STATISTICAL ANALYSIS PLAN

Study Title:	MOSAIC - A Phase 2b, Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Multicenter Study Evaluating the Efficacy and Safety of Selonsertib in Subjects with Moderate to Advanced Diabetic Kidney Disease
Name of Test Drug:	Selonsertib
Study Number:	GS-US-223-1017
Protocol Version (Date):	Original: 01 February 2019 Amendment 1: 10 June 2019 Amendment 2: 13 April 2020
Analysis Type:	Final Analysis
Analysis Plan Version:	Version 1.0
Analysis Plan Date:	03 December 2021
Analysis Plan Author(s):	PPD

CONFIDENTIAL AND PROPRIETARY INFORMATION

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

LIST OF ABBREVIATIONS

ACEi	angiotensin converting enzyme inhibitor
AE	adverse event
ANCOVA	analysis of covariance
ARB	angiotensin receptor blocker
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BLQ	below the limit of quantitation
BMI	body mass index
CI	confidence interval
COVID-19	coronavirus disease 2019
CRF	case report form
CSR	clinical study report
CTCAE	Common Toxicity Criteria for Adverse Events
DKD	diabetic kidney disease
DMC	data monitoring committee
EAIR	exposure-adjusted incidence rate
ECG	Electrocardiogram
EOS	end of study
EOT	end of treatment
eGFR	estimated glomerular filtration rate
$eGFR_{cr}$	estimated glomerular filtration rate calculated by CKD-EPI Creatinine Equation (2009)
$eGFR_{cys}$	estimated glomerular filtration rate calculated by CKD-EPI Cystatin C Equation (2012)
ESKD	end stage kidney disease
FAS	Full Analysis Set
GLP1-RA	glucagon-like peptide-1 receptor agonists
GLPS	Global Patient Safety
HbA1c	hemoglobin A1c
HLT	high-level term
IXRS	interactive voice or web response system
LTT	lower-level term
LOQ	limit of quantitation
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed-effect model repeated measures
PP	per protocol
PT	preferred term
PTM	placebo to match
PY	patient year
Q1, Q3	first quartile, third quartile

QRS	electrocardiographic deflection between the beginning of the Q wave and termination of the S wave representing time for ventricular depolarization
QT	electrocardiographic interval between the beginning of the Q wave and termination of the T wave representing the time for both ventricular depolarization and repolarization to occur
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate using Fridericia's formula
RR	electrocardiographic interval representing the time measurement between the R wave of one heartbeat and the R wave of the preceding heartbeat
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SEL	selonsertib
SGLT-2i	sodium-glucose co-transporter-2 inhibitors
SI (units)	international system of units
SOC	system organ class
sTNFR1	soluble tumour necrosis factor receptor-1
T2DM	type 2 diabetes mellitus
TEAE	treatment-emergent adverse event
TFLs	tables, figures, and listings
UACR	urine albumin to creatinine ratio
ULN	upper limit of normal
VR	ventricular rate
WHO	World Health Organization

PHARMACOKINETIC ABBREVIATIONS

AUC_{last}	area under the concentration versus time curve from time zero to the last quantifiable concentration
AUC_{tau}	area under the concentration versus time curve over the dosing interval
C_{last}	last observed quantifiable concentration of the drug
C_{max}	maximum observed concentration of drug
C_{tau}	observed drug concentration at the end of the dosing interval
CLss/F	apparent oral clearance after administration of the drug: at steady state: CLss/F = Dose/AUC_{tau} , where "Dose" is the dose of the drug
$t_{1/2}$	estimate of the terminal elimination half-life of the drug, calculated by dividing the natural log of 2 by the terminal elimination rate constant (λ_z)
T_{last}	time (observed time point) of C_{last}
T_{max}	time (observed time point) of C_{max}
λz	terminal elimination rate constant, estimated by linear regression of the terminal elimination phase of the concentration of drug versus time curve

1. INTRODUCTION

This statistical analysis plan (SAP) describes the statistical analysis methods and data presentations to be used in tables, figures, and listings (TFLs) in the clinical study report (CSR) for Study GS-US-223-1017. This SAP is based on the study protocol Amendment 2 dated 13 April 2020 and the electronic case report form (eCRF). The SAP will be finalized before database finalization. Any changes made after the finalization of the SAP will be documented in the CSR.

1.1. Study Objectives

The primary objective of this study is as follows:

- To evaluate whether selonsertib (SEL) can slow the decline in kidney function

The secondary objectives of this study are as follows:

- To evaluate whether SEL can reduce the risk of kidney failure, or reduce the risk of death due to kidney disease in subjects with diabetic kidney disease (DKD)
- To assess the safety and tolerability of SEL in subjects with DKD

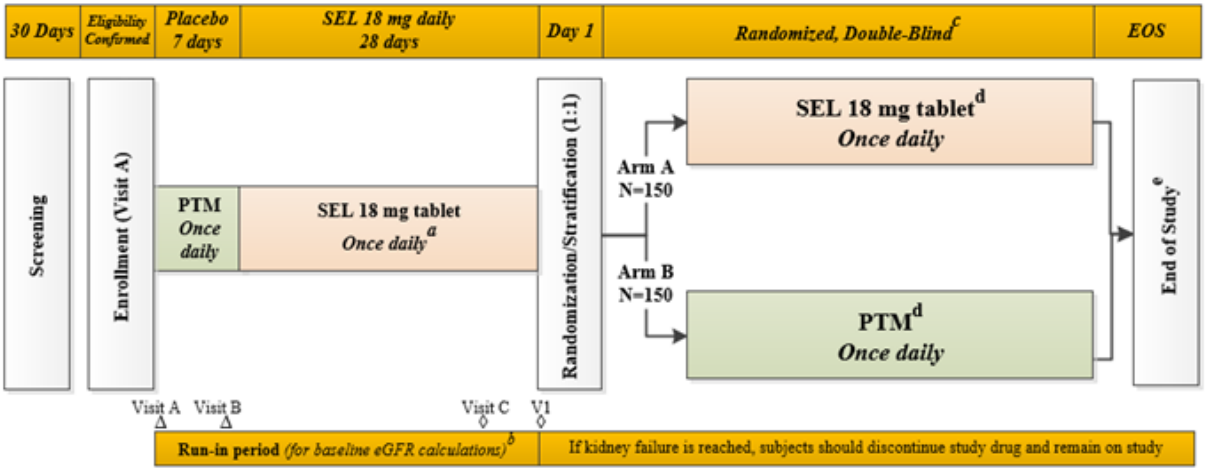
1.2. Study Design

This is a Phase 2b, randomized, double-blind, placebo-controlled, parallel group, multicenter study evaluating the efficacy and safety of SEL in subjects with type 2 diabetes mellitus (T2DM) and moderate to advanced DKD.

Subjects meeting the study's entry criteria after signing the informed consent will enroll into a Run-in period of at least 5 weeks and receive at least one week of placebo to match (PTM) and then SEL (18 mg) for at least 4 weeks. After completing the Run-in period, subjects meeting eligibility will be randomized in a 1:1 ratio to receive SEL (18 mg) or PTM orally once daily. Subjects must be on SEL for at least 7 consecutive doses prior to Visit C and Visit 1 in order to randomize.

The overall study design is presented graphically in Figure 1-1.

Figure 1-1. Study Design Schema



Abbreviations: EOS = End of Study, EOT = End of Treatment, PTM = placebo-to-match to match, SEL= Selonsertib

a Prior to randomization, subjects must have at least 7 consecutive daily doses of study drug immediately prior to Visit C and Randomization (Visit 1)

b Post-run-in Baseline eGFR is defined as the average of Visit C and Visit 1 eGFR values. Pre-run-in Baseline is defined as the average of Visit A and Visit B eGFR values.

c If kidney failure is reached, subjects should discontinue study drug and remain on study.

d If a subject permanently discontinues study drug, there will be a 30 Day EOT Follow-up visit. Subjects who permanently discontinue study drug prior to the global study end date will have an EOT visit and a 30 Day (±7 days) EOT Follow-up visit. Subjects are encouraged to complete all remaining study visits until the global study end date.

e The global study end date will occur when the last randomized subject reaches 48 weeks and/or all subjects on study have completed end of study assessments and the 30 Day EOS Safety Follow-up visit.

Randomization will be stratified by average estimated glomerular filtration rate calculated by CKD-EPI Creatinine Equation (2009) ($eGFR_{cr}$) values from Visit A and Visit B, average urine albumin to creatinine ratio (UACR) values from Visit A and B, and concomitant use of sodium-glucose co-transporter-2 (SGLT-2) inhibitors at Visit 1.

Subjects will continue to receive SEL or PTM in a double-blind fashion until death, study drug discontinuation, kidney failure (dialysis performed for at least 4 weeks, kidney transplantation, or confirmed decrease in eGFR to < 15 mL/min/1.73 m^2 for subjects without dialysis or kidney transplantation), or the global study end date.

1.3. Sample Size and Power

With a sample size of 300 subjects (150 per treatment arm), power to detect a difference in $eGFR_{cr}$ decline rate of 3.7 mL/min/1.73 m^2/year (common SD = 10 mL/min/1.73 m^2/year) between SEL 18 mg and placebo using a two-sample t-test is 99% at a 1-sided significance level of 0.15. Assuming 15% dropout, with a sample size of 254 (127 per arm), the power is 97%.

2. TYPE OF PLANNED ANALYSIS

2.1. Interim Analyses

2.1.1. DMC Analysis

An external multidisciplinary Data Monitoring Committee (DMC) will review the progress of the study and perform interim reviews of the safety data in order to protect subject welfare and preserve study integrity. To ensure the best interests of the participants, the DMC will make recommendations to the sponsor if the nature, frequency, and severity of adverse effects associated with the study treatment warrant the early termination of the study, the continuation of the study, or the continuation of the study with modifications.

The initial review will be conducted after 300 randomized subjects have completed through Week 12 or discontinued from the study. Additional meetings will be scheduled approximately every 6 months.

The DMC's role and responsibilities and the scope of analysis to be provided to the DMC are provided in a mutually agreed upon charter, which defines the DMC membership, meeting logistics, and meeting frequency.

No formal interim efficacy analysis, which may lead to early termination for efficacy or futility, is planned.

2.2. Final Analysis

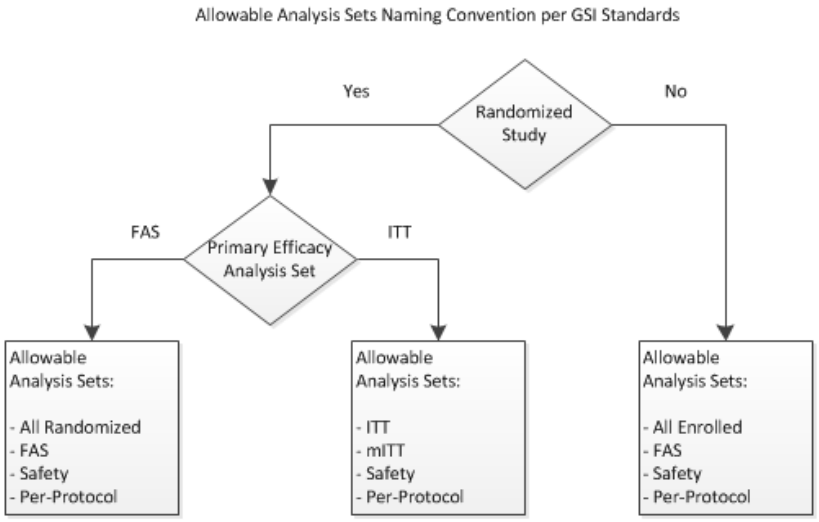
The unblinded final analysis will be performed after all subjects have completed the study, outstanding data queries have been resolved or adjudicated as unresolvable, and the data have been cleaned and finalized. The analysis of the primary endpoint will be conducted at the time of the final analysis and will be tested at 1-sided 0.15 significance level.

3. GENERAL CONSIDERATIONS FOR DATA ANALYSES

Analysis results will be presented using descriptive statistics. For categorical variables, the number and percentage of subjects in each category will be presented; for continuous variables, the number of subjects (n), mean, standard deviation (SD), median, first quartile (Q1), third quartile (Q3), minimum, and maximum will be presented.

By-subject listings will be presented for all subjects in the Safety Analysis Set and sorted by subject ID number, visit date, and time (if applicable). Data collected on log forms, such as AEs, will be presented in chronological order within the subject. For randomized subjects, the treatment group to which subjects were randomized will be used in the listings. Age, sex at birth, race, and ethnicity will be included in the listings, as space permits.

3.1. Analysis Sets



Analysis sets define the subjects to be included in an analysis. Analysis sets and their definitions are provided in this section. Subjects included in each analysis set will be determined before the study blind is broken for analysis. The analysis set will be identified and included as a subtitle of each table, figure, and listing.

