A Population Pharmacokinetic Meta-analysis of Sunitinib Malate (SU11248) and Its Primary Metabolite (SU12662) in Healthy Volunteers and Oncology Patients

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Abstract

Purpose: Sunitinib malate is an oral multitargeted tyrosine kinase inhibitor approved for advanced renal cell carcinoma and imatinib-resistant or imatinib-intolerant gastrointestinal stromal tumor. Following administration, sunitinib is metabolized by cytochrome *P*450 3A4 to an active metabolite (SU12662). The objective of this analysis was to assess sunitinib and SU12662 pharmacokinetics and to identify covariates that might explain variability in exposure following oral administration.

Experimental Design: Data from 590 subjects (73 volunteers and 517 patients) in 14 studies were analyzed. Plasma concentration-time data were analyzed using nonlinear mixed-effects modeling to estimate population pharmacokinetic parameters, as well as relationships between these parameters and gender, race, age, weight, creatinine clearance, Eastern Cooperative Oncology Group score, and tumor type. Simulations were done to determine the predicted effect of these covariates on exposure.

Results: Separate models were developed for sunitinib and SU12662 (each a two-compartment model with first-order absorption and elimination). Sunitinib parameters were estimated as CL/*F*, 51.8 L/h and $Vd/F_{central}$, 2,030 liters. SU12662 parameters were estimated as CL/*F*, 29.6 L/h and $Vd/F_{central}$, 3,080 liters. Tumor type (except acute myeloid leukemia), Asian race, gender, body weight, and elevated Eastern Cooperative Oncology Group score described a portion of the variability in CL/*F* for sunitinib and metabolite; gender and body weight explained some of the variability in $Vd/F_{central}$ for sunitinib and metabolite. Among patients, the predicted changes in sunitinib and metabolite AUC and C_{max} as a result of the individual covariates ranged up to 17%.

Conclusion: The magnitude of the predicted changes in exposure with the covariates studied minimizes the necessity for dose adjustment in any of these subpopulations.

Sunitinib malate (SU11248; SUTENT) is an oral multitargeted tyrosine kinase inhibitor that selectively inhibits class III, V, and XII split-kinase domain receptor tyrosine kinases, including vascular endothelial growth factor receptors (VEGFR1, VEGFR2, and VEGFR3), platelet-derived growth factor receptors (PDGFR-α and PDGFR-β), stem cell factor receptor (KIT), and Fms-like tyrosine kinase-3 receptor (FLT3), as well as the glial cell line–derived neurotrophic factor receptor (RET; refs. 1–5). The antitumor activity of sunitinib has been shown in a number of preclinical tumor models (3, 4), and its clinical efficacy has been shown in patients with metastatic renal cell carcinoma (6–8), gastrointestinal stromal tumor (9), metastatic breast cancer (10), and a variety of other solid tumors (e.g., neuroendocrine tumors; ref. 11). Sunitinib has received regulatory approval for the treatment of advanced renal cell carcinoma and imatinib-resistant or imatinib-intolerant gastrointestinal stromal tumor (12).

Following administration, sunitinib is primarily metabolized by cytochrome *P*450 3A4 to an active *N*-desethyl metabolite (SU12662; refs. 12, 13). The active metabolite is also metabolized by cytochrome *P*450 3A4 (12). Elimination is primarily via the feces, with <16% excreted in the urine (12, 13). Because SU12662 has an inhibitory profile similar to that of sunitinib *in vitro* and has similar plasma protein binding, the combination of sunitinib plus SU12662 (sunitinib + SU12662) represents the total active drug (total drug) in plasma.

Pharmacokinetic investigations in both healthy volunteers and cancer patients have shown that following a single oral dose, peak plasma sunitinib concentrations occur between 6 and 12 hours post-dose (12). In addition, sunitinib and SU12662 have previously been shown to display linear pharmacokinetics and have prolonged half-lives of ~40 and 80 hours, respectively (14). Sunitinib is well absorbed (14);

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Translational Relevance

Sunitinib malate (SU11248; SUTENT) is an oral multitargeted receptor tyrosine kinase inhibitor that is approved in the United States and European Union for the treatment of advanced renal cell carcinoma and imatinib-resistant or imatinib-intolerant gastrointestinal stromal tumor.

This article describes an analysis using a population approach to assess the pharmacokinetics of sunitinib and its primary active metabolite (SU12662) and to identify covariates that might explain variability in exposure following oral administration. Simulations were done to assess the effect of the identified covariates on sunitinib and total drug (sunitinib and SU12662) exposure. The magnitude of the predicted changes in exposure with the covariates studied minimizes the necessity for dose adjustment in any of these subpopulations.

bioavailability is not affected by food intake (12, 15); and no significant changes in pharmacokinetics are observed with repeat versus single dosing (12).

No differences in pharmacokinetics have been observed between healthy volunteers and cancer patients in individual studies (12, 16). However, when analyzed across multiple studies, factors such as patient status, age, gender, race, body weight, and clinical performance status may affect the pharmacokinetics of sunitinib in individuals, resulting in increased or decreased exposure to sunitinib, SU12662, or total drug. Therefore, an analysis using a population approach was done to assess the pharmacokinetics of sunitinib and SU12662 and to identify covariates that might explain variability in exposure following oral administration. The analysis focused on factors that increased exposure to sunitinib and SU12662 and may subsequently increase the incidence or severity of adverse events. Simulations were then done to assess the effect of these covariates on sunitinib and total drug exposure.

