Physiologically Based Pharmacokinetic Modeling of Quizartinib to Assess Drug-Drug Interaction as an Inhibitor of Breast Cancer Resistance Protein

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BACKGROUND

- Quizartinib is an orally-administered, highly-potent type II FMS-like tyrosine kinase 3 inhibitor. Quizartinib was approved by FDA in 2023 for the treatment of patients with newly diagnosed FLT3-internal tandem duplication (ITD)-positive acute myeloid leukemia (AML) based on the results of the phase 3 clinical trial (QUANTUM-First) [1].
- In vitro study revealed that quizartinib has an inhibitory effect on P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) with the half-maximal inhibitory concentration (IC_{50}) of 9.55 μM and 0.813 μM, respectively.
- A clinical drug-drug interaction (DDI) study between quizartinib and a P-gp substrate, dabigatran etexilate, resulted in minimal increases (12%) of Cmax and AUC of quizartinib [2].

OBJECTIVES

The aim of this study is to develop a physiologically based pharmacokinetic (PBPK) model of quizartinib incorporating the inhibitory effect on BCRP and assess the DDI risk of quizartinib as a BCRP inhibitor.

METHODS

The PBPK model of quizartinib consisting of the first-order absorption model and full PBPK distribution model was previously developed for the assessment of the inhibitory potential of UDP-glucuronosyltransferase 1A1 [3]. In this study, the model was updated in Simcyp Simulator V23.2 to evaluate the potential of quizartinib to inhibit BCRP (Figure 1). The Simcyp built-in compound files were used for rosuvastatin and sulfasalazine.

RESULTS

Model development

Single-dose PK in healthy subjects and multiple-dose PK in AML patients

- The developed model reasonably recovered the PK of quizartinib. The predicted PK parameters were within approximately 1.5-fold (Figure 2 and 3, Table 1).
- By reducing Fa from 0.735 in healthy subjects to 0.336 in AML patients, the PK of quizartinib in AML patients was reproduced, aligned with population PK analysis showing that quizartinib exposures were approximately 1.7-fold higher in non-AML subjects compared to AML patients [4].

DDI with a P-gp substrate, dabigatran etexilate

- The quizartinib PBPK model sufficiently predicted the clinically observed DDI result with dabigatran etexilate which exhibited negligible DDI (1.13- and 1.11-fold increases in Cmax and AUC, respectively) (Table 2).
- Sensitivity analysis of the quizartinib P-gp $K_{i,u}$ showed that the observed Cmax and AUC ratios of around 1.1-folds were in the range of P-gp $K_{i,u}$ of 0.094 to 0.19 μM, indicating that the input value of the quizartinib P-gp $K_{i,u}$ (0.0955 μM) was within the range of reasonable DDI prediction.
- The in vitro $K_{i,u}$ value allowed us to adequately predict the inhibitory effect of quizartinib on intestinal efflux transporters in vivo, suggesting the applicability for DDI prediction with BCRP substrates (Figure 4).

Model application

DDI with BCRP substrates, rosuvastatin and sulfasalazine

- The validated PBPK model predicted that oral multiple-dose co-administration of 60 mg quizartinib QD would increase the Cmax and AUC_{48h} by 3.31- and 2.44-fold, respectively, for rosuvastatin and by 2.66- and 2.66-fold, respectively, for sulfasalazine (Table 3).

Table 3. Predicted Cmax and AUC_{48h} ratios for BCRP substrates in the DDI studies of 60 mg quizartinib QD with 20 mg rosuvastatin and 1000 mg sulfasalazine

Substrate	Cmax ratio	AUC_{48h} ratio
Rosuvastatin	3.31 (2.83 – 3.87)	2.44 (2.00 – 2.68)
Sulfasalazine	2.66 (2.29 – 3.01)	2.66 (2.29 – 3.03)

Values are expressed as geometric mean ratios with trial geometric mean ranges (min – max) of 10 trial simulations of 10 subjects.

