

Clinical Pharmacokinetics

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

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Supplementary Methods

Studies and Data

For all studies introduced, documented approval from appropriate independent ethics committee(s) or institutional review board(s) was obtained for all participating centers/countries before the start of the study. All individuals provided written informed consent for participation. For ARTS-DN and ARTS-DN Japan, the primary analysis as well as further details including rationale, design, participants' baseline characteristics, and study protocols have been published [1, 2, 3]. Table 1 and Table 2 provide summary characteristics and statistics of the studies relevant for the analysis presented here.

ARTS-DN (NCT01874431) was a multicenter, randomized, double-blind, placebo-controlled, parallel-group, phase IIb study designed to compare the effects of finerenone, 1.25–20 mg once daily (OD), with placebo, added to standard of care with a RAS blocker; further details have been published previously [1, 3]. ARTS-DN Japan (NCT01968668) had the same design as ARTS-DN, with differences, besides ethnicity, in terms of a lower number of patients and a higher number of visits [2]. The primary efficacy endpoint in these studies was effect of treatment on UACR after 90 days compared with baseline; main safety markers were change in serum potassium concentration and eGFR-EPI. For the three parameters only central laboratory measurements were used for model building.

Analytical Methods

Plasma concentrations of finerenone were determined using a fully validated high-performance liquid chromatography/mass spectrometry assay after protein precipitation with acetonitrile. 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 [4]. Further details of the efficacy and safety parameters have also been published along with the studies described above. Plasma concentrations below the lower limit of quantification (LLOQ) of 0.1 µg/L were reported as such and excluded from the analysis.

Data Analysis

Previously, a popPK model had been developed to describe the PK of finerenone in healthy volunteers (Caucasians) and subjects with renal impairment using data from the phase I studies described in the Introduction. This model was applied and further developed based on data from the phase IIa ARTS, see Supplementary Phase IIa Models.

For the current analysis, this phase IIa PK model was updated by parameter re-estimation first with ARTS-DN data, and then using the ARTS-DN^{+JP} dataset (Table 1 and Table 2). A similar stepwise approach was followed for the development of the PKPD models for the efficacy marker UACR and the safety markers serum potassium concentration and eGFR-EPI. The previously developed phase IIa PKPD models for the three biomarkers (as detailed in Supplementary Phase IIa Models) were updated by parameter re-estimation and, if needed, the structural models were re-evaluated.

Phase IIb PK Model Development

The phase IIa PK model (Supplementary Phase IIa Models) was able to describe the ARTS-DN PK data reasonably well and the optimization process was focused on re-estimation of parameters, re-evaluation of covariate effects, and the random-effects structure, without structural model changes. Previously determined covariate relationships were re-evaluated and updated by means of backward elimination. In the backward elimination procedure, the covariate effects were removed one by one, and the covariates that produced non-significant minimum value of the objective function (MVOF) increases (< 10.83 points) were discarded. In addition, possible differences in PK between the global population and the Japanese population were evaluated by extending the dataset accordingly and including parameters for inter-ethnic differences in the models and testing for significance.

Phase IIb PK/PD Model Development

For the three biomarkers, a sequential PKPD modeling approach was followed in which the individual post hoc estimates of the structural parameters from the final PK model were included in the dataset to simulate individual PK time-profiles as input for the development of the PKPD models. The time delay that was observed between the increase in finerenone concentration and the effect on UACR, serum potassium concentration, and eGFR-EPI was described by turnover (indirect response) models [5]. Parameters of the three phase IIa PKPD models were re-estimated and alternative concentration–effect relationships were evaluated including linear, log-linear, power, maximum effect (I_{\max}), and sigmoid I_{\max} models (Supplementary Functional Forms). For all three models, inter-ethnic differences between Japanese and non-Japanese patients from the global study (Table 1) were investigated.

Model Evaluation

Goodness-of-fit (GOF) was determined using the MVOF, defined as minus twice the log-likelihood. For nested models, a decrease of 10.8 points in the MVOF (theoretically corresponding to $p < 0.001$ in a chi-squared distribution) after adding an additional parameter was considered significant. The GOF was also investigated by visual inspection of diagnostic plots of individual predictions and plots of (weighted) residuals. In addition, a visual predictive check was performed, in which the median and 90% inter-quantile range of simulated data with the model developed were plotted in overlay with the observations at day 90 versus the model-predicted area under the curve (AUC) at steady state (AUC_{SS}) (Figure 2). For plotting purposes, the data were binned into 20 categories based on equal numbers of observations per bin. In addition, the predictive performance of the PKPD models was assessed by comparing the model-predicted percentage of subjects who reach the predefined thresholds with the observed percentages. The UACR target was defined as the percentage of subjects with a $UACR \leq 0.5$, ≤ 0.6 , ≤ 0.7 , or ≤ 0.8 at day 90 calculated as $UACR_{day90}/UACR_{baseline}$. For serum potassium concentration the percentages of subjects with one or more concentrations > 5.5 mmol/L and > 6.0 mmol/L during the active treatment period were evaluated, and for eGFR-EPI the thresholds were defined as the percentage of subjects with a decrease in eGFR-EPI $\geq 30\%$, $\geq 40\%$, and $\geq 57\%$ at day 90.

Simulations

The PKPD models developed using data from ARTS-DN were used to simulate the drug effect of finerenone on the efficacy and safety markers for several dosing regimens (placebo and 5, 7.5, 10, 15, 20, or 30 mg finerenone OD, with 30 mg presenting an extrapolation beyond the ARTS-DN^{+JP} dose range). Again, the aforementioned predefined thresholds were evaluated; however, at day 180 in order to investigate steady state PD effects that the model predicts only beyond 90 days, and with the addition of an eGFR-EPI threshold decrease of > 25%. In total, 5000 subjects in each treatment group were simulated. Apart from the determined variability in the population, the NONMEM-reported parameter uncertainty was also taken into account for these simulations. The hypothetical phase III simulation scenario is further detailed in Table 3.

Computation

Data were analyzed using a non-linear mixed-effects modeling approach implemented in NONMEM (version 7 level 2; Icon Development Solutions, Ellicott City, MD, USA) [6, 7]. The NONMEM software package was implemented on an Intel QuadCore (Intel® Core™ i7 CPU860, 2.80 GHz, 3.24 GB RAM); Compaq Visual Fortran (version 6.6, Compaq Computer Corporation, Houston, TX, USA) was used as the compiler. Diagnostic graphics, exploratory analyses, and post-processing of NONMEM output were performed using S-Plus (version 8.2 Professional, Insightful Corp., Seattle, WA, USA) or in R (version 3.1.2 [2014-10-31]) [8] facilitated via R-Studio (version 0.98.501) [9].

Parameters were estimated using the first-order conditional estimation method with interaction between the two levels of stochastic effects (first-order conditional estimation interaction). Random effects were included as exponential terms reflecting log-normal distributions of model parameters. The residual variability was explored with proportional and additive error models.

