Physiologically Based and Population PK Modeling in Optimizing Drug Development: A Predict–Learn–Confirm Analysis

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Physiologically based pharmacokinetic (PBPK) modeling and classical population pharmacokinetic (PK) model-based simulations are increasingly used to answer various drug development questions. In this study, we propose a methodology to optimize the development of drugs, primarily cleared by the kidney, using model-based approaches to determine the need for a dedicated renal impairment (RI) study. First, the impact of RI on drug exposure is simulated via PBPK modeling and then confirmed using classical population PK modeling of phase 2/3 data. This methodology was successfully evaluated and applied to an investigational agent, orteronel (nonsteroidal, reversible, selective 17,20-lyase inhibitor). A phase 1 RI study confirmed the accuracy of model-based predictions. Hence, for drugs eliminated primarily via renal clearance, this modeling approach can enable inclusion of patients with RI in phase 3 trials at appropriate doses, which may be an alternative to a dedicated RI study, or suggest that only a reduced-size study in severe RI may be sufficient.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC? ☑ A renal impairment (RI) study represents the gold-standard requirement for drug development when assessing the effect of RI on drug exposures and informing clinical dosing. • WHAT QUESTION DID THIS STUDY ADDRESS? ☑ By comparing the results with prospective data from an RI study, this analysis evaluated whether physiologically based pharmacokinetic (PBPK) and population PK modeling and simulation could predict the impact of RI on the PK of orteronel. • WHAT THIS STUDY ADDS TO OUR KNOWLEDGE ☑ PBPK and population PK modeling and simulation seem to accurately predict the impact of RI on the systemic exposure to orteronel, which suggests the potential to predict for renally cleared drugs and help determine clinical dosages. • HOW THIS MIGHT CHANGE CLINICAL PHARMACOLOGY AND THERAPEUTICS ☑ For drugs cleared mainly via renal clearance, PBPK and population PK modeling can estimate the impact of RI on PK thereby allowing participation of patients with RI at appropriately reduced doses in pivotal phase 3 trials and potentially obviating the need for or reducing the design of an RI study.

Modeling and simulating changes in pharmacokinetics (PKs) in subjects with renal impairment (RI) may help to guide appropriate clinical dosing. Although classical population PK modeling is very useful in this regard, physiologically based pharmacokinetic (PBPK) modeling and simulation allows *in vitro–in vivo* extrapolation and simultaneous incorporation of multiple pathophysiological factors as system parameters, not easily performed when using a traditional compartmental PK modeling approach.[1,2] PBPK modeling and simulation, which is increasingly being used to aid drug development,[3–5] can help predict the PK characteristics of drugs in humans, and evaluate the effects of intrinsic (e.g., organ dysfunction, age, genetics) and extrinsic (e.g., drug–drug interactions) factors on drug exposure.[5,6] Such PBPK models can predict drug absorption, metabolism, and disposition by combining the physicochemical characteristics of the drug and nonclinical characterization of human total clearance (CL) mechanisms (and associated enzymology) before the availability of clinical data.[5,7] Ideally, however, the PBPK model should be strengthened with actual human PK parameter values when clinical PK data become available.[5,7] The model can then be used to predict the behavior of a drug in more complex clinical situations characterized by multivariate changes to intrinsic/extrinsic factors.[5,7] Availability of data to guide evaluation of the effects of disease states is crucial for the development of a reliable PBPK model for certain disease populations. In particular, Jones *et al.*[5] noted a low level of confidence in the application of PBPK modeling to populations with renal insufficiency in which the impact of renal insufficiency on metabolism and transporter activities is not known. Various examples of PBPK modeling to predict clinical PK in RI have been reported.[1,8–10]

In this study, we present an application of PBPK modeling to a simpler system for orteronel, a drug that is primarily cleared by

This article was published online 14 July 2015. Subsequently, the authors noted an error in one of the percentages and in the following sentence 37% has been changed to 28%: CLcr seemed to have the most profound impact on plasma orteronel concentrations; in the final PK model, it was predicted that a reduction in CLcr from 92 to 46 mL/min would lead to a **28%** decrease in CL/F. This revised version was published online 18 July 2015.

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Received 18 March 2015; accepted 27 May 2015; advance online publication 1 June 2015. doi:10.1002/cpt.155

Table 1 Simulated $AUC_{0\text{-}tau,ss}$ and AUC ratios to healthy subjects in subjects with varying degrees of renal impairment derived from physiologically based pharmacokinetic (PBPK) modeling and simulation

Scenario[a]	$AUC_{0\text{-}tau,ss}$ (h*ng/mL)	AUC ratio
Healthy subjects (400 mg BID)	27,460	N/A
Moderate renal impairment (400 mg BID) (GFR 30–60 mL/min)	41,670	1.52
Severe renal impairment (400 mg BID) (GFR <30 mL/min)	50,280	1.83
Dose adjustment to 220 mg BID in severe renal impairment subjects (to match healthy exposure)	27,650	1.01
Dose adjustment to 200 mg BID in severe renal impairment subjects (for available dose strengths)	25,140	0.92

Abbreviations: AUC, area under the concentration-vs.-time curve; $AUC_{0\text{-}tau,ss}$, AUC over the steady-state dosing interval (from 228–240 hours in the simulation) at steady state; GFR, glomerular filtration rate.
Values are presented as the mean of 100 simulations.
[a]Assuming 100% fraction absorbed with all uncharacterized metabolism treated as hepatic clearance (orteronel dose 400 mg BID for 10 days). Clinical pharmacokinetic data for healthy subjects (high-fat diet group, $n = 42$) were obtained from clinical study C21007.

