Studying Telmisartan Plasma Exposure, Kidney Distribution, Receptor Occupancy, and Response in Patients With Type 2 Diabetes Using [^{11}C]Telmisartan

Sjoukje van der Hoek[1] (iD), Douwe J. Mulder[2] (iD), Antoon T.M. Willemsen[3], Ton Visser[4], Andre Heeres[4,5], Riemer H.J.A. Slart[3], Philip H. Elsinga[3], Hiddo J.L. Heerspink[1] and Jasper Stevens[1,*] (iD)

The angiotensin receptor blocker telmisartan slows progression of kidney disease in patients with type 2 diabetes (T2D), yet many patients remain at high risk for progressive kidney function loss. The underlying mechanisms for this response variation might be attributed to differences in angiotensin-1 receptor occupancy (RO), resulting from individual variation in plasma drug exposure, tissue drug exposure, and receptor availability. Therefore, we first assessed the relationship between plasma telmisartan exposure and urinary-albumin-to-creatinine-ratio (UACR) in 10 patients with T2D and albuminuria (mean age 66 years, median UACR 297 mg/g) after 4 weeks treatment with 80 mg telmisartan once daily. Increasing telmisartan exposure associated with a larger reduction in UACR (Pearson correlation coefficient (PCC) = −0.64, P = 0.046, median change UACR: −40.1%, 95% confidence interval (CI): −22.9 to −77.4%, mean telmisartan area under the curve (AUC) = 2927.1 ng·hour/mL, 95% CI: 723.0 to 6501.6 ng·hour/mL). Subsequently, we assessed the relation among plasma telmisartan exposure, kidney distribution, and angiotensin-1 RO in five patients with T2D (mean age 60 years, median UACR 72 mg/g) in a separate positron emission tomography imaging study with [^{11}C]Telmisartan. Individual plasma telmisartan exposure correlated with telmisartan distribution to the kidneys (PCC = 0.976, P = 0.024). A meaningful RO could be calculated in three patients receiving 120 mg oral telmisartan, and although high exposure seems related to higher RO, with AUC_{0-last} of 31, 840, and 274 ng·hour/mL and corresponding RO values 5.5%, 44%, and 59%, this was not significant (P = 0.64). Together these results indicate, for the first time, a relationship among interindividual differences in plasma exposure, kidney tissue distribution, RO, and ultimately UACR response after telmisartan administration.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

☑ Angiotensin receptor blockers reduce the risk of kidney failure but a large and unexplained interindividual response variability leads to suboptimal therapy in many patients with diabetic kidney disease.

WHAT QUESTION DID THIS STUDY ADDRESS?

☑ Whether there is a relationship among the interindividual differences in plasma exposure, kidney tissue distribution, receptor occupancy (RO), and ultimately urinary-albumin-to-creatinine-ratio (UACR) response after telmisartan administration.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

☑ UACR response variability is associated with interindividual differences in plasma telmisartan exposure. Furthermore, plasma telmisartan exposure is positively associated with telmisartan kidney distribution, although its relationship with angiotensin-1 receptor occupancy was less clear.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

☑ Understanding of the pharmacological relationship among telmisartan dose, exposure, kidney distribution, RO, and UACR response in individual patients may lead to improved individual telmisartan dosing regimens.

Approximately 30% of patients with type 2 diabetes (T2D) ultimately develop diabetic kidney disease (DKD) and this has now become the leading cause of renal replacement therapies, accounting for ~ 50% of cases in developed countries. In addition, DKD results in high cardiovascular morbidity and mortality and decreased patients' health-related quality of life.[1] Among others, current treatment of DKD includes tight blood pressure control with angiotensin converting enzyme inhibitors (ACEis) and angiotensin receptor blockers (ARBs).[2]

ARBs are the guideline recommended treatment for kidney protection, based on clinical trials demonstrating that these agents reduce the risk of kidney failure.[3,4] Yet, a substantial proportion of patients remains at high risk for progressive kidney function loss during ARB treatment, which can be, in part, attributed to an interindividual variation in therapeutic response.[5,6] This individual variation in long-term efficacy closely correlates with the individual variation in urinary-albumin-to-creatinine-ratio (UACR), an accepted surrogate for progressive kidney function loss. Indeed, ~ 30% of patients do not achieve a reduction in the UACR during ARB treatment.[5] This provides a clear rationale to pay more attention to studying the individual patient and unravel determinants of response variability and therapy resistance in order to personalize treatment. We hypothesize that the underlying mechanisms of the interindividual response variability can be attributed to variability in plasma- and tissue drug disposition and receptor interaction.