Supplementary Phase IIa Models

Pharmacokinetics

A population pharmacokinetics (PK) model was available to describe the PK of finerenone in stable Caucasian patients with chronic heart failure using data from the phase IIa Mineralocorticoid Receptor Antagonist Tolerability Study (ARTS) [10]. The PK of finerenone was adequately described by a two-compartment model with first-order elimination. The central and peripheral volumes of distribution were assumed to be equal to avoid over-parameterization. The absorption was described by a series of first-order processes using three transit compartments with an additional lag time to absorption. Body weight was found to have a significant influence on the volume of distribution (V_d/F). Furthermore, estimated glomerular filtration rate (eGFR), as calculated using the Modification of Diet in Renal Disease (MDRD) study equation (eGFR-MDRD) [11], was found to have a significant influence on clearance (CL/F) and on the relative bioavailability (F), which was assumed to be 1 for a typical subject.

Urinary Albumin:Creatinine Ratio

The distribution of the urinary albumin:creatinine ratio (UACR) data in the phase IIa population was skewed to the right. Therefore, the UACR data were log-transformed and the distribution of the baseline UACR values was described using a Box–Cox transformation of the inter-individual variability of UACR at baseline. This Box–Cox transformation was not needed for the ARTS-Diabetic Nephropathy (ARTS-DN) population. The relationship between individual exposure and log-transformed UACR values in the phase IIa population was described by an indirect response model with an inhibiting drug effect on the zero-order UACR production rate k_{in} (Supplementary Functional Forms Eq. S2), resulting in a decrease in UACR from baseline. The concentration–effect relationship was described by a maximum inhibition (I_{max}) model (Supplementary Functional Forms Eq. S7), in which I_{max} was fixed to 1.

Serum Potassium Concentration

The absolute serum potassium concentrations were described by a turnover model with an inhibiting linear drug effect on the dissipation rate k_{out} (Supplementary Functional Forms Eq. S3 and S4) describing the loss of serum potassium, resulting in an increase in serum potassium concentrations from baseline.

Estimated Glomerular Filtration Rate

In contrast to ARTS-DN, in ARTS, eGFR-MDRD [11] was used both as a covariate for PK and as a pharmacodynamics biomarker. The effect of finerenone on eGFR-MDRD was described by a turnover model with an inhibiting, linear drug effect on the zero-order production rate constant k_{in} , resulting in a decrease in eGFR-MDRD from baseline (Supplementary Functional Forms Eq. S2 and S4). Subjects with moderate renal impairment typically had lower baseline eGFR-MDRD values (approximately one-third lower) compared with subjects with mild renal impairment.

Supplementary Functional Forms

Exposure–Response

The time delay that was observed between the increase in finerenone concentration and the effect on urinary albumin:creatinine ratio (UACR), estimated glomerular filtration rate (eGFR-MDRD in phase IIa and eGFR-EPI in phase IIb), and serum potassium concentration was described by turnover models, also known as indirect response models (Equation S1) [5].

$$\frac{dR}{dt} = k_{in} - k_{out} * R \quad \text{Eq. S1}$$

k_{in} represents the zero-order production rate constant; k_{out} represents the first-order rate constant describing the loss of response; R is the response variable (UACR, serum potassium concentration, eGFR-MDRD or eGFR-EPI); t represents time.

The effect of finerenone on UACR and eGFR-MDRD or eGFR-EPI was described by an inhibiting effect on k_{in} (Equation S2), resulting in a decrease in UACR and eGFR-MDRD or eGFR-EPI with increasing finerenone concentrations. The effect on serum potassium concentration was described by an inhibiting effect on k_{out} (Eq. S3), resulting in an increase in serum potassium concentration with increasing finerenone concentration.

$$\frac{dR}{dt} = k_{in} * (1 - EFF) - k_{out} * R \quad \text{Eq. S2}$$

$$\frac{dR}{dt} = k_{in} - k_{out} * (1 - EFF) * R \quad \text{Eq. S3}$$

In these equations EFF represents the finerenone drug effect as detailed below. Linear (Eq. S4), log-linear (Eq. S5), power (Eq. S6), maximum effect (I_{max}) (Eq. S7), and sigmoid I_{max} (Eq. S8) models were evaluated to characterize the concentration–effect relationships.

$$\text{Linear: } EFF = SLP * C \quad \text{Eq. S4}$$

$$\text{Log – linear: } EFF = SLP * LOG(C + 1) \quad \text{Eq. S5}$$

$$\text{Power: } EFF = SLP * C^{POW} \quad \text{Eq. S6}$$

$$I_{MAX}: EFF = \frac{I_{max} * C}{IC_{50} + C} \quad \text{Eq. S7}$$

$$\text{Sigmoid } I_{MAX}: EFF = \frac{I_{max} * C^{nH}}{IC_{50}^{nH} + C^{nH}} \quad \text{Eq. S8}$$

C represents the drug concentration; SLP represents the slope of the linear, log-linear, and power models; POW represents the power of the power model; I_{max} represents the maximum effect; IC_{50} represents the concentration resulting in a half-maximal effect of the sigmoid I_{max} concentration–effect relationships; nH is the Hill coefficient of the sigmoid I_{max} model.

Estimated Glomerular Filtration Rate

eGFR-MDRD and eGFR-EPI were calculated as follows

$$eGFR_{MDRD} = 175 * SCR^{-1.154} * AGE^{-0.203} * g * r \quad \text{Eq. S9}$$

$$eGFR_{EPI} = \alpha * \frac{SCR^\gamma}{\beta} * 0.993^{AGE} \quad \text{Eq. S10}$$

with SCR representing the serum creatinine, AGE representing the age; g a gender factor that is 1 for male and 0.742 for female; and r a factor that is 1.210 for black/African(-Americans), 0.808 for Japanese, and 1 otherwise; α is 166 for black females, 163 for black males, 144 for white/Caucasian/other females, 141 for white males; β is 0.7 for females and 0.9 for males; γ is -0.329 for females with $SCR \leq 0.7$ mg/dL, -1.209 for females with $SCR > 0.7$ mg/dL, -0.411 for males with $SCR \leq 0.9$ mg/dL, and -1.209 for males with $SCR > 0.9$ mg/dL [18-22]. The result of Eq. S10 is multiplied by 0.813 for Japanese.

