced between the 2 study groups (Table 1); mean age was 61.5 years, 70% were men, and 62% were White. Mean baseline UACR was 459.1 ± 824.7 (SD) mg/g in the verinurad plus febuxostat group and 411.6 ± 547.8 mg/g in the placebo group. Overall, 47% of patients had a baseline eGFR < 60 mL/min/1.73 m^2. Mean eGFRs were 59.2 and 68.1 mL/min/1.73 m^2 in the verinurad plus febuxostat and placebo groups, respectively (Table 2).

In the verinurad plus febuxostat group, 81% and 75% of patients completed 12 and 24 weeks of treatment, respectively. In the placebo group, 89% of patients completed both 12 and 24 weeks of treatment.

Effect of Verinurad Plus Febuxostat Therapy on UACR

The study met the primary objective with a reduction in UACR from baseline at 12 weeks for verinurad plus febuxostat versus placebo (Table 2; Fig 2). At week 12, mean percentage change from baseline in UACR was −48.7% (95% CI, −64.8% to −25.1%) for verinurad plus febuxostat and −15.3% (95% CI, −43.2% to 26.4%) for placebo. A difference between the 2 treatment arms was apparent as early as 1 week after starting treatment (mean percent change for verinurad plus febuxostat vs placebo: −38.6% [90% CI, −60.9% to −3.6%]) and persisted throughout the 24-week study period (Fig 2). At 12 weeks, the primary end point assessment, mean percentage change in UACR for verinurad plus febuxostat versus placebo, was −39.4% (90% CI, −61.8% to −3.8%).

Post hoc changes in UACR at 24 weeks showed similar trends to those recorded at 12 weeks (Table 2; Figs 2 and S1). Mean percent change from baseline in UACR was −38.4% (95% CI, −58.1% to −9.5%) for verinurad plus febuxostat and 21.4% (95% CI, −18.9% to 81.8%) for placebo. A difference between verinurad plus febuxostat versus placebo of −49.3% (90% CI, −68.2% to −19.0%) was observed. The treatment effect with the verinurad plus febuxostat combination was consistent with a true pharmacologic effect, as shown by an increase from baseline in

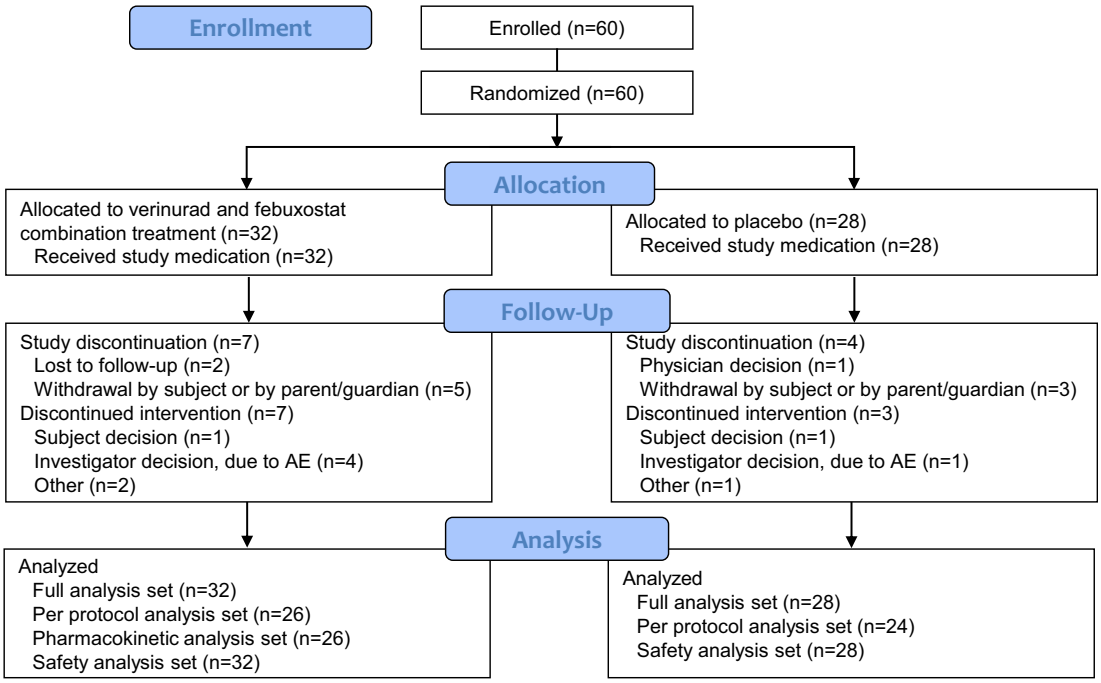

Figure 1. Patient disposition. Abbreviation: AE, adverse event.

