Application of a Physiologically Based Pharmacokinetic Model to Predict OATP1B1-Related Variability in Pharmacodynamics of Rosuvastatin

RH Rose¹, S Neuhoff¹, K Abduljalil¹, M Chetty¹, A Rostami-Hodjegan¹,² and M Jamei¹

Physiologically based pharmacokinetic (PBPK) models are increasingly being used to predict the impact of physiological and pathophysiological patient factors and concomitant medication on drug exposure to support drug development and regulatory submissions.¹,² Typically, the end point of a PBPK model is a prediction of the pharmacokinetics of a drug, while the ultimate success of a drug is dependent on demonstration of efficacy without toxicity. Because PBPK models can predict drug concentration in tissues and in plasma, a natural progression is to link them to pharmacodynamic (PD) models via the concentration at the site of action.³,⁴ Compared with the traditional approach of pharmacokinetic/pharmacodynamic (PK/PD) modeling that uses plasma concentration to drive the response, this may allow a better understanding of true PD variability vs. variability that results from drug disposition to the site of action.⁴ This is particularly pertinent where transporters are involved in drug disposition to its effect site. In this case, interindividual variability in transporter activity can result in a lack of correlation between plasma concentration and concentration at the site of action between individuals.⁵

Rosuvastatin is a 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor, thus reduces the conversion of acetyl-CoA to mevalonic acid (MVA), which is the rate-limiting step in hepatic cholesterol biosynthesis.⁶ Rosuvastatin has low passive permeability across biological membranes that limits distribution to tissues and oral absorption.⁷ However, rosuvastatin is extensively distributed into the liver, its major site of action, through the action of specific uptake transporters, including the organic anion-transporting polypeptides OATP1B1, OATP1B3, and OATP2B1 and the sodium-dependent taurocholate cotransporting polypeptide.⁸,⁹ Both liver canalicular and intestinal efflux of rosuvastatin are mediated by the breast cancer resistance protein.¹⁰ Multidrug resistance–associated protein-2 also contributes to the liver canalicular efflux of rosuvastatin but plays a more significant role in rats than in humans.¹¹,¹² The liver is a site of elimination of rosuvastatin, predominantly through biliary elimination and to a lesser extent metabolic elimination (~10%).¹³

Genetic variants of OATP1B1 and breast cancer resistance protein have been identified that contribute to interindividual variability in rosuvastatin disposition, exposure, and therapeutic or side effects.¹⁴,¹⁵ In this study, we focus on the OATP1B1 c.521T>C single-nucleotide polymorphism (SNP). This SNP has been associated with increased exposure to rosuvastatin because of reduced clearance¹⁶,¹⁷ and a significant increase in the risk of myopathy for the statins simvastatin and atorvastatin, although a statistically significant increase in risk has not been found for rosuvastatin.¹⁸–²⁰

A PK/PD model describing the effect of rosuvastatin on plasma MVA concentration has been published that uses an indirect response model with a circadian rhythm on the input rate.²¹ This model is typical of PK/PD models in that it uses the total plasma concentration to drive the PD model. However, the concentration of rosuvastatin at the site of action, i.e., the hepatic unbound intracellular water concentration (Cu₁), is a more relevant driving concentration for the PD model. This is supported by a recent publication that showed an improved correlation in the cholesterol-lowering effect between humans and a mouse model when hepatic extraction was accounted for.²² PBPK models have previously been described for rosuvastatin that account for transporter-mediated disposition and allow prediction of hepatic Cu₁.¹¹,²³,²⁴

The aim of this study was to demonstrate the added utility of linking the PBPK model-predicted concentration at the site of action to the PD response compared with the plasma concentration, using rosuvastatin as an example. PBPK and PD models were integrated, creating a PBPK/PD model that...
links the unbound hepatocellular concentration, predicted by a permeability-limited liver model within a full PBPK model, to the rate of cholesterol synthesis over time (Figure 1). The developed model was then used to predict the impact of OATP1B1 c.521TT, TC, and CC genotypes on the PK and PD of rosuvastatin, and to compare the predictions with those when plasma concentration was used to drive the PD response and with clinical data. Simulations also investigated the impact of reduced hepatic uptake transporter function on plasma, liver, and muscle concentration, which relates to the myopathy side effect of statins, in addition to the rate of cholesterol synthesis.

