Supplementary Appendix

Effects of Selonsertib in Patients with Diabetic Kidney Disease (DKD)

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Table of Contents

Supplemental Table 1. Inclusion and Exclusion Criteria

Inclusion Criteria

- Prior diagnosis of DKD
- Male or female between 30 and 75 years of age, inclusive
    - Anyone between 18 and 30 years of age may have been screened if the diagnosis of type 2 DM was confirmed with a documented C-peptide level and in consultation with the medical monitor
- Type 2 DM ≥6 months
- eGFR and UACR at screening within protocol-defined criteria by disease stage (Stage 3a: eGFR 45 to <60 mL/min/1.73m^2 and UACR ≥600 mg/g; Stage 3b: eGFR 30 to <45 mL/min/1.73m^2 and UACR ≥300 mg/g; Stage 4: eGFR 15 to <30 mL/min/1.73m^2 and UACR ≥150 mg/g)
- ACE inhibitors or ARBs at a protocol-specified minimum dose deemed appropriate for the subject by the investigator and at a stable dose for the previous 3 months, or documented intolerance to such medications
- Negative serum pregnancy test in female subjects of childbearing potential
- Serum total bilirubin ≤ 1.5 × the ULN
- Serum alanine aminotransferase or aspartate aminotransferase ≤1.5 × ULN
- Negative blood screen for HIV, hepatitis B virus, or hepatitis C virus by protocol-specified testing
- Willing and able to give informed consent prior to any study-specific procedures being performed

Exclusion Criteria

- Type 1 DM
- HbA1c >9.5%;
- Nondiabetic kidney disease
- UACR >5000 mg/g on any measurement during screening
- ESRD
- Unstable cardiovascular disease
- Concurrent use of aliskiren with either an ACE inhibitor or an ARB
- Concurrent use of an ACE inhibitor with an ARB
- Concurrent use of 2 or more ACE inhibitors or ARBs
- Diagnostic or interventional procedure that required intravenous contrast agent during or within 30 days prior to screening, and during the study treatment period
- Pregnant or lactating females

- Known hypersensitivity to selonsertib/placebo, the metabolites, or formulation excipient

DKD, diabetic kidney disease; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; UACR, urine albumin-to-creatinine ratio; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; ULN, upper limit of normal range; HIV, human immunodeficiency virus; ESRD, end-stage renal disease

Supplemental Table 2. Statistical Methods

MMRM

The MMRM includes terms for treatment group, baseline eGFR, visit, and treatment-by-visit interaction for the comparison of change from baseline in eGFR between selonsertib and placebo. The change from baseline values at Weeks 4, 8, 12, 16, 24, 36, and 48 were included in the model as response variables. Treatment comparisons at Week 48 were generated within the MMRM model using the estimated LSM at Week 48. Adjusted means and 95% CIs were presented. Within-subject variance covariance was modeled as unstructured.