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Supplementary Figures

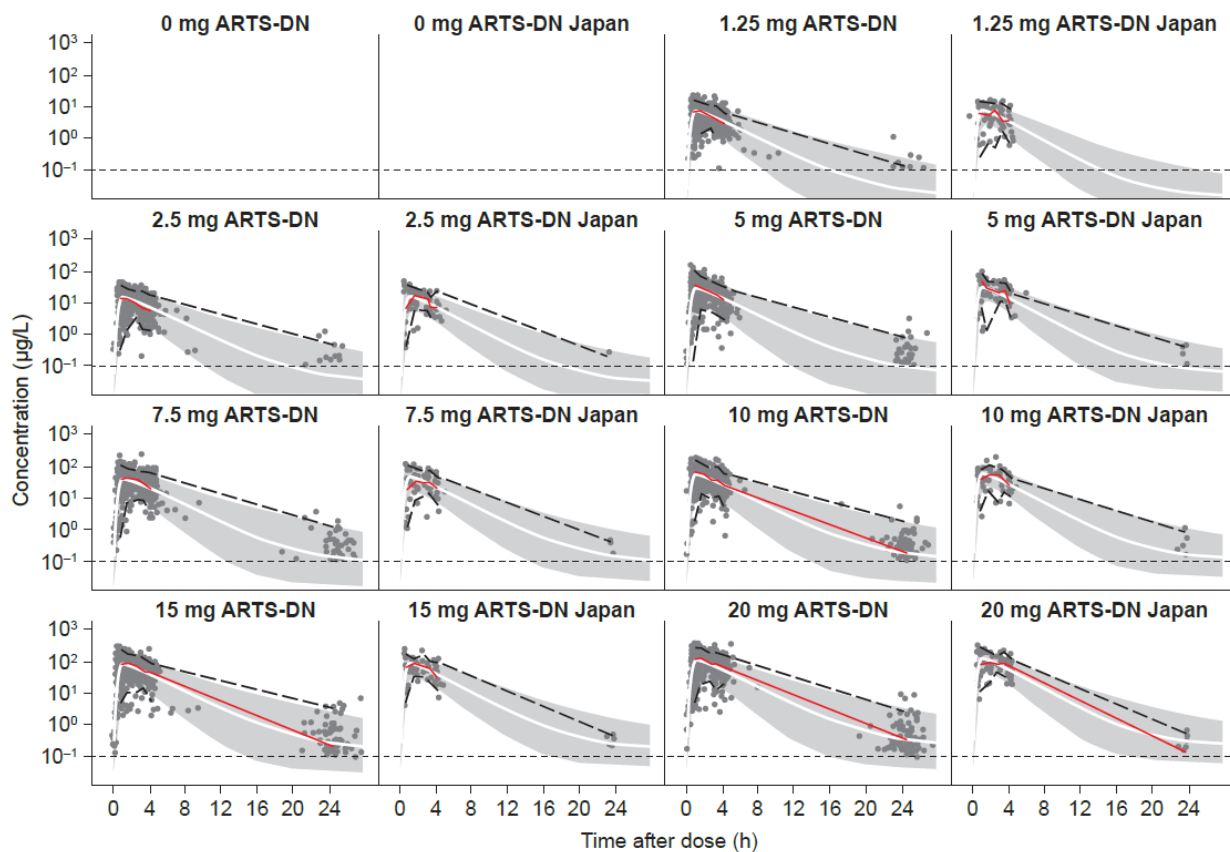


Figure S1.

Visual predictive checks of the description of the pharmacokinetics of finerenone in ARTS-DN and ARTS-DN Japan. Dots: observed concentrations; red lines: median of observations; black dashed lines: 90% intervals of observations; white lines and gray shading: median prediction and 90% prediction intervals; dashed horizontal lines: LLOQ. Observations were grouped at intervals of 0.5–1, 1–2, 3–4, 4–5 and 22–26 h post-dose, and the median, 5th and 95th percentiles were calculated for these bins. The calculated values were connected by a straight line. Therefore, the observed and predicted values should be compared only between 0–5 and 22–26 h after dose. The median and 5th or 95th percentiles of the observations are not shown if they are below the LLOQ. ‘0 mg’ denotes placebo-treated subjects.

ARTS-DN MinerAlocorticoid Receptor Antagonist Tolerability Study-Diabetic Nephropathy, *LLOQ* lower limit of quantification

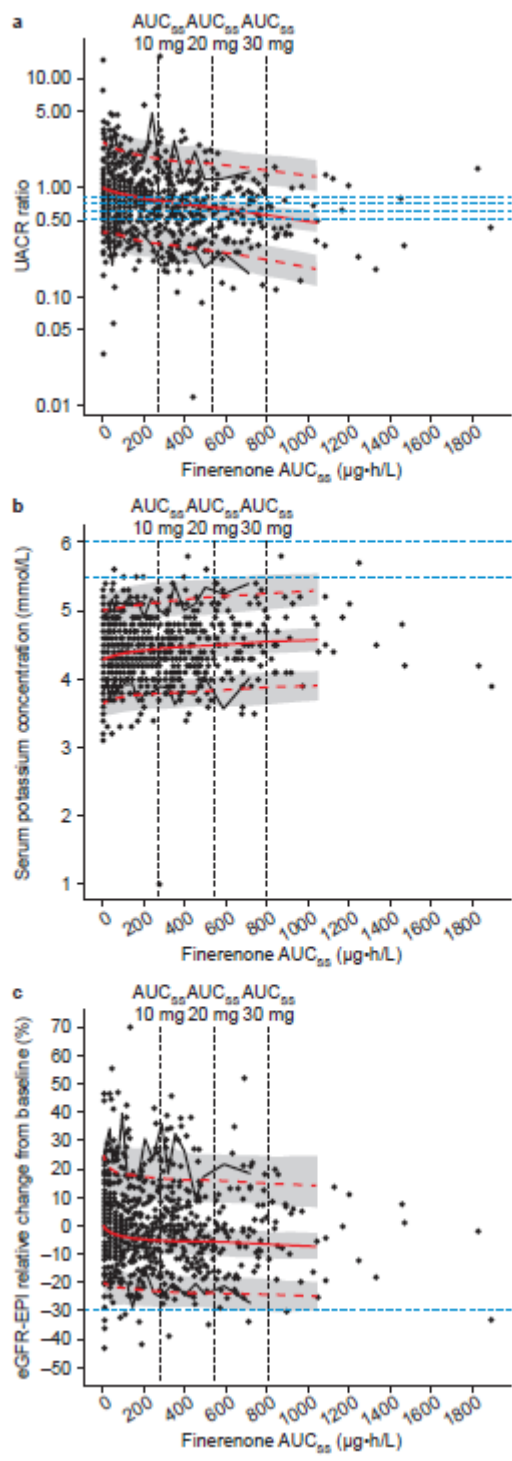


Figure S2. Predicted and observed **a** UACR, **b** absolute serum potassium concentration, and **c** relative change from baseline eGFR-EPI versus finerenone AUC_{SS}. The model was fitted to individual data. Blue dashed lines: reference/threshold lines; dark gray dashed lines: simulated AUC_{SS} for a typical subject for doses of 10, 20, and 30 mg; black solid lines: 5th and 95th percentiles of the observations; black dots: observations; red solid and dashed lines: median predictions and 5th and 95th percentiles of the predictions; gray areas: 90% CIs of the median and 5th and 95th percentiles.