However, in patients with T2D, there are no data on ARB disposition and receptor interaction in the kidneys. Accordingly, it is unknown to what extent interindividual variability in plasma- and kidney tissue drug exposure and receptor binding of ARB determine the individual response.

Therefore, our first aim was to assess the relationship between plasma drug exposure and UACR response of the ARB telmisartan in patients with T2D and albuminuria. Our second aim was to assess the relation between plasma telmisartan exposure and angiotensin II type 1 (AT-1) receptor occupancy (RO) in patients with T2D in a separate clinical positron emission tomography (PET) imaging feasibility study with [11C]Telmisartan.

MATERIALS AND METHODS

Both clinical trials were performed in accordance with the Declaration of Helsinki and Good Clinical Practice and the study protocols were approved by the local medical ethics committees. All participants signed written informed consent before any study-specific procedure commenced.

Individual telmisartan exposure-response analysis on ROTATE-2 data

Exposure and response data of 10 participants were obtained from the telmisartan arm in the pharmacokinetic (PK) substudy of ROTATE-2 (www.trialregister.nl: NL5459). In short, ROTATE-2 was a double-blind, 48-week, multicenter, crossover study to determine the individual albuminuria lowering response of four different albuminuria lowering drug classes in adult patients with T2D, an estimated glomerular filtration rate (eGFR) > 45 mL/minute/1.73 m^2 and elevated albuminuria (> 30 and ≤ 500 mg/g). Individuals with a cardiovascular disease event within 6 months of study enrollment, using glucagon like peptide-1 receptor agonists, or pregnant women were excluded. Inclusion for the PK substudy was based on willingness to participate. Most important

exclusion criterium for the substudy was the use of medication, and a surgical or medical condition that might significantly alter the absorption, distribution, metabolism, or excretion of telmisartan.

In the 4-week PK telmisartan substudy, at the first day of oral 80 mg telmisartan dosing, blood samples were obtained at predose and 0.25, 0.5, 0.75, 1, 1.5, 2, 4, or 6 and 24 hours and stored at −80°C before shipping to a central laboratory for analysis of plasma telmisartan concentrations using a validated liquid chromatography with tandem mass spectroscopy method (Nuvisan, Neu-Ulm, Germany; calibration range 0.500–1,000 ng/mL, lower limit of quantification (LLOQ) 0.500 ng/mL, inter-assay precision 2.9–7.4%, and accuracy 100.4–101.9%). UACR data were available from morning urine voids collected at days −2, −1, and 0 and week 4, and measured at a local laboratory.

Pharmacokinetic telmisartan data points below the LLOQ, but before time to maximal plasma concentration were set to zero prior to data analysis. Individual telmisartan concentration–time profiles were described using population approach nonlinear mixed effects modeling in NONMEM with first-order conditional estimation method and interaction. One-, two-, and three compartment models with linear elimination and various absorption models were fitted to the data to determine the optimal model structure. Models were parameterized in apparent clearances (clearance/bioavailability (CL/F)) and apparent volumes of distribution (V/F) and were assumed to be log-normally distributed. Proportional, additive, or combined residual error structures were explored. Demographic (age, sex, and body mass index) and clinical laboratory covariates (eGFR, blood pressure, albumin, bilirubin, creatinine, blood urea nitrogen, LDL, HDL, and total cholesterol) were formally tested as covariates during model development if they showed a correlation ($r^2 > 0.5$) with the empirical Bayesian *post hoc* parameter estimates. Model selection and evaluation was based on numerical and graphical evaluation, as described previously.[7] Area under the curve from time zero to infinity (AUC_{0-inf}) was calculated per patient by dividing the administered dose over CL/F.

UACR was calculated as the geometric mean of the three first morning void urine collections at days −2, −1, and 0 prior to the visit to the clinic for baseline measurements and at week 4. Change from baseline UACR was calculated as the log-ratio of UACR at week 4 and baseline UACR and used as response measure.

The exposure–response analysis was performed in R using linear regression analysis (2-sided, $P < 0.05$) and Pearson correlation coefficient (PCC) was used as an estimate for association.

Clinical trial to explore [11C]Telmisartan kidney exposure and receptor occupancy

Patients. In this randomized, open label feasibility study (GUMDROPS, www.trialregister.nl: NL6637), nine patients with T2D, aged between 45 and 70 years, were eligible. Main exclusion criteria were occurrence of a cardiovascular event in the 6 months prior to inclusion, major gastrointestinal surgery, severe liver disease, pregnancy, or child-bearing potential without using reliable contraception. Patients came to the hospital in fasted state and received a standardized breakfast and lunch, avoiding components high in salt.

