CLINICAL STUDY PROTOCOL

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
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404
IND Number:	117513
Clinical Trials.gov Identifier:	NCT04026165
Indication:	Diabetic Kidney Disease
Protocol ID:	GS-US-223-1017
Protocol Version/Date:	Original: 01 February 2019 Amendment 1: 10 June 2019 Amendment 2: 13 April 2020

This study will be conducted under US Food & Drug Administration IND regulations (21 CFR Part 312); however, sites located in the European Economic Area and Switzerland are not included under the IND and are considered non-IND sites.

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PROTOCOL SYNOPSIS

Gilead Sciences, Inc.
333 Lakeside Drive
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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
IND Number:	117513
Clinical Trials.gov Identifier:	NCT04026165
Study Centers Planned:	Approximately 190 centers globally
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 CCI [redacted]

Study Design:

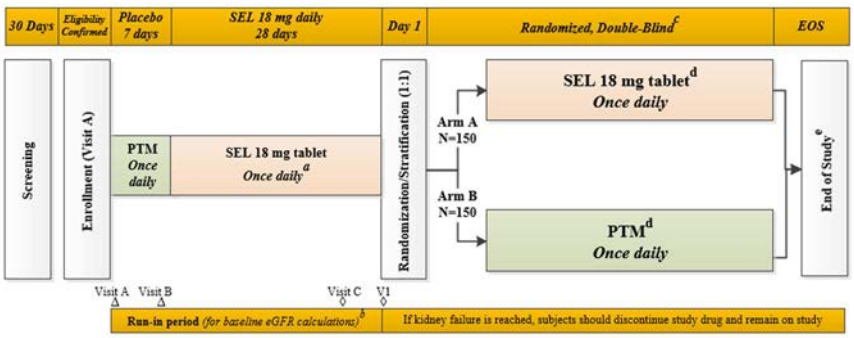
This is a Phase 2b, randomized, double-blind, placebo-controlled, parallel group, multicenter study evaluating the efficacy and safety of SEL in subjects with type 2 diabetes mellitus (T2DM) and moderate to advanced DKD.

Following the screening period, eligible subjects will enroll into a Run-in period of at least 5 weeks. During the Run-in period, all subjects will receive placebo-to-match (PTM) for at least 7 consecutive days. Subsequently, all subjects will receive SEL (18 mg) for at least 4 weeks.

After completing the Run-in period, subjects eligible for randomization will be randomized in a 1:1 ratio to receive SEL (18 mg) or PTM, orally once daily. Randomization will be stratified by estimated glomerular filtration rate (eGFR), urine albumin to creatinine ratio (UACR), and concomitant use of sodium-glucose co-transporter-2 (SGLT-2) inhibitors.

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.

Study Design Schema



Abbreviations: EOS = End of Study, EOT = End of Treatment, PTM = placebo 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.

Number of Subjects Planned:	Approximately 300 randomized subjects
Target Population:	Subjects with T2DM and eGFR ranging from ≥ 20 mL/min/1.73 m² to < 60 mL/min/1.73 m² with albuminuria receiving standard of care (SOC) therapy (angiotensin converting enzyme inhibitor [ACEi], or angiotensin receptor blocker [ARB], or intolerant to both ACEi and ARB)
Duration of Treatment:	At least 52 weeks (4 weeks during the Run-in period and at least 48 weeks post randomization)
Diagnosis and Main Eligibility Criteria:	**Inclusion Criteria** Subjects must meet *all* of the following inclusion criteria to be eligible for enrollment in this study: 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 prior to 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 ACEi or ARB as a single agent at the maximum labeled or tolerated dose deemed appropriate for the subject by the investigator and/or per local SOC 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) Subjects already receiving SGLT-2 inhibitors must be on a stable dose at least 2 weeks prior to Enrollment
6) For females of childbearing potential (unless permanently sterile or post-menopausal, as described in Appendix 6), a negative serum pregnancy test at Screening
7) For male and female subjects of childbearing potential who engage in heterosexual intercourse, agreement to abstain or use protocol specified method(s) of contraception as described in Appendix 6
8) Male subjects must refrain from sperm donation from the Screening visit through 30 days following the last dose of study drug
9) Female subjects must refrain from egg donation or harvest from the Screening visit through 30 days following the last dose of study drug
10) Subjects must refrain from blood product donation from the Screening visit through 30 days following the last dose of study drug
11) 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)

12) Required baseline laboratory data, analyzed by central laboratory, within 30 days prior to Enrollment (Visit A) as shown in the table below

Organ System	Parameter	Required Value
Hematologic	WBC, neutrophil, lymphocyte, and platelet count	≥ 0.75 x LLN to ≤ 1.5 x ULN
Hepatic	Serum total bilirubin	≤ 1.5 × ULN
	Serum ALT	
	Serum AST	
Pregnancy	β-HCG[a]	Negative
Infection	HIV[b]	Negative HIV antibody
	HBV	Negative HBsAg and negative HBc antibody or positive HBc and negative for HBV DNA by quantitative PCR
	HCV	Negative HCV antibody or negative viral RNA (if HCV antibody is positive)

a For women of childbearing potential only; serum β-HCG must be negative during Screening
b If screening test is positive, a negative confirmatory test will be required for eligibility
Abbreviations: β-HCG = beta human chorionic gonadotropin, ALT = alanine aminotransferase, AST = aspartate aminotransferase, DNA = deoxyribonucleic acid, LLN = lower limit of normal, HBc antibody = anti-hepatitis B core antibody, HBsAg = hepatitis B surface antigen, HBV = hepatitis B virus, HCV = hepatitis C virus, HIV = human immunodeficiency virus, PCR = polymerase chain reaction, RNA = ribonucleic acid, ULN = upper limit of normal, WBC = white blood count

13) Have either a normal 12-lead electrocardiogram (ECG) or an ECG with abnormalities that are not considered to be clinically significant by the investigator within 30 days prior to Enrollment (Visit A)

14) In the judgment of the investigator, participation in the study offers an acceptable benefit to risk ratio, taking into consideration the subject's current DKD status, medical condition, and the potential benefits and risks of alternative treatments for DKD

15) Willing and able to comply with scheduled visits, drug administration plan, laboratory tests, other study procedures, and study restrictions

16) Willing and able to give informed consent prior to any study specific procedures being performed

Exclusion Criteria

Subjects who meet *any* of the following exclusion criteria are not to be enrolled in this study:

1) 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 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) Diagnostic or interventional procedure that requires intravenous or intra-arterial iodinated contrast agent within 30 days prior to Enrollment (Visit A) and/or planned during the study Run-in period
10) 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
11) Pregnant or lactating females or planning to become pregnant or breastfeed during the study

12) Concurrent use of either
    a) ACEi and ARB or
    b) Mineralocorticoid receptor antagonist (MRA) or direct renin inhibitor (DRI) in combination with an ACEi or ARB for at least 2 weeks prior to Enrollment
13) Requiring chronic administration of prohibited medications as per protocol
14) Participation in another investigational study within 1 month or within 5 half-lives of the prior investigational agent (whichever is longer) prior to Enrollment (Visit A)
15) Concurrent participation in another therapeutic clinical study
16) Prior participation in any clinical trial of SEL
17) Known hypersensitivity to the study drug (SEL/placebo-to-match), the metabolites, or formulation excipients
18) Prior or ongoing clinically significant illness, medical condition, surgical history, physical finding, ECG finding, or laboratory abnormality that, in the investigator's opinion, could adversely affect the safety of the subject or impair the assessment of study results
19) Presence of any condition that could, in the opinion of the investigator, compromise the subject's ability to participate in the study, such as history of substance abuse, alcoholism, or a psychiatric condition

Randomization Eligibility Criteria:

Subjects must meet *all* of the following criteria to be eligible for randomization:

1) eGFR ≥ 15 mL/min/1.73 m² at all central laboratory assessments during the Run-in period prior to Randomization (Visit 1)
2) At least 7 consecutive daily doses of SEL, without interruption, immediately prior to Visit C and prior to Randomization (Visit 1)
3) Subject did not permanently discontinue study drug during the Run-in period
4) Subject did not withdraw consent
5) Subject did not initiate, change dose, or discontinue SGLT-2 inhibitor during the Run-in period or is not anticipated to initiate, change dose or discontinue SGLT-2 inhibitor within 12 weeks after Randomization (Visit 1)
6) Negative urine pregnancy test for female subjects of childbearing potential

7) No ongoing clinically significant illness, medical condition, surgical history, physical finding, or laboratory abnormality that, in the investigator's opinion, could adversely affect the safety of the subject or impair the assessment of study results

Stratification Factors:

- eGFR Strata:

eGFR (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 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 and Albuminuria will be transferred directly from the central laboratory to the interactive web response system (IWRS) for stratification but eGFR values will not be released to sites, investigators, or the sponsor.

Study Procedures/ Frequency:

Subjects who meet eligibility criteria at Screening will enroll into the Run-in period. Starting at Visit A, subjects will receive PTM once daily for at least 7 consecutive days. Starting at Visit B, subjects will begin to receive SEL (18 mg) once daily for at least 4 weeks.

During the Run-in period, subjects will be monitored for safety and study drug compliance. After Enrollment (Visit A), subjects will be required to return to the study site on Visit B (7-14 days after Visit A), Visit C (21-28 days after Visit B), and Visit 1 (7-14 days after Visit C). Immediately prior to Visit C and Visit 1, subjects must be on SEL for at least 7 consecutive days. Visit windows are provided in the unlikely event that a subject misses a dose within 7 days prior to Visit C and Visit 1.

Following the Run-in period, eligible subjects will be randomized at the study site on Visit 1 to enter the blinded treatment phase. Subjects will have study visits on Weeks 4, 8, 12, 24, 36, 48, and every 12 weeks thereafter. SEL/PTM will continue to be administered until 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), death, study drug discontinuation (e.g., unacceptable toxicity, subject's refusal of treatment, kidney transplantation), or the global study end date.

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. They will then resume all study visits per the schedule of procedures and attend all subsequent study visits in the same manner as subjects who are still receiving study drug.

Subjects who permanently discontinue study drug can have limited follow-up as defined in the schedule of procedures table, if requested. If full consent has not been withdrawn, subjects who permanently discontinue study drug and are no longer willing or able to attend clinic visits in-person will be asked to continue study participation via remote assessments. Subjects will be contacted approximately every 24 weeks until the global study end date. Subjects who have reached kidney failure will be followed via remote assessments as well.

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.

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Test Product, Dose, and Mode of Administration:

SEL 18 mg or PTM to be taken orally once daily

Criteria for Evaluation:

Safety:

The safety of SEL will be assessed during the study through the reporting of adverse events (AEs) and serious adverse events (SAEs), physical examinations (PEs), clinical laboratory tests, vital sign assessments, concomitant medications, and ECGs at various time points during the study.

A data monitoring committee (DMC) will meet regularly to evaluate all available safety data accumulated during the study. In addition, endpoints of interest (kidney and CV events) will be reviewed and adjudicated.

Efficacy:

Primary efficacy endpoint:

- $eGFR_{cr}$ slope from treatment-specific baselines

Secondary endpoints:

- Proportion of Kidney Clinical Events at Week 48 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

- Time from randomization to first occurrence of a Kidney Clinical Event
- $eGFR_{cys}$ slope from pre-run-in baseline

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Statistical Methods:

Primary Efficacy Analyses

Analysis Methods

The primary analysis set for efficacy analyses is the ITT Analysis Set, which includes all subjects who were randomized in the study.

Definition of Baseline

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

- SEL arm (Arm A): 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 (Arm B): The average of the measurements at Visit A (Enrollment) and Visit B. This baseline will also be referred to as pre-run-in baseline.

The primary analysis of $eGFR_{cr}$ slope will be performed after all subjects in the ITT Analysis Set complete the Week 48 visit or discontinue from the study. Pre-run-in baseline $eGFR_{cr}$ and post-run-in baseline $eGFR_{cr}$ will be used for the placebo and SEL arms, respectively. Baseline $eGFR_{cr}$ as well as all on- and off-treatment $eGFR_{cr}$ values collected after Visit 1 through time of the analysis for all subjects with available data will be included. $eGFR_{cr}$ slope will be compared between SEL and placebo using a random slope model. The random slope model will have $eGFR_{cr}$ values starting from Baseline as the outcome and will include terms for pre-run-in baseline $eGFR_{cr}$ as a continuous variable, pre-run-in baseline UACR category (< 1500 mg/g vs. ≥ 1500 mg/g), concomitant use of SGLT-2 inhibitors, treatment group, visit, and treatment-by-visit interaction. The difference in $eGFR_{cr}$ slope between SEL and placebo groups will be estimated and tested.

Multiplicity Adjustment

The primary endpoint and each secondary endpoint will be evaluated at a one-sided Type 1 error level of 0.15. No formal multiplicity adjustment will be performed.

Sample Size Determination

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-to-match 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%.

Safety Analysis	Safety analyses include summaries of extent of exposure, AEs, laboratory evaluations, and vital sign assessments.
CCI [redacted]	[redacted]

This study will be conducted in accordance with the guidelines of Good Clinical Practice (GCP) including archiving of essential documents.

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

ACEi	angiotensin converting enzyme inhibitor
AE	adverse event
ALT	alanine aminotransferase
ARB	angiotensin receptor blocker
ASK1	apoptosis signal-regulating kinase 1
AST	aspartate aminotransferase
BCRP	breast cancer resistance protein
BLQ	below the limit of quantitation
BMI	body mass index
C_{max}	maximum concentration
CI	confidence interval
CKD EPI equation	Chronic Kidney Disease Epidemiology Collaboration equation
CMH	Cochran-Mantel-Haenszel
CRP	C-reactive protein
CTCAE	Common Terminology Criteria for Adverse Events
CV	cardiovascular
CXCL1	chemokine (C-X-C motif) ligand 1
CYP	cytochrome P450 enzyme
DBP	diastolic blood pressure
DDI	drug-drug interaction
DKD	diabetic kidney disease
DRI	direct renin inhibitors
DMC	data monitoring committee
ECG	electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
EOS	end of study
EOT	end of treatment
ESKD	end stage kidney disease
EU	European Union
FDA	United States Food and Drug Administration
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GFR	glomerular filtration rate
HbA1c	Hemoglobin A1c
HBV	Hepatitis B virus
HCV	Hepatitis C virus

HIV	Human immunodeficiency virus
HR	hazard ratio
HRQoL	health-related quality of life
IB	Investigator's Brochure
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IEC	independent ethics committee
IMP	investigational medicinal product
IRB	institutional review board
ITT	Intent-to-treat
IWRS	interactive web response system
JNK	c-Jun N-terminal kinase
LLN	lower limit of normal
LLOQ	lower limit of quantitation
MAPK	mitogen activated protein kinase
MATE1	multidrug and toxin extrusion protein 1
MATE2K	multidrug and toxin extrusion protein 2
MDRD	modification of diet in renal disease
MedDRA	Medical Dictionary for Regulatory Activities
mGFR	measured glomerular filtration rate
MI	myocardial infarction
MRA	mineralocorticoid receptor antagonist
MODY	maturity onset diabetes of the young
mmHg	millimeter of mercury
NASH	nonalcoholic steatohepatitis
NYHA	New York Heart Association
OATP	organic anion-transporting polypeptide
OCT	organic cation transporter
P-gp	P-glycoprotein
PAH	pulmonary hypertension
PBMC	peripheral blood mononuclear cell
PE	physical examination
PK	pharmacokinetics
PT	preferred term
PTM	placebo to match
PVE	Pharmacovigilance & Epidemiology
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
QT_c	QT interval corrected for heart rate
ROS	reactive oxygen species

SAE	serious adverse event
SBP	systolic blood pressure
SD	standard deviation
SEL	selonsertib
SGLT-2	sodium-glucose co-transporter-2
SOC	system organ class
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reaction
TDAR	T-cell-dependent antibody response
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus
cTnI	troponin
Trx	thioredoxins
UACR	urine albumin to creatinine ratio
UGT1A1	uridine diphosphate glucuronosyltransferase 1A1
ULN	upper limit of normal
VAS	visual analog scale

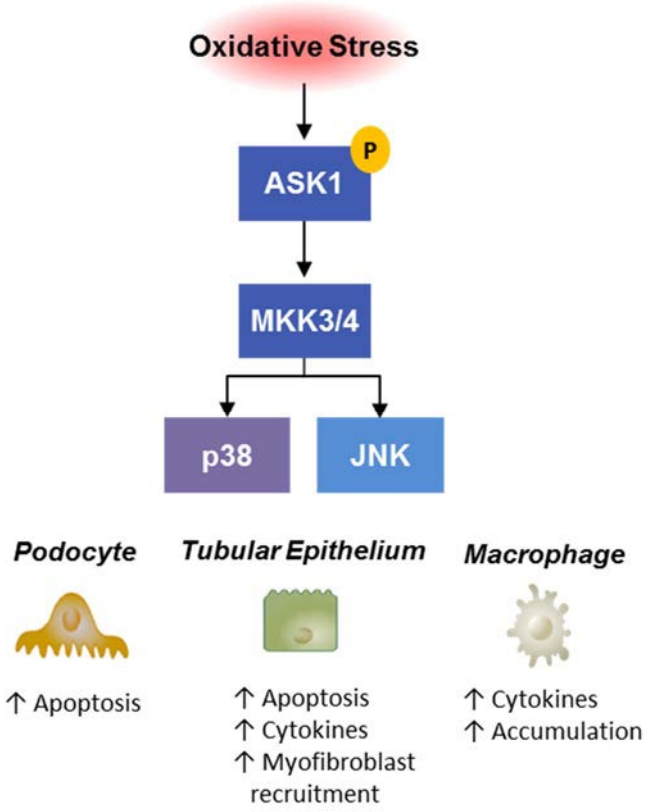
1. INTRODUCTION

1.1. Background

Apoptosis signal-regulating kinase 1 (ASK1) is an important signaling node through which oxidative stress promotes inflammation, proliferation, apoptosis, and fibrosis (Figure 1-1). The ASK1 protein is ubiquitously expressed and normally bound and repressed by thiol-containing antioxidant proteins, including thioredoxins (Trx) in the cytosol and mitochondria {Borroni 2013, Derkay 2013, Fujino 2007}. In settings of elevated oxidative stress and/or reactive oxygen species (ROS), Trx undergoes oxidation and dissociation from ASK1 leading to trans-autophosphorylation of ASK1 homodimers at threonine 845 within the activation loop {Tobiume 2002}.

Threonine (Thr) 845-phosphorylated ASK1 (pASK1) has increased catalytic activity and phosphorylates mitogen activated protein kinase kinases (MAPKKs) 3, 4, 6, and 7, which in turn phosphorylate and activate the mitogen activated protein kinases (MAPKs) p38 and c-Jun N-terminal kinase (JNK) {Fujisawa 2007, Sturchler 2010}. In response to pathological oxidative stress, ASK1 activation of p38 and JNK mediates diverse stress response pathways in cell type– and context-dependent manners. For example, in experimental models of acute and chronic kidney disease, these downstream MAPKs drive inflammation, fibrosis, and apoptosis, and are implicated as contributors to kidney disease in humans {Liles 2018}. ASK1, p38 and JNK activity are all increased in the glomerulus, and tubulointerstitium of kidneys from diabetic and nondiabetic patients with chronic kidney disease (CKD) and associated with driving progression through apoptosis, inflammation and fibrosis {Adhikary 2004, Liles 2018, Verzola 2007}. Notably, ASK1 is required for sustained activation of p38 and JNK; therefore, ASK1 serves as a mechanistic link between oxidative stress and the downstream pathological processes mediated by these 2 kinases {Tobiume 2001}. In pathological settings of oxidative stress, ASK1 is required for sustained activation of p38 and JNK, which mediate diverse cellular responses by phosphorylating both cytosolic substrates and nuclear transcription factors {Tobiume 2001}. The ASK1 pathway promotes the expression of inflammatory cytokines (eg, interleukin [IL]-1β, IL-2, and IL 6), chemokines (eg, monocyte chemotactic protein 1 [MCP-1], chemokine ligand 1 [CXCL1], and chemokine ligand 2 [CXCL2]), and matrix remodeling genes (i.e., transforming growth factor beta [TGF – β], tissue inhibitor of metalloproteinase [TIMP], plasminogen activator inhibitor-1 [PAI-1]) (Figure 1-1) {Matsuzawa 2005, Mnich 2010, Nakamura 2009, Takeda 2008, Terada 2007, Yokoi 2006}.

Figure 1-1. ASK-1 Signaling in DKD



In vivo, mice that are ASK1 deficient ($ASK1^{-/-}$) develop normally, have no histological evidence of abnormality under controlled standard laboratory settings, and possess normal wound healing responses {Osaka 2007, Yamaguchi 2003}. In settings of diabetes, obesity, hypertension, and ischemia, $ASK1^{-/-}$ mice are protected from pathological organ remodeling and fibrosis, and display decreased cell loss by apoptosis, decreased macrophage infiltration into tissues, decreased vascular intimal hyperplasia, and improved vascular function {Kataoka 2011, Nakagawa 2008, Nakamura 2009, Terada 2007, Watanabe 2005, Yamaguchi 2003, Yamamoto 2008, Yamashita 2007, Yokoi 2006}.

