

Supplementary Information

Clinical Pharmacokinetics

Finerenone dose-exposure-serum potassium response analysis of FIDELIO-DKD phase 3 - The role of dosing, titration, and inclusion criteria

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Supplementary Methods

Clinical Study Informed Consent and Ethics

The study protocol (provided as a Supplement to Bakris et al.[1]) was approved by International Review Boards, independent Ethics Committees, and competent authorities according to national and international regulations. FIDELIO-DKD is conducted in accordance with the ICH Harmonized Tripartite Guideline for Good Clinical Practice. All study participants provided written informed consent before entering the study.

Simulation workflow for dose-titration (used for simulations and VPC)

In the first stage of model development (i.e. development of structural model on the central laboratory data of the FIDELIO study population), VPCs used the observed dosing and observation times from the dataset. However, this VPC approach gives biased simulations of the serum potassium levels in the active treatment arm, as it ignores the fact that (local laboratory) serum potassium levels were used to up-titrate or temporarily interrupt finerenone dosing during FIDELIO-DKD. Therefore, from the second stage onwards (i.e. after adding the local laboratory data) a different VPC approach was used where dose-titration decisions were incorporated in the Monte Carlo simulations of the VPCs of all models that included both central and local laboratory data. Therefore, the dosing in the simulations were not copied from the observed dosing records, but rather based on the starting dose and subsequent simulated serum potassium levels. Because the decision to permanently discontinue treatment was not based on a specific serum potassium-based rule, the time of permanent treatment interruption could not be simulated using the PopPKPD model. As such, the time of permanent treatment discontinuation was taken from the observed data.

Additionally, the Monte Carlo simulations also accounted for the fact that FIDELIO-DKD used a dynamic sampling design for serum potassium by adding additional up-titration and safety visits:

- A dummy record for an up-titration visit was added to the simulation input dataset at 34 days after each scheduled study visit (34 days is the median time between up-titration visits and the regular visit in FIDELIO-DKD). In case the patient was up-titrated at the previous visit or re-started drug treatment after a drug-holiday, serum potassium observations (local and central laboratory data) were simulated for this dummy record. If this was not the case, it was assumed that this up-titration visit would not occur.
- Two dummy records for safety visits were added to the simulation input dataset at 72 and 144 hours after each scheduled or up-titration visit. These safety visits were assumed to only occur when locally analysed serum potassium levels were >5.5 mmol/L on the previous visit.

Finally, after adding the run-in and screening data in the final step of the model development process, the simulation workflow for the VPCs was further refined. For these models, the Monte Carlo simulations for the VPC also incorporated the run-in and screening visits, and excluded simulated subjects with serum potassium levels >4.8 mmol/L (i.e. simulated central laboratory data that include residual variability) at these visits (allowing one re-assessment per visit) to accurately reflect the study design of FIDELIO-DKD and serum potassium levels at baseline.

Because serum potassium levels in FIDELIO-DKD are reported with a single decimal (e.g., 4.5 mmol/L), the thresholds for inclusion, up-titration and hyperkalemia in the simulation code are adjusted to reflect this. For example, if observations ≤ 4.8 mmol/L are required for up-titration, than the simulated code uses a threshold of <4.85 mmol/L for the (non-rounded) simulated data, as a value of 4.83 mmol/L would be rounded to 4.8 and would therefore meet the ≤ 4.8 mmol/L threshold.

During exploratory tests of the simulation workflow, VPC simulations that only accounted for serum potassium levels in dose-titration decisions over-estimated the occurrence of 20 mg dosing. Because the serum potassium levels over time were relatively well described, it was concluded this mismatch likely originates from the combined influence of multiple, non-potassium related, reasons for dose-titration decisions (e.g. general safety concerns by the clinical investigator, or eGFR-EPI drops of more than 30% since the last visit). This mismatch between the observed and predicted dosing patterns was greater for patients with lower eGFR-EPI. To empirically address this mismatch in dosing pattern, the simulations included a subset of patients that would never be up-titrated from 10 mg to 20 mg, even if serum potassium levels were ≤ 4.8 mmol/L. The random chance of a patient being in this subset was empirically selected to align the simulated dosing pattern with the observed dosing pattern, and was dependent on baseline eGFR-EPI, as shown in Table S 1.