Trial design. At screening, a physical examination was performed, demographics were collected, and blood was collected for clinical chemistry assessment. After screening, eligible patients using an ACEi or ARB entered a "run in period," lasting a maximum of 4 weeks, in which the use of ACEi or ARB was discontinued to avoid interference with the study drug while the patients' blood pressure was stabilized with a calcium antagonist or metoprolol (i.e., ≤ 10 mmHg change from screening values) if necessary and at the discretion of the investigator.

At the study day and prior to breakfast, venous blood samples were taken for routine clinical laboratory assessment and 24-hour urine was collected and analyzed for urinary albumin, protein, sodium, potassium, creatinine, and urea excretion.

After a low-dose computed tomography scan for attenuation correction, 400 MBq [^{11}C]Telmisartan was intravenously administered as a bolus at $t = 0$ hours followed by a 1.5 hours baseline dynamic PET scan (Biograph Vision, Siemens Healthcare GmbH, Erlangen, Germany) to measure selective uptake and accumulation of [^{11}C]Telmisartan. After a 1.5-hours washout period (at $t = 3$ hours), an oral dose of 20, 80, or 120 mg telmisartan was administered to the patient ($n = 3{:}3{:}3$). N-desmethyl telmisartan was commercially bought and labeled by the Hospital Pharmacy at the UMCG.[8] Then, at the approximate time of maximal oral telmisartan plasma concentration ($t = 4$ hours; 1 hour after telmisartan administration) and after a second low-dose computed tomography scan for attenuation correction, a second intravenous [^{11}C]Telmisartan dose of ~ 400 MBq was administered followed by a second 1.5-hours dynamic PET scan. In this postdrug scan, a part of the receptor binding sites are occupied by telmisartan, hence the reduction in [^{11}C]Telmisartan uptake compared with the baseline scan can be used to determine the RO of telmisartan.[9] PET images were reconstructed into a series of 26 frames (7×10, 2×30, 3×60, 2×120, 2×180, 5×300, and 5×600 seconds) with corrections for detector normalization, deadtime, isotope decay, photon attenuation, random, and scattered coincidences.

During both PET scans, arterial samples were collected and the activity concentration was measured to obtain the [^{11}C]Telmisartan arterial input function. Via an arterial line placed in the radial artery, blood was sampled continuously during the first 30 minutes of both PET scans using an online blood sampler and seven manual whole blood and plasma samples were collected during the course of the PET scans.

From the start of oral telmisartan administration, 10 venous blood samples were taken at $t =$ predose, 5, 10, 20, 40, 60, 80, 100, 120, and 150 minutes and stored at $-20°C$ until shipment for analysis of plasma telmisartan concentrations using a validated liquid chromatography with tandem mass spectroscopy method (Nuvisan, Neu-Ulm, Germany).

[^{11}C]Telmisartan production and dosing. The synthesis and labeling of [^{11}C]Telmisartan was performed as described previously[8] under Good Manufacturing Practice (GMP) conditions. In short, the precursor N-desmethyl telmisartan (Symeres, Groningen, The Netherlands) was radiolabeled with [^{11}C]Methyl iodide (Department of Nuclear Medicine, UMCG) to yield [^{11}C]Telmisartan. The radiochemical purity of [^{11}C]Telmisartan was 99.4% (range: 97.6–100%, $n = 10$). The mean administered dose for the baseline PET scan was 385 MBq (range: 292–429 MBq), with a molar activity of 43,289 GBq/mmol (range: 37,994–47,713 GBq/mmol), and for the postdrug PET scan 308 MBq (range: 196–400 MBq), with a molar activity of 44015.8 GBq/mmol (range: 41,449–48,573 GBq/mmol). The [^{11}C]Telmisartan is the isotopologue of the extensively characterized ARB telmisartan and thus shares its toxicological as well as pharmacological characteristics, enabling its immediate use in patients.[10]

Data analysis. For each baseline PET scan, a volume of interest (VOI) of the left kidney was created using the PET data acquired from 4 to 12 minutes. The right kidney was excluded for analysis, as its apparent uptake is affected by spill-in from the liver, the main metabolizing organ for telmisartan.[11] First, a three-dimensional ellipsoid was manually drawn covering the whole left kidney. Parts of the colon overlapping this ellipsoid were manually removed and the final VOI was defined as the isodensity contour within the ellipsoid at 50% of the range (i.e., $0.5 \cdot (\text{max}-\text{min})$). After matching the baseline and postdrug PET scan, the baseline VOI was also used for the postdrug scan. Applying the VOI to the dynamic scans resulted in time-activity curves for both baseline- and postdrug PET scans. Next, also for each scan, the arterial input function was calibrated by fitting the