RESULTS

The OATP1B1 hepatic uptake clearance (CL_{int,T}) for the OATP1B1 c.521TT, TC, and CC genotypes was fit using published plasma concentration–time data for subjects stratified by this genotype to obtain values of 126, 30, and 0 μl/min/10^6 cells, respectively. Parameter estimates were able to satisfactorily recover the clinical plasma concentration profiles for subjects grouped by genotype (Figure 2).

For all three genotype groups, the mean observed maximum concentration (C_{max}) and area under the plasma concentration–time curve (AUC_{0–48h}) were within the range of those for the 10 simulated profiles matched in terms of subject age, proportion of females, and study size for each genotype (Supplementary Table S1). However, in all cases, the simulated time after administration to maximum plasma concentration (T_{max}) underestimated the observed data (Supplementary Table S1). The simulations predict that the mean AUC_{0–∞} and C_{max} were increased by 86 and 90% for the c.521CC genotype and 62 and 60% for the c.521TC genotype, relative to the c.521TT genotype. The clinically observed increases in AUC_{0–∞} and C_{max} were reported as 62 and 79%, respectively, for the c.521CC genotype group and 57 and 52%, respectively, for the c.521TC genotype group.17

The estimated IC_{50} and Hill coefficient for the drug effect based on rosuvastatin liver Cu_{IW} were 0.13 μmol/l and 1.3, respectively. The final model incorporating fitted the parameters allowed adequate recovery of PK and PD profiles (Figure 3). The simulated reduction in MVA AUC relative to...
Simulations were performed to predict the effect of the OATP1B1 c.521T>C sequence variation on the PD response using the established PBPK/PD model (Figure 4). Analysis of the simulated data showed that the mean rosuvastatin plasma AUC$_{0-\infty}$ was increased by 63 and 111% for the heterozygote and CC-homozygote genotypes relative to the wild type (Table 1). The liver CuIW AUC$_{0-\infty}$ was reduced by 5.7 and 9.6%, respectively (Table 1). The average MVA AUC relative to baseline corresponding to these sequence variations was increased by 30 and 35% when plasma concentration was used as the input to the PD response model, as in the original model²¹ (Table 1). However, when liver CuIW was used as the input to the PD response in our modified model, the simulated average MVA AUC relative to baseline was reduced by 3.1 and 5.8%, respectively (Table 1). The latter model is more consistent with clinical data and with mechanistic understanding of statin action (see Discussion), so this was used in further analysis.

There was a large interindividual variability in both the plasma AUC$_{0-\infty}$ of rosuvastatin and the reduction in MVA AUC from baseline (Figure 5), resulting in overlap between the interquartile ranges for the three OATP1B1 genotype groups. This overlap is most pronounced for the PD response, in which median values for each group are within the interquartile range for all groups. Further analysis of the impact of the total hepatic uptake transporter CL$_{int,T}$ on the plasma, muscle, and liver CuIW rosuvastatin AUC$_{0-24}$ and MVA AUC relative to baseline predicted by the integrated PBPK/PD model was performed using sensitivity analysis for a range between 0 and 250 μl/min/10⁶ cells. Both plasma and muscle exposure to rosuvastatin decreased as the overall hepatic uptake CL$_{int,T}$ increased (Figure 6a, c). In contrast, both liver CuIW and PD response increased as the overall hepatic uptake CL$_{int,T}$ increased (Figure 6b, d). In all cases, sensitivity to the value of CL$_{int,T}$ is greatest when the value of CL$_{int,T}$ is low. The elasticity index (EI) (Figure 6e) is a measure of the relative change in selected variable to the relative change in the CL$_{int,T}$ normalizing the scale for comparison of the sensitivity of multiple model output parameters. The EI of the muscle rosuvastatin AUC to uptake transporter CL$_{int,T}$ is identical to the plasma AUC and has its greatest absolute value, indicating the greatest proportional change.
in AUC, when hepatic uptake transporter $CL_{int,T}$ is between 175 and 225 $\mu$l/min/10^6 cells. Changes are in the opposite direction for liver CuIW and PD response (positive rather than negative), with greatest elasticity at overall hepatic $CL_{int,T}$ of 25 $\mu$l/min/10^6 cells. The PD response shows a lower elasticity to changes in $CL_{int,T}$ than the liver CuIW.

