Development of physiologically-based pharmacokinetic model (PBPK) to evaluate the relative systemic exposure to quetiapine after administration of IR and XR formulations to adults, children and adolescents

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Background & Objectives

➢ Quetiapine is an atypical antipsychotic drug with efficacy demonstrated in clinical trials for the treatment of schizophrenia, bipolar disorder, major depressive disorder, and generalized anxiety disorder in adult patients.
➢ The clinical utility of the quetiapine formulations has also been evaluated in pediatric patients for the treatment of schizophrenia, bipolar mania and bipolar depression.
➢ Quetiapine has a short half-life (~7 h) and twice daily administration is recommended for the immediate-release (IR) formulation. An extended-release (XR) formulation has been developed to allow for once-daily dosing.
➢ Quetiapine is mainly metabolized by CYP3A, with minor contribution from CYP2C9 and CYP2D6.

➢ The pharmacokinetics of the quetiapine IR formulation has been studied in children and adolescents. However a formal pharmacokinetic study of the XR formulation has not been conducted in similar age groups.

➢ The objective of this study was to support to Pediatric Research Equity Act (PREA) commitment, by applying PBPK modeling and integrating the wealth of *in vitro* and *in vivo* information available for quetiapine to predict the PK of quetiapine XR formulation in pediatrics and to estimate the relative bioavailability between IR and XR formulation in pediatrics.

Methods

➢ The strategy for building and validating the PBPK and projecting the PK of the XR formulation in children and adolescents is illustrated in scheme on right. The *in vitro* data, *in vivo* drug-drug inhibition and induction data in human, clinical PK data from the pediatric PK study with IR formulation, and PK data from bioavailability studies with the IR and XR formulation in adults were used to build and validate the quetiapine PBPK model (Table 1).

➢ The PBPK model was constructed for quetiapine using a population based ADME simulator, Simcyp v11 (Sheffield, UK). Default parameter values for creating a virtual North European Caucasian population (population, physiological parameters including liver volume and blood flows, enzyme abundances) have been applied for adults.

➢The Simcyp pediatric module that includes PBPK model together with extensive libraries on pediatric demography (age, height, weight, body surface area), developmental physiology (liver size, renal function, liver blood flow) and biochemistry (albumin, CYP ontogeny) was used to construct PBPK model in pediatrics [1].

➢ The advanced dissolution absorption metabolism (ADAM) model contains information on how the size of the GI tract changes with age from birth onwards; other parameters such as gastric emptying and intestinal transit times are assumed to be at adult values.

Scheme 1. The strategy for building and validating the PBPK and projecting the PK of the quetiapine XR formulation in children and adolescents.

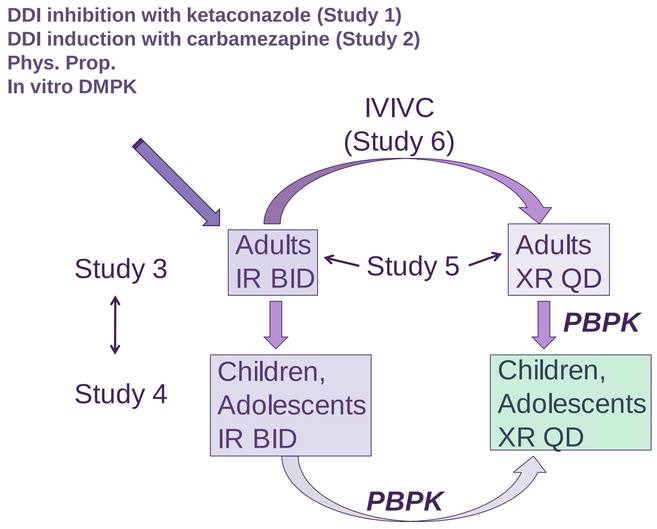

Table 1. Input parameter values used to simulate the kinetics of quetiapine.