radioactivity data of the online blood sampler to the manual plasma- and whole blood samples. Metabolite correction of the arterial input function was not considered necessary, as the proportion of the only telmisartan metabolite, 1-O-acylglucuronide, does not exceed 12.5% in plasma.[12] Finally, the kinetic analysis was performed on the time-activity curves of the kidneys and their arterial input function. The radioactivity in blood is incorporated in the model to fit the PET scan data using the general equation:

$$C_{\text{Model}}(t) = (1 - v\text{B}) \times C_{\text{Tissue}}(t) + v\text{B} \times C_{\text{Blood}}(t) \cong C_{\text{PET}}(t)$$

where C_{Model} is the model result, $v\text{B}$ the apparent blood volume fraction in the kidney, C_{Tissue} the [^{11}C]Telmisartan concentration in kidney tissue (either free or bound), C_{Blood} the [^{11}C]Telmisartan concentration in blood (measured via arterial sampling), and C_{PET} the PET signal. $v\text{B}$ was fitted during the kinetic modeling process for each scan individually, as was the delay in time of radioactivity measurement between the arterial sampling and influx of blood in the kidneys. Weighting was applied to the residuals based on frame duration and decay. When choosing the most optimal kinetic analysis method, it was decided to use a single kinetic analysis method on all participants to allow comparison between participants. Kinetic model selection and evaluation was based on visual inspection to appropriately describe all participants data, Akaike Information Criterion, and standard errors of the parameters. The total volume of distribution (V_T) was the primary parameter of interest, from which the apparent RO was calculated as[13]:

$$\text{RO}(\%) = \frac{V_{\text{T,baseline}} - V_{\text{T,post-drug}}}{V_{\text{T,baseline}}} \cdot 100$$

As measure for total plasma telmisartan exposure, the AUC from time zero to the last data point ($\text{AUC}_{0-\text{last}}$) was calculated per patient by noncompartmental analysis by trapezoidal rule. Second, the mean telmisartan concentration during PET scan (C_{mean}) per patient was calculated by dividing the AUC from the sampling point closest to tracer administration until the last data point by the time interval. Telmisartan kidney distribution (in ng/minute/mL kidney tissue) was then calculated by multiplying C_{mean} (ng/mL plasma) and the telmisartan transport rate constant (K1, in mL plasma/minute/mL kidney tissue, obtained from the kinetic model). The correlation between mean telmisartan plasma exposure and kidney distribution was assessed using linear regression analysis (2-sided, $P < 0.05$) and PCC was used as an estimate for association.

Software

Population PK model development was performed in NONMEM version 7.3.0 (ICON Development Solutions, Ellicott City, MD). Clinical trial data of GUMDROPS was collected in Castor EDC (version 2021.6.2, Castor Electronic Data Capture; Ciwit BV, Amsterdam, The Netherlands). Analysis of the PET images and kinetic modeling was performed using PMOD (version 4.105, PMOD Technologies LLC, Zürich, Switzerland). All data preparation, statistical analysis, and graphical presentation was performed in R version .3.6.3.[14]

RESULTS

Individual telmisartan exposure-response analysis in ROTATE-2

The demographics of the participants in the PK substudy in ROTATE-2 and of the entire ROTATE-2 population ($n = 37$) are represented in **Table 1**. Five participants in the substudy experienced an adverse event (itching ($n = 2$), muscle pain ($n = 1$), worsening of hypertension ($n = 1$), headache ($n = 1$), and peripheral edema ($n = 1$)). For this analysis, 79 plasma telmisartan

Table 1 Baseline characteristics of the PK substudy in ROTATE-2 and the entire ROTATE-2 population

	PK substudy (n = 10)	ROTATE-2 (n = 37)
Age, years	66 (9)	67 (8)
Male sex, n (%)	7 (70)	33 (89)
Body mass index, kg/m²	32.7 (2.7)	30.7 (3.5)
Systolic blood pressure, mmHg	139 (11)	139 (12)
Diastolic blood pressure, mmHg	74 (10)	78 (20)
eGFR, mL/minute/1.73 m²[a]	76 (26)	78 (20)
HbA1c, mmol/mol	62 (13)	61 (12)
UACR, mg/g	297 [139–742]	149 [73–285]

Data as mean (±SD) or median [IQR].
eGFR, estimated glomerular filtration rate; IQR, interquartile range; PK, pharmacokinetic; UACR, urinary-albumin-to-creatinine-ratio.
[a]Estimated by modification of diet in renal disease (MDRD) formula.

concentration measurements and 58 first morning void UACR values were available. PK plasma data were best described by a two-compartment model with first order elimination and a transit absorption model (ADVAN13). Interindividual variability was identified on CL/F, V2/F, and mean transit time. The residual error was best described by a proportional error model. No covariates could be identified. The population parameter estimates of the PK model are provided in **Table S1**. Overall, the model described the individual data accurately (**Figure S1**). The resulting mean (95% confidence interval (CI)) telmisartan AUC_{0-inf} was 2927.1 (723.0 to 6501.6) ng·hour/mL.