**DISCUSSION**

This study aimed to demonstrate the added utility of linking the PBPK model-predicted concentration at the site of action to the PD response compared with that of the use of plasma concentration. Rosuvastatin was selected as an example drug because there are clinical data demonstrating the contrasting effect of hepatic transporter activity, specifically for the OATP1B1 c.521T>C genotype, on the plasma concentration and PD response. In addition, both a PBPK model that includes hepatic transporter activity and a PD model for rosuvastatin have been published. Thus, using these models, a combined PBPK/PD model could be generated with changes to only three parameter values to account for genotype-specific OATP1B1 uptake activity and altered

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**Table 1** Mean simulated plasma and liver exposure and pharmacodynamic response to rosuvastatin for the three OATP1B1 genotypes investigated

| OATP1B1 genotype | Plasma $AUC_{0-\infty}$ (ng/ml-h) | Liver CuIW $AUC_{0-\infty}$ (ng/ml-h) | MVA 24h $AUC_{relative}$ relative to baseline (%) | MVA 24h $AUC_{relative}$ relative to baseline (%) |
|------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
| c.521TT          | 35                              | 120                             | 35                              | 36                              |
| c.521TC          | 57                              | 114                             | 46                              | 35                              |
| c.521CC          | 74                              | 109                             | 51                              | 34                              |

Mean simulated plasma area under the curve ($AUC_{0-\infty}$), liver unbound concentration in intracellular water (CuIW) $AUC_{0-\infty}$, and mevalonic acid (MVA) $AUC_{relative}$ relative to baseline of rosuvastatin for the three organic anion transporting polypeptide 1B1 (OATP1B1) genotypes investigated. MVA $AUC_{relative}$ was simulated by using either plasma concentration or liver CuIW as the input to the PD model. Data are the mean of 100 simulated individuals based on a population that was 50% female with an age range 20–50 years. Individuals were dosed with 10 mg oral rosuvastatin, either at single dose (plasma and liver CuIW $AUC_{0-\infty}$) or at 18:00 daily for 5 days (MVA $AUC_{relative}$, results for final dose).
sensitivity of the PD response to the different input concentration used. Compared with using plasma concentration as the driving concentration for the PD response, the model is better able to capture the clinical effect of the OATP1B1 c.521T>C SNP on the therapeutic effect of rosuvastatin.

The genotype-specific OATP1B1 CL\text{int,T} for rosuvastatin, considering only the c.521T>C SNP, was estimated using clinical data from Pasanen et al.\textsuperscript{17} The fitted values of 126, 30, and 0 μl/min/10^6 cells for the c.521TT, c.521TC, and c.521CC genotypes, respectively, are consistent with an average OATP1B1 CL\text{int,T} of 109 μl/min/10^6 cells determined for rosuvastatin for the north European Caucasian population,\textsuperscript{13} in which the c.521T allele predominates. Simulations using the parameter estimates for the different OATP1B1 genotype groups and a simulated study design matched to that reported by Pasanen et al.\textsuperscript{17} were able to recover the clinical data well (Figure 2). The simulated average increase in plasma AUC for the OATP1B1 c.521CC genotype relative to the TT genotype (111%) is also in close agreement with that reported in a separate clinical study for white subjects, in which a 117% increase was also in close agreement with that reported in a separate study.\textsuperscript{111%}

The simulation was able to recover the clinical data well (Figure 2). The estimated IC\textsubscript{50} for inhibition of 3-hydroxy-3-methylglutaryl coenzyme A reductase activity by rosuvastatin (0.13 μmol/l) is considerably higher than the reported IC\textsubscript{50} for the c.521CC genotype relative to the TT genotype (111%) is also in close agreement with that reported in a separate clinical study for white subjects, in which a 117% increase in activity was observed.\textsuperscript{25} However, estimation of complete loss of transport activity for the OATP1B1 c.521CC genotype, which tends to underestimate mean observed data with current settings (Figure 2).

