

Population pharmacokinetics of imatinib mesylate and its metabolite in children and young adults

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Received: 7 November 2007 / Accepted: 6 March 2008 / Published online: 9 April 2008
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Abstract

Background Imatinib mesylate (Gleevec®) is a small molecule tyrosine kinase inhibitor approved for use in the management of chronic myeloid leukemia in adults and children and in gastrointestinal stromal tumors in adults. Population pharmacokinetic (PPK) studies evaluating the effect of population covariates on the pharmacokinetics of imatinib and its active metabolite have been developed in adults with chronic myeloid leukemia (CML) and gastrointestinal stromal tumor (GIST). However, this still remains to be described in children.

Purpose The objectives of the analysis were to develop a PPK model of imatinib and its active metabolite, CGP74588, to describe exposure in children and young adults and to identify covariates that are predictors of variability in disposition.

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Methods Plasma concentrations from 26 subjects with Philadelphia (Ph+) leukemia (Phase I study) and 15 subjects with refractory solid tumors (Phase II study), who received oral imatinib at doses ranging from 260 to 570 mg/m², were available for the PPK analysis in NON-MEM. Blood samples were drawn prior to dosing and over 24–48 h on days 1 and 8 of the studies. Covariates studied included weight, age, albumin, alanine aminotransferase and the study population.

Results The pharmacokinetics of imatinib and CGP 74588 were well described by one and two compartment models, respectively. Total body weight was the only covariate found to significantly affect Cl/F and V/F . The final imatinib-CGP 74588 model is summarized as follows: Cl/F_{imatinib} (L/h) = $10.8 \times (WT/70)^{0.75}$, V/F_{imatinib} (L) = $284 \times (WT/70)$ and $D1_{\text{duration of zero order absorption, imatinib}}$ (h) = 1.67 and $Cl/F_{\text{CGP 74588}}$ (L/h) = $9.65 \times (WT/70)^{0.75}$, $V1/F_{\text{CGP 74588}}$ (L) = $11.6 \times (WT/70)$, $Q_{\text{CGP 74588}}$ (L/h) = $2.9 \times (WT/70)^{0.75}$ and $V2/F_{\text{CGP 74588}}$ (L) = $256 \times (WT/70)$. Model evaluation indicated that the final model was robust and satisfactory.

Conclusions Current imatinib dosing guidelines in pediatrics is based on the achievement of exposures consistent with doses known to be safe and efficacious in adults. Dose adjustments in children are guided empirically by the observance of drug-related toxicities. While, the pharmacokinetics of imatinib and its active metabolite, CGP 74588 in children are consistent with prior knowledge in adults, the model will form the basis to support the design of future trials, particularly with a view to managing toxicities and exploring dosing in this population.

Keywords Imatinib · Population pharmacokinetics · Pediatric · Ph+ leukemia · Refractory solid tumors

Introduction

Imatinib mesylate (Gleevec[®], Novartis Pharmaceuticals, Hanover, NJ) is a small molecule tyrosine kinase inhibitor approved for use in the management of chronic myeloid leukemia in adults and children and in gastrointestinal stromal tumors in adults [7, 8, 13]. A daily oral dose of 400 or 600 mg is recommended in adults with CML and GIST, respectively [21].

Imatinib was designed to selectively target the aberrant fusion protein *bcr-abl* tyrosine kinase generated by the Ph+ chromosome [12]. This fusion protein is a strong inhibitor of apoptosis and is expressed in high levels in leukemic cells of patients with CML [26]. Imatinib competitively binds to the ATP binding site of *bcr-abl* tyrosine kinase, inhibiting tyrosine phosphorylation of proteins involved in *bcr-abl* signal transduction and ultimately leading to selective inhibition of proliferation and induction of apoptosis of *bcr-abl* positive cells [12]. Imatinib also inhibits c-KIT and PDGFR mediated signal transduction via a similar mechanism [15, 28]. Both c-KIT and PDGFR on binding to their respective ligands, the stem cell factor and PGDF respectively, play an important role in signal transduction leading to cell proliferation.

Imatinib is completely absorbed following oral administration [14]. It is over 95% bound to plasma proteins, mainly to albumin and α 1-acid glycoprotein. The drug is metabolized in the liver, predominantly by CYP3A4, to its *N*-demethylated piperazine derivative (CGP74588). CGP74588 has similar potency, selectivity and plasma binding profile as imatinib [14, 24]. Peak plasma concentrations of CGP 74588 are attained within 1–2 h following oral administration. The metabolite is reported to have a longer plasma half-life than its parent, with a plasma exposure of about 10% of that of the parent drug [14, 18, 20, 24]. Both imatinib and CGP74588 are excreted mainly via the feces. Following oral dosing, about 20% of the dose is recovered as CGP74588 and another 20% is recovered as unchanged imatinib [14, 24].

In a phase I dose ranging study in adults with CML, daily oral doses of 400 mg and above were found to result in concentrations over 570 ng/mL ($\geq 1 \mu\text{mol/L}$) 24 h after administration. This observed concentration exceeded the threshold concentration necessary for *bcr-abl* inhibition determined from cell-based assays [10, 23]. Evaluation of the exposure–response data showed that the hematologic response [white blood cell (WBC) on day 28] was highly dependent on the dose administered [23]. In addition, the model predicted achieving normalization of WBCs by day 28 with daily doses of 400 mg in 76% of the patients [24]. Further, a study in adults with GIST has reported a linear correlation between toxicity and exposure to

unbound imatinib [11]. These relationships have not been demonstrated in the pediatric populations thus far.