UACR at 4 weeks after the end of treatment (mean change in UACR from baseline at follow-up, 184.28 mg/g for verinurad plus febuxostat and 71.94 mg/g for placebo).

Effect of Treatment on Serum Urate Levels and Markers of Kidney Function

The reduction in serum urate levels from baseline was notably greater with verinurad plus febuxostat compared with placebo at both week 12 and week 24 (Table 2) despite the sample collection scheme being optimized for pharmacokinetic rather than serum urate assessment, resulting in underestimation of the effect on serum urate levels. Mean percentage changes from baseline were −56.8% (95% CI, −63.9% to −48.4%) and −61.9% (95% CI, −68.3% to −54.3%) for the verinurad plus febuxostat combination and 6.9% (95% CI, −11.8% to 29.5%) and 4.7% (95% CI, −13.8% to 27.2%) for placebo at each time point, respectively (Fig 3). Mean percentage changes for verinurad plus febuxostat versus placebo at weeks 12 and 24 were −59.6% (90% CI, −67.6% to −49.6%) and −63.7% (90% CI, −71.0% to −54.5%), respectively.

Verinurad plus febuxostat had no apparent effect on eGFR versus placebo in patients at the end of treatment (week 24; Table 2; Fig 4).

No pronounced differences between the verinurad plus febuxostat and placebo arms were noted for serum creatinine or cystatin C levels at weeks 12 and 24 (Table 2).

Additional Secondary Outcomes

No clinically meaningful changes were observed for any of the other secondary outcomes. Of note, serum high-sensitivity C-reactive protein and serum high-sensitivity troponin I levels did not appear to differ notably from baseline or between the 2 treatment groups at weeks 12 or 24 (Table 3). Baseline cardiac magnetic resonance imaging findings indicated that patients had better cardiac structure and function across a range of parameters than was expected, leaving limited scope for improvement in these during the study period. No changes from baseline in blood oxygenation level–dependent magnetic resonance imaging measurements of renal oxygenation were detected. No clinically significant changes in blood pressure from baseline occurred with verinurad plus febuxostat treatment.

Plasma trough concentrations of verinurad and febuxostat remained steady during the course of the study and were similar to those reported in other studies.

Exploratory Outcomes

Flow-mediated vascular dilatation at baseline was comparable between the verinurad plus febuxostat (mean of 60.4% ± 28.8%) and placebo (60.6% ± 30.9%) groups. Mean changes from baseline at weeks 12 and 24 were not notably different: verinurad and febuxostat, 0.8 (95% CI, −10.6 to 12.2) and 0.5 (95% CI, −9.4 to 10.5), respectively; and placebo, −5.9 (95% CI, −17.0 to 5.3) and −5.5 (95% CI, −15.5 to 4.4), respectively.

Table 1. Baseline Patient Characteristics

	Verinurad + Febuxostat (n = 32)	Placebo (n = 28)	All (N = 60)
Male sex	22 (69%)	20 (71%)	42 (70%)
Age at screening, y	62.0 ± 9.5	60.9 ± 12.2	61.5 ± 10.7
Age at randomization			
<65 y	16 (50%)	17 (61%)	33 (55%)
≥65 y	16 (50%)	11 (39%)	27 (45%)
Race			
White	22 (69%)	15 (54%)	37 (62%)
Black or African American	6 (19%)	5 (18%)	11 (18%)
Asian	3 (9%)	4 (14%)	7 (12%)
Native Hawaiian or other Pacific Islander	1 (3%)	0 (0%)	1 (2%)
Other	0 (0%)	4 (14%)	4 (7%)
Weight, kg	93.7 ± 20.2	96.8 ± 19.6	95.1 ± 19.8
BMI, kg/m^2	32.0 ± 5.1	33.0 ± 4.7	32.4 ± 4.9
eGFR			
<30 mL/min/1.73 m^2	2 (6%)	1 (4%)	3 (5%)
30-<60 mL/min/1.73 m^2	16 (50%)	9 (32%)	25 (42%)
60-<90 mL/min/1.73 m^2	9 (28%)	12 (43%)	21 (35%)
≥90 mL/min/1.73 m^2	5 (16%)	6 (21%)	11 (18%)
Prior concomitant medications			
Agents acting on the renin-angiotensin system	25 (78%)	25 (89%)	50 (83%)
ACE inhibitors	16 (50%)	11 (39%)	27 (45%)
Angiotensin II antagonists	4 (13%)	11 (39%)	15 (25%)

