A Non-purine Xanthine Oxidoreductase Inhibitor Reduces Albuminuria in Patients with DKD: A Randomized Controlled Trial

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Key Points
- Whether xanthine oxidoreductase inhibitors (XORIs) can be renoprotective for type 2 diabetic kidney disease (T2DKD) is unclear.
- In this randomized trial, a novel XORI, TMX-049 200 mg, reduced albuminuria by 35% in patients with T2DKD, without any relevant safety concerns.
- Aside from lowering uric acid levels, xanthine oxidoreductase inhibition in the kidney may play a key role for the management of T2DKD.

Abstract
Background Diabetic kidney disease (DKD) is characterized by albuminuria and reduced renal function. Whether xanthine oxidoreductase inhibitors (XORIs) have a renoprotective effect in DKD patients with type 2 diabetes remains controversial. We conducted a proof-of-concept study to investigate the renal effects of a novel XORI, TMX-049, in patients with DKD and type 2 diabetes.

Methods This is a multicenter, 12-week, randomized, double-blind, placebo-controlled phase 2a trial conducted at 49 centers across the United States between April 2018 and June 2019. In total, 130 patients with type 2 diabetes, urine albumin-creatinine ratio (UACR) 200–3000 mg/g, eGFR $\geq$ 30 ml/min per 1.73 m², and serum uric acid (sUA) 4–10 mg/dl were randomized 1:1:1 to TMX-049 200 mg (n = 44) or 40 mg (n = 44), or placebo (n = 42). The primary endpoint was change in log-transformed UACR at week 12 from baseline. The secondary end points included changes in UACR, eGFR, and sUA from baseline.

Results The least squares mean differences for changes in log-transformed UACR from baseline to week 12 compared with placebo were $-0.43$ (95% confidence interval [95% CI], $-0.82$ to $-0.04$, $P = 0.03$) for TMX-049 200 mg and $-0.05$ (95% CI, $-0.44$ to $0.34$, $P = 0.80$) for 40 mg; a 35% reduction in UACR was observed with TMX-049 200 mg (ratio versus placebo, 0.65; 95% CI, 0.44 to 0.96) but not 40 mg (0.95; 95% CI, 0.64 to 1.41). Throughout the treatment period, marked reductions in sUA levels but no changes in eGFR were observed with both TMX-049 doses. TMX-049 was generally well tolerated, although two patients with TMX-049 200 mg developed gout.

Conclusions TMX-049 200 mg reduced albuminuria at 12 weeks in patients with DKD and type 2 diabetes. TMX-049 may exert a renoprotective effect independent of its sUA-lowering effect.

Introduction
Diabetic kidney disease (DKD), defined as a persistently increased urine albumin-creatinine ratio (UACR) $\geq$ 30 mg/g and/or sustained reduction in eGFR $<60$ ml/min per 1.73 m² (1–3), is a major cause of CKD, and afflicts approximately 40% of people with type 2 diabetes (3–5). Standard pharmacotherapy for DKD with hypertension has been traditionally the administration of renin-angiotensin-aldosterone system (RAAS) blockers, such as angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) (6). Recently, sodium-glucose cotransporter 2 (SGLT2) inhibitors were approved for the treatment of DKD (6–8). However, an effective treatment option with a different mechanism of action for patients with DKD in addition to available therapies is desired.
Xanthine oxidoreductase inhibitors (XORIs), such as allopurinol, febuxostat, and topiroxostat, have been widely used for the treatment of hyperuricemia and gout due to their uric acid-lowering effect (9–11); however, whether XORIs have a renoprotective effect has been controversial (12–14). In addition to reducing circulating uric acid levels, XORIs may ameliorate renal damage through various mechanisms at the kidney level, including the reduction of inflammation and oxidative stress and the prevention of glomerular hypertension, afferent arteriolar thickening, and ischemic renal histologic changes (14–18). Recently reported large-scale randomized controlled trials (RCTs) of XORIs failed to demonstrate the clinical benefit compared with placebo in slowing the progression of CKD after 2–3 years (19–21). Due to the varied background characteristics of patients with CKD, the evaluation of treatment effect of XORIs should target a specific patient population (19,22,23). Several RCTs have evaluated the XORIs in patients with DKD in type 2 diabetes (24–29); however, these studies were relatively small, and the results were not conclusive. Well-designed RCTs to evaluate the renoprotective effect of XORIs in patients with DKD in type 2 diabetes are thus awaited.