the kidneys (decreasing the impact of uncertainty in system parameters with respect to RI effects on metabolism) and has clinical data available for validation. Orteronel (TAK-700) is an oral, nonsteroidal, reversible, selective 17,20-lyase inhibitor that was, until recently, in development for the treatment of patients with metastatic castration-resistant prostate cancer (mCRPC).[11,12] Data from a human radioactive carbon (^{14}C) mass balance and urine metabolite profiling study revealed that orteronel is predominantly cleared through renal excretion as the intact parent compound (unpublished data; Suri, A., Pusalkar, S., Li, Y., & Prakash, S. *Clin. Pharmacol. Drug Development* 2015). In this study, a mean of 78% of orteronel was cleared via the urine (including 50% as the parent drug and 16% as the primary metabolite) compared to 18% via the feces (unpublished data; Suri, A., Pusalkar, S., Li, Y., & Prakash, S. *Clin. Pharmacol. Drug Development* 2015). The extent of orteronel metabolism is minimal, with cytochrome P450 isozymes having only a minor role. Metabolism by hydrolysis was the primary biotransformation pathway in humans. Given the importance of renal CL, patients with RI may have increased exposure to orteronel because of impaired urinary excretion (unpublished data; Suri, A., Pusalkar, S., Li, Y., & Prakash, S. *Clin. Pharmacol. Drug Development* 2015). Clinical PK data from a phase 1 food-effect study showed that the oral bioavailability of orteronel was increased with a high-fat meal; the least-squares mean ratio for area under the plasma concentration-time curve was 142% compared to fasting conditions (unpublished data; Suri, A., Pham, T., & MacLean, D.B. *Clin. Pharmacol. Drug Development* 2015).

In this analysis, PBPK and classical population PK modeling and simulation (both utilizing clinical PK data) have been evaluated as complementary approaches for predicting the impact of varying grades of RI on the PK of orteronel. We herein also report the results of an RI study (i.e., the traditional gold-standard requirement for drug development) and compare it to the model-based predictions. Collectively, the analyses presented here constitute a retrospective assessment of predictive performance of the two modeling and simulation methods (PBPK and population PK from phase 2/3) for a small molecule that is cleared primarily via the renal route. Consequently, the modeling approach described here, if applied prospectively, can inform inclusion of patients with moderate-severe RI in phase 3 trials at the appropriate dosage, and may have the potential to eliminate the need for or simplify the design of a dedicated RI study.

RESULTS

Simulation of orteronel pharmacokinetics using PBPK modeling

A PBPK model was built with physicochemical and preclinical data and oral clearance from a human phase 1 trial because orteronel had no appreciable *in vitro* clearance in human hepatocytes and liver microsomes (**Supplementary Appendix** online). The predicted PK was then validated using clinical PK data (from the fed state in a phase 1 food effect study to represent maximum oral absorption[14]) before applying the model to simulate PK of orteronel in moderate (glomerular filtration rate (GFR), 30–60 mL/min) or severe (GFR, <30 mL/min) RI for comparisons vs. the simulated PK of orteronel in healthy subjects with normal renal function.

The area under the concentration-vs.-time curve (AUC) for orteronel was predicted to increase 1.52-fold in moderate RI and 1.83-fold in severe RI compared with healthy subjects with normal renal function (**Table 1**). As shown in **Figure 1**, subjects with RI were predicted to have a higher maximum plasma concentration and a longer terminal half-life ($t_{1/2}$), leading to an increase in the AUC of orteronel at steady-state, which was greatest in the severely impaired population. The simulation also demonstrated that a reduced dose of orteronel 220 mg twice daily (BID; or a rounded dose of 200 mg BID to match available dose strengths) would achieve exposures in severe RI that are comparable to exposures in subjects with normal renal function given orteronel 400 mg BID (**Table 1**).

The prospective predictions of increases in orteronel exposure in subjects with RI were close to actual observed clinical values: 52% predicted vs. 38% observed in moderate RI; and 83% predicted vs. 87% observed in severe RI.