Although the estimated CL\text{int,T} for the OATP1B1 c.521TC genotype group was able to recover clinical data from Pasanen et al.,\textsuperscript{17} a much smaller increase in plasma AUC of 6.3% for the c.521TC relative to the c.521TT genotype was reported in another clinical study of white subjects.\textsuperscript{25} Thus, this study was poorly predicted by our model and the impact of the c.521TC genotype on plasma concentration is controversial. A large interindividual variability in rosuvastatin exposure is predicted for the different genotype groups (Figure 5), indicating the influence of many covariates, most of which remain unknown in clinical studies. Discrepancies between the impact of OATP1B1 c.521T>C sequence variation between clinical studies and between clinical and in vitro data may reflect limitations of the fitting approach, which fixed parameter values for all but the fitted parameter and used average clinical data from a small study. The availability of more clinical plasma concentration data stratified by genotype or data that are required for in vitro–in vivo extrapolation (such as absolute transporter abundance and in vitro activity data with extrapolation factors) would help investigate kinetic phenomenology of more clinical plasma concentration data stratified by genotype or data that are required for in vitro–in vivo extrapolation (such as absolute transporter abundance and in vitro activity data with extrapolation factors) would help investigate kinetic phenomenology of more clinical plasma concentration data stratified by genotype or data that are required for in vitro–in vivo extrapolation.\textsuperscript{27}

The PD model was an adaptation of that reported by Aoyama et al.,\textsuperscript{21} which describes the change in plasma MVA concentration in healthy subjects receiving 10 mg oral rosuvastatin daily. The model was modified by refitting the drug effect parameters (the IC\textsubscript{50} and Hill coefficient) when the hepatic CoA reductase activity of a purified catalytic fragment (3.5–5.4 × 10^{-3} μmol/l) and in isolated rat hepatocytes (1.3×10^{-3} μmol/l)\textsuperscript{18,29} This suggests that the PD model may lack sufficient mechanistic detail to make in vitro–in vivo extrapolation of the IC\textsubscript{50} appropriate or that the in vitro methodology fails to reflect the in vivo situation.

The final PBPK/PD model maintained the ability to describe the plasma MVA profile adequately (Figure 3). The simulated reduction in MVA AUC relative to baseline of 34 and 27%, respectively, for the evening and morning dose of rosuvastatin is in reasonable agreement with the reduction of 40 and 32% simulated by Aoyama et al.\textsuperscript{21} using their PK/PD model with plasma concentration as the PD model input. The study used in fitting of the model\textsuperscript{1} is the only published clinical study that has reported the change in plasma MVA concentration after rosuvastatin administration. Consequently, the PD model has not been tested against other datasets, including those using a dose other than 10 mg rosuvastatin or in different ethnic or disease populations. Therefore, caution should be taken in generalizing the model to other populations or dosing regimens, particularly in terms of the precise quantitative description of the MVA profile. The model also assumes that there is no influence of OATP1B1 activity on the concentration of MVA at baseline. An increased baseline cholesterol synthesis rate has been reported for the OATP1B1 c.521CC genotype, although there was no effect on the total plasma cholesterol.\textsuperscript{30} Mechanistically, the increased cholesterol synthesis rate may be related to reduced OATP-mediated hepatic bile acid uptake, leading to reduced hepatic bile acid concentration and removal of the inhibitory effect of hepatic bile acid on cholesterol catabolism.\textsuperscript{30}
allele. Large interindividual variability in the PD response is fractional low-density lipoprotein cholesterol reduction per c.521T>C SNP was associated with a 2.6% reduction in to receive rosuvastatin 20 ple, in a genome-wide study of over 3,000 patients allocated the cholesterol-lowering response to statins. For exam-

response associated with the OATP1B1 c.521T>C SNP for have shown either no effect or a slightly reduced therapeutic line (30% for c.521TC and 35% for c.521CC) was predicted in the present model.

AUC relative to baseline for individuals with the OATP1B1 genotype), and the biomarker for cholesterol synthesis was not the plasma MVA concentration, so this was not included in the present model.

