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This study will be performed in compliance with Good Clinical Practices.

A Randomized, Placebo-Controlled, Double-Blind, Multicenter, Phase 2 Study to Assess Safety, Tolerability, and Renal Effects of TMX-049 in Subjects with Type 2 Diabetes and Albuminuria

Product: TMX-049
Protocol No.: TMX-049DN-201
Phase: Phase 2

for

Teijin America, Inc.

[redacted]

by

[redacted]

Date of Protocol: 07 FEB 2018

STUDY IDENTIFICATION

CRO Medical Monitor: [redacted]

Sponsor's Study Contact: [redacted]

Protocol Biostatistician: [redacted]

SYNOPSIS

Study Number:	TMX-049DN-201
Title of Study:	A Randomized, Placebo-Controlled, Double-Blind, Multicenter, Phase 2 Study to Assess Safety, Tolerability, and Renal Effects of TMX-049 in Subjects with Type 2 Diabetes and Albuminuria
Indication under Investigation:	Diabetic kidney disease (DKD)
Number of Investigators and Study Centers:	Up to 48 study sites in the United States.
Development Phase:	Phase 2
Objectives:	The primary objective of this study is: • To assess the effect of 2 dose levels of TMX-049 on urinary albumin excretion in subjects with Type 2 diabetes and albuminuria (a urinary albumin-to-creatinine ratio (UACR) 200 to 3000 mg/g and an estimated glomerular filtration rate (eGFR) ≥30 ml/min/1.73m^2). Effects of each TMX-049 dose on UACR will be assessed in terms of ratios using log-transformed UACR at Baseline and after a 12-week period of treatment The secondary objectives of this study are: • To assess the effect of each dose of TMX-049 on eGFR during the 12-week period of treatment • To determine the percentage of subjects with >30% decrease in UACR with placebo and each dose of TMX-049 after 12 weeks of treatment • To assess the effect of each dose of TMX-049 on exploratory renal biomarkers during the 12-week period of treatment • To assess the effect of each dose of TMX-049 on serum uric acid (sUA) during the 12-week period of treatment • To assess the pharmacokinetics (PK) of TMX-049 in subjects with Type 2 diabetes and albuminuria • To assess safety and tolerability of TMX-049
Study Population:	Subjects with Type 2 diabetes with UACR 200 to 3000 mg/g and eGFR ≥30 ml/min/1.73m^2.
Methodology/ Study Design:	This will be a randomized, placebo-controlled, double-blind, multicenter Phase 2 study in subjects with Type 2 diabetes, UACR 200 to 3000 mg/g, and eGFR ≥30 ml/min/1.73m^2. Potentially eligible subjects will attend an initial Screening Visit (Visit 1) and sign an informed consent document. After the subject's medical history is reviewed and inclusion/exclusion criteria for the trial assessed, urine and blood samples will be obtained and sent to a [redacted] Subjects who have a UACR 200 to 3000 mg/g and eGFR ≥30 ml/min/1.73m^2 and meet all other protocol-specified eligibility criteria at Visit 1 will return for Visit 2. At Visit 2, subjects will have a physical examination including triplicate blood pressure measurements, a standard 12-lead electrocardiogram (ECG), provide blood samples for repeat eGFR, and submit 2 consecutive day mid-stream, first-morning void urine samples for Baseline UACR determination for confirmation of eligibility. Subjects will be given study medication to be used during a single-blind, placebo run-in phase and instructed to return their study medication to the site at Visit 3. Study medication will be self-administered by the subject once-daily (qd). Study medication should be taken in the morning at about the same time each day, and taken with food

	(breakfast or a snack) rather than on an empty stomach beginning on the day after Visit 2. Subjects who meet all eligibility criteria, including UACR 200 to 3000 mg/g and eGFR ≥30 ml/min/1.73m^2 at both Visit 1 and Visit 2 and who also have ≥80% study medication compliance during the 2-week placebo run-in phase will be randomized at Visit 3 in a 1:1:1 ratio to 1 of 3 treatment groups: placebo, 40 mg TMX-049, or 200 mg TMX-049. Randomization will be stratified by sUA (< 6.0 vs ≥6.0 mg/dL) and UACR (200 to < 300 mg/g vs 300 to ≤3000 mg/g) levels obtained at Visit 2. Study medication will be self-administered by the subject qd in the morning at about the same time each day and taken with food (breakfast or a snack), rather than on an empty stomach during the randomized treatment phase beginning on the day after Visit 3 and continued until the morning prior to Visit 6. The time of dosing and time of any food intake will remain consistent during the period of randomized treatment. Randomized study participants will return to the site after 2 (Visit 4), 6 (Visit 5), and 12 weeks (Visit 6) of double-blind treatment. Study medication compliance will be assessed by pill count at each visit. First-morning void urine samples will be collected on 2 consecutive days prior to each visit. Urine and blood samples for determination of eGFR, sUA levels, and other laboratory tests will also be obtained prior to and after initiation of randomized treatment. Results of sUA and UACR will not be reported to Investigators, subjects, and the Sponsor staff during the randomized treatment phase of the study. The time of PK sample acquisition, the time of dosing prior to the PK sample acquisition, and whether the subject took study medication with or without food will be recorded in the appropriate sections of the case report form (CRF) based on verbal communications with the subjects. At Visit 4, a sample will be obtained prior to TMX-049 dosing (trough sample). At Visit 5, a sample will be obtained 3 ± 1 hours after study medication dosing (time of maximum observed plasma concentration [t_{max}] sample). The timing of dosing can be adjusted to the time of visiting. At Visit 6, a sample will be obtained ≥6 hours (the ideal target is ≥8 hours) after study medication dosing (elimination phase sample). If a subject cannot visit within the time window, a sample will be obtained when the subject visits, even out of the time window. If the trough sample is not obtained at Visit 4, the trough sample should be obtained at Visit 6, instead of the elimination phase sample. If the trough sample is obtained at Visit 4 and the t_{max} sample is not obtained at Visit 5, the t_{max} sample should be obtained at Visit 6, instead of the elimination phase sample. Sites have the option to have a study participant return to the site on a separate day to obtain a properly-timed Visit 4, 5, or 6 sample for PK analysis. Safety assessment will be based on clinical laboratory evaluations, vital signs, physical examinations, and 12-lead ECG will be obtained prior to and during the period of randomized treatment. All study participants will attend a follow-up visit (Visit 7) 4 weeks after the last dose of study medication (Visit 6 or the Early Termination Visit). Two consecutive day urine samples for UACR determination will be submitted by all subjects at this final visit. Urine and blood samples for determination of eGFR, sUA levels, and other laboratory safety tests will be obtained at Visit 7 or at Visit 6 (or the Early Termination Visit).
Number of Subjects (Planned and Analyzed):	It is anticipated that approximately 132 subjects will be randomized into the study resulting in approximately 40 subjects per treatment group for inclusion in the primary endpoint assessment.

Diagnosis and Main Criteria for Inclusion:	The randomized population will include males or females (using a highly effective birth control method or not of childbearing potential) who are at least 18 years of age, have Type 2 diabetes treated with ≥1 glucose-lowering medication for at least 12 months, UACR 200 to 3000 mg/g at Visit 1 and Visit 2, eGFR ≥30 ml/min/1.73m^2 at Visit 1 and Visit 2, and have been treated with at least the minimal recommended dose of an angiotensin converting enzyme inhibitor (ACEI) or an angiotensin II receptor blocker (ARB), but not both, for at least 3 months prior to Visit 1, without any adjustments to this therapy for at least 4 weeks prior to the Visit 1. Compliance (based on pill count) of ≥80% during the 2-week single-blind, placebo run-in phase of the study is also required for inclusion.
Main Exclusion Criteria:	History of Type 1 diabetes; women who are breast feeding; treatment with any uric acid-lowering therapy (eg xanthine oxidase [XO] inhibitors or uricosuric agents) within 2 weeks of Visit 1; history of intolerance to any XO inhibitor; history of a gout flare requiring pharmacologic treatment; history or presence of tophaceous gout; history of immunosuppressant treatment for any known or suspected renal disorder at any time prior to Visit 1; history of a non-diabetic form of renal disease; glycosylated hemoglobin (HbA1c) >11%; sUA <4.0 mg/dL or >10.0 mg/dL; positive urinary pregnancy test; dialysis for acute renal failure within the previous 6 months prior to Visit 1; renal allograft in place or a scheduled kidney transplant within the next 22 weeks; congenital or acquired solitary kidney.
Test Product, Dose, and Route of Administration:	TMX-049 tablets (40 mg), TMX-049 capsules (80-mg capsule containing 2 x 40-mg tablets), and matching placebo tablets/capsules will be administered orally. All eligible subjects will receive qd doses of placebo during a 2-week placebo run-in phase. During the treatment phase, subjects will be randomized at a 1:1:1 ratio to receive 1 of the following treatments: • 40 mg TMX-049 (1 x 40-mg TMX-049 tablet and 2 x placebo capsules) • 200 mg TMX-049 (1 x 40-mg TMX-049 tablet and 2 x 80-mg TMX-049 capsules) • Placebo (1 placebo tablet and 2 placebo capsules) Study medication will be self-administered qd in the morning at about the same time each day, and taken with food (breakfast or a snack) rather than on an empty stomach.
Dose Modification Guidelines	Interruption of dosing can be implemented at any time to manage adverse events (AEs) considered potentially treatment related. If study medication is interrupted, no study medication must be taken (as opposed to reducing the number of study medication tablets/capsules taken).
Duration of Treatment:	There will be a single-blind 2-week placebo run-in phase followed by a double-blind 12-week treatment phase.
Duration of Subject Participation in Study:	All pre-randomization study visits will be completed in ≤6 weeks. The randomized treatment phase of the study will be 12 weeks in duration. A post-treatment follow-up visit will be carried out 4 weeks after the last administered dose of study medication. The maximum duration of study participation will be 22 weeks.

Study Populations:	The All Subjects Population will consist of any subjects who enrolled in the study (signed informed consent) and had study assessments recorded on the database as per the protocol. The Safety Population will consist of all randomized subjects who received at least one study medication tablet or capsule. The Modified Intention-to-Treat (mITT) Population will be used for the efficacy analysis and will consist of all subjects according to their randomization scheme regardless of whether they experienced protocol deviations. The last post-randomization UACR will be carried forward (LOCF) for subjects who did not have a Week 12 UACR determination. Randomized subjects with no post-randomization UACR will be excluded from the mITT analysis. The PK Population will consist of all subjects who received at least one dose of TMX-049 and have evaluable PK data. The Per Protocol Population will be used as a sensitivity analysis for the primary efficacy endpoint and will consist of all subjects according to their randomization scheme who experienced no major protocol deviations.
Study Assessments	Efficacy: UACR, eGFR, exploratory renal biomarkers, and sUA. Safety: Physical examination, vital signs, body weight and height, concomitant medications, 12-lead ECG, AE reports, measurement of HbA1c, clinical laboratory evaluations (hematology, serum chemistry, thyroid testing, lipid panel, and urinalysis parameters). PK: Plasma concentrations of TMX-049.
Efficacy Endpoints	Primary Endpoint: • Change from Baseline to Week 12 in log-transformed UACR Secondary Endpoints: • Proportion of subjects with >30% reduction from Baseline to Week 12 in UACR • Change in eGFR (Baseline compared to each post-treatment assessment) • Change in UACR (Baseline compared to each post-treatment assessment) • Change in renal biomarkers (Baseline compared to each post-treatment assessment) • Change in sUA (Baseline compared to each post-treatment assessment)
Safety Endpoints	• Proportion of subjects with reported AEs, discontinuation due to AEs or serious adverse events (SAEs) • Proportion of subjects with AEs considered by the Investigator to be related to study medication • Proportion of subjects with mild, moderate, or severe AEs as assessed by the Investigator • Changes in vital signs, ECGs, and laboratory parameters

Statistical Methods:	General Statistical Considerations: Data will be summarized using descriptive statistics and include mean, standard deviation (SD), median, minimum, maximum, and corresponding number of subjects (n). For log-transformed data, the geometric mean and geometric coefficient of variation will be provided. For categorical variables, the number and percent in each category will be presented. Tables will include the placebo group and each of the TMX-049 dose groups and a separate category that combines all TMX-049 dose groups. Efficacy Analysis: The UACR values from the 2 consecutive day mid-stream, first-morning void urine samples that are submitted at Visits 2 to 7 will be based on the mean result of measurements in each of the paired samples. If only one sample is available, the results from that sample will be used. The change from Baseline to Week 12 (or the LOCF) in log-transformed UACR will be analyzed in an analysis of covariance model with a fixed effect for treatment, baseline log-transformed UACR and baseline serum uric acid as covariates. The least squares mean, p-value, and the corresponding 95% confidence interval (CI) for the treatment difference will be provided. The last post randomization UACR will be carried forward (LOCF) for subjects who did not have a Week 12 UACR determination. To analyze the effect of LOCF on missing data, the above analysis will be repeated using a mixed model repeated measures approach. The statistical model will feature a repeated statement and include treatment, timepoint, and treatment-by-timepoint interaction as fixed effects, baseline as a covariate, and subject as a random effect. The above analysis of covariance model and repeated measures models will also be used to analyze the secondary endpoints, change in eGFR, change in UACR, change in sUA, and change in renal biomarkers at each post-treatment assessment. The proportion of subjects with >30% reduction from Baseline to Week 12 in UACR will be analyzed using a Fisher's exact test and logistic regression. Renal Biomarker Analysis: Descriptive statistics will be used for renal biomarker assessment. No inferential statistical analysis will be performed for the exploratory renal biomarkers. PK Analysis: PK samples that are obtained at Visits 4, 5, and 6 will be used to assess TMX-049 plasma concentrations and be used in a population PK analysis. Results will be summarized in each of the TMX-049 treatment groups. Safety Analysis: Descriptive statistics will be used in assessment of all safety parameters. No inferential statistical tests will be performed using safety data. Safety analyses will be performed on the Safety Population, and safety variables, including treatment-emergent AEs, laboratory tests, vital signs, and ECGs, will be summarized.

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1. CONTACTS

1.1 Emergency Contacts

Contact the person indicated below for questions concerning serious adverse events and other emergencies:

CRO Medical Monitor:

2. INVESTIGATOR/SPONSOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out the study as described. I will conduct this protocol as outlined therein, including all statements regarding confidentiality. I will make a reasonable effort to complete the study within the time designated. I will provide copies of the protocol and access to all information furnished by the Sponsor to study personnel under my supervision. I will discuss this material with them to ensure that they are fully informed about the drug and the study. I understand that the study may be terminated or enrolment suspended at any time by the Sponsor, with or without cause, or by me if it becomes necessary to protect the best interests of the study subjects. I agree to conduct this study in full accordance with all applicable regulations and Good Clinical Practice (GCP).

Principal Investigator — Date

Sponsor Signature:

[redacted]

9 Feb. 2018
Date

Co-ordinating Investigator Signature:

[redacted]

9 February 2018
Date

3. LIST OF ABBREVIATIONS

Table 1: List of Abbreviations

Abbreviation	Definition
0.5% MC	0.5 w/v% methylcellulose solution
ACEI	angiotensin converting enzyme inhibitor
AE	adverse event
ALT	alanine aminotransferase
ARB	angiotensin II receptor blocker
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
AUC_{0-24h}	area under the plasma concentration-time curve from time zero to 24 hours postdose
AUC_{inf}	area under the plasma concentration-time curve from time zero to infinity
AUC_t	area under the plasma concentration-time curve from time zero to the final quantitative point
BCRP	breast cancer resistance protein
CCLS	[redacted]
CI	confidence interval
CKD	chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
C_{max}	maximum observed concentration
C_{min}	minimum concentration
CRF	Case Report Form
CTA	Clinical Trial Authorization
CYP	cytochrome P450
DDI	drug-drug interaction
DKD	diabetic kidney disease
ECB	Early Clinical Biometrics
ECG	Electrocardiogram
eGFR	estimated glomerular filtration rate
ESKD	end-stage kidney disease
FSH	follicle-stimulating hormone
HbA1c	glycosylated hemoglobin
HDL-C	high-density lipoprotein cholesterol
IB	Investigator's Brochure
IC_{50}	concentration at which 50% inhibition is observed
ICF	informed consent form
IMP	investigational medicinal product
IRB	Institutional Review Board
IUD	intrauterine device
IXRS	interactive voice/web response system
LOCF	last observation carried forward
MATE	multidrug and toxin extrusion
mITT	Modified Intention-to-Treat Population
NAG	N-acetyl-β-D-glucosaminidase
NOAEL	no observed adverse effect level
OATP	organic anion-transporting polypeptide
OCT	organic cation transporter
PD	pharmacodynamics(s)
PK	pharmacokinetic(s)
PV&DSS	Pharmacovigilance and Drug Safety Services

Table 1: List of Abbreviations

Abbreviation	Definition
qd	once-daily
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate using Fridericia's formula
SAE	serious adverse event
SD	standard deviation
SOC	system organ class (MedDRA classification)
sTNFR1	soluble tumor necrosis factor receptor 1
sUA	serum uric acid
$t_{1/2}$	terminal half-life
TEAE	treatment-emergent adverse event
t_{max}	time of maximum observed plasma concentration
TMF	Trial Master File
t_{min}	time of minimum concentration
UACR	urinary albumin-to-creatinine ratio
UGT	uridine 5'-diphospho-glucuronosyltransferase
ULN	upper limit of normal
XO	xanthine oxidase
XOR	xanthine oxidoreductase
ZDF	Zucker diabetic fatty
ZL	normoglycemic ZDF lean

4. ETHICAL CONSIDERATIONS

4.1 Institutional Review Board or Independent Ethics Committee

This study will be considered by an Institutional Review Board (IRB). It is the responsibility of the Investigator to submit this protocol, the informed consent document (approved by the Sponsor), all relevant supporting information, and study-specific advertisements to the IRB for review. Before study onset, the protocol, any protocol amendments, informed consent form (ICF), advertisements to be used for subject recruitment, and any other written information regarding this study to be provided to a subject must be approved by the IRB. Sites will not enroll subjects for the study until the IRB has given their written approval of the protocol and ICF.