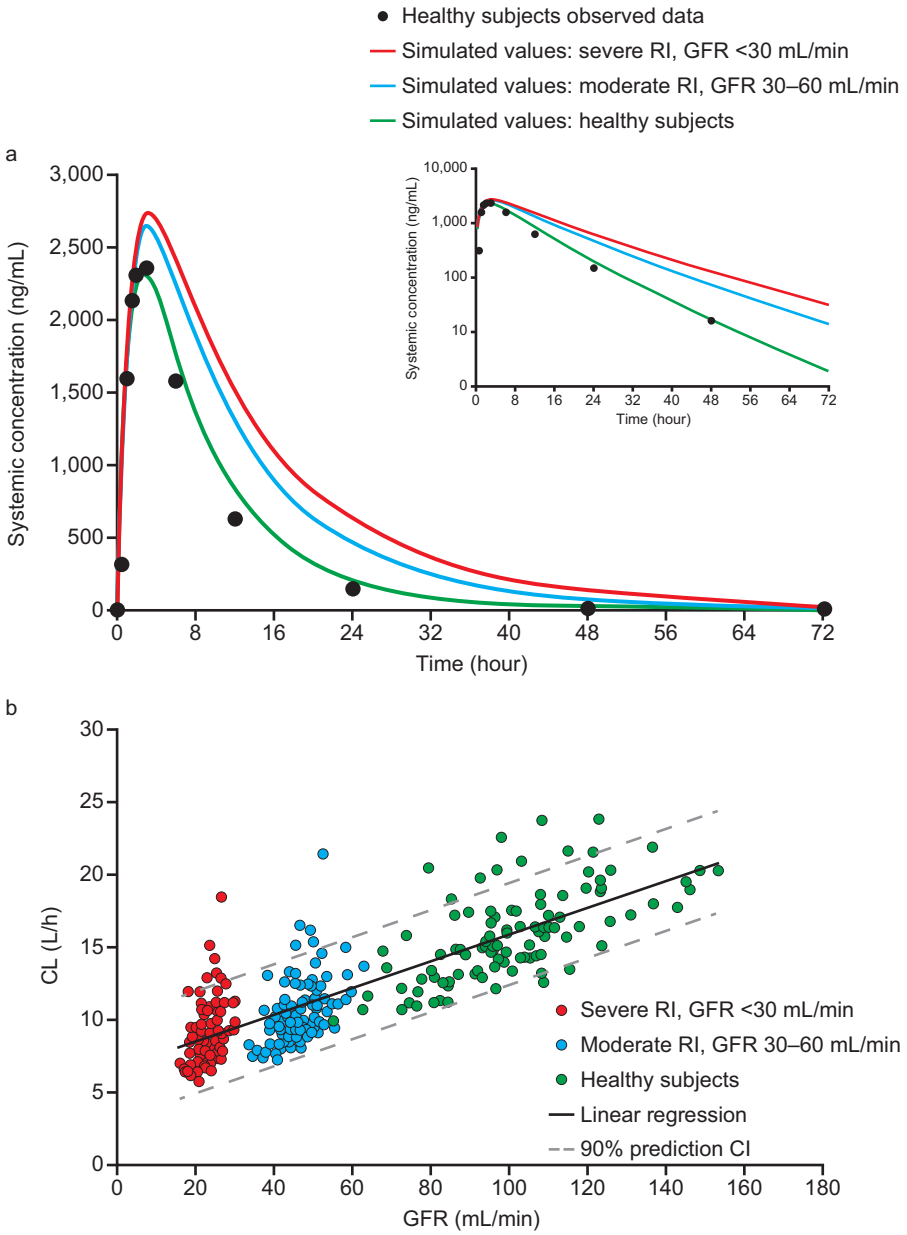

Figure 1 Physiologically based pharmacokinetic (PBPK) simulation of orteronel in (**a**) healthy subjects (observed and simulated values), subjects with moderate renal impairment (simulated values), and subjects with severe renal impairment (simulated values), and (**b**) regression of orteronel clearance vs. glomerular filtration rate (GFR) based on PBPK simulations in healthy subjects, subjects with moderate renal impairment, and subjects with severe renal impairment. Observed data for healthy subjects (high-fat diet group, $n = 42$) were obtained from clinical study C21007. The clinical scenario assumed 100% bioavailability with all uncharacterized metabolism treated as hepatic clearance (orteronel dose: 400 mg BID for 10 days). CL, total clearance; RI, renal impairment.

Orteronel population pharmacokinetic modeling

To complement the PBPK modeling and simulation approach, a population PK analysis was undertaken to quantitatively evaluate the sources of variability in orteronel PK in patients with mCRPC and to determine if dose adjustments might be required for RI in the clinical setting.

The final population PK model was developed using 3,599 orteronel plasma concentrations from 1,417 patients with mCRPC in two phase 3 studies (C21004 (NCT01193244) and C21005 (NCT01193257)) (see **Supplementary Table S1** online). Of this population, 743 patients had normal renal function (per creatinine clearance, CL_{cr}, ≥90 mL/min); 488, 183, and 3 patients had mild (CL_{cr} 60–89 mL/min), moderate (CL_{cr} 30–59 mL/min), and severe (CL_{cr} 15–29 mL/min) RI, respectively. A one-compartment disposition population PK model with first-order absorption and elimination adequately described plasma orteronel concentrations from patients with mCRPC. The model incorporated inter-individual variability for apparent total clearance (CL/F) and apparent volume of distribution (V/F), and both additive and

Table 2 Base model and final model parameters in the orteronel population pharmacokinetic analysis

Parameter	Base model	Final model[a,b]
OFV	52,861	
CL/F, L/h	18.0 (0.3)	17.7 (0.2)
V/F, L	266 (10.4)	261 (9.7)
ka, h^{-1}	2.1 (0.2)	2.2 (0.3)
Study on V/F	–0.19 (0.03)	–0.20 (0.03)
BMI on V/F		0.64 (0.11)
Race O/M on V/F		
CL_{cr} on CL/F		0.47 (0.03)
Age on CL/F		
Race Asian on CL/F		
BILI on ka		–0.46 (0.20)
BSA on ka		
CL_{cr} on ka		
AST on ka		
Additive error	222 (44.60)	105 (38.60)
Proportional error	0.45 (0.01)	0.48 (0.01)

Abbreviations: AST, aspartate aminotransferase; BILI, bilirubin; BMI, body mass index; BSA, body surface area; CL_{cr}, creatinine clearance; CL/F, apparent clearance; ka, absorption rate constant; OFV, objective function value; O/M, other or missing; V/F, apparent volume of distribution.
All values are given as mean (SD).
[a]The equation for the final model was: $TVKa=\theta_1\left(\frac{BILI}{6}\right)^{\theta_{52}}$
$TVV_2=\theta_2\left(\frac{BMI}{27}\right)^{\theta_{26}}$
$TVCL=\theta_3\left(\frac{CL_{cr}}{92}\right)^{\theta_{21}}$
[b]Includes final unblinded updated data from clinical study C21005.

proportional residual error. Population parameter estimates for CL/F, V/F, and the absorption rate constant (ka) were 17.7 L/h, 261 L, and 2.2 h^{-1}, respectively (**Table 2**). Respective inter-individual variability values for CL/F and V/F were 25% and 12% coefficients of variation. Of the covariates examined, statistically significant ($P < 0.001$) effects were observed for CL_{cr} on CL/F, body mass index (BMI) on V/F, and a patient population effect (chemotherapy-naive patients (C21004) and post-chemotherapy patients (C21005)) on V/F (**Table 2**). Additionally, a statistically significant effect of bilirubin on ka ($P < 0.001$) was observed. Although the pharmacologic plausibility of this observation in a non-cirrhotic patient population with bilirubin <1.5 times upper limit of normal is not readily apparent, the covariate was retained in the final model based purely upon statistical considerations. CL_{cr} seemed to have the most profound impact on plasma orteronel concentrations; in the final PK model, it was predicted that a reduction in CL_{cr} from 92 to 46 mL/min would lead to a 28% decrease in CL/F.