In a subsequent phase I trial in children with refractory or recurrent Ph+ leukemias, Champagne et al. [6] evaluated escalating oral doses of 260, 340, 440 and 570 mg/m² of imatinib. Daily oral doses of 260 and 340 mg/m² were found to provide similar plasma exposure as adult doses of 400 and 600 mg, respectively. No maximum tolerated dose was defined in this study. Currently a daily dose of 340 mg/m² (not to exceed 600 mg) is recommended in children with newly diagnosed Ph+ CML and 260 mg/m² in children who are resistant to interferon therapy or have Ph+ chronic phase CML recurrent after stem cell transplant [21].

The population pharmacokinetics (PPK) of imatinib has been studied in adults with CML. The clearance and the volume of distribution of imatinib were affected to a small extent by weight, hemoglobin and white blood cell count [27]. According to the model, doubling body weight increased clearance by 23% and the volume of distribution by 32%. Doubling the hemoglobin concentration increased the clearance and volume of distribution by 44 and 32%, respectively, while halving the white blood cell count increased clearance and volume of distribution by 12 and 8%, respectively. The model also predicted an overall decrease in CL/F from day 1 to 29 [27]. A similar relationship between body weight and granulocyte count with CL/F was reported in adults with GIST [17]. In contrast to the results reported in adults with CML, the model predicted an increase in the overall CL/F of imatinib with chronic exposure [17]. The objective of this study was to develop a PPK model of imatinib and its metabolite, CGP74588, in children and young adults.

Methods

Study design

Pharmacokinetic data from two Children's Oncology Group clinical trials were used in conducting the population analysis. A brief description of each of the studies is presented as follows.

Study 1 (POG 9973)

The detailed study design and patient characteristics were described by Champagne et al. [6]. Patients younger than 22 years who had recurrent or refractory Ph+ leukemia received a daily oral dose of 260, 340, 440 or 570 mg/m² of imatinib. If the dose was ≥ 800 mg/day it was given twice daily in two equal parts. Serial blood samples for plasma pharmacokinetic studies were obtained from 26 patients during the first cycle on days 1 and 8. A validated

HPLC/MS/MS method was used to assay total plasma imatinib and its main metabolite CGP 74588. The lower limit of quantification for the assay was 1 and 2 ng/mL for the parent and the metabolite, respectively [2].

Study 2 (ADVLO122)

The detailed study design and patient characteristics were described by Bond et al. [5]. Patients younger than 30 years with recurrent solid tumors of childhood including osteosarcoma, Ewing sarcoma, neuroblastoma, desmoplastic small round cell tumor, synovial cell sarcoma or gastrointestinal stromal tumor were enrolled. All patients received a daily oral dose of 440 mg/m² of imatinib. Doses of 600 mg/day or more were administered as divided doses, given twice daily. Pharmacokinetic samples were collected prior to the dose, between 1 and 3 h, 6 and 9 h and at 12 h post-dosing on day 1 for the first six patients enrolled in the study. Trough levels on days 8 and 18 were measured in all the patients. Total plasma imatinib concentrations were measured using a validated UV-HPLC method with a lower limit of quantification of 10 ng/mL [5, 19].

Study protocols were approved by institutional review boards or ethics committees of participating institutions and written informed consent was obtained from the patient or their legal guardian prior to study entry.

Population pharmacokinetic analysis

NONMEM (version 5, level 1.1, GloboMax, Hanover MD) was used for population nonlinear mixed effects modeling. The observed concentrations were transformed to the log scale and models were fit to the log transformed data. Both one and two compartment pharmacokinetic models, parameterized in terms of CL/F and V/F , were evaluated. Several input models, including first order, zero order, a combined first and zero order expression, the Weibull function and the transit compartment model were evaluated to describe the absorption process of imatinib.

Initially, the structural model was developed without any covariates. An exponential error model, as shown below, was used to describe the interindividual variance (IIV) on the pharmacokinetic parameters.

$$P_i = \hat{P} \exp(\eta^{P_i}) \quad (1)$$

P_i is the estimated parameter value for individual i , \hat{P} is the typical population value (geometric mean) of the parameter and η^{P_i} are individual-specific interindividual (between subject) random effects for individual i and parameter P assumed to be distributed: $\eta \sim N(0, \omega^2)$ with covariances defined by the interindividual covariance matrix Ω . The

random residual error was modeled using an additive error model as stated below.

$$\ln C_{ij} = \ln \hat{C}_{ij} + \varepsilon_{aij} \quad (2)$$

C_{ij} is the j th measured observation in individual i , \hat{C}_{ij} is the j th model predicted value in individual i , ε_{aij} is the additive residual random error, for individual i and measurement j and are assumed to be independently and identically distributed: $\varepsilon \sim \text{NID}(0, \sigma^2)$. A combined additive and proportional error model was also evaluated. Additionally, estimation of separate residual error terms, a possible result of the different assay methodologies used in the two studies, was also examined. The first order conditional estimation method (FOCE) with η - ε interaction was used throughout the model building procedure [4]. Model building was performed with the assumption of covariance between the random effects and so a block covariance matrix was evaluated.