When rosuvastatin liver CuIW was linked to the PD response, the PBPK/PD model predicted a small reduction in the MVA AUC relative to baseline for individuals with the OATP1B1 c.521T>C SNP (3.1% for c.521TC and 5.8% for c.521CC). In contrast, a larger increase in the MVA AUC relative to baseline (30% for c.521TC and 35% for c.521CC) was predicted if the PD response was linked to the plasma concentration. The former is in agreement with a number of studies that have shown either no effect or a slightly reduced therapeutic response associated with the OATP1B1 c.521T>C SNP for the cholesterol-lowering response to statins. For example, in a genome-wide study of over 3,000 patients allocated to receive rosuvastatin 20mg daily for a year, the OATP1B1 c.521T>C SNP was associated with a 2.6% reduction in fractional low-density lipoprotein cholesterol reduction per allele. Large interindividual variability in the PD response is predicted by the PBPK/PD model with considerable overlap in the distributions (Figure 5), suggesting that a large study size is required to detect the small effect of the OATP1B1 genotype on the PD response to rosuvastatin. A limitation of this study is that interindividual variability was not included for the parameters describing the PD response because the published PD model adapted for this study was estimated from average profiles. As a result, variability is only introduced by the PBPK model parameters, and PD variability is likely to be underestimated, possibly to a large extent because PD variability can be much greater than PK variability.

Taken together, the results indicate that reduced OATP1B1 activity results in a relatively large increase in plasma rosuvastatin concentration and a small decrease in PD response. These results are in agreement with the predictions of Wata-

nabe et al. for the effect of uptake transporter activity on plasma and liver concentration of pravastatin. Reduced uptake activity may be expected to decrease liver CuIW but this effect is countered by increased plasma concentration of rosuvastatin because reduced liver exposure leads to reduced hepatic drug elimination. The higher plasma concentration results in increased liver unbound concentration in extracellular water (CuEW), which drives both passive and active uptake into the liver. Because the PD response is driven by the liver CuIW both show a similar sensitivity to uptake transporter activity, but the relative sensitivity of the PD response is slightly lower because of the nonlinearity in the PD model (Figure 6e). A limitation of the study by Wata-

nabe et al. is that predictions were based on sensitivity analysis to probe model behavior that was not confirmed by clinical or preclinical data. Our study provides verification that the modeling approach is able to recover clinical data for the impact of hepatic uptake transporter activity on the pharma-

cokinetics (plasma concentration) and pharmacodynamics of rosuvastatin for specific OATP1B1 genotypes.

The EI, a normalized measure of sensitivity, for the effect of uptake transporter activity on muscle AUC exactly matched with that of the plasma AUC (Figure 6e). This is expected because prediction of muscle concentration was based on the perfusion-limited model, thus assuming uptake by rapid, passive diffusion into the tissue. The results are in agreement
with the association that has been observed between the plasma concentration of statins and the risk of muscle-related side effects, such as myopathy and rhabdomyolysis. Thus, in contrast to the results for the cholesterol-lowering effect of rosuvastatin, this supports the use of plasma concentration as a surrogate for the concentration at the site of action (muscle) in assessing risk of statin-induced muscle toxicity in individuals with different hepatic uptake transporter activity. One study has suggested a role for transporter-mediated uptake, by OATP2B1, and efflux in skeletal muscle exposure to rosuvastatin. However, at present, the importance of transporter-mediated uptake of rosuvastatin into muscle remains unclear. Expression of mRNA for OATP2B1 was considerably lower in skeletal muscle than in the liver, and insufficient data are available to model the impact of specific transporters on rosuvastatin uptake into muscle.

The potential power of linking PBPK to PD models has previously been recognized; however, there are few published examples that demonstrate successful application of this approach and the added value it can offer. To our knowledge, this is the first published study to use the liver concentration from a full PBPK model to drive the PD response and demonstrate improved ability to assess the impact of transporters involved in the uptake to the site of action compared with using plasma concentration to drive the PD model. This study also adds to existing knowledge by providing a specific application example validated against clinical data that confirms predictions of the discordant effect of transporter activity on the concentration of the statins in plasma and liver. It is anticipated that the approach used is applicable to other drugs with intracellular sites of action that rely on transporter-mediated processes for distribution to the site of action. It would be useful in the prediction of the impact of transporter-mediated drug–drug interactions on PD response in addition to the effect of genetic variations in transporter activity.

