NCT01559363

STATISTICAL ANALYSIS PLAN

A Phase 1b/2a, Safety, Pharmacokinetic and Dose-Escalation Study of KD019 in Subjects with Autosomal Dominant Polycystic Kidney Disease

Protocol Number: KD019-101

[redacted]

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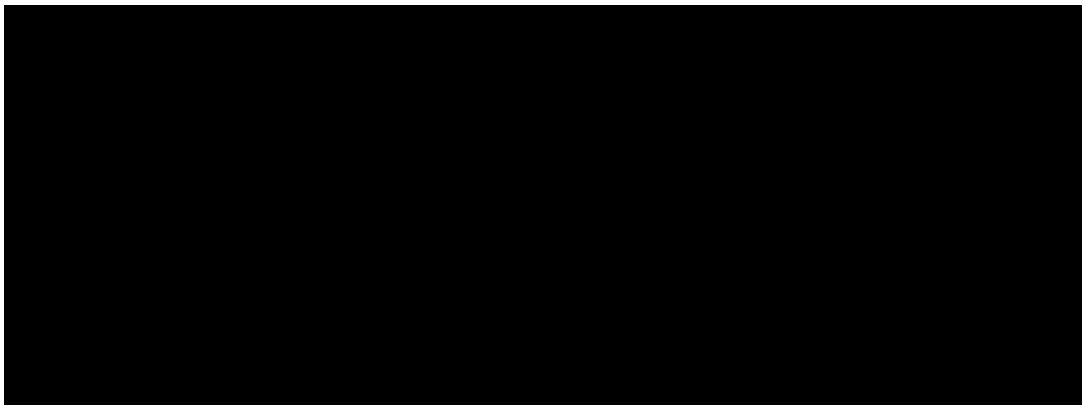

DOCUMENT HISTORY

Version	Author	Description
1.0	[redacted]	10-Sep-2021 New Document

Table of Contents

LIST OF ABBREVIATIONS

Abbreviation	Full Term
ADI	Actual dose intensity
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine transaminase
ATC	American Therapeutic Chemical (Classification)
BID	Twice daily
C1D1	Cycle 1 Day 1
CI	Confidence interval
CM	Concomitant medication
CNI	Calcineurin inhibitor
CR	Complete response
CRF	Case report form
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DOR	Duration of response
ECG	Electrocardiogram
EOT	End of treatment
HCT	Hematopoietic cell transplantation
FVC	Forced vital capacity
ICH	International Conference on Harmonisation
LR	Lack of response
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-to-treat
KPS	Karnofsky Performance Scale
NE	Not evaluable
ORR	Overall response rate
OS	Overall survival
OS-9	Overall survival at 9 months
PD	Pharmacodynamics
PDI	Planned dose intensity
PFS	progression-free survival
PFS-6	progression-free survival at 6 months
PK	Pharmacokinetics
PR	Partial response
PT	Preferred Term
RANO	Response Assessment in Neuro-Oncology criteria
RDI	Relative dose intensity
RV	Residual volume
QD	Once daily
ORR	Overall response rate

Abbreviation	Full Term
QTcF	Corrected QT interval using Fridericia's formula
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SOC	System Organ Class
STB	Stable
TEAE	Treatment-emergent adverse event

1 INTRODUCTION

Tesevatinib (formerly named KD019) was originally developed for a solid tumor indication, and is currently being investigated for the treatment of cancer. In nonclinical studies, tesevatinib selectively inhibited key kinases and validated targets in animal models of polycystic kidney disease (PKD). In addition, it has shown either no or extremely weak inhibitory activity of other kinases that should reduce off-target effects. Tesevatinib has also been shown to be a potent inhibitor of receptor and cytoplasmic tyrosine kinases (TKs). The product was specifically optimized to simultaneously inhibit EGFR, human epidermal growth factor receptor 2 (HER2), Src, vascular endothelial growth factor receptor 2 (VEGFR2/ KDR), and ephrin receptor B4 (EphB4) tyrosine kinases with high potency, and demonstrated excellent activity in target-specific cellular functional assays. In nonclinical animal models, tesevatinib had acceptable oral bioavailability and has shown sustained inhibition of its targets in vivo following a single oral dose.