The influence of covariates was also evaluated on the pharmacokinetics of imatinib and its metabolite following a stepwise forward inclusion process. In order to identify clinically meaningful covariates, the number of covariates explored was determined based on mechanistic plausibility and prior scientific knowledge of factors that may affect the pharmacokinetics of the drug. Graphical inspection of plots of maximum a posteriori (MAP) Bayes estimates of individual random effects (η_i) from the final structural model versus covariates was performed to assess the presence of any covariate effects. The covariates examined were body weight, age, albumin, alanine aminotransferases and the study population.

Initially, the population pharmacokinetic parameters of imatinib were fixed to the values obtained from the imatinib PPK model building step in order to develop the metabolite structural model. In the absence of data following intravenous administration of the metabolite, the estimation of fraction metabolized (F_m) will be confounded and is therefore typically fixed to a known value. About 20% of an oral dose of imatinib was recovered in the feces as the metabolite [14, 24]. Based on this observation, the fraction of imatinib metabolized was fixed to 0.2 in the present analysis. The metabolite model was developed following the same procedure as the imatinib PPK model. Once the metabolite structural model was determined, all parameters in the model were estimated simultaneously.

Visual inspection of diagnostic plots, plausibility and precision of parameter estimates and estimates of random residual variances for the parameters were used to guide model development. A drop in objective function value of >10.83 (considered significant at $p < 0.001$) was used to discriminate among alternative nested models.

Model evaluation

In order to assess the adequacy of the imatinib–CGP74588 PPK model, the final model was evaluated by the predictive check method [16, 31]. One thousand Monte Carlo replicates of the data set were generated using the final PPK model. Distributions of C_{avg} of the simulated data were compared with the distribution of C_{avg} in the observed imatinib and CGP 74588 data set, using exploratory graphics (quantile–quantile plots and histograms). This was also summarized across all simulation replicates as the population first quartile, mean, and third quartile values. Most of the available observed plasma concentrations in the phase II study ADVL0122 were single trough measures. C_{avg} , the average concentration across all data points within each individual, was therefore selected as the metric for predictive check. A predictive check p value was then calculated for each summary statistic as the proportion of simulated values that were greater than the observed value for that statistic. This p value defined the probability that the simulated data (under the model and parameter point estimates) could be more extreme than the observed data. Any p values more extreme than 0.05 or 0.95, or any systematic deviations evident on visual inspection of exploratory graphics were investigated and further model development was conducted as necessary.

Results

A total of 842 plasma imatinib and 424 metabolite plasma observations were available for building the population model. Summary demographic information for the patients is provided in Table 1. The median age of the patients included in the analysis was 16 years (6–24 years). The median body weight was 40.3 (14.6–119.2 kg).

Figure 1 presents the observed imatinib and CGP 74588 plasma concentration–time profiles for all individuals in

the study on days 1 and 8, respectively. The observed imatinib concentrations ranged from 9 to 11,200 ng/mL on day 1 and from 61 to 14,699 ng/mL on day 8. The metabolite concentrations ranged from 2 to 807 ng/mL on days 1 and 65 to 2,450 ng/mL on day 8, respectively. As seen in Fig. 1, there is considerable variability observed in the absorption profiles between individuals. Additionally, there appeared to be random differences in exposure in the same individual, between days 1 and 8. The area under the concentration time curve was higher on day 1 than on day 8 in some of the individuals and vice versa in some others, while a few individuals showed no difference. The imatinib and CGP plasma profiles in three individuals displayed a secondary peak.

Based on the diagnostic plots and OFV from the initial analysis, a one-compartment model was found to provide a better fit to the imatinib plasma concentration than a two-compartment model. Also, amongst the various absorption models evaluated, a zero order process best described the absorption of imatinib following oral administration. Interindividual variance was estimated on clearance, volume of distribution and on the duration of absorption. The value of the objective function for this structural model was 0.288. Clearance was estimated at 6.81 L/h (IIV 52%), volume of distribution at 149 L (IIV 55%) and the duration of absorption at 2.11 h (IIV 69%). The residual error was estimated at 49%.

Visual inspection of plots of MAP Bayes estimates of individual random effects (η_i) on CL/F and V/F versus body weight showed a correlation between the two parameters and the total body weight. Body weight was then incorporated in the model following the standard allometric expressions for clearance and volume. Accordingly, the exponents on CL/F and V/F were fixed to 0.75 and 1, respectively. Inclusion of body weight as a covariate on CL/F and V/F resulted in substantial drop in the objective function and a marked improvement in the diagnostic plots as seen in Fig. 2. Further, in order to

Table 1 Summary demographic information for patients

	POG 9973	ADVL0122
Phase/population	Phase I/Ph+ leukemia	Phase II/refractory or relapsed solid tumors
Dosage	Escalating oral doses of 260, 340, 440 and 570 mg/m ²	Target oral dose of 440 mg/m ²
PK sampling	Predose, 0.5, 1, 1.5, 2, 4, 8 and 24 h on day 1 and at predose, 0.5, 1, 1.5, 2, 4, 8, 24 and 48 h on day 8	Predose, 1–3, 6–9 and 24 h and at 24 h on day 8
No. of subjects	26	15
Age (year)	Range 7–24 Below 12 year: $n = 7$ Above 12 year: $n = 19$	Range 6–22 Below 12 year: $n = 9$ Above 12 year: $n = 6$
Weight (kg)	50 (14.6–119.2)	47.2 (19–95.3)
Sex (M/F)	17/9	–