For each analysis set, the number and percentage of subjects eligible for inclusion, as well as the number and percentage of subjects who were excluded and the reasons for their exclusion, will be summarized by treatment group.

A listing of reasons for exclusion from analysis sets will be provided by subject.

3.1.1. All Enrolled Analysis Set

The All Enrolled Analysis Set includes all subjects who were enrolled in the study.

3.1.2. All Randomized Analysis Set

The All Randomized Analysis Set includes all subjects who were randomized in the study.

3.1.3. Full Analysis Set

The Full Analysis Set (FAS) includes all subjects who were randomized in the study, and received at least one dose of study drug in the Randomization Phase.

This is the primary analysis set for the primary, secondary CCI efficacy analyses.

3.1.4. Per-Protocol Analysis Set

The Per-protocol (PP) Analysis Set includes subjects who are in the Full Analysis Set, **excluding** subjects who met **any** of the following criteria:

Violated any of the following major inclusion criteria as determined by the Inclusion/Exclusion Criteria CRF page:

1) Male or female between 18 (or ≥ age of majority in each jurisdiction if different than 18) and 80 years of age, inclusive

2) Prior diagnosis of T2DM with diagnostic modalities as per local guidelines. Must have hemoglobin A1c (HbA1c) > 6% within 30 days of Enrollment (Visit A) or be on active treatment for T2DM for at least 6 weeks prior to Enrollment (Visit A)

3) eGFR value calculated by central laboratory utilizing samples collected during Screening and prior to Enrollment (Visit A) of ≥ 20 mL/min/1.73 m² to < 60 mL/min/1.73 m² with albuminuria as measured by UACR

   a) eGFR values will be calculated using the Chronic Kidney Disease Epidemiology (CKD-EPI) Creatinine Equation (2009); UACR will be determined by urine collection, preferably early morning void. Subjects can have up to 3 eGFR and 3 UACR collections during the Screening period. Any one of the eGFR values and any one of the UACR values collected during Screening may be used to satisfy this inclusion criterion. Qualifying eGFR and UACR values do not need to be collected on the same day

   b) eGFR and UACR must meet criteria a, b, or c

Criteria	eGFR (mL/min/1.73 m²)	UACR (mg/g)
A	≥ 45 to < 60	≥ 600 to 5000
B	≥ 30 to < 45	≥ 300 to 5000
C	≥ 20 to < 30	≥ 150 to 5000

4) Treatment with either an angiotensin converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB) as a single agent at the maximum labeled or tolerated dose deemed appropriate for the subject by the investigator and/or per local standard of care for at least 6 weeks prior to Enrollment, with a stable dose for at least 2 weeks prior to Enrollment

    a) Subjects not receiving an ACEi or ARB may be enrolled if there is documented intolerance to ACEi and ARB

    b) Subjects receiving less-than-maximal dose of an ACEi or ARB may be enrolled if there is a documented reason that the maximum labeled dose of ACEi and ARB could not be reached

5) Mean systolic blood pressure (SBP) must be < 160 mmHg and mean diastolic blood pressure (DBP) must be < 100 mmHg taken at two time-points at least five minutes apart within 30 days prior to Enrollment (Visit A)

6) Subjects already receiving SGLT-2 inhibitors must be on a stable dose at least 2 weeks prior to Enrollment

Met any of the following major exclusion criteria as determined by the Inclusion/Exclusion Criteria CRF page:

1) Hemoglobin A1c (HbA1c) > 12.0% within 30 days prior to Enrollment (Visit A)

2) In the investigator's opinion, a condition other than T2DM is the primary etiology of DKD

3) Subjects with diagnosis of type 1 diabetes mellitus (T1DM) or maturity onset diabetes of the young (MODY)

4) Body mass index (BMI) > 50 kg/m^2 at Enrollment (Visit A)

5) UACR > 5000 mg/g on any measurement during Screening

6) End stage kidney disease (ESKD) (i.e., chronic hemodialysis, chronic peritoneal dialysis, or history of kidney transplantation)

7) Anticipated progression to ESKD (need for chronic hemodialysis, chronic peritoneal dialysis or receipt of kidney transplant) within 3 months after Enrollment (Visit A)

8) Unstable cardiovascular (CV) disease as defined by *any* of the following:

    a) Myocardial infarction (MI), coronary artery bypass graft surgery, or coronary angioplasty within 3 months prior to Enrollment (Visit A)

    b) Transient ischemic attack or cerebrovascular accident within 3 months prior to Enrollment (Visit A)

    c) Hospitalization for heart failure within 3 months prior to Enrollment (Visit A)

    d) New York Heart Association (NYHA) Class IV congestive heart failure

9) History of a malignancy within 5 years prior to Enrollment (Visit A). However, the following are not exclusions, and subjects may enroll if there is any history of:

   a) Carcinoma in situ of the cervix, or

   b) Basal or squamous cell cancer or other localized non-melanoma skin cancer that has been adequately treated

10) Requiring chronic administration of prohibited medications as per protocol

Violated any of the following major randomization eligibility criteria as determined by central laboratory data, the Study Drug Administration and Concomitant Medication CRF pages:

1) eGFR $\geq$ 15 mL/min/1.73 m^2 at all central laboratory assessments during the Run-in period prior to the day of Randomization.

2) At least 7 consecutive daily doses of SEL, without interruption, immediately prior to the day of nominal Visit C and prior to the day of nominal Visit 1. If Run-in SEL is taken on the day of nominal Visit C or nominal Visit 1, it will be counted towards the 7 consecutive daily doses of SEL. The day of nominal Visit C (or Visit 1) is the calendar day when Visit C (or Visit 1) was performed.

3) Subject did not initiate, change dose, or discontinue SGLT-2 inhibitor during the Run-in period prior to the day of Randomization and did not initiate, change dose or discontinue SGLT-2 inhibitor within 12 weeks after the day of Randomization.

Had any of the following major protocol deviations:

- Adherence to study drug is less than 80% in the Randomization Phase as determined by the Study Drug Accountability CRF page.

The PP Analysis Set is the secondary analysis set for selected efficacy endpoints.

3.1.5. Safety Analysis Set

The Safety Analysis Set includes all subjects who took at least 1 dose of Run-in SEL. This is the primary analysis set for safety analyses.

CCI [redacted]

CCI [redacted]

CCI [redacted]

3.2. Subject Grouping

For analyses based on the Full Analysis Set, subjects will be grouped according to the treatment to which they were randomized. For analyses based on the PP Analysis Set, subjects will be grouped according to the actual treatment received in the Randomization phase. For exposure-adjusted incidence rate (EAIR) analyses based on the Safety Analysis Set, subjects and events will be grouped according to exposure (SEL or placebo). Please refer to Section 7 for details on EAIR analyses. The actual treatment received will differ from the randomized treatment only when their actual treatment differs from randomized treatment for the entire treatment duration.

For the PK Analysis Set, subjects will be grouped according to the actual treatment they received.

3.3. Strata and Covariates

Subjects will be randomly assigned to treatment groups via the interactive voice or web response system (IXRS) in a 1:1 ratio using a stratified randomization schedule. Stratification will be based on the following variables:

- $eGFR_{cr}$ Strata:

$eGFR_{cr}$ (mL/min/1.73 m²)
≥ 45
≥ 30 to < 45
≥ 15 to < 30

- Albuminuria Strata: UACR < 1500 mg/g vs. ≥ 1500 mg/g
- Concomitant SGLT-2 Inhibitor Use Strata: Yes vs. No

Randomization will be stratified by the average $eGFR_{cr}$ values from Visit A and Visit B; the average values of UACR from Visit A and Visit B; and concomitant use of SGLT-2 inhibitors assessed at Visit 1. Visit A and B values for $eGFR_{cr}$ and Albuminuria will be transferred directly from the central laboratory to the IXRS for stratification but $eGFR_{cr}$ values will not be released to sites, investigators, or the sponsor.

If there are discrepancies in stratification factor values between the IXRS and the clinical database, the values recorded in the clinical database will be used for analyses. Additionally, stratification discrepancies will be reviewed and assessed. Based on the assessment of stratification discrepancies, a sensitivity analysis of the primary endpoint may be performed.

3.4. Examination of Subject Subgroups

Subgroup analyses based on the following Baseline characteristics will be performed for primary and secondary endpoints:

- Age (< 65 years and ≥ 65 years)
- Sex (male and female)
- Race (white and all other races)
- Ethnicity (Hispanic and non-Hispanic)
- Pre-run-in $eGFR_{cr}$ (mL/min/1.73m^2) stratum (>=45, >= 30 to < 45, and >= 15 to < 30)
- Pre-run-in $eGFR_{cr}$ (mL/min/1.73m^2) and UACR (mg/g) stratum (45 <= eGFRcr < 60 and 600 <= UACR < 5000, 30 <= eGFRcr < 45 and 300 <= UACR < 5000, 15 <= eGFRcr < 30 and 150 <= UACR < 5000)
- SGLT-2i use at Randomization (yes and no)
- Glucagon-like peptide-1 receptor agonist (GLP1-RA) use at Randomization (yes and no)
- Pre-run-in Baseline UACR categories (< 1500 mg/g and ≥ 1500 mg/g)
- ACEi or ARB use at Randomization (yes)
- Baseline N-terminal pro-B-type natriuretic peptide (Nt-proBNP) categories (Normal and High Normal)
- Day 1 soluble tumour necrosis factor receptor-1 (sTNFR1) subgroups (<= 4.3 ng/mL and > 4.3 ng/mL)

3.5. Multiple Comparisons

The study has 1 primary efficacy endpoint: $eGFR_{cr}$ slope from treatment-specific Baselines. The primary endpoint and each secondary endpoint will be evaluated at a 1-sided Type 1 error level of 0.15. No formal multiplicity adjustment will be performed. All other efficacy endpoints will also be tested using 1-sided tests at the 0.15 significance level without multiplicity adjustment.

3.6. Missing Data and Outliers

3.6.1. Missing Data

In general, missing data will not be imputed unless methods for handling missing data are specified. Exceptions are presented in this document.

For missing last dosing date of study drug, imputation rules are described in Section 4.2.1. The handling of missing or incomplete dates for AE onset is described in Section 7.1.5.2, and for prior and concomitant medications in Section 7.4.

3.6.2. Outliers

Outliers will be identified during the data management and data analysis process, but no sensitivity analyses will be conducted. All data will be included in the data analysis.

3.7. Data Handling Conventions and Transformations

The following conventions will be used for the imputation of date of birth when it is partially missing or not collected:

- If only month and year of birth is collected, then "15" will be imputed as the day of birth
- If only year of birth is collected, then "01 July" will be imputed as the day and month of birth
- If year of birth is missing, then date of birth will not be imputed.

In general, age collected at Randomization (in years) will be used for analyses and presented in listings. If age at Randomization is not available for a subject, then age derived based on date of birth and the Randomization visit date will be used instead. If an enrolled subject was not randomized, age collected at Enrollment will be used. For screen failures, the date the first informed consent was signed will be used for the age derivation. Age required for longitudinal and temporal calculations and analyses (e.g., estimates of creatinine clearance, age at date of AE) will be based on age derived from date of birth and the date of the measurement or event, unless otherwise specified.

Non-PK data that are continuous in nature but are less than the lower limit of quantitation (LOQ) or above the upper LOQ will be imputed as follows:

- A value that is 1 unit less than the LOQ will be used to calculate descriptive statistics if the datum is reported in the form of "< x" (where x is considered the LOQ). For example, if the values are reported as < 50 and < 5.0, values of 49 and 4.9, respectively, will be used to calculate summary statistics. An exception to this rule is any value reported as < 1 or < 0.1, etc. For values reported as < 1 or < 0.1, a value of 0.9 or 0.09, respectively, will be used to calculate summary statistics.
- A value that is 1 unit above the LOQ will be used to calculate descriptive statistics if the datum is reported in the form of "> x" (where x is considered the LOQ). Values with decimal points will follow the same logic as above.
- The LOQ will be used to calculate descriptive statistics if the datum is reported in the form of "≤ x" or "≥ x" (where x is considered the LOQ).

If methods based on the assumption that the data are normally distributed are not adequate, analyses may be performed on transformed data or nonparametric analysis methods may be used, as appropriate.

Sparse PK concentration values that are below the limit of quantitation (BLQ) will be presented as "BLQ" in the data listing.

Natural logarithm transformation will be used for analyzing concentrations and PK parameters in intensive PK samples. Concentration values that are BLQ will be presented as "BLQ" in the concentration data listing. Values that are BLQ will be treated as 0 at predose time points, and one-half the value of the LOQ at postdose time points for summary purposes.