Each simulated scenario was repeated 30 times, resulting in 30 simulated datasets for each scenario. Statistics of interest (such as the median or 95th percentile of the simulated data within a single bin) were calculated separately for each of these 30 simulated datasets. The 95% prediction interval of the statistics of interest in each bin were calculated as: $mean \pm 1.96 * stdev$, where the *mean* and *stdev*, are the mean and standard deviation of the statistics in calculated for each of the 30 simulated datasets.

This method for calculating the prediction interval was used for the VPC simulations, as well as the potassium simulations, with the later simulations also including parameter uncertainty.

Software

Non-linear mixed-effects modelling and simulation was performed using NONMEM (version 7.4.3). Graphical analysis and processing of NONMEM output was performed using R version 3.6.2.

Example NONMEM simulation code

The code below shows how the simulation of finerenone dose-titration and dynamic sampling of serum potassium was implemented in NONMEM. The parameter estimates were sampled from the covariance matrix of the final model.

```
$INPUT RECN SID ID TIME DV MDV EVID FLOBSC FLOBSL TREA EGFR_EPI0 UACR0 RACA SEX TAFD ICL
      IF1 BTIME FAIL FLPLAC FLSAF FLUPT FLREG TTD1
$SUBROUTINES ADVAN13 TOL=9
$ABBREVIATED COMRES=2
$MODEL COMP=(EFFECT)
$PK
IF(ICALL.EQ.4) THEN
IF (NEWIND.NE.2) THEN ; For every new individual
COM(1) = 5.1 ; COM(1) keeps track of previous local laboratory serum potassium. Set at value at which
      no dose-titration occurs for new individuals, will be replaced by first non-baseline observation
COM(2) = 0 ; COM(2) keeps track of dose level at previous observation of local laboratory serum
      potassium (or set to starting dose before first post-baseline observations).
CALL RANDOM (2, R) ; for probability that subject will never be uptitrated beyond 10 mg, despite being
      eligible
NO20UP = 0
IF(R.LT.0.35.AND.EGFR_EPI0.LT.30) NO20UP=1
IF(R.LT.0.30.AND.EGFR_EPI0.LT.45.AND.EGFR_EPI0.GE.30) NO20UP=1
IF(R.LT.0.25.AND.EGFR_EPI0.LT.60.AND.EGFR_EPI0.GE.45) NO20UP=1
IF(R.LT.0.18.AND.EGFR_EPI0.GE.60) NO20UP=1
ENDIF
IF (NEWIND.NE.2) THEN ; For every new individual
```

```

COM(1) = 5.1 ; Dummy observation at which no dose-titration occurs, will be replaced by first non-
baseline observation
COM(2) = 0
ENDIF
IF (NEWIND.NE.2.AND.TREA.EQ.1) THEN ; set starting dose to 10 mg, for those in 10 mg starting dose
group (TREA=1)
COM(2) = 10
ENDIF
IF (NEWIND.NE.2.AND.TREA.EQ.2) THEN ; ; set starting dose to 20 mg, for those in 20 mg starting dose
group (TREA=1)
COM(2) = 20
ENDIF
IF (NEWIND.NE.2.AND.TREA.EQ.3.AND.EGFR_EPI0.GE.60) THEN ; has to keep track of the placebo dose as
it determines the sampling schedule
COM(2) = 20
ENDIF
IF (NEWIND.NE.2.AND.TREA.EQ.3.AND.EGFR_EPI0.LT.60) THEN ;
COM(2) = 10
ENDIF
; DOSE TITRATION SCHEME, based on last observations, COM(1), and the dose prior to the last
observations, COM(2)
;Current dose is 0 mg
IF(COM(1).GE.5.05.AND.COM(2).EQ.0) THEN ; no restart of dose if serum potassium is above 5.0
SIMDOSE = 0
ENDIF
IF(COM(1).LT.5.05.AND.COM(2).EQ.0) THEN ; no restart of dose if serum potassium is above 5.0
SIMDOSE = 10
ENDIF
;Current dose is 10 mg
IF(COM(1).LT.4.85.AND.COM(2).EQ.10.AND.NO20UP.EQ.0) THEN ;Uptitration from 10 mg to 20 mg if
serum potassium is <= UPT_THRESHOLD mmol/L.
SIMDOSE = 20
ENDIF
IF(COM(1).LT.4.85.AND.COM(2).EQ.10.AND.NO20UP.EQ.1) THEN ;No uptitration to 20 mg if NO20UP==1
SIMDOSE = 10
ENDIF
IF(COM(1).GE.4.85.AND.COM(1).LT.5.55.AND.COM(2).EQ.10) THEN ;Subject on lower dose will not be
uptitrated when between UPT_THRESHOLD and 5.5
SIMDOSE = 10
ENDIF
; Current dose is 20 mg
IF(COM(1).LT.5.55.AND.COM(2).EQ.20) THEN
SIMDOSE = 20
ENDIF
; dose titration regardless of dose
IF(COM(1).GE.5.55) THEN ;Withhold treatment if serum potassium above 5.5
SIMDOSE = 0
ENDIF
IF(TIME.GE.TTD1) THEN
SIMDOSE = 0
ENDIF
ENDIF
; posthoc PK parameters from PK model for calculating AUCss
CL = ICL
F1 = IF1
;