Results of the simulation to evaluate the effects of mild or moderate RI on the PK profile of orteronel suggested that patients with mild RI may not require dose adjustments as they were predicted to have only a 20% higher exposure compared with subjects with normal renal function after dosing with orteronel 400 mg BID for one week (**Figure 2A**). For patients with moderate RI, the simulation predicted approximately 50% higher plasma orteronel concentrations compared with normal patients at 400 mg BID (**Figure 2A**). Among these patients with moderate RI, an orteronel dose of 300 mg BID (or 400 mg in the morning and 200 mg in the afternoon/evening, or vice versa)

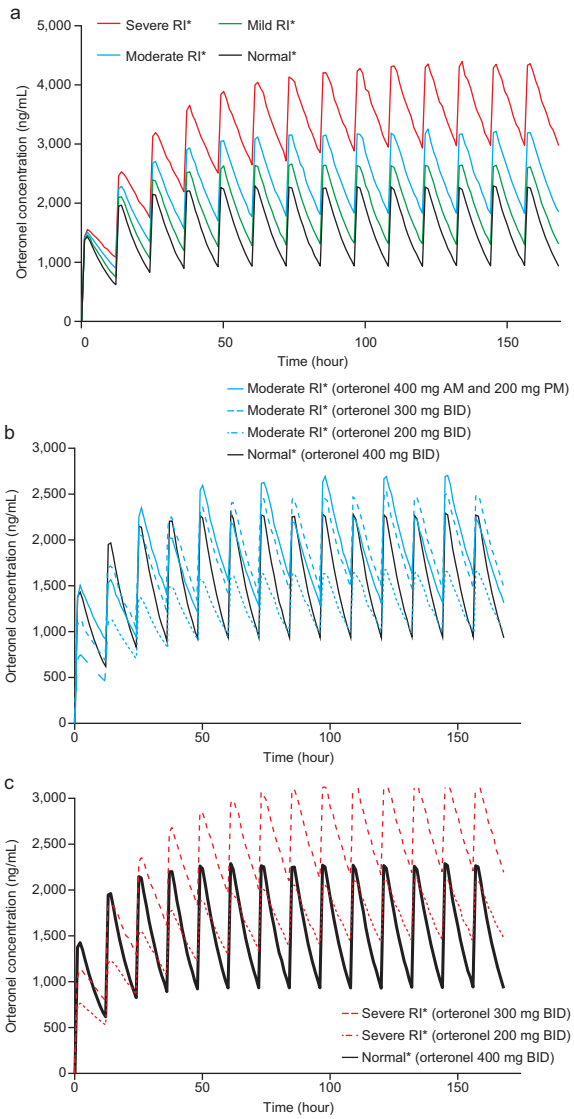

Figure 2 Simulated median population orteronel pharmacokinetic profiles for patients with metastatic castration-resistant prostate cancer (mCRPC) with normal renal function given orteronel at a dose of 400 mg BID for one week and: (**a**) patients with mild, moderate, and severe renal impairment given orteronel at a dose of 400 mg BID for one week; (**b**) patients with moderate renal impairment given orteronel at a dose of 200 mg BID, 300 mg BID, or 400 mg in the morning and 200 mg in the afternoon/evening for one week; and (**c**) patients with severe renal impairment given orteronel at a dose of 200 or 300 mg BID for one week. *Normal, normal renal function (creatinine clearance (CL_{cr}) ≥90 mL/min); mild renal impairment (CL_{cr} 60–89 mL/min); moderate renal impairment (CL_{cr} 30–59 mL/min); severe renal impairment (CL_{cr} 15–29 mL/min, not requiring dialysis). AM, morning; PM, afternoon/evening; RI, renal impairment.