The following conventions will be used for the presentation of summary and order statistics for intensive PK concentrations:

- If at least 1 subject has a concentration value of BLQ for the time point, the minimum value will be displayed as "BLQ."
- If more than 25% of the subjects have a concentration data value of BLQ for a given time point, the minimum and Q1 values will be displayed as "BLQ."
- If more than 50% of the subjects have a concentration data value of BLQ for a given time point, the minimum, Q1, and median values will be displayed as "BLQ."
- If more than 75% of the subjects have a concentration data value of BLQ for a given time point, the minimum, Q1, median, and Q3 values will be displayed as "BLQ."
- If all subjects have concentration data values of BLQ for a given time point, all order statistics (minimum, Q1, median, Q3, and maximum) will be displayed as "BLQ."

PK parameters that are BLQ will be imputed as one-half LOQ before log transformation or statistical model fitting.

3.8. Analysis Visit Windows

3.8.1. Definition of Study Day

Study Day will be calculated from the first dosing date of blinded SEL/placebo treatment and derived as follows:

- For postdose study days: Assessment Date – First Blinded SEL/placebo Dosing Date + 1
- For days prior to the first dose: Assessment Date – First Blinded SEL/placebo Dosing Date

Therefore, Study Day 1 is the day of first dose of blinded SEL/placebo administration.

3.8.2. Analysis Visit Windows

Subject visits might not occur on protocol-specified days. Therefore, for the purpose of analysis, observations will be assigned to analysis windows.

3.8.2.1. Analysis Visit Windows for the Run-in Phase

The analysis windows for the Run-in phase will be defined based on nominal visit date, as detailed in Table 3-1.

Table 3-1. Analysis Visit Windows for Visits in the Run-in Phase

Nominal Visit	Analysis Visit Window Definition	
	Lower Limit	Upper Limit
Visit A	None	Earlier of (Nominal Visit **B** date – 4, Run-in SEL first dosing date – 1)
Visit B	Earlier of (Nominal Visit B date – 3, Run-in SEL first dosing date)	Run-in SEL first dosing date
Visit C	Run-in SEL first dosing date + 1	For randomized subjects: Earlier of (Nominal Visit C date + 5, DB SEL/placebo first dosing date – 1) For not randomized subjects: None

3.8.2.2. Analysis Visit Windows for the Randomization Phase

The analysis windows are provided in Table 3-2 through Table 3-4.

Table 3-2. Analysis Visit Windows for eGFR, UACR, Vital Signs, Hematology Tests, Chemistry Tests and Pregnancy Tests in the Randomization Phase

Nominal Visit	Nominal Study Day	Visit Window Study Day	
		Lower Limit	Upper Limit
Day 1	1	Earlier of (Nominal Visit C date + 6, Study Day 1)	1
Week 4	29	2	43
Week 8	57	44	71
Week 12	85	72	127
Week 24	169	128	211
Week 36	253	212	295
Week 48	337	296	379
Week 60	421	380	463
Week 72	505	464	547
Week 84	589	548	631
Week 96	673	632	715
Week 108	757	716	799
Week 120	841	800	883
Week 132	925	884	967
Week 144	1009	968	1051
Week 156	1093	1052	1135
Week 168	1177	1136	1219

For $eGFR_{cr}$ and $eGFR_{cys}$ based on the CKD-EPI creatinine 2009 and CKD-EPI cystatin C 2012 equations, the analysis visit windows will be the same as in Table 3-2.

Table 3-3. Analysis Visit Windows for HbA1c in the Randomization Phase

Nominal Visit	Nominal Study Day	Visit Window Study Day	
		Lower Limit	Upper Limit
Day 1	1	Earlier of (Nominal Visit C date + 6, Study Day 1)	1
Week 24	169	2	239
Week 48	337	240	379
Week 60	421	380	463
Week 72	505	464	547
Week 84	589	548	631
Week 96	673	632	715
Week 108	757	716	799
Week 120	841	800	883
Week 132	925	884	967
Week 144	1009	968	1051
Week 156	1093	1052	1135
Week 168	1177	1136	1219

Table 3-4. Analysis Visit Windows for Insulin, Lipid, c-peptide, Nt-proBNP, cTnI, CRP, sTNFR1, Waist Circumference, ECG, KDQOL-36, KCCQ, Work Productivity and Activity Impairment, and Sit-to-Stand Tests in the Randomization Phase

Nominal Visit	Nominal Study Day	Visit Window Study Day	
		Lower Limit	Upper Limit
Day 1	1	Earlier of (Nominal Visit C date + 6, Study Day 1)	1
Week 48	337	2	None

3.8.3. Selection of Data in the Event of Multiple Records in an Analysis Visit Window

Depending on the statistical analysis method, single values may be required for each analysis window. For example, change from Baseline by visit usually requires a single value, whereas a time-to-event analysis would not require 1 value per analysis window.

If multiple valid, nonmissing measurements exist in an analysis window, records will be chosen based on the following rules if a single value is needed:

- For pre-SEL-treatment values (Visit A and Visit B):
  - In general, the last nonmissing value on or prior to the first dosing date of Run-in SEL will be selected, unless specified differently. If there are multiple records with the same time or no time recorded on the same day, the Baseline value will be the average of the measurements for continuous data, or the measurement with the lowest severity (e.g., normal will be selected over abnormal for safety electrocardiogram (ECG) findings) for categorical data.
  - For $eGFR_{cr}$, $eGFR_{cys}$, UACR (including urine albumin, urine creatinine), serum creatinine and serum cystatin C, a single value within each of the Visit A and/or Visit B analysis window will be used to calculate pre-run-in and/or post-run-in Baselines.
    - Within each analysis window, the latest record will be selected.
    - If there is more than 1 record on the selected day, the record with the latest time will be selected. If all records have the same time, or time is missing for at least one record, the average will be taken.
- For post-SEL-treatment values (Visit C, Day 1 and post-Randomization visits):
  - The record closest to the nominal day for that visit will be selected.
  - If there are 2 records that are equidistant from the nominal day, the later record will be selected.
  - If there is more than 1 record on the selected day, the record with the latest time will be selected. If all records have the same time, or time is missing for at least one record, the average will be taken.

Definition of pre-run-in Baseline: The average of the measurements at Visit A and Visit B.

Definition of post-run-in Baseline: The average of the measurements at Visit C and Day 1.

Definition of treatment-specific Baselines: For subjects in the placebo arm, Baseline is defined as pre-run-in Baseline. For subjects in the SEL arm, Baseline is defined as post-run-in Baseline.

4. SUBJECT DISPOSITION

4.1. Subject Enrollment and Disposition

A summary of subject enrollment will be provided by randomization status and treatment group for each country, investigator within a country, and overall. The summary will present the number and percentage of subjects enrolled. For each column, the denominator for the percentage calculation will be the total number of subjects analyzed for that column.

A table will be provided to summarize discrepancies in the value used for stratification assignment between the IXRS and the clinical database. The denominator for the percentage of subjects in the stratum will be the total number of randomized subjects. A listing of subjects with discrepancies in the value used for stratification assignment between the IXRS and the clinical database at the time of data finalization will be provided.

The randomization schedule used for the study will be provided as an appendix to the CSR.

A summary of subject disposition will be provided by randomization status and treatment group. This summary will present the number of subjects screened, the number of subjects enrolled, the number of subjects randomized, and the number of subjects in each of the categories listed below:

- All Enrolled Analysis Set
- Safety Analysis Set
- All Randomized Analysis Set
- Full Analysis Set
- Of subjects in the All Enrolled Analysis Set:
  - Completed study drug
  - Did not complete study drug with reasons for premature discontinuation of study drug
  - Completed study
  - Did not complete study with reasons for premature discontinuation of study

For the status of study drug and study completion and reasons for premature discontinuation, the number and percentage of subjects in each category will be provided. The denominator for the percentage calculation will be the total number of subjects in the All Enrolled Analysis Set corresponding to that column. In addition, a flowchart will be provided to depict the disposition.

A by-subject listings of reasons for premature discontinuation of study drug will be provided by subject identification (ID) number in ascending order. A similar listing of reasons for study discontinuation will also be provided.

4.2. Extent of Study Drug Exposure and Adherence

Extent of exposure to study drug will be examined by assessing the total duration of exposure to study drug and the level of adherence relative to the study drug regimen specified in the protocol.

4.2.1. Duration of Exposure to Study Drug

Total duration of exposure to study drug will be defined as last dosing date minus first dosing date plus 1, regardless of any temporary interruptions in study drug administration, and will be expressed in weeks using up to 1 decimal place (e.g., 4.5 weeks).

If the last study drug dosing date is missing or partial (month and year available or only year available), the following rules will be used to impute the last dosing date:

For the purpose of calculating the duration of exposure, the last contact date is the latest clinical visit date (including follow-up phone calls when the site was able to reach the subject), laboratory sample collection date, or vital signs assessment date collected in the study.

If the last study drug dosing date is missing, then the last contact date will be used.

If the last study drug dosing date is partial:

- If the month and year are the same as the month and year of the last contact date (defined as above), then the last contact date will be used.
- If the month and year are earlier than the month and year of the last contact date, the last day of the month (or the last day of the year if only year is available) will be used.
- There should not be any partial dosing date with the month and year later than the month and year of the last contact date.

The total duration of exposure to study drug will be summarized using descriptive statistics and using the number (i.e., cumulative counts) and percentage of subjects exposed through the following time periods: 1 day, 4 weeks, 8 weeks, and every 4 weeks after Week 8. Summaries will be provided by treatment group (for randomized subjects) and overall for the Safety Analysis Set, for Run-in and Randomization Phases separately.

No formal statistical testing is planned.

4.2.2. Adherence to Study Drug

In this study, the subjects will orally take 1 tablet of the study drug daily. The total number of tablets administered will be summarized using descriptive statistics.

The presumed total number of tablets administered to a subject will be determined by the data collected on the drug accountability CRF using the following formula:

$$\text{Total Number of Tablets Administered} = \left(\sum \text{No. of Tablets Dispensed}\right) - \left(\sum \text{No. of Tablets Returned}\right)$$

4.2.2.1. On-Treatment Adherence

The level of on-treatment adherence to the study drug regimen will be determined by the total amount of study drug administered relative to the total amount of study drug expected to be administered during a subject's actual on-treatment period based on the study drug regimen.

The level of on-treatment adherence will be expressed as a percentage using the following formula:

$$\text{On-Treatment Adherence (\%)} = \left(\frac{\text{Total Amount of Study Drug Administered}}{\text{Study Drug Expected to be Administered on Treatment}}\right) \text{x } 100$$

Descriptive statistics for the level of on-treatment adherence with the number and percentage of subjects belonging to adherence categories (e.g., {< 75%, ≥ 75 to < 90%, ≥ 90%}) will be provided by treatment group for the Safety Analysis Set.

No formal statistical testing is planned.

A by-subject listing of study drug administration and drug accountability will be provided by subject ID number (in ascending order) and visit (in chronological order).

4.3. Protocol Deviations

Subjects who did not meet the eligibility criteria for study entry but enrolled in the study will be summarized regardless of whether they were exempted by the sponsor or not. The summary will present the number and percentage of subjects who did not meet at least 1 eligibility criterion and the number of subjects who did not meet specific criteria by randomization status and treatment group based on the All Enrolled Analysis Set. A by-subject listing will be provided for those subjects who did not meet at least 1 eligibility (inclusion or exclusion) criterion and enrolled. The listing will present the eligibility criterion (or criteria if more than 1 deviation) that subjects did not meet and related comments, if collected.

A by-subject listing will also be provided for subjects who did not meet at least 1 randomization eligibility criterion and randomized. The listing will present the eligibility criterion (or criteria if more than 1 deviation) that subjects did not meet and related comments, if collected.

Protocol deviations occurring after subjects entered the study are documented during routine monitoring. The number and percentage of subjects with important protocol deviations by deviation reason (e.g., nonadherence to study drug, violation of select inclusion/exclusion criteria) will be summarized by treatment group and randomization status for the Safety Analysis Set. A by-subject listing will be provided for those subjects with important protocol deviations.

4.4. Assessment of COVID-19 Impact

This study was ongoing during the coronavirus disease 2019 (COVID-19) pandemic which has an impact on the study conduct. Some subjects were unable to attend onsite visits due to shelter in place guidelines, site closures, or other reasons. This section describes how special situations due to COVID-19 will be handled in the analysis.

4.4.1. Study Drug or Study Discontinuation Due to COVID-19

A by-subject listing of reasons for premature study drug or study discontinuation due to COVID-19 will be provided.

4.4.2. Protocol Deviations Due to COVID-19

A by-subject listing will be provided for subjects with important protocol deviations related to COVID-19. A separate listing will be provided for subjects with non-important protocol deviations related to COVID-19.