```

```

; PD
JAP = 0
IF(RACA.EQ.3.2) JAP = 1
CV1 = 1
CV4 = 1
IF(UACR0.GT.0) THEN ;UACR0 set to -999 for screening failures
CV1 = 1 + (UACR0-800)*THETA(12)
CV4 = 1 + (UACR0-800)*THETA(18)
ENDIF
CV2 = 1 + (SEX-1)*THETA(14)
CV3 = 1 + (SEX-1)*THETA(15)
TVBSL = THETA(2)* (1+JAP*THETA(5)/100) * (EGFR_EPI0/45)**THETA(7)*CV3
BXPARTHETA(20)
ETATR = (EXP(ETA(1))**BXPARTHETA(20)-1)/BXPARTHETA(20)
BSL=TVBSL *EXP(ETATR)
Kin = THETA(3)
Kout = Kin/BSL
EMAX = THETA(4)* (1+ETA(2))*CV1*(EGFR_EPI0/45)**THETA(13)*CV2
EC50 = THETA(8)
HILL = THETA(9)
TSLOPE = THETA(16) * (1 + (BSL-4.4)*THETA(17)) * CV4
IF(TREA.LT.3.AND.TAFD.GT.0) THEN
TSLOPE = THETA(19) * (1 + (BSL-4.4)*THETA(17)) * CV4
ENDIF
;
A_0(1) = BSL
;
$DES
AUCSS = 0
IF(TAFD.GT.0.AND.T.LT.TTD1.AND.TREA.LT.3) THEN ; only simulated non-zero exposure between first
dose and last dose, for subjects in active treatment arm (TREA = 1 or 2)
AUCSS = IF1*SIMDOSE/CL
ENDIF
EFF = EMAX * AUCSS**HILL/(EC50**HILL + AUCSS**HILL)
IF(AUCSS.LE.0) EFF =0
TEFF = TSLOPE * (T/(24*365.25))
DADT(1)= Kin-Kout*(1-EFF)*(1-TEFF)*A(1)
;
$ERROR
AUCSS2 = 0
IF(TAFD.GT.0.AND.TIME.LT.TTD1.AND.TREA.LT.3) THEN
AUCSS2 = IF1*SIMDOSE/CL
ENDIF
EFF2 = EMAX * AUCSS2**HILL/(EC50**HILL + AUCSS2**HILL)
IF(AUCSS2.LE.0) EFF2 =0
IPRED = A(1)
IF(JAP.EQ.0) W = SQRT(THETA(1))*IPRED
IF(JAP.EQ.1) W = SQRT((THETA(6)/100)*THETA(1))*IPRED
DF = THETA(10) ; degrees of freedom of Student distribution
SIG1 = W ; scaling factor for standard deviation of RUV
POTAS = IPRED*(1 + THETA(11)*FLOBSL)+W*EPS(1)*(1+ ((EPS(1)**2+1)/(4*DF)) +
((5*EPS(1)**4+16*EPS(1)**2+ 3)/(96*DF**2)) + ((3*EPS(1)**6+19*EPS(1)**4 + 17*EPS(1)**2-
15)/(384*DF**3)))
Y = -999
OBS = 0 ; uses to determine if a post-baseline visit would have occurred

