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Individual Atrasentan Exposure is Associated With Long-term Kidney and Heart Failure Outcomes in Patients With Type 2 Diabetes and Chronic Kidney Disease

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Atrasentan, an endothelin receptor antagonist, showed clinically significant albuminuria reduction with minimal signs of fluid retention in phase II trials. We evaluated whether plasma exposure was associated with long-term outcomes for kidney protection and heart failure in the phase III SONAR trial (*n* = 3668) in type 2 diabetics with chronic kidney disease. A population pharmacokinetic model was used to estimate plasma exposure of atrasentan 0.75 mg/day. Parametric time-to-event models were used to quantify the association between plasma exposure and long-term outcomes. Mean atrasentan plasma exposure was 41.4 ng.h/mL (2.5th to 97.5th P: 14.2 to 139.9). Compared with placebo, a mean atrasentan exposure translated in a hazard ratio of 0.76 (95% confidence interval (CI): 0.28–0.85) for kidney events and 1.13 (95% CI: 1.03–2.20) for heart failure events. At the mean atrasentan exposure, the kidney protective effect was larger than the increase in heart failure supporting the atrasentan 0.75 mg/day dose in this population.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

☑ The phase III SONAR trial demonstrated that the endothelin receptor antagonist atrasentan reduced the risk of kidney outcomes in patients with type 2 diabetes and chronic kidney disease.

WHAT QUESTION DID THIS STUDY ADDRESS?

☑ The atrasentan dose used in the SONAR trial assumed that plasma exposure in the SONAR trial would be comparable to the dose-finding trial (RADAR) and that the surrogate outcomes were adequate proxies for long term outcomes. We re-evaluated these assumptions.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

☑ Atrasentan plasma exposure in the SONAR trial followed a similar distribution as observed during the dose-finding trial. The mean atrasentan plasma exposure favored long-term kidney protection over heart failure, which supports the use of the 0.75 mg dose.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

☑ This study demonstrates that re-evaluation of exposure-response relationships in phase III trials is important to confirm the adequacy of the dose that is intended for clinical practice.

Endothelin receptor antagonists (ERAs) are a promising new treatment option for the prevention of end-stage kidney disease in patients with type 2 diabetes and chronic kidney disease (CKD). Experimental and clinical studies have shown that ERAs have favorable effects on risk markers of progression of CKD, such as albuminuria and systolic blood pressure, in addition to direct

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anti-inflammatory and antifibrotic effects.[1–4] However, ERAs also cause fluid retention, which can lead to edema and heart failure in high-risk patients.[1–4] The degree of fluid retention is dose-dependent and is aggravated in patients with type 2 diabetes and CKD, who are at significant risk for fluid retention and heart failure as part of their underlying disease.[5] Consequently, ERAs have a relatively narrow therapeutic window in diabetic kidney disease, where the maximum tolerated dose is limited by the degree of fluid retention. Careful dose selection of ERAs is thus critical to allow safe use of ERAs.

The SONAR trial recently demonstrated that the ERA atrasentan reduced the risk of major kidney outcomes in carefully selected patients with type 2 diabetes and CKD.[6] The dose of atrasentan in the SONAR trial was selected based on a phase II trial, which demonstrated that the plasma exposure corresponding to a dose of 0.75 mg/day provided an optimal balance between surrogates for efficacy, albuminuria reduction, safety, and body weight increase as a surrogate for fluid retention.[7] Dose selection assumed that plasma exposure would be comparable between the two trials and that the selected surrogate outcomes were adequate proxies for long term kidney and heart failure outcomes.

In this *post hoc* analysis of the SONAR trial, we first aimed to investigate whether atrasentan plasma exposure in the SONAR trial was comparable to the plasma exposure observed in the phase II dose finding trial. Second, we evaluated whether atrasentan plasma exposure was associated with long-term kidney and heart failure-related outcomes.

