Supplementary Information

Clinical Pharmacokinetics

Finerenone dose-exposure-response for the primary kidney outcome in FIDELIO-DKD phase 3 – Population pharmacokinetic and time-to-event analysis

Paul van den Berg, Martijn Ruppert, Emir Mesic, Nelleke Snelder, Andreas Seelmann, Roland Heinig, Amer Joseph, Dirk Garmann, Joerg Lippert, Thomas Eissing

1 Leiden Experts on Advanced Pharmacokinetics and Pharmacodynamics (LAP&P), The Netherlands
2 Bayer AG, Pharmaceuticals R&D, Pharmacometrics, Germany
3 Bayer AG, Pharmaceuticals R&D, Clinical Pharmacology, Germany
4 Bayer AG, Pharmaceuticals R&D, Clinical Development, Germany

*Corresponding author: Thomas Eissing, Bayer AG, Pharmaceuticals R&D, Pharmacometrics, Building B106 Room 205, 51368 Leverkusen, Germany, Tel: +49 214 3054811, E-mail: thomas.eissing@bayer.com
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 was conducted in accordance with the ICH Harmonized Tripartite Guideline for Good Clinical Practice. All study participants provided written informed consent before entering the study.

Analytical Methods
Plasma concentrations of finerenone were determined using a fully validated high-performance liquid chromatography/mass spectrometry assay after protein precipitation with acetonitrile [2]. The validation and analysis of the study samples were conducted in accordance with internal standard operating procedures and performed in compliance with the US Food and Drug Administration guidance on bioanalytical method validation [3]. The lower limit of quantification (LLOQ) of the assay used to determine finerenone concentrations was 0.1 µg/L.

Further details on additional procedures applied in FIDELIO-DKD are described in the Study Protocol as part of Bakris et al. [1].

PK outlier identification
Identification of outliers was performed as follows: the existing ARTS-DN PK model for finerenone[4] was applied to the FIDELIO data without optimizing any model parameters (a so-called MAXEVAL=0 run). Subsequently, the ratio of the observed dependent values (DV) and the population predicted values from the model output (PRED) were calculated. If the value of DV/PRED was > 50 or < 0.02, then the observation was labeled as an outlier and excluded from the analysis [4]. Approximately 13% of PK observations were identified as outliers. These outliers could not be explained by any of the available covariates and were assumed to be caused by deviations between recorded and actual dosing and/or sampling times. In addition to this, outliers identified by clinical PK expert assessment were excluded as well (see below). Based on this, a total of 411 additional observations, 173 of which were above LLOQ, were flagged as outliers and excluded from the analysis (Figure S1).

Robustness of results were evaluated by including all outliers in a final model run. The outliers could not be explained by any of the available covariates and were assumed to be caused by deviations between recorded and actual dosing and/or sampling times.

PK Expert assessment
Samples collected in the ‘PEAK’ sampling window, i.e. Visit 5, 8, 11, and 14
Per study protocol, samples were taken at any time post administration, where administration and sampling were scheduled to take place at home and in the study center, respectively. It was noted that, contrary to expectations, sampling started very early (minutes) after administration in several patients. Moreover, samples were also collected very late, close to the actual ‘trough’ in others. To account for this, a refined window for plausibility/implausibility was defined. According to the original definition PEAK concentrations <LLOQ received the PC flag ‘KINETICALLY IMPLAUSIBLE, EXCLUDE FROM STATISTICS’. According to the refined definition, values < LLOQ were only implausible, if they were contained in the interval ≥2 h to ≤ 12 h (10 mg), or ≥1.5 h to ≤15 h (20 mg). A population of samples around 24 h (>12 h and >15 h post dose for 10 mg and 20 mg, respectively) post administration was identified with very high concentrations, higher than the predefined thresholds for ‘trough’, which would correctly have to be applied to this sampling time. The
population was clearly identifiable, and samples were assigned the PC flag ‘KINETICALLY IMPLAUSIBLE, EXCLUDE FROM STATISTICS’ based on the pre-defined concentration thresholds for ‘trough’ values (8 and 16 µg/L for 10 mg and 20 mg, respectively).

PEAK samples with negative sampling times, i.e. pre-dose samples, fell outside the accepted window for PEAK. Furthermore, time of sampling could not be calculated as date and time of the respective dose on the day before was missing (according to CSP). Subsequently, all affected concentrations were excluded.

Samples collected in the ‘TROUGH’ sampling window, i.e. Visit 3
Per study protocol, samples had to be taken prior to dosing. All samples which were taken post dose and were kinetically plausible were flagged as ‘SAMPLE NOT VALID FOR TROUGH, EXCLUDE FROM STATISTICS’.

Pre dose samples taken ≤12 h and ≤15 h after dosing on day before for 10 mg and 20 mg, respectively, which were assessed as kinetically plausible, were flagged as ‘SAMPLE NOT VALID FOR TROUGH, EXCLUDE FROM STATISTICS’ as ‘trough’ was defined as >12 h and 15 h post dose for 10 mg and 20 mg, respectively.

Handling of LLOQ values in model
NONMEM’s M3 method was used to evaluate the influence of LLOQ values. However, this resulted in instability of the model (terminated runs), while the model fit was not improved. Consequently, LLOQ values were not included in the analysis.

Volume of Distribution
The two volumes of distribution were assumed equal as the data did not allow the estimation of two separate volumes. This is supported by prior Phase 1 and 2 data analyses [4]. Further, it was explored that reducing to one volume worsened the description of the data and assuming other ratios, e.g. based on physiological considerations, would not improve the description of the data. Overall, the influence of alternative assumptions on PK parameter posthoc estimates is considered minor.