TMX-049 is a newly developed XOI with a nonpurine structure (30–33). In preclinical studies, TMX-049 reduced urine albumin excretion and attenuated renal damage without affecting any metabolic parameter in an experimental rodent model of type 2 diabetes (30–32). In Zucker diabetic fatty rats, an experimental rodent model of type 2 diabetes, 1 mg/kg of TMX-049 showed a 66% inhibition in renal XOR activity compared with vehicle, whereas 3 mg/kg of febuxostat did not (renal xanthine oxidase activity in rats treated with vehicle, TMX-049, and febuxostat were 6.5, 2.2, and 6.3 mU/mg protein, respectively) (30). In addition, 12 weeks’ administration of TMX-049 significantly ameliorated the urine albumin excretion compared with vehicle-treated rats, and the effect was more potent than that with febuxostat (urine albumin excretion in rats treated with vehicle, TMX-049, and febuxostat were 103.0, 60.0, and 82.3 mg/day, respectively) (30). Therefore, TMX-049 is expected to have a more potent inhibitory effect on renal XOR activity and the therapeutic potential to the DKD than other XORIs. The safety and pharmacokinetics of TMX-049 had been evaluated in phase 1 studies; multiple doses of up to 380 mg were well tolerated in healthy male adults (33). On the basis of these findings, we hypothesized that TMX-049 would have renoprotective effects in patients with DKD in type 2 diabetes. Therefore, we conducted a proof-of-concept study to investigate the renal effects of TMX-049 in patients with type 2 diabetes and DKD. The safety and tolerability of TMX-049 were also assessed.

Materials and Methods
Study Design

This study was a 12-week, randomized, double-blind, placebo-controlled, phase 2a trial (Figure 1), conducted at 49 centers across the United States, between April 2018 and June 2019. This study was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice guidelines. The study protocol was approved by Copernicus Group Institutional Review Board, Ochsner Clinic Foundation Institutional Review Board, and Western Institutional Review Board. Written informed consent was obtained from all patients before screening. The study was registered as “Phase 2 Study of TMX-049 in Subjects with Type 2 Diabetes and Albuminuria” at ClinicalTrials.gov (NCT03449199; registration date February 28, 2018).

Participants

Key inclusion criteria were age ≥18 years old; type 2 diabetes treated with at least one glucose-lowering medication for ≥12 months and at least a minimal recommended dose of either an ACEI or ARB, but not both, for ≥3 months; UACR 200–3000 mg/g at screening (with spot urine) and enrollment (with first-morning void urine); eGFR ≥30 ml/min per 1.73 m² (using the CKD Epidemiology Collaboration Equation [34]); and serum uric acid (sUA) 4–10 mg/dl. Key exclusion criteria were type 1 diabetes, treatment with uric acid-lowering therapy <2 weeks, and glycated hemoglobin >11%.

Intervention and Randomization

Eligible patients were enrolled in a single-blind, run-in phase to receive placebo once daily for 2 weeks. Patients

![Figure 1. Study design.](image-url)
with ≥80% compliance to placebo during the run-in phase moved to a double-blind treatment phase, and were randomized in a 1:1:1 ratio to receive TMX-049 200 mg, 40 mg, or placebo once daily for 12 weeks. The dose levels were selected on the basis of the dose dependency of the effects and predicted human therapeutic dose of TMX-049 (200 mg for DKD and 40 mg for lowering uric acid) (30,33). The duration of the treatment period was determined to assess the safety and effects on the UACR of TMX-049.

Randomization was stratified by UACR (<300 mg/g) and sUA level (<6.0 and ≥6.0 mg/dl), and performed through an interactive voice/web response system using a randomization plan generated by an independent statistician. All investigators, patients, and staff remained blinded to treatment allocation during the study. The double-dummy technique was used to ensure the blinding; on each dosing occasion, all patients took one tablet (TMX-049 40 mg or placebo) orally and two capsules (TMX-049 80 mg or placebo), in accordance with the assigned treatment. To maintain the blind status, the results of UACR and sUA were not reported to investigators, patients, or staff after enrollment, unless an abnormally high level of sUA was noted.

During the study, the regimens of glucose-lowering medications and RAAS blockers (either ACEI or ARB) were continued; diuretics (thiazide, nonthiazide, and loop drugs), antituberculous drugs (pyrazinamide and ethambutol), antihypertensive drugs, antilipemic drugs, contraceptives, and hormone-replacement therapy were permitted; and starting or stopping diet remedies and exercise regimes was prohibited.