Median (95% CI) percentage change in UACR from baseline after 4 weeks of treatment was −40.1 (−77.4 to −22.9). The association between individual AUC_{0-inf} to UACR change is shown in **Figure 1**. For every 100 ng·hour/mL increment in AUC, the percentage change in log transformed UACR was −0.55% (PCC = −0.64; P = 0.046).
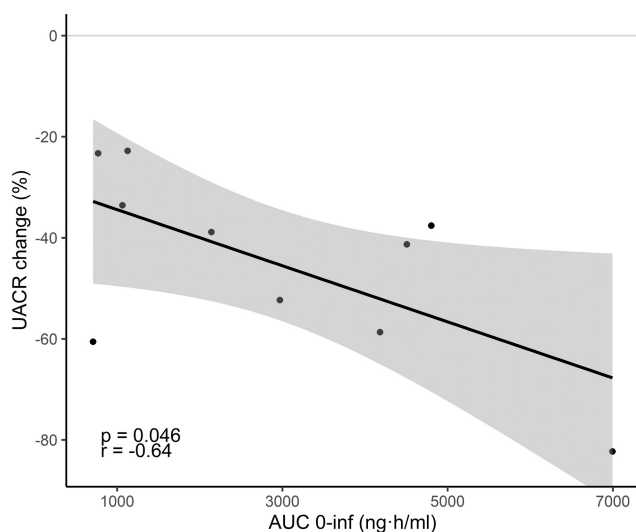

Figure 1 The association between plasma telmisartan exposure (AUC_{0-inf}) and change from baseline in urine-albumin-creatinine-ratio (UACR). Circles: observations, gray area: 95% confidence interval.

[¹¹C]Telmisartan kidney exposure and receptor occupancy

After five patients had completed the study, the trial was discontinued due to suboptimal labeling efficiency of [¹¹C]Telmisartan. Specifically, the labeling efficiency was insufficient during GMP production for PET imaging studies. The demographics of the enrolled patients are presented in **Table 2**.

The plasma exposure and kinetic analysis results are represented in **Table 3**. Telmisartan plasma exposure varied largely among the 5 participants with AUC_{0-last} ranging from 5.12 to 840.4 ng·hour/mL. The individual PK profiles and images of individual baseline and postdrug scans are shown in **Figure 2**. A reversible one-tissue compartment model proved most appropriate to describe all participants (the model structure and equations are provided in the **Supplementary Material**). In participants 1, 2, and 3, the V_T of the postdrug scan was lower compared with the V_T of the baseline scan. This resulted in RO values of 5.52%, 44.4%, and 58.6%. These participants all received 120 mg telmisartan, however, the individual plasma telmisartan exposure varied largely, with participant 1 having a relatively low AUC_{0-last} (31.1 ng·hour/mL), compared with participants 2 and 3 (840.4 and 274 ng·hour/mL).

In participant 4, the postdrug scan was performed without arterial sampling and therefore the V_T for this scan could not be obtained, and thus the kidney tissue distribution and RO of this participant could not be calculated. Kinetic analysis of the baseline scan shows a relatively high vB and large V_T. This participant received 80 mg telmisartan and had a moderate plasma exposure with an AUC_{0-last} of 53.9 ng·hour/mL.

In participant 5, the V_T of the postdrug scan was higher compared the V_T of the baseline scan, resulting in a negative RO and was therefore not taken forward in the RO analysis. This participant received the lowest dose telmisartan, 20 mg, and had a very low plasma exposure with an AUC_{0-last} of 5.12 ng·hour/mL.

The distribution of telmisartan to the kidneys varied largely among the individuals, ranging from 1.17 to 75.9 ng/minute/mL (**Table 3**) and increasing kidney distribution was correlated to increasing mean plasma telmisartan exposure (PCC = 0.976; P = 0.024). There was no significant relationship between plasma telmisartan concentrations and RO (PCC = 0.53; P = 0.64).

DISCUSSION

We performed two clinical studies to assess whether the variation of kidney disposition and receptor binding of telmisartan correlates with the variation in systemic exposure of telmisartan and pharmacodynamic response. In our first study, we showed that the albuminuria lowering response after 4 weeks of treatment with telmisartan varied largely among individuals and that this response variability is associated with interindividual differences in plasma telmisartan exposure. In our second study, we showed that the mean plasma telmisartan exposure positively associated with the kidney distribution of telmisartan, but the relationship with AT-1 receptor binding was less clear.