```

```

IF(BTIME.LE.24) Y = POTAS ;baseline, run-in and screening observations are always simulated, but do
not lead to dose titration
IF(FLREG.EQ.1.AND.MDV.EQ.0) THEN ;regular visits are always simulated
Y = POTAS
OBS = 1
ENDIF
;uptitration visit for those going from 10 to 20 mg
IF(BTIME.GT.24.AND.TAFD.GT.0.AND.MDV.EQ.0.AND.FLUPT.EQ.1.AND.COM(1).LT.4.85.AND.COM(2).EQ.1
0.AND.NO20UP.EQ.0.AND.TIME.LT.TTD1) THEN
Y = POTAS
OBS = 1
ENDIF
;uptitration visit for those going from 0 to 10 mg (uptitrated at either regular or safety visit)
IF(BTIME.GT.24.AND.TAFD.GT.0.AND.MDV.EQ.0.AND.FLUPT.EQ.1.AND.COM(1).LT.5.05.AND.COM(2).EQ.0.
AND.TIME.LT.TTD1) THEN
Y = POTAS
OBS = 1
ENDIF
;safety visit after hyperkalemia
IF(BTIME.GT.24.AND.TAFD.GT.0.AND.MDV.EQ.0.AND.FLSAF.EQ.1.AND.COM(1).GE.5.55) THEN ; possible
alternative, only safety visit when downtitrated on previous visit
Y = POTAS
OBS = 1
ENDIF
IF(BTIME.GT.24.AND.OBS.EQ.1.AND.FLOBSL.EQ.1.AND.TIME.LT.TTD1) THEN ; only local lab is used for
titration
COM(1) = POTAS
COM(2) = SIMDOSE ;Update the previous dose at each observation
ENDIF
$THETA
0.004481 ; TH1 prop res error
4.489 ; TH2 BSL
0.007824; TH3 Kin
0.06762 ; TH4 EMAX
-3.371 ; TH5 % difference in Japanese on BSL
86.22; TH6 Perc. of prop res error PD in Japanese
-0.03957 ;TH7 COV effect EGFR_EPI0 on BSL
0.2878 ; TH8 EC50 of AUC effect on Kout
1 FIX ; TH9 HILL of AUC effect on kout
6.459 ; TH10 DF of tdistribution
0.01984 ; TH11 Difference between local and central lab.
5.495e-05 ; TH12 UACRO on EMAX
-0.382 ; TH13 EGFR_EPI0 on EMAX
-0.1045 ; TH14 SEX on EMAX
0 FIX; TH15 SEX on BSL
0.003485 ; TH16 Proportional disease progression time slope placebo per year
1.726 ; TH17 impact of baseline in disease progression.
0.001218; TH18 COV effect UACRO on TSLOPE
0.001397; TH19 Proportional disease progression time slope active per year
-1.241; TH20 shape parameter boxcox transformation BSL
$OMEGA BLOCK (2)
0.007168 ; ETA1 BSL
-0.04066 1.614 ; ETA2 EMAX
$SIGMA 1 FIX ; Residual Error
$SIMULATION (82445) (63702 UNIFORM) SUBPROBLEMS=1 ONLYSIM

