Item S1: Details of Simulations of eGFR Trajectories and Clinical Events

The simulations of the eGFR trajectories and associated clinical events (death and ESKD) were performed in six steps: 1) Determination of the eGFR measurement times for each patient based on the accrual period, additional follow-up period, and eGFR measurement schedule, 2) Simulation of underlying linear trajectories in the absence of treatment, 3) Accounting for the effect of the treatment on the underlying trajectories, and 4) Simulation of observed eGFR values after accounting for random deviations of the measured eGFR values from the underlying trajectories, 5) Application of eGFR entry criteria, and 6) Simulation of clinical events (ESKD and death) which may be associated with eGFR, and accounting for loss-to-follow-up and intermittent missed visits. We provide the details of these steps below, with input parameters for the simulations designated in upper case letters.

Step 1: eGFR measurement times \( t_{ij} \) were determined for each patient \( i \) under the assumption of uniform accrual given the specified values for the accrual period, the additional follow-up period after completion of accrual, and the eGFR measurement schedule. A uniform measurement schedule at regular intervals was assumed, with the possible addition of one extra measurement shortly after randomization, and the possibility of obtaining two or more baseline measurements.

Step 2a: Random intercepts \( \alpha_i \) and slopes \( \beta_i^0 \) in absence of treatment were simulated independently for each patient \( i \) to follow a bivariate normal distribution with designated means MEAN.INT and MEAN.SLOPE, standard deviations SD.MEAN and SD.SLOPE, and Pearson correlation coefficient COR.INT.SLOPE.

Step 2b: The \( \beta_i^0 \) were transformed to follow a generalized log gamma distribution with the same mean and standard deviation as designated in Step 2a, and shape parameter K.SLOPE.

Step 3a: Simulate the effect of the treatment on the long term slope.

The long term slope was computed as $\beta_i = \beta_i^0$ for patients in the control group, and as

$$\beta_i = \text{ADDITIVE.EFFECT} + (\text{MULTIPLICATIVE.EFFECT} \times 1_{\{\beta_i^0 < 0\}}) \times \beta_i^0$$

for patients in the treatment group. Here ADDITIVE.EFFECT and MULTIPLICATIVE.EFFECT are input parameters that describe the type and size of the treatment effect. If ADDITIVE.EFFECT is set to 0, the model reduces to a proportional effect model, in which the treatment is assumed to change the magnitude of the slope by MULTIPLICATIVE.EFFECT $\times \beta_i^0$ for patients with negative $\beta_i^0$ and to have no effect on the slope for patients with positive $\beta_i^0$. If MULTIPLICATIVE.EFFECT is set to 1, the model reduces to a uniform treatment effect model in which the treatment changes each subject’s slope by ADDITIVE.EFFECT irrespective of the patient’s underlying rate of progression.


The acute effect, denoted $\Delta(t_{ij})$, is assumed to be equal to 0 in the control group.

Under the primary logarithmic acute effect model, the acute effect in the treatment group is modeled as

$$\Delta(t_{ij}) = \frac{B_{0,\text{ACUTE}} + \varepsilon_{\text{ACUTE}i}}{\log(42.5/15)} \times \max\{\log(\alpha_i + \beta_i t_{ij}) - \log(15), 0\}$$

where $B_{0,\text{ACUTE}}$ is the mean acute effect when the mean eGFR given by $\alpha_i + \beta_i t_{ij}$ is 42.5 ml/min/1.73m$^2$ and $\varepsilon_{\text{ACUTE}i}$ is a normally distributed random variable with mean 0 and standard deviation $SD._{\text{ACUTE}}$ that accounts any variation in the acute effect between patients. $SD._{\text{ACUTE}}$ was assumed to be equal to 0 in the base model, but positive values of $SD._{\text{ACUTE}}$ were considered in other models.

We also considered a linear acute effect model of the form:
A2: \[ \Delta(t_{ij}) = \frac{B_{0} \text{ACUTE} + \varepsilon \text{ACUTE}_{i}}{(42.5 - 15)} \times \max\{\alpha_{i} + \beta_{i} t_{ij} - 15, 0\}, \]

as well as a constant acute effect model

A3: \[ \Delta(t_{ij}) = B_{0} \text{ACUTE} + \varepsilon \text{ACUTE}_{i} \]

Note that the acute effect attenuates to 0 as \( \alpha_{i} + \beta_{i} t_{ij} \) declines to 15 ml/min/1.73m\(^2\) under the acute effect Models A1 and A2, but persists irrespective of \( \alpha_{i} + \beta_{i} t_{ij} \) under Model A3.

The ith patient’s underlying mean eGFR at baseline (time \( t_{i1} = 0 \)) is not affected by the acute effect and is given by the intercept \( \alpha_{i} \),

\[ \text{MEAN.eGFR}_{i1} = \alpha_{i}. \]

The ith patient’s underlying mean eGFR at times \( t_{ij} > 0 \) is

\[ \text{MEAN.eGFR}_{ij} = \alpha_{i} + \beta_{i} t_{ij} + \Delta(t_{ij}). \]

Step 4: Compute the observed eGFR values accounting for random deviations from the underlying trajectories.