If there are any changes to the approved protocol (with the exception of emergency modifications required for subject safety), a protocol amendment will be issued by [redacted] and agreed by the Sponsor. The IRB must give their written approval of any substantial amendments likely to affect the safety of the subject or the conduct of the study. The IRB must be notified of all other changes.

Each site will maintain records of all correspondence with the IRB.

4.2 Ethical Conduct of the Study

This study will be conducted in accordance with consensus ethics principles derived from the Declaration of Helsinki.

4.3 Subject Information and Consent

Written informed consent for the study will be obtained from all subjects before protocol-specific procedures are carried out. The ICF will be approved (along with the protocol) by the IRB.

The Investigator (or designee) will explain the nature of the study and the action of the test product. The subjects will be informed that participation is voluntary and that they can withdraw from the study at any time. The informed consent process shall be documented by the use of a written ICF approved by the designated IRB and will be signed by the subject prior to protocol-specific procedures being performed.

The subject will be given a copy of the signed ICF, and the original will be maintained with the subject's records.

5. INTRODUCTION

TMX-049 (compound code TEI-R04969) is a novel, potent inhibitor of xanthine oxidase (XO), which catalyzes synthesis of uric acid. TMX-049 is currently under development as a therapeutic drug for the treatment of hyperuricemia associated with gout in Japan by Teijin Pharma Limited and is also proposed for development as a therapeutic drug for diabetic kidney disease (DKD) by Teijin America Inc.

5.1 Study Rationale

In vivo non-clinical studies revealed that in addition to XO inhibition, TMX-049 showed reduction of urine albumin excretion in the rat model. The aim of this study is to obtain safety and tolerability data and also assess the renal effects in subjects with Type 2 diabetes and albuminuria treated with TMX-049 following 12 weeks of exposure. The early proof-of-concept therapeutic effect of TMX-049 on reducing urinary albumin-to-creatinine ratio (UACR) in subjects with albuminuria (Baseline UACR 200 to 3000 mg/g) compared with placebo will be assessed in this study.

5.2 Background Information

Uric acid is a final product of the metabolic breakdown of purine nucleotides in humans. Purine nucleotides are metabolized into hypoxanthine, then oxidized to xanthine, and finally further oxidized to uric acid; both oxidation reactions are catalyzed by XO. Uric acid is then excreted mainly through the kidney into the urine. Increased uric acid production or decreased renal clearance of uric acid may cause hyperuricemia, which is defined by serum uric acid (sUA) concentrations >6.8 mg/dL.[1]

Gout is arthritis induced by the accumulation of urate crystals, usually on peripheral joints, due to hyperuricemia. For the treatment of gout, uric acid-lowering therapy using XO inhibitors such as febuxostat and allopurinol is mainly applied.

In non-clinical studies, in vitro XO inhibition efficacy of TMX-049 was shown to be comparable to that of febuxostat. It was highly distributed in the liver, which is the main organ expressing XO, and persistently inhibited XO activity in this organ. TMX-049 showed a persistent plasma uric acid-lowering effect in in vivo pharmacology testing in dogs. Thus, it is expected that TMX-049 would show a longer uric acid-lowering effect than febuxostat.

The prevalence of chronic kidney disease (CKD) and end-stage kidney disease (ESKD), which is a consequence of long term CKD, is growing worldwide.[2, 3, 4] This is becoming an important issue from a health care perspective, as ESKD patients need to be treated by costly renal replacement therapy such as hemodialysis and kidney transplant. Type 2 diabetes is the one of the main causes of CKD.[3, 5, 6] Chronic kidney disease caused by Type 2 diabetes is generally recognized as DKD and defined as a persistent elevated urinary albumin excretion and/or reduction in estimated glomerular filtration rate (eGFR). At present, medication for the treatment of DKD is limited. TMX-049 decreased urine albumin excretion in Type 2 diabetes model Zucker diabetic fatty (ZDF) rats, indicating a potential renal protective effect. In addition, it is suggested that hyperuricemia could be associated with CKD onset and/or progression,[7] and it has been reported that XO inhibitors, such as allopurinol, febuxostat, and topiroxostat, improve renal function or slow the kidney disease progression of hyperuricemia patients.[8, 9, 10]

The safety, tolerability, pharmacokinetics (PK) and metabolism, and pharmacodynamics (PD) of TMX-049 have been evaluated in three Phase 1 studies. Single doses and multiple doses of up to 120 mg TMX-049 showed no significant adverse drug reactions and were well tolerated in healthy adult males in Japan. Single doses and multiple doses of up to 380 mg TMX-049 showed no significant adverse drug reactions and were well tolerated in healthy male subjects of any ethnic origin.

Based on these findings, TMX-049 is proposed as a novel XO inhibitor for the treatment of DKD and hyperuricemia with gout.

5.3 Non-Clinical Studies

Detailed data on non-clinical studies can be found in the latest version of the Investigator's Brochure (IB).[11]

5.3.1 Summary of Non-Clinical Pharmacology

5.3.1.1 In Vitro Study

The in vitro inhibition of xanthine oxidoreductase (XOR) activity by TMX-049 and febuxostat was evaluated using bovine milk XO. TMX-049 showed mixed types of inhibition (mixture of competitive and non-competitive inhibition). The inhibition constant of oxidized XO (Ki) was 0.4 ± 0.2 nmol/L and the inhibition constant of reduced XO (Ki') was 1.2 ± 0.1 nmol/L for TMX-049, while the Ki and Ki' were 0.3 ± 0.1 nmol/L and 2.0 ± 0.1 (mean ± standard error, n=3) for febuxostat, respectively.

To examine the selectivity of TMX-049 for XO, the inhibition of other purine-pyrimidine enzymes (guanine deaminase, hypoxanthine guanine phosphoribosyltransferase, purine nucleoside phosphorylase, and uridine monophosphate [UMP] synthase) and related enzymes (aldehyde oxidase) were evaluated. The concentrations at which 50% inhibition is observed (IC_{50}) values of TMX-049 for all enzymes tested were >100 μmol/L. Results indicated that TMX-049 was a potent and specific inhibitor of XOR.

5.3.1.2 In Vivo Studies

TMX-049 was assessed as a drug candidate for DKD by evaluating the effect on uric acid level and urine albumin excretion.

The effects of TMX-049 and febuxostat on liver XOR activity were evaluated using Sprague Dawley rats. TMX-049 (0.1, 1, or 10 mg/kg), febuxostat (0.1, 1, or 10 mg/kg), or vehicle (0.5 w/v% methylcellulose solution [0.5% MC]) were administered by single oral gavage to male rats. Liver was harvested at either 2 or 24 hours after administration and XOR activity was measured by pterin-based assay. Both TMX-049 and febuxostat inhibited liver XOR activity in a dose-dependent manner at 2 hours after administration, and percentages of inhibition at the respective dose levels against the vehicle-treated group were 55.5%, 97.2%, and 100.0% for TMX-049 and 62.8%, 93.1%, and 100.0% for febuxostat. Liver XOR activity was also inhibited at 24 hours after administration, and percentages of inhibition at the respective dose levels against the vehicle-treated group were 70.0%, 83.0%, and 88.9% for TMX-049, and 32.8%, 52.1%, and 64.4% for febuxostat. At 24 hours after administration, 0.1 mg/kg of TMX-049 showed comparable inhibition to 10 mg/kg of febuxostat, indicating that TMX-049 demonstrated increased liver XOR inhibition activity over febuxostat.

Hypouricemic efficacy of TMX-049 and febuxostat was evaluated in dogs by measuring allantoin in addition to plasma uric acid. TMX-049 (1, 3, or 10 mg/kg), febuxostat (1, 3, or 10 mg/kg), or vehicle (0.5% MC) were administered by single oral gavage to male beagle dogs. Plasma uric acid and allantoin concentration up to 24 hours after administration were measured and both TMX-049 and febuxostat significantly decreased area under the plasma concentration-time curve (AUC) from time zero to 24 hours postdose ($AUC_{0\text{-}24h}$) at 1 mg/kg or higher.

The effect on urine albumin excretion was evaluated in Type 2 diabetes mellitus model ZDF rats. Eight-week-old rats were orally administered TMX-049 (1 or 3 mg/kg), febuxostat (3 mg/kg), losartan potassium (10 mg/kg), or vehicle once-daily (qd) for 13 weeks. Normoglycemic ZDF lean (ZL) rats were also administered vehicle orally qd for 13 weeks (non-diabetic nephropathy control animals). Urine albumin excretion was measured up to 12 weeks. Plasma uric acid levels and XO activity in the renal cortex were determined at 13 weeks. Urine albumin excretion in vehicle-treated ZDF rats was significantly higher than ZL rats. Oral administration of both TMX-049 and losartan potassium significantly decreased urine albumin excretion compared with the vehicle-treated group, while febuxostat had no significant effect. Plasma uric acid in both the TMX-049-treated group and febuxostat-treated group was decreased compared

with the vehicle-treated group. Xanthine oxidase activity in the renal cortex was significantly inhibited by TMX-049 at doses of 1 and 3 mg/kg, whereas febuxostat and losartan potassium showed no inhibition.

5.3.2 Summary of Safety Pharmacology

The effects of TMX-049 on the central nervous system and respiratory system were investigated in male rats given a single oral dose of TMX-049 (at dose levels of 40, 120, and 500 mg/kg). No treatment-related findings were noted compared to vehicle control in general physical condition and behavior or respiratory rate, tidal volume, and minute volume (assessed up to 24 hours after administration) at any dose levels. In conclusion, under the conditions of this study, TMX-049 had no effects on the central nervous system or respiratory system in rats at doses of up to 500 mg/kg.

The effects of TMX-049 on human ether-a-go-go related gene (hERG) tail peak currents in hERG transfected Chinese hamster ovary cells were evaluated using the whole-cell patch clamp method. TMX-049 at 10, 30, and 100 μmol/L had no statistically significant effect compared with the negative control.

The effects of TMX-049 (single oral dose at dose levels of 100, 300, and 1000 mg/kg) on the cardiovascular system were investigated in 4 conscious male cynomolgus monkeys, using a telemetry system. There were no test article-related changes in blood pressure (systolic, diastolic, and mean), heart rate, electrocardiogram (ECG; PR interval, QRS duration, QT interval, and QT interval corrected for heart rate using Fridericia's formula [QTcF]), intra-abdominal body temperature, and clinical signs compared to vehicle control. In conclusion, under the conditions of this study, TMX-049 had no effect on the cardiovascular system in monkeys up to 1000 mg/kg.

5.3.3 Summary of Toxicology

Four pivotal repeat-dose toxicity studies were conducted in rats and monkeys, and TMX-049 was administered orally qd for 4 and 16 weeks for both species. The dose ranges were from 2.5 to 120 mg/kg/day in rats for 4 weeks, from 2.5 to 40 mg/kg/day in rats for 16 weeks, and from 100 to 1000 mg/kg/day in monkeys for 4 and 16 weeks.

In the 4-week rat toxicity study, the no observed adverse effect level (NOAEL) was considered to be 10 mg/kg/day (maximum plasma concentration [C_{max}] of 843 and 785 ng/mL and $AUC_{0\text{-}24h}$ of 4310 and 3030 ng·h/mL for males and females, respectively). No toxicologically significant changes related to TMX-049 were observed at 10 mg/kg/day or below. Major toxicologically significant changes at ≥40 mg/kg/day included: urinary crystals; increased neutrophil count; and histopathological changes in the kidney, urinary bladder, and thyroid gland (eg basophilic crystals, inflammatory cell infiltration, and tubular regeneration in the kidney, urothelial hyperplasia in the urinary bladder, and follicular cell hypertrophy in the thyroid gland). At the highest dose of 120 mg/kg/day, toxicologically significant changes included clinical pathological changes (eg decreased levels of red blood cell count and hemoglobin concentration, and increased levels of urea nitrogen and creatinine), increased kidney weight, renal macroscopic changes (eg yellowish granular substances and discoloration), renal microscopic changes (eg fibrosis and hyperplasia of urothelium), and microscopic changes in the urinary bladder (eg basophilic crystals and urothelial hyperplasia).

In the 16-week rat toxicity study, the NOAEL was considered to be 10 mg/kg/day (C_{max} of 792 and 830 ng/mL and $AUC_{0\text{-}24h}$ of 3720 and 3880 ng·h/mL for males and females, respectively). No toxicologically significant changes related to TMX-049 treatment were observed at 10 mg/kg/day or below. At the highest dose of 40 mg/kg/day, major toxicologically significant changes included urinary crystals, discoloration of the kidney, and renal microscopic changes (eg basophilic crystals, inflammatory cell infiltration, and tubular regeneration).

In the 4-week monkey toxicity study, the NOAEL was considered to be 1000 mg/kg/day (C_{max} of 27 900 and 34 600 ng/mL and $AUC_{0\text{-}24h}$ of 179 000 and 133 000 ng·h/mL for males and females, respectively).

There were no toxicologically significant changes in any examination, and TMX-049 was well tolerated at oral doses up to 1000 mg/kg/day for 4 weeks.

In the 16-week monkey toxicity study, the NOAEL was considered to be 300 mg/kg/day (C_{max} of 3520 and 3730 ng/mL and $AUC_{0\text{-}24h}$ of 34 100 and 39 000 ng·h/mL for males and females, respectively). There were no toxicologically meaningful changes up to 300 mg/kg/day. At the highest dose of 1000 mg/kg/day, the only toxicologically significant change observed was an increase in alanine aminotransferase (ALT). Other TMX-049-related changes observed at 1000 mg/kg/day included slight increases in aspartate aminotransferase (AST), total bilirubin, and glucose; however, these changes were not considered to be toxicologically meaningful because individual values of these parameters were slightly deviated from the range of those in the control background data at the test facility. All TMX-049-related changes showed a tendency to recover or had completely recovered by the end of the 4-week recovery period.

In vitro and in vivo genotoxicity studies for TMX-049 were conducted (bacterial reverse mutation study and in vitro chromosomal aberration study in human lymphocytes, and in vivo micronucleus study in rat bone marrow). TMX-049 showed no genotoxic potential.

Embryo fetal developmental toxicity studies were conducted in rats and rabbits. TMX-049 had no effect on reproductive function of dams and development of embryos and fetuses at up to 120 mg/kg/day in rats and 100 mg/kg/day in rabbits.

An in vivo phototoxicity study in pigmented female rats was conducted with oral administration of up to 500 mg/kg/day TMX-049 for 3 days, followed by a single exposure to ultraviolet radiation. There was no evidence of cutaneous or ocular phototoxicity.

5.3.4 Summary of Non-Clinical Pharmacokinetics

After single oral administration of TMX-049 to rats, monkeys, and dogs in the fasted condition, plasma concentration of TMX-049 reached C_{max} at 1 to 4 hours after administration and decreased with a terminal half-life ($t_{1/2}$) of 3 to 6 hours. The oral absorption of TMX-049 was high (67% to 94% in rats and 61% in monkeys). Bioavailability of TMX-049 in rats, monkeys, and dogs was 26.0% to 35.3%, 50.7%, and 46.6%, respectively. The bioavailability of TMX-049 in dogs was 5.5% following single oral administration after a meal, indicating that drug absorption decreased with meal intake. In repeat dosing of TMX-049 in rats and monkeys, C_{max} and $AUC_{0\text{-}24h}$ values generally increased dose-dependently in rats (2.5 to 120 mg/kg) and monkeys (100 to 1000 mg/kg). No clear differences due to repeated dosing were observed in the C_{max} and $AUC_{0\text{-}24h}$ values in either species. There were no apparent gender differences in C_{max} and $AUC_{0\text{-}24h}$ values in either species.

After single oral administration of [^{14}C]-TMX-049 to rats, radioactivity absorbed from the gastrointestinal tract was widely distributed in various tissues with high levels in the liver and the gastrointestinal tract. Distribution of radioactivity in the brain was low. After single oral administration of [^{14}C]-TMX-049 to pregnant rats, radioactivity was detected in fetal tissues; however, the concentration was lower than that in maternal plasma, showing limited distribution in the fetus.

In vitro plasma protein binding of TMX-049 was high in human plasma (99.6% to 99.7%) and was consistently high across species (human, rat, rabbit, dog, and monkey). The major binding protein of TMX-049 in human plasma was albumin. Distribution of TMX-049 in human blood cells was low (1.1% to 5.4%).