**METHODS**

**Development of a PBPK/PD model describing the effect of rosuvastatin on cholesterol synthesis rate**

A PBPK/PD model of rosuvastatin in the north European Caucasian healthy volunteer population was constructed in the Simcyp Simulator (version 12 Release 2) as outlined in Figure 1. Detail of the PBPK model inputs for rosuvastatin has been described previously, and further details of the calculation of the unbound concentration of a monoprotic acid in the liver extracellular and intracellular water are given in the Supplementary Methods. Briefly, the disposition of rosuvastatin was described using a whole-body PBPK model with tissue partition coefficients predicted by the method of Rodgers and Rowland, assuming perfusion-limited distribution for tissues other than the liver and gut. Distribution of rosuvastatin to the liver was described by a permeability-limited liver model that included the transporter-mediated intrinsic clearance (CL_{int,T}) for the sinusoidal uptake transporters OATP1B1, OATP1B3, OATP2B1, and sodium-dependent taurocholate cotransporting polypeptide and the canalicular efflux transporter breast cancer resistance protein. The model assumes that there is no transporter-mediated basolateral efflux from the liver, although recent work has indicated a role of basolateral efflux transporters hepatic efflux. Absorption of oral rosuvastatin was modeled using the Advanced Dissolution, Absorption and Metabolism (ADAM) model and included active efflux by breast cancer resistance protein.

Parameters describing rosuvastatin absorption, distribution, metabolism, and elimination were not changed from the previously published values, with the exception of the OATP1B1 hepatic sinusoidal uptake transporter intrinsic clearance for the three OATP1B1 c.521T>C genotypes. Using published clinically observed concentration–time data, the Simcyp Parameter Estimation module was used with the Nelder Mead optimization algorithm to obtain the uptake clearance of rosuvastatin into the liver for OATP1B1 genotypes with c.521TT, TC, and CC sequence variations. To reduce the likelihood of overestimating interindividual variability in liver disposition within the different OATP1B1 genotype groups, the variability in OATP1B1 relative activity in the liver was adjusted to maintain the same overall coefficient of variation (CV) for the OATP1B1 uptake CL_{int,T} in the northern European Caucasian population as when genotype was not considered (CV 69%). Equal variability in OATP1B1 activity was assumed for each genotype, and an adjusted CV of 44% was calculated using Eqs. 1 and 2.

\[
\sigma_w = \sqrt{\frac{\sum_{i=1}^{3} \left( N \sigma_i^2 + n_i \bar{x}_i^2 \right) - N \bar{x}_w^2}{N}}
\]

\[
CV(\%) = 100 \times \frac{\sigma}{\bar{x}}
\]

where \( \sigma_w \) is the overall weighted standard deviation for all groups, \( n_i \) is the fractional frequency of genotype \( i \) in the population, \( \sigma_i \) is the standard deviation of genotype group \( i \), \( \bar{x}_i \) is the mean value of genotype group \( i \), \( N \) is the total frequency of all genotypes in a population (\( N = 1 \)), and \( \bar{x}_w \) is the weighted mean for the population. The frequency of each genotype was calculated based on a weighted mean for the frequency of the c.521T>C SNP of 17% in the northern European Caucasian population and assuming Hardy–Weinberg equilibrium.

The structural model for the effect of rosuvastatin on cholesterol synthesis was coded using the custom PD scripting facility within the simulator (see Supplementary Data) and was based on the report by Aoyama et al. Equations describing the MVA concentration in plasma were used as reported in this publication, with the exception of the concentration input to the PD model (see Supplementary Methods). The parameters for baseline MVA concentration in plasma were kept as in the original publication. However, the drug effect (inhibition of MVA synthesis) in our model was driven by the unbound intracellular water concentration (\( C_{UM} \)) in liver, as opposed to plasma in the original model. Therefore, associated values (\( IC_{50} \) and the Hill coefficient for the inhibitory sigmoid \( E_{max} \) function) were obtained by refitting the data using the Simcyp Parameter Estimation module with the Nelder–Mead optimization algorithm and clinical data for the change in MVA concentration for morning and evening dosing of rosuvastatin in dominantly wild-type OATP1B1.
Simulations

All simulations used the Simcyp north European Cauca-
sian healthy volunteer population, and 10 trials were simu-
lated. Where simulations aimed to replicate clinical studies, the
trial design was matched as closely as possible to the
study population in terms of dosing regimen, trial size, subject
age range, and the proportion of females, as summarized in
Supplementary Table S2. For predictive simulations, all sim-
ulations used a 10 mg oral dose of rosuvastatin dosed daily
for 5 days and a trial size of 10 subjects with an age range of
20–50 years and the proportion of females as 50%. A 10 mg
dose was selected because this was used by both the PK
and PD study used in model development.7,17 The simulated
plasma concentration and PD response reached steady state
prior to the fifth dose of rosuvastatin (data not shown), thus
the results for the final dose reflect predictions at steady state.