AUC_{SS} area under the curve at steady state, CI confidence interval, eGFR-EPI estimated glomerular filtration rate according to the Chronic Kidney Disease Epidemiology Collaboration equation, UACR urinary albumin:creatinine ratio

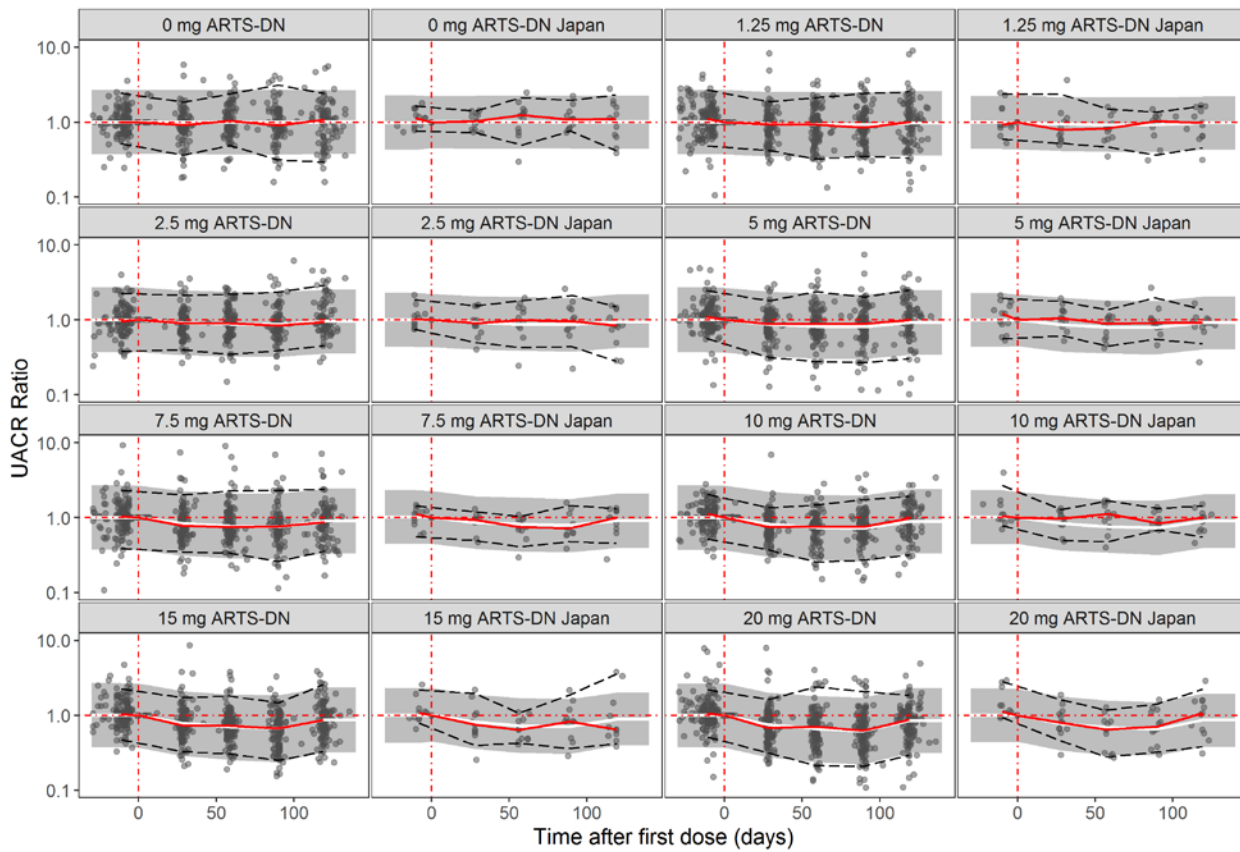


Figure S3. Visual predictive checks of the description of the effect of finerenone on UACR in ARTS-DN and ARTS-DN Japan.

Dots: observed concentrations; red lines: median of observations; black dashed lines: 90% intervals of observations; white lines and gray shading: median prediction and 90% prediction intervals; vertical red dashed line: start of treatment; horizontal red dashed lines: UACR = 1. '0 mg' denotes placebo-treated subjects.

ARTS-DN MinerAlocorticoid Receptor Antagonist Tolerability Study-Diabetic Nephropathy, UACR urinary albumin:creatinine ratio

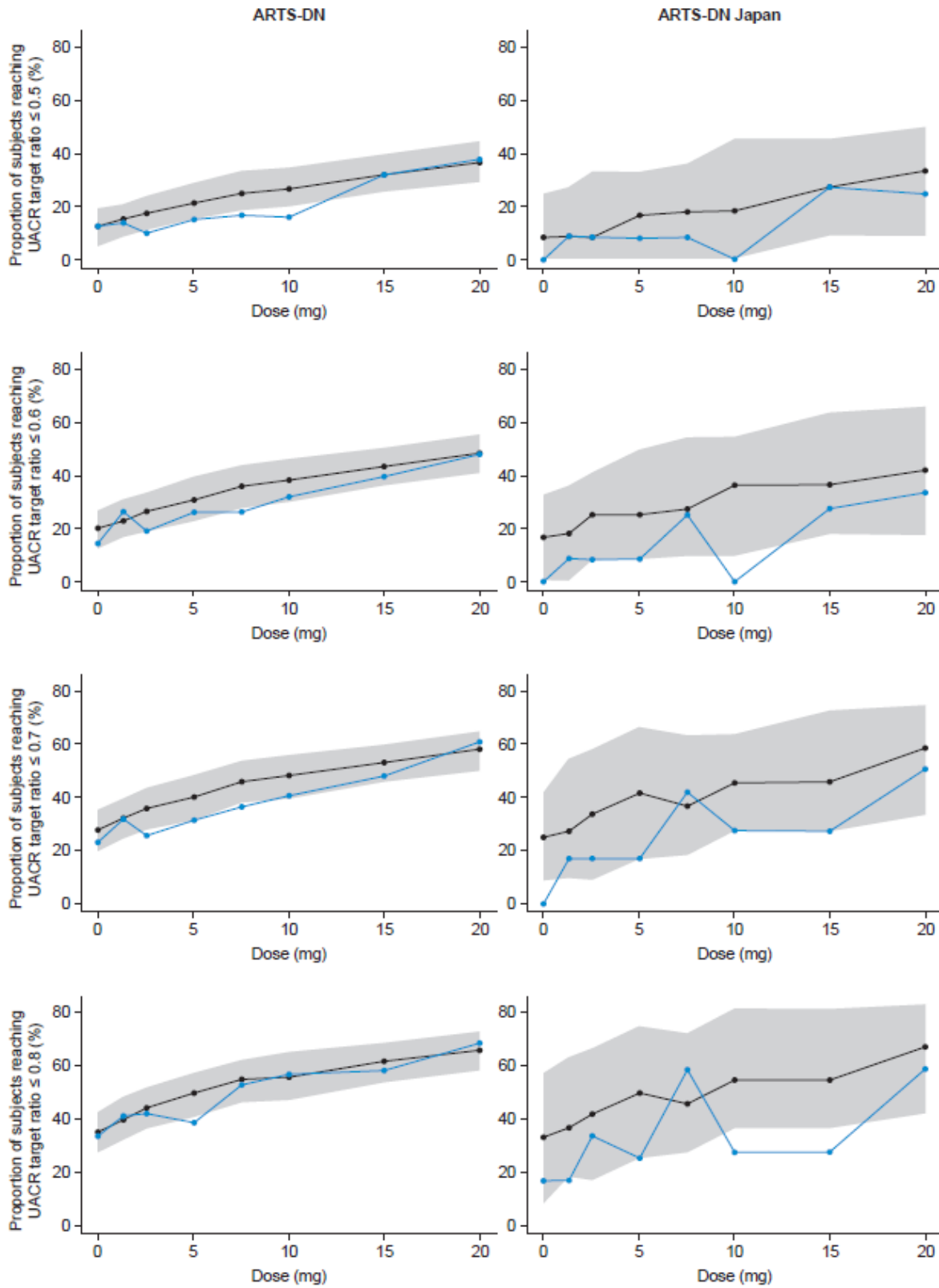


Figure S4. Predicted and observed percentages of subjects who reach a target UACR (≤ 0.5 , ≤ 0.6 , ≤ 0.7 , or ≤ 0.8) at day 90 (with 90% CIs), paneled by study and target UACR by the final ARTS-DN^{+JP} model. Blue lines: observed percentages; black lines and gray areas: median predictions and 90% CIs of the median.