Parameter	Value	Reference
MW	384	[2]
log P	2.86	[2,3,4] internal data
pKa	3.46, 6.93	[4, 5, 6] internal data
fu	0.17	[7]
V_{ss} (L/kg)	4.5	PE, internal data
SAC (L/kg)	2.2	parameter estimation
B:P ratio	1.26	Predicted in Simcyp
fa	1	Assumed in DDI studies
ka (h^{-1})	1.77	internal data
CL_{po} (L/h)	65 – 138	[8, 9]
CL_R	0.13	[8]
P_{eff} (cm/s)		
Caco-2 pH 7.4	43.3	internal data
Caco-2 pH 6.5	47.4	internal data
MDCK-II	34.8	[9]
PSA (Å)	48.3	
Intrinsic solubility	0.43	[2,5]

Results

➢ Results from ketocanozole and carbamazepine DDI studies were integrated to develop a retrograde model
➢ The model can reasonably predict the quetiapine plasma drug concentration-time profiles at steady state for both adults and children (Figure 1).
➢ The model can also reasonably predict the quetiapine plasma drug concentration-time profiles at steady state for both IR and XR formulation in adults (Figure 2).
➢ Inclusion of the colonic absorption component of the ADAM model improved the prediction of the plasma drug concentration-time profile for the XR quetiapine formulation (Figure 3).
➢ The model predicted that exposure to quetiapine after administration of 300mg daily as the XR formulation will provide similar exposure as 150 mg bid dose of IR formulation across the age ranges evaluated (10-12 yr, 13-17 yr and adults) (Figure 4 & Table 1).

Figure 1. Simulated mean plasma drug concentration-time profile (solid black line) during dosing of 200mg quetiapine bid in adults (A) and in children aged 10 to 17 years (B). The corresponding mean and individual observed data are shown by black filled and grey unfilled circles, respectively. The grey dashed lines represent the 5th and 95th percentiles for the predicted values.

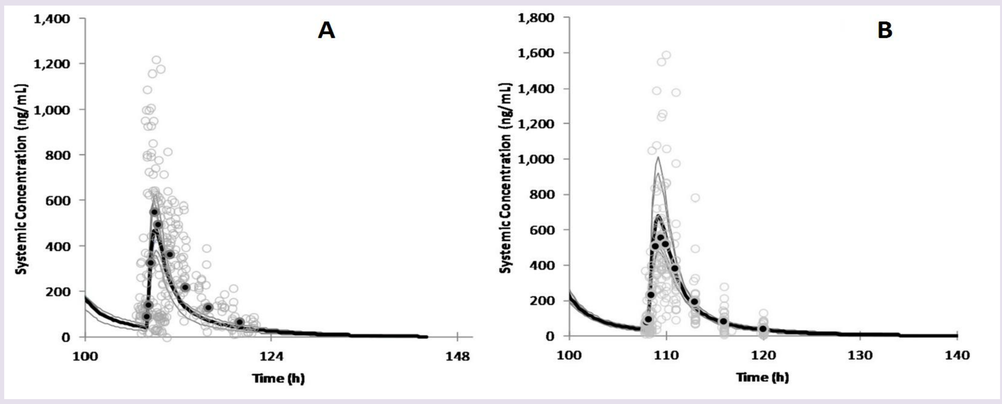

Figure 2. Simulated mean plasma drug concentration-time profile (solid black line) during dosing of 150 mg IR quetiapine bid (A) and 300 mg XR qd (B) in adults. The corresponding mean and individual observed data are shown by black filled or grey unfilled circles, respectively. The grey dashed lines represent the 5th and 95th percentiles for the predicted values.

Figure 4. Predicted mean plasma quetiapine concentration-time profiles after the last of 5 daily doses of the 300 mg XR formulation (A) and 150mg BID IR formulation (B) in adults, children and adolescents.

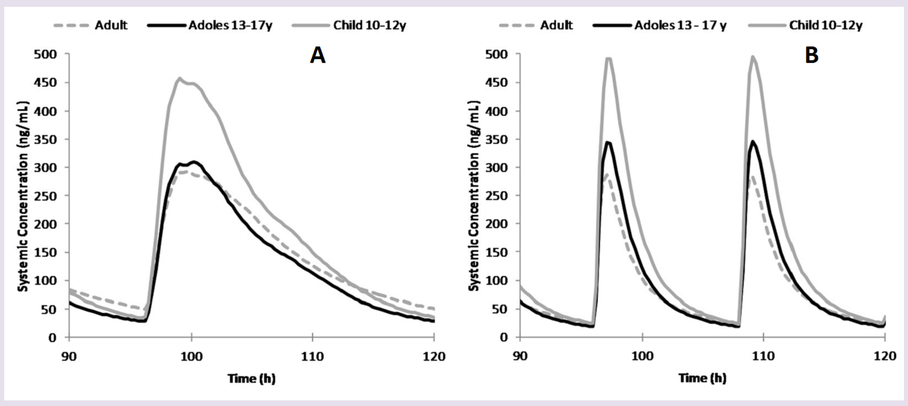

Figure 3. Regional distribution of the predicted fraction of dose absorbed in each segment of the GI tract following administration of the IR (A) and XR (B) formulation of quetiapine.