Note: Full analysis set. Values expressed as mean ± standard deviation or number (percent).
Abbreviations: ACE, angiotensin-converting enzyme; BMI, body mass index; eGFR, estimated glomerular filtration rate.

Table 2. Effect of Treatment on UACR, Serum Urate, and Markers of Kidney Function

	Verinurad + Febuxostat (n = 32)	Placebo (n = 28)
UACR, mg/g		
Baseline	459.1 ± 824.7	411.6 ± 547.8
Week 12	218.0 ± 280.7	385.3 ± 484.8
Week 24	293.6 ± 371.5	501.8 ± 734.6
Follow-up	487.5 ± 714.1	523.5 ± 597.8
Serum urate, mg/dL		
Baseline	7.5 ± 1.6	7.0 ± 0.8
Week 12	4.1 ± 2.6	7.4 ± 1.4
Week 24	4.1 ± 3.1	7.3 ± 1.2
Follow-up	7.5 ± 1.7	7.0 ± 1.2
eGFR, mL/min/1.73 m^2		
Baseline	59.2 ± 25.3	68.1 ± 23.2
Week 12	57.7 ± 21.3	64.4 ± 25.7
Week 24	53.7 ± 19.5	67.4 ± 24.3
Follow-up	51.1 ± 16.6	68.0 ± 27.1
Serum creatinine, mg/dL		
Baseline	1.40 ± 0.60	1.19 ± 0.36
Week 12	1.35 ± 0.40	1.28 ± 0.44
Week 24	1.43 ± 0.40	1.22 ± 0.41
Follow-up	1.47 ± 0.46	1.23 ± 0.47
Cystatin C, mg/L		
Baseline	1.58 ± 0.53	1.31 ± 0.35
Week 12	1.66 ± 0.53	1.35 ± 0.42
Week 24	1.71 ± 0.54	1.37 ± 0.36
Follow-up	1.75 ± 0.58	1.46 ± 0.39

Note: Values expressed as mean ± standard deviation.
Abbreviations: eGFR, estimated glomerular filtration rate; UACR, urinary albumin-creatinine ratio.

Modest changes from baseline were observed in both study arms at week 24 for the exploratory urinalysis variables but these were not considered clinically relevant. The urinary protein-creatinine ratio was numerically lower in the verinurad plus febuxostat arm compared with placebo at weeks 12 and 24 (Table S2). Urinary urate concentrations were also lower in the verinurad and febuxostat–treated group compared with placebo during follow-up (Table S2). Similarly, small changes occurred in both study arms at 24 weeks in clinical chemistry biomarker levels and were not considered clinically relevant (Table S2).

Safety

Treatment with verinurad plus febuxostat was generally well tolerated. Treatment-emergent AEs occurred in 63% of verinurad and febuxostat-treated patients and 46% of placebo-treated patients and were mostly mild to moderate in intensity. Serious AEs were reported in 5 (16%) patients treated with verinurad plus febuxostat and in 3 (11%) treated with placebo. There was a higher incidence of gastrointestinal and respiratory, thoracic, and mediastinal disorders with verinurad plus febuxostat than placebo (19% vs 7% and 19% vs 4%, respectively). Diarrhea,

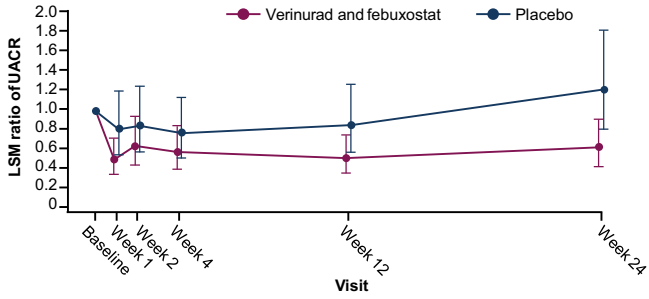

Figure 2. Estimated mean ratio of urinary albumin-creatinine ratio (UACR) with 95% CIs by treatment visit. Error bars are 95% CIs. Mixed-effects model for repeated measures with changes from baseline in ln(UACR) as the response variable; randomized treatment, visit, interaction of treatment group and visit as fixed effects; baseline ln(UACR) as a covariate; and participant as a random effect. Least squares mean (LSM) change in ln(UACR) from baseline and the 95% CI of ln(UACR) were exponentiated to yield the least square estimated mean ratio of UACR.