1.2. Investigational Medicinal Product Selonsertib

1.2.1. General Information

Selonsertib (SEL; GS-4997) is a new chemical entity and is a first-in-class small molecule inhibitor of ASK1 being developed by Gilead Sciences, Inc. Selonsertib is a potent and selective inhibitor of ASK1, a critical serine/threonine signaling kinase through which oxidative stress promotes inflammation, apoptosis, and fibrosis {Fujisawa 2007, Liles 2018, Ma 2014, Takeda 2008, Terada 2007, Tesch 2015, Tobiume 2001, Watanabe 2005}. Pathological imbalances in cellular redox homeostasis and the resultant activation and dysregulation of downstream ASK1 signaling have been implicated in the pathogenesis of diseases such as diabetic kidney disease

(DKD), nonalcoholic steatohepatitis (NASH), alcoholic hepatitis (AH), heart failure, and rheumatoid arthritis. ASK1 may also be involved in other diseases such as select solid tumors, idiopathic pulmonary fibrosis, and asthma {Chibon 2004, Hayakawa 2012, Hikoso 2007, Izumiya 2003, Noguchi 2014, Takada 2013, Taki 2008, Terada 2007, Watanabe 2005, Yamaguchi 2003, Yamaguchi 2004, Yamamoto 2008}. Clinical studies have been conducted in subjects with NASH, AH, DKD, and pulmonary hypertension (PAH); SEL is currently being developed for the treatment of DKD and as a component in combination therapy for the treatment of NASH.

In DKD, ASK1 may have a key role in maintaining the pathological cycle between oxidative stress and inflammation, leading to progressive disease noted by increased apoptosis and fibrosis, and associated damage in the kidney with a decline in glomerular filtration rate (GFR). Through inhibition of ASK1, SEL is expected to slow or halt the progression of kidney disease and the rate of GFR decline, thereby delaying dialysis and death in patients with DKD. Furthermore, ASK1 has been shown to be a key mediator of oxidative stress-induced apoptosis and fibrosis in the heart, suggesting that improvement in cardiovascular outcomes may also be observed with SEL {Gerczuk 2012, Hikoso 2007, Tobiume 2002, Toldo 2012, Yamaguchi 2003}.

The safety, tolerability, and pharmacokinetics (PK) of SEL has been evaluated in Phase 1 studies in healthy volunteers and in Phase 2 and Phase 3 studies in subjects with NASH, AH, DKD, and PAH, and potential risks based on the findings from these studies and nonclinical studies, are summarized in the Summary of Data and Guidance for the Investigator section of the Investigator's Brochure (IB).

For further information on SEL, refer to the current investigator's brochure for SEL.

1.2.2. Preclinical Pharmacology and Toxicology

1.2.2.1. Nonclinical Pharmacology

Selonsertib is a potent and selective adenosine triphosphate (ATP) competitive inhibitor of the kinase ASK1. The potency of SEL to inhibit ASK1 activation and signaling was characterized in cellular assays and in vivo models of oxidative stress. In human kidney cell line 2 (HK2) human kidney proximal tubular epithelial cells, SEL inhibited auranofin induced ASK1 autophosphorylation and inhibited the downstream phosphorylation of p38 and JNK. Selonsertib efficacy was similar to that obtained when ASK1 expression was reduced by small interfering Ribonucleic Acid (siRNA). The potency of SEL to inhibit auranofin induced p38 activation in human HK2 cells (EC_{50} 10.5 ± 1.3 nM) and human peripheral blood mononuclear cells (PBMCs) (EC_{50} 10.8 ± 1.3 nM) were congruent with the potency of SEL to inhibit ASK1 in a biochemical assay (1.76 ± 0.85 nM). Selonsertib inhibited auranofin induced production of the proinflammatory chemokine CXCL1 in human whole blood and in isolated human PBMCs with mean EC_{50} values of 131 ± 70 and 32 ± 13 nM, respectively. The approximate 4 fold difference in potency observed between whole blood and isolated PBMCs is likely due to plasma protein binding; the free fraction of SEL in human plasma is approximately 5%.

CCI [redacted]

The inhibition of ASK1 by SEL or a close structural analog (GS-444217) was efficacious and well tolerated in a number of kidney in vivo efficacy models, which together reflect the pathophysiology of human DKD. In a rat model of acute oxidative stress induced by auranofin administration, SEL dose dependently inhibited activation of ASK1 and ASK1 signaling in the kidney and inhibited the downstream expression of cytokines and chemokines in the kidney. In the unilateral ureteral obstruction (UUO) model, SEL dose dependently inhibited ASK1 pathway activation in the kidney and was efficacious in reducing both biochemical and histological indices of kidney tubulointerstitial fibrosis. In addition, SEL decreased collagen IV deposition and reduced the expression of α-smooth muscle actin (α-SMA), a marker of myofibroblasts activation. At doses ≥ 10 mg/kg, SEL treatment reduced collagen IV levels to sham control group levels; at 10 mg/kg, the mean protein free level of SEL in plasma was 8.7 nM at C_{min}. GS-444217 was evaluated in the mouse db/db eNOS$^{-/-}$ model of DKD, which is phenotypically similar to advanced human DKD {Mohan 2008, Zhao 2006}. Treatment with GS-444217 in this model markedly slowed disease progression as assessed by GFR and reduced the severity of glomerulosclerosis, proteinuria, and apoptosis in the kidney.

In safety pharmacology studies, SEL inhibited the human ether-a-go-go-related gene (hERG) channel in vitro with a concentration at which 50% inhibition occurs (IC_{50}) of 5.9 µg/mL and, based on in vivo animal studies, has the potential to prolong QT interval corrected for heart rate (QTc) and decrease systemic blood pressure at exposures (free C_{max}) that are approximately 11- and 3-fold, respectively, higher than the exposure observed at the maximum human dose of 18 mg/day.

Overall, the results from these pharmacology studies demonstrate that SEL is a potent and selective inhibitor of the ASK1 kinase, a key mediator of oxidative stress induced injury. Collectively, the data indicate that SEL has the potential to ameliorate the progression of DKD in patients.

1.2.2.2. Nonclinical Pharmacokinetics

Consistent with the moderate to high bioavailability seen in nonclinical species, SEL shows high, concentration-independent forward permeability across Caco-2 monolayers, with low efflux. Although SEL is a substrate for P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP), this is unlikely to be of relevance during absorption due to its high permeability.

CCI [redacted]

Selonsertib has a moderate volume of distribution, close to that of total body water. Selonsertib is unlikely to cross the blood-brain barrier, likely through the action of efflux transporters at the blood-brain barrier. Systemic clearance in nonclinical species is well predicted from the rates of metabolism by hepatic microsomal fractions and hepatocytes. Selonsertib has good metabolic stability with human hepatic material in vitro and low clearance in vivo. In vitro, the main route of metabolism of SEL involves *N*-dealkylation, resulting in loss of the isopropyl group CCI [redacted]. However, other routes of metabolism were detected in the rat, including oxidation (with subsequent glucuronidation) and hydrolysis of the amide. Of the major cytochrome P450 enzyme (CYP) enzymes tested, only CYP3A4 had the ability to metabolize SEL CCI [redacted], consistent with results in a clinical drug interaction study (Study GS-US-223-1434).

Selonsertib is unlikely to cause clinical interactions through inhibition of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP2D6. Substrate-dependent inhibition was observed for CYP3A, and inhibition of uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1) also was observed. CCI [redacted] A clinical study found little effect of SEL (30 mg once daily) on CYP3A activity.

As evaluated using in vitro studies, SEL is a weak inhibitor of BCRP and P-gp with IC_{50} values of > 10 µM and 3.4 µM, respectively. A Phase I clinical drug interaction study using the probe substrate digoxin (GS-US-223-1434) demonstrated that co-administration of a once-daily dose of SEL (20 mg) with digoxin (0.5 mg) resulted in a modest increase of the maximum concentration (C_{max}) and area under the concentration-time curve (AUC_{INF}) of digoxin (35% and 24%, respectively) with no change to the half-life. SEL was a weak inhibitor of intestinal P-gp in vivo.

Selonsertib was determined to be an in vitro inhibitor for hepatic transporters OATP1B1 (IC_{50} = 9.9 µM), OATP1B3 (IC_{50} > 10 µM), and organic cation transporter (OCT) 1 (IC_{50} = 2.8 µM). Based on the regulatory guidelines for determining potential DDIs and the nature of high protein binding (> 95%), SEL is unlikely to be a relevant inhibitor of these transporters in vivo.

In in vitro experiments, SEL was identified as an inhibitor of the kidney transporters OCT2 (IC_{50} = 5.5 µM), multidrug and toxin extrusion protein 1 (MATE1) (IC_{50} = 2.4 µM), and multidrug and toxin extrusion protein 2 (MATE2K) (IC_{50} = 0.94 µM). Based on in vivo plasma exposure and the 2017 FDA Guidance for Industry – In Vitro Metabolism-and Transporter-Mediated Drug-Drug Interaction studies, at clinical doses, SEL is predicted to be an in vivo inhibitor of MATE1 and MATE2K ($I_{max,u}/[IC_{50}] \geq 0.02$; $[I_{max,u}]/[IC_{50}]$ = 0.02 and 0.05, respectively) but not OCT2 ($I_{max,u}/[IC_{50}] \geq 0.1$; $I_{max,u}/[IC_{50}]$ = 0.008*)*. A Phase I study was conducted to evaluate the effect of SEL or placebo on kidney function using iohexol as an exogenous marker of GFR (GS-US-223-3973). Small, dose-dependent and reversible increases in serum creatinine with resulting decreases in calculated creatinine clearance (Cockcroft-Gault) were observed, a finding consistent with the inhibition of kidney transporters by SEL.

CCI [redacted] The metabolite was a slightly more potent inhibitor of MATE1 (IC_{50} = 6.4 µM) and MATE2K (IC_{50} = 3.4 µM), but based on the regulatory guidelines ($I_{max,u}$/ IC_{50} = 0.01) and the high plasma protein binding (~99% bound), the inhibition of these transporters by the metabolite is unlikely to be relevant in vivo.

Selonsertib CCI [redacted] are not expected to be clinically relevant inducers of human drug metabolizing enzymes and drug transporters through activation of either aryl hydrocarbon receptor (AhR) or pregnane X receptor (PXR).

Elimination of SEL and its metabolites is likely to occur through a mixture of urinary, biliary, and intestinal excretion.

1.2.2.3. Nonclinical Toxicology

Target organs/tissues identified in the repeat-dose rat and monkey toxicity studies with SEL were the gastrointestinal, kidney, hematopoietic tissue, lymphoid tissue (cynomolgus monkey only), adrenal (rat only), and lung (monkey only). In general, findings were reversible, monitorable, and only occurred at doses that exceeded the projected exposure (AUC_{24h}) at the proposed maximum human dose by at least 4-fold. Selonsertib was nongenotoxic in in vitro and in vivo assays and noncarcinogenic in transgenic RasH2 mice. In Sprague-Dawley rats, there was a reduction in the latency period for pituitary adenomas (a common spontaneous tumor in Sprague-Dawley rats) that resulted in an increased incidence of pituitary adenomas at doses associated with exposures ≥ 13-fold higher than the exposure in NASH subjects at the 18 mg dose. There was no effect of SEL on phototoxicity, ocular or skin irritation, or skin sensitization. In addition, there were no effects of SEL on fertility, early embryonic or peri- and postnatal development. However, there were embryofetal effects during organogenesis including a few visceral and/or skeletal malformations in rats and rabbits at maternally toxic doses. Therefore, appropriate precautions to prevent pregnancy should be taken in women of child-bearing potential as discussed in the Investigator Brochure (IB). There was a reduced T-cell-dependent antibody response (TDAR) in monkeys; however, this is unlikely to be clinically relevant because the TDAR finding was observed at a dose above the dose associated with systemic toxicity.

The no observed adverse effect level (NO[A]EL) (repeat-dose toxicity and immunotoxicity studies) or no observed effect level (NOEL) (reproductive toxicity studies) from key studies and exposure margins are presented in the IB. The exposure margins are based on preliminary population PK estimates of exposures from the NASH Phase 2 study (GS-US-384-1497).

Table 1-1. Estimated Exposure Margins For SEL After Oral Administration

Study Type	Species	Duration of Dosing	NO(A)EL (mg/kg/day)	SEL AUC24h (µg•h/mL)	SEL Exposure Margins[a]
Repeat-dose toxicity	Rat	26 weeks	15	164	18
	Monkey	39 weeks	5	11	1
Carcinogenicity	Mouse	26 weeks	M: 30 F: 100	M: 206 F: 194	M: 22 F: 21
	Rat	up to 96 weeks	M: 5 F: 3	M: 45.4 F: 49.5	M: 5 F: 5
Fertility	Rat	4 (males) and 2 (females) weeks prior to mating	75	—	—
Embryofetal development	Rat	Gestation Days 6 to 17	15	109	12
	Rabbit	Gestation Days 7 to 19	10	30.7	3
Peri- and postnatal development	Rat	F0: Gestation Day 6 to Lactation Day 10	30	F0: 118 F1: 18	F0: 13 F1: 2
Immunotoxicity	Monkey	4 weeks	15	59.5	6

F = female; F0 = initial generation (dams); F1 = first generation (pups); M = male; NO(A)EL = no observed (adverse) effect level
a Margins of exposure were calculated using the exposure (AUC_{24h} of 9.2 µg•h/mL) observed in NASH subjects at the 18 mg QD dose based on preliminary population PK data from the Phase 2 NASH study (GS-US-384-1497).
Source: Studies TX-223-2011, TX-223-2012, TX-223-2026, TX-223-2016, TX-223-2018 and TX-223-2027

1.2.3. Clinical Trials of Selonsertib

As of 17 July 2019, 10 Phase 1, 6 Phase 2, and 3 Phase 3 clinical studies have been conducted/are ongoing in which 390 healthy subjects, 248 subjects with DKD, an estimated 40 subjects with CKD, 1473 subjects with NASH, 50 subjects with AH, and 145 subjects with PAH have been dosed with SEL Across these studies, SEL was generally well tolerated. No adverse drug reactions with SEL have been identified to date.

Information on the completed and ongoing clinical studies can be found in the IB. Brief summaries of an additional Phase 1b study and the completed Phase 2 study relevant to this protocol are provided below.

1.2.3.1. A Phase 1b, Randomized, Blinded, Placebo-Controlled Study to Evaluate the Effect of Selonsertib on Renal Function as Assessed by Markers of Glomerular Filtration Rate in Subjects with Chronic Kidney Disease (GS-US-223-0110)

Study GS-US-223-0110 is a Phase 1b, blinded, randomized, placebo-controlled study that evaluated the effect of SEL on kidney function in subjects with CKD using markers of estimated ($eGFR_{cr}$) and measured GFR (mGFR, as assessed by iohexol clearance). Subjects (n = 82) with CKD ($eGFR_{cr}$ 20 to < 60 mL/min/1.73 m^2) were randomized 1:1 to receive SEL 18 mg or placebo once daily for 28 days followed by a 28-day washout period. After adjusting for baseline

$eGFR_{cr}$ and placebo treatment, a 4.8% decrease in mGFR on Day 7 and a decrease of 5.7% (approximately 2 mL/min/1.73 m^2) on Day 28 in the SEL treatment group was observed. This acute decrease in mGFR was reversible and deemed not clinically significant, as evidenced by no decrease in the SEL treatment group relative to placebo on Day 56. Compared with mGFR changes, there was a slightly larger decrease in $eGFR_{cr}$ in the SEL treatment group relative to placebo on Days 7 and 28 (7.0% and 6.5%, respectively) that was reversible on Day 56. Study conduct is currently complete and writing of the clinical study report is ongoing.

The results of this Phase 1b study are discordant with those of the previous Phase 1 study of SEL in healthy subjects (GS-US-223-3973). Numerically small changes in mGFR were observed during the on-treatment period in subjects with CKD that had not been observed in healthy subjects. The decrease in mGFR indicates there may be a secondary mechanism in addition to kidney transporter inhibition that is responsible for the changes in mGFR and $eGFR_{cr}$ observed in subjects with CKD. The rapid reversibility of the decrease in mGFR indicates there is no evidence of a nephrotoxic effect, and the safety profile of SEL was favorable in the Phase 1b study. Overall, the mechanism of decrease in mGFR in this population warrants further investigation with analyses ongoing while the totality of data from Study GS-US-223-0110 continues to support the development of SEL in subjects with kidney disease.

1.2.3.2. A Phase 2, Double-Blind, Placebo-Controlled, Dose-Ranging Study Evaluating the Efficacy, Safety, and Tolerability of SEL in Subjects with Diabetic Kidney Disease (GS-US-223-1015)

1.2.3.2.1. Study Design

Study GS-US-223-1015 is a completed Phase 2, double-blind, placebo-controlled, dose-ranging study that evaluated the efficacy, safety, and tolerability of SEL in subjects with DKD. A total of 334 subjects with type 2 diabetes mellitus (T2DM) and Stage 3 or Stage 4 kidney impairment and albuminuria receiving standard of care treatment for DKD were randomized (1:1:1:1) to 1 of 4 treatment groups: SEL 2, 6, or 18 mg, or matching placebo administered once daily for 48 weeks. The primary objective of this study was to determine the effect of SEL on eGFR decline in subjects with DKD.

1.2.3.2.2. Subject Disposition

Of the 334 randomized subjects, 333 subjects received at least 1 dose of study drug: 85 subjects received placebo and 248 subjects received SEL (81, 84, and 83 subjects received SEL 2, 6, and 18 mg, respectively).

A total of 256 subjects (76.9%) completed treatment and 76 subjects (22.8%) discontinued study drug (19 subjects [22.4%] in the placebo group and 57 subjects [23.0%] in the pooled SEL group [18.5%, 21.4%, and 28.9% for SEL 2, 6, and 18 mg, respectively]). The most frequent reason for discontinuation of study drug was due to an adverse event ([AE], 4 subjects [4.7%] in the placebo group and 18 subjects [7.3%] in the pooled SEL group), followed by progression to end stage kidney disease (ESKD) (4 subjects [4.7%] in the placebo group and 13 subjects [5.2%] in the pooled SEL group), and withdrawal of consent (3 subjects [3.5%] in the placebo group and 13 subjects [5.2%] in the pooled SEL group).

1.2.3.2.3. Activity and Efficacy Results

In the prespecified primary efficacy analysis, subjects receiving SEL had similar mean decreases from baseline in eGFR compared with the placebo group at Week 48 (mean [SE] difference from placebo: 0.38 [1.21] mL/min/1.73 m^2 for the SEL 2 mg group, 0.84 [1.22] mL/min/1.73 m^2 for the SEL 6 mg group, and −0.87 [1.23] mL/min/1.73 m^2 for the SEL 18 mg group; $p > 0.4$ for all pair-wise comparisons) (Figure 1-2). Differences in eGFR at Week 48 were confounded by acute effects of SEL on creatinine. Subjects receiving SEL 18 mg had a larger acute decrease in eGFR (approximately 10% of the baseline value at Week 4) than the other SEL dose groups or placebo group, which may be due, in part, to greater inhibition of the kidney transporters involved in the secretion of creatinine by SEL at this higher dose (Studies GS-US-223-0102 and GS-US-223-3973).

