Cover page

Statistical Analysis Plan

Study ID: TMX-049DN-201
Study Title: 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
NCT No.: 03449199

Teijin America, Inc.

Statistical Analysis Plan

Teijin America, Inc.

TMX-049DN-201

[redacted]

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Approvals

[redacted]

[redacted]

Reviewers

The following reviews of the SAP were conducted:

Name and Title	Role	Version Last Reviewed	Company/ Organization
[redacted] **Statistical Fellow**	Peer Review Statistician	0.1	[redacted]
[redacted] **Statistical Programmer**	Lead Programmer	0.1	[redacted]

Version History

Version #	Description of Changes	Version Date
Final Version 1.0	Not applicable	May 21, 2018
Amendment 1 Final Version 1.0	1. **Section 7.6.3**: Added a sensitivity analysis for primary efficacy endpoint. 2. **Section 7.6.4**: Added a new section to include subgroup analyses for the primary efficacy endpoint. 3. **Section 7.6.5.1** Re-arranged and added scatter plots. 4. **Section 7.8:** **1)** Added reference for population pharmacokinetic analysis. **2)** Added analyses for pharmacokinetic plasma concentration of TMX-049. 5. Minor edits were made to other sections of the SAP, as needed, for consistency with the changes described above.	April 12, 2019

Glossary of Abbreviations

Abbreviation	Term
AE	adverse event
ANCOVA	analysis of covariance
ATC	Anatomical Therapeutic Chemical
BLQ	below the limit of quantification
BMI	body mass index
BP	blood pressure
CKD-EPI	chronic kidney disease epidemiology collaboration equation
CL	confidence limit
CRF	case report form
CV	coefficient of variation
DB	double-blind
DBL	database lock
ECG	electrocardiogram
ET	early termination
HR	heart rate
ITT	intention-to-treat
LOCF	last observation carried forward
LLOQ	lower limit of quantification
MAR	missing at random
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
MMRM	mixed-effects model for repeated measures
NC	not calculated
NR	no result
OC	observed cases
PK	pharmacokinetic
PP population	per-protocol population
PT	preferred term
QTcB	Bazett corrected QT interval
QTcF	Fridericia corrected QT interval
REML	restricted maximum likelihood
SAE	serious adverse event
SD	standard deviation
SOC	system organ class
sUA	serum uric acid
TFLs	tables, figures, and listings
UACR	urinary albumin-to-creatinine ratio
WHO	World Health Organization

1. Source Documents

The Statistical Analysis Plan (SAP) was written based on the following documentation:

Document	Date	Version
Protocol	07 FEB 2018	Final version 2.0
eCRF	20 MARCH 2018	Draft version 01.014

2. Protocol Details

2.1 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 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 followings:

- The effect of each dose of TMX-049 on eGFR during the 12-week period of treatment
- The percentage of subjects with >30% decrease in UACR with Placebo and each dose of TMX-049 after 12 weeks of treatment
- The effect of each dose of TMX-049 on exploratory renal biomarkers during the 12-week period of treatment
- The effect of each dose of TMX-049 on serum uric acid (sUA) during the 12-week period of treatment
- The pharmacokinetics (PK) of TMX-049 in subjects with Type 2 diabetes and albuminuria
- Safety and tolerability of TMX-049

2.2 Overall Study Design

This is 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] central laboratory.

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. 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 versus ≥6.0 mg/dL) and UACR (200 to <300 mg/g versus 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 subjects 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.

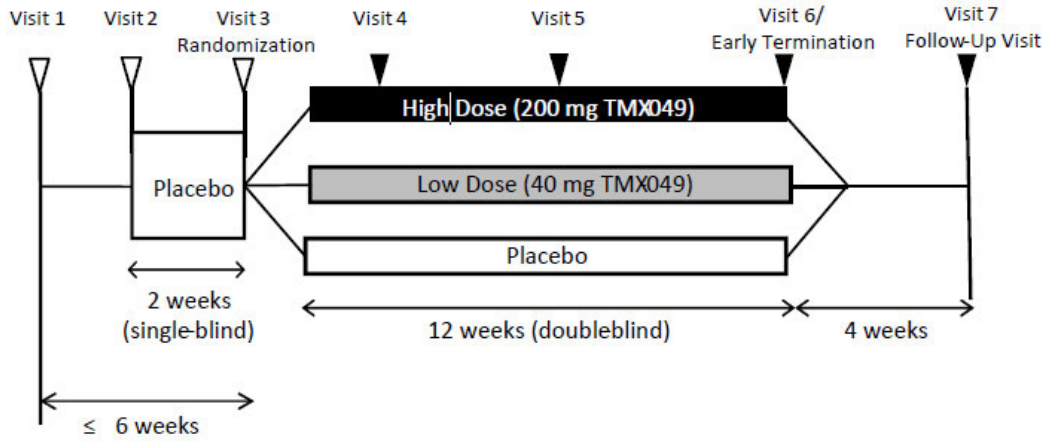
At Visit 4, a sample will be obtained prior to TMX-049 dosing (trough sample). At Visit 5, a sample will be obtained 3 ± 1 hours after study medication dosing (t_{max} sample). The timing of dosing can be adjusted to the time of visiting. At Visit 6, a sample will be obtained ≥6 hours (the ideal target is ≥8 hours) after study medication dosing (elimination phase sample). If 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.