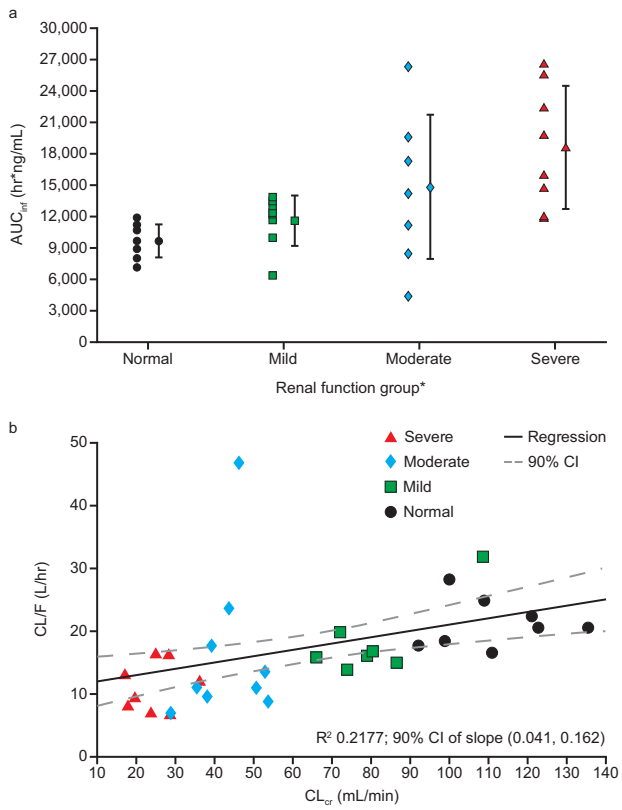

Figure 3 Pharmacokinetics of orteronel in otherwise healthy subjects with varying degrees of renal impairment: (**a**) individual area under the concentration-vs.-time curve from time 0 to infinity (AUC_{inf}) of orteronel by renal function group; and (**b**) regression of orteronel apparent total clearance (CL/F) vs. creatinine clearance (CL_{cr}). In panel **a**, individual values in each renal function group are represented by symbols on the left and the group means are represented by symbols on the right with the lines representing the (±) SD. *Normal, normal renal function (CL_{cr} ≥90 mL/min); mild, mild chronic renal impairment (CL_{cr} 60–89 mL/min); moderate, moderate chronic renal impairment (CL_{cr} 30–59 mL/min); severe, severe chronic renal impairment (CL_{cr} 15–29 mL/min, not requiring dialysis).

seemed to produce comparable exposures to 400 mg BID in patients with normal renal function (**Figure 2B**).

When the model was used to perform simulations for patients with severe RI, the results predicted plasma orteronel concentrations two-fold higher than in normal patients when dosed at 400 mg BID for one week (**Figure 2A**). Subjects with severe RI and given orteronel 200 mg BID were predicted to have similar orteronel plasma concentrations as control subjects given 400 mg BID (**Figure 2C**).

Clinical study of orteronel pharmacokinetics in subjects with varying degrees of RI

The baseline characteristics of subjects from a phase 1 study (C21010) are shown in **Supplementary Table S2** online. Mean total exposure (AUC_{inf}, area under the concentration-vs.-time curve from time zero to infinity) of orteronel increased with increasing severity of chronic RI (**Figure 3A**; see **Supplementary Table S3** online). Conversely, mean CL/F of orteronel was highest in subjects with normal renal function and decreased according to the severity of chronic RI (see **Supplementary Table S3** online). The mean percent unbound of orteronel in plasma was similar across the renal function groups and ranged from 54.7–58.9% (see **Supplementary Table S3** online). Regression analysis revealed a clearly discernible relationship between orteronel CL/F and CL_{cr} ($CL/F = 10.90 + 0.101*CL_{cr}$; 90% confidence interval of the slope: 0.041, 0.162; $r2 = 0.2177$; **Figure 3B**).

Geometric mean orteronel AUC_{inf} values are shown in **Table 3**. For subjects with mild chronic RI, mean orteronel AUC_{inf} values were increased by 18.6% compared with subjects with normal renal function. For subjects with moderate chronic RI, mean orteronel AUC_{inf} was increased by 38.4% compared with subjects with normal renal function. In subjects with severe chronic RI, mean orteronel AUC_{inf} was 87.1% higher compared with those with normal renal function.

Analysis of orteronel PK in urine revealed that renal clearance (CL_{renal}) and urinary excretion of orteronel was highest in subjects with normal renal function, and decreased with increasing RI. The geometric mean fraction of dose excreted as unchanged orteronel (Fe) was 44.9% in subjects with normal renal function, and 33.1%, 19.4%, and 13.8% in subjects with mild, moderate, and severe chronic RI, respectively. Respective geometric mean values for CL_{renal} were 9.46, 5.87, 2.95, and 1.55 L/h.

DISCUSSION

This report evaluates the impact of varying grades of RI on the PK of orteronel, an investigational selective 17,20-lyase inhibitor that was, until recently, in development for the treatment of

Table 3 Statistical analysis of orteronel AUC_{inf} by renal function in otherwise healthy subjects (from clinical study C21010) with varying degrees of renal impairment

Renal function group	No. of patients	Geometric LSM (h*ng/mL)	Ratio of geometric LSM to normal renal function (%)	90% CI of the ratio (%)
Normal renal function (CL_{cr} ≥90 mL/min)	8	9,497.51		
Mild chronic renal impairment (CL_{cr} ≥60–89 mL/min)	8	11,267.99	118.6	98.7, 142.6
Moderate chronic renal impairment (CL_{cr} ≥30–59 mL/min)	8	13,146.88	138.4	97.1, 197.3
Severe chronic renal impairment (CL_{cr} ≥15–29 mL/min)	8	17,765.62	187.1	150.3, 232.9

Abbreviations: AUC_{inf}, area under the concentration-vs.-time curve from time 0 to infinity; CI, confidence interval; CL_{cr}, creatinine clearance; LSM, least-square mean.

mCRPC. A key aspect of these analyses on orteronel is the complementary evaluation of PBPK and population PK modeling and simulation to predict RI effects, demonstrating application of a Predict-Learn-Confirm approach in the drug development setting.[9] Although development of orteronel in mCRPC was terminated in June 2014[13] because of a lack of survival benefit in phase 3 trials,[14,15] our results may have important implications for drug development in general, for they indicate the potential of PK modeling and simulation to potentially obviate the need for a full RI study for drugs cleared primarily via the renal route. This may enable a more efficient approach to define dosing in renally impaired populations.