In Phase 1 and 2 clinical studies conducted in healthy subjects and subjects with solid tumors, over 300 subjects have been treated to date; at least 185 of these have been treated at levels ≥ 300 mg daily. At least 53 subjects have received tesevatinib for ≥ 6 months, and safety and tolerability were acceptable. Tesevatinib is also in development for the treatment of breast cancer and non-small cell lung cancer (NSCLC).

In summary, both the nonclinical results in PKD models and the clinical safety results in human oncology studies suggest that tesevatinib could be a promising therapeutic in autosomal dominant polycystic kidney disease (ADPKD).

Evaluation of the safety and tolerability data from the subjects in KD019-101 led to the conclusion that tesevatinib 50 mg daily was the dose and schedule most appropriate for use in a randomized study. [redacted]

This Statistical Analysis Plan (SAP) describes detailed statistical procedures to be used for study KD019-101 . KD019-101 is specified in the protocol (Amendment No. 13, 06-Oct-2016): A Phase 2, Multicenter Study of Tesevatinib Monotherapy in Patients with Recurrent Glioblastoma.

The SAP was written in accordance with the recommendations outlined in the International Conference on Harmonisation (ICH) E9 Guideline entitled "Guidance for Industry: Statistical Principles for Clinical Trials" and the most recent ICH-E3 Guideline, entitled "Guidance for Industry: Structure and Content of Clinical Study Reports."

2 STUDY SUMMARY

2.1 Study Objectives

2.1.1 Primary Objectives

2.1.1.1 KD019-101:

- Phase 1b: To determine the safety, plasma pharmacokinetics (PK), and maximum tolerated dose (MTD) of tesevatinib when administered to subjects with ADPKD.
- Phase 2a: To evaluate the annualized change in glomerular filtration rate (GFR) in subjects with ADPKD when treated with tesevatinib.

2.1.2 Secondary Objectives

2.1.2.1 KD019-101:

- To evaluate subjects treated with tesevatinib with regard to annualized percent change from baseline in total kidney volume (TKV)
- To evaluate subjects treated with tesevatinib with regard to annualized change from baseline in the reciprocal of serum creatinine

- To evaluate subjects treated with tesevatinib with regard to safety profile
- To evaluate subjects treated with tesevatinib with regard to serum creatinine profiles
- To evaluate subjects treated with tesevatinib with regard to PK and tolerability of 2 alternative dosing schedules (dosing on Monday, Wednesday, and Friday of each week, and dosing on Monday and Thursday of each week)

[redacted]

2.1.3 Post-hoc Objectives:

- To evaluate the slope of the change in the annualized estimated GFR

2.2 Study Design

2.2.1 KD019-101

This is a Phase 1b/2a, multicenter, open-label, dose-escalation, safety, MTD, and PK study in subjects with ADPKD. The Phase 1b portion of the study has been completed and the MTD for daily dosing was determined to be 100 mg daily. In this portion of the study, subjects received 50, 100, or 150 mg of tesevatinib orally once daily for 28 days or until the development of unacceptable toxicity, noncompliance, or withdrawal of consent by the subject, or investigator decision. After the initial 28-day safety and tolerability assessment period, subjects may have, at the discretion of the investigator, continued to receive study drug for a total of 24 months from the initiation of treatment.

For those subjects who had received a minimum of 6 months of treatment at the 50 mg/day dose, dose escalation to 100 mg/day was allowed after the 100 mg/day was evaluated for safety.

In order to study the safety profile in this specific ADPKD subpopulation, up to 50 additional subjects with PKD and baseline eGFR ≥ 35 mL/min/1.73 m2 and ≤ 80 mL/min/1.73 m2, and htTKV ≥ 1000 mL will be enrolled (SILK Cohort). Up to 50 subjects will be enrolled and required to complete PK testing as described for other Phase 2a subjects in this protocol or iothalamate testing.

2.3 Visit Schedule and Study Assessment

The flow chart of visit schedule and study assessments is given in Table 4-1 of the KD019-101 Protocol .

3 STATISTICAL METHODS

3.1 General Methods

3.1.1 Computing Environment

All statistical programming and data analyses will be performed using SAS® Version 9.4 on Windows platform.