Covariate testing
Different approaches for covariate inclusion are possible and accepted, e.g. in the latest (EMA and FDA) regulatory guidelines 3 different approaches are discussed. The stepwise covariate modeling approach chosen in this manuscript is one of them and has e.g. the advantage that it requires less care to consider correlations upfront, which is not always trivial. I.e. highly correlated covariates will be filtered out by this method: when added on top of the other covariates, they will not have a significant impact on the overall fit anymore. Additional covariates are only accepted if they explain a significant part of the remaining variability and not including them would result in a statistically inferior model. Certain aspects should be interpreted with care, as leaving correlated covariates out, can change the effect size of other covariates. For specific questions of interest, e.g. what an “overall” impact may be, this can be further assess with a simulation approach for subgroups of interest considering multi-variate covariate distributions (see below).

Simulation of extent of covariate effects in the PK model
The extent of identified covariate effects included in the final model was illustrated in a forest plot. The forest plot visualized the effect of covariates on exposure when compared to a reference subject (typical subject with median (continuous) covariates and/or most prevalent (categorical) covariates). For the simulations only the covariate of interest was taken into account (other covariate effects were not included in the simulation to get a ‘pure’ covariate effect).
The following steps were followed:

1. One reference subject was simulated using the median (continuous) or most prevalent (categorical) covariates.
2. For each significant categorical covariate level in the final model, 10000 virtual subjects were generated who were different from the reference subject by changing one covariate value (e.g. male versus reference female, with equal values for all other covariates). For continuous covariates this was done similarly by simulating 10000 virtual subjects at the 5th percentile, median and 95th percentile of the covariate range with equal values for all other covariates.
3. To include uncertainty in the simulations, PK parameters were sampled from a multivariate normal distribution $N(\Theta, \Sigma)$ for the fixed-effects parameters ($P$), where $\Theta$ is the $1 \times P$ vector of the fixed-effects estimates and $\Sigma$ is the $P \times P$ covariance matrix of the $P$ fixed effects.
4. Then the exposure parameters were derived and divided by the reference subject, resulting in 10000 ratios for each level within a categorical covariate and 10000 ratios at 5th percentile, median and 95th percentile of the covariate distribution (in total 30000) for continuous covariates.
5. Per covariate evaluation, the median, 5th and 95th percentiles of the ratios were plotted to visualize uncertainty.

Simulation of finerenone exposure in subgroups of interest
PK of finerenone may be different in subgroups of interest. Even if a particular subgroup is not a covariate in the model, exposure may be different in this group, because distributions of covariates that are included in the model for this subgroup may be different compared to other subgroups. For example Japanese subjects generally have lower bodyweight and therefore, when given the same dose, generally have higher drug exposure when compared to Caucasian subjects. To compare the finerenone exposure between subgroups of interest, each subgroup of interest was simulated 1000 times, taking all covariates into account. Subgroups of interest were taken from the final PK dataset. For example, if there were 100 Japanese subjects in the final PK dataset, these 100 subjects were simulated 1000 times taking into account IV and parameter uncertainty. Simulating 1000 subsets of 100 Japanese subjects allowed to visualize the median and 5th-95th percentiles, including uncertainty in a forest plot. The simulated exposures in these subgroups of interest were compared with the ‘observed’ exposures (derived from posthoc estimates of the final model) from the study population. In addition summary statistics of simulated and posthoc exposure metrics at steady-state ($C_{max,md}$ and $AUC_{t,md}$) were provided.

The following steps were followed:

1. The overall median $C_{max,md}$ and $AUC_{t,md}$ values based posthoc estimates of the final PK model were used as a reference.
2. Using the original dataset PK was simulated 1000 times. Variability was sampled from the omega estimates of the final PK model and uncertainty was sampled from a multivariate normal distribution $N(\Theta, \Sigma)$ for the fixed-effects parameters ($P$), where $\Theta$ is the $1 \times P$ vector of the fixed-effects estimates and $\Sigma$ is the $P \times P$ covariance matrix of the $P$ fixed effects.
3. Then the exposure parameters were derived and divided by the reference.
4. For each subgroup of interest the median, 5th and 95th percentiles of the simulated ratios were plotted and compared to the median, 5th and 95th percentiles of the ratios based on
posthoc estimates. For the simulated ratio’s, the 5\textsuperscript{th} and 95\textsuperscript{th} percentiles visualized the uncertainty.

Censoring of event data
Events included in the analysis were counted from the day of randomization onwards until the planned end-of-study visit following the study sponsor’s decision to terminate the study. Only the first occurrence of an event was taken into consideration. Subjects without a primary efficacy endpoint event were censored at the date of their last contact with complete information on all components of the primary composite endpoint (up to and including the end-of-study visit). In case a non-renal death occurred within 5 months from the last visit (4 monthly visits plus maximum allowed time window of 30 days) and a subsequent clinic visit had been planned, the non-renal death date was used as the censoring date [1, 5]. As, in theory, the kidney event could have happened between visits, events were modeled as intervals, which were set to the last central lab eGFR measurement at a scheduled visit before the event until the event. During model development random dropout was assumed as per protocol subjects stay in the study, even after treatment discontinuation. More than 90\% of the subjects were still included in the study at the end-of-study date.

Lumping of prognostic factors
Categorical PFs were lumped if there were not sufficient individuals and occurred events within each PF level, set at 3\% and 1\%, respectively. As some subgroups of interest had, according to the predefined criteria, sufficient individuals (>3\%), but not sufficient events (<1\%), the latter criterion was relaxed to prevent that potentially important PFs are overlooked. Lumping was performed respecting the order of ordered categorical levels. Per PF, a reference level was chosen. When possible, this was done based on a logical choice, for example the ‘normal state’, such as the normal level for kidney function. For PFs where a logical choice was not obvious, for example for non-ordered categorical PFs, the reference was the level that includes the largest number of individuals.