Outcomes

The primary efficacy end point was the change in log-transformed UACR at week 12 from baseline. The UACR at enrollment and all subsequent study visits was on the basis of the average of the two consecutive day mid-stream, first-morning void urine samples. Secondary efficacy end points included the proportion with a >30% reduction in UACR from baseline to week 12, and the change from baseline in the UACR, eGFR, and sUA levels at weeks 2, 6, and 12 (or early termination), and follow-up visit (4 weeks after treatment completion). The UACR, eGFR, and sUA were centrally measured. The baseline was defined as the measurement at randomization. Urinary biomarkers (kidney injury molecule-1, liver fatty acid-binding protein, 8 hydroxy-2'-deoxyguanosine, and N-acetyl-β-D-glucosaminidase) and blood biomarkers (soluble TNF receptor 1 and high-sensitivity C-reactive protein) were measured as exploratory biomarkers during the study.

Safety was assessed by adverse events (AEs) after randomization identified by investigators on the basis of the clinical evaluations including vital signs (systolic and diastolic blood pressure, pulse rate, and body temperature), 12-lead electrocardiograms, and laboratory tests. The seriousness, severity (mild, moderate, and severe), and causality of AEs were recorded. AEs were coded using the terms of the Medical Dictionary for Regulatory Activities, version 20.1.

Statistical Analysis

On the basis of data from a previous study (35), we estimated that 40 participants per group would provide the trial with 80% power to detect a 35% reduction (−0.43 for log-transformed value) on the primary end point of UACR, assuming an SD of 0.67 (log-scale) using a two-group t test with a 0.05 two-sided significance level. Taking into account that 10% of patients would be excluded from the analysis, we planned to enroll 132 patients (44 per group).

Efficacy analyses were performed on a modified intention-to-treat (mITT) population, which consisted of all randomized patients who had at least one measurement of the UACR after randomization. For the primary analysis of the primary end point, an analysis of covariance (ANCOVA) model was used, with randomized treatment and randomization strata of the UACR and sUA as independent variables. The last-observation carried-forward imputation algorithm was used for missing data. The least squares mean, P value, and corresponding 95% confidence intervals (95% CIs) for the change in log-transformed UACR from baseline in each treatment group and for the difference of the change between each TMX-049 group and placebo group were presented. The adjusted geometric mean of week 12 to baseline ratio with 95% CIs in UACR for each treatment group and the relative ratio between each TMX-049 group and placebo group with its 95% CIs were presented. Because UACR is not normally distributed, log-transformation was used to calculate the means for changes from baseline.

For the secondary analysis, the primary end point was analyzed by an ANCOVA using observed cases (without imputation of missing data) and by a mixed model for repeated measures, which included randomized treatment, randomization strata of the UACR and sUA, timepoint (week), and a treatment-by-timepoint interaction as fixed effects and patient as a random effect. The restricted maximum likelihood method for estimation was used to approximate the denominator degrees of freedom. The adjusted mean change in log-transformed UACR from baseline to week 12 for each treatment group and the 95% CIs were estimated in the framework of this model, and the between-group difference and the 95% CIs for the difference. A sensitivity analysis was performed on a per-protocol population, which consisted of all patients in the mITT population who did not experience any important protocol deviations leading to exclusion.

Prespecified subgroup analyses of the primary end point were performed using the ANCOVA model, which included randomized treatment and randomization strata of the UACR and sUA as independent variables. The last-observation carried-forward imputation algorithm was used for missing data. As a post hoc analysis, the P value for interaction was evaluated by the ANCOVA model, which included randomized treatment, randomization strata of the UACR and sUA, the relevant subgroup, and the interaction between the treatment and subgroup as independent variables.

For the secondary efficacy end points, the ANCOVA model was fit for the change from baseline to each timepoint for UACR, eGFR, and sUA. The proportion of patients with a >30% reduction from baseline to week 12 in UACR was presented by treatment group. The changes in the UACR and sUA from baseline at week 12 in each treatment group were plotted to describe their correlation. Safety analyses were performed on the safety population, which included
all randomized patients who received at least one dose of the study drug. Demographic and safety data were summarized using descriptive statistics. As a post hoc analysis, the changes in the UACR and the systolic blood pressure from baseline at week 12 in each treatment group were plotted. Statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA), and all statistical tests used a two-sided significance level of 5%, with no adjustments for multiplicity for this explanatory proof-of-concept study.