4.4.3. Missed and Virtual Visits due to COVID-19

A summary of subjects affected by the COVID-19 pandemic will be provided for each scheduled study visit by treatment group and overall. For each visit, the summary will present the number and percentage of subjects who missed the visit due to COVID-19 or had a virtual visit due to COVID-19. For each column, the denominator for the percentage calculation will be the total number of subjects in the Safety Analysis Set for that column.

An overall summary of the number and percentage of subjects with missed or virtual visits (e.g., at least 1, with 1, 2, 3 or more visits) due to COVID-19 will be provided by treatment group and overall. The denominator for the percentage calculation will be the total number of subjects in the safety population for that column.

A by-subject listing of subjects with missed or virtual visits due to COVID-19 will be provided by subject ID number in ascending order.

Information regarding missed or virtual visits due to COVID-19 will be collected as free text in the CRF comment fields. The determination of missed or virtual visits due to COVID-19 will be done using Natural Language Processing (NLP) to search the CRF comment fields. A detailed explanation of the algorithm is given in Appendix 4.

4.4.4. Adverse Events Due to COVID-19

AEs of COVID-19 will be included in analyses of AEs if applicable, which will be determined through COVID-19 SMQ narrow search. A by-subject listing of AEs of COVID-19 will be provided if applicable.

4.4.5. Overall Assessment of COVID-19 Pandemic Impact

For subjects affected by COVID-19 infection and/or pandemic while participating in the study, a listing of the following individual COVID-19 related outcome categories will be provided:

- Death due to COVID-19
- Adverse event of COVID-19, as determined by COVID-19 SMQ narrow search
- Hospitalization (using data from AE eCRF) due to adverse event of COVID-19 as defined above
- Tested positive for COVID-19
- Study drug discontinuation due to COVID-19
- Study discontinuation due to COVID-19
- Missed visits due to COVID-19
- Missed key assessments due to COVID-19 (Key assessments are the central lab assessments of serum creatinine and/or serum cystatin C)

In addition, composite broad COVID-19 impact indicator will be derived based on the following individual categories defined above: death, adverse event, hospitalization, tested positive, study drug discontinuation, study discontinuation, missed visits, and missed key assessments. Composite specific COVID-19 impact indicator will be derived based on death and tested positive.

5. BASELINE CHARACTERISTICS

5.1. Demographics and Baseline Characteristics

Subject demographic variables (i.e., age, sex, race, and ethnicity) and Baseline characteristics (body weight [in kg], height [in cm], body mass index [BMI; in kg/m^2], systolic blood pressure, diastolic blood pressure, heart rate, ACEi or ARB medication use, and other variables of interest) will be summarized.

Demographic and Baseline characteristics will be summarized by randomized status, treatment group and overall using descriptive statistics (n, mean, SD, median, Q1, Q3, minimum, and maximum) for continuous variables and using number and percentage of subjects for categorical variables. For Baseline body weight, height, and BMI, descriptive statistics will also be presented by sex in the same table. The summary of demographic data will be provided for the Safety Analysis Set. No formal statistical testing is planned.

A by-subject demographic listing, including the informed consent date, will be provided by subject ID number in ascending order.

5.2. Other Baseline Characteristics

Other Baseline characteristics include serum creatinine, serum cystatin C, $eGFR_{cr}$, $eGFR_{cys}$, UACR, stage of disease (defined by $eGFR_{cr}$ and UACR), blood urea nitrogen, potassium, calcium, phosphorus, bicarbonate, fasting blood glucose, fasting blood insulin, and HbA1c. These Baseline characteristics will be summarized by randomization status, treatment group and overall using descriptive statistics (n, mean, SD, median, Q1, Q3, minimum, and maximum) for continuous variables and using number and percentage of subjects for categorical variables. The summary of these Baseline characteristics will be provided for the Safety Analysis Set. No formal statistical testing is planned.

A by-subject listing of other Baseline characteristics will be provided by subject ID number in ascending order.

5.3. Medical History

Medical history will be collected at screening for disease-specific and general conditions (i.e., conditions not specific to the disease being studied).

Disease-specific medical history will be summarized by treatment group and overall by the number and percentage of subjects with each prepopulated condition. A summary of disease-specific medical history will be provided for the Safety Analysis Set. No formal statistical testing is planned.

General medical history data will not be coded but will be listed only.

6. EFFICACY ANALYSES

6.1. Primary Endpoint

6.1.1. Definition of the Primary Endpoint

The primary efficacy endpoint of this study is $eGFR_{cr}$ slope from treatment-specific Baselines through Week 84. The values for $eGFR_{cr}$ will be calculated using the CKD-EPI Creatinine Equation (2009):

$$eGFR = 141 \times \min\left(\frac{S_{cr}}{\kappa}, 1\right)^{\alpha} \times \max\left(\frac{S_{cr}}{\kappa}, 1\right)^{-1.209} \times 0.993^{Age} \times 1.018[if\ female] \times 1.159[if\ Black]$$

S_{cr} = standardized serum creatinine (mg/dL)
κ = 0.7 (females) or 0.9 (males)
α = -0.329 (females) or -0.411 (males)
min indicates the minimum of S_{cr}/κ or 1
max indicates the maximum of S_{cr}/κ or 1
age in years

6.1.2. Statisical Hypothesis of the Primary Endpoint

The primary analysis will test the following null hypothesis (H_0) that there is no difference in $eGFR_{cr}$ slope from treatment-specific Baselines between SEL and placebo versus the alternative hypothesis (H_1) that $eGFR_{cr}$ slope in the SEL arm is larger than that in the placebo arm. Formally,

$$H_0{:}\beta_{SEL} = \beta_{PBO}\ vs.\ H_1{:}\beta_{SEL} > \beta_{PBO}$$

where β_{SEL} and β_{PBO} denote the mean slope from treatment-specific Baselines for SEL and placebo, respectively.

Statistical testing will be conducted at a 1-sided Type 1 error level of 0.15.

6.1.3. Analysis of the Primary Endpoint

The Primary Analysis Set for efficacy analyses is the Full Analysis Set.

Definition of Baseline

Baseline $eGFR_{cr}$ for the primary analysis is defined as below:

- SEL arm: The average of the measurements at Visit C and Visit 1. This Baseline will also be referred to as post-run-in Baseline.

- Placebo arm: The average of the measurements at Visit A (enrollment) and Visit B. This Baseline will also be referred to as pre-run-in Baseline.

Estimand

The Treatment Policy estimand is defined as follows. This is the primary estimand for the primary endpoint.

1) Population: Subjects in the FAS. See definition of the FAS in Section 3.1.3.

2) Variable: Primary endpoint ($eGFR_{cr}$ slope from treatment-specific Baselines through Week 84). See Section 6.1.1 for detailed definition of the primary endpoint.

3) Intercurrent events: Intercurrent events for this study include study treatment discontinuation and/or starting a concomitant medication (e.g. SGLT-2 inhibitors).

   The occurrence of an intercurrent event is irrelevant. All observed values will be used regardless of occurrence of an intercurrent event.

   - All observed values will be used regardless of occurrence of an intercurrent event (i.e, All available data defined above)

   - If a subject is lost to follow up, treat data as missing from the point of loss to follow-up onward

4) Population-level summary: $eGFR_{cr}$ slope from treatment-specific Baselines through Week 84 in each treatment arm, and difference in $eGFR_{cr}$ slope from treatment-specific Baselines through Week 84 between SEL and placebo treatment arms.

Main Estimator

A random slope model will be used to evaluate SEL treatment effect on $eGFR_{cr}$ slope from treatment-specific Baselines through Week 84. The random slope model will have $eGFR_{cr}$ change from treatment-specifc Baselines at Weeks 4, 8, 12, 24, 36, 48, 60, 72 and 84 as outcome, and will include terms for $eGFR_{cr}$ at treatment-specific Baselines as a continuous variable, pre-run-in Baseline UACR category (< 1500 mg/g vs. ≥ 1500 mg/g), concomitant use of SGLT-2 inhibitors at Randomization, treatment group, week, and treatment-by-week interaction. Within-subject variance covariance will be modeled as unstructured. If model convergence problems arise, other variance-covariance structures, such as Heterogeneous Toeplitz, will be considered and documented.

Sensitivity analyses of the $eGFR_{cr}$ slope endpoint will include the following:

- Sensitivity analysis of $eGFR_{cr}$ slope excluding off-treatment $eGFR_{cr}$ values from the SEL treatment group.

- Sensitivity analysis of $eGFR_{cr}$ slope excluding $eGFR_{cr}$ values collected after the initiation of dialysis or kidney transplantation.

- Sensitivity analysis to evaluate the impact of attenuation of the acute effect. For subjects in the SEL group, the on-treatment $eGFR_{cr}$ values will be adjusted using a regression model as described in Appendix 2, which takes into account attenuation of the acute treatment effect that may be due to the theoretical concern for loss of kidney function over time. For subjects in the placebo group, the observed $eGFR_{cr}$ values will be used. The analysis of $eGFR_{cr}$ slope will be performed using the same model as described in the primary analysis, except that pre-run-in Baseline $eGFR_{cr}$ will be used for both SEL and placebo arms.

- Sensitivity analysis of $eGFR_{cr}$ slope in subjects who completed study treatment.

- Sensitivity analysis of $eGFR_{cr}$ slope excluding subjects with randomization stratification mismatch between IXRS and Clinical Database.

- Sensitivity analysis of $eGFR_{cr}$ slope excluding subjects who took prohibited medications that may affect SEL efficacy or decrease SEL drug level in the prohibited period as detailed in Appendix 3.

- Sensitivity analysis of $eGFR_{cr}$ slope from pre-run-in Baseline for both SEL and placebo arms.

- Sensitivity analysis of $eGFR_{cr}$ slope from treatment-specific Baselines through Week 48.

- Sensitivity analysis of $eGFR_{cr}$ slope from treatment-specific Baselines through Week 60.

- Sensitivity analysis of $eGFR_{cr}$ slope from treatment-specific Baselines through Week 72.

- Sensitivity analysis of $eGFR_{cr}$ slope from treatment-specific Baselines through Week 96.

6.2. Secondary Endpoints

6.2.1. Definition of Secondary Endpoints

Secondary endpoints for this study are:

- Proportion of Kidney Clinical Events defined as any of the following events:

  — Confirmed ≥ 40% decline in $eGFR_{cr}$ from pre-run-in Baseline, or

  — Kidney failure (dialysis performed for at least 4 weeks, kidney transplantation, or confirmed decrease in $eGFR_{cr}$ to < 15 mL/min/1.73 m^2 for subjects without dialysis or kidney transplantation), or

  — Death due to kidney disease

The ≥ 40% decline in $eGFR_{cr}$ from Baseline and sustained decrease in $eGFR_{cr}$ to <15 mL/min/1.73 m^2 components need to be confirmed at the next scheduled visit but at least 4 weeks after the index measurement (i.e., the first measurement of ≥ 40% decline in $eGFR_{cr}$ from Baseline or $eGFR_{cr}$ < 15 mL/min/1.73 m^2). Events of $eGFR_{cr}$ decline ≥ 40% from Baseline or $eGFR_{cr}$ < 15 mL/min/1.73 m^2 without confirmation due to study discontinuation (e.g., death or lost to follow-up) will be included in the analysis and counted as events. Date of the index measurement will be used as the date of event in the analysis.

- Time from randomization to first occurrence of a Kidney Clinical Event

  If a subject has not experienced any Kidney Clinical Events at the time of global study end date/early discontinuation of the study, this subject will be censored at the time of the last assessment of kidney function.

- $eGFR_{cys}$ slope from pre-run-in Baseline through Week 84

  The values for $eGFR_{cys}$ will be calculated using the CKD-EPI Cystatin C Equation (2012):

$$eGFR = 133 \times \min\left(\frac{S_{cys}}{0.8}, 1\right)^{-0.499} \times \max\left(\frac{S_{cys}}{0.8}, 1\right)^{-1.328} \times 0.996^{Age} \times 0.932[if\ female]$$

$S_{cys} =$ standardized serum cystatin C (mg/L)
min indicates the minimum of $S_{cys}/0.8$ or 1
max indicates the maximum of $S_{cys}/0.8$ or 1
age in years

6.2.2. Analysis of Secondary Endpoints

The Secondary Analysis Set for efficacy analyses is the Full Analysis Set.

6.2.2.1. Analysis of proportion of Kidney Clinical Events

Number and proportion of subjects who experience a Kidney Clinical Event will be summarized by treatment group. Number and proportion of subjects who experienced each component of the Kidney Clinical Events will also be summarized by treatment group. 95% exact CI based on the Santner-Snell method (Santner and Snell, 1980) will be presented for the difference in proportions between SEL and placebo arms for the Kidney Clinial Events endpoint, as well as each component of the Kidney Clinical Events.

