Population pharmacokinetic modeling of pazopanib in healthy volunteers and patients with advanced renal cell carcinoma

Baneyx G. (1), Combes F.P. (2), Huang P-H. (4) and Elmeliegy M. (3)

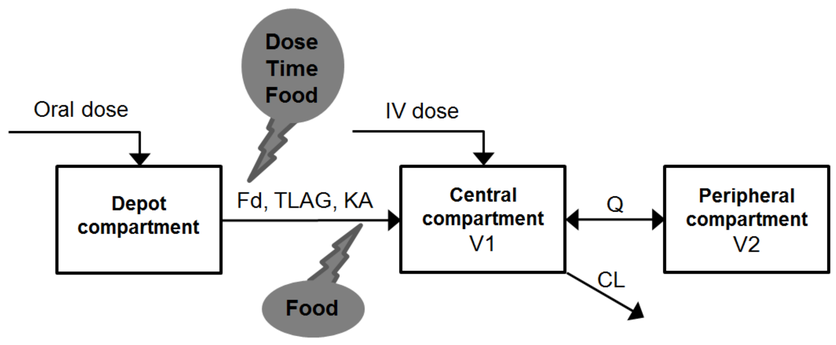
(1) Novartis Pharma AG, Biostatistical Sciences and Pharmacometrics, Basel, Switzerland. Novartis Pharmaceuticals Corporation, (2) Biostatistical Sciences and Pharmacometrics, (3) PK Sciences, (4) Integration of Randomized Clinical Trial data, East Hanover, New Jersey, USA.

Background and Objectives

- Pazopanib, a tyrosine kinase inhibitor [1], administered as oral dose of 800 mg once daily, is approved as a monotherapy treatment for advanced renal cell carcinoma and advanced soft tissue sarcoma.
- Pazopanib is classified as BCS class II and its solubility decreases with pH. Absorption is incomplete (F~21%), variable, and the exposure increases less than proportionally with dose to reach an apparent plateau from 800 mg.
- Existing popPK model had to be refined to address following aspects:
  - dose effect on oral bioavailability only characterized for 400 and 800 mg,
  - oral bioavailability predicted higher when co-administered with acid reducing agents which is in disagreement with current knowledge,
  - one compartment disposition model not adequate given the bi-exponential elimination observed after intravenous infusion.
- Objective was to update the pazopanib popPK model based on all available historical PK data and to characterize the non-linear kinetics.

Update of popPK model

- DATA: 451 subjects and 4011 PK observations (rich/sparse sampling) collected from 9 Phase I/II/III studies in healthy volunteers, patients with solid tumors and advanced renal cell carcinoma cancer after single intravenous infusion of 5 mg (7 subjects) and daily oral doses ranging from 50 to 2000 mg were used to update the structure, parameter estimates and covariate effects. PK data with food were available in 30 subjects after an oral dose of 400 and 800 mg
- ESTIMATION: Model parameters were estimated by population approach using the SAEM algorithm in Monolix 4.3.2. A logit distribution was assumed for individual bioavailability and log-normal distribution for other parameters.
- STRUCTURE (Figure 1):



- COVARIATES: Effects of dose and time (day 1 vs others) on bioavailability and effect of food on both bioavailability and absorption rate were implemented as structural covariates. Implementation of retained covariate effects for the i^{th} subject is given below:

$KA_i = \boldsymbol{KA} \cdot exp(\boldsymbol{bFOOD2} \cdot FOOD) \cdot exp(\boldsymbol{\eta_{KA,i}})$ where $\boldsymbol{KA}$ is absorption rate, $\boldsymbol{bFOOD2}$ the food effect and FOOD a time-dependent regressor indicating the presence of food (FOOD=1, otherwise 0)

$Fref_i = \boldsymbol{Fref} \cdot exp(\boldsymbol{\eta_{Fref,i}})$ where $\boldsymbol{Fref}$ is the reference absolute oral bioavailability for a subject receiving an oral dose of 800 mg on day 1 and in absence of food

An hybrid absolute oral bioavailability (TVF_i) was computed to include food effect ($\boldsymbol{bFOOD}$), dose effect ($\boldsymbol{bDOS}$) and time effect ($\boldsymbol{bTF}$) to reflect higher exposure on day 1 (DAY0=1, otherwise 0):

$$TVF_i = \ln(Fref_i/(1-Fref_i) \cdot exp(\boldsymbol{bFOOD} \cdot FOOD) \cdot (dose/800)^{\boldsymbol{bDOS}} \cdot exp(\boldsymbol{bTF} \cdot (1-DAY0))$$

Finally, a logit transformation of the quantity TVF_i was used to ensure that the value of absolute oral bioavailability (Fd_i) including both inter-subject variability and covariate effects is constraint between 0 and 1:

$$Fd_i = exp(TVF_i)/(1+exp(TVF_i))$$

References:
[1] Kumar et al. Mol Cancer Ther. 2007; 6: 2012-2021.
[2] Kuhn et al. Computational Statistics and Data Analysis 2005; 49:1020-1038.