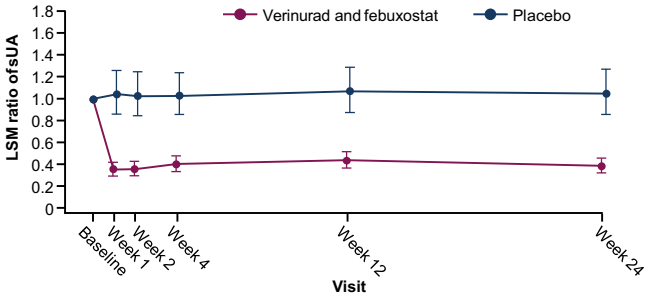

Figure 3. Estimated mean ratio of serum urate (sUA) with 95% CIs by treatment visit. Mixed-effects model for repeated measures with changes from baseline in sUA level as the response variable; randomized treatment, visit, interaction of treatment group, visit, and baseline sUA level as fixed effects; and participant as a random effect. Least squares mean (LSM) change in ln(sUA) from baseline and the 95% CI of ln(sUA) were exponentiated to yield the least square estimated mean ratio of sUA.

dizziness, and nasopharyngitis were reported most frequently by patients who received verinurad plus febuxostat (Table 4).

Twelve patients in the verinurad plus febuxostat group (38%) and 6 patients in the placebo group (21%) discontinued treatment (study treatment or the study). Reasons for discontinuation included transient changes to CL_{cr}, other AEs, and patient withdrawal from study. Five patients (16%) in the verinurad plus febuxostat group and 1 patient (4%) in the placebo group discontinued treatment due to a treatment-emergent AE, including 4 from the verinurad plus febuxostat group who discontinued because of CL_{cr} (<25 mL/min). In general, $CL_{cr} < 25$ mL/min, which required treatment discontinuation, was a result of regular daily fluctuation in patients with a reduced baseline value. In addition,

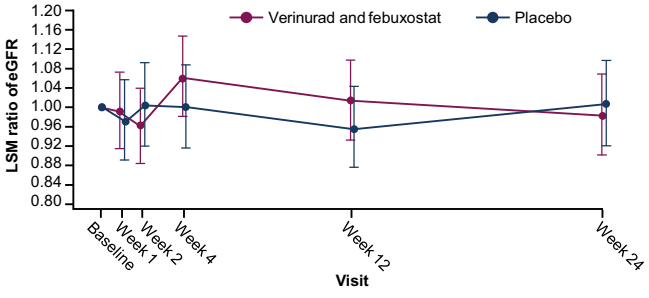

Figure 4. Estimated mean ratio of estimated glomerular filtration rate (eGFR) with 95% CIs by treatment visit. Mixed-effects model for repeated measures with changes from baseline in eGFR as the response variable; randomized treatment, visit, interaction of treatment group, visit, and baseline eGFR as fixed effects; and participant as a random effect. Least squares mean (LSM) change in ln(eGFR) from baseline and the 95% CI of ln(eGFR) were exponentiated to yield the least square estimated mean ratio of serum eGFR.

Table 3. Effect of Treatment on Biomarkers and Parameters Related to Inflammation and Cardiac Health

	Verinurad Plus Febuxostat (n = 32)	Placebo (n = 28)
Serum hsCRP, mg/dL		
Baseline	0.41 ± 0.37	0.36 ± 0.25
Week 12	0.68 ± 1.07	0.48 ± 0.58
Week 24	0.41 ± 0.40	0.50 ± 0.58
Follow-up	0.42 ± 0.37	1.54 ± 4.65
Serum hsTnT, ng/mL		
Baseline	0.016 ± 0.045	0.040 ± 0.152
Week 12	0.012 ± 0.013	0.011 ± 0.012
Week 24	0.019 ± 0.043	0.040 ± 0.102
Follow-up	0.009 ± 0.008	0.009 ± 0.009