Computation
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.
Supplementary Functional Forms
The following hazard shapes were tested: constant, Gompertz, Weibull, log-logistic and log-normal hazard.

\[
\begin{align*}
    h(t)_{\text{constant}} & = \theta_\lambda \\
    h(t)_{\text{Gompertz}} & = \theta_\lambda \cdot e^{\theta_\alpha \cdot t} \\
    h(t)_{\text{Weibull}} & = \theta_\lambda \cdot e^{\theta_\alpha \cdot \log(t+\varepsilon)} \\
    h(t)_{\text{loglogistic}} & = \frac{\theta_\alpha \cdot \theta_\lambda \cdot (t + \varepsilon)^{\theta_\alpha - 1}}{1 + \theta_\lambda \cdot (t + \varepsilon)^{\theta_\alpha}} \\
    h(t)_{\text{lognormal}} & = \frac{1}{(t + \varepsilon) \cdot \theta_{\text{scale}} \cdot \sqrt{2 \cdot \pi}} \cdot e^{-\frac{-(\log(\theta_{\text{location}}))^2}{2 \cdot \theta_{\text{scale}}^2}} \\
    & \quad \times \frac{-\log(\log(t+\varepsilon))^2}{1 - \phi\left(\frac{-\log(\log(t+\varepsilon))}{\theta_{\text{scale}}}\right)}
\end{align*}
\]

Where \( h \) is the hazard, \( t \) is time and \( \theta_\lambda, \theta_\alpha, \theta_{\text{scale}}, \theta_{\text{location}} \) are estimated parameters. \( \varepsilon \) is a small number that is added where needed to avoid computational issues such as division through zero.

Model code of PK model
\$SIZES PD=-100 ; extra input items

\$PROBLEM PK Finerenone (Study 16244)

\$INPUT C RECN DROP SID ID DROP DROP DROP PMAS TIME DROP DROP DROP TAD TAFD DROP DROP DROP DROP VISIT DV DROP EVID MDV DROP DOSE

;C RECN STUD SID ID FAS SAF PPROT PMAS TIME TIMEW TIMED TADGT0 TAFD DATE
CLK DAY DAY2 VISIT DV DVID EVID EVID MDV MDV2 DOSE

AMT DROP CMT TREA DROP DROP DROP PKFLAG AGE DROP SEX ALC SMOK RACE RACA ETHN DROP BW0 HGHT BMI BSA LBM ALT

;AMT CYCLE CMT TREA TGR LOGDV LLOQ BLO PKFLAG AGE AGEGRP SEX ALC SMOK RACE RACEASIA ETHNICIT COUNTR WGHT0 HGHT0 BMI0 BSA0 LBM0 ALT0

AST ALB BILI GGT ALP CREA PROT DROP DROP DROP DROP CPBH CKDS EGFRMD0 EGFRMD

;AST0 ALB0 BILI0 GGT0 ALP0 CREA0 PROT0 CY3A4IH0 CY3A4ID0 SGLTINH0 EGRFCAT0 CHILDPS COUNTR WGT0 HGHT0 BMI0 BSA0 LBM0 ALT0

EGFREP0 EGFREP SGLT DROP DROP DROP DROP DROP DROP DROP DROP
; EGFREPI0 EGFREPI GLYCSICN INJGLCN SCY3A4CN MCY3A4CN WCY3A4CN UCY3A4CN CY3A4SCN CY3A4MCN CY3A4WCN

DROP CYPINH CYPIND DROP DROP DROP DROP DROP FLDVP NOBS II ADDL PKASSESM MDV3

; CY3A4UCN CYPINHN CYPINDN IMPUCOV1 IMPUCOV2 IMPUDOSE EOT_DATE EOS_DATE FLDVP NOBS II ADDL PKASSESM MDV3

$DATA NM.PK.finerenone.H.v13.csv

; IGNORE=@ ; Ignore all records with 'C' value in 'C' column. These are records with EVID = 1 and AMT = 0.
IGNORE=(PMAS.EQ.0) ; Ignore all records which were NOT defined as members of the analysis dataset by the sponsor (PMAS=0).
IGNORE=(PKFLAG.EQ.1) ; Ignore all records in which TIME > TIME at last PK sample + 48h (on individual level) or if there is no PK sample.
IGNORE=(FLDVP.GT.0) ; Ignore outliers with DV/PRED<0.02 (FLDVP=1), DV/PRED>50 (FLDVP=2), DV=1630 mcg/L (FLDVP=3), and a PK observation with TADGT0=338.33h and DV=0.145 mcg/L (FLDVP=4)
IGNORE=(NOBS.EQ.0) ; Ignore subjects without valid PK observations included in the analysis
IGNORE=(PKASSESM.EQ.1) ; Ignore records flagged by sponsor as: ‘Irrelevant for statistical evaluation, exclude from statistics’
IGNORE=(PKASSESM.EQ.2) ; Ignore records flagged by sponsor as: ‘Kinetically implausible, exclude from statistics’

; $SUBROUTINES ADVAN5
$MODEL
COMP = (DEPOT )
COMP = (CENTRAL)
COMP = (PERI )
COMP = (BUFFER )
COMP = (BUFFER2)
COMP = (BUFFER3)

$PK
; Covariate effects
; Continuous covariates
CV1 = (BW0/85)**THETA(9); effect of Wght0 on V/F
CV2 = (EGFREP/39.1)**THETA(10); effect of EGFREP on CL/F and F
CV3 = (HGHT/167)**THETA(11); effect of HGHT0
CV4 = (CREA/1.51)**THETA(12); effect of CREA0
CV5 = (GGT/25)**THETA(16); effect of GGT0