In a recent study, it was concluded that quantitative information obtained from PBPK modeling was informative in helping decide whether any additional clinical studies would be required, and that this had the potential to guide further dose optimizations.[2] The PBPK model that was built for orteronel was based on a previous model,[7] and was informed by drug-specific physicochemical and nonclinical inputs, as well as single-dose clinical PK data from a healthy subject study (unpublished data; Suri, A., Pham, T., & MacLean, D.B. *Clin. Pharmacol. Drug Development* 2015). By comparing the PBPK model outputs with the population PK data and results from the phase 1 RI trial, it was evident that the PBPK model could reasonably well predict the effect of moderate and severe RI on the PK (i.e., fold increase in AUC) of orteronel. In this model, exposure to orteronel increased as a function of the estimated proportion of orteronel cleared by the kidney, together with the degree of RI (that would decrease that CL). The AUC for orteronel, when given at the clinical dose of 400 mg BID, was predicted to increase by 52% in subjects with moderate impairment and 83% in subjects with severe RI compared with controls. Furthermore, the PBPK simulation also predicted that a reduced dose of orteronel 220 mg BID (or a rounded dose of 200 mg BID) would achieve exposures in severely impaired subjects comparable to those seen in subjects with normal renal function treated at 400 mg BID. These results support the use of PBPK modeling and simulation to predict the outcome of RI scenarios when human CL_{renal} in healthy subjects with normal renal function is known.

Consistently, classical population PK modeling of data from patients with mCRPC also predicted an increase in orteronel plasma concentrations with increasing severity of RI (by approximately 20%, 50%, and 100% compared with controls at 400 mg BID in patients with mild, moderate, and severe RI, respectively). The small increase in orteronel exposure in patients with mild RI suggests that these patients are unlikely to require dose adjustments. Further simulations showed that patients with more severe RI are likely to require dose adjustments, with orteronel doses of 600 mg/day and 200 mg BID in patients with moderate and severe impairment, respectively, providing similar exposures to the 400 mg BID dose in patients with normal renal function. Thus, the results of this supportive analysis provide further evidence that population PK findings can sufficiently confirm predictions based on PBPK modeling and simulation.

In the dedicated RI trial, orteronel exposure after a single 200-mg dose increased by 19%, 38%, and 87%, compared with healthy controls in subjects with mild, moderate, and severe chronic RI, respectively. As would be expected for a renally cleared drug, CL/F, CL_{renal}, and urinary excretion of orteronel all decreased with increasing severity of RI, and there was a discernible association between CL/F and CL_{cr}. These results suggest that the dosage of orteronel may need to be reduced in subjects with moderate or severe (but not mild) RI so that the AUC values are in the range achieved with the standard clinical dose in subjects with normal renal function. Importantly, the findings also confirm the magnitude of impact of RI previously predicted based on PBPK and population PK modeling and simulation.[7]

Overall, these results provide an example of the application of modeling and simulation, and may have important implications for the drug-development process (**Figure 4**); in particular, an opportunity to streamline the clinical research plan for drugs with CL_{renal} as the major clearance mechanism by obviating the need for a traditionally designed clinical RI study or limiting the study to an abridged trial conducted only in patients with severe RI or endstage renal disease (as these patients are not fully represented in the population PK analyses). Development of a PBPK model informed by not only physicochemical and *in vitro* absorption, distribution, metabolism, and excretion data but also by human clearance and CL_{renal} information available from phase 1 clinical studies can provide a quantitative framework to enable simulation of the effects of moderate and severe RI on PK of the investigational drug. The results of these simulations together with exposure-safety relationships can guide the decision of whether to allow enrollment of each grade of RI (e.g., mild, moderate, severe) in phase 2/3 trials. When the expected magnitude of exposure increase is modest and the expected therapeutic index is not narrow, it should generally be possible to minimally include patients with mild-moderate RI, to facilitate a robust population PK analysis. Thus, population PK modeling and simulation from phase 2/3 studies has the potential to reduce the number of clinical studies required to generate PK data for an experimental drug, thereby increasing the efficiency of drug development. Averting the need for a dedicated RI study, where appropriate, or reducing its design is especially valuable when the properties of an investigational agent do not permit clinical assessment in otherwise healthy subjects, such that clinical pharmacology studies need to be conducted in patient populations. This was not the case for orteronel, as dosing of healthy subjects was possible for this agent with a noncytotoxic mechanism of action involving hormonal modulation.[16,17] However, when dealing with genotoxic/cytotoxic molecules, where volunteer clinical pharmacology studies may not be feasible, a model-based approach leveraging PBPK and population PK techniques can be extremely valuable in streamlining the design of RI studies. Importantly, a model-based approach can inform appropriate dosing of patients with RI in phase 2/3 studies and thereby enables characterization of safety, efficacy, and population PK in the target patient population with comorbid RI during drug development. Such data