3.1.2 Sample Size Justification and power calculations:

Eight subjects per cohort is a standard and reasonable sample size for determination of safety in this Phase 1b portion of the study. Given the frequency and timing of the most common AEs in prior clinical studies of tesevatinib, 8 treated subjects per dose is sufficient to describe the safety profile of tesevatinib in this subject population. These subjects who receive 50 mg daily of tesevatinib will provide 75% likelihood of having at least 1 AE if the true incidence of an AE is 5%.

In the Phase 2a cohort, the 65 subjects in the 50 mg QD dose group will allow an 80% confidence interval of approximately ± 0.64 mL/min about an expected mean 6-month change from baseline of -2.5 mL/min when the standard deviation is 4.0 mL/min.

3.1.3 General Considerations

General considerations for descriptive statistics and presentation for continuous and categorical data are given below.

3.1.3.1 Continuous variables

Continuous data will be described using descriptive statistics: number of observations (n), mean, standard deviation, median, minimum, and maximum.

Means, medians, standard deviations, and confidence intervals (CIs) will be reported to one decimal place more than the data reported on the case report form (CRF) or by the vendor. Minimum and maximum will be reported to the same number of decimal places displayed on the CRF or by the vendor. P-values will be reported to 4 decimal places.

3.1.3.2 Binary Endpoint and Other Categorical Variables

For endpoints with two possible outcomes such as alive/otherwise or response/otherwise within specific periods, the 95% confidence interval will be calculated with Clopper-Pearson method for survival rates or response rates. For other categorical variables, the counts and percent of each category within a parameter will be calculated for observed data only. The denominator for all percentages, unless otherwise specified, will be the number of subjects in the cohort or in the specified analysis population.

3.1.4 Study Day

The Study Day for all assessments prior to the first study drug administration is calculated as the difference between the date of the event or measurement (e.g., adverse event [AE] onset date, assessment date, sample collection date) and the start date of study treatment. The day before the start of study treatment is Study Day -1.

The Study Day for all post-assessments after the first study drug administration is calculated as the difference between the date of the event or measurement (e.g., AE

onset date, assessment date, sample collection date) and the start date of study treatment plus one day. The first day of study treatment is Study Day 1.

3.1.5 Baseline

Baseline value is defined as the valid and last non-missing value obtained within 28 days prior to subject receiving the first study medication, unless otherwise stated under the related assessment section. Baseline can be the day before the first study medication or on the same day as the first study medication if a pre-dose assessment is available. Subjects without data on a parameter before the first study medication will have a missing baseline for this parameter.

3.1.6 Handling of Incomplete or Missing Data

Missing data will not be imputed in general and will be reported as missing in all listings. For categorical variables, patients with missing data are not included in calculations of percentages unless otherwise specified.

3.1.6.1 Missing start and end dates for AE and concomitant medication (CM)

The assumption will be the worst or most conservative judgment when imputing AE and CM start and end dates. The purpose of imputing a start date is to help define whether the AE/CM started while taking study drug.

For a partial or missing start date:

- If the day is missing, the first day of the month will be imputed. If the missing day is the same as the month of first dose of study drug, then the first dose date will be imputed.
- If the day and month are missing, the first day of January will be imputed. If the year is the same as the first dose date, then the first dose date will be imputed.
- If the day is completely missing, the first dose date will be imputed. If the end date suggests it could have started prior to this, the first day of January of the same year as the end date will be imputed.
- When imputing a start date, the start date will ensure that the new imputed date is sensible, i.e., is prior to the end date of the AE or CM.

For a partial or missing end date:

- If the day is missing, the last day of the month or the last assessment date, whichever is earlier, will be imputed.
- If the day and month are missing, the 31st of December or the last assessment date, whichever is earlier, will be imputed

- If the date is completely missing, there will be a need to look at whether the AE/CM is still ongoing before imputing a date. If the ongoing flag is missing, then it will be assumed that AE is still present, or CM is still being taken (i.e., do not impute a date). If the AE/CM has stopped, then the last assessment date will be imputed.

These data imputations are for categorization purpose only and will not be used in the listings.