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 subjects will attend an end of study 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 [ET] Visit).

The study schema is illustrated below:



2.3 Sample Size and Power

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.

3. Efficacy and Safety Variables

3.1 Primary Efficacy Endpoint(s)

The primary efficacy endpoint is the change from Baseline to Study Week 12 (Study Visit 6) in log-transformed UACR.

3.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints include:

- Proportion of subjects with >30% reduction from Baseline to Study Week 12 (Study Visit 6) in UACR
- Change in eGFR (Baseline compared to Study Weeks 2, 6, 12/ET, and Follow-up visit)
- Change in UACR (Baseline compared to Study Weeks 2, 6, 12/ET, and Follow-up visit)
- Change in renal biomarkers (Baseline compared to Study Weeks 2, 6, 12/ET, and Follow-up visit)
- Change in sUA (Baseline compared to Study Weeks 2, 6, 23/ET, and Follow-up visit)

3.3 Safety Variables

The safety endpoints include:

- Proportion of subjects with reported adverse events (AEs), discontinuation due to AEs and serious adverse events (SAEs)
- Proportion of subjects with AEs considered by the Investigator to be related to study drug
- Proportion of subjects with mild, moderate, or severe AEs as assessed by the Investigator
- Changes from Baseline in vital signs, ECGs, and laboratory parameters

4. Pharmacokinetic/Pharmacodynamic variables

The Pharmacokinetic endpoint is the plasma concentrations of TMX-049 at Study Weeks 2, 6, and 12/ET.

5. Analysis populations

Unless otherwise specified, all efficacy analyses will be performed using the modified Intention-to-Treat (mITT) population, all sensitivity analyses will be

performed using the Per Protocol (PP) population and safety analyses will use Safety population. Pharmacokinetic (PK) analyses will be performed using the PK population.

5.1 All Subjects Population

All subjects who enrolled in the study, ie, signed informed consent, and had study assessments recorded in the database per the protocol will be included in the All Subjects population.

5.2 Randomized Population

All randomly assigned subjects will be included in the Randomized population. Randomized subjects are analyzed according to their randomized treatment.

5.3 Safety Population

All randomized subjects who received at least 1 dose of study drug will be included in the Safety population. Safety subjects are analyzed according to their actual treatment received.

5.4 Modified Intent-to-treat Population

The mITT population will consist of all randomized subjects who have at least 1 post randomization UACR assessment. Subjects in the mITT population will be analyzed according to their randomized treatment.

5.5 Per-Protocol Population

The PP population will consist of all subjects in the mITT population who do not experience any important protocol deviations leading to exclusion from the PP population. Subjects in the PP population will be analyzed according to their randomized treatment.

Protocol deviations are defined as any change, divergence, or departure from the study design or procedures defined in the study protocol. Important protocol deviations are a subset of protocol deviations and may significantly impact the correctness, accuracy, and/or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being. **Section 5.5.1** details the deviations.

All protocol deviations that occur during the study will be considered prior to database lock (DBL) for their severity and impact.

5.5.1 Important Protocol Deviations Leading to Exclusion from the Per-Protocol Population

Type	Deviation	Method of Identification
Prohibited Medications	Subjects who have taken medications that are not permitted during the double-blind treatment period. A list of permitted and prohibited concomitant medication is provided in Appendix B in the protocol.	**Manual** review of blinded concomitant medications listing. [redacted] will provide the medical monitor with the list of concomitant medications taken by subjects. The medical monitor will review this list and note any prohibited medications. Subjects will be excluded if they were taking prohibited medications during the double-blind treatment period.
Noncompliance during 12-week double-blind treatment period	Subjects who had low study drug compliance (eg, repeated occurrence of compliance <80% during the double-blind treatment period)	**Programmatic** check based on the exposure and drug accountability data. **Manual** review will be performed for identifying subjects with low compliance rate during the double-blind treatment period.
Errors in Treatment Allocation	Subjects that received a wrong treatment at 1 or more study visits due to packaging or dispensing errors	**Programmatic** check based on unblinded IVRS database after the study is unblinded. The check will be done by comparing the bottle number that IVRS had assigned to the subject/visit against the bottle number actually used.
Clinical Trial Management System	[redacted] Clinical will provide the list of protocol deviations based on the clinical monitoring.	**Manual** review: The Sponsor will review this list and finalize any important protocol deviations which will then be included in the programming.