Materials and Methods

Study methods

This analysis was done using plasma concentration data obtained from 14 clinical studies of sunitinib administered as a single agent (Table 1). Four of the studies were single-dose studies in healthy volunteers who received oral doses of sunitinib 10 or 50 mg, whereas one study investigated a single oral dose (50-350 mg) in patients with acute myeloid leukemia (AML). The remaining nine studies were multiple-dose studies in patients with metastatic renal cell carcinoma (two studies), gastrointestinal stromal tumor (three studies), or various solid tumors (four studies) who received oral doses of sunitinib ranging between 25 and 175 mg daily or every other day.

All studies were done in accordance with Good Clinical Practice and under the ethical principles established by the Declaration of Helsinki. Each study protocol was reviewed and approved by Institutional Review Board, and informed consent was obtained from each subject.

In all studies, plasma concentrations of sunitinib and the active metabolite were determined using a sensitive, specific, and validated isocratic liquid chromatographic tandem mass spectrometric method (as previously described 7, 15, 17) at either Pfizer Global Research and Development or Bioanalytical Systems, Inc.

Data from 590 subjects were analyzed; there were 73 volunteers and 517 patients (241 with gastrointestinal stromal tumor, 152 with metastatic renal cell carcinoma, 95 with other solid tumors, and 29 with AML) in the data set. The majority of subjects (>85%) were Caucasian (n = 505); other racial groups included Asian/Japanese/Pacific Islander (n = 58), Black (n = 14), and all others (n = 13). There were 398 males and 192 females. At screening (or first available measurement), mean ± SD (range) age, weight, and calculated creatinine clearance (CrCL; estimated using Cockroft-Gault) were 53 ± 15 y (18-87 y), 78 ± 19 kg (34-168 kg), and 98 ± 37 mL/min (32-347 mL/min), respectively (Table 2A and B). There were 297 subjects with a baseline Eastern Cooperative Oncology Group (ECOG) score of 0, 259 with a score of 1, 33 with a score of 2, and 1 with a score of 3 at screening. The dose range was 10 to 350 mg.

Analysis

Overview of statistical methods. Plasma concentration-time data (with plasma concentrations expressed as ng/mL) were analyzed using nonlinear mixed-effects modeling (NONMEM; version 5, level 1.1) to estimate population pharmacokinetic parameters (mean and interindividual variability) for sunitinib and SU12662 and to identify potential covariates to explain any interindividual variability in the parameters (18). Base models for both sunitinib and SU12662 were selected using first-order conditional estimation with interaction. The selected base models were analyzed for covariate influence on the interindividual error terms. Full models (inclusive of all identified potentially influential covariates) were then built using first-order conditional estimation with interaction. Covariate screening to identify significant covariates (using stepwise backward elimination) was carried out using the full models to give final models. Finally, Monte Carlo simulations were done to determine the predicted effect of these covariates on steady-state average concentration (C_{avg}), area under the plasma concentration-time curve (AUC), and maximal concentration (C_{max}) for sunitinib, SU12662, and total drug.

During the building of each model, the goodness of fit of the different models to the data was evaluated using successful minimization, successful covariance estimation, change in the objective function, visual inspection of scatter plots, precision of the parameter estimates, as well as decreases in both interindividual and residual variability (18–22). The 95% confidence intervals of the estimates of the pharmacokinetic parameters were also evaluated.

Model development. Log-transformed plasma concentration-time data were evaluated using one-, two-, and three-compartment models; the most conservative model was selected at the $P < 0.05$ level as evaluated by a 3.84-unit objective function value (ΔOFV). Interindividual variability in the main pharmacokinetic parameters [i.e., apparent oral clearance (CL/F), apparent volume of distribution (Vd/F), and absorption rate constant (K_a)] was modeled using an exponential error term. The estimate of interindividual variability was provided as percentage coefficient of variation (%CV), and residual variability was modeled as a proportional error structure. Because variability can be underestimated when presented this way, interindividual variability was also expressed as the variance [calculated as $(\%CV/100)^2$].

A two-compartment model (parameterized in terms of compartmental clearances and volumes) best described the pharmacokinetic data for both sunitinib and the active metabolite. Observed concentrations were consistent with the two-compartment model when plotted versus time after dose, and population predicted values agreed well with observed values, as did individual predicted concentrations. Final parameter estimates for the base models are shown in Table 3.

Once base models for both sunitinib and SU12662 had been identified, full models were built including all of the covariates of clinical interest. The continuous covariates evaluated were age, weight, and CrCL, whereas the categorical covariates evaluated were gender, race, ECOG score, and tumor type. All of these variables were investigated for potential effect on the CL/F of sunitinib and SU12662; only gender and weight were investigated for potential effect