MATERIALS AND METHODS

Study design and patient population

The SONAR trial was conducted or in accordance with ethical standards as described in the Declaration of Helsinki.[6,8] The study protocol and primary results of the SONAR trial have been reported previously.[6,9]

In brief, patients with type 2 diabetes mellitus and nephropathy, defined as estimated glomerular filtration rate (eGFR) of 25 to 75 mL/min/1.73 m^2 and urinary albumin to creatinine ratio (UACR) of 300 to 5000 mg/g, who were receiving a maximum tolerated dose of a renin-angiotensin-aldosterone-system inhibitor, were eligible to enter a 6-week active run-in period. Patients who were considered prone to fluid retention, defined as B-type natriuretic peptide (BNP) > 200 pg/mL, prior hospital admission for heart failure or a history of severe edema, could not participate in the trial. Following the screening and run-in period, patients proceeded to an open label active-run in period during which all patients received 0.75 mg atrasentan once daily, aimed to select patients that were likely to respond to atrasentan, defined as a UACR reduction of 30% or more, and to exclude patients that were prone to atrasentan-induced fluid retention, defined as an increase of 3 kg or more in body weight or an increase in BNP of 300 pg/mL or more.[8] All responder patients and a selection of nonresponder patients subsequently proceeded to the randomization visit and were assigned in a 1:1 ratio to continue atrasentan or to switch to placebo.[8] The primary aim of the trial was to investigate whether atrasentan could delay the progression of kidney disease in high-risk patients in the responder population. The primary kidney composite end point was defined as the time to first occurrence of doubling of serum creatinine, end-stage kidney disease (defined as chronic dialysis, kidney transplantation, or eGFR < 15 mL/min/1.73 m^2 or renal death).[8]

For this *post hoc* study we defined the safety composite outcome of the time to first occurrence of hospitalization for heart failure or development of moderate to severe peripheral edema. Both the responder and nonresponder populations in the double-blind period were included and combined in this analysis to accurately assess the relationship between plasma atrasentan exposure and kidney and heart failure outcomes across a range of plasma exposures.

Estimation of plasma exposure

Plasma samples were obtained throughout the double-blind period of the trial at several study visits prior to dosing. We used a previously developed population pharmacokinetic model to estimate atrasentan plasma exposure in the double-blind period of the trial.[10] In this model, the plasma concentration of atrasentan over time is described using patient characteristics, measured plasma concentrations, dose of atrasentan, and information about sampling and dosing times. Pharmacokinetic parameters of atrasentan, such as clearance and volume of distribution, are estimated for the entire population. Additionally, the individual deviation from the population mean parameters can be derived for each patient. This way, an individual estimate of the area under the plasma-concentration time curve (AUC), a measure that represents the overall plasma exposure of atrasentan, can be derived from the model by dividing the dose of atrasentan by the estimated model parameter representing an individual's clearance. A similar approach to estimate overall atrasentan plasma exposure has been used in the dose-finding trial. In the dose-finding trial, it was estimated that the AUC, corresponding to a 0.75 mg dose of atrasentan, ranged from 15.9 to 173.0 ng.h/mL (2.5th to 97.5th percentiles). This range in plasma exposure corresponded to a balance between kidney protection and fluid retention, which favored kidney protection, and was therefore used as reference.[7]

Association between plasma exposure and long-term outcomes

Parametric time-to-event models were developed to investigate the association between atrasentan plasma exposure and both composite outcomes. For both outcomes, model development initiated by evaluation of several model structures that could adequately describe the hazard of developing an event over time in the placebo group. Exponential, Gompertz, Weibull, log-normal, and log-logistic distributions were explored. Second, the exposure-response relationship was evaluated using a maximum effect (E_{max}) function proportional to the hazard function or, if applicable, proportional to the shape parameter using data of both the placebo and atrasentan groups. The shape parameter describes a change in the hazard over time. Third, the effect of covariates on the overall hazard and shape parameter was formally tested using data of the placebo group, followed by data of the full population. For both composite outcomes, we explored age, baseline diastolic blood pressure, baseline eGFR, baseline hemoglobin, baseline low-density and high-density lipoprotein, baseline serum albumin, diuretic medication, duration of diabetes, ethnicity, glycated hemoglobin, lipid lowering medication, sex, smoking status, race, and retinopathy. Additionally, for the kidney composite outcome, baseline albuminuria (log-transformed) and albuminuria reduction during enrichment were explored. For the heart failure and edema composite outcome, baseline BNP was also explored. Significant covariates were included in the model using a backward elimination procedure with a reduction in the minimum objective function value (MOFV) of 3.84 corresponding to a P value < 0.05. Continuous covariates were median normalized and any missing data were median imputed in the model code, except for AUC for which the geometric mean was used for imputation.

Laplacian estimation was used to obtain model parameters. Model selection and evaluation was based on numerical diagnostics (i.e., change of MOFV and relative standard error (RSE) of the population parameter estimates) and graphically using survival-based visual predictive checks.

