

Development of a pharmacokinetic model to describe the complex pharmacokinetics of pazopanib in cancer patients

Huixin Yu^{1*}, Nielka van Erp², Sander Bins³, Ron H. J. Mathijssen³, Jan H. M. Schellens^{4,5,6},
Jos H. Beijnen^{1,5,6}, Neeltje Steeghs^{4,5}, Alwin D. R. Huitema^{1,5}

¹Department of Pharmacy & Pharmacology, Netherlands Cancer Institute-Antoni van Leeuwenhoek and MC Slotervaart, Amsterdam, NL; ²Department of Clinical Pharmacy, Radboud University Medical Center, Nijmegen, NL; ³Department of Medical Oncology, Erasmus MC Cancer Institute, Rotterdam, NL; ⁴Department of Medical Oncology, Netherlands Cancer Institute-Antoni van Leeuwenhoek, Amsterdam, NL; ⁵Department of Clinical Pharmacology, Netherlands Cancer Institute-Antoni van Leeuwenhoek, Amsterdam, NL; ⁶Utrecht Institute of Pharmaceutical Sciences, Utrecht University, Utrecht, NL; *contact: h.yu@nki.nl

Introduction & Aim

- Pazopanib hydrochloride (Votient®) is a tyrosine kinase inhibitor that has been approved for the treatment of metastatic renal cell carcinoma and soft tissue sarcoma at an oral dose of 800 mg daily

Fig. 1. Chemical structure of pazopanib.

- The aim of the study was to systemically develop and evaluate a pharmacokinetic (PK) model of pazopanib to understand and quantify the complex PK characteristics of pazopanib

Data

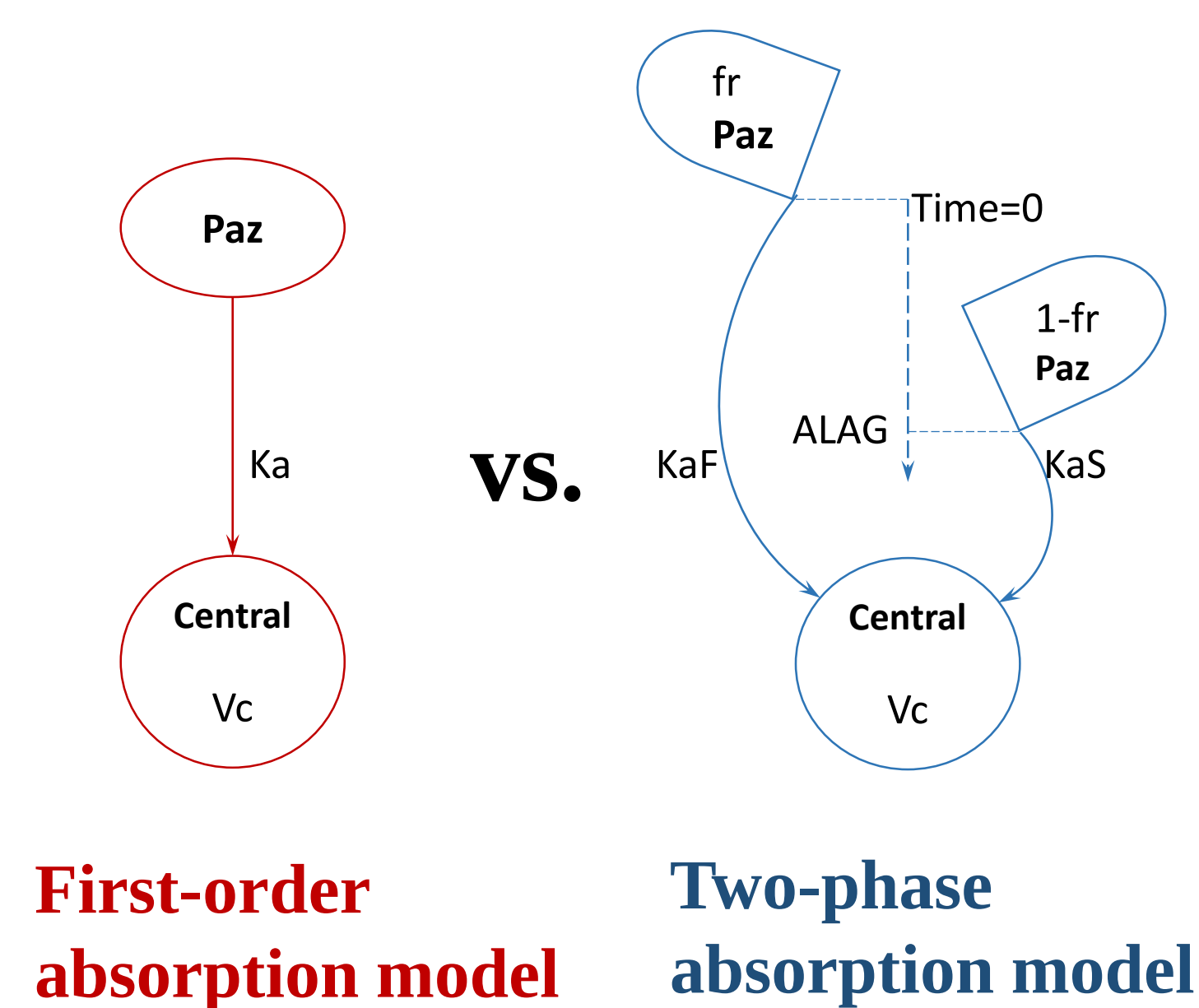
- Table 1 gives an overview of the PK data included in the study
- In study 3, ifosfamide decreased the plasma exposure of pazopanib by enzyme induction. A previously developed model for ifosfamide PK and enzyme induction was used [4].