P-value based on the Cochran-Mantel-Haenszel (CMH) approach adjusting for randomization stratification factors will be reported for the comparison of proportion of Kidney Clinical Events between treatment arms. In addition, p-value based on Fisher's exact test without adjusting for randomization stratification factors will also be reported. P-values will not be reported for the comparison of each component of the Kidney Clinical Events endpoint between treatment arms.

Subjects who do not have sufficient measurements to determine whether or not they had a Kidney Clinical Event will be considered not having a Kidney Clinical Event.

6.2.2.2. Analysis of time from randomization to a Kidney Clinical Event

A stratified log-rank test stratified by randomization stratification factors will be used to evaluate SEL treatment effect on time from randomization to a Kidney Clinical Event. Hazard ratio (HR) and 95% CI comparing the SEL and placebo arms will be estimated using a stratified Cox proportional hazard model, stratified by randomization stratification factors. Number and percent of subjects with event per treatment group, event rate, HR, 95% CI and p-value will be presented for analysis of time to the first Kidney Clinical Event, and time to each component of the Kidney Clinical Event endpoint. HR and 95% CI will only be reported for outcomes with more than 10 events, and have at least 1 event in each treatment arm. Event rate will be calculated as the number of subjects with the event, divided by the total duration of follow-up across all subjects in a given treatment group. Follow-up time for each subject will be calculated as time from Randomization to the earliest of study completion, premature study discontinuation, death and event of interest for a given outcome.

Sensitivity analyses will be performed based on different definition of events or population.

The same approaches as described in Sections 6.2.2.1 and 6.2.2.2 will be used for hypothesis testing for Kidney Clinical Events for the following:

- Sensitivity analysis where in the SEL group, a 40% reduction in $eGFR_{cr}$ will be calculated from the pre-run-in Baseline $eGFR_{cr}$ for off-treatment $eGFR_{cr}$ values and the post-run-in Baseline $eGFR_{cr}$ for on-treatment $eGFR_{cr}$ values.

- Sensitivity analysis to use treatment-specific Baselines to calculate $eGFR_{cr}$ percent decline. For all $eGFR_{cr}$ values in the SEL group, a 40% reduction in $eGFR_{cr}$ will be calculated using the post-run-in Baseline $eGFR_{cr}$.

- Sensitivity analysis to evaluate the impact of attenuation of the acute effect. For subjects in the SEL group, the on-treatment $eGFR_{cr}$ values will be adjusted using a regression model as described in Appendix 2, which takes into account attenuation of the acute treatment effect that may be due to the theoretical concern for loss of kidney function over time. This adjusted on-treatment $eGFR_{cr}$ value will be compared with the pre-run-in Baseline $eGFR_{cr}$ to calculate an adjusted percent $eGFR_{cr}$ reduction. For subjects in the placebo group, percent $eGFR_{cr}$ reduction will be calculated by comparing observed $eGFR_{cr}$ values with the pre-run-in Baseline $eGFR_{cr}$.

- Sensitivity analysis in subjects who completed study treatment.

- Sensitivity analysis excluding subjects with randomization stratification mismatch between IXRS and Clinical Database.

- Sensitivity analysis excluding subjects who took prohibited medications that may affect SEL efficacy or decrease SEL drug level in the prohibited period as detailed in Appendix 3.

- Sensitivity analysis where a 57% reduction in $eGFR_{cr}$ from pre-run-in Baseline will be used for the $eGFR_{cr}$ reduction component of the Kidney Clinical Events instead of 40% reduction.

- Sensitivity analysis for the Kidney Clinical Events based on $eGFR_{cys}$. The Kidney Clinical Events endpoint will have the same definition as in Section 6.2.1, except that the eGFR reduction and eGFR < 15 components will be based on $eGFR_{cys}$ instead of $eGFR_{cr}$.

The same approaches as described in Sections 6.2.2.1 only will be used for hypothesis testing for Kidney Clinical Events for the following:

- The proportion of Kidney Clinical Events by Week 48 will be compared between SEL and placebo treatment arms. Subjects who do not have sufficient measurements to determine whether or not they had a Kidney Clinical Event by Week 48 will be considered not having a Kidney Clinical Event by Week 48.

6.2.2.3. Analysis of $eGFR_{cys}$ slope from pre-run-in Baseline

A random slope model will be used to evaluate SEL treatment effect on $eGFR_{cys}$ slope from pre-run-in Baseline through Week 84. The random slope model will have change in $eGFR_{cys}$ values from pre-run-in Baseline at Weeks 4, 8, 12, 24, 36, 48, 60, 72, and 84 as outcome, and will include terms for pre-run-in Baseline $eGFR_{cys}$ as a continuous variable, pre-run-in Baseline UACR category (< 1500 mg/g vs. ≥ 1500 mg/g), concomitant use of SGLT-2 inhibitors at Randomization, treatment group, week, and treatment-by-week interaction. Within-subject variance covariance will be modeled as unstructured. If model convergence problems arise, other variance-covariance structures, such as Heterogeneous Toeplitz, will be considered and documented.

Sensitivity analyses of the $eGFR_{cys}$ slope endpoint will include the following:

- Sensitivity analysis of $eGFR_{cys}$ slope excluding $eGFR_{cys}$ values collected after the initiation of dialysis or kidney transplantation.

- Sensitivity analysis of $eGFR_{cys}$ slope in subjects who completed study treatment.

- Sensitivity analysis of $eGFR_{cys}$ slope excluding subjects with randomization stratification mismatch between IXRS and Clinical Database.

- Sensitivity analysis of $eGFR_{cys}$ slope excluding subjects who took prohibited medications that may affect SEL efficacy or decrease SEL drug level in the prohibited period as detailed in Appendix 3.

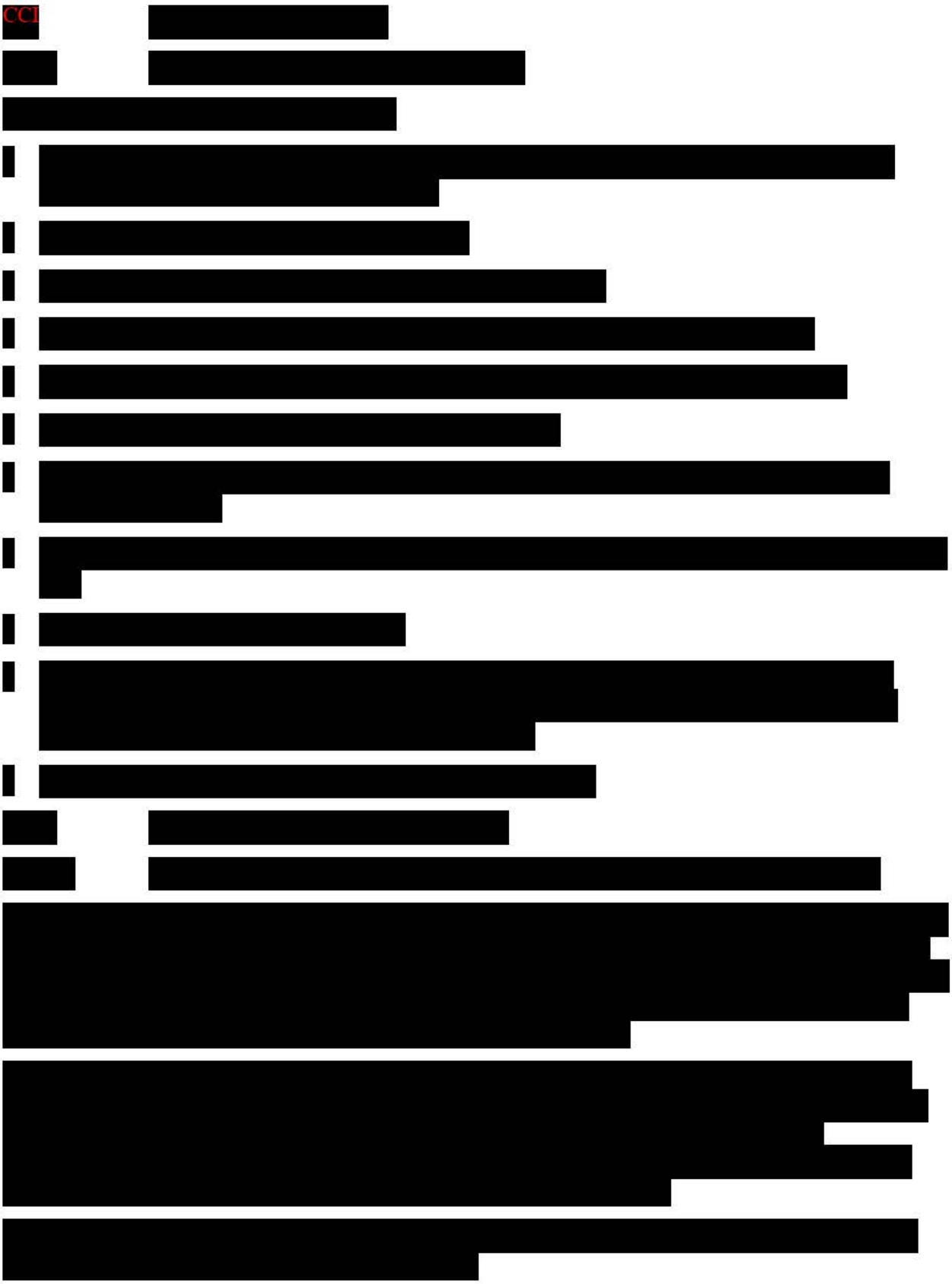
- Sensitivity analysis of $eGFR_{cys}$ slope from pre-run-in Baseline through Week 48.

- Sensitivity analysis of $eGFR_{cys}$ slope from pre-run-in Baseline through Week 60.

- Sensitivity analysis of $eGFR_{cys}$ slope from pre-run-in Baseline through Week 72.

- Sensitivity analysis of $eGFR_{cys}$ slope from pre-run-in Baseline through Week 96.

CCI



CCI [redacted]

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

CCI [redacted]

[redacted]

[redacted]

7. SAFETY ANALYSES

Unless otherwise specified, summaries of safety data will be provided for the Safety Analysis Set and will include data collected up to the last dose of study drug plus 30 days.

7.1. Adverse Events and Deaths

7.1.1. Adverse Event Dictionary

Clinical and laboratory adverse events (AEs) will be coded using the current version of MedDRA. System organ class (SOC), high-level group term (HLGT), high-level term (HLT), preferred term (PT), and lower-level term (LLT) will be provided in the AE dataset.

7.1.2. Adverse Event Severity

Adverse events are graded by the investigator as Grade 1, 2, 3, 4, or 5 according to toxicity criteria specified in the protocol. The severity grade of events for which the investigator did not record severity will be categorized as "missing" for tabular summaries and data listings. The missing category will be listed last in summary presentation.

7.1.3. Relationship of Adverse Events to Study Drug

Related AEs are those for which the investigator selected "Related" on the AE CRF to the question of "Related to Study Treatment." Relatedness will always default to the investigator's choice, not that of the medical monitor. Events for which the investigator did not record relationship to study drug will be considered related to study drug for summary purposes. However, by-subject data listings will show the relationship as missing.

7.1.4. Serious Adverse Events

Serious adverse events (SAEs) will be identified and captured as SAEs if the AEs met the definitions of SAEs that were specified in the study protocol. SAEs captured and stored in the clinical database will be reconciled with the SAE database from the Gilead Global Patient Safety (GLPS) Department before data finalization.

7.1.5. Treatment-Emergent Adverse Events

7.1.5.1. Definition of Treatment-Emergent Adverse Events

Treatment-emergent adverse events (TEAEs) are defined as follows for SEL and placebo exposures, respectively.

- SEL exposure: TEAEs are defined as 1 or both of the following:
  - Any AEs with an onset date on or after the Run-in SEL start date and no later than 30 days after permanent discontinuation of SEL
  - Any AEs leading to premature discontinuation of SEL

- Placebo exposure: TEAEs are defined as any AEs with an onset date on or after Study Day 31 (30 days after the Randomized placebo start date) and no later than 30 days after permanent discontinuation of Randomized placebo

7.1.5.2. Incomplete Dates

If the onset date of an AE is incomplete and the AE stop date is not prior to the first dosing date of Run-in SEL, then the month and year (or year alone if month is not recorded) of onset will determine whether an AE is treatment emergent.

The event is considered treatment emergent to SEL exposure if both of the following 2 criteria are met:

- The AE onset date is the same as or after the month and year (or year) of the first dosing date of Run-in SEL, and

- The AE onset date is the same as or before the month and year (or year) of the 30th day after the last dosing date of SEL

An AE with completely missing onset and stop dates, or with the onset date missing and a stop date later than the first dosing date of Run-in SEL, will be considered to be treatment emergent to SEL expsoure. In addition, an AE with the onset date missing and incomplete stop date with the same or later month and year (or year alone if month is not recorded) as the first dosing date of Run-in SEL will be considered treatment emergent to SEL exposure.

