Population Modeling Integrating Pharmacokinetics, Pharmacodynamics, Pharmacogenetics, and Clinical Outcome in Patients With Sunitinib-Treated Cancer

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The tyrosine kinase inhibitor sunitinib is used as first-line therapy in patients with metastasized renal cell carcinoma (mRCC), given in fixed-dose regimens despite its high variability in pharmacokinetics (PKs). Interindividual variability of drug exposure may be responsible for differences in response. Therefore, dosing strategies based on pharmacokinetic/pharmacodynamic (PK/PD) models may be useful to optimize treatment. Plasma concentrations of sunitinib, its active metabolite SU12662, and the soluble vascular endothelial growth factor receptors sVEGFR-2 and sVEGFR-3, were measured in 26 patients with mRCC within the EuroTARGET project and 21 patients with metastasized colorectal cancer (mCRC) from the C-II-005 study. Based on these observations, PK/PD models with potential influence of genetic predictors were developed and linked to time-to-event (TTE) models. Baseline sVEGFR-2 levels were associated with clinical outcome in patients with mRCC, whereas active drug PKs seemed to be more predictive in patients with mCRC. The models provide the basis of PK/PD-guided strategies for the individualization of anti-angiogenic therapies.


Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?
- There is a high interindividual variability (IIV) in response to sunitinib. Hence, predictive biomarkers are needed in order to maximize efficacy and minimize toxicity.
- The objective of this study was the development of PK models, linking sunitinib plasma concentrations to PD response and clinical outcome, including the identification of potential genetic predictors for patients with mRCC and patients with mCRC.

WHAT THIS STUDY ADDS TO OUR KNOWLEDGE
- The developed PK/PD models adequately describe plasma concentration-time profiles of sunitinib, SU12662, sVEGFR-2, sVEGFR-3, and clinical outcome showing the strength of an integrated modeling approach. Clinical response in patients with mRCC is best predicted by baseline sVEGFR-2 levels, whereas in patients with mCRC, active drug PKs is more predictive.

HOW MIGHT THIS CHANGE DRUG DISCOVERY, DEVELOPMENT, AND/OR THERAPEUTICS?
- The PK/PD models presented in this study provide a better understanding of the relationship between sunitinib exposure, pharmacological response, and clinical outcome, and, hence, are an important step toward finding predictive biomarkers for the clinical outcome of sunitinib.

Sunitinib is a multitarget tyrosine kinase inhibitor, which is successfully used in the treatment of metastasized renal cell carcinomas (mRCCs), gastrointestinal stromal tumors (GISTs), and other solid tumor types. Sunitinib inhibits the vascular endothelial growth factor receptors (VEGFR-1, 2, and 3), the platelet-derived growth factor receptors α and β, among other tyrosine kinases.1,2 CYP3A4 converts sunitinib into its active N-desethyl metabolite (SU12662) and subsequently into inactive metabolites. The elimination half-life of sunitinib is 40–60 hours and 80–110 hours for SU12662. An increased exposure to sunitinib is associated with improved survival but also with an increased risk for adverse events.3,4 The individual response to sunitinib is highly variable: some patients experience severe toxicity and need dose reductions or even cessation of therapy, whereas others show no response at all when using the same dose. Biomarker testing prior to the start or during therapy may help provide the...
individual patient with the most effective treatment and the lowest possible risk of adverse effects. Whereas several potential biomarkers have been identified, they are not applied in clinical routine yet. However, sunitinib meets the requirements for therapeutic drug monitoring enabling dose adjustment based on measured plasma drug concentrations.\textsuperscript{8,9–22}

Soluble VEGFR-3 (sVEGFR-3) was observed to be a potential predictive biomarker for overall survival (OS) on sunitinib treatment in a study of 303 patients diagnosed with GIST.\textsuperscript{6} Furthermore, vascular endothelial growth factor (VEGF)-A and VEGFR-3 protein expression were associated with OS and progression-free survival (PFS), respectively, in 67 sunitinib-treated patients with mRCC.\textsuperscript{7} Likewise, levels of VEGF, sVEGFR-2, and sVEGFR-3 were associated with objective responses in 63 patients with mRCC.\textsuperscript{8}