Piecewise Random Slope Model

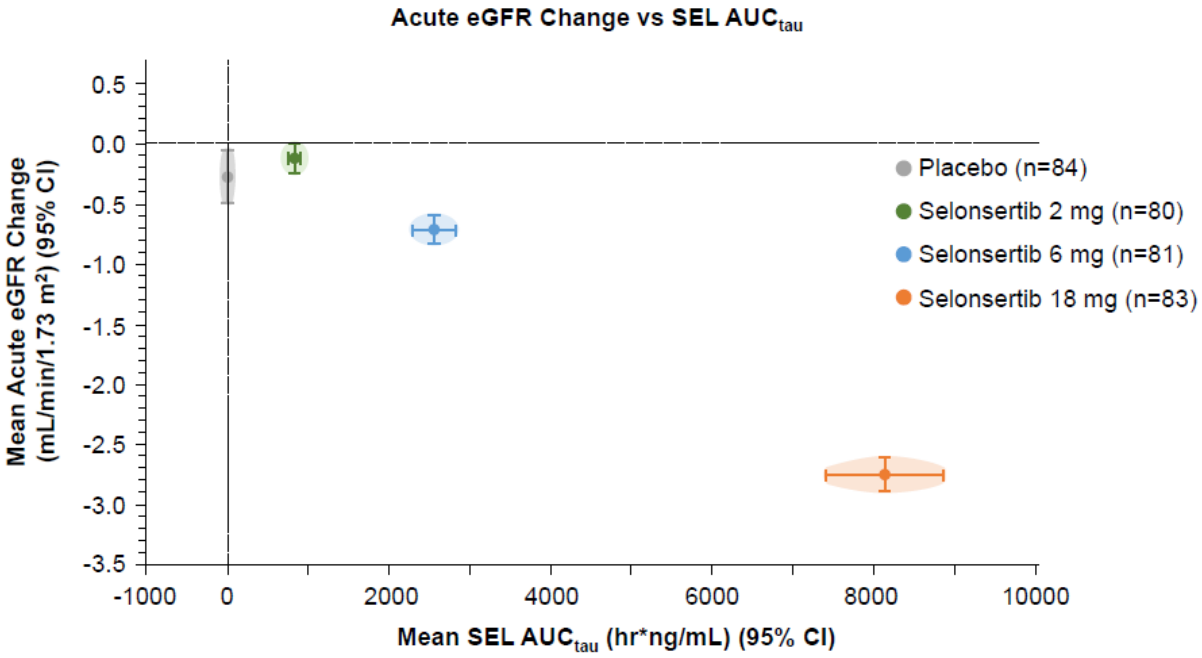
The following piecewise random slope model was used to estimate eGFR decline rate from Week 4 to Week 48 in each treatment group:

$$\Delta eGFR_{ij} = \beta_0 baseline_i + b_{1i} week_{ij} + \beta_2 weekc_{ij} + \boldsymbol{\beta_3 TRT_i} + \boldsymbol{\beta_4} week_{ij} * \boldsymbol{TRT_i} + \boldsymbol{\beta_5} weekc_{ij} * \boldsymbol{TRT_i} + \epsilon_{ij}$$

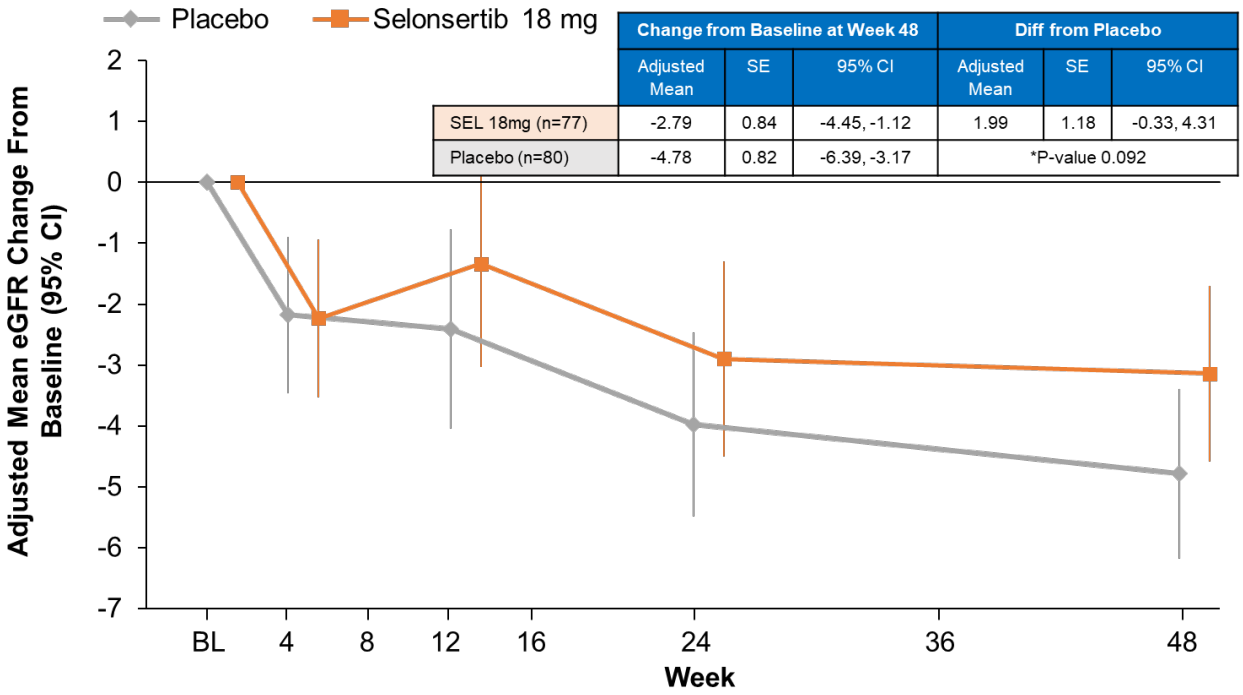
where $\Delta eGFR_{ij}$ is eGFR change from baseline for subject i at time j; $baseline$ is centered baseline eGFR on its mean; $weekc$=max($week$−4, 0); β_0, β_2, $\boldsymbol{\beta_3}$, $\boldsymbol{\beta_4}$,$\boldsymbol{\beta_5}$ are fixed effects for baseline, $weekc$, TRT ,$week*TRT$ and $weekc*TRT$; and b_{1i} is the random effect of week for subject i which follows $N(\beta_1, \sigma_b^2)$. ϵ_{ij} is the residual for subject i at time j, ϵ_{ij}~N(0, σ_e^2).