In human hepatocytes, glucuronides of TMX-049 and 2 hydroxylated metabolites were the main metabolites. There were no human-specific metabolites among human, rat, and monkey hepatocytes. In reaction phenotyping, cytochrome P450 (CYP) 1A2, CYP2C8, and CYP2C9 were involved in the oxidative metabolism of TMX-049, and uridine diphosphate glucuronate transferase (UGT1)A1/9 inhibitors (UGT1A1 and UGT1A9) were involved in the glucuronidation of TMX-049, suggesting that TMX-049 is metabolized by multiple metabolic enzymes.

After single oral administration of [^{14}C]-TMX-049 to rats, excretion was mainly into feces (83.0% to 90.8% of dose up to 168 hours). The urinary excretion of the parent compound TMX-049 was low (7.7% to 15.7% of dose up to 48 hours). After single oral administration of [^{14}C]-TMX-049 to monkeys, excretion was mainly into feces (83.0% of dose up to 168 hours). The urinary excretion of the parent compound TMX-049 was low (3.7% of dose up to 48 hours).

TMX-049 had an inhibitory effect on CYP2C8 (IC_{50}: 18.6 µmol/L), CYP2C9 (IC_{50}: 266 µmol/L), and CYP3A4 (substrates: testosterone [IC_{50}: 94.8 µmol/L] and midazolam [IC_{50}: 283 µmol/L]). There was no significant inhibition for CYP1A2, CYP2B6, CYP2C19, and CYP2D6.

TMX-049 had no inductive effect on CYP1A2 and CYP2B6 up to 300 µmol/L. TMX-049 had no inductive effect on CYP3A4 up to 100 µmol/L, but had an inductive effect at 300 µmol/L. However, the inductive effect was 20% or less of the positive control (20 µmol/L rifampicin).

TMX-049 was a substrate of breast cancer resistance protein (BCRP), organic anion-transporting polypeptide (OATP) 1B1, and OATP1B3. There was no significant inhibition for P-glycoprotein (IC_{50}: >250 µmol/L), organic cation transporter (OCT) 2 (IC_{50}: >10 µmol/L), and multidrug and toxin extrusion (MATE) 1 (IC_{50}: >10 µmol/L), but TMX-049 had an inhibitory effect on BCRP (IC_{50}: 18.6 µmol/L), OATP1B1 (IC_{50}: 3.71 µmol/L) and OATP1B3 (IC_{50}: 10.9 µmol/L), organic anion transporter (OAT) 1 (IC_{50}: 7.37 µmol/L), MATE2-K (IC_{50}: 0.887 µmol/L), and bile salt export pump (IC_{50}: 37.7 µmol/L). Also, TMX-049 inhibited the OAT3 and multidrug resistance-associated protein (MRP) 2-mediated active transport by 45% and 36% at the highest concentration, respectively (IC_{50}: OAT3: >10 µmol/L, MRP2: >100 µmol/L).

5.4 Summary of Clinical Experience

5.4.1 Study TMX-049-101

A Phase 1 first-in-human study has been completed to investigate the safety, tolerability, PK, and PD of TMX-049 in healthy male subjects in Japan (study TMX-049-101). TMX-049 was administered as single ascending oral doses from 1 to 120 mg in the fasted condition. Single oral doses of 5 and 40 mg TMX-049 were also administered after a meal to investigate food effect.

Over the dose range tested in the fasted condition, the time of maximum observed plasma concentration (t_{max}) ranged from 1.75 to 3.000 hours, with mean C_{max} ranging from 16.672 to 1675.657 ng/mL. Mean $t_{1/2}$ ranged from 5.432 to 18.708 hours. Area under the plasma concentration-time curve from time zero to infinity (AUC_{inf}) was 93.19 to 10 764.20 ng·h/mL. Plasma drug concentration parameters (C_{max} and AUC_{inf}) showed dose proportionality over the dose range tested. After administration of 5 mg TMX-049, the fed/fasted geometric mean ratio (90% confidence intervals [CIs]) was 0.758 (0.498 to 1.155) for C_{max} and 0.961 (0.599 to 1.542) for AUC_{inf}, showing no significant food effect. However, at 40 mg TMX-049, the fed/fasted geometric mean ratio (90% CIs) was 0.495 (0.300 to 0.818) for C_{max} and 0.610 (0.395 to 0.943) for AUC_{inf}, showing that plasma exposure to TMX-049 was decreased when administered with food. After single oral administration of TMX-049 at doses of 1 to 120 mg in the fasted condition, or 5 and 40 mg in the fed condition, the mean cumulative urinary excretion rate up to 72 hours after administration was low, ranging from 3.17% to 6.03%. Renal clearance of TMX-049 ranged from 0.24 to 0.62 L/h.

In the fasted condition over the dose range tested, sUA concentrations decreased compared with the placebo group. The time to reach minimum concentration (t_{min}) for serum uric acid tended to increase (from 18.0 hours at 1 mg to 38.7 hours at 120 mg) with increasing dose. The ratio of minimum concentration (C_{min}) of sUA relative to Baseline value decreased from -8.30% to -45.51% as the dose increased from 1 to 120 mg. Mean t_{max} of plasma xanthine increased from 5.3 to 22.7 hours and mean C_{max} of plasma xanthine increased from 0.0857 to 0.2405 mg/dL as the dose of TMX-049 increased from 1 to 120 mg. In the fed condition, sUA concentrations decreased which was consistent with the results following administration in the fasted state. Minimum plasma concentration and t_{min} values following a dose of 5 mg TMX-049 were 5.30 mg/mL and 12.7 hours in the fasted condition, and 4.63 mg/dL and 12.7 hours in the fed condition, respectively; and following a dose of 40 mg TMX-049 were 4.30 mg/dL and 27.0 hours in the fasted

condition, and 4.12 mg/dL and 23.3 hours in the fed condition, respectively, showing no significant food effect.

Single oral doses of TMX-049 from 1 to 120 mg had no safety issues and were well tolerated. Six adverse events (AEs) were reported by 4 out of 48 subjects administered TMX-049 in the fasted condition, including C-reactive protein increased, testicular neoplasm, foot deformity, ALT increased, and blood lactate dehydrogenase increased. One AE (urine ketone body present) was reported by 1 out of 20 subjects in the placebo group. There was no tendency to onset of AEs associated with dose increase and causal relationship with TMX-049 was ruled out for all of the AEs.

One serious adverse event (SAE) was observed (testicular neoplasm). The Principal Investigator judged that the event did not have a causal relationship with TMX-049 and the Sponsor considered that the judgment by the Principal Investigator was appropriate.

No subjects died or discontinued the study treatment during the study period.

Based on non-clinical study findings, urinary sediment and endocrine parameters were monitored in the clinical study; however, no abnormal changes in urinary sediment or abnormal changes related with thyroid hormone in the endocrine test were detected. Also, no AEs related to deposition of xanthine crystals in the kidney or bladder or AEs related with the thyroid gland were observed. No other clinically significant abnormal findings were observed.

5.4.2 Study TMX-049-102

A Phase 1 multiple dose study has been conducted in healthy male subjects in Japan to investigate the safety, tolerability, PK, and PD of TMX-049 administered qd for 10 days at dose levels ranging from 3 to 120 mg in the fed state.

Following the initial administration of TMX-049 at 3 to 120 mg, median t_{max} ranged from 2.50 to 4.00 hours, with mean C_{max} ranging from 37.487 to 2088.050 ng/mL. Mean $t_{1/2}$ ranged from 4.148 to 7.029 hours. The plasma drug concentration parameters C_{max}, $AUC_{0\text{-}24h}$, AUC from time zero to the final quantitative point (AUC_t), and AUC_{inf} showed dose proportionality over the dose range studied. Following the final administration in the repeated qd administration of TMX-049 for 10 days at 3 to 120 mg, median t_{max} ranged from 2.00 to 4.00 hours, with mean C_{max} ranging from 46.165 to 1873.007 ng/mL. Mean $t_{1/2}$ ranged from 7.883 to 15.166 hours. The C_{max}, $AUC_{0\text{-}24h}$, and AUC_t of the plasma unchanged drug showed dose proportionality over the dose range studied. The AUC_{inf} increased dose-dependently, but dose proportionality could not be confirmed. The mean accumulation ratio ranged from 0.9092 to 1.2548 for C_{max} and 0.9152 to 1.1608 for $AUC_{0\text{-}24}$ across the dose range studied, showing no increase in the blood exposure. Based on the changes in trough plasma concentrations of unchanged drug, steady-state was reached by Day 7 at the latest in all the groups treated with TMX-049.

After the initial administration of TMX-049, sUA levels remained low depending on the dose of TMX-049. The mean C_{min} of sUA was 5.35 mg/dL in the placebo group compared with 5.55, 4.67, 4.40, and 4.08 mg/dL in the groups treated with 3, 10, 40, and 120 mg of TMX-049, respectively. Compared with Baseline sUA levels, the mean percent change in C_{min} was -7.96% in the placebo group and -15.64%, -22.07%, -30.55%, and -35.79% in the groups treated with at 3, 10, 40, and 120 mg of TMX-049, respectively, showing that the C_{min} decreased with an increase in TMX-049 dose.

When TMX-049 was administered qd for 10 days at 3 to 120 mg, the sUA levels reached steady-state by Day 9 at the latest in any group, based on the changes in the trough sUA concentrations. The sUA levels after the last administration remained low depending on the dose of TMX-049. The mean C_{min} of sUA was 5.54 mg/dL in the placebo group compared with 4.95, 3.50, 2.45, and 1.13 mg/dL in the groups treated with 3, 10, 40, and 120 mg of TMX-049, respectively. The mean C_{min} of sUA was lower after the last administration compared with after the initial administration. Compared with Baseline sUA levels, the mean percent change in C_{min} was -4.61% in the placebo group and -24.04%, -41.32%, -61.30%,

and -82.33% in the groups treated with 3, 10, 40, and 120 mg of TMX-049, respectively, showing that the C_{min} decreased with an increase in TMX-049 dose. The mean percent change in C_{min} of sUA decreased after the repeated administration compared with that after the initial administration. After the completion of administration on Day 10, the mean sUA levels returned to the same levels as Baseline (0 h on Day 1) by Day 17, the final observation day, in all the groups.

After oral administration of TMX-049 at 3 to 120 mg, the urinary uric acid excretion decreased in association with a decrease in the sUA levels. The plasma xanthine increased after oral administration of TMX-049 at 3 to 120 mg and the urinary xanthine excretion also increased in association with the increased plasma xanthine. Likewise, the plasma hypoxanthine increased after administration of TMX-049 and the urinary hypoxanthine excretion also increased in association with the increased plasma hypoxanthine.

Adverse events were noted in 3 of 24 subjects treated with TMX-049 at 3, 10, 40, and 120 mg, and in 1 of 8 subjects treated with placebo. The incidence of AEs was 50.0% (3/6 subjects) in the group treated with 120 mg of TMX-049 and 12.5% (1/8 subjects) in the placebo group. No AEs were noted in the groups treated with 3, 10, and 40 mg of TMX-049. One occurrence each of dizziness postural, white blood cell count increased, and transaminases increased were noted in the group treated with 120 mg of TMX-049. The event of transaminases increased was considered to be an adverse drug reaction (ADR), but this occurred on Day 11, its severity was mild, and this reaction disappeared without any treatment. No deaths, other SAEs, or AEs leading to discontinued administration of the investigational drug were noted. Apart from abnormal laboratory values counted as AEs, no safety concerns were noted in the laboratory values, vital signs, and physical findings. No AEs related to standard 12-lead ECG were noted. In summary, the repeated qd oral administration of TMX-049 for 10 days at 3 to 120 mg was well tolerated by healthy male subjects, and no safety concerns were noted.

5.4.3 Study TMX-049DN-101

A further Phase I study has been completed to investigate the safety, tolerability, PK, and PD of single and multiple oral doses of TMX-049 in healthy male subjects of any ethnic origin. TMX-049 was administered as single ascending doses from 10 to 380 mg in the fasted condition and as multiple oral doses from 40 to 380 mg, administered qd for 10 days in the fed condition.

Following single and multiple qd oral dose administration in the fasted and fed states, TMX-049 was characterised by rapid to steady absorption with median t_{max} between 1.5 and 3.5 hours. Plasma concentrations declined in a biphasic manner with $t_{1/2}$ ranging from 10 to 19 hours. Systemic exposure to TMX-049 increased in a dose-proportional manner across the fasted 10 to 380 mg single oral dose range. Following 40 to 380 mg qd multiple dosing of TMX-049 in the fed state, dose-proportional increases in AUC values and slightly greater than dose-proportional increases in C_{max} were indicated; however, these assessments of dose proportionality were not entirely conclusive due to high between-subject variability and wide confidence intervals. Following multiple qd oral dosing, minimal accumulation of TMX-049 in plasma was observed. Steady-state was generally achieved within 5 days of dosing and no time-dependent change in exposure was detected with multiple dosing. Urinary excretion was low with arithmetic means ranging from approximately 3% to 5% of the dose excreted as unchanged drug following single fasted doses of TMX-049.

Regarding PD parameters, the sUA level reached C_{min} (mean: 3.62 to 5.12 mg/dL) at a median t_{min} of 12, 16, 24, 24, and 24 hours, following single oral administration of 10, 40, 120, 220, and 380 mg TMX-049, respectively, and then increased. There was a delay in time to C_{min} with an increase in dose between 10 and 120 mg TMX-049 and then t_{min} reached 24 hours for the 120 to 380 mg dose levels. The percent change from baseline of C_{min} (mean) of sUA decreased from −17.0% to −41.5% as the dose of TMX-049 increased from 10 to 380 mg.

Following single doses of 10 to 380 mg TMX-049 under fasted conditions, and multiple qd oral dosing for 10 days under fed conditions, plasma xanthine increased after administration, and the urinary xanthine excretion also increased in association with the increased plasma xanthine. Likewise, the plasma hypoxanthine, and oxypurine increased after administration of TMX-049, and the urinary hypoxanthine and

oxypurine excretion also increased in association with the increased plasma hypoxanthine.

When TMX-049 was orally administered repeatedly qd for 10 days at 40 to 380 mg after breakfast, the sUA concentrations reached a steady state by Day 9 in all dosing groups. On Day 10 in the qd oral dosing regimen of TMX-049, the sUA levels in the groups treated with 40, 120, 240, and 380 mg TMX-049 decreased with an increase in the doses of TMX-049 compared with baseline (sUA level at predose, Day 1). The mean percent change from baseline in C_{min} for sUA was -61.8%, -75.9%, -83.4% and -85.4% for the 40, 120, 240, and 380 mg TMX-049 dose levels, respectively. After the completion of administration on Day 10, the mean sUA levels returned to the same levels as baseline (predose, Day 1) by Day 17/18, the final observation day, in all the groups.

There was no formal food effect analysis performed on the PD parameters. Different groups of subjects in Part A and Part B received 40, 120, and 380 mg TMX-049 on Day 1 under fasted (Part A) or fed (Part B) conditions. Changes from baseline in mean sUA levels in the 40, 120 and 380 mg TMX-049 dose groups were similar following administration under fed and fasted conditions. The C_{min} occurred at a similar time for the fed and fasted TMX-049 doses.

After administration of single doses of 10 to 380 mg TMX-049 under fasted conditions, and multiple qd oral doses of 40 to380 mg TMX-049 under fed conditions, there was a decrease in urinary uric acid..

Overall, in Part A (single ascending-dose), 9 treatment emergent adverse event (TEAE)s were noted in 7 (17.5%) subjects administered single oral doses of between 10 and 380 mg TMX-049 as tablets under fasting conditions. Headache was the most frequently reported TEAE being reported by 3 subjects (1 subject following placebo and 2 subjects following 220 mg TMX-049). All 4 instances of headache were mild and only one instance was considered possibly related to the study drug (220 mg TMX-049). Two subjects received concomitant medication for the treatment of headache. There were no other TEAEs in Part A reported by more than 1 subject. Overall, in Part B (multiple ascending dose), 40 TEAEs were noted in 15 (46.9%) subjects administered qd oral doses of between 40 and 380 mg TMX-049 qd as tablets under fed conditions. Headache and pollakiuria were the most frequently reported TEAEs, each being reported by 3 subjects. A total of 4 events of headache were reported. Three headache events were reported by 2 subjects receiving placebo; 2 of which were mild in severity and 1 which was moderate and considered to be possibly related to treatment, requiring concomitant medication. One event of headache was reported by 1 subject receiving 40 mg TMX-049 (considered to possibly related and mild in severity). All events of headache had an onset day between Day 1 and Day 8, and the duration varied from approximately 1 to 4 days. A total of 3 events of pollakiuria were reported (2 events for 2 subjects receiving 380 mg and 1 event by 1 subject receiving placebo). These events of pollakiuria were mild in severity and considered to be possibly related to the study drug. No concomitant medication was required for any event. All events of pollakiuria had an onset day of Day 3, however the duration varied from approximately 1 to 5 days. Rash, nausea, dizziness, and nasopharyngitis were the only other TEAEs reported by more than 1 subject in Part B, each being reported by 2 subjects. With the exception of rash (120 mg TMX-049 qd), these TEAEs were generally considered to be not related or unlikely related to the study drug and were mild in severity, with the exception of 1 moderate TEAE of nasopharyngitis. One subject reported mild nasopharyngitis on Day 6 that developed to moderate severity on Day 7, requiring concomitant medication. There were no deaths or SAEs reported during the study and none of the subjects discontinued from the study due to a TEAE. There were no treatment-or dose-related trends and no clinically significant findings in the clinical laboratory evaluations, endocrine data, vital signs data, 12-lead ECG measurements, or physical examination findings during the study. In summary, single oral administration of TMX-049 from 10 to 380 mg under fasted conditions, and the repeated qd oral administration of TMX-049 for 10 days from 40 to 380 mg under fed conditions, were well tolerated by healthy male subjects, and no safety concerns were noted.