With regard to genetic predictors, previous studies associated single nucleotide polymorphisms (SNPs) in genes encoding metabolizing enzymes or transporters related to pharmacokinetics (PKs) and pharmacodynamics (PDs) of sunitinib with efficacy and toxicity.\textsuperscript{8–22}

In order to find predictive biomarkers for the clinical outcome of sunitinib, a better understanding of the relationships between sunitinib exposure, the pharmacological response, and the clinical outcomes is vital. This is part of the objectives of the European collaborative project EuroTARGET.\textsuperscript{23} Several PK models for sunitinib have previously been published. Here, we used a nonlinear mixed-effects PK model for analyzing data of both patients with mRCC and patients with metastasized colorectal cancer (mCRC) in a pooled dataset.\textsuperscript{23–26} This model was linked to PD models for sVEGFR-2 and sVEGFR-3, which were previously developed by our group.\textsuperscript{27} The purpose of our study was the development of PK models, linking sunitinib plasma concentrations to PD response, and clinical outcome in a model-based time-to-event (TTE) analysis, including the identification of potential genetic predictors.

METHODS

Patient population

For the underlying PK/PD analysis, data were used from two PK studies, which focused on sunitinib treatment in patients with mRCC and patients with mCRC.\textsuperscript{23,25} Both studies were designed as prospective, open label, single arm, multicenter, nonrandomized studies and performed in accordance with the Declaration of Helsinki. Patients gave written informed consent to give venous blood for PK/PD analysis. Blood was drawn, immediately centrifuged (1000 g, 4 °C, 15 minutes) and stored at −80 °C. In the C-IV-001 study, up to 12 plasma samples were collected within 3 cycles during routine checkups. Except for a mandatory baseline sample before treatment start, each center was free to develop a schedule according to their specific clinical routine. In the C-II-005 study, plasma samples were collected within 2 cycles at baseline, day 2 of each cycle, and afterward approximately every 2 weeks, always before sunitinib intake.

Plasma concentrations of sunitinib and SU12662 were determined using high-performance liquid chromatography tandem mass spectrometry (MD SciEX API 5000 triple quadrupole mass spectrometer; Applied Biosystems/MD SciEX, Thornhill, Ontario, Canada). Between-run precision and accuracy ranged from 1.6–6.1% and 0.2–9.1% for sunitinib and from 1.1–5.3% and −0.1 to 6.2% for SU12662, respectively.\textsuperscript{26} The sVEGFR-2 concentrations were determined by commercially available enzyme-linked immunosorbent assay kits (R&D Systems, Minneapolis, MN). The sVEGFR-3 was measured using a validated immunoassay.\textsuperscript{26} Within-laboratory precision and accuracy of all assays were within the acceptance criteria of the European Medicines Agency\textsuperscript{29} with 2.2–4.3% and 6.2–14.3% for sVEGFR-2, and 0.4–14.7% and −3.8 to +16.2% for sVEGFR-3, respectively. Quality control samples were analyzed in all assays and runs to determine run acceptance.

SNP selection and genotyping

The selection of SNPs was based on previously reported SNP associations (\(P < 0.05\)) with sunitinib treatment outcome with regard to efficacy and toxicity. Herein, we have focused on SNPs that were very likely to have an effect on VEGF or VEGFRs, or SNPs that have a high biomarker potential because of confirmatory findings in large cohorts. Thirteen SNPs were selected located in CYP3A5, ABCB1, VEGF-A, VEGF-2, VEGF-3, and interleukin-8 (details are provided in Supplementary Material S1).

Germline DNA was isolated from whole blood samples taken at baseline (before treatment initiation), using the Chemagic blood kit (PerkinElmer), and genotyping was performed using the LightCycler 480 Real-Time polymerase chain reaction Instrument (Roche Applied Science, Almere, The Netherlands)
Pharmacokinetic/pharmacodynamic modeling

Data from all patients were analyzed together using the first-order conditional estimation method with interaction implemented in NONMEM, version 7.3.30 The PK/PD models were built in a sequential manner. The structure of the models is shown in Figure 1.