If the assessment of the relationship of the AE to tesevatinib is missing, then it will be assumed that the AE is related to tesevatinib and the AE considered as such in the frequency tables of possibly related AEs. No imputation should be done at the data level.

3.1.6.2 Missing event dates

Event date will be imputed only when day is missing, and the purpose of imputing an event date is to most conservatively calculate time to event.

If the day is missing, the first (mid, last) day of the month will be imputed for undesired (neutral, desired) event. If the missing day is the same as the month of first dose of study drug, then the first dose date will be imputed for undesired event.

These data imputations are for time to event calculation only and will not be used in the listings.

3.2 Analysis Populations

The following populations will be analyzed:

Modified Intent-to-treat (mITT) Population: The primary population for efficacy analyses will be a Modified Intent-to-treat (mITT) Population. For KD019-101 it is defined as all subjects who completed 28 days (for subjects in the Phase 2a portion of the study this will be 25 or 26 days in the Monday/Thursday and Monday/Wednesday/Friday cohorts, and 28 days in the 50 mg daily dosing cohort).

[redacted]

The mITT Population will be used for tables of demography, baseline characteristics, and efficacy.

Safety Population: The Safety Population is defined as all subjects who receive at least 1 dose of tesevatinib.

3.3 Subject Disposition and Evaluability

Subjects who failed screening (i.e., subjects who signed the informed consent were screened but never started the study treatment, and their basic demographics and any AE after signing the informed consent may have been collected in the CRF) will be excluded from any populations defined in Section 3.2. Therefore, these subjects will be excluded from any summary tables or listings.

The number of subjects discontinuing from the study and the primary reason for discontinuation will be summarized.

3.4 Protocol Deviations

All protocol deviations will be identified and classified as major or minor before clinical database lock and all major protocol deviations will be presented in a listing.

Major Deviation: Protocol deviation that may impact the accuracy, and/or reliability of the study data or that may impact subject rights, safety or well-being.

Minor Deviation: Protocol deviation that does not impact the accuracy, and/or reliability of the study data or subject rights, safety or well-being.

3.5 Demographics and Baseline Characteristics

3.5.1 Demographics

Subject demographics and baseline characteristics will be summarized for the mITT Population by cohort and study. Descriptive statistics will be provided for age, height, and weight.

3.5.2 Medical History

Medical history will be summarized by primary System Organ Class (SOC) and Preferred Term (PT). Medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 18.1 (or higher) terminology.

3.6 Prior and Concomitant Medications

Concomitant medications will be coded using the World Health Organization Drug Dictionary. Prior medications are defined as those medications that began and stopped before the start of study treatment. Concomitant medications are defined as medications taken after the start of study treatment and during the study period, including those began before but ongoing at the start of study treatment. If a medication start date is partially or fully missing and it is unclear as to whether the medication is prior or concomitant, it will be assumed that the medication is concomitant.

Number and percentage of incidence of prior and CM will be summarized according to study, cohort, Anatomical Therapeutic Class (ATC) and preferred drug name.

3.7 Primary Endpoint Analysis

The primary endpoint for the Phase 1b portion of KD019-101 is safety and tolerability. This will be covered in Section 3.9. [redacted] The primary endpoint is annualized change in glomerular filtration rate (GFR) in subjects with ADPKD when treated with tesevatinib. The annualized change in GFR will be calculated as the percent change from baseline divided by total duration in days times 365.25.

This analysis will be done using the mITT population. Descriptive statistics will be provided for each cohort [redacted]. The annualized GFR will be calculated for the 6, 12, 18 and 24 months timepoints.

GFR will be estimated using three equations; MDRD-4**,** CKD-EPI$_{2012cys}$, and CKD-EPI$_{2012Scr-cys}$.