MMRM, mixed model for repeated measures; eGFR, estimated glomerular filtration rate; LSM, least squares mean; CI, confidence interval

Supplemental Figure 1. Acute selonsertib dose- and exposure-dependent change in eGFR between Weeks 0 and 4 of treatment (post-hoc efficacy analysis set). eGFR, estimated glomerular filtration rate; SEL, selonsertib; AUC_{tau}, area under the plasma concentration time curve over the dosing interval; CI, confidence interval



Supplemental Figure 2. Adjusted mean (95% CI) of eGFR (cystatin C-based CKD-EPI) change from baseline by visit: post-hoc analysis (full analysis set with available samples for cystatin C from selonsertib 18 mg and placebo arms, excluding data collected from two sites with GCP compliance findings; n=148). CI, confidence interval; eGFR, estimated glomerular filtration rate; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; GCP, International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use guidelines for Good Clinical Practice; SE, standard error, BL, baseline; MMRM, mixed model for repeated measures

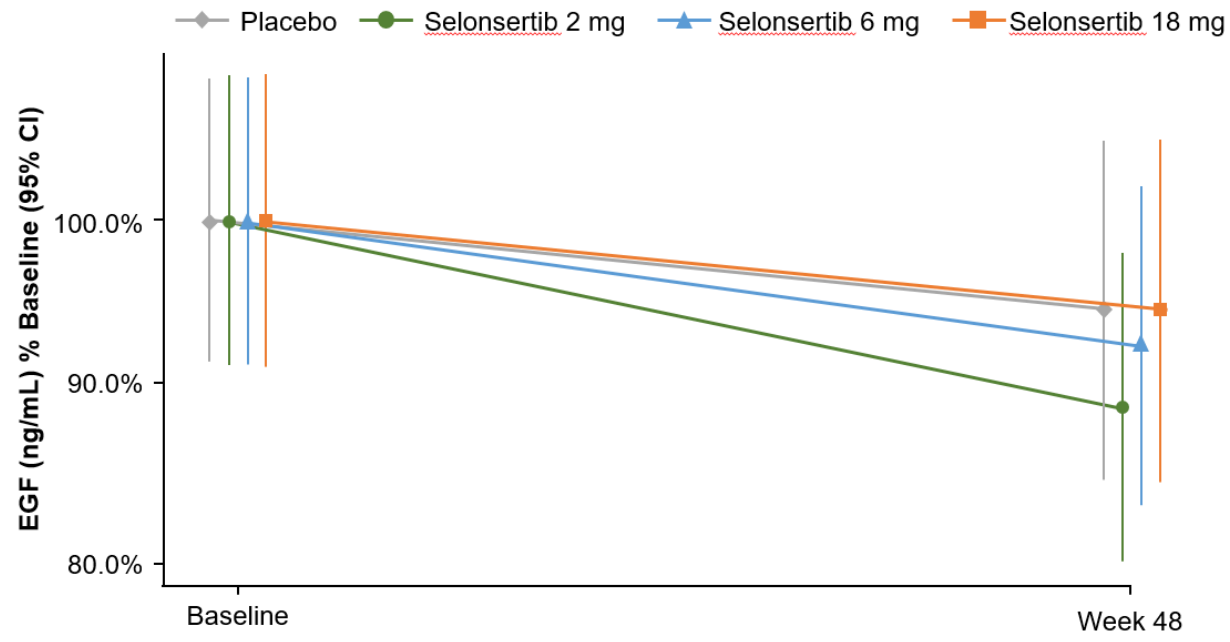


	Change from Baseline at Week 48			Diff from Placebo		
	Adjusted Mean	SE	95% CI	Adjusted Mean	SE	95% CI
SEL 18mg (n=77)	-2.79	0.84	-4.45, -1.12	1.99	1.18	-0.33, 4.31
Placebo (n=80)	-4.78	0.82	-6.39, -3.17	*P-value 0.092		

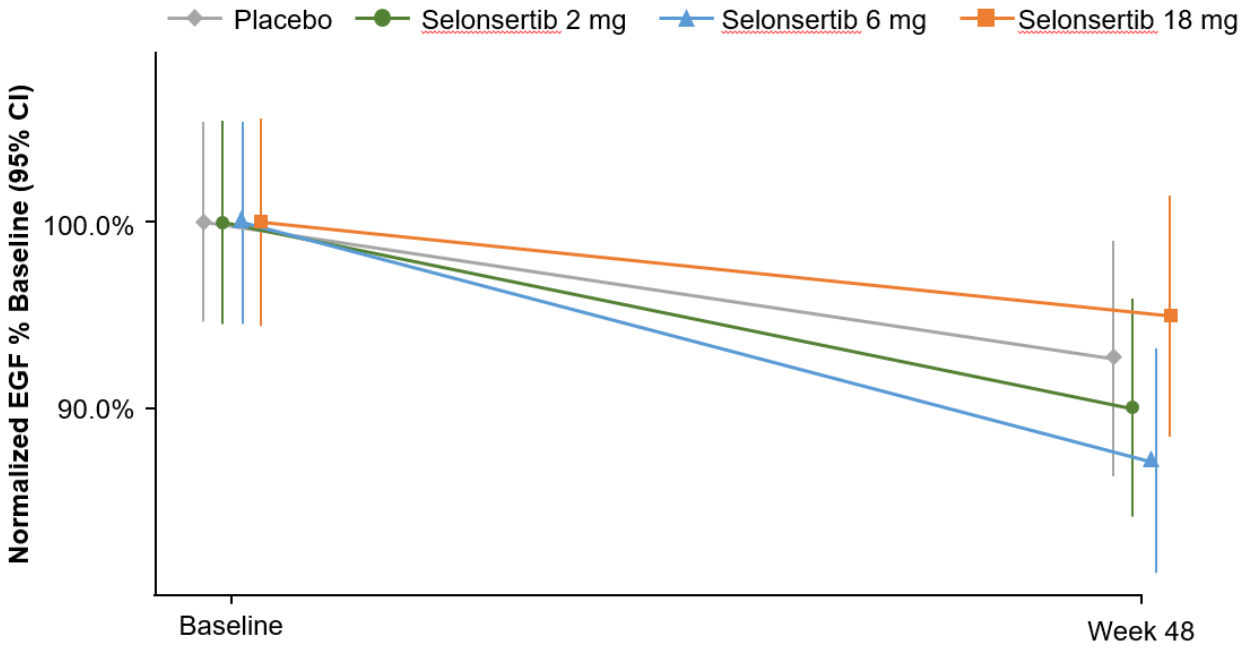
*MMRM analysis did not adjust for the acute effect.