; Categorical covariates

; RACA
SRACA1=0; RACA=1+non-significant categories
IF(RACA.EQ.3.3) SRACA1=1; RACA=3.3
ERACA = THETA(13)**SRACA1

; SGLT (GLYCSI CATN)
SSGLT1=0; GLYCSI CATN=1+3
IF(SGLT.EQ.2) SSGLT1=1; GLYCSI CATN=2
ESGLT = THETA(14)**SSGLT1

; SMOK
SSMOK1=0; SMOK=1
IF(SMOK.GE.2) SSMOK1=1; SMOK=2+3
ESMOK = THETA(15)**SSMOK1

; CYPINH reduced categories (CYPINHR) on CL/F and F
SCYPINHR1=0; CYPINH=9(None)
SCYPINHR2=0; CYPINH=9(None)
IF(CYPINH.EQ.4.OR.CYPINH.EQ.6.OR.CYPINH.EQ.8) SCYPINHR1=1; CYPINH=4(Strong Cyp inh >50%) or CYPINH=6(Moderate Cyp inh >50%) or CYPINH=8(Weak Cyp inh >50%)
IF(CYPINH.EQ.1) SCYPINHR2=1; CYPINH=1(Unclassified Cyp inh <50%)
IF(CYPINH.EQ.2) SCYPINHR2=1; CYPINH=2(Unclassified Cyp inh >50%)
IF(CYPINH.EQ.3) SCYPINHR2=1; CYPINH=3(Strong Cyp inh <50%)
IF(CYPINH.EQ.5) SCYPINHR2=1; CYPINH=5(Moderate Cyp inh <50%)
IF(CYPINH.EQ.7) SCYPINHR2=1; CYPINH=7(Weak Cyp inh <50%)
ECYPINHR = (THETA(17)**SCYPINHR1) * (THETA(18)**SCYPINHR2)
K14 = THETA(2)
K45  = K14
K56  = K14
K62  = K14
;
TVCL  = THETA(3)*CV2*CV3*CV4*ESMOK*CV5*ESGLT*ECYPINHR
CL    = TVCL*EXP(ETA(1))
TVV2  = THETA(4)*CV1*ERACA
V2    = TVV2*EXP(ETA(2))
Q     = THETA(5)
V3    = THETA(6)*V2
;
ALAG1 = THETA(7)
;
F1    = THETA(8)/(CV2*CV3*CV4*ESMOK*ESGLT*ECYPINHR)
;
S2    = V2
K23   = Q/V2
K32   = Q/V3
K20   = CL/V2
;
$ERROR
IPRED = A(2)/V2
W = SQRT(THETA(1))*IPRED
IRES = IPRED-DV
IWRES = IRES/W
Y = IPRED+W*ERR(1)
;
A1=A(1)
A2=A(2)
$\text{THETA}$

(0, 0.05) ; RES ERR residual error

(0, 22.6) ; TH2, Ka (1/h)

(0, 30.0) ; TH3, CL/F (L/h)

(0, 113) ; TH4, Vc/F (L)

(0, 0.336) ; TH5, Q/F (L/h)

(1 FIX) ; TH6, Ratio between Vp/F and Vc/F : FIXED

(0.215 FIX) ; TH7, Absorption lagtime (h) : FIXED

(1 FIX) ; TH8, Relative bioavailability : FIXED

(0.502) ; TH9, effect of WGHT0 on V/F

(0.156) ; TH10, effect of EGFREP on CL/F and F

(0.716) ; TH11, effect of HGHT0 on CL/F and F

(0.120) ; TH12, effect of CREA0 on CL/F and F

(0, 1.29) ; TH13, effect of RACA (RACA=3.3) on V/F

(0, 1.10) ; TH14, effect of SGLT (GLYCSI CATN=2) on CL/F and F

(0, 1.04) ; TH15, effect of SMOK (SMOK=2 or SMOK=3) on CL/F and F

(-0.0712) ; TH16, effect of GGT0 on CL/F

(0.949) ; TH17, effect of Cyp3A4 inhibitor use (Strong or Moderate or Weak Cyp inh >50% (CYPINH=4 or 6 or 8)) on CL/F and F

(0.958) ; TH18, effect of Cyp3A4 inhibitor use (other CYPINH use (CYPINH=1, 2, 3, 5, or 7)) on CL/F and F

$\text{OMEGA BLOCK(2)}$

0.0965 ; OM1, CL/F

0.044 0.103 ; OM2, Vc/F and Vp/F

$\text{SIGMA}$

1 FIX ; SIG1

$\text{EST MAXEVAL}=9999\ PRINT=5\ NOABORT\ METHOD=1\ INTERACTION\ POSTHOC ;\ No\ CWRES$

MSFO=Q.T.AB.2.3x4.v2.r.nmv

$\text{COV COMP PRINT=E}$

$\text{TABLE}$

ID SID TIME TAD TAFD VISIT DOSE TREA IPRED CWRES ETAS(1:LAST) TVCL CL Q TVV2 V2

V3 F1 AGE SEX ALC SMOK RACA ETHN BW0 HGHT LBM BMI BSA ALT AST ALP BILI GGT CREA PROT

CYPINH CYPIND SGLT CKDS CPGH EGFRMD0 EGFRMD EGFRREP0 EGFRREP NOBS CV1 CV2 CV3 CV4 CV5
ESMOK ERACA ESGLT ECYPINHR PKASSESM MDV3
NOPRINT ONEHEADER FORMAT=s1PE15.8
FILE=par
Model code of TTE model