Results

Patient Disposition and Characteristics

Between April and December 2018, 344 patients were screened for eligibility, and 177 were enrolled in the run-in phase. In total, 130 patients were randomized and received the study treatment at 33 study sites, thus being included in the safety population: TMX-049 200 mg (n = 44), 40 mg (n = 44), and placebo (n = 42). The distribution of randomized patients by study site is presented in the Supplemental Table 1. After excluding one patient with TMX-049 40 mg who was lost to follow-up, 129 patients were included in the mITT population: TMX-049 200 mg (n = 44), 40 mg (n = 43), and placebo (n = 42). Overall, 126 patients completed the study (Figure 2).

Baseline characteristics of the patients in the mITT population were similar among the three groups (Table 1). The majority of patients were >65 years old, male, and White. The median UACR was 474.0 (interquartile range, 256.0–915.0) mg/g. The mean of eGFR and sUA was 59 (SD, 21) ml/min per 1.73 m2 and 6.3 (SD, 1.5) mg/dl, respectively. The mean duration of study treatment for the safety population was 82.3 days; all patients had a compliance of ≥80% with the exception of one patient in the TMX-049 40 mg group. All patients received concomitant therapy with RAAS blockers; ACEIs 49% and ARBs 51%. SGLT2 inhibitors and insulin therapy were administered to 7% and 61% of patients, respectively.

Efficacy

Primary End Point

The least squares mean for changes in log-transformed UACR from baseline to week 12 were −0.53 (95% CI, −0.83 to −0.23) for TMX-049 200 mg (P=0.001), −0.15 (95% CI, −0.45 to 0.15) for 40 mg (P=0.32), and −0.10 (95% CI, −0.40 to 0.21) for placebo (P=0.52, Figure 3A). The least squares mean difference for changes in log-transformed UACR from baseline to week 12 compared with placebo were −0.43 (95% CI, −0.82 to −0.04) for TMX-049 200 mg (P=0.03) and −0.05 (95% CI, −0.44 to 0.34) for 40 mg (P=0.80). For TMX-049 200 mg, 40 mg, and placebo, the adjusted geometric mean of week 12 to baseline ratios in UACR were 0.59 (95% CI, 0.44 to 0.79), 0.86 (95% CI, 0.64 to 1.16), and 0.91 (95% CI, 0.67 to 1.23), respectively (Figure 3B). Compared with placebo, the relative ratio of adjusted geometric means of week 12 to baseline ratio in UACR for TMX-049 200 mg and 40 mg were 0.65 (95% CI, 0.44 to 0.96) and 0.95 (95% CI, 0.64 to 1.41), respectively; thus, a 35% reduction in UACR relative to the placebo group was achieved in the TMX-049 200 mg group but not in the 40 mg group. The secondary and sensitivity analyses showed similar results (Supplemental Table 2). For both TMX-049 200 mg and 40 mg, the results were consistent across the prespecified subgroups including baseline sUA, systolic blood pressure, and glycohemoglobin levels (Supplemental Figure 1).

Secondary End Points

There were no reductions in UACR at weeks 2 or 6 with either dose (Figure 3A). The proportion of patients with a >30% reduction in UACR from baseline to week 12 in the TMX-049 200 mg, 40 mg, and placebo groups was 43% (19 out of 44 patients), 33% (14 out of 43 patients), and 24% (10 out of 42 patients), respectively. No changes in eGFR were observed with either TMX-049 dose at any timepoint; a declining trend in eGFR was observed in the placebo group (Figure 4). In both TMX-049 groups, sUA levels sharply decreased at week 2, remained stable until week 12, and...
returned to baseline levels at the follow-up visit, whereas no changes were observed in the placebo group (Figure 5). No correlation was apparent between the changes in UACR and sUA in any group (Figure 6). Regarding the exploratory biomarkers, there were no relevant findings for the urinary biomarkers (kidney injury molecule-1, liver fatty acid-binding protein, 8 hydroxy-2'-deoxyguanosine, and N-acetyl-b-D-glucosaminidase) or blood biomarkers (soluble TNF receptor 1 and high-sensitivity C-reactive protein) in either treatment group.