Supplemental Figure 3. Percent change in EGF (A, uncorrected; B, normalized for creatinine) and KIM-1 (C, uncorrected; D, normalized for creatinine) from baseline by visit. EGF, endothelial growth factor; KIM-1, kidney injury molecule-1; CI, confidence interval

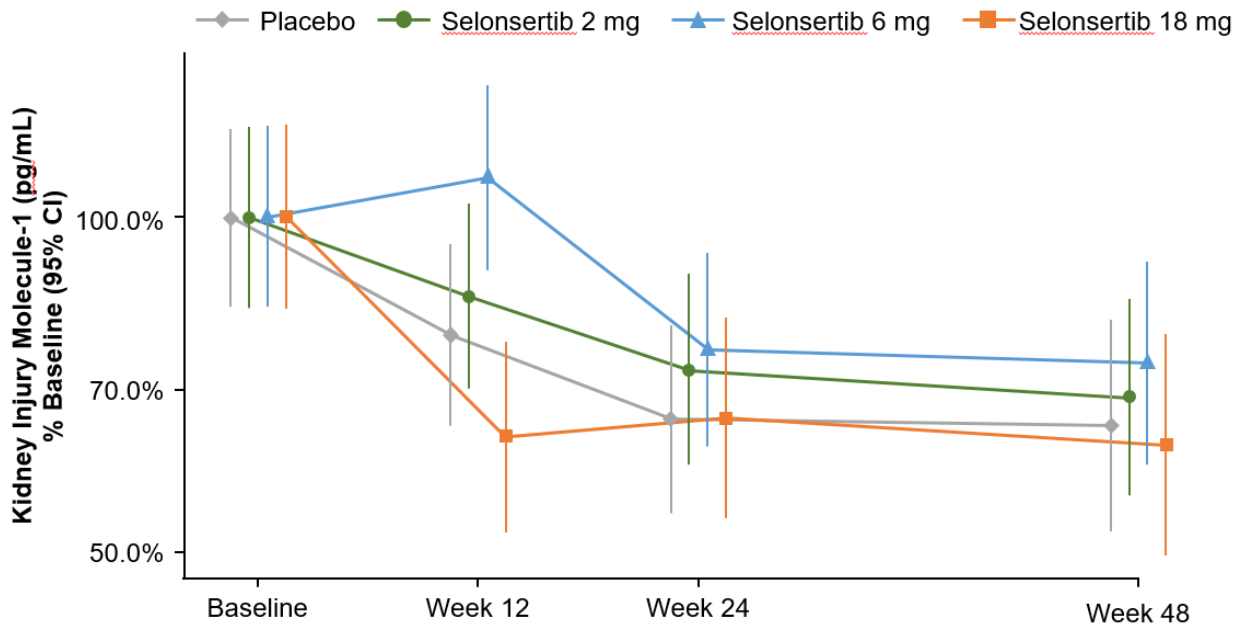
(A)