As defined in the table, the majority of the protocol deviations will be determined programmatically from the data. Those criteria which require clinical or medical monitoring interpretation will be reviewed prior to DBL, following discussion with the medical monitor and Teijin.

All the important protocol deviations leading to exclusion from the PP population occurring during the study will be reviewed and approved by Teijin prior to DBL and unblinding. Should other categories of important protocol deviations, not anticipated at the time of preparing this SAP, be identified during the study (and prior to unblinding), they will be documented in a separate document and included in all relevant protocol deviation reviews and approvals.

5.6 Pharmacokinetic Population

The PK population will consist of all subjects who received at least 1 dose of TMX-049 and had evaluable PK data. Subjects in the PK population will be analyzed according to their actual treatment received.

6. DATA Handling

6.1 Time points and Visit Windows

Day 0 is defined as the Baseline/Randomization visit (Study Visit 3). Day 1 is the first day of treatment. Relative days after Day 1 are calculated as (assessment date – Day 1 date) + 1. Relative days prior to Day 1 are calculated as (assessment date – Day 1 date).

The visit windows defined in the following table will be used for the by-visit analyses of the primary, the secondary and other endpoints. All other analyses will use the nominal study visit as defined in the study schedule and eCRF.

If there are multiple visits (scheduled or unscheduled) within a visit window, the measurement closest to the target day of the visit will be used in the analysis. If the measurements are equally distant to the target day, then the later one will be used in the analysis.

Time Point (Target Study Day)	**Study Day Range for UACR***	**Study Day Range for Serum Chemistry, Hematology, Lipid Panel, Urinalysis, Blood and Urine Samples for Biomarkers, Vital Signs**	**Study Day Range for ECG, Physical Examination**	**Study Day Range for HbA1C**
Baseline	≤ 1	≤ 1	< 1	≤ 1
Week 2 (Day 14)	2 – 21	2 - 21		
Week 6 (Day 42)	22 – 63	22 - 63		
Week 12/ET (Day 84)	64 – 104	64 – 104	≥ 1	> 1
Week 12/ET + 28 Days (Day 112)	≥ 105	≥ 105		

*: This is for the first morning void UACR sample collection.

6.2 Handling of Dropouts, Missing Data, and Outliers

Missing data will not be imputed for safety analyses. The safety evaluations will be performed on observed data only.

For AEs with partial or missing onset or stop dates:

AE stop date will be imputed first as:

- If stop date is complete missing, assume it is ongoing (no imputation);
- For a partial AE stop date (day is missing, or both day and month are missing): December 31st if both day and month are missing, or last day of the month if only day is missing.

Then AE onset date will be imputed as:

- If onset date is complete missing: the first dose date;
- For a partial AE onset date (day is missing, or both day and month are missing):
  - Partial date < the first dose date: December 31st, or last day of the month
  - Partial date = the first dose date: the first dose date
  - Partial date > the first dose date: January 1st if both day and month are missing, or first day of the month if only day is missing.

If the imputed AE onset date is after the AE stop date/imputed AE stop date, then the onset date will be set to the AE stop date/imputed AE stop date.

The imputed dates will not be listed. Study day relative to the first dose of double-blind study drug associated with missing or partial dates will not be displayed in AE listings.

In the event that a partial date (month/year or year) for concomitant medication is available, this information will be used as follows:

- When both month and year are available – first day of the month will be used for start date and the last day of the month will be used for the stop date.
- When only year is available – January 1st will be used for the start date and December 31th will be used for the stop date.

The imputed dates will only be used to determine whether a concomitant medication will be classified as prior medication or concomitant medication.

6.2.1 Observed Cases Datasets

Mixed-effects model for repeated measurements (MMRM) will be performed based on a missing at random (MAR) assumption using data actually observed - observed cases (OC) dataset. OC datasets will be used for analysis of the primary efficacy as well as all secondary efficacy endpoints. This dataset will not impute any values for missing observations.

7. Statistical Methods

7.1 General Principles

All data processing, summarization and analyses will be performed using the Hosted SAS (d-Wise) Environment / Version 9.4 (or later) of the SAS® (SAS Institute, Cary, NC) statistical software package.

Unless specified otherwise, data will be displayed using the following treatment group labels, in the order presented:

- Placebo
- TMX-049 40 mg QD
- TMX-049 200 mg QD
- TMX-049 Overall

All data collected will be presented in listings by treatment group, center, subject, and visit (where applicable), unless otherwise specified.