The event is considered treatment emergent to placebo exposure if both of the following 2 criteria are met:

- The AE onset date is the same as or after the month and year (or year) of the 30th day after the first dosing date of Randomized placebo (Study Day 31), and

- The AE onset date is the same as or before the month and year (or year) of the 30th day after the last dosing date of Randomized placebo

7.1.6. Summaries of Adverse Events and Deaths

Exposure-adjusted treatment-emergent AE incidence rates will be summarized based on the Safety Analysis Set, by exposure type (SEL or placebo) and overall. SEL exposure includes Run-in SEL exposure and Randomized SEL exposure.

7.1.6.1. Calculation of Treatment Exposure

Treatment exposure will be calculated as follows, for SEL and placebo respectively:

- SEL: Total exposure (Patient Year) is calculated as the sum of Run-in SEL and Randomized SEL exposure time (in years) for all subjects who have been exposed to Run-in SEL and/or Randomized SEL in the Safety Analysis Set, starting from the first dosing date of Run-in SEL to the last dosing date of SEL (Run-in SEL or Randomized SEL).

In other words,

$$\begin{aligned} &Total\ SEL\ Exposure \\ &= \sum_{i \in \{Subjects\ randomized\ to\ SEL\}} Ex(first\ dose\ of\ Runin\ SEL\ to\ last\ dose\ of\ Randomized\ SEL)_i \\ &+ \sum_{i \in \{Subjects\ randomized\ to\ Placebo\}} Ex(first\ dose\ of\ Runin\ SEL\ to\ last\ dose\ of\ Runin\ SEL)_i \\ &+ \sum_{i \in \{Subjects\ not\ randomized\}} Ex(first\ dose\ of\ Runin\ SEL\ to\ last\ dose\ of\ Runin\ SEL)_i \end{aligned}$$

- Placebo: Total exposure (Patient Year) is calculated as the sum of Randomized placebo exposure time (in years) for all subjects who exposed to Randomized placebo in the Safety Analysis Set, starting from Study Day 1 to the last dosing date of Randomized placebo.

In other words,

$$\begin{aligned} &Total\ Placebo\ Exposure \\ &= \sum_{i \in \{Subjects\ randomized\ to\ Placebo\}} Ex(first\ dose\ of\ Randomized\ Placebo\ to\ last\ dose\ of\ Randomzied\ Placebo)_i \end{aligned}$$

7.1.6.2. Calculation of Exposure-Adjusted AE Incidence Rate

EAIR for AEs will be calculated as follows for SEL and placebo exposure periods, respectively:

$$EAIR(SEL) = \frac{\#\ of\ Subjects\ who\ experienced\ at\ least\ 1\ TEAE\ of\ interest\ to\ SEL\ exposure}{Total\ SEL\ Exposure}$$

$$EAIR(Placebo) = \frac{\#\ of\ Subjects\ who\ experienced\ at\ least\ 1\ TEAE\ of\ interest\ to\ Placebo\ exposure}{Total\ Placebo\ Exposure}$$

7.1.6.3. Summaries of Exposure-Adjusted AE Incidence Rate

A brief, high-level summary of the number of subjects who experienced at least 1 TEAE in the categories described below will be provided by exposure type (SEL or placebo) and overall. EAIRs (per 100 Patient Years) will also be presented. All deaths observed in the study, as well as EAIRs per 100 Patient Years will also be included in this summary by exposure type (SEL or placebo) and overall.

The number subjects who experienced at least 1 TEAE in the AE categories described below will be provided and summarized by SOC, PT, by exposure type (SEL or placebo) and overall. EAIRs (per 100 Patient Years) for AEs in these categories will also be provided.

- TEAEs
- TEAEs with Grade 3 or higher
- TE treatment-related AEs
- TE treatment-related AEs with Grade 3 or higher
- TE SAEs
- TE treatment-related SAEs
- TEAEs leading to premature discontinuation of study drug
- TEAEs leading to temporary interruption of study drug
- TEAEs leading to Death

Multiple events will be counted only once per subject per exposure type in each summary. Adverse events will be summarized and listed first in alphabetic order of SOC, and then by PT in descending order of total frequency within each SOC. For summaries by severity grade, the most severe grade will be used for those AEs that occurred more than once in an individual subject during one exposure type (SEL or placebo) during the study.

In addition to the above summary tables, all TEAEs, TE SAEs, TE treatment-related AEs, and TE treatment-related SAEs will be summarized by PT only, in descending order of total frequency.

In addition, data listings will be provided for the following in the All Enrolled Analysis Set:

- All AEs, indicating whether the event is treatment emergent
- All AEs of Grade 3 or above

- All SAEs
- All Deaths
- All AEs leading to premature discontinuation of study drug
- All AEs leading to temporary interruption of study drug

7.1.7. Additional Analysis of Adverse Events

Categories of AEs of special interest will be summarized (number and percentage) by treatment group. Table 7-1 presents the method of selecting preferred terms for each specified AE category.

Table 7-1. Methods in Selecting Preferred Terms for Specified AE of Interest Categories

AE of Interest Category	Methods in Selecting Preferred Terms
Cardiac failure	Broad Standardized MedDRA Query (SMQ) Cardiac Failure
Acute Renal Failure	Narrow SMQ Acute Renal Failure
COVID-19	Narrow SMQ COVID-19

7.2. Laboratory Evaluations

Central laboratory data collected during the study will be analyzed and summarized using both quantitative and qualitative methods. Summaries of central laboratory data will be provided for the Safety Analysis Set and will include data collected up to the last dose of study drug plus 30 days for subjects who have permanently discontinued study drug. The analysis will be based on values reported in conventional units. When values are below the LOQ, they will be listed as such, and the closest imputed value will be used for the purpose of calculating summary statistics as specified in Section 3.7. Hemolyzed test results will not be included in the analysis, but they will be listed in by-subject laboratory listings.

A by-subject listing for central laboratory test results will be provided by subject ID number and visit in chronological order for hematology, serum chemistry, and urinalysis separately. For central laboratory data, values falling outside of the relevant reference range and/or having a severity grade of 1 or higher on the CTCAE severity grade will be flagged in the data listings, as appropriate.

A by-subject listing for local laboratory test results will also be provided by subject ID number and collection date in chronological order. Test values and corresponding reference ranges reported by the local laboratories will be presented.

No formal statistical testing is planned.

7.2.1. Summaries of Numeric Laboratory Results

Descriptive statistics will be provided by treatment group for each central laboratory test specified in the study protocol as follows:

- Baseline values
- Values at each postbaseline visit
- Change from Baseline at each postbaseline visit

A Baseline laboratory value will be defined as the last nonmissing measurement obtained on or prior to the date/time of first dose of Run-in SEL, with the exception that Baseline laboratory values for serum creatinine, serum cystatin C, $eGFR_{cr}$, $eGFR_{cys}$, urine albumin, urine creatinine and UACR will be defined as the average values of Visit A and Visit B measurements. Change from Baseline to a postbaseline visit will be defined as the visit value minus the Baseline value. The mean, median, Q1, Q3, minimum, and maximum values will be displayed to the reported number of digits; SD values will be displayed to the reported number of digits plus 1.

Median (Q1, Q3) of the change from Baseline values for white blood cells, neutrophis, lymphocytes, hemoglobin, platelet count, serum creatinine, $eGFR_{cr}$, serum cystatin C, $eGFR_{cys}$, UACR, total bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT) and alkaline phosphatase (ALP) will be plotted using a line plot by randomization status, treatment group and visit.

In the case of multiple values in an analysis window, data will be selected for analysis as described in Section 3.8.3.

7.2.2. Graded Laboratory Values

The modified CTCAE v5.0 criteria as specified in the protocol will be used for assigning toxicity grades (0 to 4) to central laboratory results for analysis.

Severity grading for serum creatinine will be defined with the following criteria for reporting purposes. Any serum creatinine within the normal range should be grade 0 regardless of the criteria specified.

Grade 1	Grade 2	Grade 3	Grade 4
1.25 to < 1.5 x Baseline	1.5 to < 1.75 x Baseline	1.75 to ≤ 3 x Baseline	>3 x Baseline

Severity grading for serum cystatin C will be defined with the following criteria for reporting purposes. Any serum cystatin C within the normal range should be grade 0 regardless of the criteria specified.

Grade 1	Grade 2	Grade 3	Grade 4
1.25 to < 1.5 x Baseline	1.5 to < 1.75 x Baseline	1.75 to ≤ 3 x Baseline	>3 x Baseline

Grade 0 includes all values that do not meet the criteria for an abnormality of at least Grade 1. For laboratory tests with criteria for both increased and decreased levels, analyses for each direction (ie, increased, decreased) will be presented separately.

7.2.2.1. Treatment-Emergent Laboratory Abnormalities

Treatment-emergent laboratory abnormalities are defined as follows for SEL and placebo exposures, respectively. Treatment-emergent laboratory abnormalities will only be evaluated for central laboratory testing results.

- SEL exposure: values that increase at least 1 toxicity grade from Baseline at any time point after the first dosing date of Run-in SEL, up to and including the date of last dose of SEL plus 30 days.

- Placebo exposure: values that increase at least 1 toxicity grade from Baseline at any time point on or after Study Day 31, up to and including the date of last dose of Randomized placebo plus 30 days.

Baseline is defined as the last nonmissing value prior to the first dose of Run-in SEL.

If the relevant Baseline laboratory value is missing, any abnormality of at least Grade 1 observed within the time frame specified above will be considered treatment emergent.

7.2.2.2. Treatment-Emergent Marked Laboratory Abnormalities

Treatment-emergent marked laboratory abnormalities are defined as follows for SEL and placebo exposures, respectively. Treatment-emergent marked laboratory abnormalities will only be evaluated for central laboratory testing results.

- SEL exposure: values that increase at least 2 toxicity grades from Baseline at any time point after the first dosing date of Run-in SEL, up to and including the date of last dose of SEL plus 30 days.

- Placebo exposure: values that increase at least 2 toxicity grades from Baseline at any time point on or after Study Day 31, up to and including the date of last dose of Randomized placebo plus 30 days.

Baseline is defined as the last nonmissing value prior to the first dose of Run-in SEL.

If the relevant Baseline laboratory value is missing, any Grade 2, 3 or 4 values observed within the time frame specified above will be considered treatment emergent.

7.2.2.3. Summaries of Laboratory Abnormalities

Laboratory data that are categorical will be summarized using the number and percentage of subjects in the study with the given response at Baseline and each scheduled postbaseline visit.

The following summaries (number and EAIR per 100 Patient Years) for treatment-emergent central laboratory abnormalities will be provided by lab test and exposure type (SEL or placebo); subjects will be categorized according to the most severe postbaseline abnormality grade for a given lab test:

- Treatment-emergent laboratory abnormalities
- Treatment-emergent Grade 3 or 4 laboratory abnormalities
- Treatment-emergent marked laboratory abnormalities

EAIR for treatment-emergent laboratory abnormalities will be calculated in the same manner as EAIR for TEAEs (Section 7.1.6.2).

A by-subject listing of treatment-emergent Grade 3 or 4 laboratory abnormalities will be provided by subject ID number and visit in chronological order. This listing will include all test results that were collected throughout the study for the lab test of interest, with all applicable severity grades displayed.

7.2.3. Liver-related Laboratory Evaluations

Liver-related abnormalities after initial study drug dosing will be examined and summarized using the number and EAIR of subjects who were reported to have the following central laboratory test values for postbaseline measurements:

- AST: (a) > 3 times of the upper limit of reference range (ULN); (b) > 5 x ULN; (c) > 10 x ULN; (d) > 20 x ULN
- ALT: (a) > 3 x ULN; (b) > 5 x ULN; (c) > 10 x ULN; (d) > 20 x ULN
- AST or ALT: (a) > 3 x ULN; (b) > 5 x ULN; (c) > 10 x ULN; (d) > 20 x ULN
- Total bilirubin: (a) > 1 x ULN; (b) > 2 x ULN
- ALP: > 1.5 x ULN
- AST or ALT > 3 x ULN and (a) total bilirubin > 1.5 x ULN; (b) total bilirubin > 2 x ULN; (c) total bilirubin > 2 x ULN and ALP < 2 x ULN

The summary will include data for the following exposure periods for SEL and placebo exposures, respectively:

- SEL exposure: at any time point after the first dosing date of Run-in SEL, up to and including the date of last dose of SEL plus 30 days.
- Placebo exposure: at any time point on or after Study Day 31, up to and including the date of last dose of Randomized placebo plus 30 days.