Covariates were also evaluated graphically by stratification of survival-based visual predictive checks.

Software

All datasets were prepared in R version 3.2.4 (R Foundation for Statistical Computing, Vienna, Austria). Ggplot2 version 3.0.0 was used for all graphs. NONMEM version 7.3.0 (ICON Development Solutions, Ellicott City, MD) was used for the estimation of plasma exposure, development of the parametric time-to-event models, and model simulations.

RESULTS

A total of 3,668 patients with type 2 diabetes and CKD were randomized to either atrasentan 0.75 mg/day (N = 1,834) or to placebo (N = 1,834). Baseline characteristics were well balanced between treatment groups (**Table 1**). A total of 1,756 patients had evaluable plasma-concentrations of atrasentan and, for the remaining 78 patients, we imputed plasma exposure using the geometric mean plasma exposure of the population.

Comparison of plasma exposure

A mean trough concentration of atrasentan of 1.61 ng/mL (2.5th to 97.5th percentiles (P): 0.55 to 5.10 ng/mL) was observed during the SONAR trial. The vast majority of the observed plasma trough concentrations (92.4%) were within the previously observed range of the atrasentan phase II dose-finding trial. The geometric mean model-derived AUC was 41.4 ng.h/mL (2.5th to 97.5th P: 14.2 to 139.9 ng.h/mL), which was slightly lower than the geometric mean model-derived AUC of 52.2 ng.h/mL (2.5th to 97.5th P: 15.9 to 173.0 ng.h/mL) reported in the atrasentan phase II trial. Nonetheless, for 1,653 patients of the 1,756 patients (94.2%) with evaluable plasma-concentrations, the AUC was within the 2.5th to 97.5th percentiles of the AUC observed in the atrasentan phase II trial (**Figure 1**).

Association between plasma exposure and long-term outcomes

During a median follow-up of 2.2 years, the kidney composite outcome occurred in 152 (8.3%) patients who received atrasentan as compared with 192 (10.5%) patients in the placebo group (hazard ratio (HR) 0.72, 95% confidence interval (CI): 0.58 to 0.89, P = 0·0023).[6] The composite of hospitalization for heart failure or moderate to severe oedema occurred in 285 (15.6%) patients in the atrasentan group vs. 233 (12.7%) patients in the placebo group (HR 1.26, 95% CI: 1.06 to 1.51, P = 0.008).

For the kidney composite outcome, a log-logistic hazard model best described the placebo data. Individual atrasentan exposure was implemented in the model using an E_{max} function on the overall hazard, which significantly improved overall model fit (−11.5 Δ MOFV, P < 0.05). The AUC_{50} parameter, which represents the AUC value at which 50% of the maximum effect of atrasentan is achieved, was estimated to be 128.5 ng.h/mL (95 CI: 16.4 to 240.6 ng.h/mL). Inclusion of the covariates age, baseline UACR, serum albumin, eGFR, and race (Asians and Whites) on the overall hazard as well as adding the covariate UACR reduction during the enrichment period on the shape parameter significantly improved overall model fit. Model parameters were accurately estimated (RSE < 50%; **Table 2**). In general, the structural trend of the data over time was generally accurately described (**Figure 2**).

For the composite of hospitalization for heart failure or moderate to severe edema, a log-normal hazard model best described the placebo data. Individual atrasentan exposure was implemented in

Table 1 Demographics of patients included in the double-blind period of the SONAR trial