CONCLUSION

- The quizartinib PBPK model was developed and validated as a fit-for-purpose perpetrator model for predicting DDI with BCRP substrates.
- The PBPK modeling results could inform that the impact of quizartinib on BCRP substrate would be moderate (2.44-fold AUC increase for rosuvastatin and 2.66-fold AUC increase for sulfasalazine) in the clinic.

REFERENCES

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[3] Zhang M et. al., Poster presentation in ACoP Annual Meeting 2022.
[4] Vaddady P et. al. Clin transl Sci. 2024;17:e70074.

DISCLOSURES

AW, HA, HT and SN are employees of Daiichi Sankyo Co., Ltd. KK and YX are employees of Daiichi Sankyo, Inc. SY and NO are employees of Certara UK Ltd.

Figure 1. Overview of PBPK model development, validation and application

Model development

- In vitro and physicochemical data
- Unbound competitive inhibition constant ($K_{i,u}$) values for P-gp (0.0955 μM) and BCRP (0.00813 μM)
  - ✓ Corrected IC_{50} with the unbound fraction (0.01) in the incubation media of the cell-based assay
- Absolute bioavailability study [2]
  - ✓ Single IV (50 μg) + PO (60 mg) in healthy subjects

Model validation

- Single-dose and multiple-dose PK data [2]
  - ✓ Single oral dose of 30 and 60 mg in healthy subjects
  - ✓ Multiple oral dose of 30 and 60 mg QD in AML patients
- DDI study with a P-gp substrate, dabigatran etexilate [2]
  - Quizarinib 60 mg QD and dabigatran etexilate 150 mg
  - To confirm whether an in vitro $K_{i,u}$ value for an efflux transporter such as P-gp could recover the in vivo inhibitory potential

Model application

- DDI prediction with BCRP substrates
  - ✓ Quizartinib 60 mg QD for 21 days
  - ✓ Substrate: Rosuvastatin 20 mg and sulfasalazine 1000 mg on Day 20

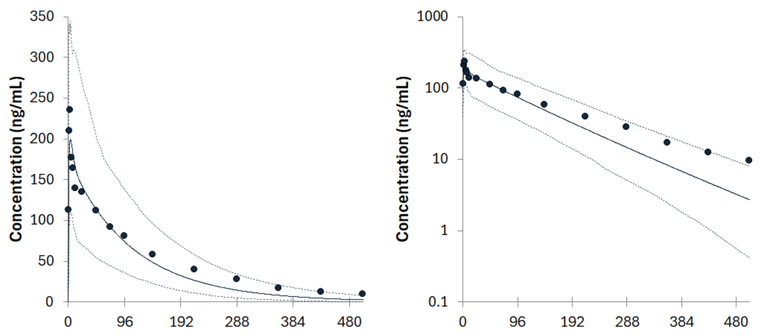

Figure 2. Predicted and observed plasma concentrations of quizartinib in healthy subjects following a single oral-dose administration at 60 mg

Solid lines and symbols represent the simulated mean plasma concentrations of quizartinib with dashed lines of 5th and 95th percentiles (n = 160) and the observed mean plasma concentrations (n = 16) on linear (left) and logarithmic (right) scales

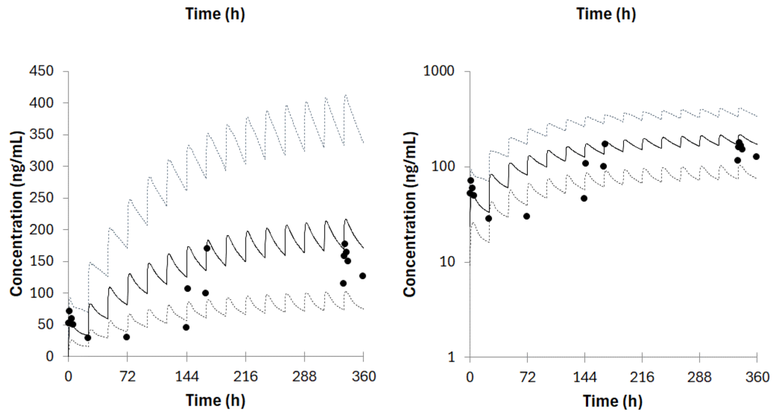

Figure 3. Predicted and observed plasma concentrations of quizartinib in AML patients following multiple oral-dose administration at 60 mg QD