$SIZES   LIM6=90000 PD=-150 NO=15000

$PROBLEM   TTE Finerenone Renal (Study 16244)

$INPUT   C RECN SID ID TREA TGR TIME DROP DROP TAD TAD2 TADGT0 TAFD
          DOSE AMT II ADDL DVID_L DV_L=DV
          EVID_L=EVID TTETYPE MDV FAS SAF STUD PPROT DAY DAY2 VISIT
          CYCLE TTR TTC TTH1 TTD1 TTD2 TTRF TTCF TTH1F DROP DROP ; dropped are EOS_DATE and
          EOT_DATE
          AGE AGEGRP SEX ALC SMOK RACE RACE_ASIAN ETHNICITY COUNTR
          WGH0 TMO0 HBA1C0 CYP3A4_INH0 CYP3A4_IND0 SGLT_INH0
          EGRF_CAT0 CHILD_PUGH_SCR RENAL_IMP_CAT0 K0 UACR0
          EGRF_MDRD0 EGFR_MDRD EGFR_EPI0 EGFR_EPI GLYCSI_CATN
          INJCGL_CATN S_CYP3A4_CATN M_CYP3A4_CATN W_CYP3A4_CATN
          UCYP3A4_CATN CYP3A4S_CATN CYP3A4M_CATN CYP3A4W_CATN
          CYP3A4U_CATN CYPINHN CYPINDN
          IMPUCOV1   IMPUCOV2
          IMPUTED_DOSE
          DSINT1 DSINT2 DSINT3 NMINT1 NMINT2 NMINT3
          NMMIS1 NMMIS2 NMMIS3 SWITCH1 SWITCH2 SWITCH3
          TTEFL1 TTEFL2 TTEFL3
          SUBJSTAT
          PK_ETA1 PK_ETA2 CREA GGT HGHT

$DATA   NM.finerenone.TTE.D.v32_RENAL.csv
          IGNORE=@
          IGNORE(FAS.NE.1)
          IGNORE(DV.EQ.1)
          IGNORE(TIME.LT.0)
          IGNORE(TTETYPE.EQ.-99)
          IGNORE(TTETYPE.EQ.-1)
$SUBROUTINE ADVAN13 TOL=6

$MODEL  COMP=(DEPOT, DEPDOSE) ; 1
      COMP=(CENTRAL) ; 2
      COMP=(PERI) ; 3
      COMP=(BUFFER) ; 4
      COMP=(BUFFER2) ; 5
      COMP=(BUFFER3) ; 6
      COMP=(ELIMITED) ; 7
      COMP=(AUC) ; 8 -- AUC of central conc
      COMP=(NOTUSED) ; 9
      COMP=(CUMHZRD) ; 10

$PK

dummyETA = ETA( 1) ; dummy

; Values used in the final PK model (H.PK.mod)

BW0 = WGHT0
EGFREP = EGFR_EPI
RACA = RACE_ASIAN
SGLT = GLYCSI_CATN
SSMOK1 = SMOK
CYPINH = CYPINHN
PK_THETA02 = 22.4943
PK_THETA03 = 29.9365
PK_THETA04 = 113.053
PK_THETA05 = 0.334720
PK_THETA06 = 1
PK_THETA07 = 0.215
PK_THETA08 = 1
PK_THETA09 = 0.501018
PK_THETA10 = 0.154506
PK_THETA11 = 0.719710
PK_THETA12 = 0.117879
PK_THETA13 = 1.29221
PK_THETA14 = 1.09913
PK_THETA15 = 1.04077
PK_THETA16 = -0.0693831
PK_THETA17 = 0.951379
PK_THETA18 = 0.996089

; The following part is taken from the final PK model
CV1 = (BW0 / 85)**PK_THETA09       ; effect of BW0 on V
CV2 = (EGFREP / 39.1)**PK_THETA10 ; effect of EGFREP on CL and F1
CV3 = (HGHT / 167)**PK_THETA11    ; effect of HGHT
CV4 = (CREA / 1.51)**PK_THETA12   ; effect of CREA
CV5 = (GGT / 25)**PK_THETA16      ; effect of GGT

; Categorical covariates
; RACA
SRACA1=0                 ; RACA=1+other categories
IF(RACA.EQ.3.3) SRACA1=1 ; RACA=3.3 (Korean)
ERACA = PK_THETA13**SRACA1

; SGLT (GLYCSI CATN)
SSGLT1=0                 ; GLYCSI CATN=1+3 (SGLT use 0-50% of at-risk period)
IF(SGLT.EQ.2) SSGLT1=1   ; GLYCSI CATN=2 (SGLT use >50% of at-risk period)
ESGLT = PK_THETA14**SSGLT1

; SMOK
SSMOK1=0                 ; SMOK=1 (non-smokers)
IF(SMOK.GE.2) SSMOK1=1 ;SMOK=2+3 (current/former smokers)

ESMOK = PK_THETA15**SSMOK1

;CYPINH
SCYPINHR1=0 ;CYPINH=9(None)
SCYPINHR2=0 ;CYPINH=9(None)

IF(CYPINH.EQ.4.OR.CYPINH.EQ.6.OR.CYPINH.EQ.8) SCYPINHR1=1 ;CYPINH=4(Strong Cyp inh >50%) or CYPINH=6(Moderate Cyp inh >50%) or CYPINH=8(Weak Cyp inh >50%)

IF(CYPINH.EQ.1) SCYPINHR2=1 ;CYPINH=1(Unclassified Cyp inh <50%)
IF(CYPINH.EQ.2) SCYPINHR2=1 ;CYPINH=2(Unclassified Cyp inh >50%)
IF(CYPINH.EQ.3) SCYPINHR2=1 ;CYPINH=3(Strong Cyp inh <50%)
IF(CYPINH.EQ.5) SCYPINHR2=1 ;CYPINH=5(Moderate Cyp inh <50%)
IF(CYPINH.EQ.7) SCYPINHR2=1 ;CYPINH=7(Weak Cyp inh <50%)