	Placebo	Atrasentan
Number of patients	1,834	1,834
Age, years	64.4 (± 8.7)	64.6 (± 8.8)
Sex, males	1,376 (75.0)	1,346 (73.4)
Race		
Asian	609 (33.2)	589 (32.1)
Black	115 (6.3)	109 (5.9)
White	1,044 (56.9)	1,066 (58.1)
Other	66 (3.6)	70 (3.8)
Ethnicity, Hispanic or Latino	401 (21.9)	424 (23.1)
Body weight, kg	84.9 (± 18.7)	85.6 (± 19.8)
BMI, kg/m^2	30.3 (± 6.4)	30.4 (± 6.2)
Duration of diabetes, years	16.5 (± 8.9)	16.6 (± 9.0)
Current smoker	270 (14.7)	302 (16.5)
Retinopathy	599 (32.7)	605 (33.0)
Systolic blood pressure, mmHg	133.3 (± 15.4)	133.3 (± 15.3)
Diastolic blood pressure, mmHg	71.4 (± 10.1)	71.7 (± 9.8)
Serum creatinine, µmol/L	153.3 (± 46.9)	153.4 (± 46.0)
Estimated glomerular filtration rate, mL/min/1.73 m^2	43.1 (± 13.7)	43.5 (± 13.9)
Low-density lipoprotein	2.5 (± 1.0)	2.5 (± 1.0)
High-density lipoprotein	1.2 (± 0.4)	1.2 (± 0.4)
Glycated hemoglobin (%)	7.6 (± 1.5)	7.6 (± 1.4)
Hemoglobin, g/L	128.6 (± 16.9)	129.9 (± 17.3)
Serum albumin, g/L	39.1 (±3.6)	39.2 (±3.6)
Brain natriuretic peptide, pg/mL	47.0 [25.0–87.8]	48.0 [26.0–86.0]
UACR, mg/g	492.0 [246.7–986.2]	482.4 [247.2–957.1]
UACR responders*	1,323 (72.1)	1,325 (72.2)
Lipid-lowering drugs	1,476 (80.5)	1,437 (78.4)
Diuretic	1,530 (83.4)	1,535 (83.7)

Variables are displayed as mean (SD) or median [IQR]. Sex, ethnicity, and race are displayed as number of patients (% of patients).
BMI, body mass index; UACR, albumin-to-creatinine ratio.
*Urinary UACR responders were defined as patients with a UACR reduction ≥ 30% from baseline at the end of the 6-weeks enrichment period.

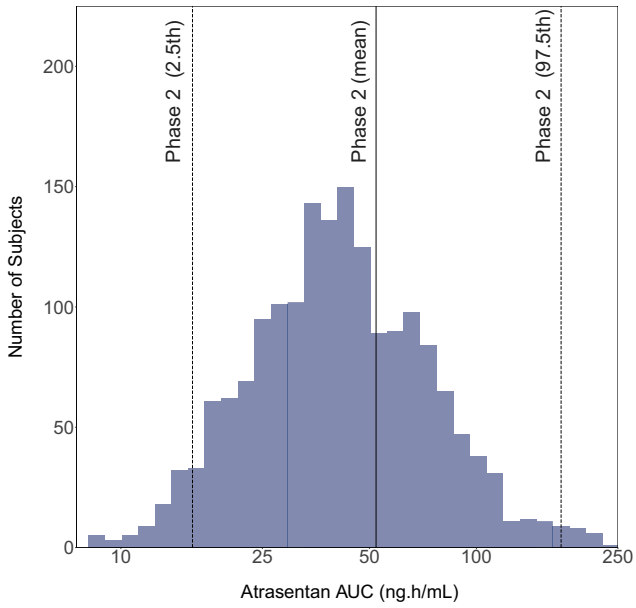

Figure 1 Distribution of plasma exposure in the double-blind period of the SONAR trial. Vertical lines represent the mean, 2.5th, and 97.5th percentiles of the plasma exposure reported in the phase II dose-finding trial. AUC, area under the plasma-concentration time curve.

the model using an E_{max} function on the shape parameter, which significantly improved overall model fit (−7.2 ΔMOVF, $P < 0.05$). The AUC_{50} parameter was estimated to be 174.0 ng.h/mL (95% CI: 1.3 to 346.7 ng.h/mL). Inclusion of BNP, diuretic medication, duration of diabetes, eGFR, ethnicity, and race (Asians) on the overall hazard improved overall model fit. Model parameters were accurately estimated (RSE < 50%; **Table 2**) and the structural trend of the data over time was accurately described (**Figure 2**). Model codes for both composite outcomes are provided in the **Supplementary Materials**.

The associations between plasma exposure and kidney and heart failure composite outcomes are displayed in **Figure 3**. The proportion of patients with a kidney event decreased as atrasentan plasma exposure increased. The proportion of patients with hospitalization for heart failure or worsening of edema event increased as atrasentan plasma exposure increased (**Figure 3**). At the geometric mean AUC, the HR was 0.76 (95% CI: 0.28–0.85) for the kidney composite outcome and the HR was 1.12 (95% CI: 1.03–3.38) for the heart failure or edema composite outcome.