Most guideline- and literature information on the PKs of telmisartan is obtained in dose finding- and safety studies in healthy individuals. However, little is known about the variability in plasma telmisartan exposure of ARBs in patients with T2D. The

Table 2 Demographic characteristics at baseline

Subject	Sex	Age, years	BMI, kg/m²	eGFR, mL/minute/ 1.73 m²	HbA1c, mmol/mol	24-hours-UAE, mg/24 hours	Chronic RASi use	T2D duration, years	Hypertension
1	F	61	35	98	110	72	No	27	No
2	M	50	42	100	53	103	ACEi	11	Yes
3	M	55	35	103	49	17	ARB	10	Yes
4	M	65	44	83	93	2843	ACEi	16	Yes
5	M	69	27	90	71	32	ACEi	8	Yes

ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; T2D, type 2 diabetes; UAE, urinary albumin excretion.

reported telmisartan mean AUC (from time 0 until 28 hours) and time to maximum concentration (T_{max}) after administration of 80 mg oral telmisartan to 37 healthy volunteers is 3,728 (range: 582–14,099) ng·hour/mL and 1 (range: 0.5–1) hours.[15] In our first study (ROTATE-2), the values in patients with T2D are in the same order of magnitude (mean AUC_{0-inf}: 2927, range: 709–6,995 ng·hour/mL, and median T_{max}: 0.75, range 0.5–1.5 hours).[15] A relation between plasma systemic exposure to telmisartan and blood pressure lowering response has been reported before,[16] but a possible relation with albuminuria lowering response in patients with T2D is a new finding. Given the relatively small number of participants in this data analysis ($n = 10$), these findings should be confirmed in a larger patient cohort.

In the second study, we explored the association between systemic telmisartan exposure and kidney distribution. An important finding was the linear relationship between increasing mean plasma telmisartan concentrations and increasing kidney distribution of telmisartan during the postdrug PET scan. This indicates that, in the observed exposure range, the distribution of telmisartan into the kidneys is not restricted by, for example, concentration-dependent distribution or saturable absorption processes.

Our data were best described by a one-tissue compartment model and therefore the V_T represents the total volume of distribution of [¹¹C]Telmisartan and no distinction can be made between specifically bound tracer to the AT-1 receptor, non-specially bound and free tracer in the tissue. However, the only difference between the two PET scans was the administration of oral telmisartan. We therefore believe it reasonable to assume that the concentration [¹¹C]Telmisartan specifically bound to the AT-1 receptors is affected and the non-displaceable concentration is the same between the two PET scans. Therefore, we consider it unlikely that the total distribution volumes of [¹¹C] Telmisartan between the postdrug and baseline scan will also be affected and thus can be used as a proxy for RO. In the postdrug-vs. the baseline PET scans of the 3 participants receiving 120 mg oral telmisartan, a reduction in V_T of the tracer in kidney tissue was observed, indicating displacement of [¹¹C]Telmisartan due to binding of telmisartan to the AT-1 receptor. The blocking by telmisartan, with RO values of 5.5%, 44%, and 58.6% and their corresponding telmisartan plasma exposures of 31.1, 840, and 274 ng·hour/mL indicate a trend toward a positive correlation between plasma exposure and RO. The lack of statistical

Table 3 Results kinetic analysis (±SE), plasma exposure to and kidney distribution of telmisartan after oral dosing of telmisartan

Subject	Scan[a]	Dose,[b] mg	Blood delay, seconds	vB	K1, mL/ minute/mL	K2, min⁻¹	VT, mL/cm³	AUC₀₋ₗₐₛₜ, ng·hour/mL	Kidney distribution[c] ng/minute/mL	RO, %
1	1		40.6	0.23 (3.2)	0.22 (1.1)	0.07 (1.7)	3.07 (1.5)			
	2	120	39.6	0.19 (9.4)	0.25 (4.7)	0.09 (4.1)	2.90 (3.1)	31.1	3.58	5.52
2	1		40.2	0.25 (4.7)	0.11 (3.0)	0.03 (3.3)	3.41 (2.5)			
	2	120	48	0.26 (5.0)	0.17 (3.7)	0.09 (4.6)	1.89 (2.2)	840.4	75.9	44.42
3	1		50.2	0.36 (6.6)	0.15 (3.3)	0.01 (6.2)	14.23 (6.9)			
	2	120	54.4	0.34 (9.7)	0.19 (3.4)	0.03 (4.1)	5.90 (5.3)	274	33.51	58.56
4	1		63.5	0.74 (5.3)	0.62 (14.0)	0.03 (4.6)	22.08 (15.7)			
	2[d]	80	NA	NA	NA	NA	NA	53.9	NA	NA
5	1		12.2	0.24 (9.4)	0.13 (2.3)	0.05 (4.5)	2.78 (4.0)			
	2	20	17.9	0.47 (6.7)	0.44 (4.9)	0.06 (3.4)	7.63 (6.0)	5.1	1.17	−174.64