Table 1. Characteristics of PK data of pazopanib

	Study 1 [1]	Study 2 [2]	Study 3 [3]
Type of study	TDM	paz + doc	paz + ifo
Number of patients	13	41	42
Number of PK occasions	3	1	3
Doses (mg/day)	400, 600, 800, 1,200	200, 400, 600	200, 400, 800, 1,000
PK sampling time (hours)	0, 1, 2, 3, 4, 6, 8, 10, 24	0, 0.5, 1, 2, 4, 6, 8, 24	0, 0.5, 1.5, 3.5, 6, 8, 24

Doc, docetaxel; ifo, ifosfamide; TDM, therapeutic drug monitoring

Absorption models



- The first-order absorption model showed underestimation of maximum concentration and misspecification in elimination; the two-phase absorption model improves the model fit (Fig.2)

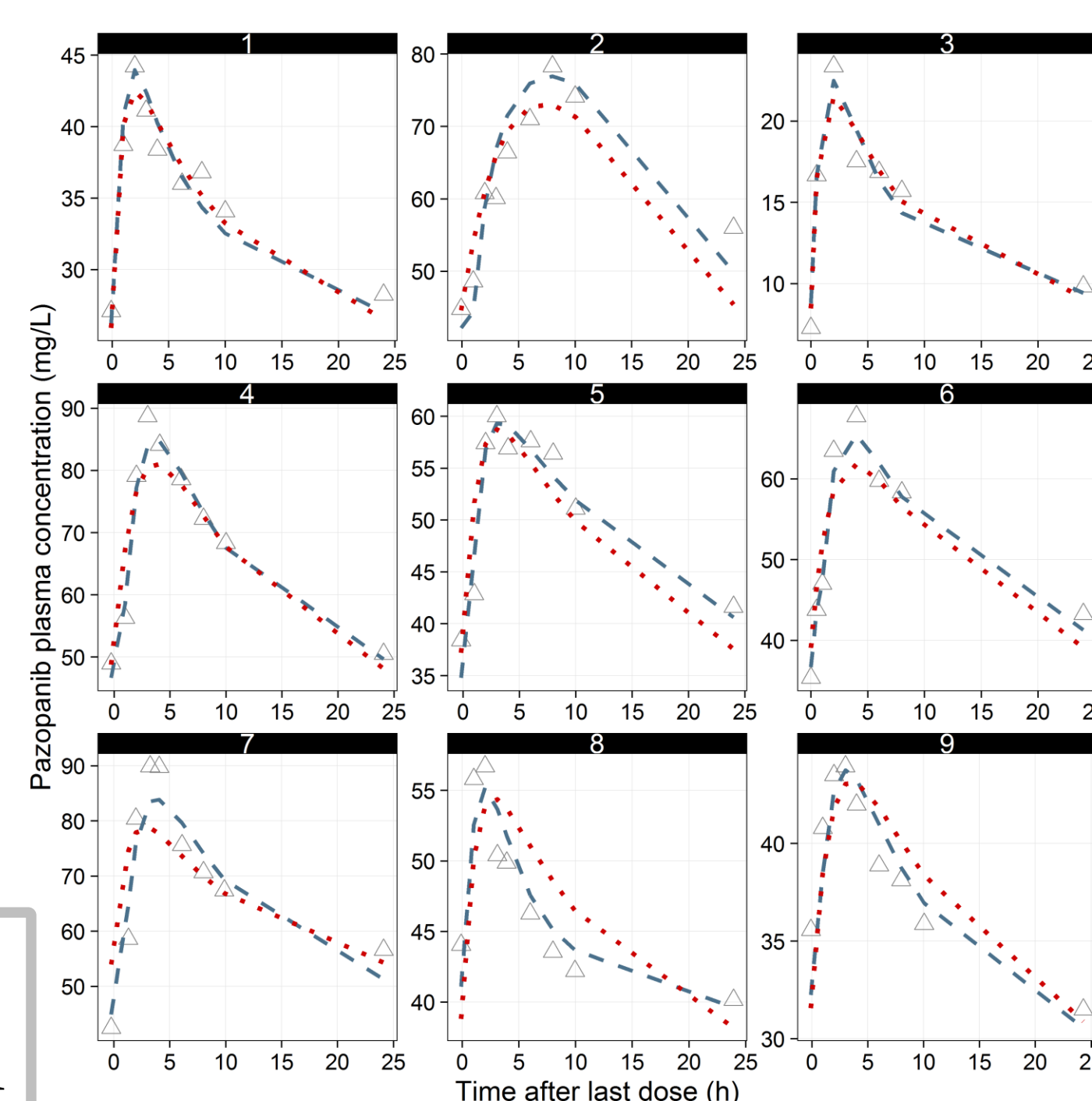


Fig. 2. Representative observed (symbols) concentration-time curves of pazopanib and the associated model fit of first-order (red lines) and two-phase (blue lines) absorption models.