```

```
$TABLE ID TIME DV AUCSS2 ETA1 ETA2 SIMDOSE TREA FLOBSC FLOBSL NO20UP FLSAF FLREG  
FLUPT NOPRINT ONEHEADER FORMAT=s1PE15.8 FILE=par
```

Snippet of simulation input data

Shown below (Table S 2) is an illustration of the simulation input dataset for a single scheduled visit (in this case, the visit 2 (month 1) scheduled visit) + the associated five visits that may occur depending on the serum potassium and dose level of previous visits. For visits that do not occur, no observation is simulated, and records associated with such visits are removed in post-processing step of the simulated data.

Final PKPD model code

```
$SUBROUTINES ADVAN13 TOL=9
$MODEL COMP=(EFFECT)
$PK
; posthoc PK parameters from PK model for calculating AUCs
CL = ICL
F1 = IF1
;
; PD
JAP = 0
IF(RACA.EQ.3.2) JAP = 1
;
CV1 = 1
CV4 = 1
IF(UACR0.GT.0) THEN ;UACR0 set to -999 for screening failures
CV1 = 1 + (UACR0-800)*THETA(12)
CV4 = 1 + (UACR0-800)*THETA(18)
ENDIF
;
CV2 = 1 + (SEX-1)*THETA(14)
CV3 = 1 + (SEX-1)*THETA(15)
;
TVBSL = THETA(2)* (1+JAP*THETA(5)/100) * (EGFR_EPI0/45)**THETA(7)*CV3
BXPARG=THETA(20)
ETATR = (EXP(ETA(1))**BXPARG-1)/BXPARG
BSL=TVBSL *EXP(ETATR)
;
Kin = THETA(3)
Kout = Kin/BSL
EMAX = THETA(4)* (1+ETA(2))*CV1*(EGFR_EPI0/45)**THETA(13)*CV2
EC50 = THETA(8)
HILL = THETA(9)
;
TSLOPE = THETA(16) * (1 + (BSL-4.4)*THETA(17)) * CV4
IF(TREA.LT.3.AND.TAFD.GT.0) THEN
TSLOPE = THETA(19) * (1 + (BSL-4.4)*THETA(17)) * CV4
ENDIF
;
A_0(1) = BSL
;
$DES
AUC = 0
IF(TAFD.GT.0) THEN
AUC = F1*DOSE/CL
ENDIF
;
TEFF = TSLOPE * (T/(24*365.25))
EFF = EMAX * AUC**HILL/(EC50**HILL + AUC**HILL)
IF(AUC.LE.0) EFF =0
;
DADT(1)= Kin-Kout*(1-EFF)*(1-TEFF)*A(1)
;
```



```

$ERROR
IPRED = A(1)
IF(JAP.EQ.0) W = SQRT(THETA(1))*IPRED
IF(JAP.EQ.1) W = SQRT((THETA(6)/100)*THETA(1))*IPRED
;
DF = THETA(10) ; degrees of freedom of Student distribution
SIG1 = W ; scaling factor for standard deviation of RUV
IWRES=(DV-IPRED*(1+THETA(11)*FLOBSL))/SIG1
;
PHI=(DF+1)/2
GAMMA=EXP(GAMLN(PHI))
;
PHI2=DF/2
GAMMA2=EXP(GAMLN(PHI2))
;
COEFF=GAMMA/(GAMMA2*SQRT(DF*3.14159265))/SIG1
BASE=1+(IWRES*IWRES)/DF
IF(BASE.EQ.0) BASE=0.000001
POW=-(DF+1)/2
;
L=COEFF*BASE**POW ; PDF of t-distribution
MIN2LL = -2*LOG(L)
Y= -2*LOG(L)
;
$THETA
(0,0.00457) ; TH1 sigma2, scalar of residual error
(0,4.53) ; TH2 BSL
(0,0.011) ; TH3 Kin
(0, 0.093, 0.99) ; TH4 EMAX
(-4) ; TH5 % difference in Japanese on BSL
(0, 83) ; TH6 Relative sigma in Japanese (%)
-0.05 ; TH7 COV effect EGFREPI0 on BSL
(0.01, 0.40) ; TH8 EC50 of AUC effect on Kout
1 FIX ; TH9 HILL of AUC effect on kout
(3, 7, 20) ; TH10 degrees of freedom of t-distribution
(0.021) ; TH11 Difference between local and central laboratory data
0.00007 ; TH12 UACRO on EMAX
(-0.33) ; TH13 EGFREPI0 on EMAX
-0.16 ; TH14 SEX on EMAX
0 FIX ; TH15 SEX on BSL
(0.0035) ; TH16 TSLOPEplacebo, progression rate in placebo arm
(-0.5, 1.8, 40) ; TH17 Relation between BSL and TSLOPE
0.0015 ; TH18 COV effect UACRO on TSLOPE
(0.0019) ; TH19 TSLOPEactive, progression rate in active treatment arm
(-10, -1, -0.01) ; TH20 shape parameter boxcox transformation BSL
$OMEGA BLOCK (2)
0.125 ; ETA1 BSL
-0.13 1.2 ; ETA2 EMAX
$ESTIMATION MAXEVAL=9999 PRINT=5 NOABORT -2LL METHOD=1 LAPLACE POSTHOC
NUMERICAL SLOW ATOL=9 SIGL=9 NSIG=3