The overall PD effect was summarized by calculating the
% reduction in 24-h MVA AUC from baseline at steady state
using the trapezium rule and as described previously.21

Sensitivity analysis for the impact of total uptake
transporter CL_{int,T} on rosuvastatin disposition and PD
response

The automated sensitivity analysis option within the Simcyp
Simulator was used to investigate the effect of total uptake
transporter CL_{int,T} on the plasma, liver, and muscle exposure
to rosuvastatin and the change in PD response. The specific
output variables investigated were plasma, liver C_{u,W} and
muscle AUC_{0–24 h} and % reduction in MVA AUC from baseline.

Sensitivity analysis was selected to investigate overall CL_{int,T}
over the range of normal transporter activity for rosuvastatin
uptake (250 μl/min/10^6 cells; approximately the sum of uptake
over the range of normal transporter activity for rosuvastatin
uptake (250 μl/min/10^6 cells)).13

The EI is a dimensionless expression of sensitivity that
measures the relative change in an output variable Q (e.g.,
AUC) for a relative change in the input parameter P (in this
case, CL_{int,T}).46 EI was calculated as follows for each input
parameter value n:

$$EI_n = \left( \frac{P_n}{Q(P_n)} \right) SI$$

where Q(P_n) is the value of Q when P = P_n and SI is a mea-
sure of the change in the output variable Q per unit change
in the input parameter value P_{n-1} from its initial value P_n,
calculated using Eq. 4.

$$SI_n = \frac{Q(P_n) - Q(P_{n-1})}{P_{n-1} - P_n}$$

For the highest input parameter value, N, SI is approximated
as follows:

$$SI_N = 2SI_{N-1} - SI_{N-2}$$

Acknowledgments. This work was funded by Simcyp Limited
(a Certara Company). The Simcyp Simulator is freely avail-
able, after completion of the training workshop, to approved
members of academic institutions and other non-for-profit
organizations for research and teaching purposes. The
authors thank Eleanor Savill for help in preparing the manu-
script and Theresa Cain for advice on statistical analysis.

Conflict of Interest. R.H.R., S.N., K.A., M.C., and M.J. are
employees of Simcyp Limited (a Certara company). A.R.-H.
is an employee of the University of Manchester and part-time
secondee to Simcyp Limited (a Certara Company).

Author Contributions. R.H.R., S.N., and M.J. designed
the research. R.H.R. performed the research and analyzed
the data. R.H.R., S.N., K.A., M.C., A.R.-H., and M.J. wrote
the manuscript.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

✓ Disposition of rosuvastatin to its target organ, the
liver, involves the action of several uptake trans-
porters, including the polymorphic transporter
OATP1B1. Reduced hepatic uptake of statins
has been shown to increase plasma concentra-
tion but has little effect on liver concentration.

WHAT QUESTION DID THIS STUDY ADDRESS?

✓ The question addressed was whether using a
PBPK model predicted unbound liver concen-
tration as opposed to the plasma concentration
to drive the PD model would improve predictions
of the effect of genetic variation of OATP1B1
activity on the therapeutic response.

WHAT THIS STUDY ADDS TO OUR KNOWLEDGE

✓ This study demonstrates a method that allowed
improved ability to predict the impact of the
activity of transporters involved in uptake to the
site of action on the PD effect.

HOW THIS MIGHT CHANGE CLINICAL
PHARMACOLOGY AND THERAPEUTICS

✓ The approach used is applicable to other drugs
that rely on transporter-mediated processes for
distribution to an intracellular site of action and
offers a means to better differentiate variability
resulting from drug disposition from true PD
variability.

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