Relative bioavailability

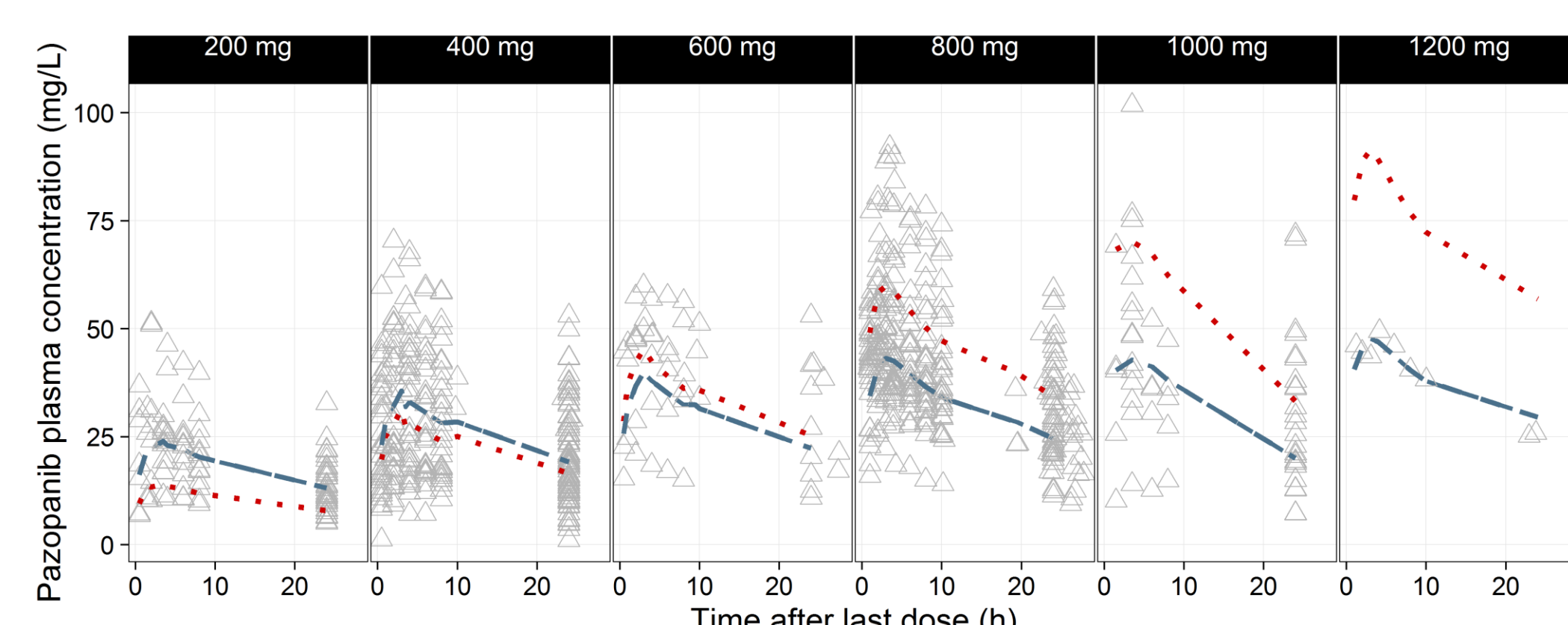


Fig. 3. Observed PK of pazopanib (symbols) at different dose levels and associated model fit with linear (red lines) and non-linear (blue lines) dose-concentration relationship.

- Model with linear dose-concentration relationship underestimated at low doses, while overestimated at high doses. The model with non-linear dose-concentration relationship improves the model fit (Fig. 3)
- The inclusion of over-time decrease in bioavailability dropped OFV by 16 points