Data will be presented in summary tables by treatment group, assessment, and visit (where applicable).

The category "Missing" will be presented if the number missing is greater than zero for at least 1 treatment group.

Descriptive summary statistics for continuous variables will include the number of observations (N), mean, standard deviation (SD), median, minimum, and maximum. For UACR of original scale, the geometric mean, geometric coefficient of variation (CV), and CV will also be provided.

Descriptive summary statistics for categorical variables will include frequency counts and percentages [n (%)]. Unless stated otherwise in the table shells, the denominator for percentage calculations will be the number of subjects in the pertinent analysis population.

Dates will be displayed as DDMMMYYYY.

Analysis and summarization of treatment group comparisons for the primary and secondary efficacy endpoints will be reported in their original measurement units and converted values to accommodate regulatory review by FDA and external authorities, where appropriate.

All significance tests will be 2-sided and use a 0.05 α-level.

7.2 Subject Disposition and Data Sets Analyzed

Subject disposition will be listed and summarized by treatment group, and will include the number and percentage of subjects:

- Screened
- Entered single-blind Placebo run-in period
- Discontinued single-blind Placebo run-in period

• Randomized

• Treated

• Included in each study population (All subjects, Randomized, mITT, Safety, PP, and PK)

The number and percentage of subjects who complete the study and those who discontinue early (including a breakdown of the primary reasons for discontinuation), will be presented for the subjects randomized in each treatment group.

A summary of subject enrollment by site will be provided by treatment group and overall. A summary of subject randomized by randomization strata (sUA and UACR levels) will also be provided by treatment group.

7.3 Protocol Deviations

All the important protocol deviations leading to exclusion from the PP population will be listed and summarized by treatment group for the mITT population.

7.4 Demographics and Other Baseline Characteristics

Demographic and baseline characteristics will be listed and summarized by treatment group for the mITT, Safety, and PP population. Standard descriptive statistics will be presented for the continuous variables of:

- Age at study entry (years)
- Weight (kg)
- Height (cm)
- Body mass index (BMI) (kg/m^2)
- Supine systolic blood pressure (SBP) (mm Hg)
- Supine diastolic blood pressure (DBP) (mm Hg)
- Pulse rate (beats/min)
- Temperature (^oC)

The total counts and percentages of subjects will be presented for the categorical variables of:

- Age group (years) (<65;≥65)
- Sex (Male; Female)
- Race
- Ethnicity
- BMI categories (≤30 kg/m^2; >30 kg/m^2)
- Tobacco use (Yes, number of cigarettes/day; No)

- Alcohol Drinking (Yes, number of units/week; No)

Baseline laboratory characteristics for a select number of tests will also be summarized by treatment group for the mITT, Safety, and PP population. Standard descriptive statistics will be presented for the following laboratory tests:

- Urinary albumin-to-creatinine ratio (UACR) (mg/g)
- Log-transformed UACR (mg/g)
- HbA1C (%)
- eGFR (CKD-EPI) (ml/min/1.73m^2)
- Serum creatinine (mg/dL)
- Serum uric acid (mg/dL)
- Total cholesterol (mg/dL)
- High-density lipoprotein cholesterol (HDL-C) (mg/dL)
- Non-HDL-C (mg/dL)

A summary of physical examination data will be presented by treatment group for the mITT, Safety, and PP population.

No formal tests of statistical significance will be performed on the demographic and Baseline data.

7.4.1 Medical History

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 20.5 (or a later version if updated during the study). All medical history will be listed, and the number and percentage of subjects with any medical history will be summarized for the mITT population by system organ class (SOC) and preferred term (PT) for each treatment group.

7.4.2 Previous and Concomitant Medications

Medications received prior to or concomitantly with treatment will be coded by [redacted] using the World Health Organization (WHO) Drug Dictionary, Version September 2017 (or a later version if updated during the study), Anatomical Therapeutic Chemical (ATC) Classification codes.

Prior medications and concomitant medications are defined as follows:

- Prior medications are those taken prior to the first dose date of double-blind study drug.
- Concomitant medications are those with a start date on or after the first dose date of double-blind treatment, or those with a start date before the first dose date of double-blind treatment and a stop date on or after the first dose date of study drug.

If a medication cannot be classified as "prior" or "concomitant" after applying imputation rules for missing/incomplete dates, it will be classified as concomitant.

Prior medications, prohibited medications (See Protocol Appendix B for the full list of prohibited medications defined in this study) taken during the double-blind treatment period, and concomitant medications taken during the double-blind treatment Period will be listed and summarized separately for the mITT population.

The number and percentage of subjects using each medication will be displayed together with the number and percentage of subjects using at least one medication within each therapeutic class (Anatomical Therapeutic Chemical [ATC]-Level 2), chemical subgroup (ATC-Level 4), and generic term.