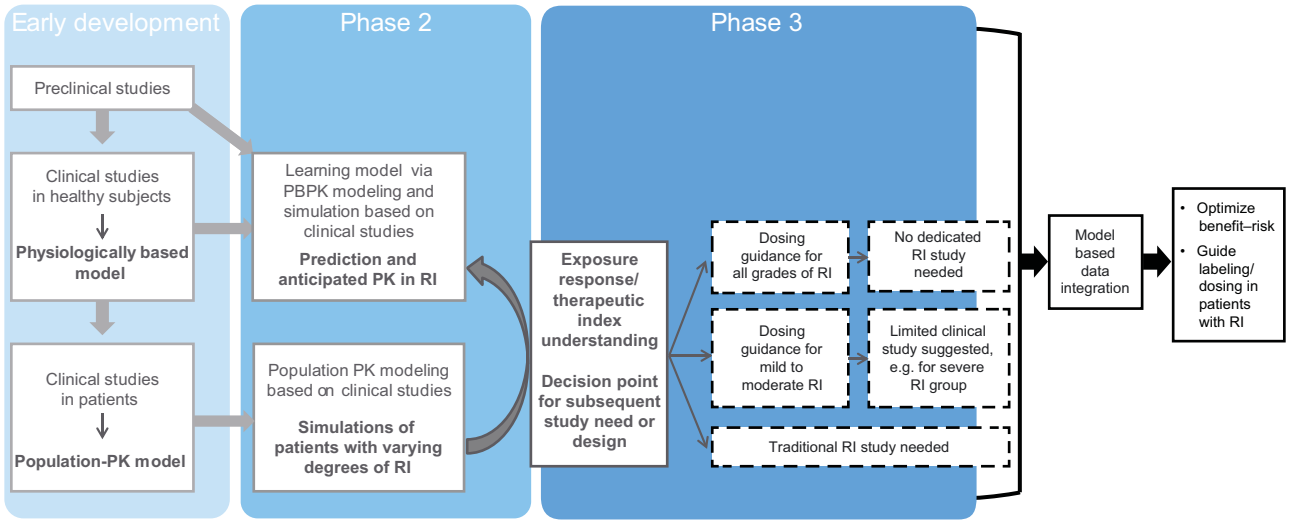

Figure 4 Role of pharmacokinetic (PK) modeling and simulation for guiding dosing according to renal function as part of the drug development continuum. In early clinical development, initial physiologically based pharmacokinetic (PBPK) model is developed along with population PK model based on availability of data from healthy and/or patient studies. The PBPK model is refined in phase 2 and predictions for patients with renal impairment (RI) are conducted. Population PK model and simulations from phase 2 data then aid in reaching a decision point for informing enrollment and dosing guidelines for patients with RI in phase 3 study(ies) and/or the need for or design of a subsequent RI study. Integrated population PK and exposure-response model-based integration of data from phase 2–3 studies should support final decisions around dosing for patients with varying grades of RI to optimize benefit-risk balance and guide labeling.

from phase 2/3 studies help in more accurately qualifying the benefit/risk profile of the recommended posology for these special patient populations as it is based on data from patients with the disease intended to be treated and not solely based on PK data from otherwise healthy subjects in a traditional RI study.

METHODS

Simulation of orteronel pharmacokinetics using PBPK modeling

A PBPK modeling and simulation approach was used to predict the impact of varying grades of RI on the PK of orteronel. This involved combining *in vitro* and *in vivo* data on the physicochemical properties of orteronel with observed clinical PK data. The modeling and simulation was performed using Simcyp (Simcyp Limited version 11, Sheffield, UK) commercial software.[18] The detailed PBPK methodology used here is based on a previously published model used for predicting drug-drug interactions.[7] This model was considered adequate based on visual predictive plots and by accuracy of predicting orteronel PK for normal healthy volunteers.

In a previous food-effect study, a high-fat meal produced a 1.42-fold increase in orteronel exposure (unpublished data; Suri, A., Pham, T., & MacLean, D.B., *Clin. Pharmacol. Drug Development* 2015). As diet was not restricted in any other orteronel clinical trial, clinical PK data in the fed state was used as the reference for model qualification using the healthy subject population in Simcyp to provide a conservative assessment of exposures achievable under conditions of maximum bioavailability.

In the PBPK model, orteronel apparent oral CL in humans (CL/bioavailability(F) of 16.9 L/h with percent coefficient of variation of 15.7%) derived from the food-effect study (unpublished data; Suri, A., Pham, T., & MacLean, D.B., *Clin. Pharmacol. Drug Development* 2015) was divided into three pathways (renal CL, hepatic CL, or other CL) based on the results of the aforementioned ^{14}C-orteronel human mass balance and urine metabolite profiling study (unpublished data; Suri, A., Pusalkar, S., Li, Y., & Prakash, S. *Clin. Pharmacol. Drug Development* 2015). The results from this previous study showed that 53% of orteronel CL (intact parent compound in urine) was characterized as renal CL, 19% of the CL (metabolites formed via hydrolysis) was characterized as other CL (neither renal nor hepatic CL pathways), and 28% of the CL was uncharacterized. For the present assessment, uncharacterized CL (metabolism via glucuronidation and dehydration) was assigned as hepatic CL.

Three Simcyp populations (N = 100 men, aged 50–65 years, for each population) were evaluated based on available clinical PK data for: (1) healthy subjects with normal renal function in the fed state (condition of maximum oral absorption for orteronel); (2) subjects with moderate RI, defined as a GFR of 30–60 mL/min; and (3) subjects with severe RI, GFR <30 mL/min (observed GFR, 16–30 mL/min). For the purpose of PBPK simulations, orteronel was dosed BID for 10 days at 400 mg BID (in all three Simcyp populations), and 220 mg BID or 200 mg BID (in severe RI). Inputs that were used to build the orteronel compound profile in the Simcyp population-based simulator are described in the **Supplementary Appendix** online.

Orteronel population pharmacokinetic modeling

The effects of RI on orteronel PK were investigated in patients with mCRPC using a classical population PK modeling approach to determine the need for dose adjustments. For this analysis, PK data from two phase 3 trials in mCRPC (C21004 and C21005) were included in the final model. The analysis was performed using nonlinear mixed-effects modeling, with NONMEM (version VI) and S-PLUS (version 8.2) used for postprocessing and graphical evaluation of output. The first-order conditional estimation method in NONMEM was utilized.