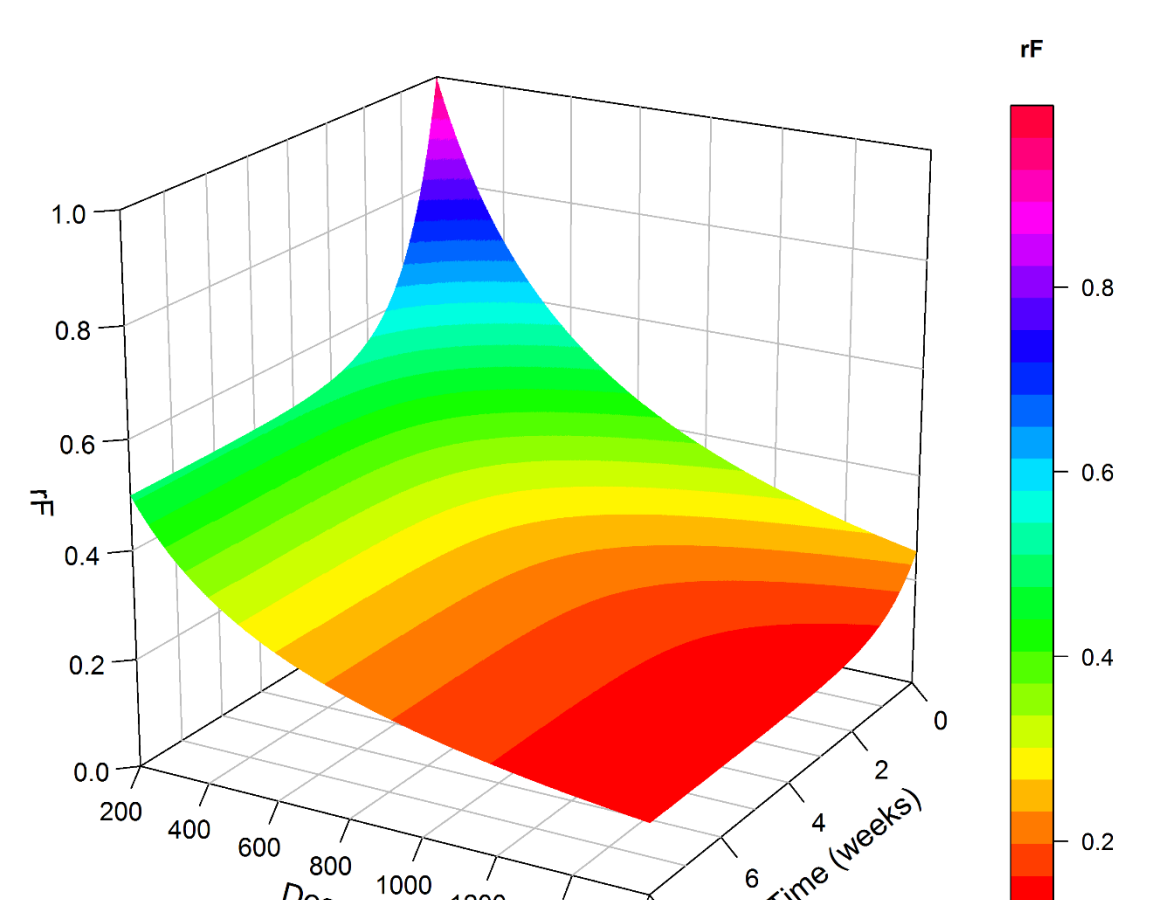


Fig. 4. Relative bioavailability (rF) vs. dose and time. rF decreases with increment of dose levels and treatment period.