7.5 Treatment Compliance and Exposure

Duration of exposure to double-blind study drug is defined as:

Date of last dose – Date of first dose + 1

For each subject, percentage of compliance is calculated as: total number of days taken study drug / the total number of days exposed to study drug. The total number of days on study drug can be calculated as: total number of days exposed to study drug minus the total number of days missing doses.

The number and percentage of compliant subjects will be presented for the Safety population, where compliant is defined as percentage compliance between 80.0% and 120.0% inclusive. The following percentage compliance categories will also be presented:

- <80.0%
- 80.0% to 120.0%
- >120.0%

Treatment duration (days) and percentage compliance will be summarized descriptively by treatment group for the Safety population.

- <28 days
- ≥28 days and <56 days
- ≥56 days and <84 days
- ≥84 days

7.6 Efficacy

7.6.1 Primary Efficacy Analysis

The primary efficacy endpoint is the change from Baseline to Study Week 12 (Study Visit 6) in log-transformed UACR. The analysis will be based on the mITT population.

The UACR values from Study Visits 2 to 7 are calculated as the mean result from 2 consecutive day mid-stream, first morning void urine samples that are submitted on the morning before and on the day of study visits. If only 1 sample is available, the measurement from that sample is used.

Baseline UACR is defined as the mean of UACR from urine samples collected on Study Visit 3 (Randomization day).

For the primary analysis of the primary efficacy endpoint, the last-observation-carried-forward (LOCF) imputation algorithm will be used, where the last recorded post-baseline value for the same subject is carried forward to the missing Study Week 12 visit.

The change from Baseline to Study Week 12 in log-transformed UACR will be analyzed in an analysis of covariance (ANCOVA) model with randomized treatment, randomization strata of sUA (<6.0 vs ≥6.0 mg/dL) and UACR (200 to <300 mg/g vs 300 to ≤3000 mg/g) levels as independent variables. The least square mean (LS mean), p-value, and the corresponding 95% confidence limit (CL) for the change in log-transformed UACR in each treatment group, and the difference of change in log-transformed UACR between each TMX-049 treatment group versus Placebo group will be presented. The adjusted geometric mean of Week 12 to Baseline ratio in UACR with the corresponding 95% CLs for each treatment group, and the ratio of the adjusted geometric mean of Week 12 to Baseline ratio achieved within each treatment group relative to that achieved with Placebo group with 95% CLs will also be provided.

7.6.2 Secondary Efficacy Analysis

Secondary analysis of the primary efficacy endpoint will use mixed model repeated measures (MMRM) and all observed data. The model will include randomized treatment, randomization strata of sUA (<6.0 vs ≥6.0 mg/dL) and UACR (200 to <300 mg/g vs 300 to ≤3000 mg/g) levels, timepoint (Study Week), a treatment-by-timepoint interaction as fixed effects, and subject as a random effect. All post-baseline (excluding data collected at Follow-up visit) observations collected will be used in the MMRM. The MMRM statistics will be based on the restricted maximum likelihood (REML) method for estimation. An unstructured (co)variance structure will be used to model within-subject errors. The Kenward-Roger approximation will be used to approximate the denominator degrees of freedom. The adjusted mean change in log-transformed UACR from Baseline to Study Week 12 for each treatment group and the 95% CLs will be estimated in the framework of the this model, as well as the between-group difference and the 95% CLs for the difference.

Summarization of the inferential statistics will include the LS means, standard error (SE) of the estimates, p-value, and 2-sided CLs. These statistics will be provided for the within treatment group changes from Baseline and for the comparison of TMX-049 versus Placebo for the change from Baseline values. The adjusted

geometric mean of Week 12 to Baseline ratio in UACR with the corresponding 95% CLs for each treatment group, and the ratio of the adjusted geometric mean of Week 12 to Baseline ratio achieved within each treatment group relative to that achieved within Placebo group with 95% CLs will also be provided.

Figures displaying the mean change from Baseline by study week, LS mean change at Week 12 in log-transformed UACR from the ANCOVA model using LOCF, as well as the adjusted geometric mean ratio to Baseline at each study week from MMRM will be presented by treatment group.

Furthermore, the ANCOVA model specified in **Section 7.6.1** will be fitted using observed data in order to check the robustness of LOCF in the primary efficacy analysis.

7.6.3 Sensitivity Analysis

The analyses described in **Sections 7.6.1** and **7.6.2** will be performed using the PP population.