To evaluate the potential treatment effect of SEL in a future DKD study population, posthoc analyses were performed with 2 changes to the analysis population. First, posthoc analyses excluded data from 20 subjects enrolled at 2 study sites that were audited and found to have compliance violations, anomalous data, or both. Second, posthoc analyses excluded subjects with baseline eGFR < 20 mL/min/1.73 m^2 (n = 50 in the Full Analysis Set excluding subjects from the 2 sites described above) to reduce the probability of subjects experiencing an immediate decrease in eGFR to the threshold that defines kidney failure (eGFR < 15 mL/min/1.73 m^2). Two dose-dependent effects were observed that correspond to acute and chronic effects: a greater decline in eGFR acutely from Weeks 0 to 4 (creatinine transport effect [inhibition of tubular secretion of creatinine by SEL]), and a smaller decline in eGFR chronically from Weeks 4 to 48 (therapeutic effect) (Figure 1-3). Between Weeks 4 and 48, the rate of eGFR decline in the SEL 18 mg group was significantly slower than that in the placebo group (mean difference from placebo: 3.70 mL/min/1.73 m^2 annualized over 1 year, or 75% reduction in eGFR decline rate compared with placebo; nominal p = 0.036) (Table 1-2 and Table 1-3)

Figure 1-2. GS-US-223-1015: Adjusted Mean (95% CI) of Estimated Glomerular Filtration Rate (MDRD) Change from Baseline by Visit (Primary Analysis) (Full Analysis Set)

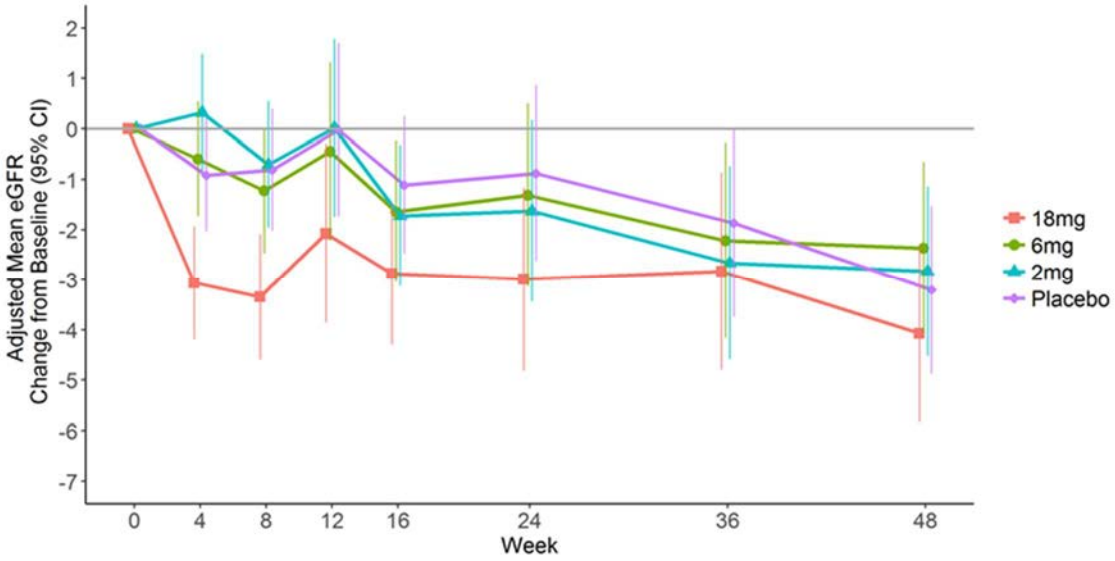


Figure displays adjusted mean (95% CI) eGFR change in randomized subjects who received at least 1 dose of study drug (N = 333). Results were obtained from mixed-effect model repeated measures (MMRM) with baseline eGFR, treatment group, visit, and treatment-by-visit interaction included in the model. MDRD = modification of diet in renal disease

Figure 1-3. GS-US-223-1015: Estimated Glomerular Filtration Rate (MDRD) Decline Rate Using a Piecewise Linear Random Slope Model (Posthoc Analysis)

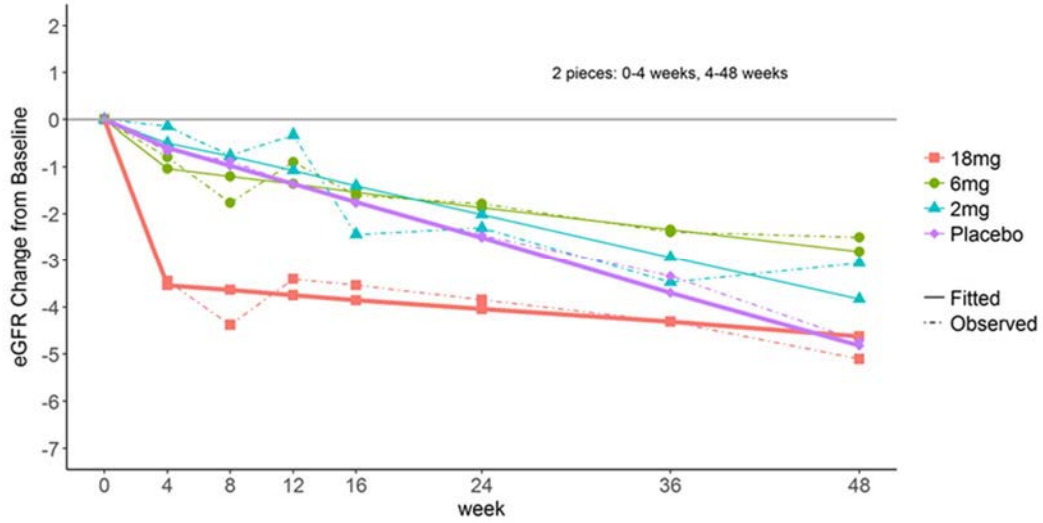


Figure displays observed and fitted eGFR change values (ml/min/1.73 m^2) from a piecewise linear random slope model in randomized subjects who received at least 1 dose of study drug, were not from the 2 excluded sites, and had a baseline eGFR ≥ 20 ml/min/1.73 m^2 (N = 263). The piecewise linear random slope model had a turning point at Week 4, with baseline eGFR, treatment group, week, and treatment-by-week interaction included in the model. MDRD = modification of diet in renal disease

Table 1-2. GS-US-223-1015: Estimated Glomerular Filtration Rate (MDRD) Decline Rate from Week 4 to Week 48 (Posthoc Analysis)

	SEL 18 mg (N = 67)	SEL 6 mg (N = 65)	SEL 2 mg (N = 67)	Placebo (N = 64)
eGFR decline rate (mL/min/1.73 m^2/year)				
Adjusted Mean (SE)	−1.27 (1.28)	−2.05 (1.23)	−3.90 (1.18)	−4.97 (1.21)
95% CI	−3.78, 1.24	−4.46, 0.37	−6.22, −1.59	−7.35, −2.59
Difference in eGFR decline rate from Placebo				
Adjusted Mean (SE)	3.70 (1.76)	2.93 (1.72)	1.07 (1.69)	—
95% CI	0.25, 7.16	−0.46, 6.31	−2.25, 4.39	—
p-value	0.036	0.090	0.528	—

CI = confidence interval; MDRD = modification of diet in renal disease; SE = standard error
Posthoc analysis was performed for subjects who received at least 1 dose of study drug, were not from the 2 excluded sites, and had a baseline eGFR ≥ 20 ml/min/1.73 m^2 (N = 263)
eGFR (MDRD) was calculated as 175 * serum creatinine-1.154 * age at laboratory collection-0.203 * 1.212 (if black) * 0.742 (if female)
Adjusted means for rate of eGFR decline from Week 4 to Week 48 were estimated from a piecewise linear random slope model in randomized subjects who received at least 1 dose of study drug. The model had a turning point at Week 4, with baseline eGFR, treatment group, week, and treatment-by-week interaction included in the model
Difference from placebo was the difference in adjusted eGFR decline rate between each SEL group and placebo

1.2.3.2.4. Safety Results

Table 1-3 presents the overall summary of AEs by treatment group. Overall, 80.8% of subjects experienced an AE: 83.5% in the placebo group and 79.8% in the pooled SEL group (79.0%, 84.5%, and 75.9% for SEL 2, 6, and 18, respectively). Adverse events related to study drug occurred in 9.4% (8 subjects) in the placebo group and 12.5% (31 subjects) in the pooled SEL group (8.6%, 11.9%, and 16.9% for SEL 2, 6, and 18 mg, respectively). Adverse events leading to study drug discontinuation occurred in 9.4% (8 subjects) in the placebo group compared with 12.1% (30 subjects) in the pooled SEL group (8.6%, 13.1%, and 14.5% for SEL 2, 6, and 18 mg, respectively). Overall, 4 deaths occurred (1.2%), with a frequency of 1.2% in the placebo group and 1.2% in the pooled SEL group (1.2%, 1.2%, and 1.2% for SEL 2, 6, and 18 mg, respectively). Three of the deaths were nontreatment emergent, i.e., occurred more than 30 days after the last dose of study drug.

Table 1-3. GS-US-223-1015: Overall Summary of Adverse Events (Safety Analysis Set)

Number (%) of Subjects With Any	SEL 2 mg (N = 81)	SEL 6 mg (N = 84)	SEL 18 mg (N = 83)	SEL Pooled (N = 248)	Placebo (N = 85)
AE	64 (79.0%)	71 (84.5%)	63 (75.9%)	198 (79.8%)	71 (83.5%)
Grade ≥ 3 AE	21 (25.9%)	20 (23.8%)	21 (25.3%)	62 (25.0%)	15 (17.6%)
AE Related to Study Drug	7 (8.6%)	10 (11.9%)	14 (16.9%)	31 (12.5%)	8 (9.4%)
Grade ≥ 3 AE Related to Study Drug	0	3 (3.6%)	0	3 (1.2%)	1 (1.2%)
SAE	24 (29.6%)	20 (23.8%)	20 (24.1%)	64 (25.8%)	16 (18.8%)
SAE Related to Study Drug	0	2 (2.4%)	0	2 (0.8%)	1 (1.2%)
AE Leading to Temporary Interruption of Study Drug	14 (17.3%)	8 (9.5%)	10 (12.0%)	32 (12.9%)	7 (8.2%)
AE Leading to Study Drug Discontinuation	7 (8.6%)	11 (13.1%)	12 (14.5%)	30 (12.1%)	8 (9.4%)
AE Leading to Death	0	1 (1.2%)	0	1 (0.4%)	0
All Deaths During Study	1 (1.2%)	1 (1.2%)	1 (1.2%)	3 (1.2%)	1 (1.2%)

Adverse events were mapped according to MedDRA Version 19
Treatment-emergent AEs are those started on or after first study dose date up to and including 30 days after permanent discontinuation, or led to premature study drug discontinuation
Toxicity grades (1=Mild, 2=Moderate, 3=Severe, 4=Life-Threatening, 5=Death) were from modified CTCAE Version 4.03

Table 1-4 presents a summary of AEs reported for ≥ 5% of subjects in any treatment group by preferred term. The most common AEs in the pooled SEL group were upper respiratory tract infection, hypertension, hyperkalemia, diarrhea, constipation, and hypoglycemia, with no dose-dependent toxicity noted.

Table 1-4. GS US-223-1015: Adverse Events Occurring in ≥ 5% of Subjects in Any Treatment Group by Preferred Term (Safety Analysis Set)

	SEL 2 mg (N = 81)	SEL 6 mg (N = 84)	SEL 18 mg (N = 83)	SEL Pooled (N = 248)	Placebo (N = 85)
Number (%) of Subjects Experiencing Any AE	64 (79.0%)	71 (84.5%)	63 (75.9%)	198 (79.8%)	71 (83.5%)
Upper respiratory tract infection	5 (6.2%)	5 (6.0%)	8 (9.6%)	18 (7.3%)	9 (10.6%)
Hypertension	9 (11.1%)	6 (7.1%)	3 (3.6%)	18 (7.3%)	6 (7.1%)
Hyperkalaemia	6 (7.4%)	4 (4.8%)	8 (9.6%)	18 (7.3%)	4 (4.7%)
Diarrhoea	8 (9.9%)	2 (2.4%)	7 (8.4%)	17 (6.9%)	4 (4.7%)
Anaemia	4 (4.9%)	6 (7.1%)	5 (6.0%)	15 (6.0%)	5 (5.9%)
Oedema peripheral	2 (2.5%)	5 (6.0%)	4 (4.8%)	11 (4.4%)	8 (9.4%)
Constipation	6 (7.4%)	7 (8.3%)	3 (3.6%)	16 (6.5%)	2 (2.4%)

	SEL 2 mg (N = 81)	SEL 6 mg (N = 84)	SEL 18 mg (N = 83)	SEL Pooled (N = 248)	Placebo (N = 85)
Nausea	8 (9.9%)	5 (6.0%)	1 (1.2%)	14 (5.6%)	4 (4.7%)
Acute kidney injury	3 (3.7%)	6 (7.1%)	6 (7.2%)	15 (6.0%)	2 (2.4%)
Back pain	3 (3.7%)	6 (7.1%)	6 (7.2%)	15 (6.0%)	2 (2.4%)
Hypoglycaemia	7 (8.6%)	5 (6.0%)	4 (4.8%)	16 (6.5%)	1 (1.2%)
Urinary tract infection	6 (7.4%)	1 (1.2%)	5 (6.0%)	12 (4.8%)	5 (5.9%)
Dyspnoea	1 (1.2%)	5 (6.0%)	6 (7.2%)	12 (4.8%)	3 (3.5%)
End stage kidney disease	2 (2.5%)	4 (4.8%)	3 (3.6%)	9 (3.6%)	6 (7.1%)
Chronic kidney disease	2 (2.5%)	5 (6.0%)	3 (3.6%)	10 (4.0%)	4 (4.7%)
Arthralgia	6 (7.4%)	1 (1.2%)	1 (1.2%)	8 (3.2%)	5 (5.9%)
Blood creatinine increased	6 (7.4%)	1 (1.2%)	3 (3.6%)	10 (4.0%)	2 (2.4%)
Cardiac failure congestive	3 (3.7%)	2 (2.4%)	5 (6.0%)	10 (4.0%)	2 (2.4%)
Cellulitis	1 (1.2%)	3 (3.6%)	6 (7.2%)	10 (4.0%)	1 (1.2%)
Dizziness	1 (1.2%)	1 (1.2%)	5 (6.0%)	7 (2.8%)	4 (4.7%)
Hyperglycaemia	6 (7.4%)	1 (1.2%)	3 (3.6%)	10 (4.0%)	1 (1.2%)
Metabolic acidosis	3 (3.7%)	1 (1.2%)	5 (6.0%)	9 (3.6%)	2 (2.4%)
Bronchitis	1 (1.2%)	1 (1.2%)	3 (3.6%)	5 (2.0%)	5 (5.9%)
Cough	3 (3.7%)	2 (2.4%)	5 (6.0%)	10 (4.0%)	0
Gout	3 (3.7%)	5 (6.0%)	0	8 (3.2%)	1 (1.2%)
Abdominal pain	0	5 (6.0%)	1 (1.2%)	6 (2.4%)	0

Adverse events were mapped according to MedDRA Version 19
Treatment-emergent AEs are those started on or after first study dose date up to and including 30 days after permanent discontinuation, or led to premature study drug discontinuation
Multiple AEs were counted once per subject for each PT. PTs are presented by descending order of the total frequency (all treatment groups combined)

Table 1-5 presents a summary of serious adverse events (SAEs) occurring in ≥ 2 subjects in any treatment group by preferred term. In the placebo group, 18.8% (16 subjects) experienced an SAE compared with 25.8% (64 subjects) in the pooled SEL group (29.6%, 23.8%, and 24.1% for SEL 2, 6, and 18 mg, respectively). The most common SAEs were acute kidney injury, congestive cardiac failure, pneumonia, chest pain, fluid overload, and hypertension, with no dose-dependent toxicity noted.

Table 1-5. GS-US-223-1015: Serious Adverse Events Occurring in ≥ 2 Subjects in Any Treatment Group by Preferred Term (Safety Analysis Set)

	SEL 2 mg (N = 81)	SEL 6 mg (N = 84)	SEL 18 mg (N = 83)	SEL Pooled (N = 248)	Placebo (N = 85)
Number (%) of Subjects Experiencing Any SAE	24 (29.6%)	20 (23.8%)	20 (24.1%)	64 (25.8%)	16 (18.8%)
Acute kidney injury	3 (3.7%)	3 (3.6%)	1 (1.2%)	7 (2.8%)	2 (2.4%)
Cardiac failure congestive	2 (2.5%)	1 (1.2%)	4 (4.8%)	7 (2.8%)	2 (2.4%)
Pneumonia	3 (3.7%)	2 (2.4%)	1 (1.2%)	6 (2.4%)	0
Chest pain	1 (1.2%)	2 (2.4%)	1 (1.2%)	4 (1.6%)	1 (1.2%)
Fluid overload	2 (2.5%)	1 (1.2%)	1 (1.2%)	4 (1.6%)	0
Hypertension	3 (3.7%)	0	1 (1.2%)	4 (1.6%)	0
Acute myocardial infarction	1 (1.2%)	2 (2.4%)	0	3 (1.2%)	0
Chronic obstructive pulmonary disease	3 (3.7%)	0	0	3 (1.2%)	0
Dyspnoea	0	2 (2.4%)	1 (1.2%)	3 (1.2%)	0
Bradycardia	2 (2.5%)	0	0	2 (0.8%)	1 (1.2%)
Cardiac failure acute	2 (2.5%)	0	0	2 (0.8%)	1 (1.2%)
Hypovolaemia	2 (2.5%)	0	0	2 (0.8%)	0
kidney failure	2 (2.5%)	0	0	2 (0.8%)	0
Cerebrovascular accident	0	0	0	0	2 (2.4%)

Adverse events were mapped according to MedDRA Version 19
Treatment-emergent AEs are those started on or after first study dose date up to and including 30 days after permanent discontinuation, or led to premature study drug discontinuation
Preferred terms are presented by descending order of the total frequency (all treatment groups combined)

Table 1-6 presents a summary of subjects with Grade 3 or 4 laboratory abnormalities. In the placebo group, 51.8% (44 subjects) experienced a Grade 3 or 4 laboratory abnormality compared with 51.2% (127 subjects) in the pooled SEL group (44.4%, 52.4%, and 56.6% for SEL 2, 6, and 18 mg respectively). The most common Grade 3 or 4 laboratory abnormalities were hyperglycemia and fasting hyperglycemia.

Table 1-6. GS-US-223-1015: Grade 3 or 4 Laboratory Abnormalities (Safety Analysis Set)

	SEL 2 mg (N = 81)	SEL 6 mg (N = 84)	SEL 18 mg (N = 83)	SEL Pooled (N = 248)	Placebo (N = 85)
Subjects with Post-baseline Value	81	84	83	248	85
Maximum Post-baseline Toxicity Grade					
Grade 3 or 4	36 (44.4%)	44 (52.4%)	47 (56.6%)	127 (51.2%)	44 (51.8%)
Grade 3	32 (39.5%)	39 (46.4%)	44 (53.0%)	115 (46.4%)	42 (49.4%)
Grade 4	4 (4.9%)	5 (6.0%)	3 (3.6%)	12 (4.8%)	2 (2.4%)

Toxicity grades (1=Mild, 2=Moderate, 3=Severe, 4=Life-Threatening, 5=Death) were from modified CTCAE Version 4.03
For maximum post-baseline toxicity grade, the most severe graded abnormality from all tests was counted for each subject
For each individual laboratory test, the most severe graded abnormality for that test was counted for a subject
A treatment-emergent laboratory abnormality was defined as an increase of at least 1 toxicity grade from baseline at any time post-baseline up to and including the date of last study drug dose plus 30 days

1.2.3.2.5. Conclusion

This study did not meet the predefined efficacy endpoints, which did not account for the acute effects of SEL on eGFR. In post-hoc analyses, SEL demonstrated a dose-dependent reduction in decline of kidney function in subjects with advanced DKD. Differences in eGFR slope between Weeks 4 and 48 indicate that SEL may be efficacious in slowing the progression of DKD {Chertow 2019}.

Treatment with SEL was well tolerated and no dose-limiting toxicity was observed.

1.3. Rationale for This Study

Diabetes mellitus is the leading cause of CKD in the developed world, accounting for half of all incident cases of ESKD, the latter of which is associated with a 5-year survival of less than 40%. Approximately 13 million people in the United States (US) and European Union (EU) have concomitant CKD and T2DM. Approximately 10 million of these patients have CKD Stage 2-4 and the prevalence continues to increase in step with the increasing prevalence of T2DM and metabolic syndrome. Current standard of care (SOC) therapies for DKD (angiotensin converting enzyme inhibitors [ACEi] and angiotensin receptor blockers [ARB]) target glomerular hypertension and do not address the underlying pathological processes of chronic inflammation and oxidative stress that persist and drive disease progression through fibrosis. The continual decline in eGFR that occurs in many patients with DKD despite treatment with these approved therapies highlights the large unmet medical need.

Selonsertib is a potent and selective once daily, orally administered inhibitor of ASK1 that has the potential to improve pathological sequelae in the kidney leading to GFR decline. SEL is expected to delay the time to development of serious adverse clinical outcomes such as kidney transplantation, dialysis, and death in patients with DKD. SEL has demonstrated clinical activity and a favorable safety and tolerability profile in a Phase 2 study in subjects with Stage 3 and 4 DKD.

In the Phase 2 study in subjects with Stage 3 and 4 DKD, subjects receiving SEL 18 mg had a larger acute decrease in eGFR (approximately 10% of the baseline value at Week 4) than the other SEL dose groups or placebo group, which may be due, in part, to greater inhibition of the kidney transporters involved in the secretion of creatinine by SEL at this higher dose (Studies GS-US-223-0102 and GS-US-223-3973). In a Phase 1b study in subjects with CKD with a eGFR between 20 to < 60 mL/min/1.73 m^2 (GS-US-223-0110), acute reversible decreases for both eGFR and mGFR were observed with SEL 18 mg, indicating a potential secondary mechanism involved in the acute decrease observed in eGFR upon initiation of SEL.

Due to this acute (potentially artefactual) effect observed in prior studies, this Phase 2b study has incorporated a Run-in design to account for the acute eGFR effect in order to better characterize the chronic (long-term) effect of SEL on eGFR. To maintain the integrity of the study, other than eGFR values < 15 mL/min/1.73 m², eGFR results collected at Visits A, B, C, and Visit 1 will not be released to subjects, investigators or sponsor before study unblinding. All eGFR values starting at week four will be released to subjects, investigators and the sponsor for safety monitoring and treatment decisions.

1.4. Rationale for Dose Selection of Selonsertib

A SEL dosing regimen of 18 mg once daily was selected for evaluation in this Phase 2b DKD study based on results from the dose-ranging Phase 2 studies in subjects with DKD, NASH, and PAH and an examination of pharmacokinetic/pharmacodynamic (PK/PD) relationships between SEL exposure and response.