Safety
During the treatment, 17 out of 44 (39%), 19 out of 44 (43%), and 19 out of 42 (45%) patients receiving TMX-049 200 mg, 40 mg, and placebo, respectively, reported AEs (Table 2), of which the majority were either mild or moderate, and not drug related. The most common AEs (observed in three patients per group) were nausea and diarrhea in the TMX-049 200 mg group, nausea and peripheral edema in the TMX-049 40 mg group, and urinary tract infection and nasopharyngitis in the placebo group. Drug-related AEs occurred more frequently with TMX-049 200 mg (six patients) and 40 mg (five patients) than placebo (two patients), and were most likely due to gout attack or low uric acid levels. Gout was reported in two patients in the TMX-049 200 mg group within 30 days after treatment initiation.

No deaths were reported during the study. Ten patients experienced serious AEs, of which one was considered to be related to the TMX-049 (myelodysplastic syndrome). This patient with TMX-049 40 mg was anemic before randomization and taking azathioprine (a prohibited medication). Moderate anemia was observed during the study, and the patient was found to have myelodysplastic syndrome and discontinued the TMX-049 and azathioprine; the hemoglobin and hematocrit levels recovered to baseline level after 1 month. No other patient discontinued the study treatment due to AEs. Clinically relevant changes were not found regarding vital signs, 12-lead electrocardiograms, or laboratory tests, except for in one patient with a decreased GFR during the administration of TMX-049 40 mg. No marked differences in blood pressure were observed among the treatment groups throughout the treatment. The mean change in the systolic blood pressure from baseline to each study visit is shown in the Supplemental Figure 2. The post hoc analysis did not show any correlation between the changes in UACR and systolic blood pressure in any group (Supplemental Figure 3).

Discussion
In this study, TMX-049 200 mg reduced the primary end point of the UACR after 3 months by 35% compared with placebo in patients with DKD and type 2 diabetes who had normal or high baseline sUA levels. On the basis of the latest recommendations (23), early changes (e.g., within 6 months) in albuminuria can be a reliable surrogate end point for DKD;
the threshold of 30% reduction in the geometric mean UACR can be used for evaluations in phase 2 trials to determine which interventions have the greatest promise for advancing to phase 3 trials. The effect of other XORIs on albuminuria in patients with DKD and type 2 diabetes was investigated in several small RCTs (24–29); however, most of these studies lacked a placebo control (26–28). In an RCT conducted in 80 patients with DKD and hyperuricemia in type 2 diabetes, febuxostat 80 mg/day did not reduce the secondary end point of UACR after 6 months compared with placebo (24). In another RCT conducted in 40 Iranian patients with DKD in type 2 diabetes (25), allopurinol 100 mg/day reduced the urine protein after 4 months compared with placebo (P=0.05), but this study did not report the prespecified primary end point or the effect size between the groups (36). An RCT of topiroxostat (up to 160 mg/day) in 65 Japanese patients with DKD, hyperuricemia, and type 2 diabetes (>95% of participants) did not show any difference in the primary end point of the UACR change after 7 months compared with placebo (29). Due to a lack of evidence from well-designed RCTs, it is premature to conclude the treatment effect of other XORIs in patients with DKD in type 2 diabetes.

Several findings in this study raise the possibility that the observed effects of the 200 mg TMX-049 dose on albuminuria were not entirely due to the reduction in sUA per se. TMX-049 200 mg, the predicted therapeutic dose for DKD, was much higher than the dose predicted to reduce uric acid levels (40 mg) (30,33), and thus was expected to inhibit XOR strongly. In fact, although marked reductions in sUA levels were observed with both doses of TMX-049, the UACR was reduced only with the dose of 200 mg; no apparent relationship between the changes in UACR and sUA with TMX-049 200 mg was observed. In addition, the reduction in UACR with TMX-049 200 mg was not accompanied by any change in eGFR or blood pressure, and the reduction at week 12 was similar among subgroups with low/high baseline sUA or blood pressure levels. These findings suggest the observed effects of TMX-049 200 mg may not be hemodynamically mediated. Increased oxidative stress is a major

![Graph of mean change in the log-transformed UACR from baseline to each study visit and adjusted geometric mean of week 12 to baseline ratio in UACR.](image-url)
factor influencing the development of diabetic complications, such as DKD (37).