DISCUSSION

In this study, we found that atrasentan plasma exposure in the SONAR trial was overall slightly lower than the plasma exposure observed in the primary dose-finding trial. Nonetheless, plasma exposures were for the vast majority of patients in SONAR within the anticipated range observed in the phase II dose-finding trial. We also demonstrated that atrasentan plasma exposure was associated with long-term kidney and heart failure outcomes. An increase in exposure translated into a higher probability of kidney protection. Yet, it increased the risk of hospitalization for heart failure or moderate to severe edema. Importantly, the AUC_{50} values for hospitalization for heart failure or oedema were higher than for kidney outcomes suggesting that the exposure-response relationship for heart failure or edema seemed to be shifted to higher atrasentan exposures. At the average plasma exposure of a 0.75 mg atrasentan dose, the balance between kidney protection and hospitalization for heart failure or edema favors kidney protection, which confirms the adequacy of the selected atrasentan dose in SONAR.

Dose selection of a new drug is a critical element for the success of confirmatory phase III clinical trials and consequently for a successful overall drug development program.[11,12] In ~ 16.0% of first time marketing authorization applications, uncertainties in dose selection resulted in refusal of marketing authorization.[11] Moreover, postapproval dose adaptions occurred in ~ 20% of new chemical entities, mainly as a result of safety findings.[12] This implies that phase III dose selection is often suboptimal, even in case of a successful phase III trial.

Dose selection for endothelin receptor antagonists is particularly critical because of their narrow therapeutic window in patients with diabetic kidney disease, who are at significant risk for fluid retention and heart failure as part of their underlying disease. The atrasentan dose selection for the SONAR phase III outcome trial was therefore carefully performed.[7] In the SONAR trial, plasma-concentrations were collected throughout the double-blind period, which enabled further assessment of the atrasentan exposure-response relationship. To this end, we first compared the atrasentan plasma exposure observed in the SONAR trial with the plasma exposure observed in the primary phase II dose-finding trial. In doing so, we confirmed that the selected 0.75 mg dose in the SONAR trial provided the anticipated distribution in plasma exposure. By using similar inclusion and exclusion criteria in the dose-finding and confirmatory atrasentan trials it is not a surprise that a majority of patients in the SONAR trial had plasma exposures within the anticipated reference range.[1,8] Furthermore, the enrichment period in the SONAR trial has likely contributed to the favorable benefit risk ratio observed in the trial by excluding patients who did not tolerate the drug or who did not have a favorable response to atrasentan possibly due to either high or low exposure to atrasentan. This has likely resulted in exclusion of patients at the extremes of the plasma exposure distribution and an increase in the proportion of patients within the anticipated reference range. Overall, this analysis confirms that the dose of 0.75 mg in the setting of the SONAR trial provides the anticipated distribution in atrasentan plasma exposure.

Of course, a comparable distribution in plasma exposure between the phase II and phase III trials is only relevant if there is also an association with long-term treatment outcomes. We therefore developed parametric time-to-event models to quantify the association between atrasentan plasma exposure and long-term treatment outcomes. In general, the models were able to accurately describe the association between plasma exposure and long-term treatment response. Numerical diagnostics indicated that all model parameters were estimated with reasonable precision, which provides reassurance in adequate model performance. Upon visual inspection, the central trend of the data (i.e., the proportion of patients experiencing a composite outcome over time) was adequately

Table 2 Model parameters composite outcomes

Model structure	Parameter	Estimate	RSE (%)	2.5% Lower limit	97.% Upper limit
Composite kidney outcome					
Structural model	Baseline hazard	380.51	32.38	139.02	622.00
	Shape parameter	2.14	4.43	1.96	2.33
Drug effect on overall hazard	AUC_{50}, ng.h/mL	128.49	44.50	16.42	240.56
Covariates on overall hazard	log UACR, mg/g	1.14	6.10	1.00	1.27
	Serum albumin, g/L	−2.40	24.19	−3.54	−1.26
	Age, years	−2.35	16.52	−3.11	−1.59
	eGFR, ml/min/1.73 m^2	−2.28	10.71	−2.76	−1.80
	Whites	−0.75	22.90	−1.09	−0.41
	Asians	−0.40	44.10	−0.75	−0.05
Covariates on shape parameter	UACR reduction %	0.48	24.22	0.25	0.71
Composite heart failure and edema outcome					
Structural model	Baseline hazard	1.89	4.64	1.72	2.07
	Shape parameter	3.88	27.10	1.82	5.94
Drug effect on shape	AUC_{50}, ng.h/mL	174.00	50.62	1.32	346.68
Covariates on overall hazard	BNP, pg/mL	0.10	22.65	0.06	0.15
	eGFR, mL/min/1.73 m^2	−0.44	29.60	−0.69	−0.18
	Asians	−0.54	19.98	−0.75	−0.33
	Ethnicity (Hispanic / Latino)	−0.39	29.45	−0.61	−0.16
	Duration of diabetes, years	0.17	38.74	0.04	0.31
	Diuretic comedication	−1.03	17.72	−1.39	−0.67