For individual laboratory tests, subjects will be counted once based on the most severe values in corresponding period. For both the composite endpoint of AST or ALT and total bilirubin, subjects will be counted once when the criteria are met at the same postbaseline visit date. A listing of subjects who met at least 1 of the above criteria will be provided.

7.3. Vital Signs and BMI

Descriptive statistics (n, mean, SD, median, Q1, Q3, minimum, and maximum) will be provided by treatment group for vital signs and BMI as follows. Body weight will be summarized as described in Section 5.1.

- Baseline value
- Value at each postbaseline visit
- Change from Baseline at each postbaseline visit

A Baseline value will be defined as the last available value collected on or prior to the date of first Run-in SEL administration. Change from Baseline to a postbaseline visit will be defined as the postbaseline value minus the Baseline value.

In the case of multiple values in an analysis window, data will be selected for analysis as described in Section 3.8.3. No inferential statistics will be generated.

7.4. Prior and Concomitant Medications

Medications collected at screening and during the study will be coded using the current version of the World Health Organization (WHO) Drug dictionary.

7.4.1. Prior Medications

Prior medications are defined as any medications taken before a subject took the first Run-in SEL.

Prior medications will be summarized by preferred name using the number and percentage of subjects for each treatment group and overall. A subject reporting the same medication more than once will be counted only once when calculating the number and percentage of subjects who received that medication. The summary will be ordered by preferred term in order of descending overall frequency. For drugs with the same frequency, sorting will be done alphabetically.

For the purposes of analysis, any medication with a start date prior to the first dosing date of Run-in SEL will be included in the prior medication summary regardless of when the stop date is. If a partial start date is entered the medication will be considered prior unless the month and year (if day is missing) or year (if day and month are missing) of the start date are after the first dosing date of Run-in SEL. Medications with a completely missing start date will be included in the prior medication summary, unless otherwise specified.

Summaries will be based on the Safety Analysis Set. No formal statistical testing is planned.

All prior medications will be provided in a listing sorted by subject ID number and start date in chronological order.

Disease-specific prior medications (ACEi, ARB, and ARB or ACEi) will be summarized and listed in a similar manner.

Prior use of SGLT-2 inhibitors, statins and GLP1-RAs will also be summarized and listed in a similar manner.

7.4.2. Concomitant Medications

Concomitant medications are defined as medications taken while a subject took study drug. Use of concomitant medications will be summarized by preferred name using the number and percentage of subjects for each treatment group and overall. A subject reporting the same medication more than once will be counted only once when calculating the number and percentage of subjects who received that medication. The summary will be ordered by preferred term in descending overall frequency . For drugs with the same frequency, sorting will be done alphabetically.

For the purposes of analysis, any medications with a start date prior to or on the first dosing date of Run-in SEL and continued to be taken after the first dosing date, or started after the first dosing date but prior to or on the last dosing date of study drug will be considered concomitant medications. Medications started and stopped on the same day as the first dosing date of Run-in SEL or the last dosing date of study drug will also be considered concomitant. Medications with a stop date prior to the date of first dosing date of Run-in SEL or a start date after the last dosing date of study drug will be excluded from the concomitant medication summary. If a partial stop date is entered, any medication with the month and year (if day is missing) or year (if day and month are missing) prior to the date of first Run-in SEL administration will be excluded from the concomitant medication summary. If a partial start date is entered, any medication with the month and year (if day is missing) or year (if day and month are missing) after the study drug stop date will be excluded from the concomitant medication summary. Medications with completely missing start and stop dates will be included in the concomitant medication summary, unless otherwise specified.

Summaries will be based on the Safety Analysis Set. No formal statistical testing is planned.

All prior and concomitant medications (other than per-protocol study drugs) will be provided in a by-subject listing sorted by subject ID number and administration date in chronological order.

Disease-specific concomitant medications (ACEi, ARB, and ARB or ACEi) will be summarized and listed in a similar manner.

Concomitant use of SGLT-2 inhibitors, statins and GLP1-RAs will also be summarized and listed in a similar manner.

7.5. Electrocardiogram Results

ECG analysis results are intended to identify meaningful changes in the QT interval. If potential abnormalities of interest are identified, further analyses may be conducted. Summaries of investigator assessment of ECG readings will be provided for the Safety Analysis Set for each scheduled time point. No formal statistical testing is planned.

7.5.1. Investigator Electrocardiogram Assessment

A shift table of the investigators' assessment of ECG results at each postbaseline visit compared with Baseline values will be presented by randomization status and treatment group using the following categories: normal; abnormal, not clinically significant; abnormal, clinically significant; or missing. Baseline ECG value will be defined as the last nonmissing value before the first dose of Run-in SEL. The number and percentage of subjects in each cross-classification group of the shift table will be presented. Subjects with a missing value at Baseline or postbaseline will not be included in the denominator for percentage calculation. No formal statistical testing is planned.

A by-subject listing for ECG assessment results will be provided by subject ID number and visit in chronological order.

7.5.2. Corrected QT Intervals

The QT interval (measured in millisecond [msec]) is a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle. The QT interval represents electrical depolarization and repolarization of the ventricles. The QT interval is affected by heart rate, and a number of methods have been proposed to correct QT for heart rate.

Corrected QT (QTc) intervals will be derived using Fridericia's correction (QTcF) as follows:

$$QTcF = \frac{QT}{\sqrt[3]{RR}}$$

where QT is measured in msec; RR = 60/Heart Rate (beats per min [bpm]) and RR is measured in seconds

The maximum postbaseline QTcF interval values obtained during the study will be summarized within the following categories:

- > 450 msec
- > 480 msec
- > 500 msec

The maximum postbaseline change in QTcF interval values obtained during the study will also be summarized within the following categories:

- > 30 msec
- > 60 msec

QTcF and uncorrected QT values at each visit and change from Baseline at each visit will be summarized for the Safety Analysis Set by treatment group and randomization status using descriptive statistics.

7.5.3. PR and QRS Intervals

The PR interval (measured in msec) is a measure of the time between the start of the P wave (the onset of atrial depolarization) and the beginning of the QRS complex (the onset of ventricular depolarization). The QRS interval measures the duration of the QRS complex. The maximum postbaseline ventricular rate (VR) and PR and QRS intervals observed during the study will be categorized. The number and percentage of subjects having values in the following ranges will be presented by treatment group and randomization status:

- VR > 100 bpm
- PR interval > 200 msec
- QRS interval > 110 msec

In addition, VR, PR, RR, and QRS values at each visit and change from Baseline at each visit will be summarized for the Safety Analysis Set by treatment group and randomization status using descriptive statistics.

7.6. Other Safety Measures

7.6.1. Pregnancy Report

A data listing will be provided for subjects experiencing pregnancy during the study, from screening to subjects' last study visit.

7.6.2. HIV-1, HBV, and HCV Serology

Data for HIV-1, HBV, and HCV serology will be listed and summarized.

7.6.3. Digoxin and C-Peptide Testing Results

A data listing will be provided for digoxin levels; a separate listing will be provided for C-peptide testing results.

7.7. Changes From Protocol-Specified Safety Analyses

There are no deviations from the protocol-specified safety analyses.

8. PHARMACOKINETIC (PK) ANALYSES

8.1. PK Sample Collection

Sparse (single) PK samples will be collected at Weeks 4, 12, 24, 48 and EOT visit for PK analysis of SEL and metabolite(s), as applicable. Date and time of last dose of study drug prior to PK sample collection as well as date and time of PK sample collection will be recorded. Additionally, whether the previous dose of study drug was taken fed or fasted will be recorded.

Sparse (single) PK samples will not be collected for subjects who permanently discontinue study drug and remain on study.

A single PK blood sample will be collected at any time during each On-Treatment Visit for all subjects.

CCI [redacted]

Concentrations of SEL and GS-607509 in plasma will be determined using validated bioanalytical assays. A population PK model will be developed to characterize the PK of SEL and its metabolite (as applicable). Data from this study (single PK CCI) will be combined with data from other studies in a meta-population analysis using nonlinear mixed-effects modeling techniques. Details of the population PK analysis will be provided in a separate population PK analysis report.

CCI [redacted]

8.2. PK Analyses Related to Intensive PK Sampling

CCI [redacted] Concentrations of SEL and its metabolite GS-607509 in plasma will be determined using validated bioanalytical assays.

8.2.1. Estimation of PK Parameters

PK parameters will be estimated using Phoenix WinNonlin® software using standard noncompartmental methods. The linear up/log down rule will be used in conjunction with the appropriate noncompartmental model, with input values for dose level, dosing time, plasma concentration, and corresponding real-time values, based on drug dosing times whenever possible.

All predose sample times before time-zero will be converted to 0.

For area under the curve (AUC), samples BLQ of the bioanalytical assays occurring prior to the achievement of the first quantifiable concentration will be assigned a concentration value of 0 to prevent overestimation of the initial AUC. Samples that are BLQ at all other time points will be treated as missing data in WinNonlin. The nominal time point for a key event or dosing interval (τ) may be used to permit direct calculation of AUC over specific time intervals. The appropriateness of this approach will be assessed by the PK scientist on a profile-by-profile basis.

Pharmacokinetic parameters such as AUC_{tau}, λ_z and $t_{1/2}$ are dependent on an accurate estimation of the terminal elimination phase of drug. The appropriateness of calculating these parameters will be evaluated upon inspection of PK data on a profile-by-profile basis by the PK scientist.

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI

[redacted]

9. REFERENCES

Mallinckrodt CH, Sanger TM, Dube S, DeBrota DJ, Molenberghs G, Carroll RJ, et al. Assessing and interpreting treatment effects in longitudinal clinical trials with missing data. Biological psychiatry 2003;53 (8):754-60.

Santner, T. J., and Snell, M. K. Small-Sample Confidence Intervals for and in Contingency Tables. Journal of the American Statistical Association 1980; 75:386–394.

10. SOFTWARE

SAS® Software Version 9.2. SAS Institute Inc., Cary, NC, USA.

East 6 Version 6.5. Copyright © Cytel Inc., 1994-2018

11. SAP REVISION

Revision Date (DD MMM YYYY)	Section	Summary of Revision	Reason for Revision
3 DEC 2021			Original Version 1.0

12. APPENDICES

Appendix 1. Schedule of Assessments

Study Procedures Table – Screening to Randomization

	Period	Screening	Enrollment	Run-In		Randomization
	Visit		**A**	**B[a]**	**C[b]**	**1[b]**
	Visit Window (days)	**30 day screening period**		**7 – 14 days after visit A**	**21 – 28 days after visit B**	**7 – 14 days after visit C**
Clinical Assessments	Written Informed Consent	X				
	Medical History & Demographics	X				
	Complete Physical Examination[c]	X				
	Vital Signs including Weight[d]	X	X	X	X	X
	Height	X				
	Waist Circumference	X				
	12 Lead ECG	X				
	CCI					
	Adverse Events	X	X	X	X	X
	Concomitant Medications	X	X	X	X	X
	Study Drug Dispensing		X	X	X	X
	Study Drug Dosing		X	X	X	X
	Study Drug Bottle Return			X	X	X

	Period	Screening	Enrollment	Run-In		Randomization
	Visit		A	B[a]	C[b]	1[b]
	Visit Window (days)	30 day screening period		7 – 14 days after visit A	21 – 28 days after visit B	7 – 14 days after visit C
Laboratory Assessments	Subject Fasting[g]			X		X
	eGFR[h]	X	X	X	X	X
	Early Morning Void Urine ACR & Urinalysis[i]	X	X	X	X	X
	Chemistry & Hematology	X	X	X	X	X
	HbA1c	X				
	HIV-1, HBV, HCV Serology	X				
	Blood Biomarkers			X		X
	CCI					
	Prothrombin Time	X				
	Insulin, Lipid, c-peptide			X		X
	Nt-proBNP			X		X
	cTnI			X		X
	Digoxin[k]				X	
	Pregnancy Testing[l]	X		X		X
	FSH Testing[m]	X				
	Urine Biomarkers			X		X

a. Samples to be collected pre-dose
b. Subject can have no missed doses of study drug during the 7 consecutive days immediately prior to Visit C and Visit 1
c. On visits without a scheduled complete physical examination, a symptom-driven physical examination may be performed if necessary
d. Vital signs include resting blood pressure, pulse, respiratory rate, temperature and weight. Measurements of blood pressure should be taken per institutional guidelines. Subject position should be consistent for each subsequent measure
e. Subject-reported outcomes should be completed at the start of the study visit and prior to the clinical and laboratory assessments. The subject should read the questionnaires by himself/herself and record the answers by himself/herself. The HRQoL questionnaires to be completed at Enrollment are KDQOL-36, KCCQ, and WPAI-GH

[redacted]

g. Subjects should abstain from all food for at least 8 hours prior to laboratory draw, water is allowed
h. eGFR value to be calculated by the Chronic Kidney Disease Epidemiology Creatinine Equation (2009); if eGFR value at Screening does not meet inclusion criteria, subject may repeat 2 additional times during Screening and prior to Enrollment (Visit A). Subject must have eGFR $\geq$ 15 mL/min/1.73 m^2 at all central laboratory assessments during the Run-in period prior to Randomization (Visit 1)
i. First morning void collection is preferred when possible, but early morning void is accepted. Bring sample to clinic within 1 hour, if not possible, refrigerate and bring to clinic within 12 hours. If UACR value at Screening does not meet inclusion criteria, subject may repeat 2 additional times during Screening and prior to Enrollment (Visit A)

[redacted]

k. For subjects taking digoxin only, digoxin level should be measured at Visit C and Week 4. PI may continue checking after Week 4 as part of digoxin management as needed. Monitor and adjust digoxin dose as necessary based on prescribing information.
l. Females of childbearing potential as defined by protocol only (refer to Protocol Appendix 6): Serum pregnancy test at Screening and urine pregnancy test at Visit B, Randomization and every 4 weeks through the 30 Day EOT Follow-up visit.
m. FSH testing to determine female subject's postmenopausal state as described in Protocol Appendix 6.