4-Variable Modification of Diet in Renal Disease (MDRD-4) Equation

High Level Formula for Black or African-American Males: Estimated GFR = $175 \times (Scr^{-1.154}) \times (Age^{-0.203}) \times 1.212$
High Level Formula for Males NOT Black or African-American (any other option): Estimated GFR = $175 \times (Scr^{-1.154}) \times (Age^{-0.203})$
High Level Formula for Black or African-American Females:

Estimated GFR = $175 \times (Scr^{-1.154}) \times (Age^{-0.203}) \times 1.212 \times 0.742$
High Level Formula for Females NOT Black or African-American (any other option): Estimated GFR = $175 \times (Scr^{-1.154}) \times (Age^{-0.203}) \times 0.742$

Note: Age is shown in years. Scr = serum creatinine

CKD-EPI$_{2012cys}$ Equation to Predict Glomerular Filtration Rate (GFR)

Gender	Scys (mg/L)	Equation
Female	≤ 0.8	$133 \times (Scys/0.8)^{-0.499} \times 0.996^{age}$ (× 0.932)
	> 0.8	$133 \times (Scys/0.8)^{-1.328} \times 0.996^{age}$ (× 0.932)
Male	≤ 0.8	$133 \times (Scys/0.8)^{-0.499} \times 0.996^{age}$
	> 0.8	$133 \times (Scys/0.8)^{-1.328} \times 0.996^{age}$

Note: Age is shown in years. Scys= serum cystatin

CKD-EPI$_{2012Scr-cys}$ Equation to Predict Glomerular Filtration Rate (GFR)

Gender	Scr (mg/L)	Scys (mg/L)	Equation
Female	≤ 0.7	≤ 0.8	$130\times (Scr/0.7)^{-0.248}\times (Scys/0.8)^{-0.375}\times 0.995^{age}$ (× 1.08, if black)
		> 0.8	$130\times (Scr/0.7)^{-0.248}\times (Scys/0.8)^{-0.711}\times 0.995^{age}$ (× 1.08, if black)
	> 0.7	≤ 0.8	$130\times (Scr/0.7)^{-0.601}\times (Scys/0.8)^{-0.375}\times 0.995^{age}$ (× 1.08, if black)
		> 0.8	$130\times (Scr/0.7)^{-0.601}\times (Scys/0.8)^{-0.711}\times 0.995^{age}$ (× 1.08, if black)
Male	≤ 0.7	≤ 0.8	$130\times (Scr/0.9)^{-0.207}\times (Scys/0.8)^{-0.375}\times 0.995^{age}$ (× 1.08, if black)
		> 0.8	$130\times (Scr/0.9)^{-0.207}\times (Scys/0.8)^{-0.711}\times 0.995^{age}$ (× 1.08, if black)

	> 0.7	≤ 0.8	$130\times (Scr/0.9)^{-0.601}\times (Scys/0.8)^{-0.375}\times 0.995^{age}$ (× 1.08, if black)
		> 0.8	$130\times (Scr/0.9)^{-0.601}\times (Scys/0.8)^{-0.711}\times 0.995^{age}$ (× 1.08, if black)

Note: Age is shown in years. Scys= serum cystatin, Scr = serum creatinine

3.7.1 Secondary Endpoint Analyses

3.7.1.1 Total Kidney Volume

The annualized percent change from height adjusted baseline in total kidney volume (hTKV) will be summarized by cohort and study using the mITT population. hTKV will be determined by MRI at screening (baseline measurement), at the 6-month visit, and every 6 months thereafter. Descriptive statistics will be provided for each timepoint and cohort [redacted]. The annualized percent change from baseline will be calculated as the percent change from baseline divided by total duration in days times 365.25.

3.7.1.2 Serum Creatinine

The annualized percent change from baseline in the reciprocal of serum creatinine will be summarized by cohort using the mITT population. Descriptive statistics will be provided for each cohort [redacted]. The change from baseline in the reciprocal of serum creatinine will be calculated using the first and last timepoint for each subject. The annualized percent change from baseline will be calculated as the percent change from baseline divided by total duration in days times 365.25.

3.7.2 Post-hoc Endpoint Analysis

3.7.2.1 Slope of the change in eGFR

The slope of the change in the estimated GFR was derived from the individual slopes for each patient using the MDRD-4 equation. Descriptive statistics will be provided for each cohort [redacted]. The change from baseline in the estimated GFR will be calculated two ways. The first using the first and last timepoint for each subject and the second using all of the available timepoints.

3.8 Safety Analysis

Safety assessments will include AEs, serious adverse events (SAEs), vital sign measurements, clinical laboratory evaluations (hematology and chemistry), and electrocardiograms (ECGs). Unscheduled visits for safety assessments will not be presented in summary tables but will be in listings. All safety analyses will be performed using the safety population for all cohorts and both studies.