XORIs are hypothesized to exert nephroprotective effects by reducing production of reactive oxygen species at the kidney level, thus alleviating oxidative stress (12). XORIs can also exert renoprotective effects via mechanisms such as suppression of superoxide production, or salvage of high-energy adenine nucleotides by XOR inhibition in the kidney (13,38). TMX-049 may have a more potent inhibitory effect on the renal XOR activity than other XORIs (30), and the extent of XOR inhibition in the kidney may play a pivotal role in the treatment of DKD. Furthermore, it has also been hypothesized that hyperuricemia may accelerate DKD progression via a mechanism linked to the RAAS (39,40). Allopurinol has been reported to lower blood pressure, an effect that may be RAAS mediated (41–43). In patients with TMX-049 treatment, we did not observe changes in blood pressure during the treatment, or an acute decline in eGFR immediately after the treatment initiation, as is typically observed with RAAS blockers (44) or SGLT2 inhibitors (7,8).

The safety data of TMX-049 obtained from this study were consistent with those from previous studies (30–33), or

Table 2. Patients with adverse events

| Adverse events                  | TMX-049 200 mg (n=44), n (%) | TMX-049 40 mg (n=44), n (%) | Placebo (n=42), n (%) |
|--------------------------------|-------------------------------|-------------------------------|----------------------|
| Total adverse events           | 17 (39)                       | 19 (43)                       | 19 (45)              |
| Drug-related adverse events    | 6 (14)                        | 5 (11)                        | 2 (5)                |
| Adverse events leading to study drug discontinuation | 0                             | 1 (2)                         | 0                    |
| Serious adverse events         | 2 (5)                         | 4 (9)                         | 4 (10)               |
| Drug-related serious adverse events | 0                             | 1 (2)                         | 1 (2)                |
| Adverse events occurred in ≥2 patients in any group |                               |                               |                      |
| Nausea                         | 3 (7)                         | 3 (7)                         | 0                    |
| Diarrhea                       | 3 (7)                         | 0                             | 2 (5)                |
| Hypoglycemia                   | 1 (2)                         | 2 (5)                         | 1 (2)                |
| Edema peripheral               | 0                             | 3 (7)                         | 1 (2)                |
| Arthralgia                     | 2 (5)                         | 0                             | 0                    |
| Blood uric acid decreased      | 2 (5)                         | 0                             | 0                    |
| Dizziness                      | 2 (5)                         | 0                             | 0                    |
| Gout                           | 2 (5)                         | 0                             | 0                    |
| Urinary tract infection        | 1 (2)                         | 1 (2)                         | 3 (7)                |
| Edema                          | 0                             | 2 (5)                         | 1 (2)                |
| Hyperkalemia                   | 0                             | 2 (5)                         | 0                    |
| Hypothyroidism                 | 0                             | 2 (5)                         | 0                    |
| Influenza                      | 0                             | 2 (5)                         | 0                    |
| Upper respiratory tract infection | 0                             | 2 (5)                         | 0                    |
| Weight increased               | 0                             | 2 (5)                         | 0                    |
| Nasopharyngitis                | 1 (2)                         | 0                             | 3 (7)                |
| Headache                       | 1 (2)                         | 0                             | 2 (5)                |

Data are presented for the safety population (n=130).
known safety profiles of other XORIs (9–11,45), and no
new or unexpected safety concerns were observed. In our
study, treatment-related gout was reported early in the
treatment in two patients receiving TMX-049 200 mg, but
not in those receiving TMX-049 40 mg or placebo. An in-
crease in gout flares is frequently observed during initiation
of antihyperuricemic therapy (9–11,45). One patient in the
TMX-049 40 mg group experienced worsening anemia and
discontinued study treatment due to drug interaction (with
azathioprine) and myelodysplastic syndrome, which was
reported as a serious and drug-related AE. The deterioration
of anemia was likely due to a drug-drug interaction that led

Table 1. Mean sUA (mg/dL) and change from baseline to each visit

|                  | Baseline | Week 2 | Week 6 | Week 12/early termination | Follow-up |
|------------------|----------|--------|--------|---------------------------|-----------|
| Placebo (n=42)   | 6.16 [0.22] | 6.22 [0.21] | 6.06 [0.24] | 6.17 [0.21] | 6.49 [0.22] |
| TMX-049 40 mg (n=43) | 6.47 [0.25] | 4.09 [0.28] | 4.07 [0.28] | 3.94 [0.32] | 6.37 [0.28] |
| TMX-049 200 mg (n=44) | 6.17 [0.21] | 2.74 [0.23] | 3.00 [0.31] | 2.95 [0.30] | 6.11 [0.24] |

Figure 5. Mean change in the sUA level from baseline to each study visit. Data are shown as mean±SEM. In the table, mean [SEM] is pre-
sented, and changes from baseline are shown in parentheses. Data are presented for the modified intention-to-treat population (n=129): TMX-
049 200 mg (n=44), TMX-049 40 mg (n=43), and placebo (n=42).