```

Supplementary References

1. Bakris GL, Agarwal R, Anker SD, Pitt B, Ruilope LM, Rossing P, et al. Effect of Finerenone on Chronic Kidney Disease Outcomes in Type 2 Diabetes. *The New England journal of medicine*. 2020 Dec 3;383(23):2219-29.

Supplementary Figures

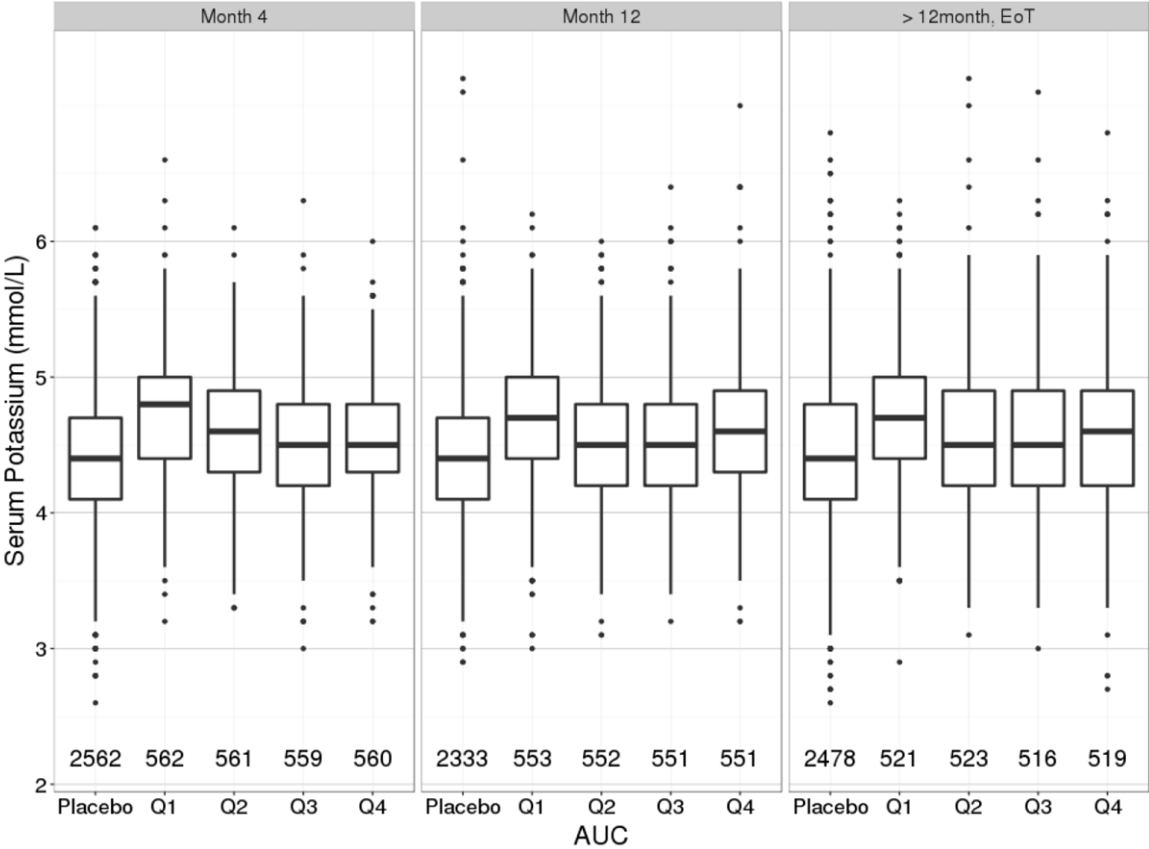


Figure S 1. Serum Potassium versus area under the drug concentration versus time curve (AUC) exposure quartiles (Q1-Q4) boxplots at three representative timepoints. The line in the boxplots marks the median with the surrounding box from 25th to 75th percentiles, whisker extensions defined as 1.5 interquartile range (IQR) and outliers shown as points above and below. The quartiles are based on the exposure at the respective timepoint indicated at the top of the figure; the number in the lower part of the figure represents the number of subjects per quartile; EoT = End of Treatment.