AUC, area under the plasma-concentration time curve; BNP, B-type natriuretic peptide; eGFR, estimated glomerular filtration rate; RSE, relative standard error; UACR, albumin-to-creatinine ratio.

captured by both models, although a slight bias was observed for the kidney composite outcome. This bias occurs at ~ 600 days, from which a small underprediction of the proportion of patients that reached the composite outcome was visible. The reason for this bias is unclear, but could be due to a reduced number of patients with a follow-up of more than 600 days. The underprediction appears to be more abundant in the placebo group, and, as a consequence, the estimated kidney protective treatment effect of atrasentan is expected to be on the conservative side.

A benefit of the used parametric approach to model outcome data, as compared with the more often used semiparametric Cox proportional hazard model, is that an E_{max} function can be estimated in the parametric approach to determine the AUC_{50} parameter. The AUC_{50} aids in clinical interpretation of the association between plasma exposure and response. AUC_{50} values obtained in our analysis indicate that maximum effects in the composite kidney outcome are reached at a lower atrasentan plasma exposure, as compared with the maximum effect in the heart failure and edema composite outcome. Kidney protection is therefore favored over heart failure or edema with low atrasentan exposures. On an individual level, an estimate of plasma exposure can be obtained using the population pharmacokinetic model using dosing information, sampling information, and plasma-concentration. This plasma exposure can then be used to determine the individual benefit / risk balance but should ideally also take into account other relevant patient characteristics that determine the long-term risk on kidney and heart failure outcomes as well as likelihood to respond to atrasentan.[10]

Dose selection, based on short-term changes in risk markers for kidney protection and fluid retention, translated in a favorable balance toward long-term kidney protection. In addition to plasma exposure, we found that other patient characteristics also influenced long-term treatment outcome. For instance, for efficacy, patients with high albuminuria at baseline were more vulnerable for the composite kidney outcome, consistent with the recognition of albuminuria levels as an important predictor of kidney outcomes. Furthermore, the albuminuria reduction during the enrichment period positively influenced the shape parameter in the time-to-event model, which translates in a lower risk of kidney events with additional albuminuria lowering. Similar patient characteristics were identified in another *post hoc* analyses of the enrichment period of the SONAR trial that influenced atrasentan treatment response in surrogate outcomes for kidney protection and fluid retention. In future diabetic kidney disease studies, these patient characteristics might be used to set different plasma exposure targets depending