In addition, the primary efficacy endpoint, ie, the change from Baseline to Study Week 12 in log-transformed UACR will also be analyzed in an analysis of covariance (ANCOVA) model with randomized treatment, randomization strata of sUA (<6.0 vs ≥6.0 mg/dL) and UACR (200 to <300 mg/g vs 300 to ≤3000 mg/g) levels as independent variables, Baseline log-transformed UACR as a covariate. The least square mean (LS mean), p-value, and the corresponding 95% confidence limit (CL) for the change in log-transformed UACR in each treatment group, and the difference of change in log-transformed UACR between each TMX-049 treatment group versus Placebo group will be presented. The adjusted geometric mean of Week 12 to Baseline ratio in UACR with the corresponding 95% CLs for each treatment group, and the ratio of the adjusted geometric mean of Week 12 to Baseline ratio achieved within each treatment group relative to that achieved within Placebo group with 95% CLs will also be provided. These analyses will be performed in both mITT and PP population, using LOCF and observed data, respectively.

7.6.4 Subgroup Analysis

Standard descriptive statistics of UACR (both Log-scale and original scale) and change from Baseline to Study Week 12 will be provided for different categories of the following Baseline demographics and lab characteristics subgroups. If data allowed, the primary efficacy endpoint, ie, the change from Baseline to Study Week 12 in log-transformed UACR, with LOCF imputation algorithm will be analyzed using ANCOVA model described in **Section 7.6.1** for each subgroup. The analyses will be based on mITT population.

- Age at study entry (years) (<65; >=65)
- Sex (male; female)

- Race (African American; not African American)
- eGFR (CKD-EPI) at Baseline (ml/min/1.73m^2) (<60; >=60)
- BMI (kg/m^2) (below the median; at or above the median)
- SBP (mm Hg) (below the median; at or above the median)
- sUA (mg/dL) (below the median; at or above the median)
- UACR (mg/g) (below the median; at or above the median)
- HbA1C (%) (below the median; at or above the median)Oxidative stress markers (below the median; at or above the median)
  - 8 hydroxy 2' deoxyguanosine (8-OhdG)
  - high sensitivity C reactive protein (hs-CRP)
  - soluble tumor necrosis factor receptor 1 (sTNFR1)

7.6.5 Secondary Efficacy Endpoints Analysis

Analysis of the secondary efficacy endpoints will be based on mITT population and PP population. Descriptive statistics for secondary efficacy endpoints will be presented by treatment group and by study visit where appropriate. All post-baseline data collected will be used in the analyses, including observations occurring after discontinuation of study drug.

7.6.5.1 Change in eGFR, UACR, and sUA from Baseline to Study Weeks 2, 6, 12/ET, and Follow-up Visit

For each of these secondary efficacy endpoints, the ANCOVA model using LOCF described for the primary efficacy endpoint in **Section 7.6.1** will be fitted for the change from Baseline to each specific timepoint, ie, Study Week 2, Week 6, Week 12, and Follow-up Visit.

The MMRM and all observed data (excluding data collected at Follow-up visit) described for the primary efficacy endpoint in **Section 7.6.2** will be fitted for each of these endpoints also.

Note: In the above ANCOVA and MMRM models, Baseline eGFR will be included as a covariate to model change in eGFR from Baseline.

For each of these endpoints, 3 figures will be generated by treatment group: figure to present the mean change from Baseline by visit; figure to present the LS mean change from Baseline to Study Week 12 from the ANCOVA model, and figure to present the LS mean change from Baseline to each post-baseline study weeks from the MMRM.

In addition, the following scatter plots will be generated by treatment group:

- Change in UACR at Study Week 12 from Baseline versus Baseline UACR

- Change in UACR at Study Week 12 versus change in eGFR at Study Week 12 from Baseline
- Change in UACR at Study Week 12 from Baseline versus Baseline eGFR
- Change in UACR at Study Week 12 from Baseline versus Baseline sUA
- Change in UACR at Study Week 12 from Baseline versus Change in sUA at Study Week 12
- Change in UACR at Study Week 12 from Baseline versus Baseline BMI
- Change in UACR at Study Week 12 from Baseline versus Baseline SBP
- Change in UACR at Study Week 12 from Baseline versus Baseline HbA1C
- Change in UACR at Study Week 12 from Baseline versus Baseline 8-OhdG
- Change in UACR at Study Week 12 from Baseline versus Baseline hs-CRP
- Change in UACR at Study Week 12 from Baseline versus Baseline sTNFR1
- Change in eGFR at Study Week 12 from Baseline versus Baseline eGFR
- Change in eGFR at Study Week 12 from Baseline versus Baseline sUA
- Change in sUA at Study Week 12 versus change in eGFR at Study Week 12 from Baseline

7.6.5.2 Proportion of Subjects with >30% Reduction from Baseline to Study Week 12 in UACR

The frequency and percent of subjects with >30% reduction from Baseline to Study Week 12 in UACR will be presented by treatment group. Subjects with missing observations at Study Week 12 are imputed as non-responders for this analysis.