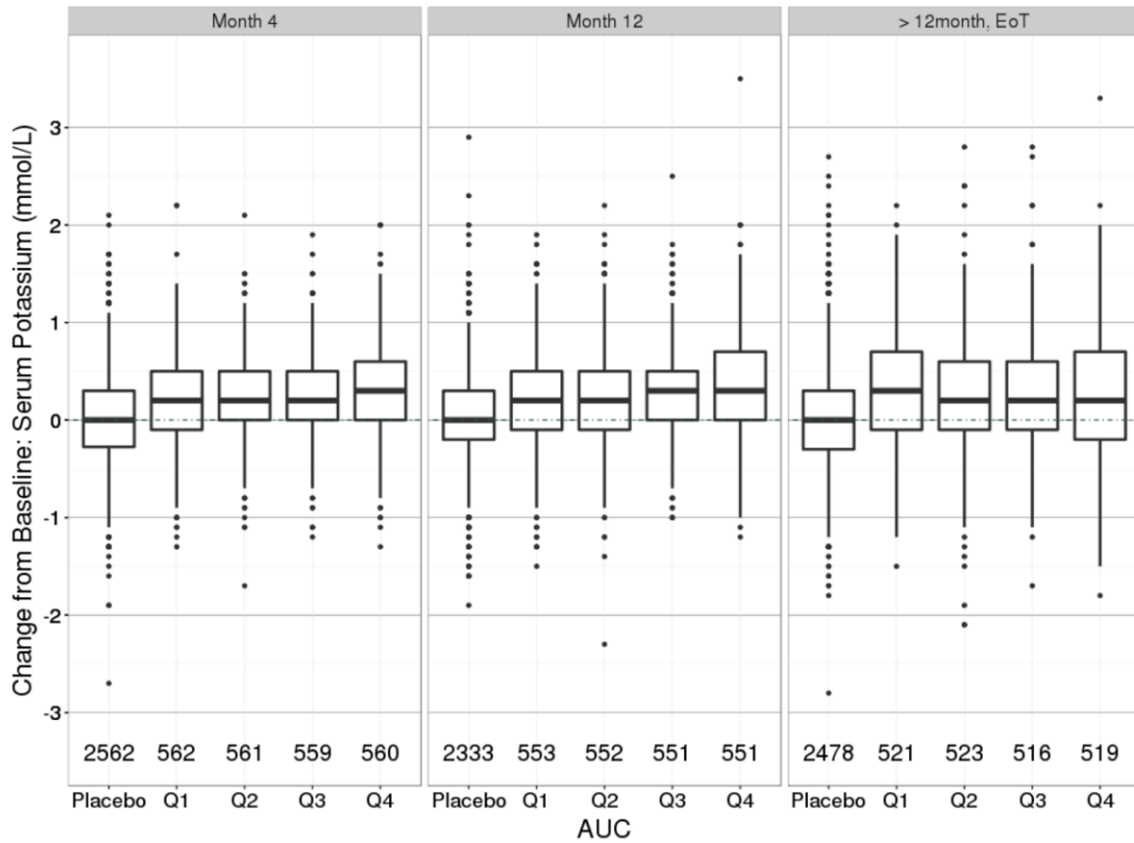


Figure S 2. Change from Baseline: Serum Potassium versus area under the drug concentration versus time curve (AUC) exposure quartiles (Q1-Q4) boxplots at three representative timepoints. The line in the boxplots marks the median with the surrounding box from 25th to 75th percentiles, whisker extensions defined as 1.5 interquartile range (IQR) and outliers shown as points above and below. The quartiles are based on the exposure at the respective timepoint indicated at the top of the figure; the number in the lower part of the figure represents the number of subjects per quartile; EoT = End of Treatment.

Supplementary Tables

Table S 1. Random chance for simulated subjects to be in subset without 10 to 20 mg up-titration.

Baseline eGFR (ml/min/1.73m ²)	Random chance of being in subset without 10 mg to 20 mg up-titration (%)
<30	35
≥30-<45	30
≥45 - <60	25
≥60	18

Table S 2. Simulation input dataset illustration.

ID	TIME	DV	VISIT	FLREG	FLUPT	FLSAF	FLOBSC	FLOBSL	<i>When does visit occur?</i>