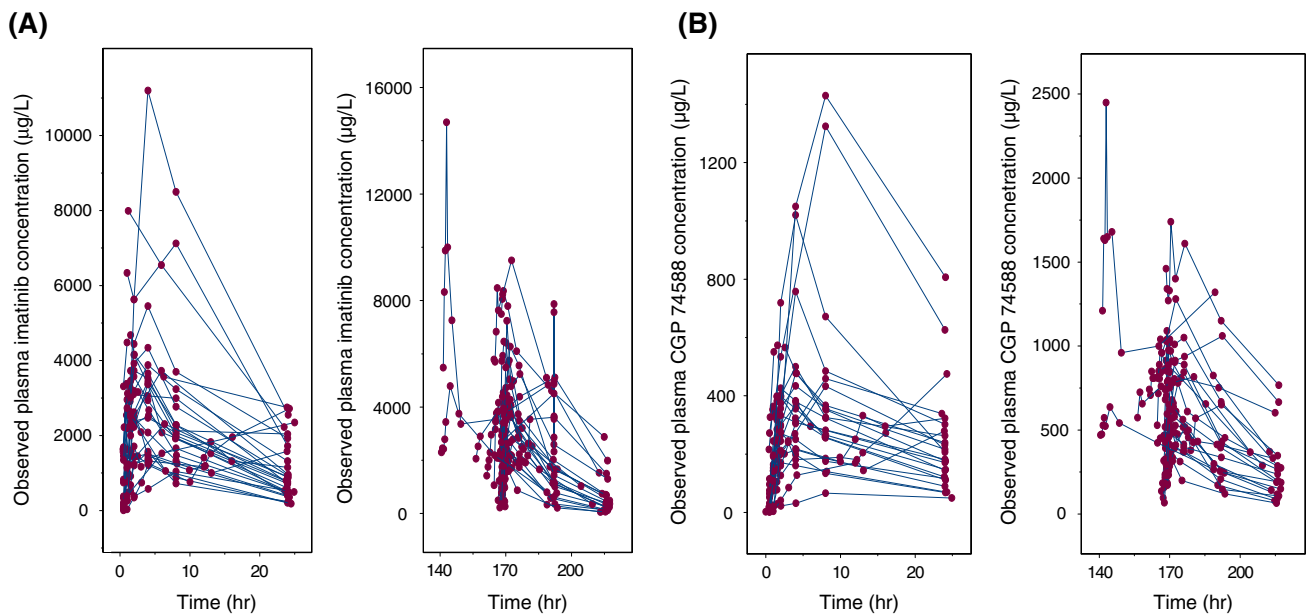


Fig. 1 Observed plasma concentration–time profile of **a** imatinib on days 1 and 8 from POG 9973 and ADVL 0122 and **b** CGP 74588 on days 1 and 8 from POG 9973

account for the observed random variability in absorption/exposure (Fig. 1), a bioavailability term ($F1$) was included in the model. This parameter was fixed to 1 in the general population and interoccasion variability (IOV) in $F1$ was estimated. This resulted in a decrease of over 30 points in the objective function value. The final imatinib model estimated imatinib CL/F and V/F at 10.4 L/h and 255 L, respectively. The estimates of interindividual variability on CL/F decreased to 31.7% and that on V/F was estimated to be close to zero. Interoccasion variability on $F1$ was estimated at 44%. There was no discernible relationship between the parameters and any of the other covariates tested. A summary of the model building process is presented in Table 2. The plasma disposition of CGP 74588 was best described by the two-compartment model. Body weight was the only covariate found to significantly affect CL/F and V/F . The parameter estimates for the final imatinib–CGP 74588 model are presented in Table 3. Figure 3 (left panel) shows population and individual predicted concentrations obtained from the final model plotted against observed concentration. Figure 3 (right panel) shows the weighted residuals plotted against predicted concentrations. The plots do not exhibit any trends and are generally featureless indicating that the structural and statistical models are satisfactory.

Individual CL/F and V/F estimates for imatinib ranged from 3.6 to 22 L/h and 59 to 482 L, respectively. Median values for CL/F and V/F in children (<12 years) were 5.06 L/h and 98.4 L. In adolescents and young adults (>12 years) median CL/F and V/F were 10.3 L/h and

273.4 L, similar to those reported in adults. Figure 4 presents plots of individual CL/F and V/F in relation to body weight and body surface area. There is a moderate variability in the observed CL/F , similar to that observed in adults. Since estimation of a random effect on V/F was not supported by the data, weight alone contributed to the differences in the volume of distribution between individuals.

Model evaluation

The distributions of the simulated C_{avg} in comparison with the observed C_{avg} for imatinib and CGP 74588 are presented in Fig. 5. No systematic deviations from the observed data were seen.

Discussion

The results of a population pharmacokinetic analysis for imatinib mesylate and its major active metabolite CGP74588 in children and young adults are reported here. Data from a COG phase I study in children with Ph-leukemias and a phase II study in children with recurrent or refractory solid tumors were analyzed simultaneously.