ARTS-DN MinerAlocorticoid Receptor Antagonist Tolerability Study-Diabetic Nephropathy, ARTS-DN^{+JP} combined ARTS-DN and ARTS-DN Japan dataset, CI confidence interval, UACR urinary albumin:creatinine ratio

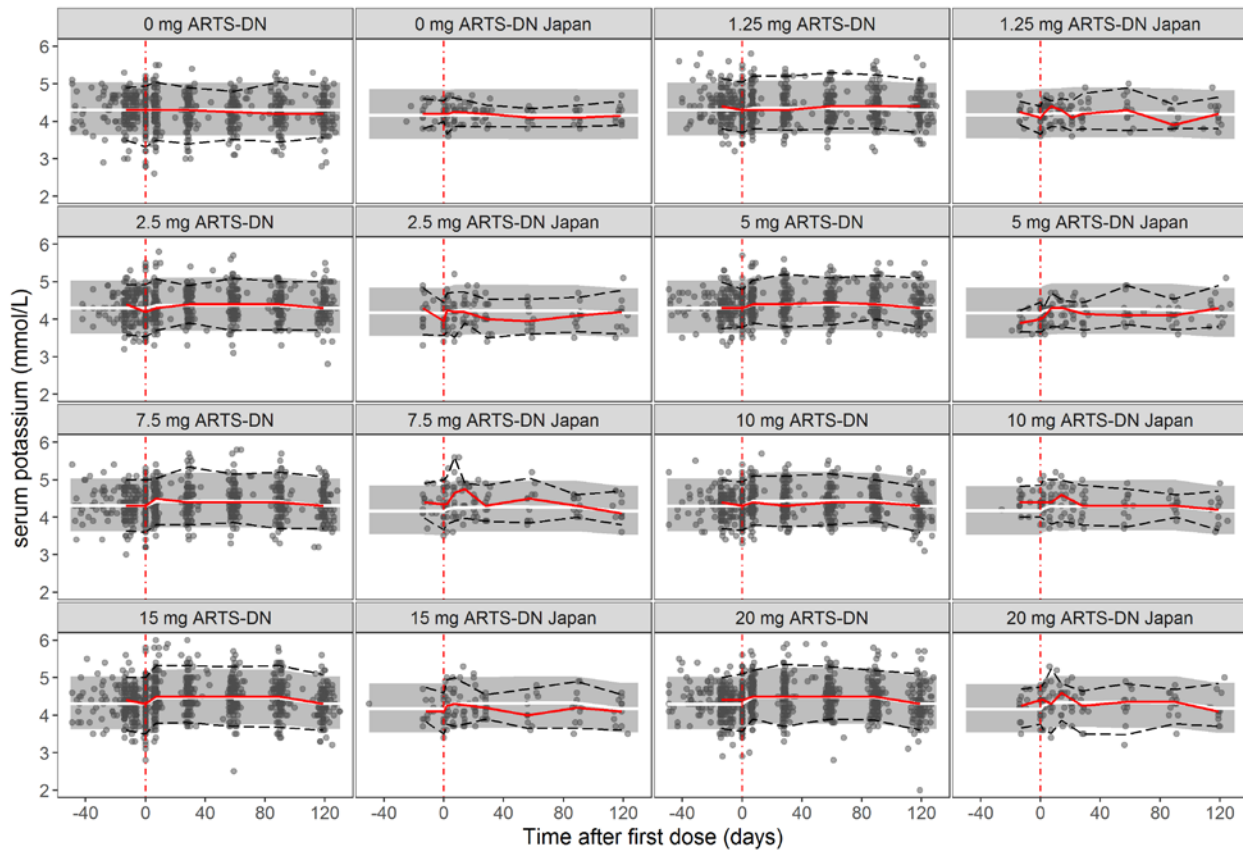


Figure S5. Visual predictive checks of the description of the effect of finerenone on serum potassium in ARTS-DN and ARTS-DN Japan. Dots: observed concentrations; red lines: median of observations; black dashed lines: 90% intervals of observations; white lines and gray shading: median prediction and 90% prediction intervals; vertical red dashed line: start of treatment. '0 mg' denotes placebo-treated subjects.

ARTS-DN MinerAlocorticoid Receptor Antagonist Tolerability Study-Diabetic Nephropathy