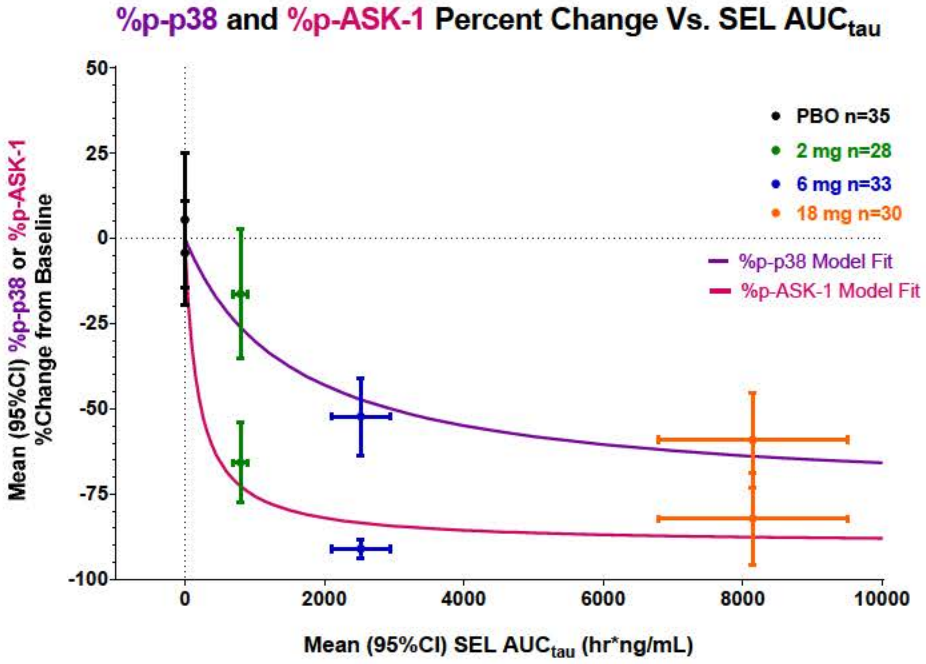
Across the clinical development program, SEL administered for up to 48 weeks has been well tolerated with no clear exposure relationship for the incidence or severity of adverse events or laboratory abnormalities. Collectively, the efficacy, safety, and PK/PD data support evaluation of a single dose of SEL 18 mg in the proposed Phase 2b study in subjects with DKD.

Dose selection for SEL in the Phase 2bDKD study was based on results from the dose-ranging Phase 2 study in subjects with DKD indicating near maximal inhibition of p38 phosphorylation in blood cells, and near maximal slowing of the chronic rate of eGFR decline between week 4 and 48 of treatment. In addition, the percent change from baseline in phosphorylation of ASK-1 was measured in whole blood lysates with a sandwich immunoassay using anti-phospho-ASK-1 antibody to capture phospho-ASK-1 (p-ASK-1) and anti-ASK-1 antibody for detection. This was determined at Week 12 with all remaining samples from study GS-US-223-1015 (N = 126: 35, 28, 33, 30 from the placebo, 2 mg, 6 mg, and 18 mg daily SEL treatment arms, respectively) and provides additional data supporting the 18 mg dose of SEL. As the p-ASK-1 analysis was conducted on a subset of samples from the dataset previously presented in the IB, PK/PD analyses for both % phospho-p38 (p-p38) and p-ASK-1 have been reconstructed in this subset for a direct comparison to the observed p-ASK-1 results (Figure 1-4).

Across the range of SEL doses evaluated, a consistently greater degree of inhibition of the more proximal measure of ASK-1 engagement, %p-ASK-1, is observed compared to %p-p38 (Figure 1-4). Pharmacokinetic/pharmacodynamic model fits for %p-ASK-1 and %p-p38 in this analysis set indicate the maximum predicted inhibition of ASK-1 and p-38 phosphorylation to be

89.6% and 75.8%, respectively, with SEL exposure resulting in half-maximal inhibition of 185 hr*ng/mL and 1520 hr*ng/mL, respectively. These analyses of ASK-1 engagement support dose selection of 18 mg SEL which provides near maximal effect and any further increased dose of SEL is not expected to provide meaningfully greater PD response, or increased efficacy.

Figure 1-4. PK/PD Relationships for SEL Exposure (AUCtau) and %p-p38 or %p-ASK-1 (Study GS-US-223-1015)



Similar to p38 phosphorylation, in the Phase 2 DKD study, a dose- and exposure (AUC_{tau})-dependent response relationship was observed for the rate of eGFR decline (slope) from Week 4 to 48. The mean eGFR slope in the 18 mg group was -1.27 mL/min/1.73 m^2/year, significantly smaller than the placebo group slope (-4.97 mL/min/1.73 m^2/year), and residing on the flat portion of the dose- and exposure-response curves. Additionally, the relationship between p-p38 inhibition and chronic eGFR slope by dose group showed a trend in improved efficacy with increasing dose of SEL with minimal overlap between SEL 18 mg and placebo.

In the Phase 2 DKD study, there was a small difference in change in eGFR between the 6 mg and 18 mg doses of SEL that trended in favor of the 18 mg dose at 48 weeks but was not statistically significant. This improvement with the 18 mg dose in slowing the rate of eGFR decline may be clinically significant over longer periods of time. For example, for patients starting with an eGFR of 30 ml/min/1.73 m^2, this difference between doses would increase time to kidney failure from approximately 4 years with SEL 6 mg to approximately 6 years with SEL 18 mg. In the context of such large therapeutic differences and a disease course that spans many years, SEL 18 mg is the optimal dose for the long-term prevention of kidney failure among patients with moderate to advanced DKD.

Across the clinical development program, SEL administered for up to 48 weeks has been well tolerated with no clear exposure relationship for the incidence or severity of adverse events or laboratory abnormalities. Collectively, the efficacy, safety, and PK/PD data support evaluation of SEL 18 mg in this Phase 2b study in subjects with DKD.

1.5. Rationale for Placebo Use

All subjects, including those randomized to the placebo arm, will continue to receive standard of care therapy (e.g., ACEi, ARB, etc.) as part of their treatment for T2DM and moderate to advanced DKD. Thus, the use of placebo will not interfere with their current treatment plan.

1.6. Risk/Benefit Assessment for the Study

Chronic kidney diseases, including DKD, are serious diseases that have broad and negative public health, social, and economic impacts. New agents that prevent long-term decreases in kidney function are needed to improve the efficacy, safety, and tolerability of treatments for these diseases.

This study will provide additional information regarding the safety and efficacy of SEL in patients with T2DM and moderate to severe DKD. Transient increases in serum creatinine have been observed in a dose-dependent manner with SEL and are consistent with the inhibitory effect of SEL on transporters involved in tubular creatinine secretion (MATE1 and MATE2K, IC_{50} = 2.4 μM and 0.94 μM). The potential benefits of SEL for the treatment of DKD were shown in the Phase 2 study GS-US-223-1015. SEL appeared to be safe and well-tolerated without significant dose-related toxicity and demonstrated a clinically meaningful reduction in decline of kidney function among subjects with advanced DKD. Differences in eGFR slope between SEL and placebo from 4 to 48 weeks demonstrate that SEL is expected to slow the progression of DKD. These data support further evaluation of the 18 mg dose in a Phase 2b study. No events considered to be adverse drug reactions (ADRs) to SEL have been identified in the clinical studies conducted to date. Thus, at this time, no significant clinical risks are expected with administration of SEL.

Potential risks of this study include those related to the fact that SEL is a new chemical entity. Although a long term safety profile has yet to be established, SEL, administered at doses up to 100-mg in Phase 1 studies and up to 18 mg in Phase 2 studies in subjects with NASH, AH, DKD, or PAH, appears to be well tolerated.

A concentration QT analysis demonstrated that SEL at doses up to 100-mg did not cause clinically relevant prolongation of the QTc interval. To mitigate the potential risk of liver injury, subjects are monitored closely; defined rules for close observation and drug cessation due to elevated liver tests are specified in the protocols. In addition, embryofetal toxicity was observed in nonclinical studies; therefore to prevent potential fetal exposure, adherence to highly effective methods of contraception will be required.

Additional risks to study subjects include those attributable to study participation in general, including risks associated with frequent clinic visits and laboratory blood draws, and the associated pain and discomfort of phlebotomy. Strategies to mitigate these risks include close monitoring of lab values as well as AEs. Parameters for discontinuation of the study drugs due to AEs and non-kidney laboratory abnormalities are also defined and will be closely followed.

For this study, frequent assessments of kidney function will be performed from the collection of both blood and urine samples. Parameters for discontinuation of the study drugs due to adverse events are defined in this study protocol and will be closely followed.

While the potential benefits and risks described above must be confirmed, available data in DKD subjects treated for 48 weeks, as well as the favorable safety profile seen across the Phase 2 studies in NASH, DKD, and PAH, provide strong rationale for a favorable benefit/risk ratio in support of the study in subjects with DKD.

1.7. Compliance

This study will be conducted in compliance with this protocol, Good Clinical Practice (GCP), and all applicable regulatory requirements.

2. OBJECTIVES

The primary objective of this study is:

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

The secondary objectives of this study are:

- 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

CCI

3. STUDY DESIGN

3.1. Endpoints

Primary efficacy endpoint:

$eGFR_{cr}$ slope from treatment-specific baselines

The secondary endpoints of this study are:

- Proportion of Kidney Clinical Events at Week 48 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

- Time from randomization to first occurrence of a Kidney Clinical Event
- $eGFR_{cys}$ slope from pre-run-in baseline

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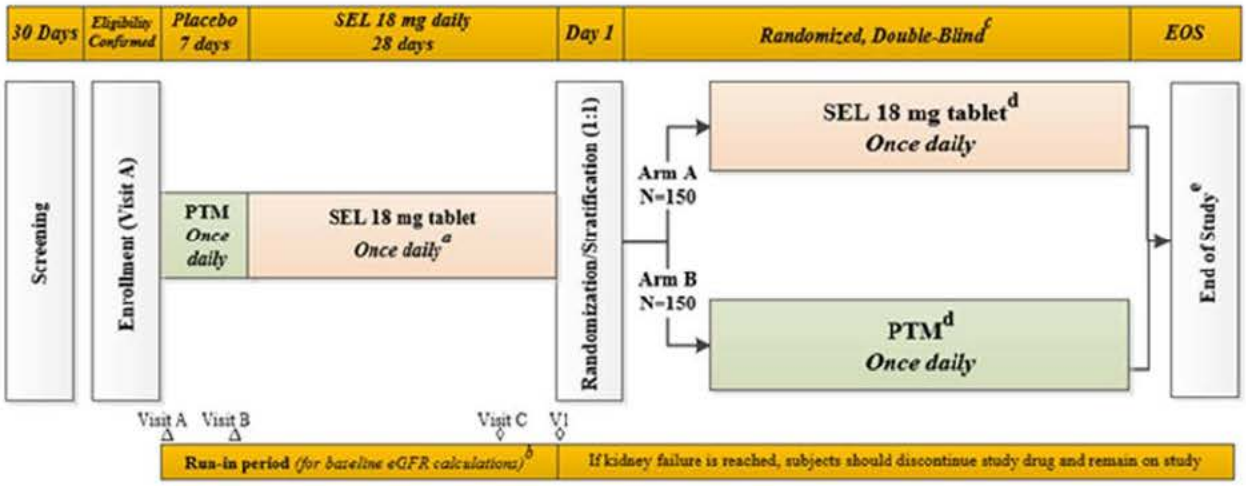
3.2. Study Design

This is a Phase 2b, randomized, double-blind, placebo-controlled, parallel group, multicenter study evaluating the efficacy and safety of SEL in subjects with 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 3-1.

Figure 3-1. 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 eGFR 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.

3.3. Duration of Treatment

At least 52 weeks (4 weeks during the Run-in period and at least 48 weeks post randomization)

3.4. Discontinuation of Study Drug

Selonsertib or PTM should be discontinued for any of the following reasons in consultation with the Gilead Medical Monitor and/or sponsor designee:

- Death
- 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)
- Pregnancy during the study; refer to Appendix 6
- Participation in another therapeutic clinical study
- Clinically significant adverse event in the opinion of the subject or investigator
- Significant protocol violation that impacts subject safety
- Significant subject noncompliance with study drug administration, study procedures, or study requirements per judgement of the investigator
- Intercurrent illness that would, in the judgment of the investigator, ***permanently*** affect assessments of clinical status to a significant degree
- Unacceptable toxicity, or toxicity that, in the judgment of the investigator, compromises the ability to continue study-specific procedures or is considered to not be in the subject's best interest
- Study blinding is intentionally broken by the subject or the study site
- Discontinuation of the study at the request of Gilead, a regulatory agency, or an institutional review board or independent ethics committee (IRB/IEC)

Subjects who permanently discontinue study drug will have an end of treatment (EOT) visit scheduled as soon as possible after the decision to discontinue study drug is made. If an ECG, 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. In addition to the EOT visit, subjects who permanently discontinue study drug prior to global study end date will have a 30 day (±7 days) EOT Follow-up visit which will include an assessment of eGFR and UACR.

Every attempt should be made to keep these subjects in the study and complete all subsequent study visits in the same way as subjects who are still on study drug. If this is not possible, subjects off study drug will have the option to be followed via limited assessments as defined in Section 6.7.2.

Subjects who have permanently discontinued study drug, reached kidney failure, or are no longer able to continue to attend clinic visits in-person, and have not withdrawn full consent will be asked to continue to participate in this study via remote assessments as defined in Section 6.7.3.

3.5. Discontinuation Criteria from Study

Subjects may discontinue from study for the following reasons:

- Death
- Pregnancy during the study; refer to Appendix 6
- Participation in another therapeutic clinical study
- Withdrawal of consent and refusal to allow any subsequent data collection, including passive methods. If a subject is amenable to any degree of limited follow-up or data collection, including passive methods, the subject must not be discontinued from the study
- Significant subject noncompliance with study drug administration, study procedures, or study requirements per judgement of the investigator
- The subject is lost to follow-up after exhaustion of all contact efforts until the global study end date; see Section 6.7.3.
- Investigator's decision to remove the subject from the study
- Discontinuation of the study by the Sponsor, a Regulatory Agency, or an IRB or EC

For subjects who discontinue from study for reasons other than death, withdrawal of full consent or loss to follow-up, the subject should complete the end of study (EOS) visit. Subjects who permanently discontinue study drug and study on the same day should complete the EOT visit and return to clinic for their EOT Follow-up visit 30 days (±7 days) for assessments. If an ECG or STS was conducted at a previous visit within 24 weeks of the EOT/EOS visit, the assessment does not need to be performed at the EOT/EOS visit.

3.6. End of Study

The primary analysis of $eGFR_{cr}$ slope will be performed after all subjects in the ITT Analysis Set complete the Week 48 visit or discontinue from the study. The global study end date is defined as 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.

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CCI [redacted]

4. SUBJECT POPULATION

4.1. Number of Subjects and Subject Selection

This study will enroll approximately 300 subjects with T2DM and eGFR ranging from ≥ 20 mL/min/1.73 m² to < 60 mL/min/1.73 m² with albuminuria receiving standard of care therapy (ACEi or ARB, or intolerant to ACEi and ARB).

4.2. Inclusion Criteria

Subjects must meet *all* of the following inclusion criteria to be eligible for enrollment in this study:

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 prior to 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 ACEi or ARB as a single agent at the maximum labeled or tolerated dose deemed appropriate for the subject by the investigator and/or per local SOC 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) Subjects already receiving SGLT-2 inhibitors must be on a stable dose at least 2 weeks prior to Enrollment

6) For females of childbearing potential (unless permanently sterile or post-menopausal, as described in Appendix 6), a negative serum pregnancy test at Screening

7) For male and female subjects of childbearing potential who engage in heterosexual intercourse, agreement to abstain or use protocol specified method(s) of contraception as described in Appendix 6

8) Male subjects must refrain from sperm donation from the Screening visit through 30 days following the last dose of study drug

9) Female subjects must refrain from egg donation or harvest from the Screening visit through 30 days following the last dose of study drug

10) Subjects must refrain from blood product donation from the Screening visit through 30 days following the last dose of study drug

11) 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)

12) Required baseline laboratory data, analyzed by central laboratory, within 30 days prior to Enrollment (Visit A) as shown in the table below

Organ System	Parameter	Required Value
Hematologic	WBC, neutrophil, lymphocyte, and platelet count	≥ 0.75 x LLN to ≤ 1.5 x ULN
Hepatic	Serum total bilirubin	≤ 1.5 × ULN
	Serum ALT	
	Serum AST	

Organ System	Parameter	Required Value
Pregnancy	β-HCG[a]	Negative
Infection	HIV[b]	Negative HIV antibody
	HBV	Negative HBsAg and negative HBc antibody or positive HBc and negative for HBV DNA by quantitative PCR
	HCV	Negative HCV antibody or negative viral RNA (if HCV antibody is positive)

a For women of childbearing potential only; serum β-HCG must be negative during Screening
b If screening test is positive, a negative confirmatory test will be required for eligibility
Abbreviations: β-HCG = beta human chorionic gonadotropin, ALT = alanine aminotransferase, AST = aspartate aminotransferase, DNA = deoxyribonucleic acid, LLN = lower limit of normal, HBc antibody = anti-hepatitis B core antibody, HBsAg = hepatitis B surface antigen, HBV = hepatitis B virus, HCV = hepatitis C virus, HIV = human immunodeficiency virus, PCR = polymerase chain reaction, RNA = ribonucleic acid, ULN = upper limit of normal, WBC = white blood count

13) Have either a normal 12-lead electrocardiogram (ECG) or an ECG with abnormalities that are not considered to be clinically significant by the investigator within 30 days prior to Enrollment (Visit A)

14) In the judgment of the investigator, participation in the study offers an acceptable benefit to risk ratio, taking into consideration the subject's current DKD status, medical condition, and the potential benefits and risks of alternative treatments for DKD

15) Willing and able to comply with scheduled visits, drug administration plan, laboratory tests, other study procedures, and study restrictions

16) Willing and able to give informed consent prior to any study specific procedures being performed

4.3. Exclusion Criteria

Subjects who meet *any* of the following exclusion criteria are not to be enrolled in this study:

1) 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 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) Diagnostic or interventional procedure that requires intravenous or intra-arterial iodinated contrast agent within 30 days prior to Enrollment (Visit A) and/or planned during the study Run-in period

10) 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

11) Pregnant or lactating females or planning to become pregnant or breastfeed during the study

12) Concurrent use of either

    a) ACEi and ARB or

    b) Mineralocorticoid receptor antagonist (MRA) or direct renin inhibitor (DRI) in combination with an ACEi or ARB for at least 2 weeks prior to Enrollment

13) Requiring chronic administration of prohibited medications as per protocol

14) Participation in another investigational study within 1 month or within 5 half-lives of the prior investigational agent (whichever is longer) prior to Enrollment (Visit A)

15) Concurrent participation in another therapeutic clinical study

16) Prior participation in any clinical trial of SEL

17) Known hypersensitivity to the study drug (SEL/placebo-to-match), the metabolites, or formulation excipients

18) Prior or ongoing clinically significant illness, medical condition, surgical history, physical finding, ECG finding, or laboratory abnormality that, in the investigator's opinion, could adversely affect the safety of the subject or impair the assessment of study results

19) Presence of any condition that could, in the opinion of the investigator, compromise the subject's ability to participate in the study, such as history of substance abuse, alcoholism, or a psychiatric condition

4.4. Eligibility Criteria for Randomization

Subjects must meet *all* of the following criteria to be eligible for randomization:

1) eGFR ≥ 15 mL/min/1.73 m² at all central laboratory assessments during the Run-in period prior to Randomization (Visit 1)

2) At least 7 consecutive daily doses of SEL, without interruption, immediately prior to Visit C and prior to Randomization (Visit 1)

3) Subject did not permanently discontinue study drug during the Run-in period

4) Subject did not withdraw consent

5) Subject did not initiate, change dose, or discontinue SGLT-2 inhibitor during the Run-in period or is not anticipated to initiate, change dose or discontinue SGLT-2 inhibitor within 12 weeks after Randomization (Visit 1)

6) Negative urine pregnancy test for female subjects of childbearing potential

7) No ongoing clinically significant illness, medical condition, surgical history, physical finding, or laboratory abnormality that, in the investigator's opinion, could adversely affect the safety of the subject or impair the assessment of study results

5. INVESTIGATIONAL MEDICINAL PRODUCTS

5.1. Randomization, Blinding and Treatment Codes

An Interactive Web Response System (IWRS) will be used to maintain a central log documenting screening, enrollment and randomization and study drug bottle numbers. It is the investigator's responsibility to ensure that the subject is eligible for the study prior to enrollment and randomization. Subjects will be assigned a screening number at the time of consent. Once eligibility for enrollment has been confirmed, the subjects will be assigned a unique subject number via IWRS and enter the Run-in period. During the Run-in, treatment will be unblinded and subjects will receive PTM for at least 7 consecutive days and SEL for at least 4 weeks. Subjects must be on SEL for at least 7 consecutive doses prior to Visit C and Visit 1 in order to randomize.

Subjects who meet randomization eligibility criteria will be randomized in a 1:1 ratio to either SEL or PTM. Randomization will be stratified by average eGFR values from Visit A and Visit B, average UACR values from Visit A and B, and concomitant use of SGLT-2 inhibitors at Visit 1. The unique subject number assigned at enrollment will remain the same in the randomized phase of the study.