A one-compartment model adequately fit the plasma concentration data for imatinib while a two-compartment pharmacokinetic model best fit the observed CGP74588 plasma concentrations. The estimates of CL/F and V/F for

Fig. 2 *Top panel:* Plot of clearance residuals (CLR) and volume residuals (VR) versus weight from the base model. *Bottom panel:* Plot of clearance residuals (CLR) and volume residuals (VR) versus weight after weight was incorporated into the model. The open circles are the individual data and the line is a local regression smooth. The horizontal line marks $x = 0$

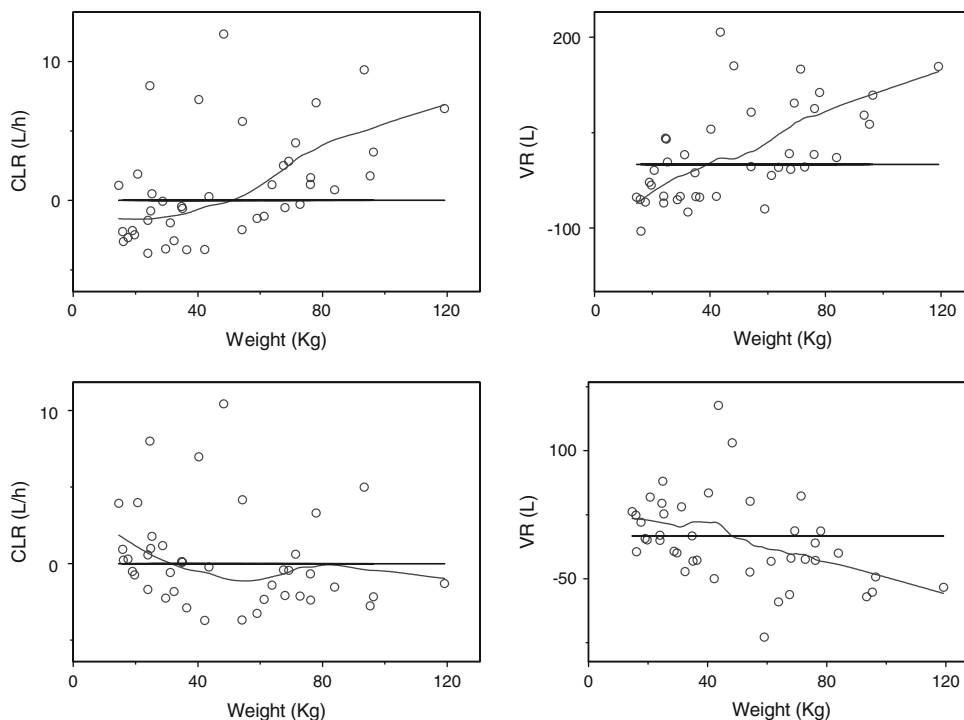


Table 2 Summary of model building for imatinib

Description of the model	Parameter	Point estimate	Comments
One-compartment with first order elimination and zero order absorption ($D1$), interindividual variability estimated on all parameters (base model)	CL/F (L/h)	6.81	OFV = 0.288
	V/F (L)	149	Correlation between CL/F , V/F , and total body weight
	$D1$ (h)	2.11	
	$\eta_{CL/F, \%CV}$	52.1%	
	$\eta_{V/F, \%CV}$	53%	
	$\eta_{D1, \%CV}$	69%	
	$\sigma_{\%CV}$	49%	
Base model + total body weight on CL/F and V/F	CL/F (L/h)	10.3	-14.16
	V/F (L)	255	
	$D1$ (h)	2.29	
	$\eta_{CL/F, \%CV}$	45%	
	$\eta_{V/F, \%CV}$	41%	
	$\eta_{D1, \%CV}$	65%	
	$\sigma_{\%CV}$	49%	
Base model + total body weight on CL/F and V/F + IOV on F1	CL/F (L/h)	10.3	-46.242
	V/F (L)	251	
	$D1$ (h)	2.32	
	$\eta_{CL/F, \%CV}$	33%	
	$\eta_{V/F, \%CV}$	7%	
	$\eta_{D1, \%CV}$	69%	
	$\sigma_{\%CV}$	45%	
	IOV on F1	44%	

Table 3 Parameter estimates from the final imatinib–CGP 74588 model

Parameter (units)	Point estimate (%CV)	IIV (%) (%CV)
Imatinib		
CL/F (L/h)	10.8 (7.5)	31.5 (26.5)
V/F (L)	284 (6.5)	–
$D1$ (h)	1.67 (0.5)	92.6 (37.3)
F1	1 (fixed)	–
IOV on F1		41 (24.8)
CGP74588		
CL/F (L/h)	9.65 (7.8)	33.4 (30.1)
$V1/F$ (L)	11.6 (16.6)	–
Q (L/h)	2.9 (21.9)	–
$V2/F$ (L/h)	256 (23.5)	–
Residual error		
Imatinib (%CV)	40.8 (14.8)	
CGP74588 (%CV)	34.7 (17.4)	

$$CL/F_{\text{imatinib}} \text{ (L/h)} = 10.8 \times (WT/70)^{0.75}; V/F_{\text{imatinib}} \text{ (L)} = 284 \times (WT/70)^{0.75}; D1_{\text{imatinib}} \text{ (h)} = 1.67; CL/F_{\text{CGP 74588}} \text{ (L/h)} = 9.65 \times (WT/70)^{0.75}; V1/F_{\text{CGP 74588}} \text{ (L)} = 11.6 \times (WT/70); Q_{\text{CGP 74588}} \text{ (L/h)} = 2.9 \times (WT/70)^{0.75}; V2/F_{\text{CGP 74588}} \text{ (L)} = 256 \times (WT/70)$$

imatinib obtained in children and young adults are consistent with the prior knowledge on imatinib and CGP 74588 in adults. The final model predicts the total imatinib clearance and volume of distribution in a 70 kg adult to be 10.8 L/h and 284 L, respectively [$CL/F = 10.8 \times (WT/70)^{0.75}$ and