Final PK model

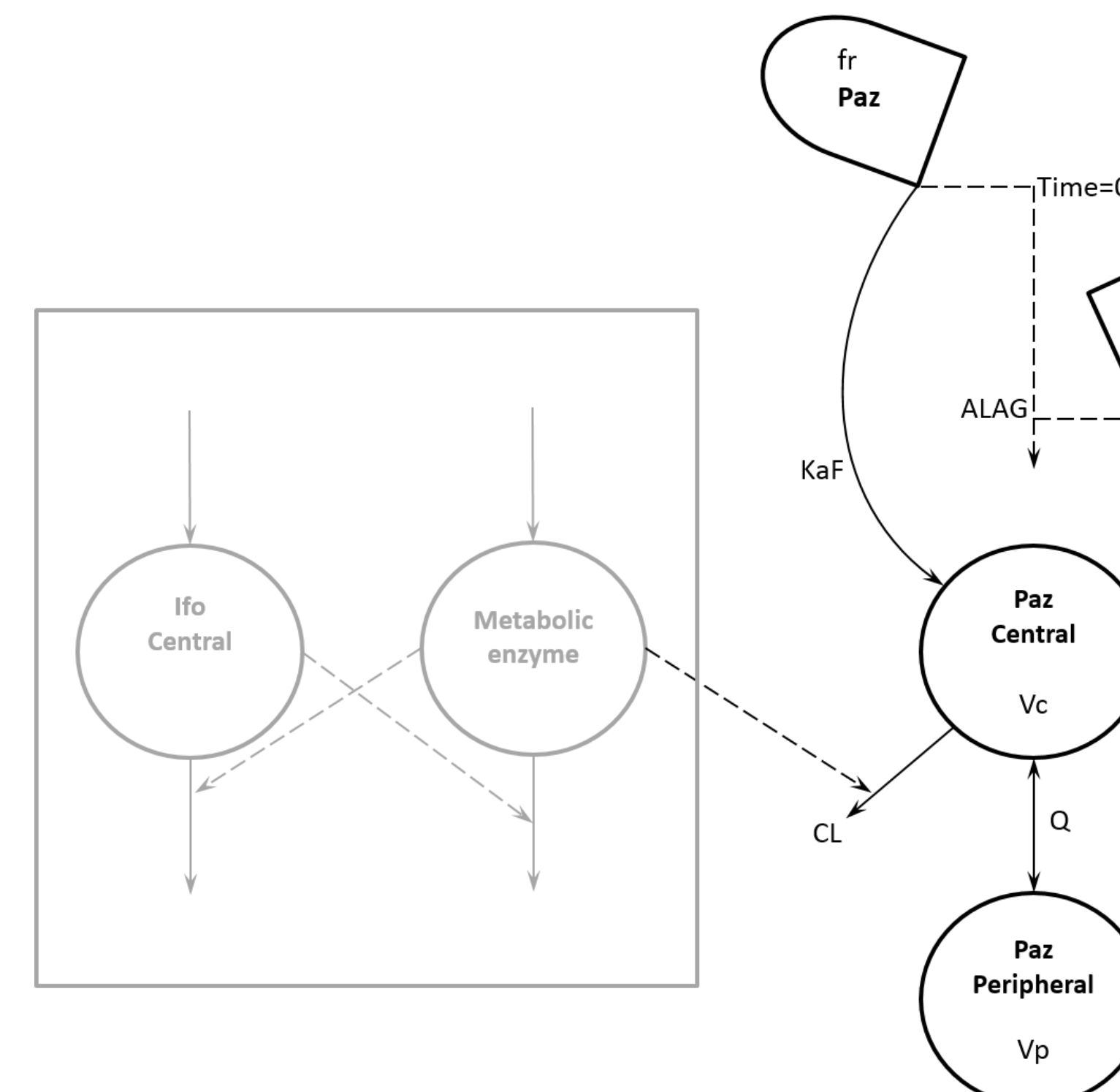


Fig. 5. Structure of final PK model of pazopanib. The grey square area represents the ifosfamide PK model [4]. ALAG, lag time; CL, clearance; fr, fraction of pazopanib; Ifo, ifosfamide; KaF, fast absorption rate constant; KaS, slow absorption rate constant; Q, between compartmental clearance; Paz, pazopanib; Vc, central volume of distribution; Vp, peripheral volume of distribution.

Table 2. Parameter estimates of pazopanib PK model

Parameters	Units	Estimate	RSE (%)
Population parameter			
KaF	h ⁻¹	0.40	31
KaS	h ⁻¹	0.12	28
fr	%	36.1	34
ALAG	h	0.98	6
CL	L/h	0.27	23
Vc	L	2.43	34
Q	L/h	0.99	29
Vp	L	25.1	27
rF ₂₀₀	—	1 FIX	—
E _{max}	—	1 FIX	—
ED ₅₀	mg	480	23
A ₁	%	50.1	27
λ	d ⁻¹	0.15	43
Between-subject variability			
KaF	CV%	140	20
L	CV%	30.9	20
Vp	CV%	98.2	17
rF	CV%	35.6	16
Between-occasion variability (rF)			
CV%	CV%	74.5	22
Residual unexplained variability			
Proportional residual error	CV%	8.0	6
Additive residual error	mg/L	3.1	13