Pharmacokinetic model

The PK model was partially based on a semiphysiological model published by Yu et al.24 This model features a one-compartment model for sunitinib and a biphasic distribution for SU12662. Presystemic formation of SU12662 is handled via a hypothetical enzyme compartment incorporated into the central compartment of sunitinib. The central compartment and the enzyme compartment are connected by an intercompartmental clearance, which was fixed to the liver blood flow. The addition of a peripheral compartment for sunitinib was tested because other published models featured this structure and the underlying data indicated a similar distribution as the active metabolite.3,4,27 Interindividual variability (IIV) was initially included for all model parameters and removed in case the model did not significantly worsen after exclusion.

Sensitivity analysis

The effect of fixed parameters on the model predictions was tested by varying the respective parameters between +50 and −50% in 10% steps of the base value derived from literature. As time of drug intake or sampling time was corrected VPCs, were performed using the PsN software.33 Both procedures, bootstrap and prediction-corrected VPCs, were performed using the PsN software.33
missing in some patients, administration time was set to 
8:00 AM, assuming that an intake in the morning is the most 
likely scenario. A similar approach was used for missing 
sampling times. Here, 12:00 PM was chosen, because most 
likely scenario. A similar approach was used for missing

distributions were tested using NONMEM. 35 Although a 
constant hazard is usually a viable assumption in patients

where 

\[ h(t) = \lambda_0 \cdot e^{\beta t} \] (5)

Time-dependent hazard (Gompertz) 

\[ h(t) = \lambda_0 \cdot e^{\beta t \cdot t} \] (6)

Time-dependent hazard (Weibull) 

\[ h(t) = \lambda_0 \cdot e^{\beta \ln(t)} \] (7)

Dichotomous covariates were divided by their characteristic 
values, whereas continuous covariates were grouped. Sta-
tistical significance of the difference between groups was 
determined using the log-rank test.

In addition, the Kaplan-Meier analysis as the classical 
nonparametric method was used to determine the median 
PFs in patients with mRCC and the TTP in patients with 
mCRC. 36,37 Kaplan-Meier analysis and Cox regression 
were performed using the survival package in R. 36

### Results

#### Patients

Clinical characteristics of the included patients are pre-

presented in Table 1. Twenty-seven patients with mRCC 
treated with sunitinib were recruited of which one patient 
was excluded from the analysis due to lack of PK data. 
Twenty-eight patients with mCRC were recruited of which 
seven patients were excluded because of missing drug 
administration \((n = 5)\), missing data \((n = 1)\), or uncertainty 
in the documentation of sunitinib intake \((n = 1)\). Thus, 26 
patients with mRCC and 21 patients with mCRC treated 
with sunitinib were included into the combined PK/PD 
analysis.

Outcome analysis was performed for each tumor entity 
separately with regard to the different end points of each 
study using data of 24 patients with mRCC and 21 patients 
with mCRC. Two of the 26 patients with mRCC were 
excluded from the outcome analysis as both received suni-
tinib as second-line therapy.

Moreover, 25 patients with mRCC and 14 patients with 
mCRC could be genotyped on the 13 selected SNPs. Here, 
we observed SNP call rates of 94–100% and 10 of 13 
SNPs were in the Hardy-Weinberg equilibrium with \(P\) 
values > 0.05. Only the SNPs \(ABCB1\) rs1045642, and \(VEGFA\) 
rs699947 and rs2010963 were not in the Hardy-Weinberg 
equilibrium with \(P = 0.009, P = 0.002,\) and \(P = 0.030,\) 
respectively.

#### Pharmacokinetic model

A PK model previously published by Yu et al. 24 was 
adapted as the basis for the structural model. To allow 
comparison of the estimated parameters, volume and clear-
ance parameters were, as in the reference model, allome-

| Table 1 Patient characteristics (median and range) |
|---------------------------------|---------------------------------|
| Patients with mRCC \((n = 26)\) | Patients with mCRC \((n = 21)\) |
| Age, years (range) | 64 (43–75) | 61 (33–85) |
| Gender, M/F | 25/1 | 12/9 |
| Weight, kg (range) | 83 (65–106) | 73 (57–106) |
| Height, cm (range) | 180 (155–186) | 172 (149–184) |
| BMI, kg/m² (range) | 25.7 (22.5–34.5) | 26.0 (13.3–39.3) |

BMI, body mass index; mCRC, metastasized colorectal cancer; mRCC, metastasized renal cell carcinoma.