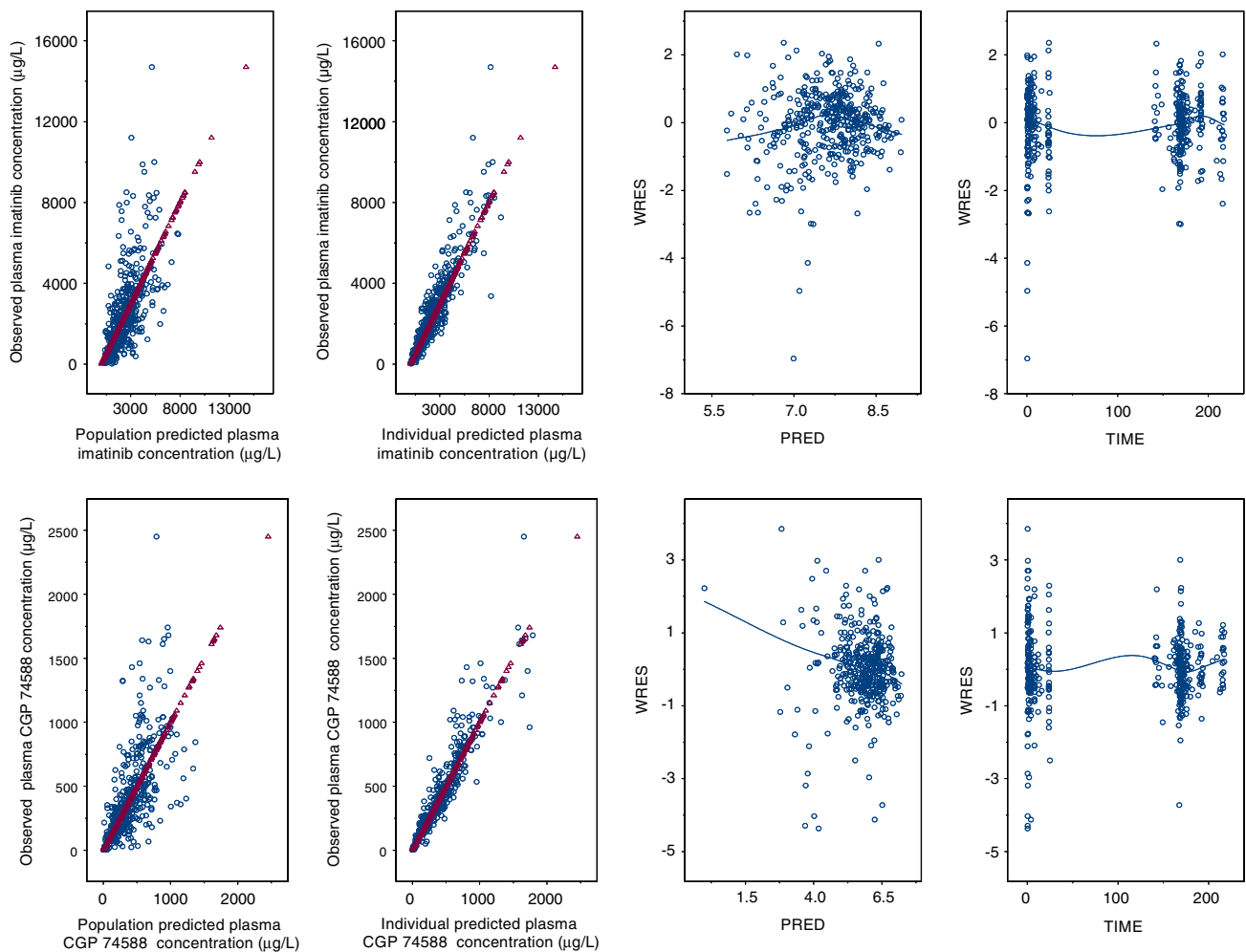


Fig. 3 Left panel: Individual (IPRED) and population (PRED) predicted concentrations of imatinib and CGP 74588 plotted as function of the observed concentrations (DV). The open circles are the individual data and the line is the $y = x$ (unity) line. Right panel:

Weighted residuals versus predicted concentrations and weighted residuals versus time for the final model. The open circles are the individual data and the line is a local regression smooth

$V/F = 284 \times (WT/70)^1$. These values compare well with the average values reported in adults [7, 17, 27]. Further, in a typical 5-year-old child weighing 18 kg, the model predicts a total clearance of 4 L/h [0.22 L/(h kg)].

A few of the previously published PPK studies in adults have reported a statistically significant change in the overall clearance of imatinib between single dose and steady state. In their study in adults with CML, Schmidli et al. reported a decrease of about 25% in the total clearance of imatinib between days 1 and 29 of treatment. A study in adults with GIST reported an overall increase in imatinib clearance on chronic exposure. Hence this relationship was investigated in the present analysis. Unlike the above observations in adults, clearance estimates remained the same between single dose (day 1) and steady state (day 8).