- eGFR Strata:

eGFR strata (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

During the randomized phase, subjects and all personnel directly involved in the conduct of the study will be blinded to treatment assignment. Study drug will be dispensed in a blinded fashion to the subjects. Additionally, to maintain the blinding of treatment assignment, serum creatinine and eGFR results collected at Visits A, B, C, and 1 will not be released to subjects, investigators or sponsor before study unblinding, with the exception of eGFR values < 15 mL/min/1.73 m². The IWRS will be utilized to maintain the blinding of eGFR values required for stratification. A third party vendor, who is independent of Gilead, or Biometrics personnel at Gilead who are not associated with the study team will be unblinded to baseline eGFR values in order to monitor and calculate the decrease in eGFR of ≥ 40% relative to baseline.

Other specified Gilead personnel or independent vendors may be unblinded based on their study role. The Pharmacokinetics File Administrator, or designee, in Bioanalytical Operations and/or Clinical Data Management, who facilitates the data transfer of PK files between Gilead and vendors, will remain unblinded. Individuals in Clinical Packaging & Labeling or Clinical Supply Management who have an Unblinded Inventory Manager role in the IXRS system for purposes of IMP inventory management will remain unblinded. Individuals in PVE responsible for safety signal detection, IND safety reporting and/or expedited reporting of suspected unexpected serious adverse reactions (SUSARs) may be unblinded to individual case data and/or group level summaries. External (ie, contract research organizations) biostatisticians and programmers will be unblinded for data monitoring activities. Regulatory Compliance personnel may also be unblinded for purposes of identifying subjects for whom study drug concentrations are to be determined for blinded studies in which Quality Assurance audits of bioanalytical or research reports are necessary.

5.1.1. Procedures for Breaking Treatment Codes

In the event of a medical emergency where breaking the blind is required to provide medical care to the subject, the investigator may obtain treatment assignment directly from the IWRS system for that subject (refer to the IWRS Site User Manual for unblinding instruction). Gilead recommends but does not require that the investigator contact the Gilead Medical Monitor and/or sponsor designee before breaking the blind. Treatment assignment should remain blinded unless that knowledge is necessary to determine subject emergency medical care. The rationale for unblinding must be clearly explained in source documentation and on the electronic case report form (eCRF), along with the date on which the treatment assignment was obtained. The investigator is requested to contact the Gilead Medical Monitor and/or sponsor designee promptly in case of any treatment unblinding, and retain this information at the study site team level only.

Blinding of study drug is critical to the integrity of this clinical study and therefore, if a subject's treatment assignment is disclosed to the investigator, during the blinded treatment phase, the subject will have study drug discontinued. All subjects will be followed until the global study end date unless consent to do so is specifically withdrawn by the subject.

Gilead Pharmacovigilance & Epidemiology (PVE) may independently unblind cases for expedited reporting of suspected unexpected serious adverse reactions (SUSARs).

5.2. Description and Handling of Selonsertib (SEL)

5.2.1. Formulation

SEL 18 mg tablets will be supplied as round, film-coated gray tablets debossed with an underscored "18" on one side and "GSI" on the other side. The tablets are approximately 7.14 mm in diameter. In addition to the active ingredient, SEL 18 mg tablets contain the following inactive ingredients: lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, magnesium stearate, polyvinyl alcohol, polyethylene glycol, titanium dioxide, talc, and iron oxide black.

PTM 18 mg tablets are available for blinding purposes. Each placebo-to-match tablet is identical to SEL 18 mg tablets in their size, shape, and appearance and contains the same inactive ingredients.

5.2.2. Packaging and Labeling

SEL and PTM tablets are packaged in white, high-density polyethylene (HDPE) bottles. Each bottle contains 30 tablets, silica gel desiccant and polyester packing material. Each bottle is capped with a child-resistant polypropylene screw cap fitted with an induction-sealed, aluminum-faced liner.

Study drugs to be distributed to centers in the United States (US) and other participating countries shall be labeled to meet applicable requirements of the US Food and Drug Administration (FDA), European Union (EU) Guideline to Good Manufacturing Practice - Annex 13 (Investigational Medicinal Products), and/or other local regulations.

5.2.3. Storage and Handling

SEL 18 mg and PTM tablets should be stored at controlled room temperature of 25°C (77°F); excursions are permitted between 15°C and 30°C (59°F and 86°F). Storage conditions are specified on the label. Until dispensed to the subjects, all bottles of study drug should be stored in a securely locked area, accessible only to authorized site personnel. To ensure the stability and proper identification, study drug should not be stored in a container other than the containers in which they were supplied.

Consideration should be given to handling, preparation, and disposal through measures that minimize drug contact with the body. Appropriate precautions should be followed to avoid direct eye contact or exposure when handling.

5.3. Dosage and Administration of Selonsertib / Placebo-to-Match

The administration of study drug will be recorded in the source documentation and in the eCRF. Study drug will be self-administered by the subject orally once daily at approximately the same time each day. The study drug should be swallowed whole with water and may be taken with or without food. A dose is considered missed if the subject cannot take the dose within 12 hours of their regular dosing time. If a subject misses a dose, the subject should take their next dose at the regular dosing time.

Following completion of screening assessments, eligible subjects will enroll into the Run-in period. Subjects will self-administer PTM orally once daily from Enrollment (Visit A) to Visit B for at least 1 week, at approximately the same time each day. Following Visit B subjects will receive at least 4 weeks of SEL (18 mg) orally once daily at approximately the same time each day.

After completing the Run-in period, subjects meeting randomization eligibility criteria will be randomized 1:1 to receive either SEL 18 mg or PTM orally once daily.

5.3.1. Dose Interruption

The Gilead Medical Monitor and/or sponsor designee should be consulted prior to study drug interruption when medically feasible. Prior to resumption of study drug, the investigator should discuss the case with the Gilead Medical Monitor and/or sponsor designee. Study drug interruption should be considered in the following situations:

- Intercurrent illness that would, in the judgment of the investigator, affect assessments of clinical status to a significant degree. Following resolution of intercurrent illness, the subject may resume study dosing at the discretion of the investigator
- Subject is scheduled for elective or emergency procedures that require nothing by mouth; timing of study drug pause should be determined in consultation with the Gilead Medical Monitor and/or sponsor designee
- See Section 7.5 for dose interruptions related to toxicity including liver enzyme abnormalities and eGFR decline
- If study drug is withheld, restart study drug as soon as clinically appropriate and check eGFR at next scheduled visit, preferably with study drug taken for at least 7 consecutive days.

NOTE: While study drug is interrupted for any of the above reasons, the subject may continue to have study visits and to take part in procedures and assessments, if deemed medically appropriate by the investigator.

5.4. Prior and Concomitant Medications

All concomitant medications will be recorded in the source documents and eCRFs. This includes concomitant medications taken within 30 days prior to Screening; concomitant medications of interest, as defined in Section 6.4.2, up to 1 year prior to Screening; and any taken during the study through the 30 Day EOS Safety Follow-up visit or until subjects are being followed via remote assessments as defined in Section 6.7.3.

The following medications are prohibited:

- Any investigational medication or device within 30 days or within 5 half-lives of the prior investigational agent (whichever is longer) prior to Enrollment and throughout the study
- Concurrent use of study drug with both an ACEi and ARB
- Strong cytochrome P4503A4 (CYP3A4) inducers may decrease the exposure of SEL and could lead to decreased efficacy. Use of strong CYP3A4 inducers is prohibited from 2 weeks prior to Enrollment through end of treatment
- Inhibitors of kidney transporter-mediated creatinine secretion may impact the assessment of efficacy. Use of inhibitors of creatinine secretion is prohibited from 2 weeks prior to Enrollment through end of study

Caution should be exercised when co-administering sensitive P-gp substrates with narrow therapeutic index with SEL as it may increase the concentrations of these agents. Investigators should refer to the full prescribing information for additional guidance on use of concomitant medication with a P-gp inhibitor.

Examples of representative medications that are prohibited 2 weeks prior to enrollment or which should be used with caution starting at enrollment are listed in Table 5-1. This is not an exhaustive list of medications that are prohibited or to be used with caution. If there are questions about concomitant medications, please contact the Gilead Medical Monitor or Sponsor Designee.

Table 5-1. Examples of Medications that are Prohibited or to be Used with Caution[a]

	Agents Prohibited
Drug Class	**Prohibited 2 weeks prior to enrollment through the end of study**
Antianginals[b]	ranolazine[c]
Antiarrhythmics[b]	amiodarone[d], dronedarone[c], dofetilide[c]
Antibiotics[b]	trimethoprim
Antifungals[b]	isavuconazole[c]
Antiparasitics[b]	pyrimethamine[c]
Direct renin inhibitors (DRI)[e]	aliskiren[f]
H2 Blockers[b,i]	cimetidine, famotidine
Mineralocorticoid receptor antagonists (MRA)[e]	spironolactone, eplerenone
Nuclear factor erythroid 2–related factor 2 (Nrf2) activator	bardoxolone[c]
	Agents Prohibited
Drug Class	**Prohibited 2 weeks prior to enrollment through the end of treatment**
Anticonvulsants[g]	phenobarbital, phenytoin
Antimycobacterials[g]	rifampin
Herbal/Natural Supplements[g]	St. John's Wort

Category	Agents to be used with caution Use with caution from enrollment through end of treatment
Cardiac Medications[f]	digoxin[h], dabigatran etexilate, flecainide
Antineoplastic/immunosuppressant[f]	methotrexate

a Not all of these example medications may be approved in each of the countries where the study is being conducted; please refer to local product information
b May increase serum creatinine and decrease eGFR.
c Not approved in Japan
d Due to the long half-life of amiodarone, prohibited 90 days prior to enrollment through end of the study
e Disallowed if concurrent use with ACEi or ARB for at least 2 weeks prior to Enrollment. If subject cannot tolerate ACEi or ARB, subject may use either a DRI OR an MRA as a single agent. If medically necessary after Week 12, concurrent use of MRA with ACEi or ARB is permitted. However, concurrent use with ACEi or ARB is associated with risk of hyperkalemia, so caution must be exercised. Please refer to full prescribing information for additional guidance.
f SEL may increase the exposure of these medications and must be used with caution. Please refer to the full prescribing information for additional guidance
g May result in a decrease in the concentration of SEL
h 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 Permissible H2 blockers include ranitidine, nizatidine, roxatidine, and lafutidine.

5.5. Accountability for Study Drug

The investigator is responsible for ensuring adequate accountability of all used and unused study drug bottles. This includes acknowledgement of receipt of each shipment of study drug (quantity and condition). All used and unused study drug bottles dispensed to subjects must be returned to the site, and any study drug losses must be explained.

Study drug accountability records will be provided to each study site to:

- Record the date received and quantity of SEL/PTM bottles
- Record the date, subject number and the SEL/PTM bottle numbers dispensed
- Record the date, quantity of used and unused SEL/PTM bottles returned, along with the initials of the person recording the information.

5.5.1. Investigational Medicinal Product Return or Disposal

The study drug (SEL/PTM) should be retrieved from each subject at the end of each dispensing interval. The quantity of study drug and the date returned by the subject should be recorded in the subject's study drug accountability records. All study drug returned by the subject should be retained for review by the study site monitor prior to return of study drug to Gilead Sciences or destruction at the site.

Please see Section 9.1.8 for more information.

6. STUDY PROCEDURES

The study procedures to be conducted for each subject enrolled in the study are presented in the Study Procedures Table (Appendix 2) and described in the text below.

In the event a study visit is delayed, all attempts should be made to complete a visit as close as possible to the missed visit. All subsequent visits should be completed on the original schedule based on time from randomization. If a subject is on a drug hold or permanently off study drug, they should still return for regular assessments according to the schedule of procedures.

If a subject experiences drug interruption or is unable to undergo study assessments at their site due to an SAE or other emergent reasons (e.g., pandemic, natural disasters or other reasons including recommendations by national, state, or local authorities, site institution or investigator), document the deviation from the protocol along with the reason in source documentation and consult with the sponsor on a case-by-case basis. Sites should attempt alternative means (such as phone calls, text messages, e-mails, or other suitable means) to maintain contact with subjects to follow up on assessments including AEs, IP, and concomitant medication usage.

The investigator must document any deviation from protocol procedures and notify the sponsor or contract research organization (CRO).

6.1. Informed Consent

All subjects must sign and date the most recent Institutional Review Board/Institutional Ethics Committee (IRB/IEC) approved informed consent form before any study-specific procedures are performed. CCI [redacted] It is recommended sites make every effort to obtain the name, address, and phone number of a relative or friend of the subject. This information will be stored at the site, and not shared with the sponsor or sponsors representatives, but used for remote assessments as defined in protocol Section 6.7.3.

6.2. Subject Enrollment

Entry into screening does not guarantee enrollment into the study. To manage the total study enrollment, Gilead, at its sole discretion, may suspend screening and/or enrollment at any site or study-wide at any time.

Subjects meeting all of the inclusion criteria and none of the exclusion criteria will return to the clinic within the 30 day screening window for enrollment into the study.

Any consented subject who is excluded from the study before enrollment will be considered a screen failure. All screen failures must be documented along with an adequate description of the reason the subject was considered a screen failure. If available, information should be provided

as to why the subject did not meet eligibility criteria, withdrew consent, experienced an intercurrent illness, or had other events that precluded enrollment. Of note, subjects may be rescreened only once for study eligibility under a new screening number.

From time of obtaining informed consent and prior to study drug initiation, the following type of events should be reported on the eCRFs: all SAEs and AEs which are related to protocol-mandated procedures. All other untoward medical occurrences observed during the Screening period, including exacerbation or changes in medical history are to be captured on the medical history eCRF. See Section 7 Adverse Events and Toxicity Management for additional details.

6.3. Randomization and Treatment Assignment

After the Run-in period, subjects who meet randomization eligibility will be randomized to SEL or PTM based on a randomization schedule prepared by Gilead and/or a designee before the start of the study. Any consented subject who is excluded from the study before randomization will be considered a Run-in failure.

Eligible subjects will be centrally randomized via IWRS. See Section 5.1 Randomization, Blinding and Treatment Codes for additional details.

6.4. Study Procedure Descriptions

6.4.1. Medical History & Medication History

A complete medical and surgical history will be obtained prior to Enrollment (Visit A) and recorded on the eCRF, including a history of the subject's DKD.

Medical history should include, but not be limited to (as applicable): T2DM, DKD, diabetic neuropathy, diabetic retinopathy, diabetic gastroparesis, congestive heart failure NYHA (Class I, II, IIIa, IIIb), valvular heart disease, coronary artery disease, coronary revascularization (coronary artery bypass graft, percutaneous coronary intervention), dyslipidemia, stroke, PVD, peripheral revascularization, NASH, fatty liver disease, gout, kidney stones, cancer, and history of smoking tobacco.

6.4.2. Concomitant Medications

Concomitant medications include prescription medication, over-the-counter preparations, and herbal/homeopathic remedies and therapies used within 30 days prior to Screening, concomitant medications of interest up to 1 year prior to Screening, and any taken during the study through the 30 Day EOS Safety Follow-up visit or until subjects are being followed via remote assessments as defined in Section 6.7.3.

Concomitant medications of interest on this study are defined as the following categories of medications:

a) Glucose-lowering (oral and injectable medications)

b) Cardiovascular risk reduction: blood pressure and/or heart failure (e.g., calcium channel blockers, beta blockers, diuretics, other medications for blood pressure and/or heart failure); lipid-lowering (e.g., statins, fibrates, PCSK9 inhibitors, other lipid-lowering medications); blood thinners (anti-platelets, anti-thrombotics, anti-coagulants); anti-arrhythmics

c) Kidney disease risk reduction: renin-angiotensin-aldosterone system inhibitors [RAASi] (e.g., angiotensin converting enzyme inhibitors [ACEi], angiotensin receptor blockers [ARB], and other medications); sodium-glucose cotransporter 2 [SGLT2] inhibitors

d) Kidney disease complications: potassium binders, bicarbonate, erythropoiesis-stimulating agents, hypoxia-inducible factor prolyl hydroxylase inhibitor (HIF-PHI), iron, phosphate binders, vitamin D analogs, calcimimetics, etc.

6.4.3. Physical Examination

A complete physical examination (PE) will be performed at Screening and End of Treatment. The PE will be performed by a physician, physician's assistant, or nurse practitioner qualified to perform the assessment.

A complete PE should include source documentation of general appearance and the following body systems including head, neck, and thyroid; eyes, ears, nose, throat, mouth, and tongue; chest (excluding breasts); respiratory; CV; lymph nodes; abdomen; musculoskeletal; neurological.

At each subsequent visit where a complete PE is not scheduled, a symptom-driven PE may be performed if necessary, if a new symptom or a worsening symptom is reported by the subject or is identified upon assessment by the physician, physician's assistant or nurse practitioner, or qualified. Significant changes should be recorded as AEs, if applicable.

Height, waist circumference and body mass index will be collected at specified time points.

6.4.4. Vital Signs

Assessment of vital signs will include measurement of resting blood pressure, pulse, respiratory rate, temperature and weight performed by a qualified designee as per standard institutional guidelines at each study visit.

Screening Subjects must meet Inclusion Criteria #11: 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).

Blood pressure is to be obtained when the subject has been seated for ≥ 5 minutes with feet flat on the floor and measurement arm supported so that the midpoint of the manometer cuff is at heart level. The subject's position during blood pressure assessments should remain consistent and a consistent arm should be used throughout the study. Measure and record the blood pressure to the nearest 2 millimeter of mercury (mmHg) mark on the manometer or to the nearest whole number on an automatic device.

CCI [redacted]

[redacted]

[redacted] [redacted]

[redacted]

6.4.7. Pregnancy Testing

All females of childbearing potential as defined in Appendix 6 will have a serum pregnancy test at Screening and urine pregnancy tests at Visit B during the Run-in period, Visit 1 and every 4 weeks thereafter until the 30 Day EOT Follow-up visit. After Week 4, every 4 week pregnancy testing may be performed at home in between clinic visits, where possible, or in clinic, if at home pregnancy tests are unavailable. Pregnancy testing will continue every 4 weeks through the 30 Day EOT Follow-up visit. At home pregnancy testing kits will be provided. Females of childbearing potential who perform at home pregnancy tests will be contacted by the site at 4 week intervals and asked to report the result of the at home pregnancy test.

In the event of a positive urine home pregnancy result, subjects will be instructed to stop study drug immediately (if applicable) and return to the clinic as soon as possible for a serum pregnancy test.

6.4.8. Electrocardiogram

A single 12-lead ECG will be collected at Screening, every 48 weeks, and at EOT and EOS visits. Collection of additional ECGs for routine safety monitoring at additional time points or days is at the discretion of the Investigator based on GCP.

ECGs should always be collected prior to PK (or any other blood draw) if they are to be collected at the same nominal time point. Subjects should be resting quietly and free of distraction (e.g., television, conversation) for 10 minutes prior to and during the ECG collection. Electrocardiograms will be recorded using the site's standard ECG equipment and will include ventricular rate, PR interval, QRS interval and QT interval. ECGs will be interpreted by the investigator (or qualified designee) for clinical significance and results will be entered into the eCRF.

6.4.9. Clinical Outcome Assessments

Clinical outcome assessments CCI [redacted] should be completed at the start of the study visit and prior to the clinical and laboratory assessments. Questionnaires should be administered prior to conducting the CCI test when performed on the same day.

CCI [redacted]

CCI [redacted]

6.4.10. Laboratory Assessments

All blood and urine samples for laboratory assessments will be sent to the central laboratory for analysis. Specific instructions for collection, processing, labeling and shipping samples will be provided in a central laboratory manual. Laboratory samples will be collected as specified in Appendix 2. A list of clinical laboratory analytes to be collected are listed in Appendix 3.

For fasting laboratory visits, subjects should abstain from all food for at least 8 hours prior to laboratory draw. Water is allowed.

6.4.11. Urine Albumin to Creatinine Ratio

Collection of the first urine void after the subject awakes from sleep is the preferred urine collection option because more concentrated urine allows for enhanced detection of analytes in small quantities. When possible, the subject should capture the first morning void and bring the sample to the clinic within 1 hour of collection. If that is not possible, the specimen should be refrigerated and brought in within 12 hours of collection. As the first morning void may be difficult to obtain, an early morning or early waking sample is accepted in situations where the subject cannot collect a first void.

Subjects can have up to 3 UACR collections during the Screening period. Any one of the UACR values and any one of the eGFR values collected during Screening may be used to satisfy the inclusion criterion. Qualifying eGFR and UACR values do not need to be collected on the same day. UACR stratification will be the average of Enrollment (Visit A) and Visit B measurements.

6.4.12. Estimated Glomerular Filtration Rate

- Screening: Subjects can have up to 3 eGFR 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 the inclusion criteria. Subjects must have an 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.

- Run-in period: Other than eGFR values < 15 mL/min/1.73 m², eGFR and serum creatinine results collected at Visit A, B, C, and Visit 1 will not be released to subjects, investigators or sponsor before study unblinding. Local labs assessing eGFR or creatinine should not be collected during the Run-in period or during the time after the Run-in period leading up to the Week 4 visit unless required for safety.

- Run-in prior to Week 4: If there is a ≥50% decline in eGFR compared to Screening during the Run-in period prior to Week 4, a central laboratory flag will be issued to notify the site of this drop. Sites will be notified of the ≥50% eGFR decline but will continue to be blinded to the eGFR values. Local labs assessing eGFR or creatinine should not be collected during the Run-in period or during the time after the Run-in period leading up to the Week 4 visit unless required for safety.