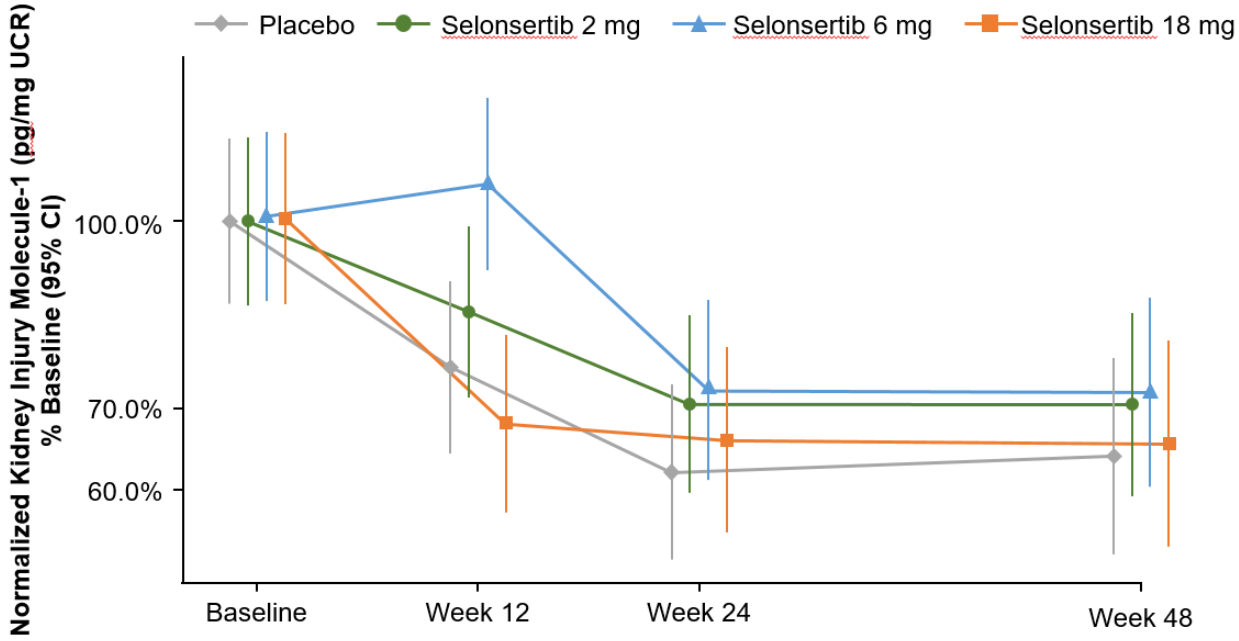
(B)



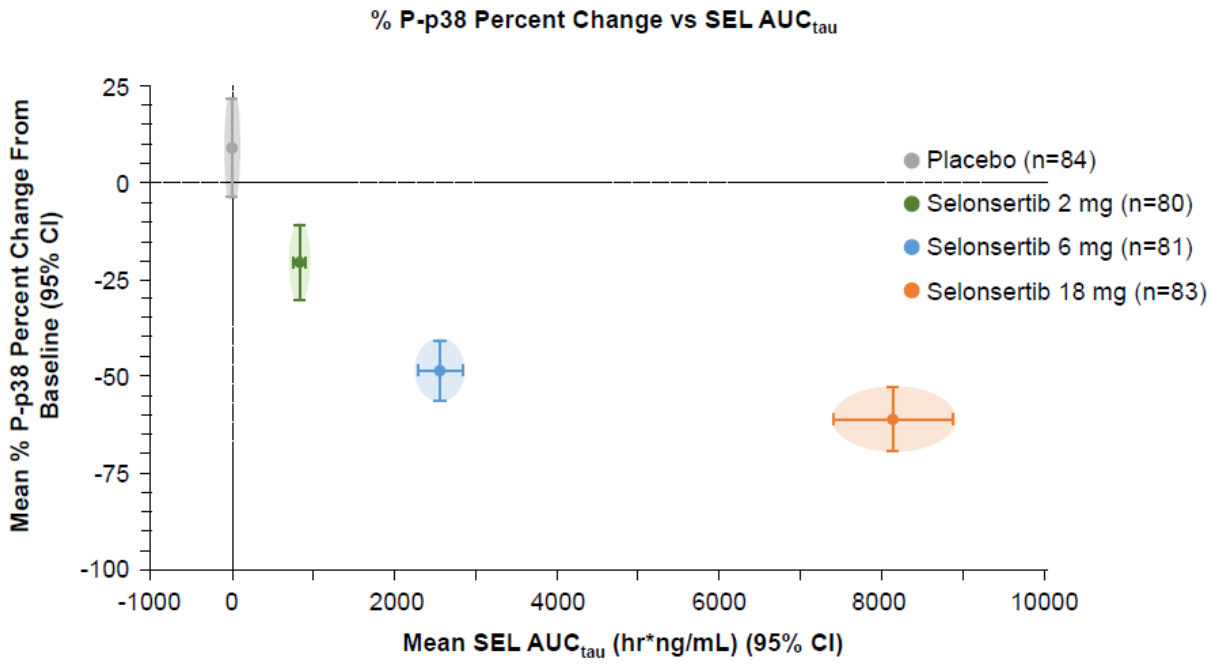
(C)