In the present analysis, interoccasion variability in absorption was assessed by incorporating a bioavailability term (F1) in the model. F1 was fixed to a value of 1. Although the absolute bioavailability of imatinib is close to 1 the term F1 in the model does not estimate true bioavailability. The model estimated this random variability to be about 40%. Considerable variability in the absorption of imatinib has been observed in previous studies, although the reason for this is not clear. In a study estimating the absolute bioavailability of imatinib capsules, the observed variability in the exposure ($AUC_{0-\infty}$) more than doubled following an oral dose of 400 mg when compared to an IV infusion of 100 mg [22]. Further, in some patients clinically important lower absorption and low bioavailability has been reported [24]. Imatinib exhibits high intrinsic permeability and undergoes rapid dissolution at $pH \leq 5.5$,

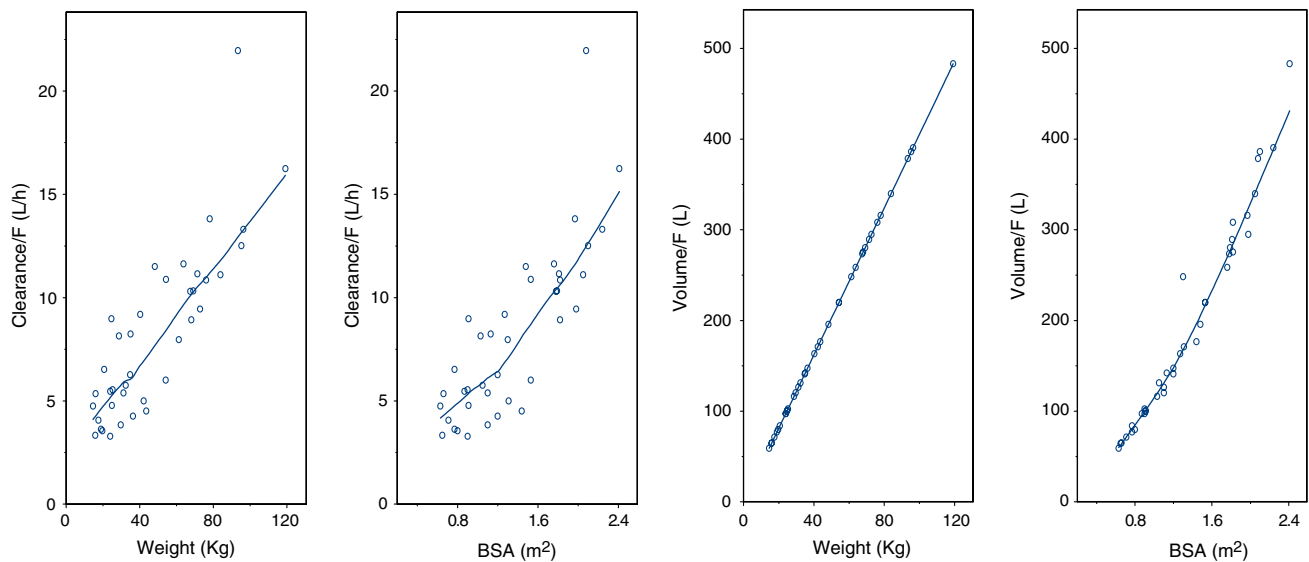


Fig. 4 Model predicted total imatinib clearance (CL/F) (a) and volume of distribution (V/F) (b) plotted against body weight and body surface area

resulting in rapid absorption following oral administration. Such pH dependent aqueous solubility could result in considerable within subject variability in absorption. In addition, it is reported to undergo biliary clearance and subsequent enterohepatic recirculation [14, 25]. This may also contribute to the observed variability in absorption. As major changes in the physiology of the gastrointestinal tract take place within the first weeks of life [3], variability in absorption in children, as observed in this analysis, is expected to be similar to that in adults.

CGP 74588 is the pharmacologically active *N*-demethylated metabolite of imatinib. Peak plasma levels of CGP 74588 are observed 1–2 h post oral dosing. The plasma exposure of the metabolite (AUC_{0-24}) has been reported to be around 10% that of imatinib [14]. About 20% of an oral dose of imatinib was recovered in the feces as the metabolite [14, 24]. Based on this observation, the fraction of imatinib metabolized was fixed to 0.2. Although this is a fair assumption, estimates of metabolite clearance and volume of distribution would depend on the value of F_m to a large extent. There is large variability reported in both the expression and activity of CYP3A4 between individuals [9, 30]. This variability in CYP3A4 expression and activity would result in large differences between individuals in the fraction of the parent compound metabolized. Overall, the model described the disposition of CGP 74588 well. The estimate of the elimination half-life calculated for CGP 74588 under the model is in good agreement with the reported value of 20.6 ± 1.7 h, estimated via noncompartmental analysis of CGP 74,588 data from a biotransformation study employing a similar sampling scheme [14].

Several pediatric solid tumors have shown abnormally high expression of PDGFR and c-KIT [1, 29]. In the phase I trial in children with Ph+ leukemias (study 1, POG 9973), daily oral doses in the range of 260–570 mg/m² were found to be safe and effective in achieving a complete hematologic response [6]. However, no clinical activity was observed in the phase II trial (ADVL 0122) which was designed to assess the response of pediatric solid tumors to treatment with imatinib [5]. The results of the present analysis show that the pharmacokinetics of imatinib in the two populations were similar. There were no differences observed in estimates of CL/F and V/F between the two study populations. The average plasma imatinib concentrations attained on days 1 and 8 were also comparable in patients receiving the same dose in the two populations. It could be inferred that the reason for the observed difference in efficacy between the two populations is due to pharmacological rather than dispositional differences. For instance, the presence of activating mutations rather than high expression of c-KIT and PDGF-r are required for effective inhibition by imatinib [5]. Further dose adjustments to achieve higher imatinib concentrations in these populations may be of little or no value.