Table 1. Summary of design of single-agent studies from which data were analyzed

Design (study number)	Population (*n*)	Dosing schedule*	Study day for full PK sampling	Full PK sampling time points post-dose (h)
Single-dose studies				
R, DB, PC (001)	Healthy volunteers (6)	50 mg †	1	Pre-dose (0), 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 9, 10, 11, 12, 16, 24, 30, 36, 48
R, OL, three-way CO of sunitinib free base, L-malate salt, and the effect of food (004)	Healthy volunteers (15)	50 mg ‡	1	0, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 9, 10, 11, 12, 16, 24, 30, 36, 48, 72, 216
		3 single doses (free base fasted; L-malate salt fasted; L-malate salt fed)		
R, OL, two-way CO study with/without concomitant ketoconazole (009)	Healthy volunteers (27)	10 mg§	1	0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 16, 24, 30, 36, 48, 72, 120, 168, 216, 312, 408, 504
		Ketoconazole: 400 mg p.o. qd ×7 d		
OL, CO study with/without concomitant rifampin (1001)	Healthy volunteers (25)	50 mg	1	0, 2, 4, 7, 8, 9, 12, 16, 24, 36, 48, 72, 144, 240, 288, 336, 408
		Rifampin: 400 mg p.o. qd ×7 d		
OL, dose escalation (006)	AML (29)	50-350 mg ‡	1	0, 4, 6, 8, 10, 12, 24, 48
Multiple-dose studies				
OL, single-arm, NR, dose-escalating study of three treatment schedules (013)	GIST (68, of which 18 with full PK)	25, 50 or 75 mg qd (2/2, 4/2 or 2/1)	Schedule 2/2‖	
			Cycle 1: 1, 14 Cycle 2: 14	0, 1, 4, 6, 8, 10, 12, 24, 48
			Schedule 4/2‖	
			Cycle 1: 1 and 28 Cycle 2: 28	As above
			Schedule 2/1‖	
			Cycle 1: 1, 14 Cycle 2: 14	As above
DB, PC, R (1004)	GIST (154)	50 mg qd (4/2)	Schedule 4/2	
			Cycle 1: 1, 14, 28 Additional cycles: 1, 28	Trough sampling only
OL, NR (1045)	GIST (12)	25, 50, 75 mg qd (4/2)	Schedule 4/2‖	
			Cycle 1: 1	0, 1, 2, 4, 6, 8, 10
			Cycle 1: 2, 7, 14, 21	0
			Cycle 1: 28	0, 1, 2, 4, 6, 8, 10, 24, 48

(*Continued on the following page*)

on Vd/*F*. Continuous covariates identified were then incorporated into the base model as a power model centered on a median value, where

$$\text{Typical\_Value} = \theta_1 \left(\frac{\text{Cov}}{\text{Cov}_{\text{reference}}} \right) \theta_2$$

Cov is the covariate of interest and $\text{Cov}_{\text{reference}}$ is the median value of that covariate.

Categorical covariates were incorporated as a linear proportional model, where

$$\text{Typical\_Value} = \theta_1 (1 + \theta_2 \cdot \text{Indicator})$$

Indicator is a coding variable equal to 1 when the covariate is present and 0 when it is absent. θ_2 is the proportional change, coded as relative to the most common covariate value.

To identify significant ($P < 0.01$) covariates for sunitinib and the active metabolite, a stepwise backward elimination from the full model procedure was used. Individual covariates were eliminated one at a time, and the resulting change in the NONMEM ΔOFV was noted. Nonsignificant covariates were removed and a second round of stepwise backward elimination was done. This process was repeated until all remaining covariates in the model were significant at the $P < 0.01$ level as judged by ΔOFV. (The results of this process are described in Results.).

Finally, Monte Carlo simulations were done to determine the effect of these significant covariates on model parameters for sunitinib and SU12662 (including interindividual variability in absorption rate, CL/*F*, and Vd/*F*). Covariates that increased plasma concentrations were tested, as well as various combinations of these covariates. Ten thousand subjects were simulated per covariate combination, at steady

Table 1. Summary of design of single-agent studies from which data were analyzed (Cont'd)

Design (study number)	Population (*n*)	Dosing schedule*	Study day for full PK sampling	Full PK sampling time points post-dose (h)
OL, NR (014)	mRCC (56)	50 mg qd (4/2)	Schedule 4/2 Cycles 1-4: 1, 14, 28 Additional cycles: 1	Trough sampling only
OL, NR (1006)	mRCC (92)	50 mg qd (4/2)	Schedule 4/2 Cycle 1: 1, 14, 28Cycles 2-4: 1, 28 Additional cycles: 1	Trough sampling only
OL, NR, dose escalation (002)	Solid tumor (27)	25, 50, 75 or 100 mg ‡ qd or qod (4/2)	Schedule 4/2‖ Cycle 1: 1 and 27 or 28	0, 1, 2, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 8, 10, 12, 14, 16, 24
OL, NR, dose escalation (005)	Solid tumor (41)	50, 75 mg ‡ qd or qod (2/2 or 4/2)	Schedule 2/2‖ Cycle 1: 1 and 13 or 14 Cycles 2 and 3: 13 or 14 Schedule 4/2‖ Cycle 1: 1 and 28 Cycles 2 and 3: 28 Schedule 4/2‖ Cycle 1: 14	0, 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 20, 24, 48 As above 0, 4, 6, 8, 10, 12, 24
OL, NR (016)	Solid tumor (12)	50 mg qd (2/1)	Schedule 2/1‖ Cycle 1: 1 and 14 Cycle 2: 14 Cycle 3: 14	0, 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 20, 24
OL, dose escalation (018)	Solid tumor (26)	50-175 mg loading dose on day 1; 50 mg qd (2/1)	Schedule 2/1‖ Cycle 1: 1 Cycle 2: 1 and 14 Cycle 3: 14 (for >50 mg) Cycle 1: 14	0, 4, 6, 8, 10, 12, 24 0, 4, 6, 8, 10, 12, 24, 72, 120

Abbreviations: CO, crossover; DB, double-blind; MD, multiple dose; mRCC, metastatic renal cell carcinoma; GIST, gastrointestinal stromal tumor; *n*, number of subjects evaluable for PK; NR, nonrandomized; OL, open-label; PC, placebo-controlled; p.o., oral; PK, pharmacokinetics; qd, everyday; qod, every other day; R, randomized; SD, single dose.
*Information provided: dose of sunitinib (in all studies sunitinib was administered in the form of L-malate salt capsules unless stated); frequency of dosing and dosing schedule (weeks on treatment/weeks off treatment).
†Free base powder in bottle.
‡Free base and L-malate salt capsule.
§L-Malate salt powder in bottle.
‖Trough PK sampling was also done.