6. STUDY OBJECTIVES

The primary objective of this study is:

- To assess the effect of 2 dose levels of TMX-049 on urinary albumin excretion in subjects with Type 2 diabetes and albuminuria (a UACR 200 to 3000 mg/g and an eGFR ≥30 ml/min/1.73m^2). Effects of each TMX-049 dose on UACR will be assessed in terms of ratios using log-transformed UACR at Baseline and after a 12-week period of treatment

The secondary objectives of this study are:

- To assess the effect of each dose of TMX-049 on eGFR during the 12-week period of treatment
- To determine the percentage of subjects with >30% decrease in UACR with placebo and each dose of TMX-049 after 12 weeks of treatment
- To assess the effect of each dose of TMX-049 on exploratory renal biomarkers during the 12-week period of treatment
- To assess the effect of each dose of TMX-049 on sUA during the 12-week period of treatment
- To assess the PK of TMX-049 in subjects with Type 2 diabetes and albuminuria
- To assess safety and tolerability of TMX-049

7. INVESTIGATION PLAN

7.1 Overall Study Design and Plan Description

This will be a randomized, placebo-controlled, double-blind, multicenter, Phase 2 study in subjects with Type 2 diabetes, UACR 200 to 3000 mg/g and eGFR ≥30 ml/min/1.73m^2.

Potentially eligible subjects will attend an initial Screening Visit (Visit 1) and sign an informed consent document. After the subject's medical history is reviewed and inclusion/exclusion criteria for the trial assessed, urine and blood samples will be obtained and sent to a [redacted].

Subjects who have a UACR 200 to 3000 mg/g and eGFR ≥30 ml/min/1.73m^2 and meet all other protocol-specified eligibility criteria at Visit 1 will return for Visit 2. At Visit 2, subjects will have a physical examination including triplicate blood pressure measurements, a standard 12-lead ECG, provide blood samples for repeat eGFR, and submit 2 consecutive day mid-stream first-morning void urine samples for Baseline UACR determination for confirmation of eligibility. Subjects will be given study medication to be used during a single-blind, placebo run-in phase and instructed to return their study medication to the site at Visit 3. All pre-randomization study visits will be completed in ≤6 weeks. Study medication will be self-administered by the subject qd. Study medication should be taken in the morning at about the same time each day, and taken with food (breakfast or a snack) rather than on an empty stomach beginning on the day after Visit 2.

Subjects who meet all eligibility criteria, including UACR 200 to 3000 mg/g and eGFR ≥30 ml/min/1.73m^2 at both Visit 1 and Visit 2 and who also have ≥80% study medication compliance during the 2-week placebo run-in phase, will be randomized at Visit 3 in a 1:1:1 ratio to 1 of 3 treatment groups: placebo, 40 mg of TMX-049, or 200 mg of TMX-049. Approximately 132 subjects will be randomized, with the expectation that 40 subjects per treatment group will complete 12 weeks of treatment and be included in the primary endpoint assessment. Randomization will be stratified by sUA (<6.0 vs ≥6.0 mg/dL) and UACR (200 to <300 mg/g vs 300 to ≤3000 mg/g) levels obtained at Visit 2. Study medication will be self-administered by the subject qd in the morning at about the same time each day and taken with food (breakfast or a snack), rather than on an empty stomach during the randomized treatment phase beginning on the day after Visit 3 and continued until the morning prior to Visit 6. The time of dosing and time of any food intake will remain consistent during the period of randomized treatment.

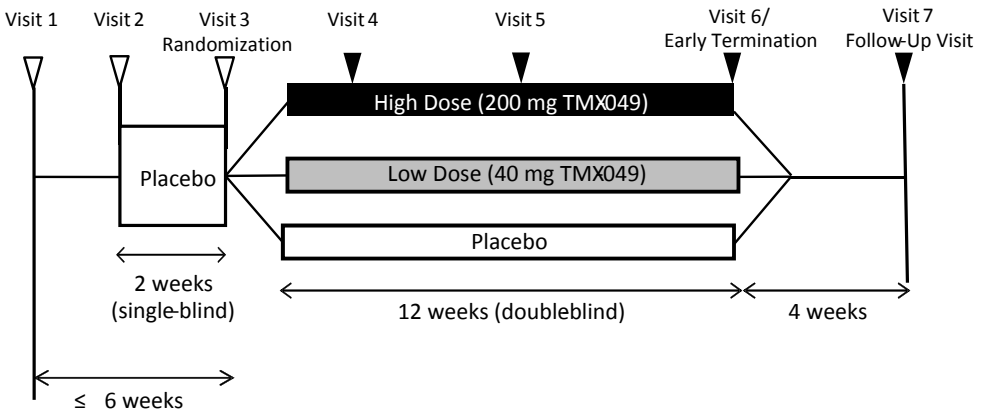
Randomized study participants will return to the site after 2 (Visit 4), 6 (Visit 5), and 12 weeks (Visit 6) of double-blind treatment. Study medication compliance will be assessed by pill count at each visit. First-morning void urine samples will be collected on 2 consecutive days prior to each visit. Urine and blood samples for determination of eGFR, sUA levels, and other laboratory tests will be obtained prior to and after initiation of randomized treatment. Results of sUA and UACR will not be reported to Investigators, subjects, and the Sponsor staff during the randomized treatment phase of the study. The time of PK sample acquisition, the time of dosing prior to the PK sample acquisition, and whether the subject took study medication with or without food will be recorded in the appropriate sections of the case report form (CRF) based on verbal communications with the subjects.

At Visit 4, a sample will be obtained prior to TMX-049 dosing (trough sample). At Visit 5, a sample will be obtained 3 ± 1 hours after study medication dosing (t_{max} sample). The timing of dosing can be adjusted to the time of visiting. At Visit 6, a sample will be obtained ≥6 hours (the ideal target is ≥8 hours) after study medication dosing (elimination phase sample). If subject cannot visit within the time window, a sample will be obtained when the subject visits, even out of the time window. If the trough sample is not obtained at Visit 4, the trough sample should be obtained at Visit 6, instead of the elimination phase sample. If the trough sample is obtained at Visit 4 and t_{max} sample is not obtained at Visit 5, the t_{max} sample should be obtained at Visit 6, instead of the elimination phase sample. Sites have the option to have a study participant return to the site on a separate day to obtain a properly timed Visit 4, 5, or 6 sample for PK analysis.

Safety assessment will be based on clinical laboratory evaluations, vital signs, physical examinations, and 12-lead ECG, which will be obtained prior to and during the period of randomized treatment.

All study participants will attend a Follow-up Visit (Visit 7) 4 weeks after the last dose of study medication. Two consecutive day urine samples for UACR determination will be submitted by all subjects at this final visit. Urine and blood samples for determination of eGFR, sUA levels, and other laboratory safety tests will be obtained at Visit 7 or at Visit 6 (or the Early Termination Visit).

Figure 1: Study Design



7.2 Discussion of Study Design, Including the Choice of Control Groups

A single-blind, 2-week placebo run-in phase will be conducted prior to randomization to study treatment in order to enter only those subjects who can be expected to have an acceptable level of treatment compliance in the randomized treatment phase of the study.

This treatment phase of the study will be double-blind and placebo-controlled in order to avoid bias in the collection and evaluation of data during its conduct. Placebo has been chosen as the control treatment to assess whether any observed effects are treatment related or simply reflect the study conditions.

The aim of the study is to obtain safety, tolerability, and PK data and to assess effects of TMX-049 on UACR in subjects with Type 2 diabetes and albuminuria. The selected doses are anticipated to be reasonably well tolerated by subjects with Type 2 diabetes and albuminuria for the duration of the investigational treatment period.

A 12-week treatment represents an adequate time to permit the assessment of safety and tolerability of TMX-049 as well as a determination of early proof-of-concept therapeutic effect on reducing UACR compared with placebo, while limiting the potential risk associated with a novel investigational drug.

7.3 Selection of Study Population

The study protocol can only fulfil its objectives if appropriate subjects are enrolled. The following eligibility criteria are designed to select subjects for whom protocol treatment is considered appropriate. All relevant medical and non-medical conditions should be taken into consideration when deciding if participation in this study is suitable for a particular subject.

Note: Subjects with exclusionary laboratory tests or other assessments at Visit 1 and/or Visit 2 may have a

single repeat test at the Investigator's discretion.

7.3.1 Inclusion Criteria

To be eligible to participate in the study, subjects must meet the following criteria:

1. Males or females using a highly effective birth control method or not of childbearing potential who are at least 18 years of age at Visit 1

2. Has Type 2 diabetes and has been treated with ≥1 glucose-lowering medication for at least 12 months prior to Visit 1

3. Treatment with at least the minimal recommended dose of an angiotensin converting enzyme inhibitor (ACEI) or an angiotensin II receptor blocker (ARB), but not both, for at least 3 months prior to Visit 1, without any adjustments to this therapy for at least 4 weeks prior to the Visit 1

4. Willingness and ability to provide written informed consent prior to any study-related procedures and to comply with all study requirements

5. Urinary albumin-to-creatinine ratio 200 to 3000 mg/g at Visit 1 and Visit 2. The average of the 2 consecutive day mid-stream, first-morning void UACR results will be used at Visit 2

6. Estimated glomerular filtration rate ≥30 ml/min/1.73m^2 (calculated using the Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] equation) at Visit 1 and Visit 2

7. Compliance (based on pill count) of ≥80% during the single-blind, placebo run-in phase of the study

7.3.2 Exclusion Criteria

Subjects who meet any of the following criteria will not be eligible to participate in the study:

1. Investigational drug use within previous 30 days prior to Visit 1

2. History of Type 1 diabetes

3. Women who are breastfeeding

4. History of drug or alcohol abuse within 1 year of Visit 1

5. Treatment with any uric acid-lowering therapy (eg XO inhibitors and uricosuric agents) within 2 weeks of Visit 1

6. Treatment with [redacted] from any time after Visit 2

7. Treatment with [redacted] from any time after Visit 2

8. Treatment with [redacted] from any time after Visit 2

9. Treatment with [redacted] from any time after Visit 2

10. Treatment with use of [redacted] from any time after Visit 2

11. Treatment with use of [redacted] from any time after Visit 2

12. History of intolerance to any XO inhibitor

13. History of a gout flare requiring pharmacologic treatment

14. History or presence of tophaceous gout

15. History of immunosuppressant treatment for any known or suspected renal disorder at any time prior to Visit 1

16. History of a non-diabetic form of renal disease

17. History of hospitalization for treatment of uncontrolled cardiac arrhythmia, unstable angina, myocardial infarction, any arterial revascularization procedure, or heart failure within 3 months of Visit 1

18. History of hospitalization for treatment of a major psychiatric disorder within 5 years of Visit 1

19. History of any cancer with the exception of basal cell carcinoma of skin or in-situ cervical carcinoma within 5 years of Visit 1. Subjects with a history of cancer who have been disease free for more than 5 years prior to Visit 1 do not require exclusion from the trial

20. Positive test for human immunodeficiency virus (HIV), hepatitis B, or hepatitis C at Visit 2

21. Hemoglobin <10.0 g/dL at Visit 1

22. Glycosylated hemoglobin [HbA1c] >11% at Visit 1

23. Alanine aminotransferase or AST >2 x upper limit of normal (ULN) at Visit 1 or Visit 2

24. Serum uric acid <4.0 mg/dL or >10.0 mg/dL at Visit 1 or Visit 2

25. Systolic blood pressure ≥160 mmHg or diastolic blood pressure ≥90 mmHg based on average of triplicate measurement at Visit 1 or Visit 2

26. Fridericia-corrected QT interval (QTcF) ≥450 ms (males) or ≥470 ms (females) on an ECG obtained at Visit 2

27. Female subjects with positive urinary pregnancy test at Visit 1 or Visit 3

28. Known bilateral clinically relevant renal artery stenosis (>75%)

29. Dialysis for acute renal failure within the previous 6 months prior to Visit 1

30. Renal allograft in place or a scheduled kidney transplant within the next 22 weeks from Visit 1 (being on a waiting list does not exclude the subject)

31. Congenital or acquired solitary kidney

32. Subjects with a clinical diagnosis of heart failure with reduced ejection fraction and persistent

symptoms (New York Heart Association [NYHA] class III-IV) at Visit 1

33. History or presence of any clinical condition which, in the opinion of the Investigator, impedes ability for the subject to complete all study protocol requirements, increases risk of participation, or is not in the best interest of the study participant

7.3.3 Withdrawal of Subjects

7.3.3.1 Replacement Procedures

Subjects who are withdrawn or who choose to withdraw from this study will not be replaced.

7.3.3.2 Guidance to Investigators on When to End Study Treatment Regimen

Subjects will be withdrawn if any of the following criteria are met:

- subject decision (withdrawal of consent)
- any clinically relevant signs or symptoms that in the opinion of the Investigator warrant subject withdrawal
- ALT or AST >8 x ULN
- ALT or AST >5 x ULN for more than 2 weeks
- ALT or AST >3 x ULN and with either a total bilirubin >2 x ULN or and International Normalized Ratio (INR) >1.5
- ALT or AST >3 x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
- eGFR ≤15 ml/min/1.73m^2, confirmed with repeat measurement
- development of an inter-current illness, condition, or procedural complication that in the opinion of the Investigator would interfere with the subject's continued participation
- development of an intolerable AE as determined by the Investigator and/or subject
- positive pregnancy test result
- significant protocol non-compliance in the study, as considered applicable by the Investigator
- if it becomes necessary to break the blinding code for a subject

A subject is free to withdraw from the study at any time for any reason without prejudice to their medical care. In addition, the Investigator may decide, for reasons of medical prudence, to withdraw a subject. In either event, the Sponsor will be notified and the date and reason(s) for the withdrawal will be documented in the subject's source data. Should the randomization code be broken for a subject, the date, time, and reason will be recorded in the subject's source data.

The Investigator will also withdraw the subject from the study upon the request of the Sponsor or if the Sponsor terminates the study. Upon occurrence of a serious or intolerable AE, the Investigator should confer with the Sponsor before discontinuing the subject.

If a subject has started the investigational medicinal product (IMP) and subsequently develops an inter-current medical problem, the Investigator may decide to withdraw IMP administration temporarily on clinical grounds. If the subject recovers and there are no clinical contraindications to resuming IMP administration this should be allowable within the protocol if the treating clinician feels it is appropriate to do so.

7.3.3.3 Follow-Up of Subjects Prematurely Discontinued from the Study Treatment Regimen or Withdrawn from Study

If a subject is withdrawn or chooses to withdraw, an early termination visit and end of study visit will be performed if possible (see Table 2). The Investigator may also request that the subject returns for an additional follow-up visit.

Where possible all subjects who discontinue due to AE will be followed up at suitable intervals to evaluate the course of the AE and to ensure reversibility or stabilization. The subsequent outcomes of these events will be recorded on the paper CRF.

If a subject is withdrawn or chooses to withdraw prior to randomization, no additional tests are required.

7.4 Treatment of Subjects

Study medication is defined as any investigational treatment(s) or placebo intended to be administered to a study participant according to the study randomization or treatment allocation.

7.4.1 Treatments Administered

All eligible subjects will receive qd doses of placebo during a 2-week placebo run-in phase. Subjects with ≥80% study medication compliance during the 2-week placebo run-in phase will be randomized to receive qd doses of 40 mg TMX-049, 200 mg TMX-049, or placebo during the double-blind 12-week treatment phase.

On each dosing occasion, subjects assigned to the placebo group will swallow 1 tablet (placebo) and 2 capsules (placebo), subjects assigned to the low-dose group (40 mg TMX-049) will swallow 1 tablet (40 mg TMX-049) and 2 capsules (placebo), and subjects assigned to the high-dose group (200 mg TMX-049) will swallow 1 tablet (40 mg TMX-049) and 2 capsules (80 mg TMX-049) with water. All tablets/capsules making up a dose must be taken at the same time (ie dividing a dose is not permitted).

Treatment group	Capsule	Tablet
TMX-049 200-mg group	2 x 80-mg TMX-049 capsules	1 x 40-mg TMX-049 tablet
TMX-049 40-mg group	2 x placebo capsules	1 x 40-mg TMX-049 tablet
Placebo group	2 x placebo capsules	1 x placebo tablet

Subjects will be instructed to take study medication qd in the morning at approximately the same time each day. Subjects should take study medication with food, rather than on an empty stomach whenever possible, although occasional administration on an empty stomach is permissible. Subjects who don't usually eat breakfast should eat something (a snack would be acceptable), prior to dosing. Study medication will begin the morning after Visit 2 in the placebo run-in phase and the morning after Visit 3 at the beginning of the randomized treatment phase. The last dose of study medication will be taken in the morning before Visit 6.