Solid lines and symbols represent the simulated mean plasma concentrations of quizartinib with dashed lines of 5th and 95th percentiles (n = 130) and the observed mean plasma concentrations (n = 13) on linear (left) and logarithmic (right) scales

Table 1. Predicted and observed PK parameters for quizartinib in healthy subjects following a single-dose 60 mg quizartinib and in AML patients following multiple-dose 60 mg quizartinib

	Single-dose 60 mg			Multiple-dose 60 mg QD					
				Day 1			Day 15		
	Cmax (ng/mL)	Tmax (h)	AUCinf (ng*h/mL)	Cmax (ng/mL)	Tmax (h)	AUCinf (ng*h/mL)	Cmax (ng/mL)	Tmax (h)	AUCinf (ng*h/mL)
Observed	226 (35)	4.0 (2.0 – 4.2)	24200 (43)	102 (83)	2.2 (1.3 – 6.0)	1180 (85)	406 (108)	2.0 (1.0 – 6.0)	6520 (119)
Predicted	201 (35)	3.7 (1.1 – 14)	18621 (43)	104 (40)	3.3 (1.1 – 15)	1822 (40)	407 (44)	2.8 (1.0 – 6.9)	8561 (47)
Pred/Obs	0.89	0.93	0.77	1.02	1.52	1.54	1.00	1.39	1.31

Values are expressed as geometric mean with coefficient of variation (CV%) except for median for Tmax with ranges (minimal to maximal).

	Cmax ratio	AUCinf ratio
Observed	1.13 [0.77, 1.65]	1.11 [0.77, 1.60]
Predicted	1.11 [1.09, 1.10]	1.10 [1.09, 1.10]
Pred/Obs	0.98	1.00

Values are expressed as geometric mean ratios [90% confidential interval] of 10 trials of 20 subjects

Table 2. Predicted and observed Cmax and AUCinf ratios for dabigatran in healthy subjects after a single oral-dose administration of 150 mg dabigatran etexilate in the presence and the absence of a single oral-dose administration of 60 mg quizartinib

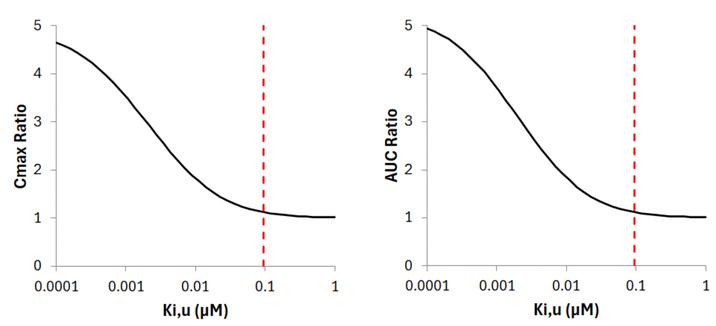

Figure 4. Sensitivity analysis for quizartinib P-gp $K_{i,u}$ on dabigatran Cmax and AUCinf ratios in the DDI study with dabigatran etexilate

Simulation was performed in a population representative following a single oral-dose administration of dabigatran etexilate at 150 mg in the presence and the absence of a single oral-dose administration of quizartinib at 60 mg. Dashed red lines represent the original input of quizartinib P-gp $K_{i,u}$ (0.0955 μM) used in the PBPK model.

Presented at ACoP 2025 Annual Meeting; Oct 18-21, 2025 in Aurora, CO