CV%, coefficient of variation; RSE, relative standard error

Model evaluation

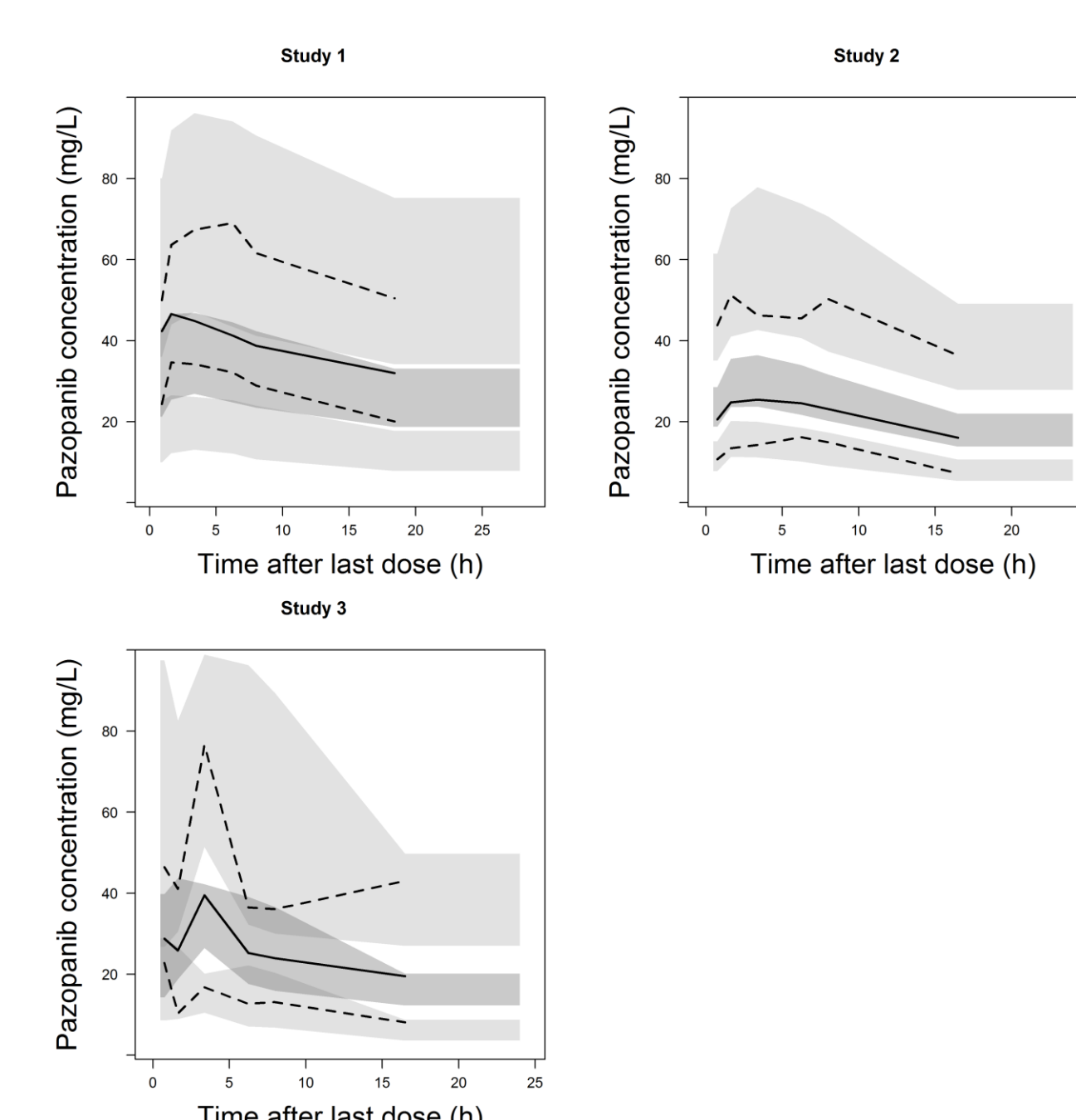


Fig. 6. Visual predictive checks stratified on the clinical studies (n = 1,000). Solid lines and dark grey areas represent the median observed values and simulated 95% confidence intervals (CIs). Dashed lines and light grey areas represent the 10% and 90% percentiles of the observed values and 95% CIs of the simulated percentiles.