ECYPINHR = (PK_THETA17**SCYPINHR1) * (PK_THETA18**SCYPINHR2)

K14 = PK_THETA02
K45 = K14
K56 = K14
K62 = K14

; TVCL = PK_THETA03 * CV2 * CV3 * CV4 * ESMOK * CV5 * ESGLT * ECYPINHR
CL = TVCL * EXP( PK_ETA1)
TVV2 = PK_THETA04 * CV1 * ERACA
V2 = TVV2 * EXP( PK_ETA2)
Q = PK_THETA05
V3 = PK_THETA06 * V2

; ALAG1 = PK_THETA07

; F1 = PK_THETA08 / (CV2*CV3*CV4*ESMOK*ESGLT*ECYPINHR)

; S2 = V2
K23 = Q / V2
K32 = Q / V3
K20 = CL / V2

;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;

CENSORING = 2 ; Interval Censoring + right censoring
IF (NEWIND.LE.1) SURVZ = 1 ; Survival(0)=1 [we use this variable for storing survival function at start of observation interval for interval censored data]

;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;

; TTE prognostic factors for renal end point:
; -------------------------------------------
; AGE_log, BMI_log, CHILD_PUGH_SCR, EGFR_EPI0_log
; GLYCSI_CATN, INJCGL_CATN, RACE_ASIAN, SMOK, UACR0_log, WGHT0_log

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; TTE continuous covariates
PFCONTC1 = EXP( LOG( AGE / 66) * THETA( 11))  ; effect of AGE
PFCONTC2 = EXP( LOG( BMI0 / 30) * THETA( 12))  ; effect of BMI
PFCONTC3 = EXP( LOG( EGFR_EPI0 / 43) * THETA( 13))  ; effect of EGFR_EPI0
PFCONTC4 = EXP( LOG( UACR0 /850) * THETA( 14))  ; effect of UACR0
PFCONTC5 = EXP( LOG(  WGHT0 / 85) * THETA( 15))  ; effect of WGHT0

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; TTE categorical covariates: CHILD_PUGH_SCR, GLYCSI_CATN, INJCGL_CATN, RACE_ASIAN, SMOK
CATC1 = CHILD_PUGH_SCR
CATC2 = GLYCSI_CATN
CATC3 = INJCGL_CATN
CATC4 = RACE_ASIAN
CATC5 = SMOK
; CHILD_PUGH_SCR: 1 = likely A; 2 = likely B; 3 = certain B; 5 = Not available
; lumping: 1+5 (ref) vs [2+3]
CATC1L2 = 0;
IF (CATC1.EQ.2) CATC1L2 = 1
IF (CATC1.EQ.3) CATC1L2 = 1
PFCATC1 = (1 + THETA( 16)) ** CATC1L2

; GLYSCI_CATN: 3 = NONE; 1 = 0-50%; 2 = 50-100% 
; lumping: 3 (ref) vs [1+2]
CATC2L2 = 0;
IF (CATC2.EQ.2) CATC2L2 = 1
PFCATC2 = (1 + THETA( 17)) ** CATC2L2

; INJCGI_CATN: 3 = NONE; 1 = 0-50%; 2 = 50-100% 
; lumping: 3 (ref) vs [1+2]
CATC3L2 = 0;
IF (CATC3.EQ.1) CATC3L2 = 1
IF (CATC3.EQ.2) CATC3L2 = 1
PFCATC3 = (1 + THETA( 18)) ** CATC3L2

; RACE_ASIAN: 12 categories
; lumping: [1+3.2+996+5+999+4+2
; [3.1+3.5+3.3+3.6+3.4]
CATC4L2 = 0;
CATC4L3 = 0;
CATC4L4 = 0;
CATC4L5 = 0;
IF (CATC4.EQ.2) CATC4L3 = 1
IF (CATC4.EQ.3.4) CATC4L5 = 1
IF (CATC4.EQ.3.1) CATC4L5 = 1
IF (CATC4.EQ.3.5) CATC4L5 = 1
IF (CATC4.EQ.3.3) CATC4L5 = 1
IF (CATC4.EQ.3.6) CATC4L5 = 1
PFCATC4 = (1+THETA(19))**CATC4L2 * (1+THETA(20))**CATC4L3 * (1+THETA(21))**CATC4L4 * 
           (1+THETA(22))**CATC4L5

; SMOK: 1 = Never; 2 = Former; 3 = Current
; lumping: no lumping (1=ref)
CATC5L2 = 0;
CATC5L3 = 0;
IF (CATC5.EQ.2) CATC5L2 = 1
IF (CATC5.EQ.3) CATC5L3 = 1
PFCATC5 = (1+THETA(23))**CATC5L2 * (1+THETA(24))**CATC5L3

; ---------------------------------------------------------
PFCONT = PFCONTC1 * PFCONTC2 * PFCONTC3 * PFCONTC4 * PFCONTC5
PFCATC = PFCATC1 * PFCATC2 * PFCATC3 * PFCATC4 * PFCATC5

EMAX = THETA(4)
EC50 = THETA(5)
HILL = THETA(6)

LAM = EXP( THETA( 1))
ALPH = THETA( 2)
DEL = 1E-8
DISTHAZPK = LAM * EXP((ALPH-1) * LOG(TIME + DEL)) ; the hazard according to the chosen distribution