Note: Values given as mean ± standard deviation.
Abbreviations: hsCRP, high-sensitivity C-reactive protein; hsTnT, high-sensitivity troponin 1.

more patients in the verinurad plus febuxostat group had eGFR < 45 mL/min/1.73 m^2 at baseline, which may have contributed to the discrepancy in discontinuation rates across groups. One patient in the verinurad plus febuxostat treatment group discontinued study drug because of nausea and diarrhea. AEs related to laboratory findings occurred in 2 patients in the verinurad plus febuxostat group and were in samples drawn pre-dose on dosing day 1; 1 AE was "acute kidney injury" and the other was "creatinine renal clearance decreased." Because both were found before treatment start, neither was considered related to verinurad or febuxostat.

No treatment-related serious AEs occurred. Serious cardiac AEs were reported in the placebo group only. Serum creatinine level elevations greater than 1.5 times baseline occurred in 2 patients in each treatment arm but resolved by the next visit. No hepatotoxicity concerns were identified. No deaths were reported.

Discussion

This proof-of-concept study showed that treatment with verinurad, 9 mg, plus febuxostat, 80 mg, once daily reduced albuminuria in patients with T2DM and

Table 4. Treatment-Emergent Adverse Events Occurring in 2 or More Patients in Either Treatment Group

Adverse Event	Verinurad Plus Febuxostat (n = 32)	Placebo (n = 28)
Diarrhea	4 (12.5%)	1 (3.6%)
Dizziness	3 (9.4%)	0 (0.0%)
Nasopharyngitis	2 (6.3%)	1 (3.6%)
Congestive heart failure	0 (0.0%)	2 (7.1%)
Troponin I increased	0 (0.0%)	2 (7.1%)

hyperuricemia receiving standard-of-care renoprotective treatment and optimal antihypertensive therapy. This intensive urate-lowering strategy led to a 39% reduction in UACR versus placebo after 12 weeks of treatment. Reductions in UACR versus placebo were observed as early as week 1 and were seen throughout the 24-week treatment period. The magnitude of reduction in albuminuria achieved with verinurad plus febuxostat suggests that this novel therapeutic approach may confer additional renoprotection for patients with T2DM and hyperuricemia beyond existing strategies.

The combination of verinurad plus febuxostat was well tolerated, consistent with findings from previous studies of verinurad alone in healthy adult men[23] and febuxostat alone in patients with gout.[24] A higher number of patients in the verinurad plus febuxostat group discontinued treatment compared with the placebo group. The reasons for discontinuation of treatment were several, including nausea and diarrhea, which are commonly reported AEs with febuxostat.[24] For 2 treatment-emergent AEs of acute kidney injury and decreased CL_{cr} in patients on the verinurad plus febuxostat arm, samples were drawn before randomization and first drug use on study day 1 and were not considered related to the study drug. It could not be ascertained whether other suspected treatment-related discontinuations constituted a real or spurious treatment effect; this will be assessed in future studies. Measurements of kidney function were closely monitored during treatment given the potential of URAT1 inhibitors to alter uric acid concentrations in the tubular lumen.[14,25] No measurable effect of verinurad plus febuxostat on serum creatinine or cystatin C concentrations was found.

No effects of verinurad plus febuxostat on eGFR were observed; however, the study was not powered to detect changes in eGFR of the magnitude that could be expected in a study of this limited duration. The verinurad and febuxostat-treated group had lower eGFR than the placebo-treated group at baseline; however, no notable differences were found between groups in eGFR assessments during follow-up. Recent clinical trials have found that urate-lowering therapies such as allopurinol or febuxostat slow the rate of decline in eGFR.[8-10] However, this has not been observed in all studies.[26-29] Differences in clinical trial designs, such as insufficient sample size, heterogeneity in study design, and short follow-up times, may account for these discrepancies.[30] Future studies will be required to assess whether verinurad in combination with an xanthine oxidase inhibitor is superior to placebo in preventing or slowing eGFR decline.