If a subject does not take a dose of study drug within +12 hours of their regular dosing time, then the dose of study drug should be skipped and the subject should be instructed to take the study drug at the next regularly scheduled time. If a dose is missed, the site notified and recorded in the appropriate sections of the CRF based on verbal communications with the subjects. If a subject takes more than the intended dose,

they should report this to the site and an AE will be recorded if there were symptoms that accompanied the additional dose taken.

At Visit 4, subjects should not take study medication in the morning before their visit. Subjects can take study medication after the PK sample is obtained provided it is taken within +12 hours of their regular dosing time.

At Visit 5, subjects should take study medication approximately 3 hours before the visit. Therefore, the time of dosing may not necessarily be in the morning and can be adjusted according to the time of the visit.

At Visit 6, subjects should take study medication in the morning.

The time of PK sample acquisition, the time of dosing prior to the PK sample acquisition and whether the subject took study medication with or without food will be recorded in the appropriate sections of the CRF based on verbal communications with the subjects.

7.4.2 Identity of Investigational Product

The IMP, TMX-049 tablets at 40-mg strength, TMX-049 capsules at 80-mg strength (the capsule will contain 2 x 40-mg tablets), and matching placebo tablets and capsules, will be supplied by the Sponsor, along with batch numbers, Transmissible Spongiform Encephalopathy statements, safety data sheets, and Certificates of Analysis.

7.4.2.1 Packaging and Labeling

The study drugs will be supplied by the Sponsor as treatment kits consisting of 1 tablet and 2 capsules for each dosing day (placebo: 1 x placebo tablet and 2 x placebo capsules; 40-mg dose group: 1 x 40-mg TMX-049 tablet and 2 x placebo capsules; 200-mg dose group: 1 x 40-mg TMX-049 tablet and 2 x 80-mg TMX-049 capsules). The treatment kits will consist of aluminum pouches containing 2 wallets, each wallet will contain sufficient tablets/capsules for 9 days qd dosing (18 days dosing per treatment kit). The treatment kits will be identical in appearance in order to maintain the double-blind status of the treatment phase.

All packaging and labeling will be in compliance with Good Manufacturing Practice (GMP) specifications, as well as applicable local regulations.

The subject will be provided with a treatment kit for the placebo run-in phase at Visit 2 and will return the empty wallet/wallet containing unused medication at Visit 3 when an assessment of compliance during the run-in phase will be made.

The subject will be provided with the relevant number of treatment kits at Visits 3, 4, and 5 for qd dosing at home during the double-blind treatment phase and the subject will return the empty wallet/wallets containing unused medication at the subsequent visit (Visit 4, 5, and 6).

7.4.2.2 Storage and Stability

The IMP may be dispensed only by the Investigator, by a staff member specifically authorized by the Investigator, or by a pharmacist, as appropriate.

The treatment kits will be stored at between 20°C and 25°C (68°F and 77°F) in each study site pharmacy, which will be locked with restricted access. No special procedures are required for the safe handling of the tablets/capsules.

Prior to dispensing of the treatment kits for home dosing, subjects will be instructed to keep the tablets/capsules in the original packaging and store the treatment kits at room temperature, and out of reach

of children. The study drug must not be given to other persons. The subject must return the empty wallet/wallets containing unused medication to the study site for a compliance check at Visit 3 (following the placebo run-in) and Visits 4, 5, and 6 (during the treatment phase). The subjects will receive instructions for medication intake from the Investigator.

7.4.2.3 Study Drug Accountability, Reconciliation, and Return

The Investigator will maintain accurate records showing the receipt and disposition of the study supplies. Records will be maintained showing the receipt and disposition of the study supplies both at site and at subject level.

The IMP accountability records and inventory will be available for verification by the Sponsor, or designee, at intervals and upon request during the study to check the supplies' storage (provided that this does not unblind the study). At the completion of the study, there will be a final reconciliation of all IMP.

The IMP must not be used for any purpose other than the present study. Study drug that has been dispensed to a subject must not be re-dispensed to a different subject.

The empty aluminum pouches and wallets will be discarded upon satisfactory completion of accountability procedures. Any unused treatment packs will be retained until completion of the study.

The Study Monitor will periodically collect the study drug accountability forms and check all study drug dispensation and returns during the entire study period.

Details of retention and reference samples will be documented in the pharmacy records. The interactive voice/web response system (IXRS) vendor can manage damaged study drug in the IXRS. Once drug is received at site, they will acknowledge receipt of the study drug. During this acknowledgement transaction, they will be asked to indicate if any of the study drug was received in damaged condition.

7.4.2.4 Study Drug Handling and Disposal

No special procedures are required for the safe handling of the tablets/capsules.

Following completion of the clinical phase of the study and Sponsor review of accountability, all unused supplies will either be returned to the Sponsor (together with the accountability records) or will be destroyed locally in agreement with the Sponsor and Certificates of Destruction provided to the Sponsor.

Only participants enrolled in the study may receive study treatment and only authorized site staff may dispense or administer study treatment.

7.4.3 Method of Assigning Subjects to Treatment Groups and Measures to Minimize/Avoid Bias

7.4.3.1 Subject Identification

Subjects will be identified by a subject number and site number.

A list identifying the subjects by subject number and site number will be kept in the Trial Master File (TMF).

7.4.3.2 Randomization

Subjects who meet all eligibility criteria and who also have ≥80% study medication compliance during the 2-week placebo run-in phase will be centrally randomized at Visit 3 to receive placebo, 40 mg TMX-049, or 200 mg TMX-049 in a 1:1:1 ratio. Randomization will be stratified by sUA (<6.0 vs ≥6.0 mg/dL) and UACR (200 to <300 mg/g vs 300 to ≤3000 mg/g) levels obtained at Visit 2. Randomization will be

performed through IXRS.

The randomization plan will be generated by an independent statistician and none of the Sponsor staff, Investigators, or study subjects will have access to the randomization schema prior to randomization and until the database is unblinded at the end of the study.

Prior to the start of the trial, the IXRS vendor will generate the master randomization code and a copy will be supplied to the biopharmaceutical analyst.

7.4.3.3 Blinding

The 2-week placebo run-in phase will be conducted in a single-blind manner. In order to ensure the subjects will remain blinded to the study treatment, the treatment packs will be identical in appearance to those used during the treatment phase.

The following controls will be employed to maintain the double-blind status of the treatment phase study:

- The placebo tablet will be identical in appearance to the TMX-049 40-mg tablet and the placebo capsules will be identical in appearance to the TMX-049 80-mg capsules.
- The treatment packs for the placebo, 40-mg dose level and 80-mg dose level will be identical in appearance. The total number of tablets and capsules making up each dose will be identical, with each subject receiving 1 tablet and 2 capsules per dose, irrespective of the treatment assigned.
- The Investigator and other members of staff involved with the study will remain blinded to the treatment and randomization code.
- Results of sUA and UACR will not be reported to Investigators, subjects, and the Sponsor staff.
- All data will be provided to [redacted] in a blinded manner.

7.4.3.3.1 Unblinding in the Event of an Emergency

All participants will be centrally randomized using an IXRS. Before the study is initiated, the directions for the IXRS will be provided to each site.

During an emergency or life-threatening situation when knowledge of the assigned treatment is essential for immediate medical management, such as in the event of possibly treatment-related SAEs or severe AEs, the Investigator or designee may unblind the subject's treatment assignment. The Investigator or designee should make every attempt to contact the Medical Monitor prior to unblinding; however, subject safety must be a priority so unblinding should not be unduly delayed. If not possible to do so in advance, the Medical Monitor must be contacted after the unblinding. The justification and process of unblinding should be appropriately documented in the Investigator Site File.

If it becomes necessary to break the code during the study, the date, time, and reason will be recorded in the subject's source data and will be witnessed by a second person. Under such circumstances, subjects will be withdrawn from the study; dosing of TMX-049 or placebo will be stopped and early termination procedures will be conducted.

7.4.4 Selection of Doses in the Study

Two dose levels of TMX-049 have been selected for this study; a 40-mg dose level and a 200-mg dose level. The 200-mg dose level sufficiently covers the maximum predicted human therapeutic dose levels of 150 mg/day approximately for the treatment of DKD based upon the pharmacological study in ZDF rats and the results of Phase 1 studies. The 40-mg dose level has been selected to evaluate the dose dependency

of the therapeutic effects. The 40-mg dose level is within the range of predicted human therapeutic dose levels (5 to 48 mg/day) for the treatment of hyperuricemia based on the results of Phase I study in Japan (TMX-049-101).

The selected doses are anticipated to be reasonably well tolerated by subjects with Type 2 diabetes and albuminuria for the duration of the investigational treatment period.

In a previous Phase 1 multiple dose study (Study TMX-049-DN-101), repeated qd oral administration of TMX-049 for 10 days at doses up to 380 mg was well tolerated by healthy male subjects, and no safety concerns were noted.

7.4.5 Dose Modification

Interruption of dosing can be implemented at any time to manage AEs considered potentially treatment related. If study medication is interrupted, no study medication must be taken (as opposed to reducing the number of study medication tablets/capsules taken).

7.4.6 Prior and Concomitant Medications

Please also see Appendix B which lists all the medications.

7.4.6.1 Permitted

Subjects must have been treated with ≥1 glucose-lowering medication for at least 12 months prior to Visit 1 and continue with this treatment for the duration of the study. It is preferable that these medications should not be changed from Visit 2 until the end of the study; however, if this is deemed clinically necessary, this is permitted and the subject does not need to be withdrawn from the study. Investigators should recognize the potential interaction between TMX-049 and metformin (see Section 7.4.6.2).

Subjects must also have been treated with at least the minimal recommended dose of an ACEI or ARB, but not both, for at least 3 months prior to Visit 1, without any adjustments to this therapy for at least 4 weeks prior to the Visit 1, and continue with this treatment for the duration of the study.

Diuretics known to have effect on excretion of uric acid (thiazide diuretics, non-thiazide diuretics, and loop diuretics); antituberculous drugs known to have effect on excretion of uric acid (pyrazinamide and ethambutol); antihypertensive drugs; and antilipemic drugs will be permitted during the study. It is preferable that these medications should not be changed from Visit 2 until the end of the study; however, if this is deemed clinically necessary, this is permitted and the subject does not need to be withdrawn from the study.

Oral, injected, or implanted contraceptives and hormone-replacement therapy are permitted during the study.

Use of all concomitant medications will be recorded on the subject's CRF. This will include all prescription drugs, herbal preparations, over-the-counter medications, vitamins, and minerals. Any changes in medications during the study will also be recorded on the CRF. Subjects will be asked to telephone the site at any time to speak to a member of the medical staff should they require concomitant medication. The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

Diet remedies and exercise regimes should not begin or stop from Visit 2 until the end of the study.

7.4.6.2 Caution

It is possible that the exposure of metformin may increase when administered in combination with TMX-049. [redacted]

[redacted]

[redacted]

- [redacted]
- [redacted]

7.4.6.3 Prohibited

The following treatments are prohibited during the study and in the timeframe preceding Screening and first dosing occasion as specified in the exclusion criteria (see Section 7.3.2):

- Treatment with any uric acid-lowering therapy (eg XO inhibitors and uricosuric agents) within 2 weeks of Visit 1 and for the duration of the study
- Immunosuppressant treatment for any known or suspected renal disorder at any time prior to Visit 1 and for the duration of the study
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- Other investigational drugs within the previous 30 days prior to Visit 1 and for the duration of the

study.

7.4.7 Contraception

Female subjects participating in the study who are of non-childbearing potential will not be required to use contraception. Women of non-childbearing potential are defined as permanently sterile (ie due to hysterectomy, bilateral salpingectomy, bilateral oophorectomy, or confirmed tubal occlusion) or postmenopausal (defined as at least 12 months postcessation of menses without an alternative medical cause). Postmenopausal status will be confirmed with a screening serum follicle-stimulating hormone (FSH) test.

Female subjects of childbearing potential will be required to follow contraception requirements from the time of signing the ICF until 3 months after the last dose of TMX-049 or placebo. Male subjects and their partners of childbearing potential will be required to follow contraception requirements from Visit 2 until 3 months after the last dose of TMX-049 or placebo.

Female subjects of childbearing potential must be willing to use a highly effective method of birth control (ie contraceptive measure with a failure rate of <1% per year) in conjunction with male contraception (ie male condom with spermicide). Highly effective methods of contraception include:

- intrauterine device (IUD; eg Mirena Coil). Steel or copper IUDs are not acceptable.
- established use of oral, injected, or implanted hormonal method of contraception associated with inhibition of ovulation.
- male sterilization, with verbal confirmation of surgical success (for female subjects on the study, the vasectomized male subjects should be the sole partner for that subject).
- bilateral tubal ligation.

Male subjects with partners of childbearing potential must use a barrier method of contraception (ie male condom with spermicide) in addition to a second method of acceptable contraception used by their female partners. In addition to the list of effective contraception methods above, other acceptable methods of contraception include:

- established use of progesterone only oral contraception, where inhibition of ovulation is not the primary mode of action.
- diaphragm, cap, or sponge in conjunction with spermicide.

Subjects who practice true abstinence, which must be due to the subject's lifestyle choice; ie the subjects should not become abstinent just for the purpose of study participation, are exempt from contraceptive requirements. Periodic abstinence (eg calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

For male subjects, sexual intercourse with female partners who are pregnant or breastfeeding should be avoided unless condoms are used from the time of the first dose of TMX-049 or placebo until 3 months after the last dose. Male subjects are required to refrain from donation of sperm from Visit 2 until 3 months after the last dose of study drug.

For subjects who are exclusively in same-sex relationships and do not have heterosexual intercourse, contraceptive requirements do not apply. However, subjects must not be intending to become pregnant during the study.

7.4.8 Treatment Compliance

Study medication compliance will be assessed following a 2-week placebo run-in phase and only subjects with ≥80% study medication compliance will be randomized to receive study treatment in the double-blind treatment phase.

The subject must return the empty packaging as well as the packaging containing unused medication to the study site for a compliance check at the visits specified in Table 2. Each site will reconcile the medication dispensed and returned by their subjects.

7.5 Study Procedures

7.5.1 Schedule of Study Procedures

Study procedures and their timing are summarized in Table 2. The order of the procedures in the sections below does not reflect the order in which they will be conducted.

Table 2: Schedule of Study Procedures

	Screening		Single-Blind, Placebo, Run-in Phase		Double-Blind Treatment Phase				Follow-up
	Visit 1	Visit 2		Visit 3	Start of study drug	Visit 4	Visit 5	Visit 6/ET	Visit 7
Study days and visit window guidelines	**Day -42 to Day -15**	**Day -14 ± 4 days**	**Day -14 ± 4 days to Day 0**	**Day 0**	**Day 1**	**Day 14 ± 4 days**	**Day 42 ± 7 days**	**Day 84 ± 7 days**	**Visit 6/ET+28 ± 7 days**
Administrative Procedures									
Informed consent	X								
Assignment of Screening number	X								
Contact IXRS	X	X		X		X	X	X	X
Check of eligibility based on inclusion/ exclusion criteria	X	X		X					
Assignment of randomization number				X					
Pre-visit telephone reminder for urine and PK [1]		X		X		X	X	X	X
Trial Compliance									
Prior/concomitant medication review	X	X		X		X	X	X	X
Dispense urine collection supplies	X	X		X		X	X	X	
Investigational Product									
Dispense study drug (placebo) for single-blind run-in		X							
Administration of placebo			qd dosing for 2 weeks						
Assess single-blind compliance				X					
Dispense double-blind study drug (placebo or TMX-049)				X		X	X		
Administration of TMX-049 or placebo					qd dosing for 12 weeks				
Assess double-blind compliance						X	X	X	
Clinical Procedures/Assessments						X	X	X	
Demographics and medical history	X								
Height	X								
Body weight	X			X			X	X	X
Vital signs (blood pressure[2], pulse rate, and body temperature)	X	X		X		X	X	X	X
Physical examination		X						X	

	Screening		**Single-Blind, Placebo, Run-in Phase**		**Double-Blind Treatment Phase**				**Follow-up**
	Visit 1	**Visit 2**		**Visit 3**	**Start of study drug**	**Visit 4**	**Visit 5**	**Visit 6/ET**	**Visit 7**
Study days and visit window guidelines	**Day -42 to Day -15**	**Day -14 ± 4 days**	**Day -14 ± 4 days to Day 0**	**Day 0**	**Day 1**	**Day 14 ± 4 days**	**Day 42 ± 7 days**	**Day 84 ± 7 days**	**Visit 6/ET+28 ± 7 days**
12-lead ECG		X						X	
AE monitoring	X	X	X	X					
TEAE monitoring					X	X	X	X	X
Laboratory Assessment									
UACR[3]	X								
First morning void UACR		X[4]		X[4,5]		X[4,5]	X[4,5]	X[4,5]	X[4,5]
Complete blood count (CBC)	X			X		X	X	X	X
Serum chemistry profile (including sUA and serum creatinine to calculate eGFR)	X	X		X[5]		X[5]	X[5]	X[5]	X[5]
Serology: HIV, hepatitis B, and hepatitis C		X							
Thyroid hormones		X		X		X	X	X	X
Lipid panel		X		X		X	X	X	X
HbA1c	X			X				X	
Urine pregnancy (females of childbearing potential)	X			X				X[6]	X
FSH (females of non-childbearing potential)	X								
Urinalysis	X			X		X	X	X	X
Blood and urine samples for biomarkers[7]				X		X	X	X	X
Pharmacokinetic sampling						X[8]	X[9]	X[10]	
Pharmacogenomics sampling				X[11]					

AE = adverse event; CRF = Case Report Form; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; ET = early termination; FSH = follicle-stimulating hormone; HbA1c = glycosylated hemoglobin; HIV = human immunodeficiency virus; IXRS = interactive voice/web response system; KIM-1 = kidney injury molecule-1; L-FABP = liver fatty acid-binding protein; NAG = N-acetyl-β-D-glucosaminidase; PK = pharmacokinetic; 8-OHdG = 8-hydroxy-2'-deoxyguanosine; qd = once-daily; sUA = serum uric acid; TEAE = treatment-emergent adverse event; t_{max} = time of maximum observed plasma concentration; UACR = urinary albumin-to-creatinine ratio.