PF = PFCONT * PFCATC

$DES

C2DES = A(2) / V2
IF (C2DES.LT.0) C2DES = 0
ERDES = 1 + EMAX * C2DES**HILL / (EC50**HILL + C2DES**HILL)

DISTHAZDES = LAM * EXP((ALPH-1) * LOG(T + DEL)) ; the hazard according to the chosen distribution
HAZNOWDES = DISTHAZDES * PF * ERDES

DADT(1) = -K14 * A(1)
DADT(2) = K62 * A(6) - K23 * A(2) + K32 * A(3) - K20 * A(2)
DADT(3) = K23 * A(2) - K32 * A(3)
DADT(4) = K14 * A(1) - K45 * A(4)
DADT(5) = K45 * A(4) - K56 * A(5)
DADT(6) = K56 * A(5) - K62 * A(6)
DADT(7) = K20 * A(2) ; ELIMINATED
DADT(8) = C2DES ; AUC
DADT(9) = 0
DADT(10) = HAZNOWDES

$ERROR

A1 = A(1)
A2 = A(2)
A7 = A(7) ; eliminated
AUC = A(8)
C2ERR = A(2) / V2

IF (C2ERR.LT.0) C2ERR = 0

ERERR = 1 + EMAX * C2ERR**HILL / (EC50**HILL + C2ERR**HILL)

DISTHAZERR = LAM * EXP((ALPH-1) * LOG(TIME + DEL)); the hazard according to the chosen distribution

HAZNOWERR = DISTHAZERR * PF * ERERR

CHAZ = A(10) ; cumulative hazard

SURV = EXP(-CHAZ) ; probability of surviving to or beyond current time

; It is the "interval + right censoring" block

IF (DV.EQ.00) Y = SURV

IF (DV.EQ.11) SURVZ = SURV

IF (DV.NE.11) SURVZ = SURVZ

IF (DV.EQ.12) Y = SURVZ - SURV

M2LL = 12345

IF (Y.GT.0) M2LL = -2*LOG(Y)

$THETA

(-30,-19.1,-10) ; TH1 LOG lambda

(0,1.80,3) ; TH2 Alpha for Weibull

0 FIX ; TH3 not used

(-1,-0.36,100) ; TH4 EMAX

(0,0.183) ; TH5 EC50

1 FIX ; TH6 HILL for ER

0 FIX ; TH7 not used

0 FIX ; TH8 not used

0 FIX ; TH9 not used

0 FIX ; TH10 not used

(-5,-1.08,5) ; TH11 Age

(-5,-0.868,5) ; TH12 BMI
\(-5,0.566,5\) ; TH13 EGFR_EPI  
\(-5,1.05,5\) ; TH14 UACR0  
0 FIX ; TH15 WGHT0  
\(-1,0.768,5\) ; TH16 CHILD_PUGH_SCR level 2+3 (vs 1+5)  
\(-1,-0.28,5\) ; TH17 GLYSCI_CATN level 2 (vs 1+3)  
\(-1,-0.1,5\) ; TH18 INJCGI_CATN level 1+2 (vs 3)  
0 FIX ; TH19 not used  
\(-1,1.02,5\) ; TH20 RACE_ASIAN level 2  
0 FIX ; TH21 not used  
\(-1,0.213,5\) ; TH22 RACE_ASIAN level 3.1+3.5+3.3+3.6+3.4  
0 FIX ; TH23 SMOK level 2 (former)  
0 FIX ; TH24 SMOK level 3 (current)  

$\text{SESTIMATION PRINT}=1 \text{ MAX}=99999 \text{ METHOD}=\text{COND LAPLACE} \text{ NUMERICAL LIKE SLOW}$  
$\text{NOTHETABOUNDTEST NOABORT NSIG}=2 \text{ SIGL}=6$  

$\text{SCOVARIANCE COMP PRINT}=E \text{ R S}$  

$\text{TABLE RECN ID TIME CHAZ SURV SURVZ AUC Y M2LL LAM ALPH DISTHAZPK MDV A1 A2 A7 C2DES C2ERR ERDES ERERR HAZNOWDES HAZNOWERR DISTHAZERR EVID DV DVID_L TAD LAM PF PFCONT PFCONTC1 PFCONTC2 PFCONTC3 PFCONTC4 PFCONTC5 PFCATC PFCATC1 PFCATC2 PFCATC3 PFCATC4 PFCATC5 VISIT DOSE TREA F1 Q TVCL CL TVV2 V2 NOPRINT ONEHEADER FORMAT}=s^{1PE15.8} \text{ FILE}=par$

**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.

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chromatography-tandem mass spectrometry and its application to a pharmacokinetic study in venous and capillary human plasma. Journal of Chromatography B. 2021;1172.

3. FDA. U.S. Department of Health and Human Services. Food and Drug Administration. Center for Drug Evaluation and Research (CDER). Center for Veterinary Medicine (CVM). Guidance for Industry: Bioanalytical method validation. 2018.

4. Snelder N, Heinig R, Drenth HJ, Joseph A, Kolkhof P, Lippert J, et al. Population Pharmacokinetic and Exposure-Response Analysis of Finerenone: Insights Based on Phase IIb Data and Simulations to Support Dose Selection for Pivotal Trials in Type 2 Diabetes with Chronic Kidney Disease. Clinical pharmacokinetics. 2020 Mar;59(3):359-70.