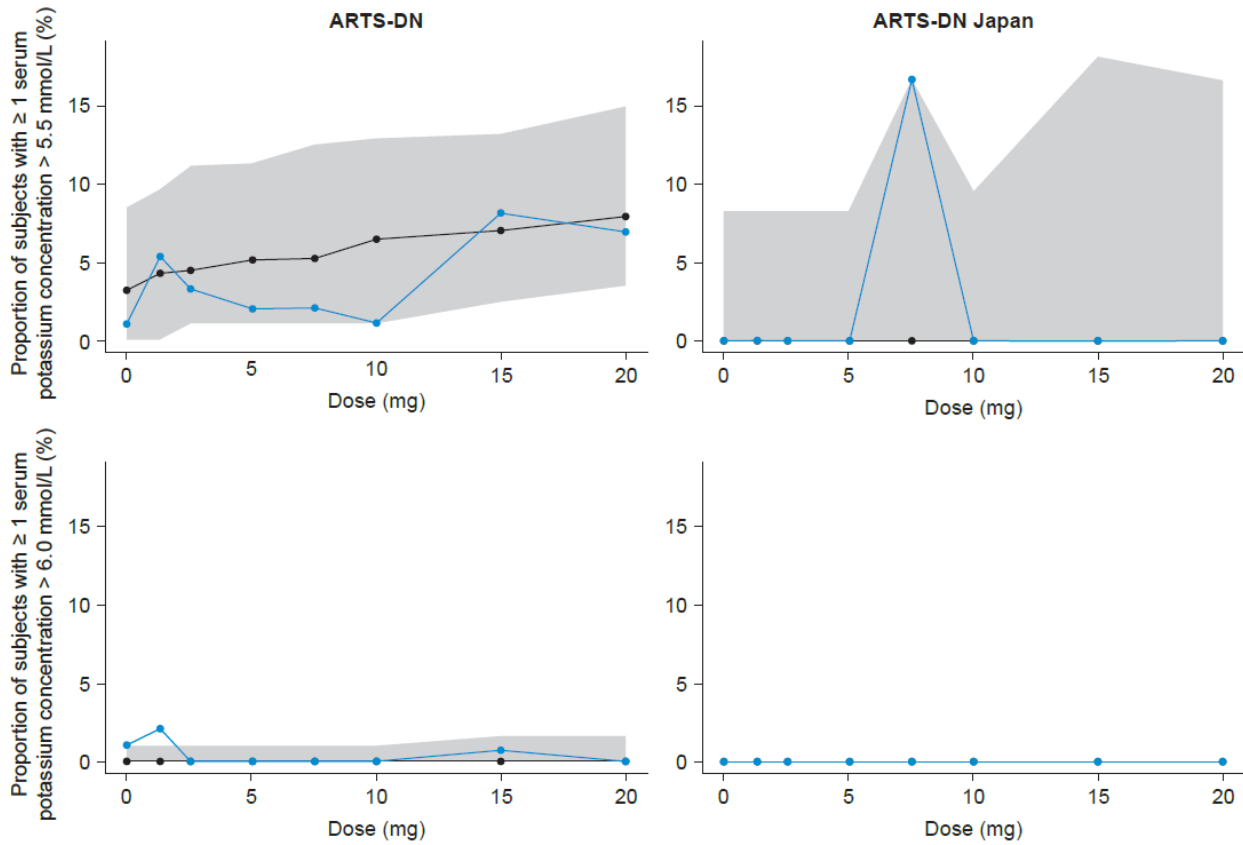


Figure S6. Predicted and observed percentages of subjects with one or more serum potassium concentrations > 5.5 mmol/L (upper row) or > 6.0 mmol/L (lower row) (with 90% CIs) paneled by population for the final ARTS-DN^{+JP} model. In the ARTS-DN Japan population the predicted percentage of subjects with one or more serum potassium concentration > 6.0 mmol/L was 0%. Blue lines: observed percentages; black lines and gray areas: median predictions and 90% CIs of the median. In cases in which the black line or gray area is not depicted, the predicted percentage of subjects reaching the threshold was 0%. ARTS-DN MinerAlocorticoid Receptor Antagonist Tolerability Study-Diabetic Nephropathy, ARTS-DN^{+JP} combined ARTS-DN and ARTS-DN Japan dataset, CI confidence interval

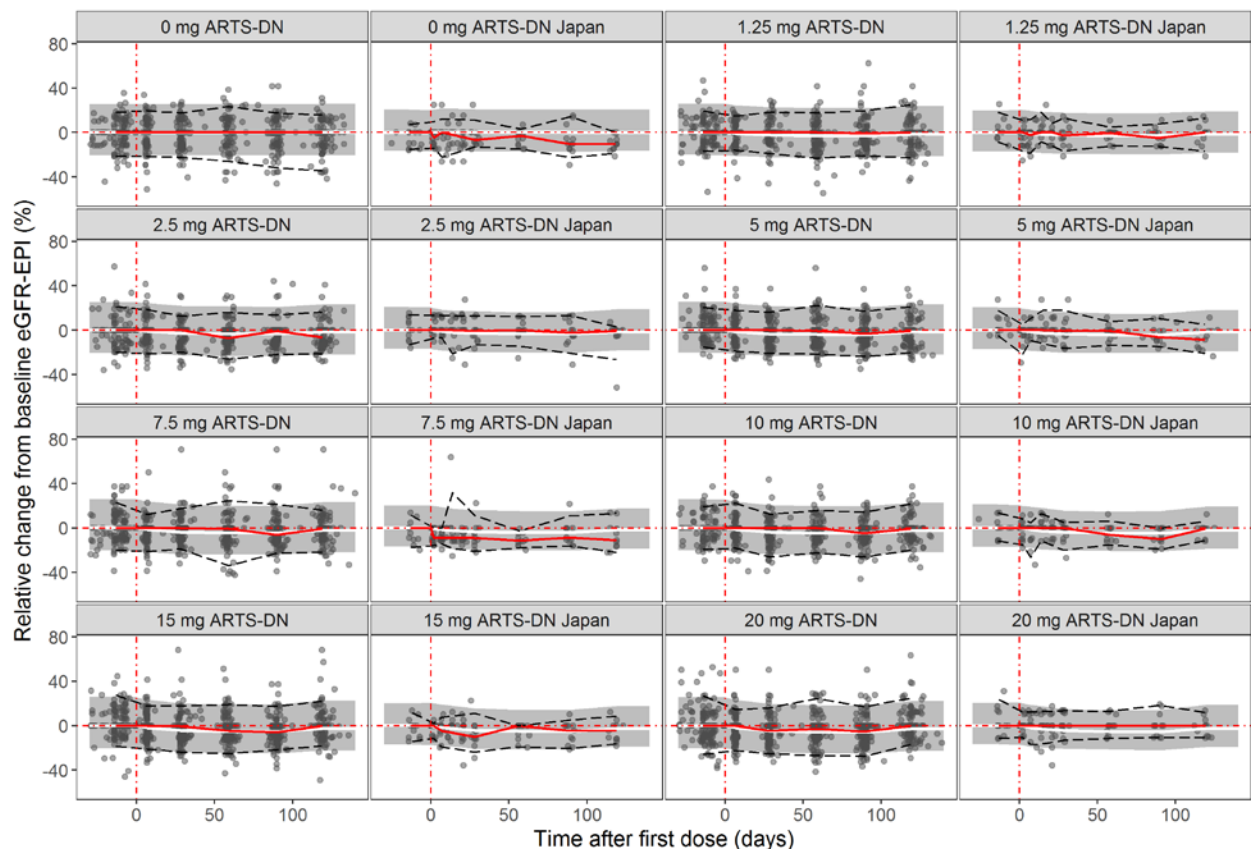


Figure S7. Visual predictive checks of the description of the effect of finerenone on eGFR-EPI (relative change from baseline) in ARTS-DN and ARTS-DN Japan. Dots: observed concentrations; red lines: median of observations; black dashed lines: 90% intervals of observations; white lines and gray shading: median prediction and 90% prediction intervals; vertical red dashed line: start of treatment; horizontal red dashed line: 0% change from baseline referenceline . '0 mg' denotes placebo-treated subjects. ARTS-DN MinerAlocorticoid Receptor Antagonist Tolerability Study-Diabetic Nephropathy, eGFR-EPI, eGFR according to the Chronic Kidney Disease Epidemiology Collaboration equation