[1]Telephone contact around 3 days prior to scheduled visits.
[2]Average of triplicate measurements.
[3]Urine sample for assessment of UACR to be collected at the study site once subjects have signed the informed consent form.

[4]The average of the 2 consecutive day mid-stream, first-morning void UACR results will be used. The 2 consecutive day first-morning void urine samples will be collected at the subject's home the morning before and the morning of each visit.

[5]Results of sUA and UACR will not be reported to Investigators, subjects, and the Sponsor staff.
[6]Only Early Termination Visit.
[7]Urine sample for the analysis of KIM-1, L-FABP, 8-OHdG, and NAG; the mid-stream, first-morning void urine samples collected by the subjects at home will be used for the analysis of exploratory biomarkers. Aliquots of serum, plasma, and urine will be stored for potential use in other biomarker assays.
[8]At Visit 4, a sample will be obtained prior to TMX-049 dosing (trough sample). The time of PK sample acquisition, the time of dosing prior to the PK sample acquisition, and whether the subject took study medication with or without food should be recorded in the CRF.
[9]At Visit 5, a sample will be obtained 3 ± 1 hours after study medication dosing (t_{max} sample). The timing of dosing can be adjusted to the time of visiting. The time of PK sample acquisition, the time of dosing prior to the PK sample acquisition, and whether the subject took study medication with or without food should be recorded in the CRF.
[10]At Visit 6, a sample will be obtained ≥6 hours (the ideal target is ≥8 hours) after study medication dosing (elimination phase sample). If a subject cannot visit within the time window, a sample will be obtained when the subject visits, even out of the time window. If the trough sample is not obtained at Visit 4, the trough sample should be obtained at Visit 6, instead of the elimination phase sample. If the trough sample is obtained at Visit 4 and t_{max} sample is not obtained at Visit 5, the t_{max} sample should be obtained at Visit 6, instead of the elimination phase sample. The time of PK sample acquisition, the time of dosing prior to the PK sample acquisition, and whether the subject took study medication with or without food should be recorded in the CRF.
Sites have the option to have a study participant return to the site on a separate day to obtain a properly-timed Visit 4, 5, or 6 sample for PK analysis.
[11]Sample will be obtained only from subjects that consent to pharmacogenomics sampling.
See full set of evaluations in Appendix A.

7.5.2 Screening Procedures

Refer to Table 2 for the timing and frequency of all assessments. The order of the procedures in the sections below does not reflect the order in which they will be conducted.

7.5.2.1 Screening Visit (Visit 1) Day -42 to Day -15

The information recorded for all subjects, regardless of their suitability for the study, will be retained and archived. The following information and procedures will be recorded and performed for all potential subjects as part of the screening assessments:

- informed consent (signed prior to any screening procedures being performed)
- assignment of screening number
- contact IXRS
- confirmation of subject eligibility based on inclusion/exclusion criteria
- complete blood count
- FSH (females of non-childbearing potential)
- demography including sex, race/ethnic origin, age, body mass index, smoking status, and alcohol consumption
- medical history (including information obtained from the subject's general practitioner)
- height, body weight
- urine pregnancy test for female subjects of childbearing potential
- urinalysis and urine sample for UACR (to be obtained at the study site)
- serum chemistry profile (including sUA and serum creatinine to calculate eGFR); see Appendix A for the evaluations to be performed
- HbA1c
- adverse event recording
- prior medication review
- vital signs, consisting of supine blood pressure, supine pulse rate, and oral body temperature
- dispense urine collection supplies (for collection of 2 consecutive day mid-stream, first-morning void urine samples on the morning before and the morning of Visit 2)

Single re-testing of laboratory parameters or other assessments may be performed at the Investigator's discretion.

7.5.3 Single-Blind, Placebo Run-in Phase (Visit 2): Day -14 ± 4 Days

The following information and procedures will be recorded and performed for all eligible subjects at

Visit 2:

- pre-Visit 2 call for reminder of urine collection
- confirmation of subject eligibility based on inclusion/exclusion criteria
- contact IXRS
- urine sample for UACR (2 consecutive day mid-stream, first-morning void urine samples to be collected at the subject's home on the morning before and the morning of Visit 2)
- serum chemistry profile (including sUA and serum creatinine to calculate eGFR); see Appendix A for the evaluations to be performed
- viral serologies
- thyroid hormones
- lipid panel
- adverse event recording
- prior/concomitant medication review
- vital signs, consisting of supine blood pressure, supine pulse rate, and oral body temperature
- resting 12-lead ECG
- physical examination
- dispense treatment kit for 2-week placebo run-in
- dispense urine collection supplies (for collection of 2 consecutive day first-morning void urine samples on the morning before and the morning of Visit 3)
- before leaving the site, each subject will be given a card to carry at all times in case of an emergency outside the site. The card gives details of the study number, start and end date of the subject's involvement in the study, subject details, name of the relevant study physician, and the address and telephone number of the site. Subjects may destroy this card 4 weeks after they have completed the study

Single re-testing of laboratory parameters or other assessments may be performed at the Investigator's discretion.

7.5.4 Treatment Phase Procedures

7.5.4.1 Pre- Visit Telephone Call

Subjects will receive a telephone call around 3 days prior to their scheduled visits to remind the subject to collect 2 consecutive mid-stream, first-morning urine samples at home, prior to the day and on the morning of the scheduled visits and bring these to the site. Subjects will also be reminded to return their treatment kits for a compliance check. During the call, the subject must ONLY be reminded about at-home urine collection, returning their treatment kits and dosing before visit. No other questions should be asked and no additional conversation should take place.

7.5.4.2 Randomization Visit (Visit 3): Study Day 0

Subjects who meet all eligibility criteria and who also have ≥80% study medication compliance during the 2-week placebo run-in phase will be randomized to study treatment at Visit 3. The following information and procedures will be recorded and performed at Visit 3 as part of the Baseline assessments:

- pre-Visit 3 call for reminder of urine collection
- subjects who don't meet eligibility criteria or the criteria of study medication compliance during the 2-week placebo run-in phase will be withdrawn from the study
- confirmation of subject eligibility based on inclusion/exclusion criteria
- contact IXRS
- assignment of randomization number
- assessment of treatment compliance during the 2-week run-in period
- urine pregnancy test for female subjects of childbearing potential
- urine sample for UACR (2 consecutive day mid-stream, first-morning void urine samples to be collected at the subject's home on the morning before and the morning of Visit 3)
- complete blood count
- serum chemistry profile (including sUA and serum creatinine to calculate eGFR); see Appendix A for the evaluations to be performed
- thyroid hormones
- lipid panel
- HbA1c
- urinalysis
- blood (plasma and serum) and urine sample for biomarkers (the mid-stream, first-morning void urine samples collected by the subjects at home will be used for the analysis of biomarkers)
- blood sample for pharmacogenomics (only from subjects that consent to pharmacogenomics sampling)
- adverse event recording
- concomitant medication review
- vital signs, consisting of supine blood pressure, supine pulse rate, and oral body temperature
- body weight
- 1 study drug treatment kit will be dispensed to the subject

- dispense urine collection supplies (for collection of 2 consecutive day mid-stream, first-morning void urine samples on the morning before and the morning of Visit 4)

7.5.4.3 Visit 4: Study Day 14 ± 4 Days

The following information and procedures will be recorded and performed at Visit 4:

- contact IXRS
- pre-Visit 4 call for reminder of urine collection and not dosing in the morning before the visit
- study drug administration; see Section 7.4.1
- urine sample for UACR (2 consecutive day mid-stream, first-morning void urine samples to be collected at the subject's home on the morning before and the morning of Visit 4)
- complete blood count
- serum chemistry profile (including sUA and serum creatinine to calculate eGFR eGFR); see Appendix A for the evaluations to be performed
- thyroid hormones
- lipid panel
- urinalysis
- blood (plasma and serum) and urine sample for biomarkers (the mid-stream, first-morning void urine samples collected by the subjects at home will be used for the analysis of biomarkers)
- treatment-emergent adverse event recording
- concomitant medication review
- vital signs, consisting of supine blood pressure, supine pulse rate, and oral body temperature
- PK sampling; see Section 7.7.1
- 2 study drug treatment kits will be dispensed to the subject
- dispense urine collection supplies (for collection of 2 consecutive day first-morning void urine samples on the morning before and the morning of the subsequent visit)
- assess double-blind compliance

7.5.4.4 Visit 5: Study Day 42 ± 7 Days

The following information and procedures will be recorded and performed at Visit 5:

- pre-Visit 5 call for reminder of urine collection and dosing approximately 3 hours before the visit before visit
- contact IXRS

- study drug administration; see Section 7.4.1
- urine sample for UACR (2 consecutive day mid-stream, first-morning void urine samples to be collected at the subject's home on the morning before and the morning of Visit 5)
- complete blood count
- serum chemistry profile (including sUA and serum creatinine to calculate eGFR); see Appendix A for the evaluations to be performed
- thyroid hormones
- lipid panel
- urinalysis
- blood (plasma and serum) and urine sample for biomarkers (the mid-stream, first-morning void urine samples collected by the subjects at home will be used for the analysis of biomarkers)
- treatment-emergent adverse event recording
- concomitant medication review
- vital signs, consisting of supine blood pressure, supine pulse rate, and oral body temperature
- body weight
- PK sampling, see Section 7.7.1
- 3 study drug treatment kits will be dispensed to the subject
- dispense urine collection supplies (for collection of 2 consecutive day first-morning void urine samples on the morning before and the morning of the subsequent visit)
- assess double-blind compliance

7.5.4.5 End of Treatment Visit 6: Study Day 84 ± 7 Days or Early Termination Visit

The following information and procedures will be recorded and performed at Visit 6:

- contact IXRS
- pre-Visit 6 call for reminder of urine collection, dosing in the morning before the visit
- dispense urine collection supplies (for collection of 2 consecutive day first morning void urine samples on the morning before and the morning of the subsequent visit)
- urine sample for UACR (2 consecutive day mid-stream, first-morning void urine samples to be collected at the subject's home on the morning before and the morning of Visit 6)
- complete blood count
- serum chemistry profile (including sUA and serum creatinine to calculate eGFR); see Appendix A

for the evaluations to be performed

- thyroid hormones
- lipid panel
- HbA1c
- urinalysis
- urine pregnancy test for female subjects of childbearing potential (only Early Termination Visit)
- blood (plasma and serum) and urine sample for biomarkers (the mid-stream, first-morning void urine samples collected by the subjects at home will be used for the analysis of biomarkers)
- treatment-emergent adverse event recording
- concomitant medication review
- vital signs, consisting of supine blood pressure, supine pulse rate, and oral body temperature
- body weight
- resting 12-lead ECG
- physical examination
- PK sampling; see Section 7.7.1
- assess double-blind compliance

7.5.4.6 End of Study Follow-up (Visit 7): Visit 6/ET+28 ± 7 days

The following information and procedures will be recorded and performed for all subjects as part of the follow-up assessments:

- contact IXRS
- pre-Visit 7 call for reminder of urine collection
- urine pregnancy test for female subjects of childbearing potential
- urine sample for UACR (2 consecutive day mid-stream, first-morning void urine samples to be collected at the subject's home on the morning before and the morning of Visit 7)
- complete blood count
- serum chemistry profile (including sUA and serum creatinine to calculate eGFR); see Appendix A for the evaluations to be performed
- thyroid hormones
- lipid panel

- urinalysis
- blood (plasma and serum) and urine sample for biomarkers (the mid-stream, first-morning void urine samples collected by the subjects at home will be used for the analysis of biomarkers)
- treatment-emergent adverse event recording
- concomitant medication review
- vital signs, consisting of supine blood pressure, supine pulse rate, and oral body temperature
- body weight

7.5.5 Procedures for Premature Discontinuation from the Study Treatment Regimen

At any time, subjects are free to discontinue the IMP without prejudice to further treatment. A subject who decides to discontinue the IMP will always be asked about the reason(s) for withdrawal and the presence of any AEs. Any such AEs will be followed up and the Medical Monitor should be notified of any ongoing AE that may delay treatment or necessitate permanent discontinuation of treatment. Subjects who are permanently discontinued from further receipt of IMP, regardless of the reason, will be identified as having permanently discontinued treatment. Subjects who are permanently discontinued will be asked to attend an early termination visit and an end of study visit for follow-up evaluations (see Table 2). Subjects who decline to return to the site for those visits should be contacted by telephone as an alternative.

7.5.6 Temporary Discontinuation

If a subject does not take a dose of study drug within +12 hours of their regular dosing time, then the dose of study drug should be skipped and the subject should be instructed to take the study drug at the next regularly scheduled time.

7.5.7 Lost to Follow-up

A subject will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. The following actions must be taken in relation to a subject who fails to attend the site for a required study visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible.
- The site must counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study.
- In cases in which the subject is deemed lost to follow-up, the Investigator must make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.

Should the subject continue to be unreachable, only then will he/she be considered to have withdrawn from the study with a primary reason of lost to follow-up.

7.6 Efficacy and Safety Variables

7.6.1 Efficacy Assessments

7.6.1.1 Urine Samples for the Calculation of Urinary Albumin-to-Creatinine Ratio

Two consecutive day mid-stream, first-morning void urine samples will be collected by the subjects at home using the urine collection vessels supplied by the study site at the times indicated in the Schedule of Assessments (Table 2). Subjects will be instructed to return the samples to the study site at their scheduled visit.

The determination of UACR will be performed by [redacted].

The results of UACR at Visits 3, 4, 5, 6, and 7 will not be reported to Investigators, subjects, and the Sponsor staff. The Investigators must not measure UACR at local sites.

7.6.1.2 Blood Samples for the Calculation of Estimated Glomerular Filtration Rate

Blood samples for the calculation of eGFR will be taken at the times indicated in the Schedule of Assessments (Table 2).

The determination of eGFR will be performed by [redacted] using the CKD-EPI formula. The calculation will be based on the serum creatinine measurement in the serum chemistry profile.

7.6.1.3 Urine Samples for the Analysis of Exploratory Biomarkers

The mid-stream, first-morning void urine samples collected by the subjects at home using the urine collection vessels supplied by the study site will be used for the analysis of exploratory biomarkers (kidney injury molecule-1 [KIM-1], liver fatty acid-binding protein [L-FABP], 8 hydroxy-2'-deoxyguanosine [8-OHdG]), and N-acetyl-β-D-glucosaminidase (NAG) at the times indicated in the Schedule of Assessments (Table 2). Aliquots of urine will be stored for potential use in other biomarker assays related to the mechanism of action, PK, safety, or renal effects of TMX-049.

The analysis of biomarkers will be performed by [redacted]

7.6.1.4 Blood Samples for the Analysis of Serum Uric Acid

Blood samples for the analysis of sUA will be taken at the times indicated in the Schedule of Assessments (Table 2).

Serum uric acid will be analyzed as part of the serum chemistry profile performed by [redacted] (see Appendix A).

7.6.1.5 Blood Samples for the Analysis of Exploratory Biomarkers

Blood samples (serum and plasma) for the analysis of exploratory biomarkers (soluble tumor necrosis factor receptor 1 [sTNFR1] and high-sensitivity C-reactive protein [hs-CRP]) will be taken at the times indicated in the Schedule of Assessments (Table 2). Aliquots of serum and plasma will be stored for potential use in other biomarker assays related to the mechanism of action, PK, safety, or renal effects of TMX-049.

The analysis of biomarkers will be performed by [redacted].

7.6.2 Safety Assessments

Safety will be monitored throughout the study for all subjects. The analysis of the safety data will be performed using the Safety Population. The timings of all measurements to be performed during the study may be subject to change based on the ongoing review of the safety, tolerability, efficacy, and PK results. All changes will be agreed with the Sponsor and documented in the TMF. The IRB will be notified of the changes, if appropriate.

7.6.2.1 Adverse Events

7.6.2.1.1 Definitions

The term "adverse event," as used by the Sponsor, is synonymous with the term "adverse experience," which is used by the Food and Drug Administration.

