Supplemental Data

TITLE: Prediction of Crizotinib-Midazolam Interaction using the Simcyp Population-based Simulator: Comparison of CYP3A Time-Dependent Inhibition between Human Liver Microsomes versus Hepatocytes

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Supplemental Data, Table S1. Comparison of clinically observed and model-predicted fold-increase in midazolam $AUC_{0-\infty}$ by crizotinib in humans after 28-day repeated oral administration of crizotinib 250 mg twice daily

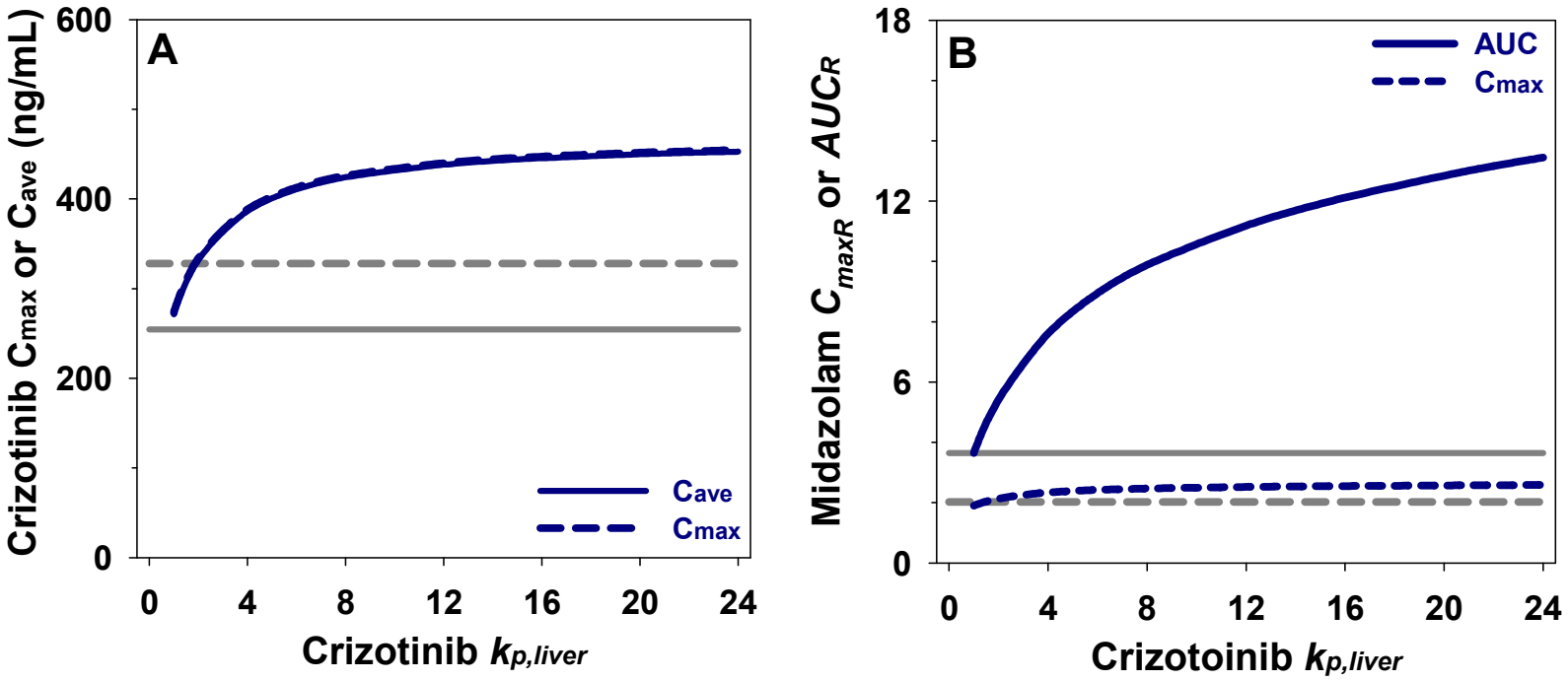
	Crizotinib $C_{ave,ss}$ [a]		Predicted fold increase in midazolam $AUC_{0-\infty}$ [b]		
	ng/mL total	nM free	Simcyp-PBPK	Simcyp-R_{ss}	Static Model
Observed	255	53	–	–	3.2
Minimal-PBPK [c]	296	61	4.0 (1.6 - 10)	3.4	3.5
Full-PBPK [c] with hepatic k_p = 1	271	56	3.6 (1.6 – 8.8)	2.3	3.3
Full-PBPK [c] with hepatic k_p = 22	451	93	13 (3.6 - 37)	2.3	4.2

Data are expressed as geometric mean or geometric mean with 90% confidence interval for Simcyp-PBPK in parentheses.