Imatinib and CGP 74588 bind to erythrocytes and the plasma protein α 1-acid glycoprotein. These were not measured in either of the two studies and their proposed relationship with CL/F and V/F could not be evaluated in this analysis. A logical extension of the current efforts in pediatrics would be to challenge the established adult therapeutic window using the current model to explore exposure targets. As the adult thresholds presumably correlate with toxicity and efficacy outcomes, simulated

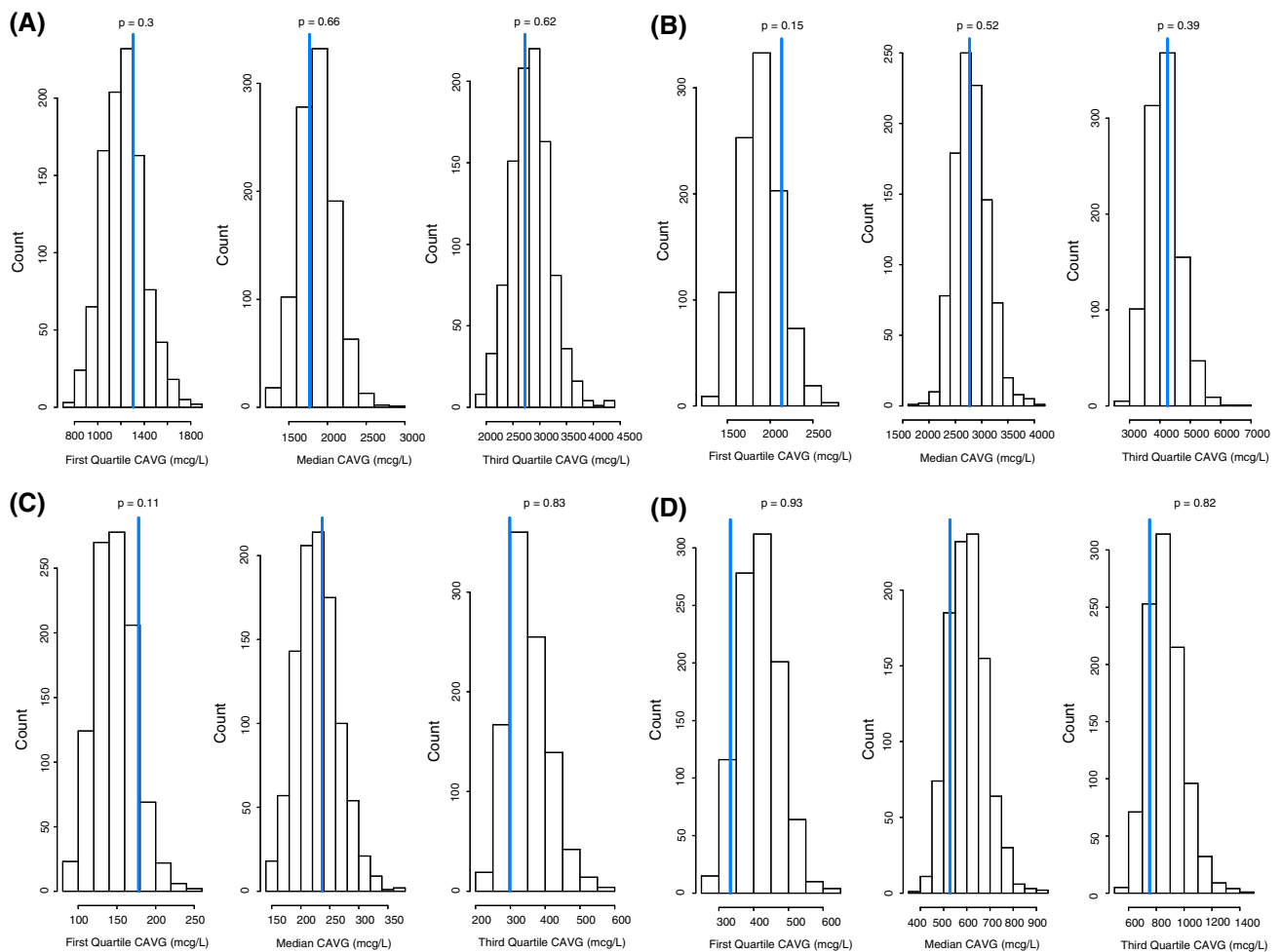


Fig. 5 Predictive check for imatinib and CGP74588 C_{avg} on days 1 and 8. *Top panel (a, b): left* Population first quartile C_{avg} ; *middle* Median C_{avg} ; *right* Population third quartile C_{avg} for imatinib on days 1 and 8. *Bottom panel (c, d): left* Population first quartile C_{avg} ;

middle Median C_{avg} ; *right* Population third quartile C_{avg} for CGP 74588 on days 1 and 8. The observed values are indicated by a vertical line, along with the predictive check p value (p value is the proportion of the simulated C_{avg} above the observed value)

pediatric thresholds can be likewise evaluated by extending the current model to consider exposure–outcome relationships. The existing clinical data in pediatrics suggest that these targets may differ and hence a model based algorithm may be useful to design and plan more targeted investigations in pediatrics and perhaps ultimately guide individual therapy with imatinib if drug levels are monitored.

Acknowledgments The authors thank Drs. Y. Wang and H. Schmidli, Novartis Pharma AG, for providing them with the NONMEM script from their previously published Gleevec PPK model in adults.

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