state with 50 mg daily oral dosing. For each simulated subject, steady-state C_{avg} [dose/(simulated clearance × 24 h)], AUC (C_{avg} × 24 h), and C_{max} of both sunitinib and metabolite were calculated, along with the 5th, 50th, and 95th percentiles for both sunitinib and total drug (i.e., sunitinib plus the active metabolite). Based on preclinical observations in monkeys given equivalent i.v. doses of sunitinib and SU12662 (1), a conversion of 21% of sunitinib to metabolite was assumed to bring the magnitude of the parameters to a more physiologically relevant level. However, all parameters estimated for both sunitinib and SU12662 were expressed in relative terms because bioavailability was unknown. For sunitinib, bioavailability was a function of fraction absorbed only, whereas for SU12662, bioavailability was a function of the fraction absorbed as well as the fraction of sunitinib metabolized to SU12662. The relevant fractions for each molecule were incorporated in the pharmacokinetic parameter estimates when fitting data to the model. In this way, percent changes in secondary exposure measures (such as AUC and C_{max}) for any subpopulation would not be affected by assumptions of absolute bioavailability.

Results

Pharmacokinetic models for sunitinib and SU12662. Sunitinib and SU12662 were modeled independently. The final model for the sunitinib molecule was a two-compartment model with first-order absorption and first-order elimination including the effects of gender, Asian race, and tumor type (except AML) on CL/*F* and of body weight on Vd/$F_{central}$. The final model for the metabolite was also a two-compartment model with first-order absorption and first-order elimination and included the effects of body weight, gender, Asian race, elevated ECOG score, and tumor type (except AML) on CL/*F* and of body weight and gender on Vd/$F_{central}$. Final parameter estimates are summarized in Table 4.

For sunitinib, CL/*F* was estimated to be 51.8 L/h and Vd/$F_{central}$ was estimated to be 2,030 liters; interindividual

Table 2. Summary of patient physiologic and demographic characteristics

(A) Summary values at screening (or first available measurement) of continuous covariates

Variable	Age (y)	Weight (kg)	CrCL (mL/min)*
Minimum	18	34.0	32.2
1st quartile	44	64.0	74.1
Mean	53	77.6	98.2
Median	55	76.9	93.5
3rd quartile	64	88.0	118
Maximum	87	168	347
Total *N*	590	590	587
SD	15	18.8	36.7

(B) No. of subjects within a range at screening (or first available measurement)

Demographic(range at screening)	Subgroup	Healthy volunteers	Patients	All
Age, y (18-87)	<40	63	36	99
	40-60	10	275	285
	60-75	0	180	180
	>75	0	26	26
Weight, kg (34-168)	≥135	0	6	6
	76-<135	36	271	307
	41-75	37	237	274
	≤40	0	3	3
CrCL, mL/min (32-347)*	>80	72	318	390
	50-80	1	168	169
	30-49	0	28	28
	<30	0	3	3

*Excludes three subjects with low CrCL values (<1 mL/min; these are thought to be an artifact of the Cockroft-Gault estimation).

variability expressed as %CV was estimated to be 38% for CL/*F* (variance, 0.14) and 43% for Vd/$F_{central}$ (variance, 0.18). The terminal half-life was estimated to be 69 hours (interindividual variability, 9%; variance, 0.008). The absorption rate constant (K_a) was estimated at 0.20/h (interindividual variability, 80%; variance, 0.64), corresponding to an absorption half-life of 3.5 hours.

For SU12662, CL/*F* was estimated at 29.6 L/h and Vd/$F_{central}$ was estimated to be 3,080 liters; interindividual variability (%CV) was estimated to be 47% for CL/*F* (variance 0.22) and 59% for Vd/$F_{central}$ (variance 0.35). The terminal half-life was estimated to be 80 hours (interindividual variability, 28%; variance, 0.08). The absorption and formation rate constant was 0.29/h (interindividual variability, 86%; variance, 0.74), corresponding to a formation or appearance half-life of 2.4 hours.

Based on these estimates, the equations shown in Fig. 1 were used to determine CL/*F* and Vd/*F* for sunitinib and SU12662.

Table 3. Values of final parameter estimates for the base models for sunitinib and SU12662

Parameter	Estimate (SE/estimate)	Interindividual variability (SE/estimate)	Interindividual variability (variance)*
Sunitinib			
CL/*F*, L/h	37.7 (1.8%)	37.9% (8.8%)	0.14
Vd/$F_{central}$, liters	1,940 (3.8%)	44.7% (13%)	0.20
K_a, 1/h	0.195 (6.8%)	81.2% (13%)	0.66
Intercompartmental flow (*Q*/*F*), L/h	6.37 (18%)	NA	NA
Vd/$F_{peripheral}$, liters	588 (8.7%)	NA	NA
Proportional error	0.147 (9.6%)	NA	NA
SU12662			
CL/*F*, L/h	20.2 (2.3%)	52.2% (8.5%)	0.27
Vd/$F_{central}$, liters	2,710 (3.9%)	65.1% (8.7%)	0.42
K_a, 1/h	0.287 (6.6%)	89.1% (13%)	0.79
Intercompartmental flow (*Q*/*F*), L/h	27.7 (26%)	NA	NA
Vd/$F_{peripheral}$, liters	345 (22%)	NA	NA
Proportional error	0.0913 (7.3%)	NA	NA

Abbreviation: NA, not applicable.
*Calculated as $[\%CV/100]^2$.