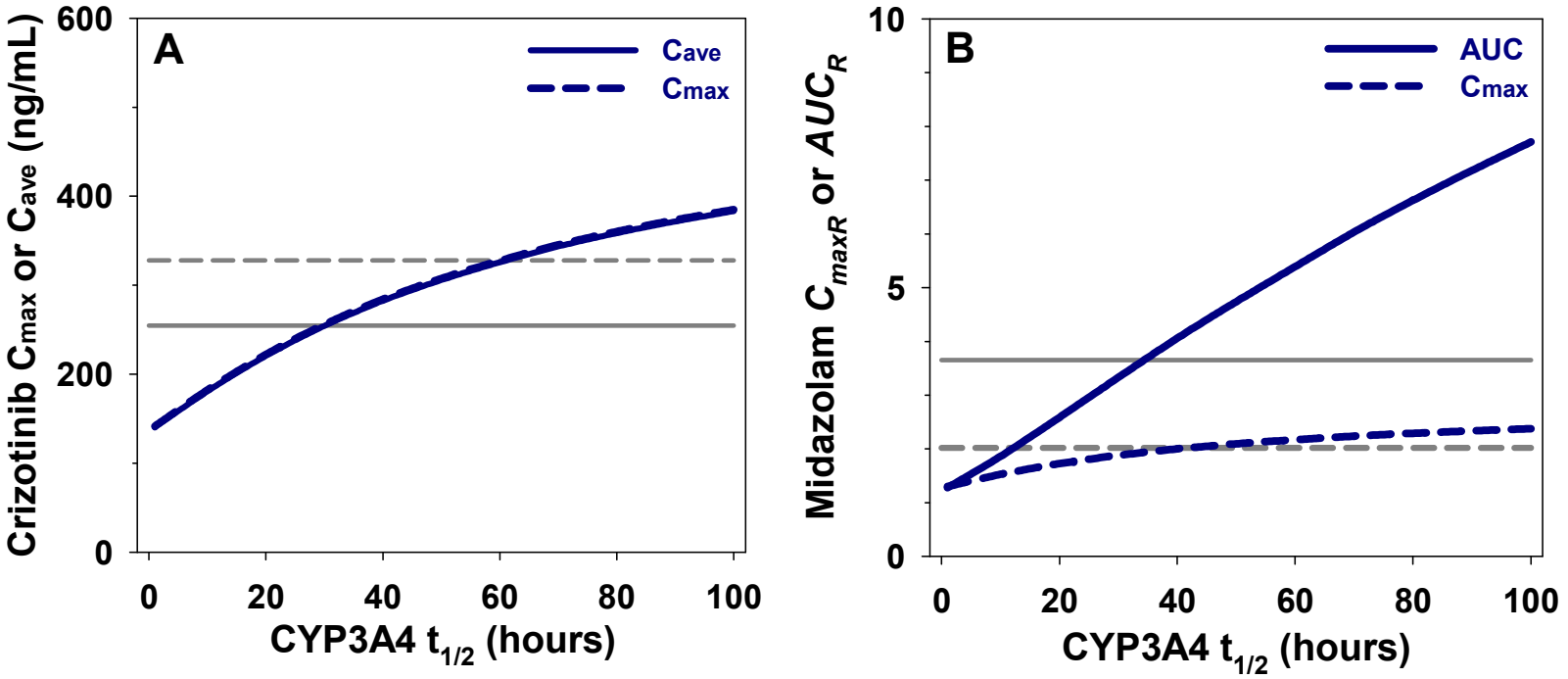
[a] Observed and Simcyp-predicted crizotinib steady-state average plasma concentrations ($C_{ave,ss}$) were calculated from $AUC_{0-\tau}$ divided by dosing interval of 12 hours.

[b] Fold-increase in midazolam $AUC_{0-\infty}$ was predicted with the Simcyp-PBPK, Simcyp-static (R_{ss}) and static mathematical models using TDI parameters from HSP. For the static mathematical model, either the observed or Simcyp-predicted crizotinib $C_{ave,ss}$ was used for the predictions. Clinically observed fold-increase in midazolam $AUC_{0-\infty}$ was 3.7 with 90% confidence interval of 2.6 - 5.1.

[c] Simcyp simulation was performed with minimal- or full-PBPK models with crizotinib hepatic k_p of either 1 or 22 in a virtual population of healthy volunteers in 8 trials of 10 subjects using CRZ-HSP.



Supplemental Data, Figure S1. Relationships between crizotinib hepatic $k_{p,liver}$ versus the predicted crizotinib C_{max} and C_{ave} (A) or the predicted fold-increase in midazolam $AUC_{0-\infty}$ and C_{max} (B) by Simcyp with CRZ-HSP. *A single oral dose of midazolam (2 mg) was co-administered on day 28 with oral doses of crizotinib (250 mg twice daily with an interval of 12 hours) for 28 days. Simcyp simulation was performed with a full-PBPK model in a virtual population of healthy volunteers in 8 trials of 10 subjects using CRZ-HSP. The x-axis represents crizotinib liver-to-plasma partition coefficient ($k_{p,li\ ver}$) and the y-axis represents the predicted crizotinib steady-state C_{max} (---) and C_{ave} (—) (A) or the fold-increase in midazolam C_{max} (---) and $AUC_{0-\infty}$ (—) (B). The horizontal lines represent the observed crizotinib steady-state C_{max} (---) and C_{ave} (—) (A) or the fold-increase in midazolam C_{max} (---) and $AUC_{0-\infty}$ (—).*



Supplemental Data, Figure S2. Sensitivity analysis of hepatic CYP3A4 turnover half-lives for the prediction of crizotinib steady-state plasma concentrations (A) or the fold-increase in midazolam $AUC_{0-\infty}$ and C_{max} with co-administration of crizotinib (B) by Simcyp with CRZ-HSP. *A single oral dose of midazolam (2 mg) was co-administered on day 28 with oral doses of crizotinib (250 mg twice daily with an interval of 12 hours) for 28 days. Simcyp simulation was performed with a full-PBPK model in a virtual population of healthy volunteers in 8 trials of 10 subjects using CRZ-HSP. The x-axis represents hepatic CYP3A4 turnover half-life in hours and the y-axis represents the predicted crizotinib steady-state C_{max} (---) and C_{ave} (—) (A) or the fold-increase in midazolam C_{max} (---) and $AUC_{0-\infty}$ (—) (B). The horizontal lines represent the observed crizotinib steady-state C_{max} (---) and C_{ave} (—) (A) or the fold-increase in midazolam C_{max} (---) and $AUC_{0-\infty}$ (—).*