Placebo
Selonsertib 2 mg
Selonsertib 6 mg
Selonsertib 18 mg
Kidney Injury Molecule-1 (pg/mL)
% Baseline (95% CI)
100.0%
70.0%
50.0%
Baseline
Week 12
Week 24
Week 48

(D)

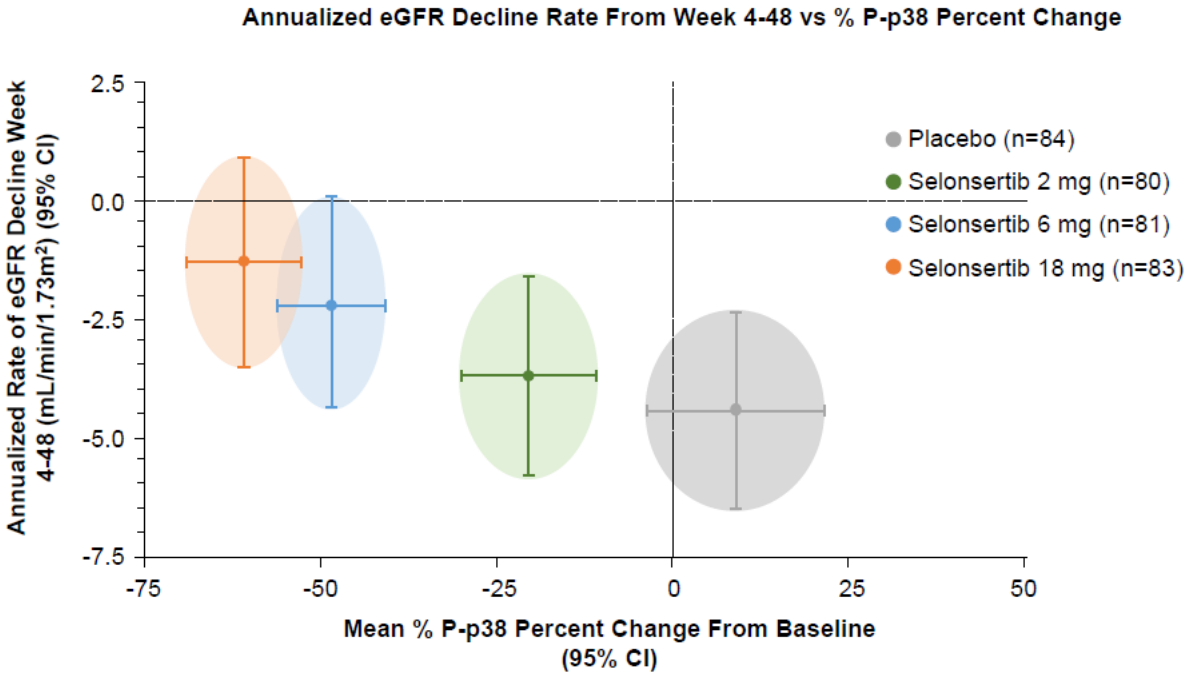

Placebo
Selonsertib 2 mg
Selonsertib 6 mg
Selonsertib 18 mg
Normalized Kidney Injury Molecule-1 (pg/mg UCR)
% Baseline (95% CI)
100.0%
70.0%
60.0%
Baseline
Week 12
Week 24
Week 48

Supplemental Figure 4. Relationship between percent change in P-p38 from baseline and selonsertib dose and exposure (AUC_{tau}). P-p38, phospho-p38; AUC_{tau}, area under the plasma concentration-time curve over the dosing interval; SEL, selonsertib; CI, confidence interval; %P-p38, percent P-p38; PBO, placebo



%P-p38 data was excluded for one outlier subject in the PBO group.

Supplemental Figure 5. Relationship between percent change in P-p38 from baseline and chronic (Week 4-48) eGFR annual slope by dose group. eGFR, estimated glomerular filtration rate; CI, confidence interval; PBO, placebo



%P-p38 data was excluded for one outlier subject in the PBO group.