A base structural model was developed followed by a random effects model. Next, a full model was developed with the addition of prespecified covariates (body weight, BMI, body surface area, age, race, region, CL_{cr}, and liver function; see **Supplementary Table S1** online). The full model underwent a covariate selection procedure (stepwise backward elimination and forward selection; P = 0.001) to generate a final parsimonious model. Standard goodness-of-fit plots were used to assess lack of fit noted with the initial model and guide further development for the base model. Model stability was assessed throughout the model development process. To avoid ill-conditioning or instability, inspection of the

correlation matrix of the estimates was performed to check for extreme pairwise correlations ($P > 0.95$) between parameter estimates. Additionally, the condition number (i.e., the ratio of the largest to smallest eigenvalues) of the correlation matrix of the parameter estimates, derived from the Hessian, should have been <1,000.

Up to four sparse PK samples were collected from each patient in studies C21004 and C21005. Only PK samples from orteronel-treated patients were analyzed.

Simulations were conducted for patients with normal renal function (CL_{cr} ≥90 mL/min), and for those with mild (CL_{cr} 60–89 mL/min) or moderate (CL_{cr} 30–59 mL/min) RI, who received orteronel at a dose of 400 mg BID for one week. One hundred CL_{cr} samples were generated for each group of 100 resampled patients using a uniform distribution; all other covariates remained the same. A total of 100 replicates (N = 10,000/group) underwent simulation using the final model. To determine a dosage for patients with RI that would produce orteronel exposures comparable to normal subjects given 400 mg BID, simulations were conducted at orteronel dosages of 200 or 300 mg BID, or 400 mg in the morning and 200 mg in the evening, for one week. These simulations were repeated for patients with severe RI (CL_{cr} 15–29 mL/min).

Clinical study of orteronel pharmacokinetics in subjects with varying degrees of renal impairment

The impact of RI on the PK parameters of orteronel in plasma and urine was evaluated in an open-label, single-dose, parallel-group phase 1 study (C21010). Otherwise healthy subjects, aged 18–80 years with a BMI of 18–35 kg/m^2 and adequate liver function (full eligibility criteria are in the **Supplementary Appendix** online), were enrolled into four groups (n = 8 per group) according to their RI status (CL_{cr} using the Cockcroft-Gault formula[19]): normal renal function (CL_{cr} ≥90 mL/min), and mild (CL_{cr} ≥60–89 mL/min), moderate (CL_{cr} ≥30–59 mL/min), and severe (CL_{cr} ≥15–29 mL/min, not requiring dialysis) chronic RI. For safety reasons, subjects with moderate or severe RI were only enrolled after all subjects with mild RI had completed day seven, and after reviewing adverse events. Healthy controls were enrolled last to ensure adequate matching of age and BMI to all RI groups.

On day 1, all subjects received a single oral 200-mg dose of orteronel after a 10-hour fast. Subjects remained fasted for four hours postdose Prior and concomitant therapies that could interfere with PK measurements were prohibited (**Supplementary Appendix** online).

Timed, serial blood samples were collected over 144 hours postdose for the determination of plasma orteronel concentrations. Urine was also collected over 72 hours postdose for PK assessment of orteronel in urine. Safety assessments were also undertaken.

Quantification of orteronel was performed using a validated ultra-high performance liquid chromatography with tandem mass spectrometry assay at PPD Bioanalytical Laboratories (Richmond, VA; **Supplementary Appendix** online). Plasma protein binding was performed using a rapid equilibrium dialysis method and unbound as well as total plasma concentrations were measured using validated bioanalytical methods at PPD Bioanalytical Laboratories.

PK parameters were estimated using noncompartmental methods (Phoenix WinNonlin version 6.1). Regression analysis evaluated relationships between baseline renal function (CLcr) and CL/F. To assess the effect of RI on AUC_{inf}, AUC_{last}, and maximum plasma concentration of orteronel, an analysis of variance on the natural log-transformed PK parameters was performed with renal function group (i.e., mildly, moderately, or severely impaired, or normal) as a fixed effect.

The study was conducted in accordance with the Declaration of Helsinki and in compliance with the Good Clinical Practice and International Conference on Harmonization guidelines. Protocols and informed consents were approved by the institutional review board at each investigational center. All subjects provided written informed consent before study initiation.

Additional details on model development, processing methods, and PK methodology are included in the **Supplementary Appendix** online.

Additional Supporting Information may be found in the online version of this article.

ACKNOWLEDGMENTS

The authors would like to acknowledge all the subjects who participated in these studies and their families, as well as all the investigators and site staff who made these studies possible. All clinical data were generated in studies sponsored by Millennium Pharmaceuticals, Inc., a wholly owned subsidiary of Takeda Pharmaceutical Company Limited. Writing assistance for this manuscript was provided by Dawn L. Lee, a medical writer with FireKite (an Ashfield Company, part of UDG Healthcare PLC) and was funded by Millennium Pharmaceuticals, Inc. All editorial procedures complied with Good Publication Practice 2 guidelines (Graf C, et al. *BMJ* 2009;339:b4330).

AUTHOR CONTRIBUTIONS

A.S., S.C., C.L., and K.V. wrote the manuscript; A.S. designed the research; A.S., S.C., and C.L. performed the research; and A.S., S.C., C.L., and K.V. analyzed the data.

CONFLICTS OF INTEREST

C.L., A.S., and K.V. are employees of Millennium Pharmaceuticals, Inc., a wholly owned subsidiary of Takeda Pharmaceutical Company Limited. C.L. and A.S. own stock of Millennium Pharmaceuticals, Inc., a wholly owned subsidiary of Takeda Pharmaceutical Company Limited. S.C. has been a consultant or held an advisory role for Millennium Pharmaceuticals, Inc., a wholly owned subsidiary of Takeda Pharmaceutical Company Limited.

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