Table 4. Values of final parameter estimates for the final models for sunitinib and SU12662

Parameter	Sunitinib			
	Estimate (SE/estimate)	Interindividual variability (%CV)	Interindividual variability (variance)*	95% CI
CL/*F*, L/h	51.8 (4%)	38%	0.14	47.9-55.7
Vd/$F_{central}$, liters	2,030 (4%)	43%	0.18	1,877-2,183
K_a, 1/h	0.195 (7%)	80%	0.64	0.170-0.220
Q/*F*, L/h	7.22 (20%)	NA	NA	4.44-10.00
Vd/$F_{peripheral}$, liters	583 (9%)	NA	NA	485-681
Weight on CL/*F*	NA	NA	NA	NA
Weight on Vd/*F*	0.459 (16%)	NA	NA	0.318-0.600
Gender on CL/*F*	-0.0876 (34%)	NA	NA	-0.145 to -0.030
Gender on Vd/*F*	NA	NA	NA	NA
Asian race on CL/*F*	-0.130 (30%)	NA	NA	-0.206 to -0.054
ECOG on CL/*F*	NA	NA	NA	NA
GIST on CL/*F*	-0.285 (14%)	NA	NA	-0.361 to -0.209
Solid tumor on CL/*F*	-0.269 (15%)	NA	NA	-0.349 to -0.189
mRCC on CL/*F*	-0.258 (13%)	NA	NA	-0.323 to -0.193
Proportional error	0.146 (10%)	NA	NA	0.118-0.174

Abbreviations: 95% CI, 95% confidence interval; NA, not available (covariates not found to have a significant effect when the full model was subjected to stepwise backward elimination were omitted from the final model).
*Calculated as $[\%CV/100]^2$.

To test the goodness of fit of the final model, plots were generated including population predicted versus observed concentrations, individual predicted versus observed concentrations, weighted residuals versus population predicted concentrations, and weighted residuals versus time (Fig. 2). Individual predicted values agreed well with observed values across the range of observations. The weighted residuals were evenly scattered across the range of predicted concentrations and time. A predictive check was done to evaluate model performance; the parameters from the final model and interindividual error estimates were used to simulate concentrations back into the observed data set. The simulated concentrations agreed well with the observed concentrations; no systematic bias was observed.

Effects of covariates. With the exception of AML (which did not influence the disposition of either sunitinib or the metabolite), the estimations suggest that the CL/*F* for both sunitinib and the metabolite is reduced in patients relative to healthy adult volunteers. In gastrointestinal stromal tumor patients, sunitinib CL/*F* was reduced by 29% and metabolite CL/*F* by 22%; metastatic renal cell carcinoma patients exhibited a reduced sunitinib and metabolite CL/*F* (by 26%); and other solid tumors patients exhibited a reduced sunitinib CL/*F* (by 27%) and metabolite CL/*F* (by 29%).

The influence of Asian race on CL/*F* was examined relative to all other races (>85% Caucasian), with CL/*F* decreased by 13% for sunitinib and 12% for the metabolite.

Relative to male gender, female gender decreased CL/*F* for both sunitinib and metabolite (by 9% and 26%, respectively) and decreased Vd/*F* for the metabolite (by 24%).

Body weight displayed no relationship with sunitinib CL/*F*, but correlated positively with Vd/*F* for sunitinib and with both Vd/*F* and CL/*F* for the metabolite. For sunitinib, Vd/*F* decreased by 26% for a 40-kg individual relative to a 77-kg individual (the median body weight for the studies included in this analysis); for a heavier individual (100 kg), Vd/*F* increased by 13%. For the metabolite, Vd/*F* decreased by 28% and CL/*F* decreased by 18%, for a 40-kg individual relative to a 77-kg individual. Conversely, for a 100-kg individual relative to a 77-kg individual, Vd/*F* for the metabolite increased by 14% and CL/*F* increased by 8%.

A small effect of elevated ECOG score ($\geq$2) was identified for metabolite CL/*F* but not for sunitinib CL/*F*. In patients with an elevated ECOG score, CL/*F* for the metabolite decreased by 7%. However, the effect was imprecisely estimated (96% CV); therefore, the clinical significance of this relationship should be interpreted with caution.

No relationship with age or renal function (CrCL) was observed for either sunitinib or metabolite CL/*F*.

Simulations. Simulations with the final models, using the demographic covariates shown to decrease CL/*F* and/or Vd/*F*, were done to predict sunitinib, metabolite, and total drug exposures in these subpopulations. Because the goal of the simulations was to describe potential changes in patients and clinical effect, changes in exposure were expressed relative to a 77-kg Caucasian male patient with metastatic renal cell carcinoma and an ECOG score of $\leq$1 (gastrointestinal stromal tumor and other solid tumor patients were expected to display similar changes, as the effect of disease on CL/*F* was similar across tumor types). These results are summarized in Fig. 3. In Asians relative to other races, AUC and C_{max} were predicted to increase by 15% for both sunitinib and total drug. In females relative to males, AUC was predicted to increase by 10% for sunitinib and by 17% for total drug; C_{max} was predicted to increase by almost as much (9% for sunitinib and 17% for total drug). Other covariates had less effect in the simulations. A baseline ECOG score $\geq$2 was predicted to increase total drug AUC by 2% (due to decreased CL/*F* of the metabolite only). In extremely low body weight subjects (40 kg), total drug AUC was predicted to increase by 6% (when compared with the median body weight of 77 kg), whereas high body weight (100 kg) was predicted to reduce total drug AUC by 2%.