AUC_{0-last}, area under the curve from zero to last telmisartan sampling point; K1, rate constant describing tracer transfer from blood to tissue; K2, rate constant describing tracer transfer from tissue to blood; NA, not applicable; PET, positron emission tomography; RO, receptor occupancy, calculated as (($V_{T,baseline}-V_{T,post-drug}$)/ $V_{T,baseline}$) 100%; vB, calculated apparent blood volume fraction; V_T, apparent calculated volume of distribution. [a]1 = baseline PET scan, 2 = postdrug PET scan. [b]Oral dose telmisartan administered 1 hour before post-drug PET scan. [c]Transport rate of telmisartan to the kidneys, calculated as plasma telmisartan exposure during PET · K_1. [d]This postdrug scan was performed without arterial sampling and therefore no kinetic modeling could be performed.
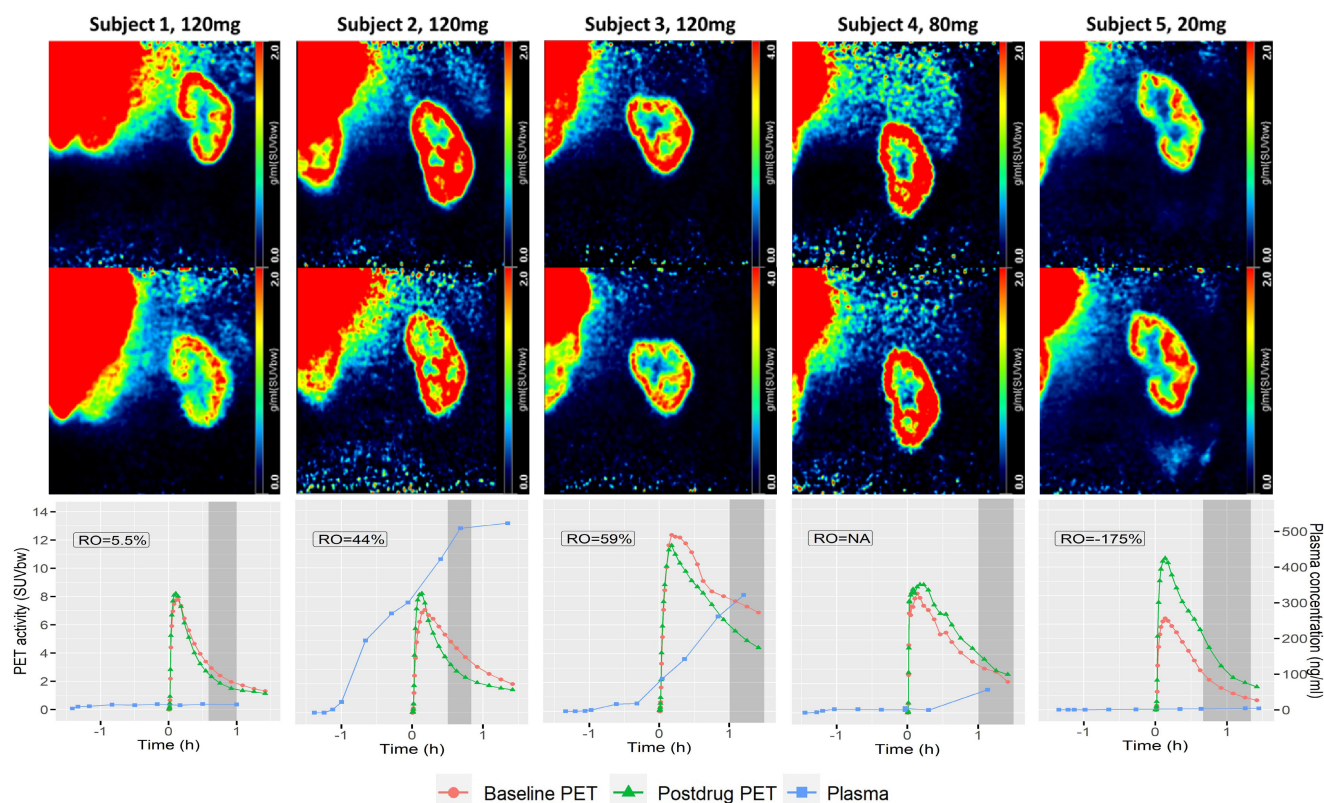
Figure 2 Combined PET and PK data per participant. Top and middle rows: A representative positron emission tomography (PET) image of the activity in the left kidney for each individual on baseline (top) and postdrug scan (middle). Bottom row: Individual time activity curves of the tissue compartment of baseline and postdrug PET scan (left y-axis) combined with the plasma telmisartan concentration (right y-axis). SUVbw: standardized uptake value, normalized to body weight, calculated as tissue radioactivity [KBq/g]/(injected dose [MBq]·body weight [kg]), Gray bars: time frames used for the depicted PET images. *Note*: for participant 6, SUVbw is replaced by the total time activity curves since the arterial input function could not be obtained.