- Randomization: Subjects must have eGFR values of ≥ 15 mL/min/1.73 m² at all central laboratory assessments during the Run-in period to satisfy randomization eligibility.

- Stratification: eGFR will be the average of Enrollment (Visit A) and Visit B measurements. This value will be transferred directly from the central laboratory to the IWRS system for stratification.

A clinical endpoint event is a confirmed decrease in eGFR to < 15 mL/min/1.73 m^2 for subjects who remain asymptomatic without initiation of dialysis or kidney transplantation. The eGFR confirmatory measure will be collected at the next scheduled study visit but at least 4 weeks after the index measurement.

Another clinical endpoint event is a confirmed change in eGFR ≥ 40% decline from pre-run-in baseline. The ≥ 40% decline confirmatory measure will be collected at the next scheduled study visit but at least 4 weeks after the index measurement. A third party vendor, who is independent of Gilead, or Biometrics personnel at Gilead who are not associated with the study or study team, will be unblinded to baseline eGFR values to provide the calculation of decrease in eGFR of ≥ 40% relative to baseline.

Only eGFR values from the central laboratory will be utilized for efficacy assessments. Following randomization, eGFR calculations will be confirmed by Gilead.

6.4.12.1. eGFR Calculations

eGFR will be calculated from measured serum creatinine using the CKD-EPI Creatinine Equation (2009).

The CKD-EPI (mL/min/1.73 m^2) Creatinine Equation (2009) is:

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

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

For secondary CCI [redacted] analyses, eGFR may be calculated from measured cystatin C using the CKD-EPI cystatin C Equation (2012) as below:

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

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

6.4.13. Digoxin Testing

Digoxin should be administered with caution from enrollment through end of treatment. Digoxin levels should be assessed at Visit C, Week 4, and per investigator discretion. Digoxin levels will continue to be checked during the study period per investigator discretion. Investigators should monitor and adjust digoxin dose as necessary based on prescribing information.

CCI [redacted]

CCI [redacted]

6.5. Assessments for Subjects who Reach Kidney Failure While on Study Drug

Subjects who reach kidney failure will be instructed to discontinue study drug, complete the EOT and 30 Day (±7 days) EOT Follow-up visits, which will include an assessment of eGFR and UACR. Following the 30 Day EOT Follow-up visit, subjects who reach kidney failure will continue on study, followed via remote assessments per Section 6.7.3, but no longer followed for the primary efficacy endpoint.

6.6 Assessments for Discontinuation of Study Drug

Prior to premature study drug discontinuation, the Gilead Medical Monitor and/or sponsor designee should be consulted. Subjects who permanently discontinue from study drug (see Section 3.4) will complete an EOT visit and return to clinic for a 30 Day (± 7) EOT Follow-up visit. If a subject has completed a 12-lead ECG, or the STS test within 24 weeks prior to the EOT visit, these assessments do not need to be performed.

6.7. Post End of Treatment Follow-up Assessments

Following permanent study drug discontinuation, subjects should remain on study and continue to attend all subsequent study visits in the same manner as subjects who are still on study drug for full assessments (see Section 6.7.1).

Alternative follow-up visits and assessments have been defined to ensure subjects remain on study through the global study end date. If a subject indicates the assessments or in-clinic visits have become burdensome, an alternative follow-up method should be implemented (see Sections 6.7.2 and 6.7.3).

6.7.1. Full Assessments

For subjects who prematurely discontinue from study drug, all efforts should be made for the subject to remain on study to complete all assessments through the global end of study. If the subject following study drug discontinuation remains on study, the subject should resume study visits as per the Study Procedures Table (see Appendix 2).

6.7.2. Limited Assessments

Subjects who permanently discontinue study drug will be encouraged to continue all study visits according to the same schedule and continue the same assessments as subjects still receiving study drug. However, if a subject requests limited follow up, at a minimum, the following assessments must be performed every 12 weeks to follow the subject for kidney and cardiovascular outcomes (see Appendix 2).

- Complete physical exam (symptom driven)
- Vital signs including weight
- AE and SAE collection per protocol Section 7

- Concomitant Medications
- eGFR
- Chemistry and Hematology

6.7.3. Remote Assessments

Subjects who have permanently discontinued study drug, reached kidney failure, or are no longer able to continue to attend clinic visits in-person, and **have not withdrawn full consent** will be asked to continue study participation through remote contact, without in-clinic study visits. Subjects will be contacted approximately every 24 weeks until the global study end date. At a minimum, subjects will be contacted at the global study end date.

Subjects will be contacted via telephone, email, or other contact methods through friends or family. Details regarding discussions via telephone, email, or other contact must be properly documented by the site in the source records, including the responses from the subject. The investigator will make every effort to contact the subject or a close relative or caretaker by phone to collect information. The investigator should show due diligence by documenting in the source documents steps taken to contact the subject (e.g., dates of phone calls, registered letters, etc.).

Follow-up for survival, kidney outcomes, and safety will continue until reasons listed in protocol Section 3.5 are met or until the global study end date.

Information gathered will include:

- Survival status
- Death details, if applicable
- Receipt of kidney transplant
- Dialysis initiation post study drug discontinuation
- AE and SAE collection per protocol Section 7

6.8. Unscheduled Visits

Unscheduled visits may occur at any time while the subject is enrolled and on study. Unscheduled procedures, including but not limited to, vital signs, laboratory assessments, 12-lead ECG and health-related quality of life questionnaires may be conducted. Data generated during an unscheduled visit will be collected on the eCRF.

6.9. Sample Storage

Residual biological samples from all visits may be frozen and stored if specific consent is obtained. These stored samples may be used by Gilead or research partners of Gilead to help answer questions about the study drugs, DKD, and its associated conditions, or clinical laboratory testing to provide additional safety data. No human genetic testing will be performed without express written consent of study subjects. CCI [redacted]

7. ADVERSE EVENTS AND TOXICITY MANAGEMENT

7.1. Definitions of Adverse Events, Adverse Reactions, and Serious Adverse Events

7.1.1. Adverse Events

An AE is any untoward medical occurrence in a clinical study subject administered a medicinal product, which does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and/or unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. AEs may also include pre- or post-treatment complications that occur as a result of protocol specified procedures, lack of efficacy, overdose, drug abuse/misuse reports, or occupational exposure. Preexisting events that increase in severity or change in nature during or as a consequence of participation in the clinical study will also be considered AEs.

An AE does not include the following:

- Medical or surgical procedures such as surgery, endoscopy, tooth extraction, and transfusion. The condition that led to the procedure may be an adverse event and must be reported.
- Pre-existing diseases, conditions, or laboratory abnormalities present or detected before the screening visit that do not worsen. Situations where an untoward medical occurrence has not occurred (eg, hospitalization for elective surgery, social and/or convenience admissions)
- Overdose without clinical sequelae (see Section 7.6.1)
- Any medical condition or clinically significant laboratory abnormality with an onset date before the consent form is signed and not related to a protocol-associated procedure is not an AE. It is considered to be pre-existing and should be documented on the medical history eCRF.

7.1.2. Serious Adverse Events

A **serious adverse event** (SAE) is defined as an event that, at any dose, results in the following:

- Death
- Life-threatening (Note: The term “life-threatening” in the definition of “serious” refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.)
- In-patient hospitalization or prolongation of existing hospitalization
- Persistent or significant disability/incapacity

- A congenital anomaly/birth defect

- A medically important event or reaction: such events may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes constituting SAEs. Medical and scientific judgment must be exercised to determine whether such an event is reportable under expedited reporting rules.

  Examples of medically important events include:

  Intensive treatment in an emergency room or at home for allergic bronchospasm

  Blood dyscrasias or convulsions that do not result in hospitalization

  Development of drug dependency or drug abuse

- For the avoidance of doubt, infections resulting from contaminated medicinal product will be considered a medically important event and subject to expedited reporting requirements

7.1.3. Clinical Laboratory Abnormalities and Other Abnormal Assessments as Adverse Events or Serious Adverse Events

Laboratory abnormalities without clinical significance are not recorded as AEs or SAEs. However, laboratory abnormalities (eg, clinical chemistry, hematology, and urinalysis) that require medical or surgical intervention or discontinuation must be recorded as an AE, as well as an SAE, if applicable. In addition, laboratory or other abnormal assessments (eg, electrocardiogram, x-rays, vital signs) that are associated with signs and/or symptoms must be recorded as an AE or SAE if they meet the definition of an AE or SAE as described in Sections 7.1.1 and 7.1.2. If the laboratory abnormality is part of a syndrome, record the syndrome or diagnosis (ie, anemia), not the laboratory result (ie, decreased hemoglobin).

For specific information on handling of clinical laboratory abnormalities in this study, please refer to Section 7.5.

For adverse events associated with laboratory abnormalities, the event clinical severity should be graded in the context of the underlying conditions; this may or may not be in agreement with the grading of the laboratory abnormality.

7.2. Assessment of Adverse Events and Serious Adverse Events

The investigator or qualified subinvestigator is responsible for assessing AEs and SAEs for causality and severity, and for final review and confirmation of accuracy of event information and assessments.

7.2.1. Assessment of Causality for Study Drugs and Procedures

The investigator or qualified subinvestigator is responsible for assessing the relationship to study drug using clinical judgment and the following considerations:

- **No**: Evidence exists that the adverse event has an etiology other than the study drug. For SAEs, an alternative causality must be provided (eg, pre-existing condition, underlying disease, intercurrent illness, or concomitant medication)
- **Yes**: There is reasonable possibility that the event may have been caused by the study drug

It should be emphasized that ineffective treatment should not be considered as causally related in the context of adverse event reporting.

The relationship to study procedures (eg, invasive procedures such as venipuncture or biopsy) should be assessed using the following considerations:

- **No:** Evidence exists that the adverse event has an etiology other than the study procedure
- **Yes:** The adverse event occurred as a result of protocol procedures, (eg., venipuncture)

7.2.2. Assessment of Severity

The severity of AEs will be graded using a modified version of the Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0, November 27, 2017 (see Appendix 4). For each event, the highest severity grade attained should be reported. The modifications to the CTCAE criteria are the addition of a Grade 1 upper respiratory infection and a revision of the Hyperglycemia grading scale (reference Appendix 4 for grading scales).

If a CTCAE criterion does not exist, the investigator should use the grade or adjectives: Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), Grade 4 (life-threatening), or Grade 5 (fatal) to describe the maximum severity of the AE. For purposes of consistency with the CTCAE, these severity grades are defined in Table 7-1.

Table 7-1. Guidelines for Grading of Adverse Event Severity

Grade	Adjective	Description*
Grade 1	Mild	Asymptomatic or mild symptoms; clinical or diagnostic observations only, intervention not indicated
Grade 2	Moderate	Minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (preparing meals, shopping, using telephone, managing money, etc.)
Grade 3	Severe	Medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living (bathing, dressing, and undressing, feeding self, using toilet, taking medications, and not bedridden)
Grade 4	Life-threatening	Life-threatening consequences; urgent intervention indicated
Grade 5	Fatal	Death related to adverse event

* A semi-colon indicates 'or' within the description of the grade.

The distinction between the seriousness and the severity of an AE should be noted. Severe is a measure of intensity; thus, a severe reaction is not necessarily a serious reaction. For example, a headache may be severe in intensity, but would not be classified as serious unless it met one of the criteria for serious events listed in Section 7.1.2.

7.3. Investigator Requirements and Instructions for Reporting Adverse Events and Serious Adverse Events to Gilead

Requirements for collection prior to study drug initiation:

After informed consent, but prior to initiation of study medication, the following types of events should be reported on the eCRFs: all SAEs and adverse events related to protocol-mandated procedures.

7.3.1. Adverse Events

Following initiation of study drug and throughout the duration of the study, including the 30 Day EOS Safety Follow-up period, collect all AEs, regardless of causal relationship. AEs must be collected and reported to the eCRF database as instructed.

Regarding subjects who permanently discontinue study drug but remain on study, AEs are collected as follows:

- Full Assessments (per Section 6.7.1): Subjects continuing on study and completing full assessments, AEs are collected throughout the duration of the study including the 30 Day EOS Safety Follow-up period.

- Limited Assessments (per Section 6.7.2): Subjects continuing on study and completing limited assessments, AEs are collected throughout the duration of the study including the 30 Day EOS Safety Follow-up period.

- Remote Assessments (per Section 6.7.3): Subjects continuing on study and completing survival outcome assessments, AEs are collected through the 30 Day EOT Follow-up period.

All AEs should be followed up until resolution or until the adverse event is stable, if possible. Gilead Sciences may request that certain AEs be followed beyond the protocol defined follow-up period.

7.3.2. Serious Adverse Events

All SAEs, regardless of causal relationship, that occurs after the subject first consents to participate in the study (ie, signing the informed consent) and throughout the duration of the study, including the 30 Day EOS Safety Follow-up period, must be reported to the eCRF database and Gilead PVE as instructed. This also includes any SAEs resulting from protocol-associated procedures performed after informed consent is signed.

If the investigator learns of any SAEs that occur after study participation has concluded and the event is deemed relevant to the use of IMP, he/she should promptly document and report the event to Gilead PVE.

Regarding subjects who prematurely discontinue study drug but remain on study, SAEs are collected as follows:

- Full Assessments (per Section 6.7.1): subjects continuing on study and completing full assessments, SAEs are collected throughout the duration of the study including the 30 Day EOS Safety Follow-up period.

- Limited Assessments (per Section 6.7.2): subjects continuing on study and completing limited assessments, SAEs are collected throughout the duration of the study including the 30 Day EOS Safety Follow-up period.

- Remote Assessments (per Section 6.7.3): subjects continuing on study and completing survival outcome assessments, SAEs are collected through the 30 Day EOT Follow-up period.

All AEs and SAEs will be recorded in the eCRF database within the timelines outlined in the eCRF completion guideline.

Electronic Serious Adverse Event (eSAE) Reporting Process

- Site personnel record all SAE data in the eCRF database and from there transmit the SAE information to Gilead PVE within 24 hours of the investigator's knowledge of the event. Detailed instructions can be found in the eCRF completion guidelines

- If for any reason it is not possible to record the SAE information electronically, ie, the eCRF database is not functioning, record the SAE on the paper serious adverse event reporting form and submit within 24 hours to:

Gilead PVE:	Fax: PPD Email: PPD

- As soon as it is possible to do so, any SAE reported via paper must be transcribed into the eCRF database according to instructions and within timelines outlined in the eCRF completion guidelines

- If an SAE has been reported via a paper form because the eCRF database has been locked, no further action is necessary

- For fatal or life-threatening events, copies of hospital case reports, autopsy reports, and other documents are also to be submitted by e-mail or fax when requested and applicable. Transmission of such documents should occur without personal subject identification, maintaining the traceability of a document to the subject identifiers

- Additional information may be requested to ensure the timely completion of accurate safety reports
- Any medications necessary for treatment of the SAE must be recorded onto the concomitant medication section of the subject's eCRF and the event description section of the SAE form

7.4. Gilead Reporting Requirements

Depending on relevant local legislation or regulations, including the applicable US FDA Code of Federal Regulations, the EU Clinical Trials Directive (2001/20/EC) and relevant updates, and other country-specific legislation or regulations, Gilead may be required to expedite to worldwide regulatory agencies reports of SAEs, serious adverse drug reactions (SADRs), or SUSARs. In accordance with the EU Clinical Trials Directive (2001/20/EC), Gilead or a specified designee will notify worldwide regulatory agencies and the relevant IEC in concerned Member States of applicable SUSARs as outlined in current regulations.

In the intended study population, Gilead anticipates the occurrence of SAEs that would not be meaningful to report on an individual basis to regulatory agencies in an expedited fashion. These events include SAEs that are manifestations of the underlying disease, commonly occur in the study population independent of drug exposure, or are components of the study endpoints. The following SAEs will not be reported to regulatory agencies in an expedited fashion throughout the conduct of this clinical trial unless they are life-threatening or fatal, or if reporting is specifically requested by any regulatory agencies:

- Kidney impairment
- Chronic kidney disease
- Diabetic nephropathy
- Diabetes mellitus
- Hypertension
- Hyperkalaemia
- Hypoglycaemia
- Hyperglycaemia
- Blood creatinine abnormal
- Blood creatinine increased
- Glomerular filtration rate abnormal
- Glomerular filtration rate decreased

- Albuminuria
- Proteinuria
- Kidney failure
- End stage kidney disease
- Dialysis
- Dialysis device insertion
- Kidney transplant
- Acute myocardial infarction
- Cardiac failure congestive
- Cardiac failure acute
- Cerebrovascular accident
- Atrial fibrillation

Assessment of expectedness for SAEs will be determined by Gilead using reference safety information specified in the investigator's brochure or relevant local label as applicable.

All investigators will receive a safety letter notifying them of relevant SUSAR reports associated with any study drug. The investigator should notify the IRB or IEC of SUSAR reports as soon as is practical, where this is required by local regulatory agencies, and in accordance with the local institutional policy.

7.5. Toxicity Management

All clinical and clinically significant laboratory toxicities will be managed according to uniform guidelines detailed in the Management of Clinical and Laboratory Adverse Events (Appendix 5).

For study-specific discontinuation and interruption criteria, refer to Section 3.4 and Section 5.3.1. Specific toxicity discontinuation criteria in Section 3.4 supersede general toxicity guidelines, and in general, where discrepancy is present, the more conservative criteria apply. The Gilead Medical Monitor and/or sponsor designee should be consulted prior to study drug discontinuation when medically feasible.

7.5.1. Grades 1 and 2 Laboratory Abnormality or Clinical Event

For Grades 1 and 2 laboratory abnormalities or clinical events not specified in Sections 3.4 or Section 5.3.1, continue study drug at the discretion of the investigator.

7.5.2. Grade 3 Laboratory Abnormality or Clinical Event

For Grade 3 laboratory abnormalities or clinical events not specified in Sections 3.4 or Section 5.3.1, the following toxicity management guidelines apply:

- For a Grade 3 clinically significant laboratory abnormality or clinical event, study drug may be continued if the event is considered to be unrelated to study drug
- For a Grade 3 clinical event or clinically significant laboratory abnormality confirmed by repeat testing, that is considered to be related to study drug, study drug should be withheld until the toxicity returns to ≤ Grade 2
- If a laboratory abnormality or clinical event recurs to ≥ Grade 3 following re-challenge with study drug and is considered related to study drug, then study drug should be permanently discontinued and the subject managed according to local clinical practice. Recurrence of laboratory abnormalities considered unrelated to study drug may not require permanent discontinuation and study drug may be continued at the discretion of the investigator

7.5.3. Grade 4 Laboratory Abnormality or Clinical Event

For Grade 4 laboratory abnormalities or clinical events not specified in Sections 3.4 or 5.3.1, the following toxicity management guidelines apply:

- For a Grade 4 clinical event or clinically significant laboratory abnormality, confirmed by repeat testing, that is considered to be related to study drug, study drug should be permanently discontinued and the subject managed according to local practice. The subject should be followed as clinically indicated until the laboratory abnormality returns to baseline or is otherwise explained, whichever occurs first. A clinically significant Grade 4 laboratory abnormality that is not confirmed by repeat testing should be managed according to the algorithm for the new toxicity grade
- Study drug may be continued without dose interruption for a clinically non-significant Grade 4 laboratory abnormality (eg, Grade 4 creatine kinase after strenuous exercise or non-fasting triglyceride elevation that can be medically managed) or a clinical event considered unrelated to the study drug

Grade 4 treatment-emergent toxicities will be noted by the investigator and brought to the attention of the Gilead Medical Monitor and/or sponsor designee, who will discuss with the investigator and determine the appropriate course of action. All subjects experiencing AEs must be monitored periodically until symptoms subside, any abnormal laboratory values have resolved or returned to baseline levels or they are considered irreversible, or until there is a satisfactory explanation for the changes observed.

7.5.4. Liver Enzymes

To mitigate the potential risk of liver injury, subjects are monitored closely; defined rules for close observation and drug cessation due to elevated liver tests are specified.

After becoming aware of any of the following abnormal laboratory values, an unscheduled visit (ie, sequential visit) should occur to retest within 3 to 7 days of receipt of the original test results. Retest may be obtained sooner if medically indicated per investigator judgement.

If ALT and/or AST:

- > 3 – 5 x ULN (Grade 2): Monitor at least weekly until < or equal to 1.5 x ULN
- > 5 – 20 x ULN (Grade 3): Withhold study drug. Monitor at least weekly until ALT/AST are < or equal to 1.5 x ULN, then may resume study drug. If Grade 3 recurrence, withhold study drug. Monitor at least weekly until ALT/AST < or equal to 1.5 x ULN, then may resume study drug. If Grade 3 recurrence, discontinue study drug permanently
- > 20 x ULN (Grade 4): Withhold study drug until ALT/AST < or equal to 1.5 x ULN, then may resume study drug. If Grade 4 recurrence, discontinue study drug permanently

7.5.5. eGFR Decline

SEL is associated with an acute decline in eGFR after study drug initiation, and in the phase 2 study of SEL in DKD (GS-US-223-1015), the median acute eGFR decline associated with SEL 18 mg at Week 4 was 10%. We observed that approximately 25% of subjects had an acute eGFR decline of 19% or greater (25^{th} percentile), and 75% of subjects had an acute eGFR decline of 4% or greater (75^{th} percentile).