In extreme cases, combinations of covariates would be predicted to increase exposure levels higher than any one covariate alone. For example, in Asian female patients, total

Table 4. Values of final parameter estimates for the final models for sunitinib and SU12662 (Cont'd)

SU12662			
Estimate (SE/estimate)	**Interindividual variability (%CV)**	**Interindividual variability (variance)***	**95% CI**
29.6 (3%)	47%	0.22	27.2-32.0
3,080 (4%)	59%	0.35	2,815-3,345
0.290 (7%)	86%	0.74	0.252-0.328
23.3 (30%)	NA	NA	9.64-37.0
289 (27%)	NA	NA	138-440
0.296 (64%)	NA	NA	-0.074 to 0.666
0.510 (49%)	NA	NA	0.024-0.996
-0.274 (15%)	NA	NA	-0.354 to -0.294
-0.241 (23%)	NA	NA	-0.339 to -0.133
-0.123 (31%)	NA	NA	-0.198 to -0.048
-0.0652 (96%)	NA	NA	-0.188 to 0.058
-0.224 (15%)	NA	NA	-0.289 to -0.159
-0.287 (14%)	NA	NA	-0.366 to -0.208
-0.257 (12%)	NA	NA	-0.316 to -0.198
0.0914 (7%)	NA	NA	0.0782-0.105

drug AUC would be predicted to increase by 34% relative to non-Asian male patients. In the case of a 40-kg female patient, total drug AUC would be predicted to increase by 25%.

Discussion

This analysis used a population approach to assess the pharmacokinetics of sunitinib and the active metabolite SU12662 and to identify covariates that might explain variability in exposure following oral administration. It included sunitinib and metabolite plasma concentration data collected from 590 subjects (healthy volunteers and oncology patients) in 14 single-dose and multiple-dose clinical studies of sunitinib as a single agent. Because studies with other tyrosine kinase inhibitors have shown correlations between elevated drug exposure and increased toxicity (23–25), this analysis focused on clinical factors that increased exposure to sunitinib and/or SU12662, which may in turn increase the incidence or severity of adverse events. The majority of patients in the sunitinib trials received the recommended 50 mg daily starting dose, enabling the present study to determine whether this dose was inappropriately high in particular patient populations.

Disposition of sunitinib was described using a two-compartment model with first-order absorption and elimination. Estimates of interindividual variability were provided as %CV and associated variance. Apparent CL/*F* of sunitinib was

A

$$CL/F_{parent} = 51.8 \cdot (1 - 0.0876 \cdot sex) \cdot (1 - 0.13 \cdot race_{Asian}) \cdot (1 - 0.285 \cdot type_{GIST}) \cdot (1 - 0.269 \cdot type_{ST}) \cdot (1 - 0.258 \cdot type_{MRCC})$$

$$Vd/F_{parent} = 2030 \cdot \left(\frac{weight(kg)}{77.2}\right)^{0.459}$$

Sex is coded 0 for male and 1 for female; Asian race ($race_{Asian}$), presence of GIST ($type_{GIST}$), other solid tumor ($type_{ST}$) and mRCC ($type_{MRCC}$) are coded 0 if not present and 1 if present.

B

$$CL/F_{metabolite} = 29.6 \cdot \left(\frac{weight(kg)}{77.2}\right)^{0.296} \cdot (1 - 0.274 \cdot sex) \cdot (1 - 0.123 \cdot race_{Asian}) \cdot (1 - 0.0652 \cdot ECOG) \cdot (1 - 0.224 \cdot type_{GIST}) \cdot (1 - 0.287 \cdot type_{ST}) \cdot (1 - 0.257 \cdot type_{MRCC})$$

$$Vd/F_{metabolite} = 3080 \cdot \left(\frac{weight(kg)}{77.2}\right)^{0.510} \cdot (1 - 0.241 \cdot sex)$$

Sex is coded 0 for male and 1 for female; ECOG is coded 0 for a score of 0 or 1, and 1 for a score of 2 or greater; Asian race ($race_{Asian}$), presence of GIST ($type_{GIST}$), other solid tumor ($type_{ST}$) and mRCC ($type_{MRCC}$) are coded 0 if not present and 1 if present.

Fig. 1. Equations used to determine CL/*F* and Vd/*F* for sunitinib (*A*) and SU12662 (*B*).