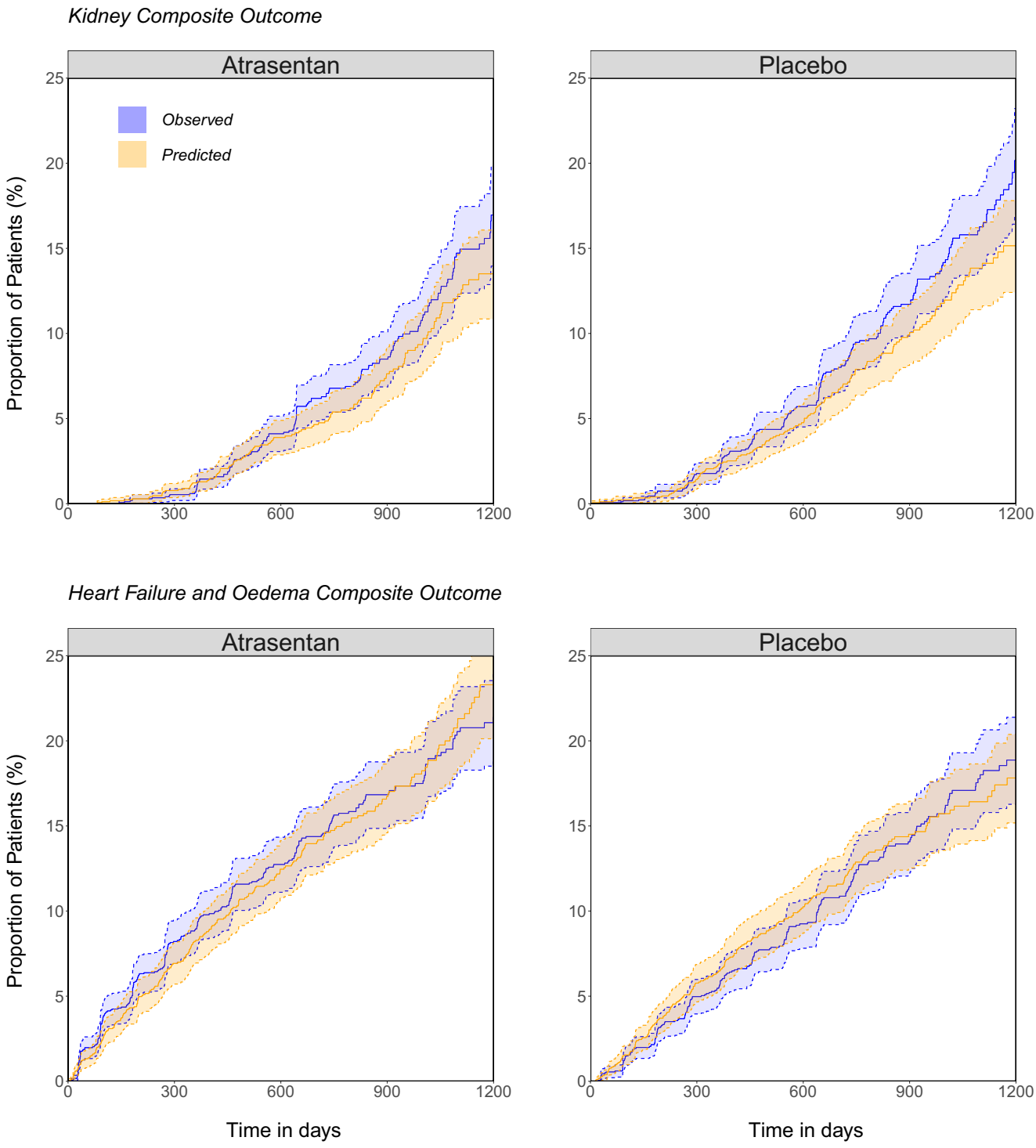

Figure 2 Model predicted and observed Kaplan–Meier curves for kidney and heart failure composite outcomes stratified by treatment.

on the individual benefits and risks. Another topic that requires further study is exploration of the utility of therapeutic drug monitoring to maintain adequate exposure levels in an individual patient to optimize benefit and risk balance in individual patients.

The main limitation of this study was that only one dose level was included in the SONAR trial. Therefore, our models cannot be used to determine the optimal dose of atrasentan to reduce the risks of long-term clinical outcomes. Second, the confidence intervals of the AUC_{50} parameters overlap for both composite kidney and heart failure outcomes, which can in part be explained by a relatively low number of patients with high plasma exposures (i.e., higher than the AUC_{50} value). Consequently, the finding that the dose-response curve for heart failure and edema is shifted to higher atrasentan exposures should therefore be interpreted with caution. Finally, the computational burden to estimate parameters of both parametric models is high. Therefore, time-varying covariates could