5. Bakris GL, Agarwal R, Anker SD, Pitt B, Rulope LM, Nowack C, et al. Design and Baseline Characteristics of the Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease Trial. American journal of nephrology. 2019;50(5):333-44.
Figure S 1. Overview of measured finerenone concentrations in the final PK dataset.
Black dots, non-outliers; red dots: outliers (DV/PRED >50); blue dots, outliers (DV/PRED <0.02); green dots, additional outliers identified by sponsor.
Figure S 2. Forest plot for subgroups of interest: Gender. The % indicates the percentage of subjects in each group. Red dots and whiskers represent the median and 5th-95th percentiles of the Cmax,md or AUCτ,md ratio using a subject with median Cmax,md or AUCτ,md as reference, based on 1000 trial simulations. The red areas indicate the uncertainty (5th-95th percentiles of the simulated 5th percentile, median and 95th percentile). Blue dots and whiskers represent the median and 5th-95th percentiles of the Cmax,md or AUCτ,md ratio using a subject with median Cmax,md or AUCτ,md as reference, based on the posthoc estimates.
Figure S 3. Forest plot for subgroups of interest: Age. The % indicates the percentage of subjects in each group. Red dots and whiskers represent the median and 5th-95th percentiles of the $C_{\text{max,md}}$ or $\text{AUC}_{\tau,\text{md}}$ ratio using a subject with median $C_{\text{max,md}}$ or $\text{AUC}_{\tau,\text{md}}$ as reference, based on 1000 trial simulations. The red areas indicate the uncertainty (5th-95th percentiles of the simulated 5th percentile, median and 95th percentile). Blue dots and whiskers represent the median and 5th-95th percentiles of the $C_{\text{max,md}}$ or $\text{AUC}_{\tau,\text{md}}$ ratio using a subject with median $C_{\text{max,md}}$ or $\text{AUC}_{\tau,\text{md}}$ as reference, based on the posthoc estimates.
Figure S 4. Forest plot for subgroups of interest: Ethnicity. The % indicates the percentage of subjects in each group. Red dots and whiskers represent the median and 5th-95th percentiles of the Cmax,md or AUCτ,md ratio using a subject with median Cmax,md or AUCτ,md as reference, based on 1000 trial simulations. The red areas indicate the uncertainty (5th-95th percentiles of the simulated 5th percentile, median and 95th percentile). Blue dots and whiskers represent the median and 5th-95th percentiles of the Cmax,md or AUCτ,md ratio using a subject with median Cmax,md or AUCτ,md as reference, based on the posthoc estimates.
Figure S 5. Forest plot for subgroups of interest: Renal impairment categories. The % indicates the percentage of subjects in each group. Red dots and whiskers represent the median and 5th-95th percentiles of the Cmax,md or AUCτ,md ratio using a subject with median Cmax,md or AUCτ,md as reference, based on 1000 trial simulations. The red areas indicate the uncertainty (5th-95th percentiles of the simulated 5th percentile, median and 95th percentile). Blue dots and whiskers represent the median and 5th-95th percentiles of the Cmax,md or AUCτ,md ratio using a subject with median Cmax,md or AUCτ,md as reference, based on the posthoc estimates.
Figure S 6. Plots illustrating the magnitude of PF effects based on the final Kidney TTE model: continuous PFs. Blue numbers indicate the values at 10-90 percentiles of the covariate distribution. Thick lines indicated the estimated effects and the ribbons indicate the 95% confidence intervals.
Figure S 7. Plots illustrating the magnitude of PF effects based on the final Kidney TTE model: continuous PFs. Black dots indicate the point estimate of the effects, the whiskers indicate the 95% confidence intervals.
Figure S 8. VPC of the final Kidney TTE model, stratified by Age quartiles. Subjects were divided in four Age quartiles. The numbers indicate the ranges in years. Thick lines indicate the KM curves of the observed data and the ribbons indicate the 95% prediction intervals.
Figure S 9. VPC of the final Kidney TTE model, stratified by BMI quartiles. Subjects were divided in four BMI quartiles. The numbers indicate the ranges in kg/m$^2$. Thick lines indicate the KM curves of the observed data and the ribbons indicate the 95% prediction intervals.
Figure S 10. VPC of the final Kidney TTE model, stratified by eGFR-EPI groups. Subjects were divided in four eGFR-EPI groups. The numbers indicate the ranges in mL/min/1.73m². Thick lines indicate the KM curves of the observed data and the ribbons indicate the 95% prediction intervals.
Figure S 11. VPC of the final Kidney TTE model, stratified by UACR quartiles. Subjects were divided in four UACR quartiles. The numbers indicate the ranges in mg/g. Thick lines indicate the KM curves of the observed data and the ribbons indicate the 95% prediction intervals.
Figure S 12. VPC of the final Kidney TTE model, stratified by likely Child-Pugh categories at screening. CPS_R, likely Child-Pugh categories at screening. Thick lines indicate the KM curves of the observed data and the ribbons indicate the 95% prediction intervals.
Figure S 13. VPC of the final Kidney TTE model, stratified by SGLT2 inhibitor use categories. GLYCSICN_R, SGLT2 inhibitor use categories. Thick lines indicate the KM curves of the observed data and the ribbons indicate the 95% prediction intervals.
Figure S 14. VPC of the final Kidney TTE model, stratified by GLP-1 agonist use categories. INJCGLCN_R, GLP-1 agonist use categories. Thick lines indicate the KM curves of the observed data and the ribbons indicate the 95% prediction intervals.
Figure S 15. VPC of the final Kidney TTE model, stratified by Race/Ethnicity.

RACEASIAn_R, 1 = Black / African-American , 2 = All Asian Ethnicities, except Japanese ,
3 = all other Races/Ethnicities. Thick lines indicate the KM curves of the observed data and
the ribbons indicate the 95% prediction intervals.
Figure S 16. Illustration of the typical PK after once daily administration of 10 or 20 mg finerenone at steady-state. Solid black line indicates the EC90 and the dashed black line indicates the EC50 of the final Kidney TTE model.