Fisher's exact test will be performed between each TMX-049 group and the placebo group and the exact p-value from each test will be provided. The difference in the percentage of responders between each treatment group and the Placebo group and the exact 95% CLs based on Clopper-Pearson method will also be provided.

Furthermore, the association between having UACR reduction greater than 30% from Baseline to Study Week 12 and the treatment group will be assessed by Logistic regression model. The model will use the incidence of subjects with >30% reduction as the dependent variable, the randomized treatment group, randomization strata of sUA (<6.0 vs ≥6.0 mg/dL), and UACR (200 to <300 mg/g vs 300 to ≤3000 mg/g) levels as independent variables, Baseline UACR and Baseline sUA levels as covariates. The estimated odds ratio (and 95% CL) of having >30% reduction versus not having >30% reduction in URCA in any active TMX-049 group versus Placebo group, will be provided.

7.6.5.3 Exploratory Renal Biomarkers

Exploratory renal biomarkers include:

- Urinary biomarkers: kidney injury molecule 1 (KIM-1), liver fatty acid binding protein (L-FABP), 8-OHdG, and N-acetyl-β-D-glucosaminidase (NAG).

- Blood biomarkers: sTNFR1, hs-CRP.

Descriptive statistics for the listed renal biomarkers will be presented by treatment group and by study visit where appropriate.

7.7 Safety

7.7.1 Adverse Events

All AEs recorded on the eCRF will be coded using the MedDRA dictionary Version 20.5 (or a later version if updated during the study) and classified as TEAEs as follows:

TEAEs are events with start date on or after the date of first dose of double-blind study drug and up to 30 days after date of last dose of double-blind study drug.

All AE data will be listed by treatment group. Treatment-emergence status, AEs leading to discontinuation of double-blind study drug, AEs resulting in death, and serious AEs will be presented in the listing.

Summary tables of TEAEs by treatment group and overall will be produced for the Safety population.

The relationship between an AE and study drug is assessed as related or not related.

An overview table will summarize the number and percentage of subjects with at least 1 of the following TEAEs, where subjects with more than 1 TEAE in a particular category are counted only once in that category:

- Any TEAE
- Drug-related TEAE
- Severe drug-related TEAE
- Treatment-emergent SAE
- Treatment-emergent drug-related SAE
- TEAE leading to study drug discontinuation
- Drug-related TEAE leading to study drug discontinuation
- TEAE leading to death

The number and percentage of subjects reporting each AE will be summarized by SOC and PT for the Safety population. Tables will be sorted, as to SOC, by Internationally Agreed Order. PTs will be sorted by PT code (variable PTCD). The following summaries will be produced:

- TEAEs by SOC and PT
- TEAEs by onset time period, SOC, and PT (<28 days; ≥28 days and <56 days; ≥56 days and <84 days; ≥84 days)

- TEAEs by PT
- TEAEs reported by at least 5% of subjects in any treatment group, by SOC and PT
- TEAEs related to treatment, by SOC and PT
- TEAEs related to treatment, by PT
- TEAEs by relationship to treatment, by SOC and PT
- TEAEs by severity, by SOC and PT
- TEAEs related to treatment by severity, by SOC and PT
- TEAEs causing discontinuation from treatment, by SOC and PT
- TEAEs related to treatment causing discontinuation from treatment, by SOC and PT
- Treatment-emergent SAEs, by SOC and PT
- Treatment-emergent SAEs related to treatment, by SOC and PT
- TEAEs leading to death, by SOC and PT
- SAEs during Single-blind, placebo run-in, by SOC and PT

In the above summaries, subjects with more than 1 AE within a particular SOC are counted only once for that SOC. Similarly, subjects with more than 1 AE within a particular PT are counted only once for that PT. For summaries by maximum intensity, subjects with multiple AEs within a particular SOC or PT will be counted under the category of their most severe AE within that SOC or PT.

No statistical comparisons of AE related data between treatment groups will be performed.

7.7.2 Laboratory Evaluations

Data for the following hematology, blood chemistry, lipid profile, and urinalysis received from central laboratory will be listed and summarized by treatment group and visit. If data for any additional analytes are also received then these will be listed only.

All summaries of laboratory test results will be presented in International System of Units (SI) and conventional units. Out-of-reference-range values will be flagged as high (H) or low (L) in the listings.

For analysis purposes, values preceded by a "<" or a ">"sign (ie, those below or above the limits of quantification) will be considered equal to the lower or upper limit of quantification, respectively.