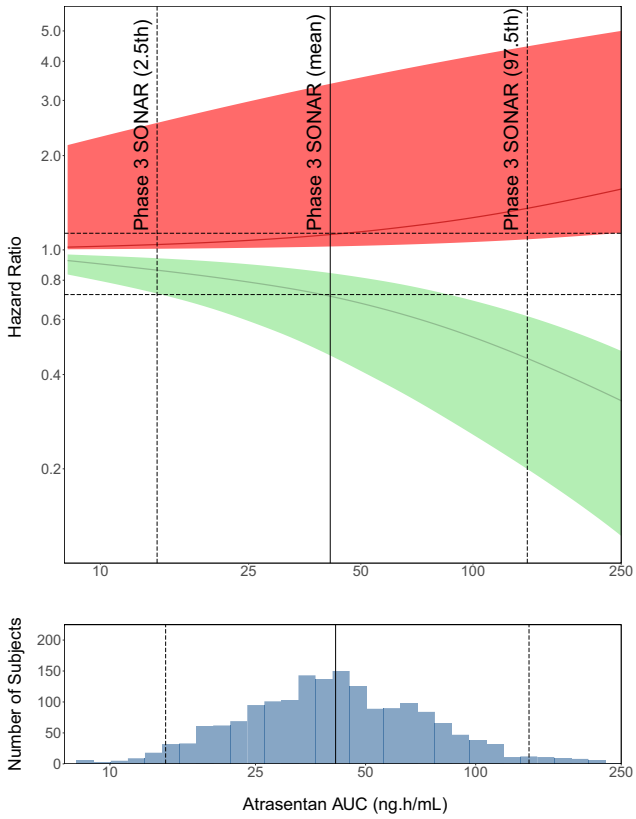

Figure 3 Association between plasma exposure and kidney (green) and heart failure (red) composite outcomes in the SONAR trial. Model predictions (-) are displayed as mean with 95% confidence interval (CI). The vertical lines represent the geometric mean, 2.5th, and 97.5th percentiles of plasma exposure in the double-blind period of the phase III SONAR trial. The horizontal lines represent the effect size at the geometric mean plasma exposure. The histogram represents the distribution of plasma exposures in the SONAR trial. AUC, area under the plasma-concentration time curve.

not be implemented in both models, which could have potentially increased model performance.

In conclusion, we successfully re-evaluated the selected phase III dose of atrasentan. Our analysis demonstrates that atrasentan plasma exposure in the phase III SONAR trial followed a similar distribution as observed during the phase II dose-finding trial. Furthermore, mean plasma exposures of atrasentan favored long-term kidney protective effects over heart failure supporting the use of the 0.75 mg dose in patients with type 2 diabetes and CKD.

SUPPORTING INFORMATION

Supplementary information accompanies this paper on the *Clinical Pharmacology & Therapeutics* website (www.cpt-journal.com).

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CONFLICTS OF INTEREST

H.J.L.H. is consultant to AbbVie, AstraZeneca, Boehringer Ingelheim, Bayer, Chinook, CSL Behring, Gilead, Janssen, Merck, Mundipharma, Mitsubishi Tanabe, Novo Nordisk, and Retrophin. He received research support from AstraZeneca, AbbVie, Boehringer Ingelheim, and Janssen. D.E.K. is a consultant to AbbVie, Chinook, Janssen, and Retrophin. G.B. is a consultant for Bayer, Relypsa, Janssen, Merck, and Vascular Dynamics. R.C.-R. serves on advisory boards for Boehringer and AstraZeneca and has been a speaker for AstraZeneca, Boehringer Ingelheim, AbbVie, Takeda, Amgen, and Janssen; he is consultant for AstraZeneca, Novonordisk, Janssen, and Boehringer Ingelheim. He received research support from AstraZeneca, AbbVie, and GlaxoSmithKline. F.F.H. is a consultant for and received honoraria from AbbVie and AstraZeneca. D.W.K. received grant funding from Bayer, Novartis, and the National Institutes of Health, and has been a consultant for AbbVie, Bayer, Merck, Boehringer Ingelheim, Corvia, CinRx, GlaxoSmithKline, Duke Clinical Research Institute, St Luke's Medical Center, and AstraZeneca. H.M. is a consultant for AbbVie, Boehringer-Ingelheim, and Teijin Pharma. V.P. has served on Steering Committees for trials funded by AbbVie, Boehringer Ingelheim, GlaxoSmithKline, Janssen, Novo Nordisk, Retrophin, and Tricida; and has participated in scientific presentations or advisory boards with AbbVie, Astellas, AstraZeneca, Bayer, Baxter, Bristol-Myers Squibb, Boehringer Ingelheim, Dimerix, Durect, Eli Lilly, Gilead, GlaxoSmithKline, Janssen, Merck, Mitsubishi Tanabe, Novartis, Novo Nordisk, Pfizer, Pharmalink, Relypsa, Retrophin, Sanofi, Servier, and Tricida. S.W.T. participates on a steering committee for Bayer Fidelio/Figaro studies, and speaker's bureau with Servier and Pfizer. D.d.Z. serves on advisory boards or is a speaker for Bayer, Boehringer Ingelheim, Fresenius, Mundipharma, and Mitsubishi Tanabe; participates in steering committees or is a speaker for AbbVie and Janssen; and is on the data safety and monitoring committees for Bayer. H.-H.P. serves as a consultant for AbbVie. All other authors declared no competing interests for this work.

AUTHORS CONTRIBUTIONS

J.V.K., J.S., and H.J.L.H. wrote the manuscript. J.V.K. and H.J.L.H. designed the research. G.B., R.C.-R., F.F.H., D.W.K., D.K., H.M., J.J.V.M., H.-H.P., V.P., S.W.T., D.d.Z., and H.J.L.H. performed the research. J.V.K. analyzed the data.

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