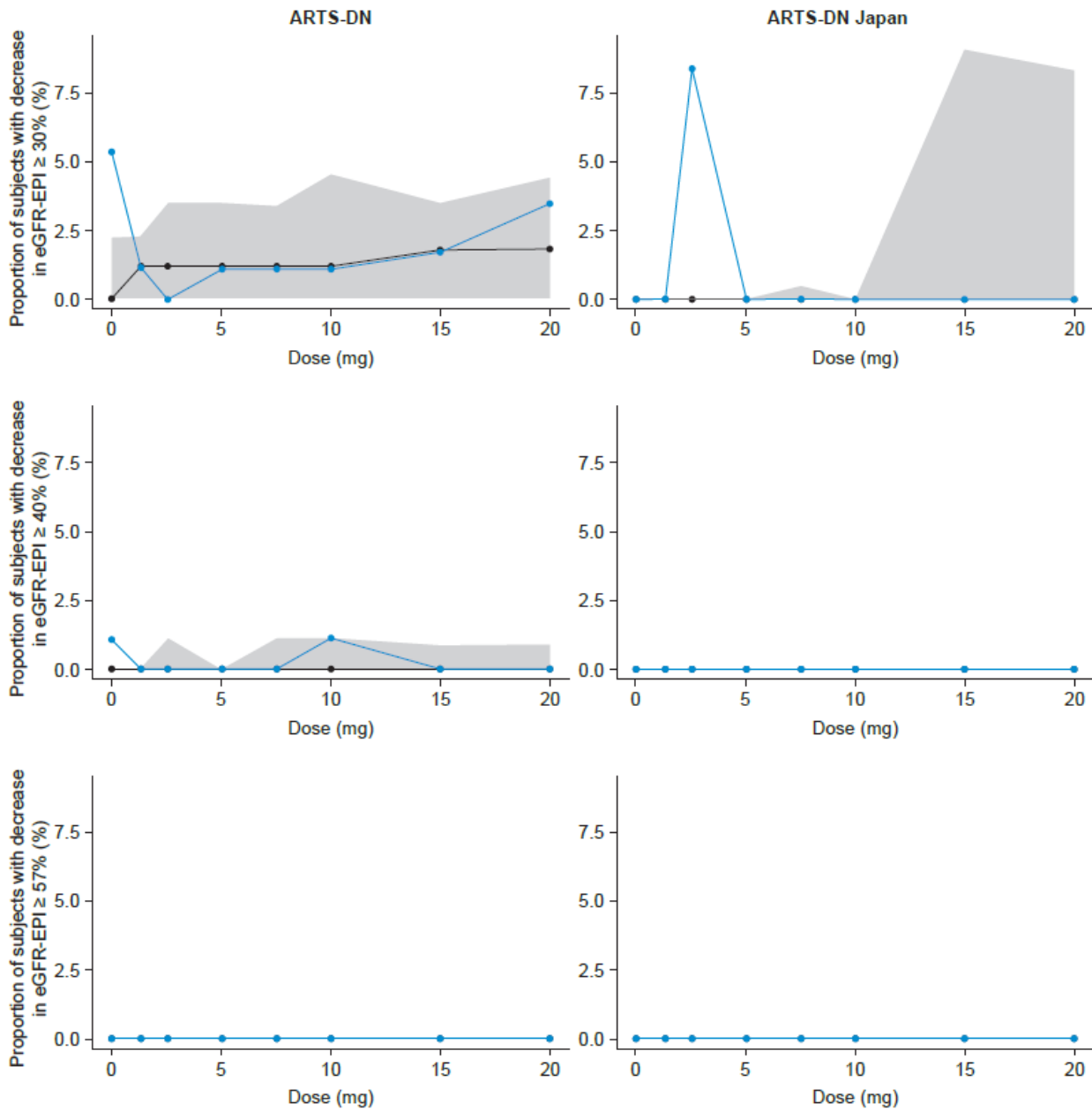


Figure S8.

Predicted and observed percentages of patients with a decrease in eGFR-EPI $\geq 30\%$, $\geq 40\%$, and $\geq 57\%$, at day 90 (with 90% CIs), paneled by study and criterion by the final ARTS-DN^{JP} model. Blue lines: observed percentages; black lines and gray areas: median predictions and 90% CIs of the median. In cases in which the black line or gray area is not depicted, the predicted percentage of subjects reaching the threshold was 0%.

ARTS-DN MinerAlocorticoid Receptor Antagonist Tolerability Study-Diabetic Nephropathy, ARTS-DN^{JP} combined ARTS-DN and ARTS-DN Japan dataset, CI confidence interval, eGFR EPI estimated glomerular filtration rate according to the Chronic Kidney Disease Epidemiology Collaboration equation

Supplementary Tables

Table S1. Parameter estimates of the final (ARTS-DN and ARTS-DN Japan) PK model and parameter estimates of the pre-existing phase IIa and intermediate ARTS-DN model.

Parameter	Phase IIa ^a	ARTS-DN only ^b	Final model ^c	SE	RSE, %	LLCI	ULCI
<i>Fixed effects</i>							
K_a^d , 1/h	17.8	11.4	10.7	0.24	2.29	10.2	11.2
CL/F, L/h	31	36.9	37.3	0.686	1.84	36	38.6
V_d/F , L	104	125	123	2.08	1.69	119	127
Q/F, L/h	0.925	0.415	0.433	0.0353	8.15	0.364	0.502
Lag time, h	0.215 (fixed)	0.215 (fixed)	0.215 (fixed)				
F	1 (fixed)	1 (fixed)	1 (fixed)				
<i>Covariate effects</i>							
SLV _{CBW} (BW effect)	0.57	0.516	0.449	0.0548	12.2	0.342	0.556
SLCL _{eGFR} (eGFR effect)	0.304	0.126	0.101	0.0136	13.5	0.0743	0.128
<i>Random effects: IIV</i>							
$\omega^2_{K_a}$ (IIV)	0.75	0.518	0.585	0.0409	6.99	0.505	0.665
$\omega^2_{CL/F}$ (IIV)	0.234	0.214	0.2	0.0153	7.65	0.17	0.23
$\omega^2_{V_d/F}$ (IIV)	0.108	0.0927	0.0927	0.0107	11.5	0.0717	0.114
$\omega^2_{CL/F \times V_d/FHT}$ (IIV)	0.109	0.0851	0.0928	0.0103	11.1	0.0726	0.113
<i>Random effects: residual error</i>							
σ_1^2 prop	0.194	0.179	0.179	0.00579	3.23	0.168	0.190

Formulae for calculating individual parameters (i) with covariate effects

$$V_d/F = V_d/F \cdot (1 + SLV_{CBW} \cdot [\ln(BW) - \ln(\text{median BW})])$$

$$CL/F = CL/F \cdot (1 + SLCL_{eGFR} \cdot [\ln(eGFR) - \ln(\text{median eGFR})])$$

$$F = F / (1 + SLCL_{eGFR} \cdot [\ln(eGFR) - \ln(\text{median eGFR})])$$

The median BW was 90.4 kg and 88.5 kg in the ARTS-DN study and the combined ARTS-DN and ARTS-DN Japan studies, respectively).

The median eGFR-MDRD was 63.9 mL/min/1.73 m² and 63.53 mL/min/1.73 m² in the ARTS-DN study and the combined ARTS-DN and ARTS-DN Japan studies, respectively.