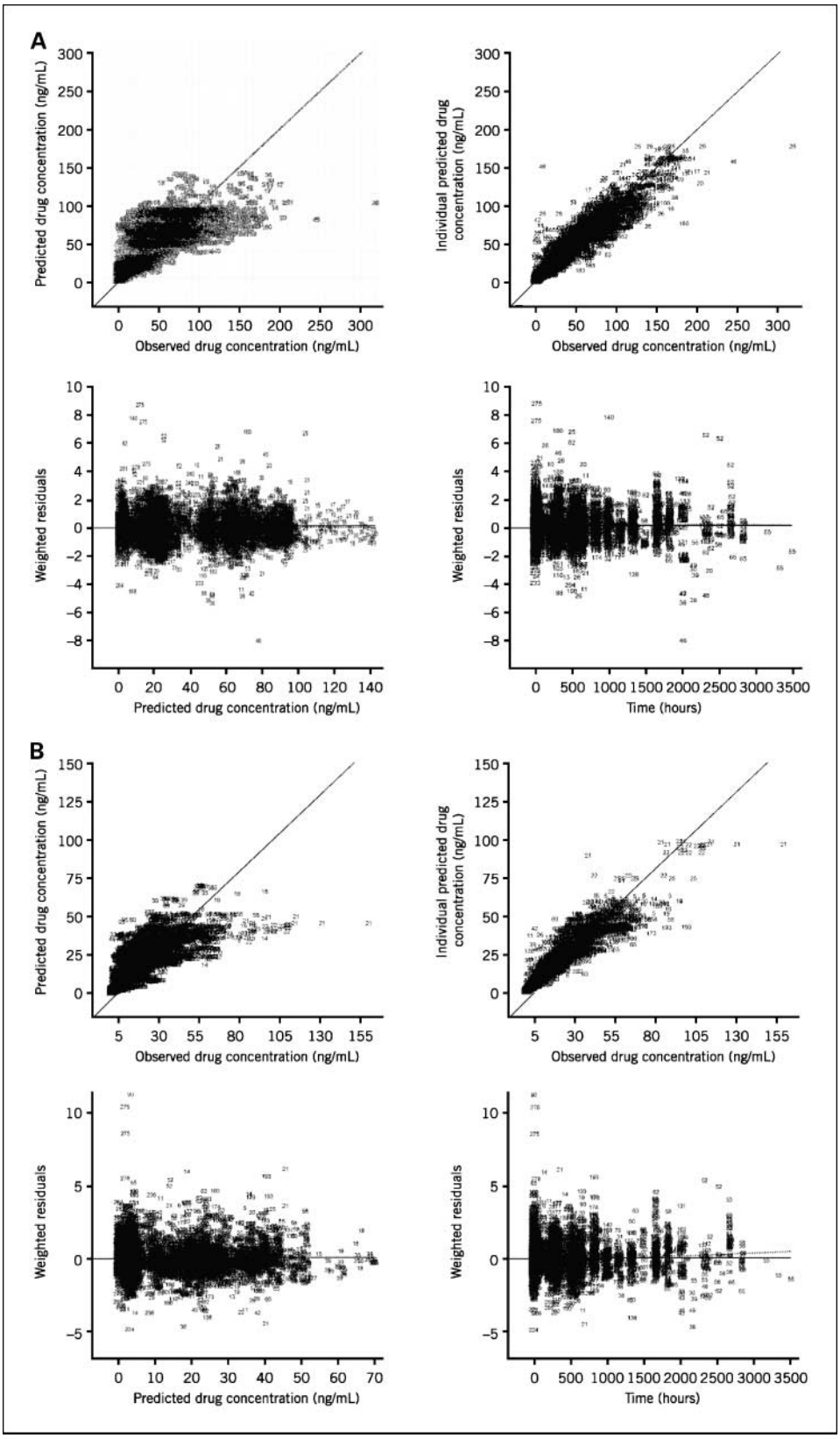

Fig. 2. Diagnostic goodness-of-fit plots for sunitinib (*A*) and metabolite (*B*) final models, showing population and individual predicted versus observed concentrations, weighted residuals versus time, and weighted residuals versus population predicted concentrations. Lines represent the unity (population and individual predicted plots) or null value (weighted residual plots).

estimated to be 51.8 L/h and Vd/*F* was estimated to be 2,030 liters for the central compartment [with interindividual variabilities (%CV) of 38% and 43% and variances of 0.14 and 0.18, respectively]. The terminal half-life was estimated to be 69 hours (interindividual variability 9%), and the absorption half-life 3.5 hours (interindividual variability 80%).

Disposition of the metabolite was also described using a two-compartment model. Based on preclinical observations (1), a

conversion of 21% of total sunitinib to metabolite was assumed to bring the magnitude of the parameters to a more physiologically relevant level. CL/F was estimated to be 29.6 L/h, and Vd/$F_{central}$ 3,080 liters [with interindividual variabilities (%CV) of 47% and 59% and variances of 0.22 and 0.35, respectively]. The terminal half-life was estimated to be 80 hours (interindividual variability, 28%), and the appearance half-life 2.4 hours (interindividual variability, 86%).

Tumor type (except AML), Asian race, gender, body weight, and elevated ECOG score (five of the seven covariates tested) described a portion of the variability in CL/F for sunitinib and metabolite; no relationship with age or renal function was observed for either sunitinib or metabolite CL/F. Gender and body weight (the two covariates tested) explained some of the variability in Vd/F for sunitinib and metabolite. Tumor type (metastatic renal cell carcinoma, gastrointestinal stromal tumor, or other solid tumor) had the greatest effect on the pharmacokinetics of sunitinib and SU12662, whereas race, gender, body weight (metabolite only), and ECOG score displayed less of an effect.