Conclusions

- Integration of all available historical PK data improved the understanding of the non-linear pharmacokinetics of pazopanib and allowed exploration of multiple factors.
- The non-linear exposure of pazopanib was characterized by an absolute oral bioavailability decreasing with the dose (limited solubility) and time as well as associated to a marked increase with food.
- Implementation of a continuous dose effect on oral bioavailability will extend the ability of the model to simulate pazopanib exposure at any dose levels.

Results and discussion

- Pazopanib PK well described by a two-compartment disposition model with delayed first order absorption, first-order elimination and absolute oral bioavailability decreasing with dose and time (Figure 3, Table 1).
- Absolute oral bioavailability (Figure 2):
  - 40 % higher at 400 mg than 800 mg
  - 30 % lower at steady state than after single administration
  - 2.9 fold increased by food after single administration 800 mg
- Effect of acid reducing agents was predicted to decrease bioavailability by 12% (in agreement with current knowledge) but not retained in the model.
- PK model suggested that the increase of exposure less than dose proportional fashion was due to the low solubility limiting the absorption.
- Time effect was implemented as a categorical covariate (day1 vs other days) due to lack of data between first administration and time to reach steady state and there is no strong evidence to support this result.

Figure 2: Impact of dose, time and food on bioavailability

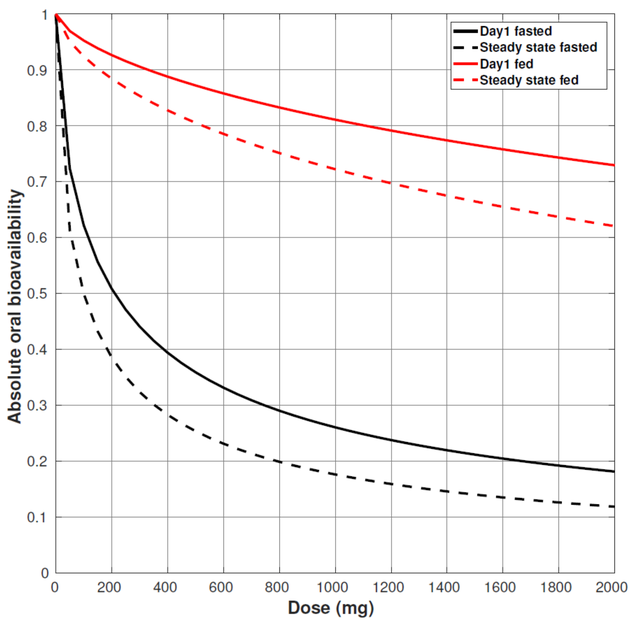


Figure 3: Model evaluation (pcVPC, NPDE)

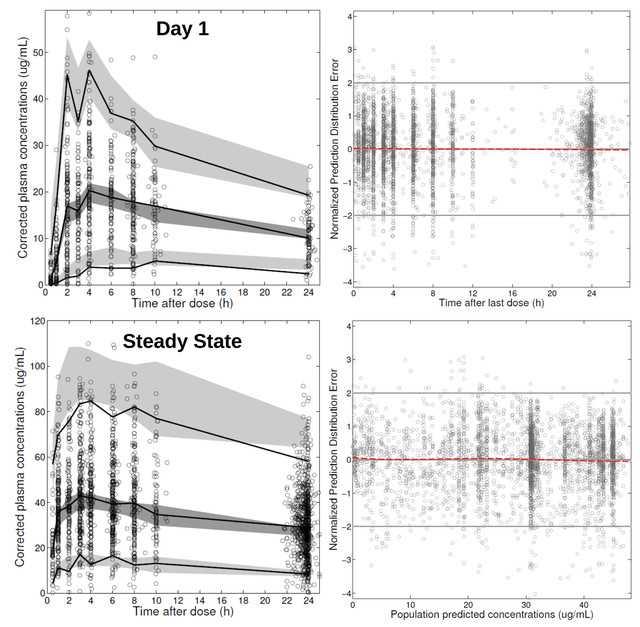


Table 1: Parameter estimates

PARAMETER			FIXED EFFECTS		INTER-SUBJECT VARIABILITY	
			Estimate	RSE%	Estimate	RSE%
TLAG	lag time	(h)	0.42	8.77	0.91	7.97
Fref	absolute oral bioavailability		0.29	4.33	0.86	4.58
bFOOD	food effect on Fref		2.50	FIX		
bDOS	dose effect on Fref		-0.67	6.07		
bTF	time effect on Fref		-0.50	7.27		
KA	absorption rate	(h-1)	0.42	6.72	0.76	6.75
bFOOD2	food effect on KA		-0.93	6.76		
V1	central volume	(L)	5.10	FIX		
V2	peripheral volume	(L)	7.82	4.66		
Q	inter-compartmental clearance	(L/h)	1.05	6.56		
CL	clearance	(L/h)	0.17	5.17	0.65	5.19
Corr(CL, Fref)	covariance CL-Fref		0.63	5.80		
a	additive error	(µg/mL)	0.12	9.05		
b	proportional error	(%)	22.8	1.53		

Fref: absolute oral bioavailability for reference dose 800 mg on day 1 and without food; RSE: relative standard error.

Poster presented at Population Approach Group Europe (PAGE), June 6-9, 2017, Budapest, Hungary.