Study Procedures Table – Week 4 to Week 48+

	Period	On Treatment						
	Visit	**2**	**3**	**4**	**5**	**6**	**7**	
	Week	**4**	**8**	**12**	**24**	**36**	**48**	**q12 weeks[l]**
	Visit Window (days)	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**
Clinical Assessments	Complete Physical Examination[a]							
	Vital Signs including Weight[b]	X	X	X	X	X	X	X
	Waist Circumference						X	
	12 Lead ECG						X	
	CCI							
	Adverse Events	X	X	X	X	X	X	X
	Concomitant Medications	X	X	X	X	X	X	X
	Study Drug Dispensing	X	X	X	X	X	X	X
	Study Drug Dosing	X	X	X	X	X	X	X
	Study Drug Bottle Return	X	X	X	X	X	X	X

	Period	On Treatment						
	Visit	**2**	**3**	**4**	**5**	**6**	**7**	
	Week	**4**	**8**	**12**	**24**	**36**	**48**	**q12 weeks[l]**
	Visit Window (days)	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**
Laboratory Assessments	Subject Fasting[e]						X	
	eGFR[f]	X	X	X	X	X	CCI	X
	Early Morning Void Urine ACR & Urinalysis[g]	X	X	X	X	X	X	X
	Chemistry & Hematology	X	X	X	X	X	X	X
	HbA1c				X		X	X
	Blood Biomarkers	X			X		X	
	Insulin, Lipid, c-peptide						X	
	Nt-proBNP						X	
	cTnI						X	
	Digoxin[h]	X						
	CRP						X	
	Sparse PK[i]	X		X	X		X	
	CCI							
	Pregnancy Testing[k]	X	X	X	X	X	X	X
	Urine Biomarkers	X			X		X	

a. On visits without a scheduled complete physical examination, a symptom-driven physical examination may be performed if necessary
b. Vital signs include resting blood pressure, pulse, respiratory rate, temperature and weight. Measurements of blood pressure should be taken per institutional guidelines. Subject position should be consistent for each subsequent measure
[redacted]
e. Subjects should abstain from all food for at least 8 hours prior to laboratory draw, water is allowed
f. eGFR value to be calculated by the Chronic Kidney Disease Epidemiology Creatinine Equation (2009)

g. First morning void collection is preferred when possible, but early morning void is accepted. Bring sample to clinic within 1 hour, if not possible, refrigerate and bring to clinic within 12 hours
h. For subjects taking digoxin only, digoxin level should be measured at Visit C and Week 4. PI may continue checking after Week 4 as part of digoxin management as needed. Monitor and adjust digoxin dose as necessary based on prescribing information.
i. Sparse PK samples should only be collected for randomized subjects on study drug
[redacted]
k. Females of childbearing potential as defined by protocol only (refer to Protocol Appendix 6): Starting after Week 4, every 4 week pregnancy testing may occur at home, where possible, in between in clinic visits or in clinic. At home pregnancy testing kits will be provided. Females of childbearing-potential performing at home pregnancy testing will be contacted every 4 weeks to report the result of the at home pregnancy tests until the 30 Day EOT Follow-up visit.
l. Repeat every 12 weeks until global study end date.

Study Procedures Table – EOT to 30 Day EOS Safety Follow-up

	Period					
	Visit					
	Week	EOT[a]	30 Day EOT Follow-up[b]	Limited Assessments[c]	EOS[d]	30 Day EOS Safety Follow-up[e]
	Visit Window (days)	±7	±7	±7	±7	±7
Clinical Assessments	Complete Physical Examination[f]	X				
	Vital Signs including Weight[g]	X		X	X	
	Waist Circumference	X				
	12 Lead ECG	X			X	
	CCI					
	Adverse Events	X	X	X	X	X
	Concomitant Medications	X	X	X	X	X
	Study Drug Dispensing					
	Study Drug Dosing					
	Study Drug Bottle Return	X				

	Period					
	Visit					
	Week	EOT[a]	30 Day EOT Follow-up[b]	Limited Assessments[c]	EOS[d]	30 Day EOS Safety Follow-up[e]
	Visit Window (days)	±7	±7	±7	±7	±7
Laboratory Assessments	Subject Fasting[j]					
	eGFR[k]	X	X	X	X	
	Early Morning Void Urine ACR & Urinalysis[l]	X	X		X	
	Chemistry & Hematology	X	X	X	X	
	HbA1c					
	Blood Biomarkers	X	X		X	
	Blood Glucose					
	Insulin, Lipid, c-peptide					
	Nt-proBNP					
	cTnI					
	CRP					
	Sparse PK[m]	X				
	Pregnancy Testing[n]	X	X		X	
	Urine Biomarkers	X	X		X	

a. EOT assessments should be completed for subjects who meet criterion for study drug discontinuation in Protocol Section 3.4. These assessments should be completed as soon as possible after the decision is made. Every attempt should be made to keep the subject in the study to complete all remaining study visits for outcome assessment. If an ECG or STS was conducted at a previous visit within 24 weeks of the EOT visit, the assessment does not need to be performed at the EOT visit
b. Subjects who permanently discontinue study drug must also return to clinic for a 30 Day EOT Follow-up visit 30 days (±7 days) after study drug discontinuation
c. Subjects who permanently discontinue study drug are encouraged to continue all study visits per schedule of procedures. However, if a subject requests limited assessments, they may perform these procedures every 12 weeks
d. EOS assessments should be completed for subjects who meet criterion for study discontinuation in Protocol Section 3.5. If the subject discontinues study drug and discontinues from the study on the same day, assessments for EOT visit should be completed. The subject will still need to return to clinic 30 days (±7 days) for a 30 Day EOT Follow-up visit and complete the 30 Day EOS Safety Follow-up visit.
e. This visit may be conducted in clinic or via telephone

f. On visits without a scheduled complete physical examination, a symptom-driven physical examination may be performed if necessary
g. Vital signs include resting blood pressure, pulse, respiratory rate, temperature and weight. Measurements of blood pressure should be taken per institutional guidelines. Subject position should be consistent for each subsequent measure
[redacted]
j. Subjects should abstain from all food for at least 8 hours prior to laboratory draw, water is allowed
k. eGFR value to be calculated by the Chronic Kidney Disease Epidemiology Creatinine Equation (2009)
l. First morning void collection is preferred when possible, but early morning void is accepted. Bring sample to clinic within 1 hour, if not possible, refrigerate and bring to clinic within 12 hours
m. Sparse PK testing should be performed for all randomized subjects while on study drug. Sparse PK testing does not need to be collected after study drug is discontinued.
n. Females of childbearing potential as defined by protocol only (refer to Protocol Appendix 6): Starting after Week 4, every 4 week pregnancy testing may occur at home where possible, in between in clinic visits, or in clinic. At home pregnancy testing kits will be provided. Females of childbearing potential performing at home pregnancy testing will be contacted every 4 weeks to report the result of the at home pregnancy tests until the 30 Day EOT Follow-up visit

Appendix 2. Adjustment of On-Treatment $eGFR_{cr}$ Values

For subjects in the SEL treatment group, the on-treatment $eGFR_{cr}$ values will be adjusted using a regression model. The statistical methods are described below. For subjects in the SEL treatment group whose off-treatment $eGFR_{cr}$ data are not collected, or who experience a decrease in eGFR of ≥ 40% relative to Baseline as a primary clinical endpoint event before treatment discontinuation, their eGFR values after treatment discontinuation will be imputed using a regression model. The statistical methods are described below.

The following linear regression model will be fitted for subjects in the SEL treatment group whose off-treatment $eGFR_{cr}$ values are collected in the study:

$$\delta = \alpha + \beta x + \epsilon$$

Where δ is the change in $eGFR_{cr}$ values after treatment discontinuation defined as the first observed $eGFR_{cr}$ value at least 7 days after treatment discontinuation minus the last observed $eGFR_{cr}$ value before treatment discontinuation; x is the last observed $eGFR_{cr}$ value before treatment discontinuation, α is the intercept, β is the coefficient for x, and ϵ is the residual.

This model will then be used to predict the unobserved $eGFR_{cr}$ change after treatment discontinuation for subjects in the SEL treatment group. Specifically, the x term in the model is the observed $eGFR_{cr}$ value at each visit, and the outcome δ is the predicted $eGFR_{cr}$ change if subject hypothetically discontinue SEL treatment at each visit.

On-treatment $eGFR_{cr}$ values will then be as adjusted by adding δ to the observed $eGFR_{cr}$ values. These adjusted $eGFR_{cr}$ values will be used in the sensitivity analyses for primary and some secondary endpoints, as described in Sections 6.1.3 and 6.2.2.

Appendix 3. Prohibited Medications That May Impact SEL Treatment Efficacy or Decrease SEL Drug Level

Medication	Prohibited Period
Amiodarone	90 days prior to Enrollment through EOS
Bardoxolone	2 weeks prior to Enrollment through EOS
Ranolazine	2 weeks prior to Enrollment through EOS
Dronedarone	2 weeks prior to Enrollment through EOS
Dofetilide	2 weeks prior to Enrollment through EOS
Trimethoprim	2 weeks prior to Enrollment through EOS
Isavuconazole	2 weeks prior to Enrollment through EOS
Pyrimethamine	2 weeks prior to Enrollment through EOS
Cimetidine	2 weeks prior to Enrollment through EOS
Famotidine	2 weeks prior to Enrollment through EOS
Phenobarbital	2 weeks prior to Enrollment through EOT
Phenytoin	2 weeks prior to Enrollment through EOT
Rifampin	2 weeks prior to Enrollment through EOT
St. John’s wort	2 weeks prior to Enrollment through EOT

Appendix 4. Data Collection of COVID-19 Data

This appendix describes the clinical trial site collection of COVID-19 data pertaining to missed/virtual visits and the data processing algorithm that will be used to determine which visits are missing and which visits are virtual.

Data Collection

A COVID-19 supplement to the eCRF Completion Guidelines (CCG) was provided by Clinical Data Management to instruct clinical trial sites with data entry expectations pertaining to scenarios related to the COVID-19 pandemic. If a visit was missed, sites were instructed to enter "Visit missed due to COVID-19" and if an in-person visit was conducted virtually, sites were instructed to enter "Virtual visit due to COVID-19".

Determination of Missed and Virtual Visits

Natural Language Processing (NLP) will be used to search the CRF comment fields to identify instances of "COVID-19", "Virtual", or synonyms (see Table 12-1). The search terms will be maintained in a global lookup table and can be modified to tune the NLP model. Any comments with COVID-19 search terms, "Missed visit" or "Virtual visit" will be assigned as follows:

i) If COVID-19 terms are identified through NLP and the visit date is missing, then result is "Missed Visit"

ii) If COVID-19 and Virtual terms are identified through NLP for a visit, then result is "Virtual Visit". When there are multiple records for the same subject and the same visit, if one record could be categorized as "Virtual Visit", all records associated with this subject and this visit will be categorized as "Virtual Visit"

iii) Otherwise result is missing

Table 12-1. Example Search Terms for "COVID-19" and "Virtual" Used to Identify Missed/Virtual Visits.

Search Terms for "COVID-19"	Search Terms for "Virtual"
COVID19 CORONA CORONAVIRUS PANDEMIC OUTBREAK CRISIS LOCKDOWN QUARANTINE SHELTER	VIRTUAL TELEMED TELEHEALTH TELEPHONE REMOTE TELEMEDICINE TELECONSULTATION TELEPHONICALLY PHONE HOME VISIT ZOOM SKYPE