Patient characteristics (median and range)
relative to the reported or imputed value had primarily an effect on the absorption rate constant (ka). The RSME was relatively high with 36.9% for this parameter. As expected, the residual error for sunitinib was also highly affected with an RSME of 25.2%

Forward inclusion and backward elimination of potential covariates did not reveal any significant effects on the tested model parameters. In addition, no statistically significant differences of PK parameters between both tumor entities were found, confirming that the underlying model can be used across different tumor types. A complete list of covariates tested is provided in Material S1. Final parameter estimates are shown in Table 2. VPCs indicated that central tendency and variability of both active compounds could be described adequately with the underlying model (Figures 2a and 2b).

Pharmacokinetic/pharmacodynamic models
The inverse-linear model previously developed for healthy volunteers was also applicable to describe the concentration-time profile of both sVEGFRs in patients with mRCC and patients with mCRC after sunitinib therapy. The shape of the concentration-time curves of both soluble receptors was comparable and their response was highly correlated in patients with mRCC (r² = 0.594; P < 0.0001) and also patients with mCRC (r² = 0.635; P < 0.0001). However, the covariate analysis performed on both models revealed PD differences between the tumor entities. Addition of a proportional covariate effect of “tumor type” on the intrinsic activity (α) of sunitinib on sVEGFR-2 levels improved the model significantly (ΔOFV = 7.45; P = 0.006). It was shown that intrinsic activity (α) was 32.8% lower in patients with mCRC compared to patients with mRCC.

Intrinsic activity on sVEGFR-2 levels was also influenced by VEGF-R3 rs6877011 genotype (1 = CG/GG; 0 = CC). Presence of the G-allele (CG and GG genotypes) showed a decreased α compared to the wildtype CC (2.31 vs. 1.00 in case of patients with mRCC and 1.55 vs. 0.65 for patients with mCRC). A decreased intrinsic activity was also observed for patients with presence of a T-allele in patients with mCRC. A decreased intrinsic activity was also observed for patients with presence of a T-allele in patients with mCRC.

Final parameter estimates of both models are shown in Table 3. Visual predictive checks indicated that central tendency and variability of both proteins could be described adequately with the underlying models (Figure 2c and 2d).
Outcome model for patients with mRCC

Median PFS for patients with mRCC was calculated with 6.9 months \((n = 24)\). The PFS could be described by a parametric TTE model assuming exponentially distributed data with a baseline hazard function \(\lambda_0\) of 0.0252 weeks\(^{-1}\) (90% CI = 0.0168–0.0336). The inclusion of the measured and estimated sVEGFR-2 baseline value led to a decrease of the OFV by 4.14 or 4.67 \((P < 0.05)\), respectively. However, the dichotomized covariate, dividing patients into two groups with baseline values above and below the population median of 8.8 \(\mu\)g/L, had a stronger effect with a decrease of the OFV by \(-6.40\) \((P < 0.025)\). The \(\beta\) was estimated with 1.45 corresponding to a hazard ratio (HR) of 4.26 (with \(\beta\) defined as the natural logarithm of the HR). Inclusion of the active, unbound sunitinib/SU12662 concentrations resulted in an estimated \(\beta\) of \(-0.14\) mL/ng indicating that a higher plasma level reduces the hazard and, hence, the probability of progression during treatment. However, the effect was not statistically significant (dOFV = \(-1.1\); \(P = 0.29\)). Likewise, plasma concentrations of sVEGFR-2 and sVEGFR-3 over time were not statistically significant predictors of PFS either (dOFV = \(-3.7\) and \(-0.99\), respectively). Besides absolute plasma levels of both proteins, also the relative decrease with respect to individual baseline values predicted by the PK/PD models was tested as a potential covariate. However, no significant improvement of the model fit could be observed either (dOFV = \(-0.31\) and \(-0.98\)).

Best prediction of PFS in patients with mRCC was achieved by a hazard function \(h(t)\), including the dichotomized baseline value of sVEGFR-2, which was independent of the developed PK/PD models:

\[
h(t) = \lambda_0 \cdot e^{\beta \cdot \text{sVEGFR-2, baseline (dichotom)}}
\]

The observed Kaplan-Meier curve describing the PFS function of the patients with mRCC was within the predicted 90% prediction interval of 1,000 simulations and could sufficiently be described by the TTE model except for later time points as a result of censored data (Figure 3a). Final parameter estimates are shown in Table 4.