ARTS-DN MinerAlocorticoid Receptor Antagonist Tolerability Study-Diabetic Nephropathy, ARTS-DN^{+JP} combined ARTS-DN and ARTS-DN Japan dataset, BW body weight, CI confidence interval, CL/F clearance, CV relative standard error, eGFR estimated glomerular filtration rate, eGFR-MDRD eGFR according to the Modification of Diet in Renal Disease study equation, F bioavailability, IIV inter-individual variability, K_a absorption rate constant, LLCI lower limit of 95% CI, PK pharmacokinetics, Q/F inter-compartmental clearance; RSE relative standard error, SE standard error, SL slope, ULCI upper limit of 95% CI, V_d/F volume of distribution

^a Pre-existing PK model based on phase IIa

^b Pre-existing PK model based on phase IIa but updated based on ARTS-DN data only

^c Pre-existing PK model based on phase IIa but updated based on combined ARTS-DN^{+JP} data

^d The absorption rate constant K_a was the same for all transits, so from the dose compartment to the first transit compartment, from the first to the second, from the second to third transit and from the third transit to the central compartment

Table S2. Parameter estimates of the final (ARTS-DN and ARTS-DN Japan) and intermediate ARTS-DN PKPD model for UACR.

Parameter	ARTS-DN only ^b	Final model ^c	SE	RSE (%)	LLCI	ULCI
Baseline UACR; cat2, mg/g	97.0	96.8	2.87	2.96	91.2	102
Baseline UACR; cat3, mg/g	639	633	25.5	4.03	583	683
k_{out} , 1/h	0.0014	0.0014	0.000165	11.8	0.00108	0.00172
I_{max}	1 (fixed)					
IC ₅₀ , µg/L	14.5	12.9	1.95	15.1	9.08	16.7
Ethnic effect on σ_{add}^2 , % ^a		69.2	7.58	11	54.3	84.1
<i>Random effects: IIV</i>						
$\omega_{baseline}^2$ (IIV)	0.526	0.512	0.0252	4.92	0.463	0.561
<i>Random effects: residual error</i>						
$\sigma_{1\ add}^2$	0.182	0.181	0.0105	5.8	0.16	0.202

ARTS-DN MinerAlocorticoid Receptor Antagonist Tolerability Study-Diabetic Nephropathy, ARTS-DN^{JP} combined ARTS-DN and ARTS-DN Japan dataset, CI confidence interval, eGFR estimated glomerular filtration rate, IC₅₀ concentration of drug producing 50% inhibition, IIV inter-individual variability, I_{max} maximum inhibition, k_{out} dissipation rate, LLCI lower limit of 95% CI, PD pharmacodynamics, PK pharmacokinetics, RSE relative standard error, SE standard error, UACR urinary albumin:creatinine ratio, ULCI upper limit of 95% CI

^a Multiplication percentage for Japanese relative to global population ($\sigma_{add}^2 = 0.125$ for Japanese population)

^b PKPD model based on ARTS-DN data only

^c PKPD model based on combined ARTS-DN^{JP} data

Table S3. Parameter estimates of the final (ARTS-DN and ARTS-DN Japan) and intermediate ARTS-DN PKPD model for serum potassium concentration.

Parameter	ARTS-DN only ^d	Final model ^e	SE	RSE, %	LLCI	ULCI
Baseline serum potassium						
concentration, mmol/L	4.31	4.31	0.0125	0.29	4.29	4.33
k_{in} , mmol/L/h	0.0673	0.0815	0.00875	10.7	0.0644	0.0986
Slope _{EFF} , mmol/ μ g ^a	0.0207	0.0204	0.00123	6.03	0.018	0.0228
Ethnic effect on baseline, % ^b		-3.13	0.702	-22.4	-4.51	-1.75
Ethnic effect on σ_{prop}^2 , % ^c		75.2	5.49	7.3	64.4	86
<i>Random effects: IIV</i>						
$\omega_{baseline}^2$ (IIV)	0.107	0.102	0.0064	6.27	0.0895	0.115
<i>Random effects: residual error</i>						
$\sigma_{1\ prop}^2$	0.0043	0.00432	0.000188	4.35	0.00395	0.00469

ARTS-DN MinerAlocorticoid Receptor Antagonist Tolerability Study-Diabetic Nephropathy, ARTS-DN^{JP} combined ARTS-DN and ARTS-DN Japan dataset, CI confidence interval, IIV inter-individual variability, k_{in} zero-order production rate constant, LLCI lower limit of 95% CI, PD pharmacodynamics, PK pharmacokinetics, RSE relative standard error, SE standard error, slope_{EFF} slope, ULCI upper limit of 95% CI

^aThe model has a log-linear concentration effect relationship

^bPercentage difference in Japanese relative to global population (baseline = 4.18 mmol/L in Japanese population).

^cMultiplication percentage for Japanese relative to global population ($\sigma_{prop}^2 = 0.00325$ for Japanese population)

^dPKPD model based on ARTS-DN data only

^ePKPD model based on combined ARTS-DN^{JP} data

Table S4. Parameter estimates of the final (ARTS-DN and ARTS-DN Japan) and intermediate ARTS-DN PKPD model for eGFR-EPI.

Parameter	ARTS-DN only ^d	Final model ^e	SE	RSE (%)	LLCI	ULCI
Baseline eGFR-EPI,						
mL/min/1.73 m ²	67.4	66.6	0.66	0.991	65.3	67.9
K_{out} , 1/h	0.0030	0.0023	0.000346	15	0.00162	0.00298
Slope _{EFF} ^a (min/ml/1.73 m ² /(μg/L))	0.371	0.0359	0.00358	9.97	0.0289	0.0429
Power drug effect	0.218	0.231	0.0454	19.7	0.142	0.32
Ethnic effect on σ^2 , % ^b		64.7	4.42	6.83	56	73.4
Ethnic effect on σ^2_{prop} , % ^c		67.5	7.43	11	52.9	82.1
<i>Random effects: IIV</i>						
$\omega^2_{baseline}$ (IIV)	453	451	17.7	3.92	416	486
<i>Random effects: residual error</i>						
σ^2_{1prop}	0.0094	0.00944	0.000408	4.32	0.00864	0.0102

ARTS-DN MinerAlocorticoid Receptor Antagonist Tolerability Study-Diabetic Nephropathy, *CI* confidence interval, *eGFR-EPI* estimated glomerular filtration rate according to the Chronic Kidney Disease Epidemiology Collaboration equation, *IIV* inter-individual variability, K_{out} dissipation rate, *LLCI* lower limit of 95% CI, *PD* pharmacodynamics, *PK* pharmacokinetics, *RSE* relative standard error, *SE* standard error, *ULCI* upper limit of 95% CI

^aThe drug effect is defined as: effect = slope • [concentration]_{power}

^bMultiplication percentage for Japanese relative to global population ($\sigma^2 = 291$ for Japanese population)

^cMultiplication percentage for Japanese relative to global population ($\sigma^2_{prop} = 0.00637$ for Japanese population)

^dPKPD model based on ARTS-DN data only

^ePKPD model based on combined ARTS-DN[†]JP data