Albuminuria is the earliest clinical signal of kidney disease in diabetic nephropathy and strategies that reduce albuminuria, such as RAS inhibition, are standard of care.[1,4,31,32] However, despite receiving maximal tolerated doses of RAS inhibitors, many patients continue to remain at considerable risk for decline in eGFR and progression to kidney failure.[33] Novel strategies to lower serum urate levels may confer additional benefits beyond RAS inhibition. There are several biological mechanisms through which hyperuricemia may induce early kidney injury, including induction of a specific afferent arteriolar vasculopathy, promotion of endothelial dysfunction through nitric oxide inhibition, and activation of the RAS.[11-13] Although our exploratory analysis did not reveal improvements in markers of endothelial function or inflammation, the addition of a urate-lowering strategy may inhibit many of these pathways, thereby reducing albuminuria. The identification and validation of clinical biomarkers to serve as surrogate end points for important clinical outcomes in nephrology is of considerable interest to clinicians. Changes in albuminuria and measured GFR over time are candidate biomarkers that continue to receive significant attention for use in clinical trials in CKD.[6] A recent scientific workshop concluded that changes in albuminuria and GFR slope fulfilled the criteria for surrogate end points in clinical studies in CKD given their strong relationships with major clinical end points in CKD.[6] The marked reduction in albuminuria observed in this early-phase study provides an important positive signal for kidney protection based on a verinurad-led urate-lowering strategy.

This study was not without limitations. The sample size was small and participation was limited to patients who had T2DM and albuminuria, thereby preventing extrapolation to the wider CKD population. Sample size was based on results of studies performed in similar populations.[34,35] Because there are few reported studies in this patient population, the SD used to calculate sample size may not reflect the true SD in ln(UACR). In addition, patients with stage 4 or 5 CKD were excluded because URAT1 inhibitors require relatively preserved kidney function for optimal effect. eGFR was used instead of measured GFR to determine eligibility for the study and in monitoring participants over time, with potential for imprecision in measurement. Finally, the effects of verinurad or febuxostat alone were not explored in this study.

In conclusion, an intensive urate-lowering strategy with a combination of verinurad plus febuxostat may lead to a reduction in albuminuria among patients with T2DM and hyperuricemia receiving standard-of-care RAS inhibition. The observed effects of this treatment were independent of blood pressure. This novel approach might confer additional benefits to patients with T2DM beyond the use of existing renoprotective strategies. A larger phase 2b clinical trial (ClinicalTrials.gov identifier NCT03990363) is ongoing to confirm these findings.

Supplementary Material

Supplementary File (PDF)

Figure S1: Mean percentage change from baseline in UACR at 12 and 24 weeks according to subgroup.

Table S1: Study inclusion and exclusion criteria.

Table S2: The effect of treatment on kidney and vascular function and on biomarkers related to heart and kidney function.

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Support: Development of this manuscript was supported by AstraZeneca. Medical writing support was provided by Minal Kotecha, PhD, and editorial support was provided by Bethany King, BSc (Hons), both of Core Medica, London, United Kingdom, supported by AstraZeneca according to Good Publication Practice guidelines. The Sponsor was involved in the study design; collection, analysis and interpretation of data; and data checking of information provided in the manuscript. However, ultimate responsibility for opinions, conclusions, and data interpretation lies with the authors.

Financial Disclosure: Dr Stack is supported by grants from the Health Research Board (HRA-2013-PHR-437 and HRA-2014-PHR-685), Midwest Kidney Disease Research and Education Foundation. He has served as consultant to AstraZeneca, Grünenthal, and Menarini. Dr Erlandsson, Dr Parkinson, Ms Johansson, Dr Dronamraju, and Dr Johnsson are employees of AstraZeneca. Dr Erlandsson, Ms Johansson, and Dr Parkinson hold stock in AstraZeneca. Dr Terkeltaub has served as a consultant to AstraZeneca, Horizon, and Selecta. Dr Terkeltaub's research is currently supported by the VA Research Service, National Institutes of Health (AR060772, AR075990), and AstraZeneca.

Acknowledgments: The authors thank the patients, their families, all investigators, and the Prosciento Clinical R&D and Pharmapace Inc staff involved in this study.

Data Sharing: Data underlying the findings described in this manuscript may be obtained in accordance with AstraZeneca's data sharing policy described at https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure.

Peer Review: Received November 12, 2019. Evaluated by 2 external peer reviewers, with direct editorial input from a Statistics/Methods Editor, an International Editor, and the Editor-in-Chief. Accepted in revised form September 2, 2020.

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