significance may be due to the small sample size and inherent wide CI. Large studies are required to confirm or refute our findings. In participant 5, an increase in V_T was found on the postdrug PET scan after administration of 20 mg telmisartan, resulting in a meaningless negative RO. Plasma telmisartan exposure was extremely low in this participant (AUC 5.12 ng·hour/mL). It thus seems likely that the AT-1 receptor was hardly occupied by telmisartan during the postdrug PET scan resulting in limited displacement of [^{11}C]Telmisartan. However, the increase in V_T is thereby not explained. Because V_T is dependent on tissue perfusion, an increase in renal blood flow during the postdrug scan, as indeed suggested by a higher estimated K1 for the second scan, could explain the results for this participant.

The T_{max} we observed in the PET imaging study was substantially longer than reported in literature[15] and this is important in the design trial, because we aimed to inject the second [^{11}C]Telmisartan dose when maximum plasma telmisartan concentrations had been reached, assuming that this correlates to maximum AT-1 receptor blockage. The time of telmisartan dosing was 80–90 minutes prior to [^{11}C]Telmisartan injection (i.e., slightly longer than the reported T_{max} of 60 minutes).[15] However, the PK profiles in **Figure 2** suggest that still none of the participants had reached maximum telmisartan concentrations at the moment of tracer administration. Assuming that maximum AT-1 receptor blockage at kidney level

follows maximum plasma telmisartan concentration, it can be reasoned that the timing of the second PET scan procedure was not optimal and the RO could have been underestimated in some individuals. It is also noteworthy that the PET models all assume a constant RO during the PET scan (steady-state condition). Because this was not the case, the time-dependent RO will influence the data fitting and thus the model parameters. This effect will depend on the dynamics of the telmisartan plasma concentration and thus introduces additional variability into the results.

The recommended telmisartan dose for the treatment of hypertension is 80 mg, based on optimization of its blood pressure lowering effect. However, telmisartan's renoprotective effect increases after 80 mg twice daily dosing and is considered to be independent of blood pressure control.[5,17] Thus, the most optimal telmisartan dose for both targets seems to differ.[18] We report a maximum AT-1 RO of 60% after administration of a 120 mg telmisartan dose. Further improvement of our understanding of the relationship among telmisartan dose, exposure, kidney distribution, RO, and UACR response is needed and confirmatory studies should ascertain whether higher doses may result in higher RO and if this improves the outcome of individual patients with DKD.

To conclude, we showed that the plasma exposure to telmisartan varied largely among individuals and was positively correlated with albuminuria response. We demonstrated a positive correlation

between plasma telmisartan exposure and its distribution to the kidneys. The results also suggested a positive relation between plasma exposure and RO, but this needs to be assessed in a larger imaging trial. Together these results indicate a relationship among the interindividual differences in plasma exposure, kidney tissue distribution, RO, and ultimately UACR response after telmisartan administration.

CONFLICT OF INTEREST
H.L.H. reports research grants paid to his employer from AstraZeneca, Boehringer Ingelheim, Janssen, and Novo Nordisk for clinical trials; consulting fees, paid to his employer, from Abbvie, Boehringer Ingelheim, Travere Pharmaceuticals, and Novo Nordisk; fees for steering committee membership, paid to his employer, from Bayer, Chinook, CSL Pharma, Janssen, and Gilead; honoraria for lectures from AstraZeneca and Mitsubishi Tanabe; and receiving honoraria for advisory board participation for Merck (paid to his employer), Mitsubishi Tanabe, and Mundipharma. R.S. reports an unrestricted research grant from Siemens Healthineers. All other authors declared no competing interests for this work.

AUTHOR CONTRIBUTIONS
S.H., A.W., R.S., P.E., H.L.H., J.S., T.V., A.H., and U.M. wrote the manuscript. S.H., A.W., R.S., P.H., H.L.H., and J.S. designed the research. S.H. performed the research. S.H., A.W., and J.S. analyzed the data.

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