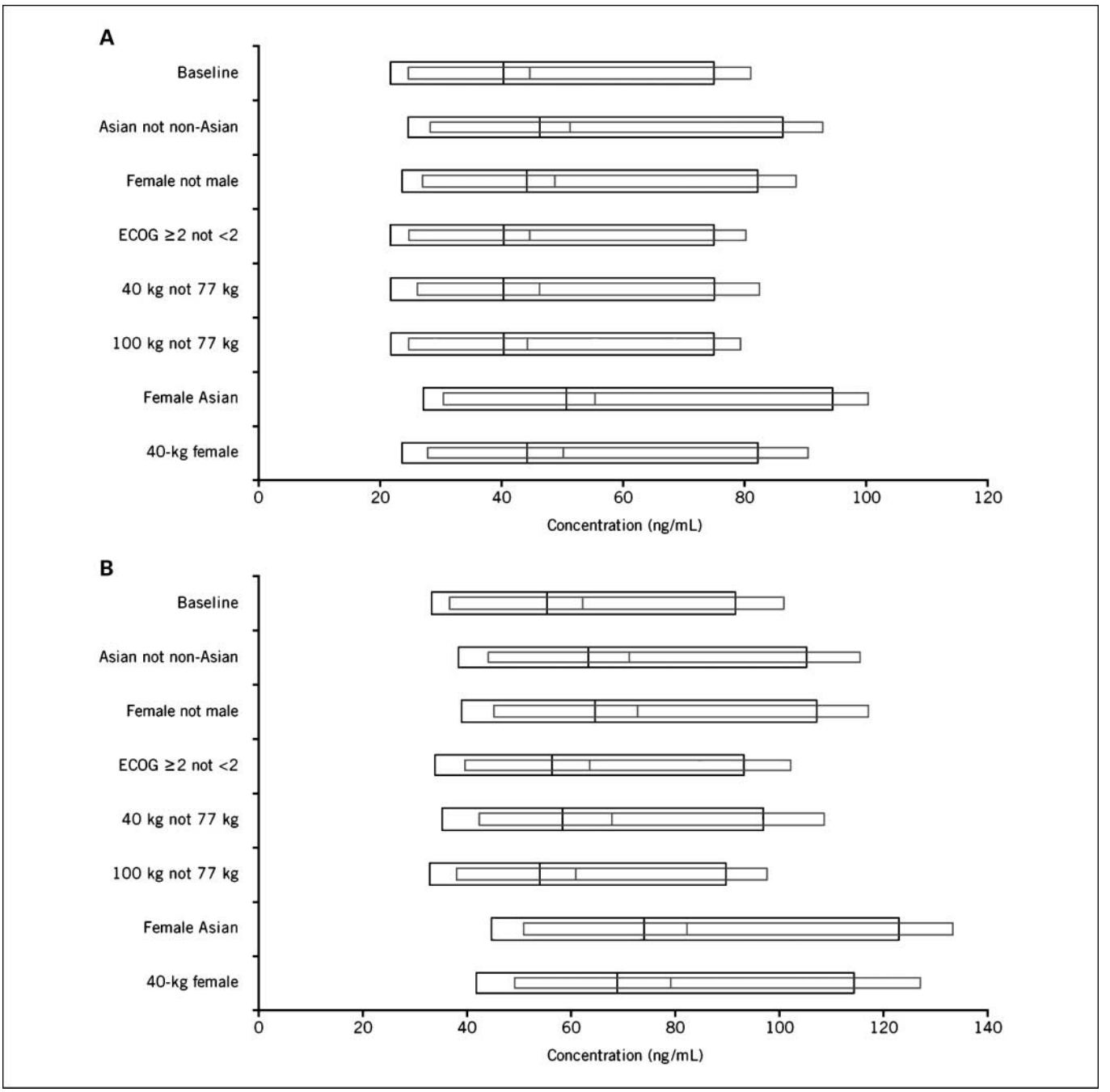

Fig. 3. Simulation predictions of sunitinib (*A*) and total drug (*B*) exposures in covariate subpopulations compared with baseline [a 77-kg Caucasian male with metastatic renal cell carcinoma and ECOG score ≤1; gastrointestinal stromal tumor and solid tumor patients were expected to display similar changes]. Wide bars represent C_{avg} ($C_{avg} \times 24$ h = AUC) and thinner bars represent C_{max}. Each bar indicates the 5th, 50th, and 95th percentiles for the subpopulation.

Simulations were done to predict the exposure increases resulting from the covariates shown to decrease CL/*F* and/or Vd/*F* in patients [i.e., Asian race, low body weight, female gender, and ECOG score ≥2 (but excluding tumor types)]. The interindividual variability of AUC and C_{max} of total drug is estimated to be 30% (expressed as %CV; variance, 0.09) in male Caucasian patients. Among patients, the predicted changes in AUC and/or C_{max} as a result of the individual covariates ranged from 2% to 17%. These findings indicate that the individual covariates investigated in this analysis minimally affected sunitinib and SU12662 pharmacokinetics and support the use of the recommended 50 mg daily sunitinib starting dose in these subpopulations.

The effects of many of the same covariates on imatinib pharmacokinetics seem to be similarly negligible (23, 26). However, factors affecting the pharmacokinetics of individual tyrosine kinase inhibitors vary, as increased CL/*F* with increasing weight has been reported for the oral tyrosine kinase inhibitor CP-724,714 (27) but not for sunitinib or imatinib.

The potential effects of body weight, mass, and/or obesity on the pharmacokinetics of anticancer drugs are of interest, particularly in Western societies with high rates of obesity and cancer. Recently, an analysis of eight different anticancer drugs in more than 1,200 patients found that obesity, defined as a body mass index of ≥30, significantly increased the absolute clearance of cisplatin, paclitaxel, and troxacitabine, as well as the steady-state volume of distribution of cisplatin and docetaxel (28). The present analysis evaluated the effect of body weight, rather than body mass index, on sunitinib pharmacokinetic parameters. However, body weight and body mass index were 90% correlated across all of the trials included in the analysis, suggesting that CL/*F* of SU12662 and Vd/*F* of both sunitinib and SU12662 are not likely to be increased to clinically significant levels in obese patients.

The identification of demographic factors associated with increased oral drug clearance, such as obesity in the case of cisplatin pharmacokinetics, was beyond the scope of the current study. However, such an investigation is of interest and warrants further analysis. In addition, correlations between total sunitinib drug exposure and specific adverse events, as well as efficacy findings, will be addressed in future studies.

Conclusion

The magnitude of the predicted changes in exposure with the covariates studied in this analysis minimizes the necessity for dose adjustment in any of these subpopulations.

Disclosure of Potential Conflicts of Interest

All authors are employed by and have an ownership interest in Pfizer.

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