An AE is any untoward, undesired, unplanned clinical event in the form of signs, symptoms, disease, or laboratory or physiological observations occurring in a human being participating in a clinical study with a Sponsor test article, regardless of causal relationship. This includes the following:

- Any clinically significant worsening of a pre-existing condition.

Note: Emergence of a new pathogen associated with a clinical event during therapy at a site other than the initial site of infection will be considered to be an AE.

- Any recurrence of a historical condition.
- An AE occurring from overdose of a Sponsor study drug whether accidental or intentional (ie a dose higher than that prescribed by a health care professional for clinical reasons).
- An AE occurring from abuse of a Sponsor study drug (ie use for non-clinical reasons).
- An AE that has been associated with the discontinuation of the use of a Sponsor study drug.

Note: A procedure is not an AE, but the underlying cause/reason for a procedure may be an AE.

A ***pre-existing condition*** is a clinical condition (including a condition being treated) that is diagnosed before the subject signs the ICF and that is documented as part of the subject's medical history.

The questions concerning whether the condition existed before the start of the active phase of the study and whether it has increased in severity and/or frequency will be used to determine whether an event is a TEAE. An AE is considered to be treatment-emergent if (1) it is not present when the active phase of the study begins and is not a chronic condition that is part of the subject's medical history, or (2) it is present at the start of the active phase of the study or as part of the subject's medical history, but the severity or frequency increases during the active phase. The active phase of the study begins at the time of the first dose of the study drug. The active phase of the study ends at the follow-up visit.

7.6.2.1.2 Reporting of Adverse Events

At each visit the Investigator, or delegate, will determine whether or not any AEs have occurred. The subject will be questioned in a general way and no specific symptoms will be suggested. If any AEs have occurred, they will be recorded in the AE section of the CRF and in the subject's medical records. If known, the diagnosis should be recorded, in preference to listing the individual signs and symptoms.

Adverse event reporting begins from the time of informed consent and ends at the Follow-up Visit (Visit 7). For subjects without the Follow-up Visit, the reporting ends 28 days after the last dose of IMP.

7.6.2.1.3 Assessment of Severity

The Investigator will be asked to provide an assessment of the severity of the AE using the following categories: mild, moderate, and severe:

- **Mild**: Easily tolerated by the subject, causes minimal discomfort, and does not interfere with everyday activities.
- **Moderate**: Sufficiently discomforting to interfere with normal everyday activities; intervention may be needed.
- **Severe**: Prevents normal everyday activities; treatment or other intervention usually needed.

7.6.2.1.4 Relationship to Study Treatment

The Investigator will make a determination of the relationship of the AE to the study drug using a 2-category system according to the following guidelines:

- Not related: There is not a reasonable possibility the adverse event is related to study drug
- Related: There is a reasonable possibility the adverse event is related to study drug

7.6.2.1.5 Follow-up of Adverse Events

Every reasonable effort will be made to follow-up subjects who have an AE at the follow-up visit, if possible, until resolution.

7.6.2.2 Serious Adverse Events

A ***serious adverse event*** (SAE) is any AE occurring at any dose that meets 1 or more of the following criteria:

- Results in death
- Is life threatening (see below)
- Requires inpatient hospitalization or prolongation of an existing hospitalization (see below)
- Results in a persistent or significant disability or incapacity (see below)
- Results in a congenital anomaly or birth defect
- Results in another important medical event (see below).

Additionally, important medical events that may not result in death, be life threatening, or require hospitalization may be considered SAEs when, based on appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias, or convulsions that do not require hospitalization, or development of drug dependency or drug abuse.

A ***life-threatening adverse event*** is any AE that places the subject at immediate risk of death from the event as it occurred. A life-threatening event does not include an event that might have caused death had it occurred in a more severe form but that did not create an immediate risk of death as it actually occurred. For example, drug-induced hepatitis that resolved without evidence of hepatic failure would not be considered life threatening, even though drug-induced hepatitis of a more severe nature can be fatal. Hospitalization is to be considered only as an overnight admission.

Hospitalization or prolongation of a hospitalization is a criterion for considering an AE to be serious. In the absence of an AE, the participating Investigator should not report hospitalization or prolongation of hospitalization. This is the case in the following situations:

- Hospitalization or prolongation of hospitalization is needed for a procedure required by the protocol. Day or night survey visits for biopsy or surgery required by the protocol are not considered serious.
- Hospitalization or prolongation of hospitalization is part of a routine procedure followed by the study center (eg stent removal after surgery). This should be recorded in the study file.
- Hospitalization for survey visits or annual physicals fall in the same category.
- Social hospitalization for purposes of respite care.

In addition, a hospitalization planned before the start of the study for a pre-existing condition that has not worsened does not constitute an SAE (eg elective hospitalization for a total knee replacement due to a pre-existing condition of osteoarthritis of the knee that has not worsened during the study).

Disability is defined as a substantial disruption in a person's ability to conduct normal life functions.

Medical and scientific judgment should be exercised in deciding whether a case is serious in those situations where important medical events may not be immediately life threatening or result in death, hospitalization, disability, or incapacity. These include events that may jeopardize the subject or may require medical intervention to prevent one or more outcomes listed in the definition of serious. Such events should usually be considered as serious.

7.6.2.2.1 Reporting Serious Adverse Events

Reporting of SAEs will be conducted in accordance with the appropriate regulatory guidelines. All SAEs that occur from the time of consent to the Follow-up Visit (Visit 7) must be reported in an expedited manner, whether or not the event is considered to be associated with the study drug.

Investigators will send the SAE report by fax or email to [redacted] immediately (within 24 hours) of becoming aware of an SAE. Covance PV&DSS will follow-up with the site in case of delayed SAE report.

[redacted]

The Investigator must also provide with urgent priority (upon receipt of a request) other relevant documentation (eg copies of diagnostic test results, hospital discharge summary, and/or autopsy report) and send this information by fax or email to [redacted].

All SAEs must be recorded in the subject's source documentation and documented in the CRF. Medications administered in association with an SAE must be documented in the CRF and in the subject's source documentation. The Investigator must also promptly notify the IRB of SAEs, including any follow-up information, in accordance with the local institutional policy and applicable regulatory requirements. Regulatory authorities will be notified of any AE associated with the use of the study drug that is both serious and unexpected, in accordance with the appropriate local regulatory guidelines. Notification of the event will be made by written, expedited safety report.

7.6.2.3 Pregnancy

A subject who becomes pregnant during the study will be instructed to stop all IMP administration. The Investigator, or designee, must report a pregnancy in a subject or the partner of a subject to the Sponsor

within 24 hours of being notified of the pregnancy. Details of the pregnancy will be reported on a pregnancy report form. The subject or partner of a subject shall receive any necessary counselling regarding the risks of continuing the pregnancy and the possible effects on the fetus. Monitoring of the subject or the partner of a subject will continue until the conclusion of the pregnancy, and the outcome of the pregnancy will be reported to the Sponsor.

7.6.2.4 Vital Signs

Supine blood pressure, supine pulse rate, and oral body temperature will be measured at the times indicated in the Schedule of Assessments (Table 2). Subjects must be supine for at least 5 minutes before blood pressure and pulse rate measurements.

Vital signs will also be performed at other times if judged to be clinically appropriate or if the ongoing review of the data suggests a more detailed assessment of vital signs is required.

Blood pressure measurements will be performed in triplicate at approximately 2-minute intervals. Pulse rate measurements will be performed singly and repeated once if outside the relevant clinical reference ranges. If repeated, the repeat value will be used in the data analysis. Site reference ranges will be applied to all vital sign determinations.

Oral body temperature will be measured singly using a digital thermometer.

7.6.2.5 12-Lead Electrocardiogram

A single 12-lead resting ECG with a 10-second rhythm strip will be recorded after the subject has been supine for at least 5 minutes at the times indicated in the Schedule of Assessments (Table 2). The 12-lead ECG will be repeated once if either of the following criteria apply:

- The QTcF is >500 msec
- The QTcF change from the Baseline is >60 msec.

If repeated, the repeat values will be used for data analysis.

Additional 12-lead ECGs will be performed at other times if judged to be clinically appropriate or if the ongoing review of the data suggests a more detailed assessment of ECGs is required.

An Investigator will perform a clinical assessment of each 12-lead ECG. Site reference ranges will be applied to all ECG parameters determined throughout the study.

The ECG machine will compute the PR and QT intervals, QTc, QRS duration, and heart rate. The QTcF will also be calculated.

7.6.2.6 Clinical Laboratory Evaluations

Blood and urine samples will be collected for clinical laboratory evaluations at the times indicated in the Schedule of Assessments (Table 2).

Additional clinical laboratory evaluations will be performed at other times if judged to be clinically appropriate or if the ongoing review of the data suggests a more detailed assessment of clinical laboratory safety evaluations is required.

An Investigator will perform a clinical assessment of all clinical laboratory data.

The evaluations to be performed are listed in Appendix A.

The results of UACR and sUA at Visits 3, 4, 5, 6, and 7 will not be reported Investigators, subjects, and the Sponsor staff. Investigators must not measure UACR or sUA at local sites.

7.6.2.7 Blood Sample for HbA1c

A blood sample will be collected for the measurement of HbA1c at the times indicated in the Schedule of Assessments (Table 2).

7.6.2.8 Physical Examinations

Full physical examinations will be performed at the times indicated in the Schedule of Assessments (Table 2).

7.6.2.9 Body Weight

Body weight (in underclothes) will be recorded at the times indicated in the Schedule of Assessments (Table 2). Body weight should be taken at the same time of day, and using the same equipment.

7.7 Pharmacokinetic Analysis

7.7.1 Blood Sampling for the Analysis of Plasma TMX-049

Blood samples (approximately 1 x 5 mL) will be taken by venipuncture or cannulation at the times indicated in the Schedule of Assessments (Table 2).

Samples taken from subjects in placebo group will not be analyzed.

At Visit 4, a sample will be obtained prior to TMX-049 dosing (trough sample).

At Visit 5, a sample will be obtained 3 ± 1 hours after study medication dosing (t_{max} sample). The timing of dosing can be adjusted to the time of visiting.

At Visit 6, a sample will be obtained ≥6 hours (the ideal target is ≥8 hours) after study medication dosing (elimination phase sample).

If a subject cannot visit within the time window, a sample will be obtained when the subject visits, even out of the time window. If the trough sample is not obtained at Visit 4, the trough sample should be obtained at Visit 6, instead of the elimination phase sample. If the trough sample is obtained at Visit 4 and t_{max} sample is not obtained at Visit 5, the t_{max} sample should be obtained at Visit 6, instead of the elimination phase sample. Sites have the option to have a study participant return to the site on a separate day to obtain a properly-timed Visit 4, 5, or 6 sample for PK analysis.

The time of PK sample acquisition, the time of dosing prior to the PK sample acquisition and whether the subject took study medication with or without food will be recorded in the appropriate sections of the CRF based on verbal communications with the subjects.

[redacted] will be responsible for the analysis of plasma TMX-049. Aliquots of plasma will be stored for potential use in possible future exploratory PK assays.

7.7.2 Population Pharmacokinetic Analysis

The sparse samples collected will be included into a population PK analysis.

7.8 Pharmacogenetic/Pharmacogenomics Testing

From subjects that consent to pharmacogenetic/pharmacogenomics sampling, a whole blood sample will be collected at Visit 3 and shipped to the Sponsor for possible future pharmacogenetic/pharmacogenomics testing. These samples may be used to explore the relationship between response to TMX-049 and pharmacogenomics differences. Pharmacogenetic testing will be limited to the genome biomarkers related to the response to TMX-049.

If the subject withdraws consent to long term storage and pharmacogenetic/pharmacogenomics testing, the Investigator will inform the Sponsor in writing and the Sponsor will destroy the sample. Samples will be de-identified by assigning a number other than the subject's study number.

The laboratory performing the testing will not be able to identify the study or the subject in any way. Samples will be stored for an indefinite period until the study drug is approved or drug development is ceased, whichever comes sooner. At this time, the Sponsor will be contacted and samples will be destroyed. The individual subject results of the analysis will not be reported to the subject, relatives, or attending physician and will not be included in the subject's medical record. There will be no follow-up contact with subjects regarding this data.

7.9 Data Quality Assurance

The Sponsor performs quality control and assurance checks on all clinical studies that it sponsors. Before enrolling any subjects in this study, the Sponsor or Sponsor's designee personnel and the Investigator will review the protocol, the brochure for clinical Investigators, the CRFs and instructions for their completion and return, the procedure for obtaining informed consent, and the procedure for reporting AEs and SAEs. A qualified representative of the Sponsor will monitor the conduct of the study, and CRFs will be verified against source documents. The Medical Monitor will review the data for safety information. Clinical data associates from the Sponsor's representative will review the data for completeness and logical consistency. Additionally, the clinical data associates will use automated validation programs to help identify missing data, selected protocol violations, out-of-range data, and other data inconsistencies. Requests for data clarification or correction will be electronically provided to the investigative site for resolution. Clinical data associates will assure that corrections have been applied properly.

7.10 Statistical Methods

The statistical analysis plan will be developed and finalized before database lock and will describe the selection of subjects to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. Below is a summary of planned statistical analyses of the outcome measures for this study.

7.10.1 Determination of Sample Size

Approximately 132 subjects will be randomized at a 1:1:1 ratio to each of the 3 treatment groups (40 mg TMX-049, 200 mg TMX-049, and placebo). Assuming that 10% of all randomized subjects will not be included in the primary endpoint analysis, this would result in approximately 40 subjects per treatment group for inclusion in the primary endpoint assessment.

A sample size of 40 per group will have more than 80% power on the primary endpoint assessment to detect a difference in means of 35% reduction (-0.431 for log-transformed value) of UACR assuming that the common standard deviation (SD) is 0.670 (log-scale) using a 2-group t-test with a 0.050 two-sided significance level.

7.10.2 Subject Populations Analyzed

The **All Subjects Population** will consist of any subjects who enrolled in the study (signed informed consent) and had study assessments recorded on the database as per the protocol.

The **Safety Population** will consist of all randomized subjects who received at least one study medication tablet or capsule.

The **Modified Intention-to-Treat (mITT) Population** will be used for the efficacy analysis and will consist of all subjects according to their randomization scheme regardless of whether they experienced protocol deviations. The last post randomization UACR will be carried forward (LOCF) for subjects who did not have a Week 12 UACR determination. Randomized subjects with no post randomization UACR will be excluded from the mITT analysis.

The **Per Protocol Population** will be used as a sensitivity analysis for the primary efficacy endpoint and will consist of all subjects according to their randomization scheme who experienced no major protocol deviations.

The **PK Population** will consist of all subjects who received at least one dose of TMX-049 and have evaluable PK data.

All protocol deviations that occur during the study will be considered prior to database lock for their severity/impact and will be taken into consideration when subjects are assigned to analysis populations. Details of subject assignment to the analysis populations will be listed.

Efficacy will be analyzed using the mITT Population (primary analysis) and the Per Protocol Population (supportive analysis), and safety will be analyzed using the Safety Population. Changes from Baseline will utilize values obtained at Visit 3 (the randomization visit) except for the change from baseline in UACR.

7.10.3 General Statistical Considerations

Data will be summarized using descriptive statistics and include mean, SD, median, minimum, maximum, and corresponding number of subjects (n). For log-transformed data, the geometric mean and geometric coefficient of variation will be provided. For categorical variables, the number and percent in each category will be presented. Tables will include the placebo group and each of the TMX-049 dose groups and a separate category that combines all TMX-049 dose groups.

7.10.4 Efficacy Analysis

7.10.4.1 Efficacy Endpoints

The primary efficacy endpoint for this study is:

- Change from Baseline to Week 12 in log-transformed UACR

The secondary efficacy endpoints for this study are:

- Proportion of subjects with >30% reduction from Baseline to Week 12 in UACR
- Change in eGFR (Baseline compared to each post-treatment assessment)
- Change in UACR (Baseline compared to each post-treatment assessment)
- Change in renal biomarkers (Baseline compared to each post-treatment assessment)
- Change in sUA (Baseline compared to each post-treatment assessment)

7.10.4.2 Statistical Analysis of Efficacy

The UACR values from the 2 consecutive day mid-stream, first morning void urine samples that are

submitted at Visits 2 to 7 will be based on the mean result of measurements in each of the paired samples. If only one sample is available, the results from that sample will be used.

The change from Baseline to Week 12 (or the LOCF) in log-transformed UACR will be analyzed in an analysis of covariance model with a fixed effect for treatment, baseline log-transformed UACR and baseline serum uric acid as covariates. The least squares mean, p-value, and the corresponding 95% CI for the treatment difference will be provided. The last post randomization UACR will be carried forward (LOCF) for subjects who did not have a Week 12 UACR determination.

To analyze the effect of LOCF on missing data, the above analysis will be repeated using a mixed model repeated measures approach and an observed case analysis. The statistical model will feature a repeated statement and include treatment, timepoint, and treatment-by-timepoint interaction as fixed effects, baseline as a covariate, and subject as a random effect.