Laboratory evaluations measured on a continuous scale will be summarized by visit using standard descriptive statistics for the Safety population. Changes from Baseline will also be summarized. For analysis by visit, the nominal study visits will be utilized.

Qualitative urinalysis laboratory results will be summarized for Baseline and all scheduled post-baseline study weeks as the number and percentage of patients having either positive or negative results. Missing category will be reported if there is more than 1 patient reported in any treatment group.

For each laboratory analyte, the Baseline value will be defined as last scheduled or unscheduled value collected prior to the first dose of treatment.

For hematology and serum chemistry, shift tables presenting movement in and out of reference range from Baseline to each scheduled post-Baseline visit will be provided for each treatment group.

Mean change from Baseline with standard deviation bars will be plotted by visit for select laboratory parameters for the Safety Analysis Set.

The lab parameters collected are presented in the following table:

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) Total bilirubin Direct bilirubin Creatinine Blood urea nitrogen (BUN) Total protein Albumin Creatinine phosphokinase (CPK) Glycosylated hemoglobin (HbA1c)	**Complete Blood Count** 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: Microscopic examination Specific gravity pH Protein Glucose Ketones Blood Urobilinogen
	For Females Only: Urine pregnancy test
	For Postmenopausal Females Only: Follicle-stimulating hormone (FSH)
Lipid Panel: Total cholesterol High-density lipoprotein cholesterol (HDL-C) non-HDL-C	**Serology:** Hepatitis B surface antigen (HBsAg) Hepatitis C antibody Human immunodeficiency virus (HIV)
Thyroid Testing: Triiodothyronine (T3) Thyroxine (T4) Free triiodothyronine (FT3) Free thyroxine (FT4) Thyrotropin/Thyroid stimulating hormone (TSH)	**Urinary Biomarkers:** Urinary albumin-to-creatinine ratio (UACR) Kidney injury molecule 1 (KIM-1) Liver fatty acid binding protein (L-FABP) 8 hydroxy 2' deoxyguanosine (8-OHdG) N-acetyl-β-D-glucosaminidase (NAG)
	Blood Biomarkers: Soluble tumor necrosis factor receptor 1 (sTNFR1) high sensitivity C reactive protein (hs-CRP) Estimated glomerular filtration rate (eGFR)

7.7.3 Vital Signs

The following vital signs will be listed and summarized by treatment group and visit.

- Supine SBP and DBP (mm Hg)

- Pulse rate (beats/min)
- Respiration rate (breaths/min)
- Body temperature (°C)

Vital signs data and changes from Baseline in vital signs will be summarized by visit using standard descriptive statistics for the Safety population.

The Baseline value will be defined as last scheduled or unscheduled value collected prior to the first dose of treatment. For analysis by visit, nominal study visits will be used.

7.7.4 Electrocardiograms

The following quantitative ECG measurements will be listed and summarized by treatment group and visit for the Safety population:

- heart rate (beats/min);
- PR interval (ms);
- QRS interval (ms);
- QT interval (ms);
- Fridericia corrected QT (QTcF) interval (ms)

An overall Investigator assessment of ECG will be summarized and listed using categories reported in the eCRF.

7.7.5 Physical Examination

Physical examination results (normal or abnormal) and details of abnormalities will be listed for each subject.

For each physical examination body system, the number and percentage of subjects with abnormalities at Baseline and post-Baseline will be summarized by treatment group for the Safety Population.

7.8 Pharmacokinetic Analysis

The population pharmacokinetic analysis was described in a separate analysis plan: Final Population Pharmacokientic Analysis and Report Plan, dated as of February 22, 2019.

Pharmacokinetic plasma concentration of TMX-049 will be summarized and listed by treatment group using descriptive statistics (including geometric mean and CV%, arithmetic mean, SD, arithmetic CV%, median, observed maximum, minimum, and N). No formal statistical tests are planned.

The following rules will be applied if there are values that are below the limit of quantification (BLQ) or if there are missing values (eg, no result [NR]) in a plasma concentration data sets to be summarized.

- For the calculation of summary statistics, BLQ values will be set to zero.
- If an embedded BLQ value is considered anomalous within the concentration time profile, this value will be excluded from the summary statistics.
- Where there is NR, these will be set to missing.
- If values are obtained from more than or equal to 50% subjects, the summary statistics will be calculated.
- If values are obtained from less than 50% subjects, all arithmetic and geometric summary statistics will be denoted as NC.

7.9 Interim Analysis

No interim analysis is planned for this study.

8. Changes in Planned Analysis

Not applicable.

9. References

The schedule of study procedures (from the Protocol) is attached for reference.	**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	

The schedule of study procedures (from the Protocol) is attached for reference.	**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]					

Note:

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; tmax = 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 (tmax 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 tmax sample is not obtained at Visit 5, the tmax 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.