However, acute declines in eGFR are expected to occur in subjects with moderate to advanced DKD and may not necessarily be associated with SEL. If acute eGFR decline occurs after the period following study drug initiation, refer to the below instructions:

- If clinically indicated, evaluate for alternative etiologies of eGFR decline and address reversible factors
- Avoid withholding or discontinuation of study drug in the setting of eGFR decline to the extent possible
- Consult with Gilead Medical Monitor and/or sponsor designee prior to withholding or discontinuing study drug
- If study drug is withheld, restart study drug as soon as clinically appropriate and check eGFR at next scheduled visit, preferably with study drug taken for at least 7 consecutive days.

Additionally, progressive decline in kidney function is expected to occur in subjects with moderate to advanced DKD. SEL is hypothesized to slow progression of DKD, and study drug should not be discontinued in the setting of expected progressive decline of underlying kidney disease.

Specific toxicity interruption and discontinuation criteria listed above supersede general toxicity guidelines, and in general, where discrepancy is present, the more conservative criteria apply.

NOTE: During the time of the study drug interruption for any of the above, the subject may continue to have study visits and to take part in procedures and assessments, if deemed medically appropriate.

In addition, embryofetal toxicity was observed in SEL nonclinical studies; therefore to prevent potential fetal exposure, adherence to highly effective methods of contraception will be required. Please see Appendix 6 for more details.

Any questions regarding toxicity management should be directed to the Gilead Medical Monitor and/or sponsor designee.

7.6. Special Situations Reports

7.6.1. Definitions of Special Situations

Special situation reports include all reports of medication error, abuse, misuse, overdose, reports of adverse events associated with product complaints, and pregnancy reports regardless of an associated AE and an AE in an infant following the potential exposure from breastfeeding and occupational exposure with an AE.

Medication error is any unintentional error in the prescribing, dispensing, or administration of a medicinal product while in the control of the health care provider, subject, or consumer.

Abuse is defined as persistent or sporadic intentional excessive use of a medicinal product by a subject.

Misuse is defined as any intentional and inappropriate use of a medicinal product that is not in accordance with the protocol instructions or the local prescribing information.

An overdose is defined as an accidental or intentional administration of a quantity of a medicinal product given per administration or cumulatively which is above the maximum recommended dose as per protocol or in the product labelling (as it applies to the daily dose of the subject in question). In cases of a discrepancy in drug accountability, overdose will be established only when it is clear that the subject has taken the excess dose(s). Overdose cannot be established when the subject cannot account for the discrepancy except in cases in which the investigator has reason to suspect that the subject has taken the additional dose(s).

Product complaint is defined as complaints arising from potential deviations in the manufacture, packaging, or distribution of the medicinal product.

Occupational exposure is defined as exposure to a medicinal product as a result of one's professional or non-professional occupation. Please refer to the Material Safety Sheet for product handling guidelines.

Infant exposure from breastfeeding that is associated with an AE is also considered a special situation report.

7.6.2. Instructions for Reporting Special Situations

7.6.2.1. Instructions for Reporting Pregnancies

The investigator should report pregnancies in female study subjects that are identified after initiation of study drug and throughout the study, including the post study drug follow-up period, to Gilead PVE using the pregnancy report form within 24 hours of becoming aware of the pregnancy.

Refer to Section 7.3 and the eCRF completion guidelines for full instructions on the mechanism of pregnancy reporting.

The pregnancy itself is not considered an AE nor is an induced elective abortion to terminate a pregnancy without medical reasons.

Any premature termination of pregnancy (eg, a spontaneous abortion, an induced therapeutic abortion due to complications or other medical reasons) must be reported within 24 hours as an SAE. The underlying medical reason for this procedure should be recorded as the AE term.

A spontaneous abortion is always considered to be an SAE and will be reported as described in Sections 7.1.1 and 7.1.2. Furthermore, any SAE occurring as an adverse pregnancy outcome post study must be reported to Gilead PVE.

The subject should receive appropriate monitoring and care until the conclusion of the pregnancy. The outcome should be reported to Gilead PVE using the pregnancy outcome report form. If the end of the pregnancy occurs after the study has been completed, the outcome should be reported directly to Gilead PVE. Gilead PVE contact information is as follows:
Email: PPD and Fax: PPD

Pregnancies of female partners of male study subjects exposed to Gilead or other study drugs must also be reported and relevant information should be submitted to Gilead PVE using the pregnancy and pregnancy outcome forms within 24 hours. Monitoring of the subject should continue until the conclusion of the pregnancy. If the end of the pregnancy occurs after the study has been completed, the outcome should be reported directly to Gilead PVE,
fax number PPD or email PPD

Refer to Appendix 6 for Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements.

7.6.2.2. Reporting Other Special Situations

All other special situation reports must be reported on the special situations report form and forwarded to Gilead PVE within 24 hours of the investigator becoming aware of the situation. These reports must consist of situations that involve study IMP and/or Gilead concomitant medications, but do not apply to non-Gilead concomitant medications.

Special situations involving non-Gilead concomitant medications does not need to be reported on the special situations report form; however, for special situations that result in AEs due to a non-Gilead concomitant medication, the AE should be reported on the AE form.

Any inappropriate use of concomitant medications prohibited by this protocol should not be reported as "misuse," but may be more appropriately documented as a protocol deviation.

Refer to Section 7.3 and the eCRF completion guidelines for full instructions on the mechanism of special situations reporting.

All clinical sequelae in relation to these special situation reports will be reported as AEs or SAEs at the same time using the AE eCRF and/or the SAE report form. Details of the symptoms and signs, clinical management, and outcome will be reported, when available.

8. STATISTICAL CONSIDERATIONS

8.1. Analysis Objectives and Endpoints

8.1.1. Analysis Objectives

The primary objective of this study is:

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

The secondary objectives of this study are:

- 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

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8.1.2. Primary Endpoint

The primary efficacy endpoint of this study is:

- $eGFR_{cr}$ slope from treatment-specific baselines

8.1.3. Secondary Endpoint

Secondary endpoints are:

- Proportion of Kidney Clinical Events at Week 48 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

- Time from randomization to first occurrence of a Kidney Clinical Event
- $eGFR_{cys}$ slope from pre-run-in baseline

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8.2. Analysis Conventions

8.2.1. Analysis Sets

8.2.1.1. Efficacy Analysis Set

The final analysis set for efficacy analysis is the Intent-to-treat (ITT) Analysis Set, which includes all subjects who were randomized in the study.

8.2.1.2. Safety Analysis Set

The final analysis set for safety analyses is the Safety Analysis Set, which includes all subjects who receive at least one dose of study drug. All data collected during treatment will be included in the safety summaries.

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8.2.1.4. Biomarker Analysis Set

The Biomarker Analysis Set will include data from subjects in the Safety Analysis Set who have the necessary baseline and on-study measurements to provide interpretable results for the specific parameters of interest.

8.3. Data Handling Conventions

Values for missing safety laboratory data will not be imputed. However, a missing baseline result will be replaced with a screening result, if available. If no pre-treatment laboratory value is available, the baseline value will be assumed to be normal (i.e, no grade [Grade 0]) for the summary of graded laboratory abnormalities. If safety laboratory results for a subject are missing for any reason at a time point, the subject will be excluded from the calculation of summary statistics for that time point.

Values for missing vital sign data will not be imputed. However, a missing baseline result will be replaced with a screening result, if available.

PK concentration values and PK parameter values below the limit of quantitation (BLQ) will be presented as "BLQ" in the data listings. BLQ values that occur prior to the first dose will be treated as 0, BLQ values at all other time points will be treated as 1/2 of the lower limit of quantitation (LLOQ).

Laboratory data that are continuous in nature but are less than the LLOQ or above the upper limit of quantitation will be imputed to the value of the lower or upper limit minus or plus one significant digit, respectively (e.g., if the result of a continuous laboratory test is < 20, a value of 19 will be assigned; if the result of a continuous laboratory test is < 20.0, a value of 19.9 will be assigned).

Procedures for handling missing data for eGFR will be described in the statistical analysis plan (SAP).

8.4. Demographic Data and Baseline Characteristics

Demographic and baseline measurements will be summarized by treatment group using standard descriptive statistics (n, mean, standard deviation [SD], median, 1st quartile [Q1], 3rd quartile [Q3], minimum, maximum for continuous variables and number and percentage of subjects for categorical variables) for the ITT Analysis Set.

Demographic summaries will include sex, race/ethnicity, and age.

Baseline characteristics may include eGFR, UACR, height, weight, BMI, concomitant use of SGLT-2 inhibitors, prior use of ACEi and/or ARB, and other variables of interest.

8.5. Efficacy Analysis

8.5.1. Primary Analysis

The Primary Analysis Set for efficacy analyses is the ITT Analysis Set, which includes all subjects who were randomized in the study.

8.5.1.1. Analysis of eGFR Slope

Definition of Baseline

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

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

The primary analysis of $eGFR_{cr}$ slope will be performed after all subjects in the ITT Analysis Set complete the Week 48 visit or discontinue from the study. Pre-run-in baseline $eGFR_{cr}$ and post-run-in baseline $eGFR_{cr}$ will be used for the placebo and SEL arms, respectively. Baseline $eGFR_{cr}$ as well as all on- and off-treatment $eGFR_{cr}$ values collected after Visit 1 through time of the analysis for all subjects with available data will be included. $eGFR_{cr}$ slope will be compared between SEL and placebo using a random slope model. The random slope model will have $eGFR_{cr}$ values starting from Baseline as the outcome, and will include terms for pre-run-in baseline $eGFR_{cr}$ as a continuous variable, pre-run-in baseline UACR category (< 1500 mg/g vs. ≥ 1500 mg/g), concomitant use of SGLT-2 inhibitors, treatment group, visit, and treatment-by-visit interaction. The difference in $eGFR_{cr}$ slope between SEL and placebo groups will be estimated and tested.

8.5.2. Secondary Analyses

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

8.5.2.1. Analysis of proportion of Kidney Clinical Events at Week 48

Kidney Clinical Event is defined as any of the following events:

- Confirmed ≥ 40% decline in $eGFR_{cr}$ from 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. Events of $eGFR_{cr}$ < 15 mL/min/1.73 m^2 or $eGFR_{cr}$ decline ≥ 40% from baseline without confirmation due to study discontinuation (e.g., death or lost to follow-up) will be included in the analysis.

The analysis of proportion of Kidney Clinical Events will be conducted when all subjects in the ITT Analysis Set reach Week 48 Visit or discontinue from the study. Number and proportion of subjects who experience a Kidney Clinical Event will be summarized. The Cochran-Mantel-Haenszel (CMH) approach adjusting for stratification factors will be used for hypothesis testing of Kidney Clinical Events.

Number and proportion of subjects who experienced each component of the Kidney Clinical Events will also be summarized.

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

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. Events of $eGFR_{cr}$ < 15 mL/min/1.73 m^2 or $eGFR_{cr}$ decline ≥ 40% from baseline without confirmation due to study discontinuation (e.g., death or lost to follow-up) will be included in the analysis. The date the first sample meets the threshold will be used as the date in the analysis.

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.

The analysis of time from randomization to a Kidney Clinical Events will be conducted when all subjects in the ITT Analysis Set reach Week 48 or discontinue from the study. Baseline as well as all on- and off-treatment $eGFR_{cr}$ values collected after Visit 1 through the end of the study will be included in the evaluation of the endpoint. The comparison will be performed between the SEL and placebo arms using a stratified log-rank test, stratified by randomization stratification factors. Median survival times and 95% Confidence Intervals (CIs) for the SEL and placebo arms will be estimated using Kaplan-Meier method. 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.

8.5.2.3. Analysis of $eGFR_{cys}$ slope from pre-run-in baseline

The analysis of $eGFR_{cys}$ slope from pre-run-in baseline will be performed after all subjects in the ITT Analysis Set complete the Week 48 visit or discontinue from the study. Pre-run-in baseline $eGFR_{cys}$ will be used for both placebo and SEL arms. Baseline $eGFR_{cys}$ as well as all on- and off-treatment $eGFR_{cys}$ values collected after Visit 1 through time of the analysis for all subjects with available data will be included. $eGFR_{cys}$ slope will be compared between SEL and placebo using a random slope model. The random slope model will have $eGFR_{cys}$ values starting from pre-run-in Baseline as outcome, and 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, treatment group, visit, and treatment-by-visit interaction. The difference in $eGFR_{cys}$ slope between SEL and placebo groups will be estimated and tested using the random slope model.

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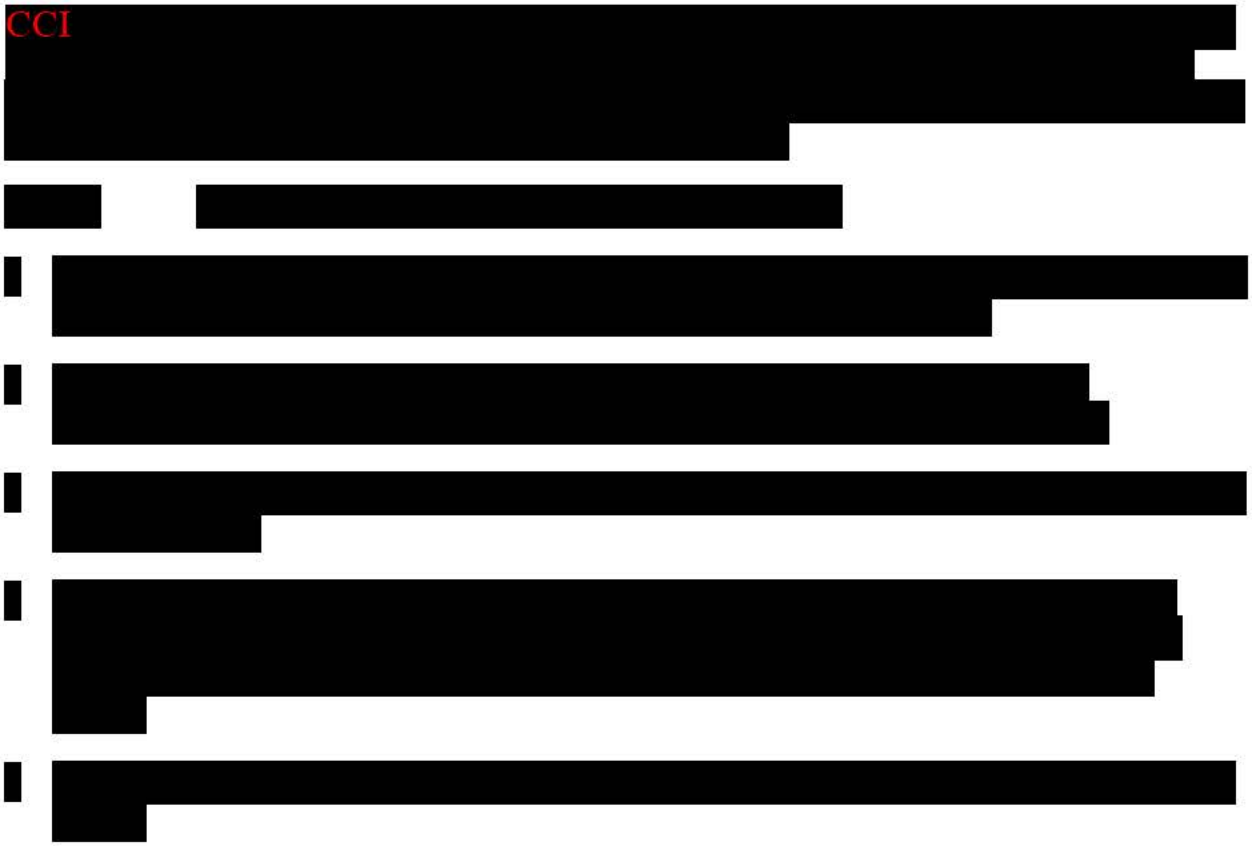

8.5.4. Multiplicity Adjustment

The primary endpoint and each secondary endpoint will be evaluated at a one-sided Type 1 error level of 0.15. No formal multiplicity adjustment will be performed.

8.6. Safety Analysis

Safety will be assessed during the study through the reporting of AEs, and by clinical laboratory tests and vital sign assessments at various time points during the study. Concomitant medication usage will also be assessed throughout the study.

All safety data collected on or after the date that SEL or PTM was first dispensed up to the date of last dose of SEL or PTM plus 30 days, including data collected during the Run-in period, will be summarized by treatment group (according to the study drug received).

8.6.1. Extent of Exposure

A subject's extent of exposure will be generated from the study drug administration eCRF. Exposure data will be summarized by treatment group.

8.6.2. Adverse Events

Clinical and laboratory adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). System Organ Class (SOC), High-Level Group Term (HLGT), High-Level Term (HLT), Preferred Term (PT), and Lower-Level Term (LLT) will be attached to the clinical database.

Events will be summarized on the basis of the date of onset for the event. Treatment-emergent adverse events (TEAEs) are defined as one or both of the following:

- Any AEs with an onset date on or after the study drug start date and no later than 30 days after permanent discontinuation of study drug
- Any AEs leading to premature discontinuation of study drug. Summaries (number and percentage of subjects) of TEAEs (by SOC, and PT) will be provided by treatment group. TEAEs will also be summarized by relationship to study drug and severity. In addition, TEAEs leading to premature discontinuation of study drug will be summarized and listed.

8.6.3. Laboratory Evaluations

Selected laboratory data (using conventional units) will be summarized using only observed data. Data and change from baseline at all scheduled time points will be summarized by treatment group and study visit.

Graded laboratory abnormalities will be defined using the grading scheme in CTCAE version 5.0 (Appendix 4).

Incidence of treatment-emergent laboratory abnormalities, defined as values that increase at least one toxicity grade from baseline at any time post baseline up to and including the date of last dose of study drug plus 30 days, will be summarized by treatment group.

8.6.4. Other Safety Evaluations

Vital sign measurements will be summarized by treatment arm and listed by subject.

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[redacted] CCI [redacted]

CCI [redacted]

[redacted]

8.9. Sample Size

8.9.1. Sample Size Determination

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%.

8.10. Data Monitoring Committee

An external multidisciplinary data monitoring committee (DMC) will review the progress of the study and perform interim reviews of safety data and provide recommendation to Gilead whether the nature, frequency, and severity of adverse effects associated with study drug warrant the early termination of the study in the best interests of the participants, whether the study should continue as planned, or the study should continue with modifications. The DMC may also provide recommendations as needed regarding study design.

The initial DMC meeting will occur after approximately 300 subjects reach Week 12 or discontinue from the study. Following this, subsequent meetings will occur approximately once every 6 months. The DMC's specific activities will be defined by a mutually agreed charter, which will define the DMC's membership, conduct and meeting schedule.

While the DMC will be asked to advise Gilead regarding future conduct of the study, including possible early study termination, Gilead retains final decision-making authority on all aspects of the study.

8.11. Endpoint Adjudication

Endpoint adjudication will be performed for major adverse kidney and CV events. If a subject has a clinical event, the data should be entered into the case report form to trigger adjudication. The adjudication may require additional source documents to support the review. The adjudication of these events will be performed in a blinded fashion for the purposes of data analysis. Detailed definitions for each event will be used in the adjudication process.

8.11.1. Events for Adjudication

Adjudicated events include, but are not limited to the following:

- Kidney failure

  Dialysis performed for at least 4 weeks

  Kidney transplantation

- Death due to kidney disease defined as death determined to be caused by kidney failure (eGFR less than 15 mL/min/1.73 m^2) and no other cause of death is determined via adjudication
- CV death
- Non-fatal MI
- Non-fatal stroke
- Hospitalization for heart failure
- Atrial fibrillation

Subjects who experience one of these confirmed clinical events will stay on study drug until kidney failure, global study end date, treatment discontinuation due to AE or other reasons.

9. RESPONSIBILITIES

9.1. Investigator Responsibilities

9.1.1. Good Clinical Practice

The investigator will ensure that this study is conducted in accordance with ICH E6 (R2) Good Clinical Practices and applicable laws and regulations.

9.1.2. Financial Disclosure

The investigator and subinvestigators will provide documentation of their financial interest or arrangements with Gilead, or proprietary interests in the investigational drug under study. This documentation must be provided prior to the investigator's (and any subinvestigator's) participation in the study. The investigator and subinvestigator agree to notify Gilead of any change in reportable interests during the study and for 1 year following completion of the study. The global study end date is defined as the date when the last subject completes the protocol-defined activities.

9.1.3. Institutional Review Board (IRB)/Independent Ethics Committee (IEC) Review and Approval

The investigator (or sponsor as appropriate according to local regulations) will submit this protocol, informed consent form, and any accompanying material to be provided to the subject (such as advertisements, subject information sheets, or descriptions of the study used to obtain informed consent) to an IRB/IEC. The investigator will not begin any study subject activities until approval from the IRB/IEC has been documented and provided as a letter to the investigator.

Before implementation, the investigator will submit to and receive documented approval from the IRB/IEC any modifications made to the protocol or any accompanying material to be provided to the subject after initial IRB/IEC approval, with the exception of those necessary to reduce immediate risk to study subjects.