1	700	.	2	1	0	0	1	0	<i>Always (scheduled visit)</i>
1	700	.	2	1	0	0	0	1	
1	772	.	2.1	0	0	1	1	0	<i>If local K+ on visit 2 ≥5.55</i>
1	772	.	2.1	0	0	1	0	1	
1	844	.	2.2	0	0	1	1	0	<i>If safety visit 2.1 occurred and local K+ was still ≥5.55</i>
1	844	.	2.2	0	0	1	0	1	
1	1516	.	2.5	0	1	0	1	0	<i>If finerenone dose is up-titrated (or re-started after interruption) during visits 2/2.1/2.2</i>
1	1516	.	2.5	0	1	0	0	1	
1	1578	.	2.6	0	0	1	1	0	<i>If local K+ on up-titration visit 2.5 is ≥5.55</i>
1	1578	.	2.6	0	0	1	0	1	
1	1660	.	2.7	0	0	1	1	0	<i>If safety visit 2.6 occurred and local K+ was still ≥5.55</i>
1	1660	.	2.7	0	0	1	0	1	

ID = unique subject identifier, TIME = time in hours, VISIT = study visit identifier, FLREG = flag/indicator of scheduled visits, FLUPT = flag/indicator of up-titration visits, FLSAF = flag/indicator of safety visits, FLOBSC = flag/indicator of central laboratory observations of serum potassium, FLOBSL = flag/indicator of local laboratory observations of serum potassium.