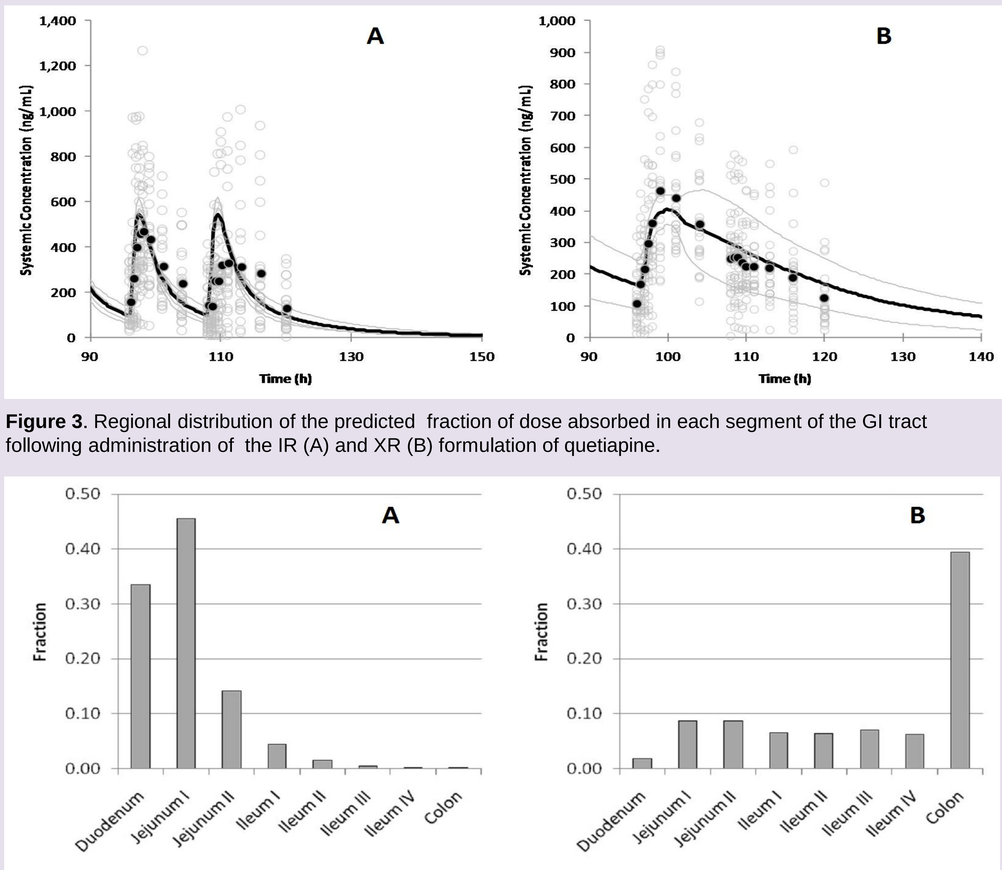

Table 2. Summary of predicted exposure to quetiapine after administration of 150 mg bid as an IR formulation in comparison with 300mg daily as the XR formulation in adults, adolescents and older children. All values are geometric means with the exception of t_{max} values which are medians.

300mg dose Minimal PBPK	AUC_{0-24} (ng/ml/h)			C_{max} (mg/ml)			t_{max} (h)		
	IR	XR	XR/IR	IR	XR	XR/IR	IR	XR	XR/IR
Adult	2464	2570	1.04	254	249	0.98	1.42	4.3	3.0
10 – 17y	3316	3738	1.13	393	447	1.14	1.61	4.5	2.8
13 – 17y	2974	2986	1.0	344	342	0.99	1.67	4.4	2.6
10 – 12y	3958	4227	1.07	517	523	1.01	1.65	4.6	2.8

Discussion and Conclusion

➢ The FDA has used information generated by PBPK to facilitate the decisions of (1) the need to conduct specific clinical pharmacology studies, (2) specific study designs and (3) appropriate labelling language. Thus, a SimCYP PBPK model for quetiapine was developed to predict the PK of quetiapine XR in children and adolescents.
➢ PBPK modeling can reasonably predict quetiapine exposure in IR and XR formulations in adults, children and adolescents by comparing with various clinical trials.
➢ The established PBPK model predicted that quetiapine XR and IR formulations would achieve similar quetiapine exposure in children and adolescents.

References

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