3.8.1 Adverse Events

AEs will be coded using the MedDRA dictionary (Version 20.1 or higher). Treatment-emergent AEs (TEAEs) are any AE occurring or worsening in severity after the first administration of study medication. All AEs (including SAEs) will be graded using the 5-point Common Terminology Criteria for Adverse Events (CTCAE) V5.0 scale (mild, moderate, severe, life-threatening, or death). Causality with KD019 will be classified as: definitely related; probably related; possibly related; unlikely related; unrelated; or not related.

The number and percentage of patients who experienced at least one TEAE as well as the number and percentage of patients who experienced AEs of each specific SOC and PT will be presented. For the presentation of AE incidences, the SOCs and the PTs within each SOC will be presented by decreasing total frequency. Tabulation by maximum severity and relationship to tesevatinib will also be included by treatment group.

The TEAEs, Grade ≥ 3 TEAEs, SAEs, and TEAEs leading to dose modification/discontinuation will be summarized by treatment arm, SOC, and PT. These analyses will be repeated for events considered related (definitely related/probably related/possibly related) to tesevatinib.

Subject listings will be provided for SAEs, AEs resulting in study drug discontinuation and deaths.

Adverse events will also be presented in listings. Time to onset and duration of AEs will be included in listings, along with action taken and outcome.

3.8.2 Clinical Laboratory Evaluation

The summary statistics (including number, mean, standard deviation, median, minimum and maximum) of all laboratory variables and changes from baseline will

be calculated for each visit or study assessment by treatment group. For parameters of white blood cell counts, neutrophils (absolute count), lymphocytes (absolute count), monocytes (absolute count), hemoglobin, platelets, ALP, ALT, aspartate aminotransaminase, total bilirubin, plots of mean/mean changes from baseline with the corresponding standard error will be displayed.

For shift tables, laboratory results will be classified using the CTCAE Version 5.0. All graded laboratory parameters will be summarized separately for hematology and biochemistry. Corresponding shift tables comparing baseline to the worst post-baseline grade within the treatment period will be provided.

3.8.3 Vital Signs

Descriptive statistics for vital signs (weight, temperature, blood pressure, pulse rate, and respiratory rate) values and the change from baseline will be presented for each scheduled assessment time point.

3.8.4 ECG

Descriptive statistics for ECG parameters (i.e., PR interval, QRS interval, and QTcF interval) at each time point with triplicate ECGs will be presented for the values and change from baseline scores. (QTcF is the QT interval using Fridericia's correction which is calculated by $QTcF = QT/RR^{1/3}$.)

The number and percentage of subjects with observed QTcF values that satisfy the following conditions will be presented by treatment group and study visit and categorized as: ≤ 450 ms; > 450 to 480 ms; > 480 to 500 ms; and > 500 ms.

The number and percentage of subjects having change from baseline QTcF values that satisfy the following conditions will be presented by treatment group and study visit and categorized as: ≤ 0 ms; > 0 to ≤ 30 ms; > 30 to ≤ 60 ms; and > 60 ms.

3.9 Pharmacokinetic Analysis Plan

PK serum concentration and all biomarkers will be summarized at each collection time-point by cohort for KD019-101.

4 LIST OF TABLES, FIGURES, AND LISTINGS

In all tables, figures and listing, results will be presented by treatment cohorts and overall, unless be otherwise specified.

Table/Listing/Figure	Title
Demographics and Baseline Characteristics	
Tables (14.1.Y.Z)	Table 14.1.1 Screen Failure
	Table 14.1.2 Patient Disposition
	Table 14.1.3 Summary of Demographics and Baseline Characteristics
	Table 14.1.4 Summary of Major Protocol Deviations
	Table 14.1.5 Summary of Medical History
Treatment Exposure and Concomitant Medication	
Tables (14.2.Y.Z)	Table 14.2.1 Summary of Treatment Compliance and Exposure
	Table 14.2.2.a Summary of Prior Medications
	Table 14.2.2.b Summary of Concomitant Medications
Efficacy	
Tables (14.3.Y.Z)	Table 14.3.1 Annualized Change in Estimated Glomerular Filtration Rate
	Table 14.3.2 Annualized Percent Change from Baseline in Height Adjusted Total Kidney Volume
	Table 14.3.3 Annualized Percent Change from Baseline in Reciprocal of Serum Creatinine