These findings were confirmed in a multivariate Cox regression analysis. The only covariates exhibiting a significant influence were the dichotomized baseline values of both soluble proteins (data not shown).

Figure 2 Prediction-corrected visual predictive checks of (a) the final pharmacokinetic (PK) model of sunitinib, (b) the final PK model of SU12662, (c) the soluble vascular endothelial growth factor receptor (sVEGFR)-2 model, and (d) the sVEGFR-3 model for one treatment cycle. Solid lines indicate the estimated mean as well as the 90% prediction interval. Dashed lines show the respective observed mean and interval. Shaded gray areas represent the 90% confidence band of the predictions. The dark gray rectangle indicates the time of treatment.
Outcome model for patients with mCRC

Median TTP for patients with mCRC was 8.4 months (n = 21). Analogous to the patients with mRCC, the TTP could be described by a parametric TTE model assuming exponentially distributed data. The baseline hazard function \( \lambda_0 \) was estimated with 0.0234 weeks\(^{-1}\) (90% CI = 0.012–0.042 weeks\(^{-1}\)). The inclusion of the current concentration of the unbound, active drug (AC\(_u\)) reduced the OFV by 6.07 (\( P < 0.05 \)). The \( \beta \) was estimated to be -0.758 mL/ng corresponding to an HR of 0.47. None of the other variables describing the individual PK or biomarker response were identified to be predictive for TTP. Therefore, TTP in patients with mCRC was best predicted by the PKs of sunitinib and SU12262 with an appropriate hazard function \( h(t) \) dependent on the current AC\(_u\)(t):

\[
h(t) = \lambda_0 \cdot e^{\beta AC_u(t)}. \tag{9}
\]

The observed Kaplan-Meier curve describing the PFS function of the patients with mCRC was within the predicted 90% prediction interval of 1,000 simulations and could sufficiently be described by the TTE model. However, TTP was difficult to predict for the time from 1 year onward due to censored data (Figure 3b). Final parameter estimates are shown in Table 4.

A multivariate Cox regression analysis confirmed these results exhibiting the area under the curve (AUC) at

\[
(\text{a}) \quad \text{Progression-free survival [%]}
\]

\[
(\text{b}) \quad \text{Time-to-progression [%]}
\]

Figure 3 Prediction-corrected visual predictive checks of (a) the final survival model for patients with metastasized renal cell carcinoma, and (b) the final survival model for patients with metastasized colorectal cancer. Shaded gray areas represent the 90% prediction interval.
steady-state of the unbound, active drug in combination with age as positive predictive covariates (data not shown).

**DISCUSSION**

In this study, we successfully integrated distinct models for sunitinib in a modeling framework, including PK, PD, pharmacogenetic, and outcome data. The developed models adequately describe plasma concentration-time profiles of sunitinib, its active metabolite SU12662, sVEGFR-2, and s-VEGFR-3, as well as clinical outcome in both tumor types. Similar models (but without pharmacogenetics) were published in patients with GIST6 and recently hepatocellular carcinoma,38 but there is no model with integrated outcome data yet published for the tumor entities investigated here.

Covariate analysis on the PK parameters did not reveal any significant findings. The significant increase of sunitinib clearance in patients with ABCB1 rs2032582 TT (18%) found in previous studies could not be confirmed.17 Presumably, this is due to the small and, with two tumor entities, relatively heterogeneous cohort. Biomarker response of sVEGFR-2 and sVEGFR-3 was highly associated in each tumor entity, which suggested a comparable predictive value of both soluble receptors. As previously reported, decreasing plasma concentrations were observed for both receptors after sunitinib administration with a subsequent increase after stop of treatment.8,27,39 Independent of tumor entity and dosing scheme, baseline levels are not fully recovered after a 2-week off phase.