Simulation

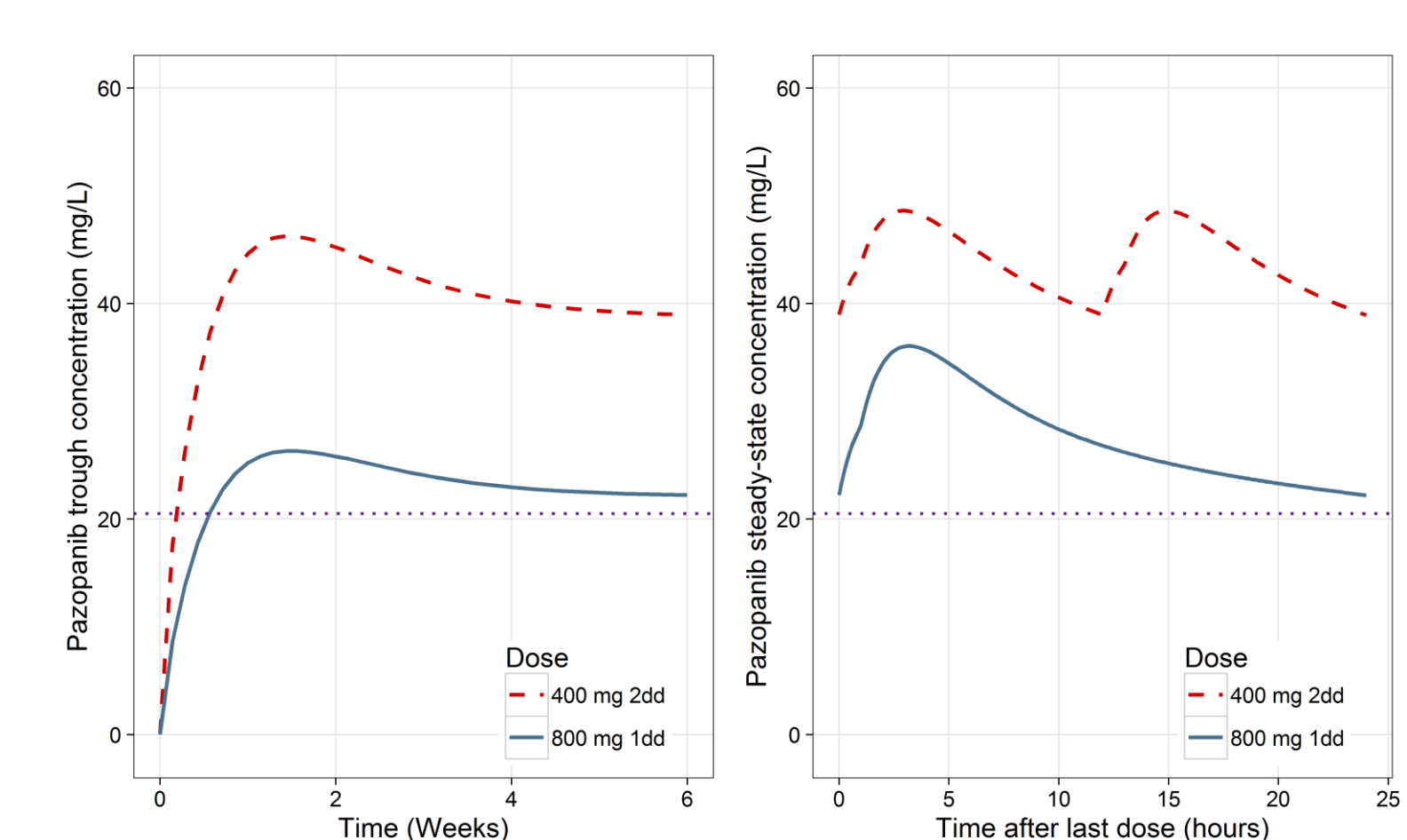


Fig. 7. Simulated pazopanib concentrations at once-daily 800 mg (approved dose) and twice-daily 400 mg. Left panel: pazopanib trough concentrations over six weeks; right panel: pazopanib concentration-time curve over 24 hours at steady-state concentrations (six weeks of treatment). The dotted lines show the concentration level of 20.5 mg/L.

- For the patients underexposed at once-daily 800 mg, a split of the dose to twice daily could potentially be effective both in treatment and costs

Conclusions

- A PK model for pazopanib was developed and evaluated
- This model illustrated multiple aspects of the PK characteristics of pazopanib: the complex absorption process, the non-linear dose-concentration relationship, the high inter-patient and intra-patient variability, and the decreased exposure over time
- Simulation of the PK model suggested that twice-daily 400 mg could result in higher exposure than once-daily dosing of 800 mg of pazopanib

References

- de Wit D et al. Ther Drug Monit. 2014;37(3):331–8
- Hamberg P et al. Cancer Chemother Pharmacol. 2014;75(2):365–71
- Hamberg P et al. Br J Cancer. 2014;110(4):888–93
- Kerbusch T et al. Br J Clin Pharmacol. 2000;49(6):555–61