	Table 14.3.3.1 Annualized Percent Change from Baseline in Reciprocal of Serum Creatinine for Study 101
Safety	
Tables (14.4.Y.Z)	Table 14.4.1 Summary of AEs
	Table 14.4.1.1 Summary of AEs for Study 101
	[redacted]
	Table 14.4.2 Summary of TEAEs
	Table 14.4.2.1 Summary of TEAEs for Study 101
	[redacted]
	Table 14.4.3 Summary of TEAEs Related to KD019
	Table 14.4.3.1 Summary of TEAEs Related to KD019 for Study 101
	[redacted]
	Table 14.4.4 AEs by Preferred Term and Maximum Severity
	Table 14.4.4.1 AEs by Preferred Term and Maximum Severity for Study 101
	[redacted]
	Table 14.4.5 AEs by Preferred Term and Strongest Relationship
	Table 14.4.5.1 AEs by Preferred Term and Strongest Relationship for Study 101
	[redacted]
	Table 14.4.6 Summary of Grade >=3 TEAEs by System Organ Class and Preferred Term
	Table 14.4.6.1 Summary of Grade >=3 TEAEs by System Organ Class and Preferred Term for Study 101
	[redacted]
	Table 14.4.7 Summary of Grade >=3 TEAEs Related to KD019 by System Organ Class and Preferred Term

	Table 14.4.8 Summary of Serious Adverse Events
	Table 14.4.9 Summary of Serious Adverse Events Related to KD019
	Table 14.4.10 Summary of TEAEs leading to Dose Modification
	Table 14.4.11 Summary of TEAEs Related to KD019 leading to Dose Modification
	Table 14.4.12 Summary of TEAEs leading to Dose Discontinuation
	Table 14.4.13 Summary of TEAEs Related to KD019 leading to Dose Discontinuation
	Table 14.4.14 Summary of Clinical Laboratory: Hematology
	Table 14.4.15 Summary of Clinical Laboratory: Chemistry
	Table 14.4.16 Summary of Clinical Laboratory: Any Other Clinical Labs
	Table 14.4.17 Shifts from Baseline for Hematology Assessment
	Table 14.4.18 Shifts from Baseline for Chemistry Assessment
	Table 14.4.19 Summary of Vital Sign Results and Change from Baseline
	Table 14.4.20 Summary of 12-Lead ECG and Change from Baseline
	Table 14.4.21 Summary of QTcF Interval Results
	Table 14.4.22 Overall Summary of AEs
	Table 14.4.23 Overall Summary of AEs for Study 101
	[redacted]
Listings (16.2.Y.Z)	Listing 16.2.1 Disposition of Subjects
	Listing 16.2.2 Protocol Deviations
	Listing 16.2.3 Patients Excluded From Efficacy Analysis
	Listing 16.2.4 Patient Demographics
	Listing 16.2.5 Dose Changes
	Listing 16.2.6.1 Estimated Glomerular Filtration Rate

	Listing 16.2.6.2 Height Adjusted Total Kidney Volume
	Listing 16.2.7.1 Adverse Events
	Listing 16.2.7.2 Adverse Events leading to Study Drug Discontinuation
	Listing 16.2.7.3 Adverse Events leading to Death
	Listing 16.2.7.4 Serious Adverse Events
	Listing 16.2.8.1 Clinical Laboratory: Hematology
	Listing 16.2.8.2 Clinical Laboratory: Chemistry
	Listing 16.2.8.3 Clinical Laboratory: Any Other Clinical Labs
	Listing 16.2.8.4 Vital Signs
	Listing 16.2.8.5 12-Lead ECG
Efficacy	
Figures (14.3.Y.Z)	Figure 14.3.1 Annualized Change in Estimated Glomerular Filtration Rate
	Figure 14.3.2 Annualized Percent Change from Baseline Height Adjusted Total Kidney Volume