The above analysis of covariance model and repeated measures models will also be used to analyze the secondary endpoints, change in eGFR, change in UACR, change in sUA, and change in renal biomarkers at each post-treatment assessment. The proportion of subjects with >30% reduction from Baseline to Week 12 in UACR will be analyzed using a Fisher's exact test and logistic regression.

7.10.4.3 Safety Endpoints

The safety endpoints for this study are:

- Proportion of subjects with reported AEs, discontinuation due to AEs or SAEs
- Proportion of subjects with AEs considered by the Investigator to be related to study medication
- Proportion of subjects with mild, moderate, or severe AEs as assessed by the Investigator
- Changes in vital signs, ECGs, and laboratory parameters

7.10.4.4 Statistical Analysis of Safety

Safety evaluation will include incidence of AEs (or TEAEs), laboratory test results, vital signs, ECG results, and physical examination findings. All summaries of safety data will be based on the Safety Population. No formal statistical analysis of the safety data will be performed. There will be safety summary tables produced and no modeling of data.

Summary tables will be provided for all AEs by treatment group. The incidence of AEs, AEs related to study medication, SAEs, and AEs leading to discontinuation of the study treatment will be presented by MedDRA (Medical Dictionary for Regulatory Activities) system organ class (SOC) and preferred term. In addition, the incidence of AEs by severity will be presented by SOC and preferred term.

The AE summary tables will include counts of subjects. Therefore, if a subject experiences more than 1 episode of a particular AE, the subject will be counted only once for that event. If a subject has more than 1 AE that is coded to the same preferred term, the subject will be counted only once for that preferred term. Similarly, if a subject has more than 1 AE within a SOC, the subject will be counted only once in that SOC.

Laboratory test variables will be summarized by treatment group and visit using descriptive statistics (number of subjects, mean, SD, minimum, median, maximum, as well as mean change from Baseline, and number and percent of subjects within specified categories). Shift tables (ie cross-tabulations of below the lower limit of the normal range, within the limits of the normal range and above the upper limit of the normal range at Baseline versus scheduled visits) will be presented by laboratory test. Laboratory tests with categorical results that cannot be analyzed by change from Baseline or shift table analysis will not be included in these summaries, but will be listed. Data obtained from laboratory tests not required by the

protocol will not be summarized, but will be listed.

Descriptive statistics of vital signs and ECG results at each visit will be presented by treatment group. Physical examination findings will be listed for each subject.

No inferential safety statistical analysis will be performed.

7.10.5 Pharmacokinetic Analysis

Pharmacokinetic samples that are obtained at Visits 4, 5, and 6 will be used to assess TMX-049 plasma concentrations and be used in a population PK analysis. Results will be summarized in each of the TMX-049 treatment groups.

TMX-049 plasma concentrations will be listed and summarized.

7.10.6 Interim Analysis

No formal interim analysis is planned for this study.

8. RISKS AND BENEFITS

TMX-049 is proposed for development as a therapeutic drug for the treatment of hyperuricemia associated with gout and DKD.

In non-clinical studies, TMX-049 was suggested to have more stable uric acid-lowering effect than existing drug, and TEI-R04969 showed a persistent XO inhibitory effect in blood vessels compared to existing drug, suggesting the possibility that TMX-049 can improve vascular endothelial function also in the clinical setting. Also, TMX-049 is considered to be a new drug candidate for the treatment of DKD.

Two important potential risks, gouty arthritis and interaction with azathioprine or mercaptopurine have been identified. No important identified risks have been identified. In this study, these important potential risks can be minimized by exclusion of gouty arthritis patients and prohibition of the concomitant use of the drug with azathioprine or mercaptopurine. There will be no restrictions on medication for gouty arthritis, so that the possible burden on subjects would not be beyond acceptable even in cases where gouty arthritis were observed.

There were 4 other safety concerns from non-clinical studies, calculi in the urinary organs, effects on the thyroid, increased ALT levels, [redacted] Since no related findings were noted in the clinical studies, these non-clinical toxicity findings (calculi in the urinary organs, effects on the thyroid, and increased ALT levels) are not identified as important risks. The interactions with transporter or metabolic enzyme-related drugs are not identified as important risks since there are no clinical data, and effects on drug exposure in humans are unknown. In this study, some of these transporter or metabolic enzyme-related drugs which possibly raise safety concerns will be prohibited.

Based on current knowledge, the benefit-risk balance of TMX-049 remains positive.

More detailed information about the known and expected benefits and risks and reasonably anticipated AEs of TMX-049 may be found in the IB.[11]

9. INVESTIGATOR'S REGULATORY OBLIGATIONS

9.1 Prestudy Documentation

This investigation will only be performed after the relevant regulatory authorities have issued a Clinical Trial Authorization (CTA) for this study. Regulatory authority approval will be sought in parallel with IRB approval.

The relevant regulatory authorities must give their written approval of any substantial amendments to the approved protocol or IMP dossier likely to affect the safety of the subjects or the conduct of the study (with the exception of emergency modifications required for subject safety).

The body responsible for making the CTA submission will maintain records of all correspondence with the relevant regulatory authorities.

9.2 Electronic Data Capture

An electronic data capture system will be used in this study. Data will be captured in source paper data documents (workbooks). At a minimum, dosing data will be entered into the electronic data capture system by staff at the clinical site when the dose is changed or missed. Following data entry, the CRF pages and the data entry will undergo quality control checks in accordance with [redacted] procedures. Any discrepancies will be resolved in the database.

Following all data validation steps, the Investigator or designee will electronically sign the completed electronic data prior to database lock.

9.3 Adverse Event Reporting

The Investigator agrees to report all AEs to the Sponsor as described in the Adverse Events section (Section 7.6.2.1). Furthermore, the Investigator is responsible for ensuring that any sub-investigator promptly brings AEs to the attention of the Investigator. If applicable, the Investigator also is responsible for informing the participating IRB of any SAEs.

9.4 Review of Source Records

The Investigator agrees that qualified representatives of the Sponsor and regulatory agencies will have the right, both during and after this study, to conduct inspections and to audit and review medical records pertinent to the clinical study as permitted by the regulations. Subjects will not be identified by name on any of the study documents or samples retained by the Sponsor for their analysis, and confidentiality of information in medical records will be preserved. Subjects will be assigned a unique identifier by the Sponsor and any participant records or datasets that are transferred to the Sponsor will contain the identifier only. The confidentiality of the subject will be maintained unless disclosure is required by regulations. Accordingly, the following statement (or similar statement) will be included in the informed consent document:

> "Representatives of regulatory agencies, IRB, the Sponsor, and your personal physician may review your medical records and all information related to this study as permitted by law."

9.5 Monitoring of the Study

A Study Monitor from [redacted] will be responsible for monitoring this clinical trial. The Study Monitor will monitor the study conduct, proper CRF completion, and source documentation completion and retention, and accurate study drug accountability. To this end, the Study Monitor will visit the study site at suitable intervals and be in frequent contact through verbal and written communication. It is essential that

the Study Monitor have access to all documents (related to the study and the individual participants) at any time these are requested. In turn, the Study Monitor will adhere to all requirements for subject confidentiality as outlined in the ICF. The Investigator and Investigator's staff will be expected to cooperate with the Study Monitor, to be available during a portion of the monitoring visit to answer questions, and to provide any missing information.

9.6 Protocol Amendments

There will be no alterations in the protocol without agreement between the Sponsor and the Investigator. There will be no alterations in the protocol affecting subject safety without the express written approval of the Sponsor, Investigator, and the IRB.

A protocol change intended to eliminate an apparent immediate hazard to subjects may be implemented immediately, but the change must then be documented in an amendment, reported to the IRB within 5 working days, and submitted to the appropriate regulatory agency in the required time frame.

9.7 Investigator Meeting

Prior to the start of the clinical study, the representative(s) of the Sponsor will meet with the Investigator(s) and appropriate clinical staff to familiarize the Investigator and clinical staff with the materials necessary for conducting the clinical study.

9.8 Change in Investigator

If any Investigator retires, relocates, or otherwise withdraws from conducting a study, the responsibility for maintaining records may be transferred to the Sponsor, IRB, or another Investigator. The Sponsor must be notified of and agree to the change. Regulatory agencies will be notified with the appropriate documentation. An updated Form FDA 1572 will be filed with the Sponsor for any changes in the study personnel reported in the current Form FDA 1572.

9.9 Termination of the Study

If, in the opinion of the Investigator, the clinical observations in the study suggest that it may be unwise to continue, the Investigator may terminate part of or the entire study after consultation with the Sponsor. In addition, the Sponsor may terminate part of or the entire study for any reason, including safety, ethical, compliance, administrative, or other reasons. A written statement fully documenting the reasons for study termination will be provided to the IRB and regulatory authorities.

9.10 Final Study Report

[redacted] will prepare an integrated clinical study report. Prior to issuing the final clinical study report, [redacted] will prepare a draft report for approval by the Sponsor. The report will be in accordance with the International Council for Harmonisation (ICH) Note for Guidance on Structure and Content of Clinical Study Reports.

The draft report may be submitted for quality assurance audit, the findings of which will be incorporated into the final version.

An electronic copy of the final report will be provided to the Sponsor. The study report will be provided in PDF format unless otherwise agreed by [redacted] [redacted] will accept no responsibility for subsequent operations carried out on this electronic information, or copies thereof, after delivery to the Sponsor. Reports requiring specialized Sponsor formats/alternative computer software packages may be possible on request from the Sponsor but may involve extra time and cost.

Delivery of a full hard copy of the final report may be possible on request from the Sponsor but may

involve extra time and cost.

9.11 Reports to the Ethics Committee and Regulatory Authorities

Upon completion of the study, the Investigator will provide the IRB with a summary of its outcome.

The relevant regulatory authorities will be provided with a Declaration of the End of a Clinical Trial form and safety report (or local equivalent) within 90 days of completion or within 15 days of a premature termination. These will also be provided to the IRB.

9.12 Confidentiality

All unpublished information that the Sponsor gives to the Investigator shall be kept confidential and shall not be published or disclosed to a third party without the prior written consent of the Sponsor.

When the Sponsor generates reports for presentations to regulatory agencies, one or more of the Investigators who has/have contributed significantly to the study will be asked to endorse the final report. The endorsement is required by some regulatory agencies.

The Investigator shall not make a patent application based on the results of this study and shall not assist any third party in making such an application without the written authorization of the Sponsor unless otherwise specified in the Clinical Study Agreement.

The subject must be informed that his/her personal study related data will be used by the Sponsor in accordance with the local data protection law. The level of disclosure must also be explained to the subject.

9.13 Records Retention

The Investigator must maintain all study documentation as confidential, and take measures to prevent accidental or premature destruction of these documents.

The Investigator must retain the study documents until at least 2 years after the last approval of a marketing application/new drug application for the indication investigated or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product (eg the Investigational New Drug application is withdrawn). These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the Sponsor.

The Investigator must notify the Sponsor prior to destroying any study essential documents.

If the Investigator can no longer ensure archiving, he/she shall inform the Sponsor. The relevant records shall be transferred to a mutually agreed upon designee.

9.14 Publications

The Sponsor holds all publication rights to the data obtained from this study. Before any data from this study are published on the initiative of the Investigator, the Investigator should obtain written approval from the Sponsor. A manuscript will be sent to the Sponsor for review and written approval at least 60 days prior to submission to the publisher, and according to any additional publication details in the Investigator Agreement.

9.15 Subject Injury

In general, if a subject is injured as a direct result of the study drug, the Sponsor will pay for reasonable and necessary medical treatment for the injury, to the extent the expenses are not covered by the subject's medical insurance, a government program, or other responsible third party. If laws or regulations of the

locality in which the trial is taking place require additional payment of expenses, the Sponsor shall comply with such law or regulation. Where applicable, the Sponsor has taken specific national insurance.

10. REFERENCES

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11. TMX-049 [Investigator's Brochure]. Teijin America, Inc. Version 4.0, 31 Oct 2017.

11. APPENDICES

Appendix A - Clinical Laboratory Evaluations

Serum Chemistry: Aspartate aminotransferase (AST) Alanine aminotransferase (ALT) Alkaline phosphatase Gamma glutamyl transferase (GGT) Lactate dehydrogenase (LDH) Sodium Potassium Chloride Calcium Bicarbonate Inorganic phosphate Glucose Urea Uric acid (sUA)[h] Total bilirubin Direct bilirubin Creatinine Blood urea nitrogen (BUN) Total protein Albumin Creatinine phosphokinase (CPK) Glycosylated hemoglobin (HbA1c)[a]	**Complete Blood Count[c]** White blood cell count (WBC) Red blood cell count (RBC) Hemoglobin Hematocrit (PCV) Mean cell volume (MCV) Mean cell hemoglobin (MCH) MCH concentration (MCHC) Platelet count Differential WBC
	Urinalysis[c]: Microscopic examination Specific gravity pH Protein Glucose Ketones Blood Urobilinogen
	For Females Only: Urine pregnancy test[d]
	For Postmenopausal Females Only: Follicle-stimulating hormone (FSH) [e]
Lipid Panel[b]: Total cholesterol High-density lipoprotein cholesterol (HDL-C) non-HDL-C	**Serology[f]:** Hepatitis B surface antigen (HBsAg) Hepatitis C antibody Human immunodeficiency virus (HIV)[g]
Thyroid Testing[b]: Triiodothyronine (T3) Thyroxine (T4) Free triiodothyronine (FT3) Free thyroxine (FT4) Thyrotropin/Thyroid stimulating hormone (TSH)	**Urinary Biomarkers:** Urinary albumin-to-creatinine ratio (UACR)[h] Kidney injury molecule 1 (KIM-1)[i] Liver fatty acid binding protein (L-FABP) [i] 8 hydroxy 2' deoxyguanosine (8-OHdG) [i] N-acetyl-β-D-glucosaminidase (NAG) [i]
	Blood Biomarkers: Soluble tumor necrosis factor receptor 1 (sTNFR1) [i] high sensitivity C reactive protein; (hs-CRP) [i] Estimated glomerular filtration rate (eGFR)

[a] At Visits 1, 3, and 6 only
[b] At Visits 2, 3, 4, 5, 6, and 7 only
[c] At Visits 1, 3, 4, 5, 6, and 7 only
[d] Females of childbearing potential only, at Visits 1, 3, 6 (Early Termination Visit only), and 7. Positive pregnancy result will result in hormone panel analyzed in serum
[e] Postmenopausal females at Visit 1 only
[f] Only analyzed at Visit 2
[g] HIV1/2 antibody test
[h] Results at Visits 3, 4, 5, 6, and 7 will not be reported to Investigators, subjects, and the Sponsor staff. Investigators must not measure UACR or sUA at local sites
[i] At Visits 3, 4, 5, 6, and 7 only. These values are corrected with urinary creatinine.

Appendix B – Permitted and Prohibited Concomitant Medication

Permitted Medications/Must be Used	Class of Compound	Study Timepoint
≥1 glucose-lowering medication	Glucose-lowering agent	At least 12 months prior to Visit 1. It is preferable that these medications should not be changed from Visit 2 until the end of the study, however, if this is deemed clinically necessary, this is permitted and the subject does not need to be withdrawn from the study.
ACEI or ARB (not both) at least the minimal recommended dose	Angiotensin II inhibitors	At least 3 months prior to Visit 1, without any adjustments to this therapy for at least 4 weeks prior to the Visit 1, and continue with this treatment for the duration of the study.
Permitted Medications/Can be Used	**Class of Compound**	**Study Timepoint**
oral, injected, or implanted contraceptives and hormone-replacement therapy are permitted during the study	Contraceptives	Any time during the study.
Antihypertensive, antilipemic, antituberculous (pyrazinamide and ethambutol), diuretics (non-thiazide diuretics, thiazide diuretics, and loop diuretics)	Antihypertensive, lipid altering, or anti-tuberculosis agents	It is preferable that these medications should not be changed from Visit 2 until the end of the study, however, if this is deemed clinically necessary, this is permitted and the subject does not need to be withdrawn from the study.
diet remedies and exercise regimes	NA	Should not begin or stop from Visit 2 until the end of the study.
Permitted but caution to be applied and avoid maximum doses, if possible, if these agents are used	**Class of Compound**	**Study Timepoint**
[redacted]	[redacted]	Any time during the study.
[redacted]	[redacted]	Any time during the study.
[redacted]	[redacted]	Any time during the study.

[redacted]		

Abbreviations: ACEI = angiotensin converting enzyme inhibitor; ARB = angiotensin II receptor blocker; BCRP = breast cancer resistance protein; CYP = cytochrome P450; NA = not applicable.

Prohibited Medications	Class of Compound	Study Timepoint
[redacted]		Any time after Visit 2 until the end of the study.
		At any time prior to Visit 1 and for the duration of the study.
		Any time after Visit 2 until the end of the study.

[redacted]		
uricosuric agents	Uric acid-lowering therapy	Within 2 weeks of Visit 1 and for duration of the study.
[redacted]	[redacted]	Any time after Visit 2 until the end of the study.
XO inhibitors	Uric acid-lowering therapy	Within 2 weeks of Visit 1 and for duration of the study.
Other investigational drugs within previous 30 days prior to Visit 1 and for the duration of the study.		

Abbreviations: [redacted]; NA = not applicable; [redacted]; XO = xanthine oxidase.