A difference in sVEGFR-2 response to sunitinib between patients with mRCC and patients with mCRC could be identified. However, decrease of sVEGFR-2 plasma levels relative to the individual baseline did not have a significant impact on PFS or TTP in both studies, hence, the clinical relevance of this effect might be negligible. Observed baseline values of sVEGFR-3 were in the same magnitude previously reported by Motzer et al.40 ranging between 22.3 and 129.2 μg/L for patients with mRCC. However, they were significantly higher compared with patients with mCRC. This finding might indicate a higher expression of this protein in patients with mRCC. However, data regarding the baseline values of sVEGFR-3 in patients with mCRC is sparse, because the first-line and second-line treatment usually does not involve tyrosine kinase inhibitors targeting sVEGFR.41

In this study, we found that the presence of the variant G-allele in SNP rs6877011 in VEGFR-3 was associated with a 56.5% decrease in intrinsic activity on sVEGFR-2 compared to the wild-type CC. The same VEGFR-3 SNP was associated with a decreased PFS in an earlier study.12 Maitland et al.42 associated variant G-allele carriers of VEGFR-2 (KDR) rs34231037 with sVEGFR2 baseline levels and a decline in sVEGFR-2 in response to treatment with pazopanib. We have recently found that rs34231037 variant G-allele carriers have a tendency toward a better response to sunitinib.43 VEGFR-1, 2, and 3 have similar binding domains.44 A SNP in any of the genes encoding these VEGFRs could result in a conformation change and prevent or stimulate binding of the drug ligand to VEGFRs, and change the ability of sunitinib to decrease sVEGFR-2 and sVEGFR-3. It is remarkable that the SNP effect of G-allele carriers of rs6877011 in VEGFR-3 was not found on the intrinsic activity of sunitinib on sVEGFR-3 but on sVEGFR-2. Possibly, a lower activity of sunitinib on sVEGFR-3 could also affect sVEGFR-2. The conformation change may have more impact on VEGFR-2 binding affinity than VEGFR-3.

In both patient groups, we succeeded in linking clinical outcome data to either PDs (mRCC) or PKs (mCRC). In patients with mRCC, baseline levels of sVEGFR-3 and sVEGFR-2 as well as the decrease in sVEGFR-2 plasma levels over the treatment duration were previously reported to be related to clinical outcome.7,45 These findings could be further confirmed by this study. Although the effect of sVEGFR-2 decrease over time was not significant in the TTE analysis, patients with a substantially higher baseline value of sVEGFR-2 showed a significantly worse PFS with an estimated HR of 4.26. The baseline value of sVEGFR-3 had a lower influence on PFS; for patients with an sVEGFR-3 baseline above the population median, the HR was 2.38 without statistical significance (P = 0.2). An effect of similar magnitude (HR = 2.4; 95% CI = 1.13–5.11) was reported by Harmon et al.46 for the same covariate. In contrast, in patients with mCRC, the TTE model showed an effect of the PKs on TTP with precise parameter estimates. Higher exposure to sunitinib and SU12662 included as active drug concentration over time was associated with a
longer TTP. Similarly, a meta-analysis with 443 patients with cancer, including advanced GIST, mRCC, and other solid tumors, suggested that an increased AUC at steady-state is associated with a longer TTP and a longer OS.4 It is not surprising that plasma concentrations of proteins related to the VEGF pathway seem to be more predictive for clinical outcome in patients with mRCC, as most RCC cells overexpress VEGF due to mutations in the von-Hippel Lindau gene.47 Furthermore, sunitinib showed no additional effects in patients with colorectal cancer,25 which is consistent with our findings that sVEGFR-2 and sVEGFR-3 levels were not correlated to outcome. The lower intrinsic activity of sunitinib on sVEGFR-2 baseline levels and the overall lower plasma concentrations of sVEGFR-3 may also underline the lower dependency of colorectal carcinomas on angiogenesis, especially via VEGF signaling.

In conclusion, a semimechanistic PK model for sunitinib could be successfully linked to PD models for sVEGFR-2 and sVEGFR-3, including various genotypes. Although we could show that sunitinib PK does not differ between the two tumor entities, we found differences in PD response with respect to the decrease of sVEGFR-2 and sVEGFR-3 plasma concentrations during therapy. Furthermore, sVEGFR-2 baseline levels seemed to be more predictive for clinical outcome in patients with mRCC in contrast to patients with mCRC where active drug PKs showed the highest impact. Nevertheless, our study provides the basis for clinical outcome in patients with mRCC in contrast to patients with metastatic renal cell carcinoma: modulation of VEGF and VEGF-related proteins. J. Transl. Med. 5, 32 (2007).

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Supplementary information accompanies this paper on the CPT: Pharmacometrics & Systems Pharmacology website (http://psp-journal.com)