Figure 6. Scatter plot of change in the UACR versus change in the sUA from baseline at week 12. Data are presented for the modified inten-
tion-to-treat population (n=129): TMX-049 200 mg (n=44), TMX-049 40 mg (n=43), and placebo (n=42).
to increased azathioprine levels. Similar to other XORIs (9–11,45), the risk of drug-drug interaction with azathioprine or mercaptopurine has been identified as a potential risk with TMX-049. Although the possible risks of febuxostat, including cardiovascular events and hepatic effects were reported (9,11,45), we did not observe an increase in liver-related or cardiovascular AEs with TMX-049 in our study.

This study has several limitations. First, this study was designed to evaluate early changes (within 3 months) in albuminuria, and thus the study period might be too short to evaluate any improvement in eGFR, which is an end point directly reflecting the renoprotective effect. A long-term study (e.g., at least 2 years) would be required to evaluate the clinical benefit on GFR decline, cardiovascular disease, and mortality and the safety of the intervention (23). Because this study proved the effect of TMX-049 on reducing albuminuria, a larger and longer study to evaluate the clinical benefit and safety of this drug in patients with DKD is warranted. Second, we obtained data that imply the role of TMX-049 in the kidney; however, the mechanism of action underlying the effects of this drug remains unclear. Further clinical and nonclinical research is needed to understand the role of XORIs in kidney diseases. Finally, although the robustness of the results of the primary end point were confirmed by the secondary and sensitivity analyses, we did not plan any multiplicity adjustment analyses for this early-phase study. The possibility of a chance finding cannot be ruled out.

In conclusion, TMX-049 200 mg ameliorated albuminuria at 12 weeks; therefore, this novel XORI showed potential clinical benefit on DKD in type 2 diabetes. Study results suggested that TMX-049 may exert a renoprotective effect that is independent of its effect on lowering uric acid. TMX-049 also exhibited an acceptable safety profile with good tolerability.

Disclosures

A. Nakajima, H. Mikami, and M. Hirata are employees of Teijin and hold Teijin stocks. G.L. Bakris reports receiving fees from Teijin for his consultation of this study and from Alynium, KBP Bioscience, Ionis, Merck, and Relypsa for consultations outside of the submitted work; and reports serving as a member of the steering committee of international outcome trials; and reports his institution received fees from Bayer, Novo Nordisk, and Vascular Dynamics. M.D. Cressman received fees from Teijin for this publication. None.

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Author Contributions

G. Bakris, M. Cressman, M. Hirata, H. Mikami, and A. Nakajima conceptualized the study; A. Nakajima was responsible for the formal analysis; M. Cressman was responsible for the methodology; M. Hirata and H. Mikami were responsible for the project administration; G. Bakris provided supervision; G. Bakris, H. Mikami, and A. Nakajima reviewed and edited the manuscript; M. Cressman and M. Hirata wrote the original draft; and each author contributed important intellectual content during manuscript drafting or revision, read and approved the final manuscript, and accepts personal accountability for the overall work.

Data Sharing Statement

The data underlying this article are available in the article and in its online supplemental material, no additional data are available.

Supplemental Material

This article contains the following supplemental material online at http://kidney360.asnjournals.org/lookup/suppl?doi=10.34067/KID.0001672021/-/DCSupplemental.

Supplemental Table 1. Distribution of randomized patients by 33 study sites (n=130).

Supplemental Table 2. Change in log-transformed UACR from baseline to week 12 with analyses using ANCOVA (LOCF), ANCOVA (OC), and MMRM.

Supplemental Figure 1. Results of a subgroup analysis according to the baseline characteristics. The relative ratio (95% CI) of adjusted geometric means of week 12 to baseline ratio in UACR between TMX-049 200 mg/40 mg group and placebo group for subgroups.

Supplemental Figure 2. Mean change (±SD) in the supine systolic blood pressure from baseline to each study visit.

Supplemental Figure 3. Scatter plot of changes in the UACR versus changes in the supine systolic blood pressure from baseline to week 12.

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