9.1.4. Informed Consent

The investigator is responsible for obtaining written informed consent from each individual participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study and before undertaking any study-related procedures. The investigator must use the most current IRB/IEC-approved consent form for documenting written informed consent. Each informed consent (or assent as applicable) will be appropriately signed and dated by the subject and the person conducting the consent discussion, and also by an impartial witness if required by IRB/IEC or local requirements. The consent form will inform subjects about genomic testing and sample retention, and their right to receive clinically relevant genomic analysis results.

9.1.5. Confidentiality

The investigator must assure that subjects' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only an identification code and any other unique identifier(s) as allowed by local law (such as year of birth) will be recorded on any form or biological sample submitted to the Sponsor, IRB/IEC, or laboratory. Laboratory specimens must be labeled in such a way as to protect subject identity while allowing the results to be recorded to the proper subject. Refer to specific laboratory instructions. NOTE: The investigator must keep a screening log showing codes, names, and addresses for all subjects screened and for all subjects enrolled in the study. Subject data will be processed in accordance with all applicable regulations.

The investigator agrees that all information received from Gilead, including but not limited to the investigator brochure, this protocol, eCRF, study drug, and any other study information, remain the sole and exclusive property of Gilead during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from Gilead. The investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study site to any third party or otherwise into the public domain.

9.1.6. Study Files and Retention of Records

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into at least the following two categories: (1) investigator's study file, and (2) subject clinical source documents.

The investigator's study file will contain the protocol/amendments, eCRF and query forms, IRB/IEC and governmental approval with correspondence, informed consent, drug records, staff curriculum vitae and authorization forms, and other appropriate documents and correspondence.

The required source data should include sequential notes containing at least the following information for each subject:

- Subject identification (name, year of birth, gender)
- Documentation that subject meets eligibility criteria, ie, history, PE, and confirmation of diagnosis (to support inclusion and exclusion criteria)
- Documentation of the reason(s) a consented subject is not enrolled
- Participation in study (including study number)
- Study discussed and date of informed consent

- Dates of all visits
- Documentation that protocol specific procedures were performed
- Results of efficacy parameters, as required by the protocol
- Start and end date (including dose regimen) of study drug, including dates of dispensing and return
- Record of all adverse events and other safety parameters (start and end date, and including causality and severity)
- Concomitant medication (including start and end date, dose if relevant; dose changes)
- Date of end of study and reason for early discontinuation, if it occurs

All clinical study documents must be retained by the investigator until at least 2 years or according to local laws, whichever is longer, after the last approval of a marketing application in an ICH region (i.e., United States, Europe, or Japan) and until there are no pending or planned marketing applications in an ICH region; or, if no application is filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and regulatory authorities have been notified. Investigators may be required to retain documents longer if specified by regulatory requirements, by local regulations, or by an agreement with Gilead. The investigator must notify Gilead before destroying any clinical study records.

Should the investigator wish to assign the study records to another party or move them to another location, Gilead must be notified in advance.

If the investigator cannot provide for this archiving requirement at the study site for any or all of the documents, special arrangements must be made between the investigator and Gilead to store these records securely away from the site so that they can be returned sealed to the investigator in case of an inspection. When source documents are required for the continued care of the subject, appropriate copies should be made for storage away from the site.

9.1.7. Case Report Forms

For each subject consented, an eCRF will be completed by an authorized study staff member whose training for this function is documented according to study procedures. eCRF should be completed as per site contract, to enable the sponsor to perform central monitoring of safety data. The Eligibility Criteria eCRFs should be completed only after all data related to eligibility have been received. Subsequent to data entry, a study monitor will perform source data verification within the electronic data capture (EDC) system. Original entries as well as any changes to data fields will be stored in the audit trail of the system. Prior to database lock (or any interim time points as described in the clinical data management plan), the investigator will use his/her log in credentials to confirm that the forms have been reviewed, and that the entries accurately reflect the information in the source documents. The eCRF capture the data required

per the protocol schedule of events and procedures. System-generated or manual queries will be issued to the investigative site staff as data discrepancies are identified by the monitor or internal Gilead staff, who routinely review the data for completeness, correctness, and consistency. The site coordinator is responsible for responding to the queries in a timely manner, within the system, either by confirming the data as correct or updating the original entry, and providing the reason for the update (e.g. data entry error). At the conclusion of the study, Gilead will provide the site with a read-only archive copy of the data entered by that site. This archive must be stored in accordance with the records retention requirements outlined in Section 9.1.6.

9.1.8. Investigational Medicinal Product Accountability and Return

Where possible, study drug should be destroyed at the site. If the site has an appropriate SOP for drug destruction as determined by Gilead, the site may destroy used (empty or partially empty) and unused study drug supplies in accordance with that site's approved SOP. A copy of the site's approved SOP will be obtained for central files. If study drug is destroyed on site, the investigator must maintain accurate records for all study drug destroyed, the method of destruction, and the person who disposed of the study drug. Upon the global study end date, copies of study drug accountability records must be filed at the site. Another copy will be returned to Gilead.

If the site does not have an appropriate SOP for drug destruction, used and unused study drug supplies are to be sent to the designated disposal facility for eventual destruction. The study monitor will provide instructions for return.

The study monitor will review study drug supplies and associated records at periodic intervals.

9.1.9. Inspections

The investigator will make available all source documents and other records for this study to Gilead's appointed study monitors, to IRB/IEC, or to regulatory authority or health authority inspectors.

9.1.10. Protocol Compliance

The investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol.

9.2. Sponsor Responsibilities

9.2.1. Protocol Modifications

Protocol modifications, except those intended to reduce immediate risk to study subjects, may be made only by Gilead. The investigator must submit all protocol modifications to the IRB/IEC in accordance with local requirements and receive documented IRB/IEC approval before modifications can be implemented.

9.2.2. Study Report and Publications

A clinical study report (CSR) will be prepared and provided to the regulatory agencies. Gilead will ensure that the report meets the standards set out in the ICH Guideline for Structure and Content of Clinical Study Reports (ICH E3). Note that an abbreviated report may be prepared in certain cases.

Investigators in this study may communicate, orally present, or publish in scientific journals or other scholarly media only after the following conditions have been met:

- The results of the study in their entirety have been publicly disclosed by or with the consent of Gilead in an abstract, manuscript, or presentation form or the study has been completed at all study sites for at least 2 years
- The investigator will submit to Gilead any proposed publication or presentation along with the respective scientific journal or presentation forum at least 30 days before submission of the publication or presentation

No such communication, presentation, or publication will include Gilead's confidential information (see Section 9.1.5).

The investigator will comply with Gilead's request to delete references to its confidential information (other than the study results) in any paper or presentation and agrees to withhold publication or presentation for an additional 60 days in order to obtain patent protection if deemed necessary.

9.3. Joint Investigator/Sponsor Responsibilities

9.3.1. Payment Reporting

Investigators and their study staff may be asked to provide services performed under this protocol, e.g. attendance at Investigator's Meetings. If required under the applicable statutory and regulatory requirements, Gilead will capture and disclose to Federal and State agencies any expenses paid or reimbursed for such services, including any clinical study payments, meal, travel expenses or reimbursements, consulting fees, and any other transfer of value.

9.3.2. Access to Information for Monitoring

In accordance with regulations and guidelines, the study monitor must have direct access to the investigator's source documentation in order to verify the accuracy of the data recorded in the eCRF.

The monitor is responsible for routine review of the eCRF at regular intervals throughout the study to verify adherence to the protocol and the completeness, consistency, and accuracy of the data being entered on them. The monitor should have access to any subject records needed to verify the entries on the CRF/eCRF. The investigator agrees to cooperate with the monitor to ensure that any problems detected through any type of monitoring (central, on site) are resolved.

9.3.3. Access to Information for Auditing or Inspections

Representatives of regulatory authorities or of Gilead may conduct inspections or audits of the clinical study. If the investigator is notified of an inspection by a regulatory authority the investigator agrees to notify the Gilead Medical Monitor and/or sponsor designee immediately. The investigator agrees to provide to representatives of a regulatory agency or Gilead access to records, facilities, and personnel for the effective conduct of any inspection or audit.

9.3.4. Study Discontinuation

Both the sponsor and the investigator reserve the right to terminate the study at any time. Should this be necessary, both parties will arrange discontinuation procedures and notify the appropriate regulatory authority(ies), IRBs, and IECs. In terminating the study, Gilead and the investigator will assure that adequate consideration is given to the protection of the subjects' interests.

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11. APPENDICES

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Appendix 1. Investigator Signature Page

GILEAD SCIENCES, INC.
333 LAKESIDE DRIVE
FOSTER CITY, CA 94404

STUDY ACKNOWLEDGEMENT

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

GS-US-223-1017 Amendment 2, 13 April 2020

This protocol has been approved by Gilead Sciences, Inc. The following signature documents this approval.

PPD

PPD (Printed)
Author

PPD

Signature

13 April 2020
Date

INVESTIGATOR STATEMENT

I have read the protocol, including all appendices, and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will conduct this study as outlined herein and will make a reasonable effort to complete the study within the time designated.

I will provide all study personnel under my supervision copies of the protocol and access to all information provided by Gilead Sciences, Inc. I will discuss this material with them to ensure that they are fully informed about the drugs and the study.

Principal Investigator Name (Printed)

Signature

Date

Site Number

Appendix 2. Study Procedures Table

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					
	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. CCI

[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 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 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							
	CCI							
	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	q12 weeks[l]
	Week	4	8	12	24	36	48	
	Visit Window (days)	±5	±5	±5	±5	±5	±5	±5
Laboratory Assessments	Subject Fasting[e]						X	
	eGFR[f]	X	X	X	X	X	X	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 [redacted]							
	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]
[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 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					
	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 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 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 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 3. Clinical Laboratory Analytes

Hematology	Chemistry	Urinalysis	Other
Hematocrit Hemoglobin Platelet count Red Blood Cell (RBC) count White Blood Cell (WBC) count Differentials (absolute and percentage), including: Lymphocytes Monocytes Neutrophils Eosinophils Basophils Mean Corpuscular Volume (MCV)	Alkaline phosphatase (ALP) Aspartate aminotransferase (AST) Alanine aminotransferase (ALT) Gamma-Glutamyl Transpeptidase (GGT) Total bilirubin Direct and indirect bilirubin Total protein Albumin Bicarbonate Blood Urea Nitrogen (BUN) Calcium Chloride CPK Cystatin-C Serum creatinine Fasting Glucose Phosphorus Magnesium Potassium Sodium Serum Uric Acid (screening and yearly) eGFR using estimating equations (e.g., CKD-EPI Creatinine (2009); CKD-EPI Creatinine-Cystatin C (2012); CKD-EPI Cystatin C (2012); MDRD Study Equation)	Appearance Blood Color Glucose Leukocyte esterase Nitrites pH Protein Specific gravity Urobilinogen Reflex to microscopic urinalysis if dipstick result is abnormal Urine albumin, urine creatinine, and UACR (early morning void on days when eGFR value is obtained)	C-reactive protein (hsCRP) Digoxin HIV-1, HBV, HCV Serology Nt-proBNP Pharmacokinetics (PK) Prothrombin time Cardiac troponin I (cTnI)
Endocrine		**Pregnancy**	
Hemoglobin A1c Fasting Insulin c-peptide FSH (for women only)		*In females of childbearing potential:* Serum β-hCG (Screening and if positive urine β-hCG) Urine β-hCG (all other visits)*	
Fasting Lipids			
Triglycerides Total Cholesterol High-density lipoprotein (HDL) Low-density lipoprotein (LDL)			

* Females of childbearing potential as defined by protocol: 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 by the sponsor. 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 through 30 day EOT Follow-up visit.

Appendix 4. Common Terminology Criteria for Adverse Events (CTCAE) v5.0

Please refer to the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0, which can be found at:

https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

The modifications to the CTCAE v5.0 criteria include a revision of the Hyperglycemia grading scale and the addition of a Grade 1 upper respiratory infection as follows:

Appendix Table 1. Hyperglycemia Grading Scale

CHEMISTRY				
CTCAE v. 5.0*modification	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Hyperglycemia, Fasting	110 to 125 mg/dL 6.08 to 6.96 mmol/L	>125 to 250 mg/dL >6.96 to 13.90 mmol/L	>250 to 500 mg/dL >13.90 to 27.79 mmol/L	>500 mg/dL >27.79 mmol/L

* CTCAE Version 5.0 currently has no provision for serum glucose levels that correlate with hyperglycemia toxicity grades. The language here represents a Gilead modification to the CTCAE Version 5.0 term 'Hyperglycemia'.

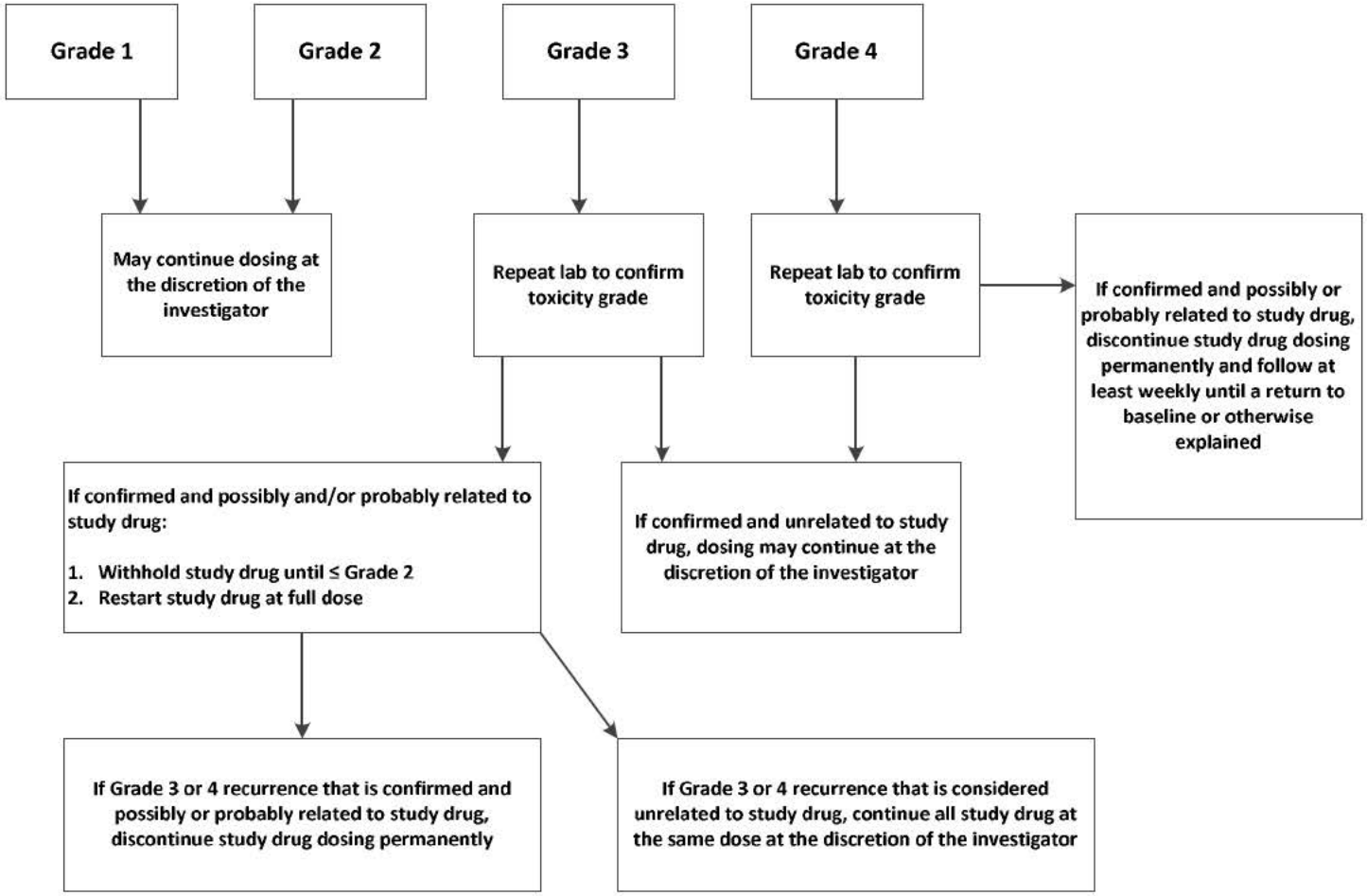
Appendix Table 2. Upper Respiratory Infection Grading Scale

CTCAE V5.0 Term	**Grade 1***	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**	**CTCAE v5.0 AE Term Definition**
Upper respiratory infection	Mild symptoms; symptomatic relief (cough suppressant, decongestant, etc.)	Moderate symptoms; oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death	A disorder characterized by an infectious process involving the upper respiratory tract (nose, paranasal sinuses, pharynx, larynx, or trachea).

* CTCAE currently has no provision for Grade 1 upper respiratory infection. The language here represents a Gilead modification to the CTCAE.

For AEs associated with laboratory abnormalities, the event should be graded on the basis of the clinical severity in the context of the underlying conditions; this may or may not be in agreement with the grading of the laboratory abnormality.

Appendix 5. Management of Clinical and Laboratory Adverse Events



* Refer to Section 7.5 for details

Appendix 6. Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements

1) Definitions

a. Definition of Childbearing Potential

For the purposes of this study, a female born subject is considered of childbearing potential following the initiation of puberty (Tanner stage 2) until becoming post-menopausal, unless permanently sterile or with medically documented ovarian failure.

Women are considered to be in a postmenopausal state when they are ≥ 54 years of age with cessation of previously occurring menses for ≥ 12 months without an alternative cause. In addition, women of any age with amenorrhea of ≥ 12 months may also be considered postmenopausal if their follicle stimulating hormone (FSH) level is in the postmenopausal range and they are not using hormonal contraception or hormonal replacement therapy.

Permanent sterilization includes hysterectomy, bilateral oophorectomy, or bilateral salpingectomy in a female subject of any age.

b. Definition of Male Fertility

For the purposes of this study, a male born subject is considered fertile after the initiation of puberty unless permanently sterile by bilateral orchiectomy or medical documentation.

2) Contraception Requirements for Female Subjects

a. Study Drug Effects on Pregnancy and Hormonal Contraception

SEL is contraindicated in pregnancy as a malformation effect is suspected, based on non-clinical data. In rats and rabbits, SEL administration was associated with effects on embryofetal development at maternally toxic doses.

Preclinical and clinical drug-drug interaction (DDI) data indicate that SEL is unlikely to alter the exposure of hormonal contraceptives through induction of human drug metabolizing enzymes or drug transporters. Please refer to the latest version of the IB for additional information.

b. Contraception Requirements for Female Subjects of Childbearing Potential

The inclusion of female subjects of childbearing potential requires the use of highly effective contraceptive measures. They must have a negative serum pregnancy test at Screening and a negative urine pregnancy test at Visit B and Visit 1. Pregnancy tests will be performed at 4 week intervals thereafter through the 30 Day EOT Follow up visit. Female subjects must agree to one of the following from Screening until 30 days following the last dose of study drug:

- Complete abstinence from intercourse of reproductive potential. Abstinence is an acceptable method of contraception only when it is in line with the subject's preferred and usual lifestyle.

  Or

- Consistent and correct use of 1 of the following methods of birth control listed below:

  Intrauterine device (IUD) with a failure rate of < 1% per year

  Tubal sterilization

  Vasectomy in the male partner (provided that the partner is the sole sexual partner and had confirmation of surgical success 3 months after procedure)

The above described methods are considered preferred methods of highly effective contraception in this protocol.

Should female subjects wish to use a hormonally based method; use of a male condom by the female subject's male partner is required. Subjects who utilize a hormonal contraceptive as one of their birth control methods must have used the same method for at least three months prior to study dosing. Hormonally-based contraceptives permitted for use in this protocol are as follows:

- Hormonal methods associated with inhibition of ovulation (each method must be used with a condom in the male partner):

  Oral contraceptives (either combined or progesterone only)

  Injectable progesterone*

  Subdermal contraceptive implant*

  Transdermal contraceptive patch*

  Contraceptive vaginal ring*

Not all of these methods may be approved in each of the countries where the study is being conducted. Please refer to local product information. Additional local regulatory requirements may apply.

NOTE: * Not approved in Japan

Female subjects must also refrain from egg donation or harvest during treatment and until at least 30 days after the last dose of study drug.

3) Contraception Requirements for Male Subjects

It is theoretically possible that a relevant systemic concentration may be achieved in a female partner from exposure of the male subject's seminal fluid. Therefore, male subjects with female partners of childbearing potential must use condoms during treatment and until 30 days after the last dose of study drug. Female partners of male study subjects are asked to select one of the above methods.

Male subjects must also refrain from sperm donation from the screening visit through 30 days following the last dose of study drug.

4) Unacceptable Birth Control Methods

Birth control methods that are unacceptable include periodic abstinence (eg. calendar, ovulation, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM). Female condom and male condom should not be used together.

5) Procedures to be Followed in the Event of Pregnancy

Subjects will be instructed to notify the investigator if they become pregnant at any time during the study, or if they become pregnant within 30 days of last study drug dose. Subjects who become pregnant or who suspect that they are pregnant during the study must report the information to the investigator and discontinue study drug immediately. Male subjects whose partner has become pregnant or suspects she is pregnant during the study or within 30 days of last study drug dose must report the information to the investigator. Instructions for reporting pregnancy, partner pregnancy, and pregnancy outcome are outlined in Section 7.6.2.

CCI [redacted]

[redacted]

CCI

CCI

[redacted]