We first simulated the random deviations \( \varepsilon_{ij} \) of the actual observed eGFRs about \( \text{MEAN.eGFR}_{ij} \) for each patient \( i \) as

\[ \varepsilon_{ij} = \left\{ \text{VAR.RESIDUAL} \times \left( \text{BETARESIDUAL} \times Z_{ij} + (1 - \text{BETARESIDUAL})^{2} \times W_{ij} \right) \right\} \]

where BETA.RESIDUAL is between 0 and 1, the \( Z_{ij} \) are standard normal random variables which follow a first order auto-regression (AR(1)) process over the time points \( t_{ij} \) with auto-correlation given by the input parameter AUTO.RESIDUAL. The \( W_{ij} \) are independent t-distributed random variables with \( n \) degrees of freedom scaled to have variance equal to 1, and, finally,
VAR.RESIDUAL = VAR.RESIDUAL.A0 + VAR.RESIDUAL.A1 × MEAN.eGFR_{ij}

defines the variances of the eGFR random deviations. Here BETA.RESIDUAL, AUTO.RESIDUAL, VAR.RESIDUAL.A0, VAR.RESIDUAL.A1, and the degrees of freedom n all represent input parameters. The $Z_{ij}$ can be viewed as random biological variation of the eGFRs around the underlying linear trajectory which are correlated over time, with the $W_{ij}$ representing random measurement error which is independent between measurements. The input parameters AUTO.RESIDUAL and BETA.RESIDUAL together determine the correlations in the $\varepsilon_{ij}$ between time points. The combination of BETA.RESIDUAL and the degrees of freedom of the $W_{ij}$ controls the contribution of outliers to the $\varepsilon_{ij}$, with an infinite degrees of freedom producing normally distributed $\varepsilon_{ij}$. The input parameters VAR.RESIDUAL.A0 and VAR.RESIDUAL.A1 define the variance of $\varepsilon_{ij}$ for a given mean eGFR.

Finally, after simulating the $\varepsilon_{ij}$, the observed eGFR at time $t_{ij}$ is computed as

$$eGFR_{ij} = MEAN.eGFR_{ij} + \varepsilon_{ij}.$$  

Step 5: Apply eGFR entry criteria

Exclude subjects whose baseline eGFRs $eGFR_{i1}$ fall outside of lower and upper entry criteria limits INT.LOW and INT.UP designated by the user. Values of INT.LOW and INT.UP used in the simulations were:

Case 1: Mean $\alpha_i = 27.5$ ml/min/1.73m$^2$, SD $\alpha_i = 10$ ml/min/1.73m$^2$, INT.LOW = 15 ml/min/1.73m$^2$, INT.UP = 40 ml/min/1.73m$^2$

Case 2: Mean $\alpha_i = 42.5$ ml/min/1.73m$^2$, SD $\alpha_i = 17.5$ ml/min/1.73m$^2$, INT.LOW = 20 ml/min/1.73m$^2$, INT.UP = 65 ml/min/1.73m$^2$
Case 3: Mean $\alpha_i = 67.5 \text{ ml/min/1.73m}^2$, SD $\alpha_i = 22.5 \text{ ml/min/1.73m}^2$, INT.LOW = 40 ml/min/1.73m$^2$

INT.UP = 95 ml/min/1.73m$^2$

Step 6: Simulation of ESKD and death.

Step 6a: Determine time of ESKD

The patient is assumed to reach ESKD at the first time $t$ at which $\alpha_i + \beta_i t + \Delta(t) \leq K.\text{ESRD}_i$, or at the first visit time $t_{ij}$ at which the observed $eGFR_{ij} \leq K.\text{ESRD}_i$, where $\Delta(t)$ = is given by A1, A2 or A3 evaluated at time $t$ and $K.\text{ESRD}_i$ is a patient specific threshold for ESKD which is simulated as a uniform random variable between 6 and 15 ml/min/1.73m$^2$.

Step 6b: Determine time of Death

The death time for patient $i$ is simulated as a random variable with hazard $h(t)$ defined as:

$$h(t) = \text{LAMBDA.B}0 + \text{LAMBDA.B2} \times (\alpha_i + \beta_i t) + \text{LAMBDA.B4} \times \beta_i$$ in the control group, and

$$h(t) = \text{LAMBDA.B1} + \text{LAMBDA.B3} \times (\alpha_i + \beta_i t) + \text{LAMBDA.B4} \times \beta_i$$ in the treatment group.

Step 6c: Simulate loss to follow-up and intermittent missing eGFRs.

Loss to follow-up was simulated as an exponential random variable with hazard rate LAMBDA.FU.

Measured eGFRs at individual visits were designated as missing according to independent Bernoulli random variables with probability PMISS.