NO DOSE ADJUSTMENT OF METFORMIN WITH FOSTEMSAVIR COADMINISTRATION BASED ON MECHANISTIC STATIC AND PHYSIOLOGICALLY BASED PHARMACOKINETIC MODELS

Dung Nguyen,[1] Xiusheng Miao,[1] Mindy Magee,[2] Pete Gorycki,[1] Katy Moore,[3] Guoying Tai[1]

[1]Drug Metabolism and Pharmacokinetics, GlaxoSmithKline, Upper Providence, PA, USA; [2]Clinical Pharmacology Modeling Simulation, GlaxoSmithKline, Upper Providence, PA, USA; [3]Clinical Pharmacology, ViiV Healthcare, Research Triangle Park, NC, USA

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Introduction

- Fostemsavir (FTR) is an oral prodrug of the first-in-class attachment inhibitor temsavir (TMR) that is approved for patients with multidrug resistant HIV-1 infection. In vitro studies indicated that TMR and its 2 major metabolites are inhibitors of organic cation transporters (OCT) 1, OCT2, and multidrug and toxin extrusion transporters (MATEs)
- To assess the clinical relevance of OCT and MATE inhibition, mechanistic static drug-drug interaction (DDI) prediction with calculated free maximum exposure ($I_{max,u}$ of TMR or individual metabolite) over IC_{50} ratios were below the cutoff limits for a DDI flag based on US FDA guidelines and above the cutoff limits for MATEs only based on EMA guidelines
- A physiologically based pharmacokinetic (PBPK) modeling approach to further investigate the potential clinical DDI risk for TMR as a perpetrator with OCT1, OCT2, and MATE substrates (eg, metformin)

Methods

- A mechanistic PBPK model for TMR as a perpetrator was developed using the Simcyp® v18.1 simulator based on its physicochemical properties and in vitro and in vivo data. The model was verified and validated through comparison with clinical data. The Simcyp models for metformin[1] and ritonavir[2] were qualified using literature data before applications of DDI prediction for TMR (Figure 1)
- In vitro renal transporter inhibition IC_{50} parameters of OCTs and MATEs for TMR and its 2 metabolites were used in the model for the DDI simulation to evaluate the effect of TMR on the sensitive substrate of OCTs and MATEs, metformin

Figure 1. Workflow for TMR PBPK Model Development, Verification, and Application

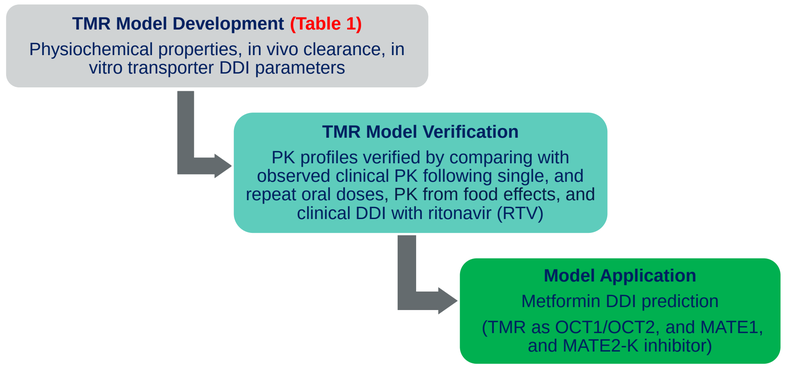


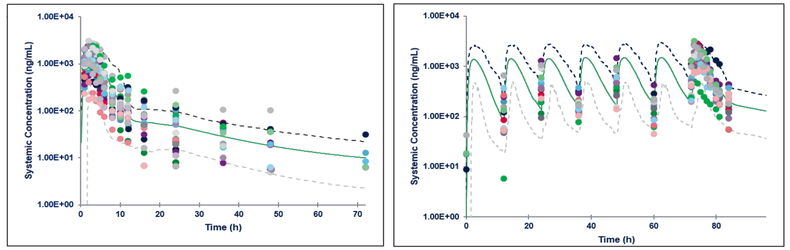
Table 1. TMR Model Input

Parameter	Value	Source
Molecular weight	473.5	
LogP	1.58	Measured
pKa	8.4-Monoprotic acid	Measured
Blood/Plasma ratio	0.869	Measured
Plasma unbound fraction (fu)	0.182	Measured
Caco-2 permeability (10^{-6} cm/s)	11.1x 10^{-6} cm/s with absorption scaling factor global model 10 and 0.02 for colon session	Measured
In vitro dissolution	89% release at 24 h	Measured
Vss (L/kg)	0.38	Predicted
Clearance Enzyme clint (uL/min/mg) Additional systemic CL (L/h) CLr (L/h)	 CYP3A4-11 Esterase-16 2.0 0.39	 Predicted based on human PK of temsavir IV dosing Measured
Transporter Inhibition Ki (uM)	Liver OCT1-4.3 Liver MATE1-15.2 Kidney OCT2-33.3 Kidney MATEs-9.4	Measured

Results

- The developed PBPK model was able to reproduce the systemic exposure of TMR after SD and RD of FTR 600 mg BID (Figure 2)
- The TMR PBPK model was further verified and qualified
  - Statistical analysis demonstrated that TMR PBPK model accurately predicted TMR PK parameters within 30% after a single and repeat oral dose of FTR 600 mg BID
  - Simulated PK profiles of TMR had reproduced the observed data from various clinical studies in healthy and patient subjects, including PK at higher dose (1200 mg), food effects, and RTV DDI

Figure 2. Simulated (Line) and Observed (Symbols) TMR Plasma Profiles After SD and RD Oral FTR 600 mg Dosing (With 5th and 95th Percentile)



- The TMR PBPK model was used to predict the DDI potential with metformin through OCT1, OCT2, and MATE inhibition by TMR and its metabolites. The most potent IC_{50} values (of major metabolites or parent) were used as a surrogate for transporter Ki values for worst-case scenario DDI prediction (Tables 2 and 3)

Table 2. Simulation Trial Design for TMR OCT1/OCT2, MATE1/2K Inhibition Prediction

Drug (substrate-inhibitor pair)	N (no. of subjects in trial)	Age range mean (SD)	% of Females	Dose regimen
Metformin - FTR	10	20-50 y	0.5	FTR 600 mg was administered orally twice a day for 10 days and a single 1000 mg metformin dose was administered 2 hours after FTR dose on Day 6

Table 3. Simulated OCT1/OCT2, MATE1/2k-Mediated DDI Following Coadministration of Metformin and FTR 600 mg BID

	Simulated with and without FTR 600 mg BID		
Substrate drug (transporter)	AUC ratio geometric mean (5th-95th percentile)	C_{max} ratio geometric mean (5th-95th percentile)	Mean liver CuIW* of metformin ratio
Metformin (OCT1/OCT2 and MATE substrate)	1.05 (1.02-1.09)	1.05 (1.02-1.09)	0.84

*CuIW = unbound concentration of metformin in liver intracellular water.

Discussion

- A TMR PBPK model was constructed and validated that reproduced the observed human PK in healthy participants from 6 clinical studies
- The model was used to further predict the DDI between FTR and metformin
- The simulations predicted no significant increase in metformin systemic exposure (AUC or C_{max}) with FTR coadministration
- Further sensitivity analyses indicated that a 10-fold more potent Ki value for TMR would result in <15% increase in metformin exposure

Conclusions

- Based on mechanistic static models and PBPK modeling and simulation, the OCT1/2 and MATE inhibition potential of TMR and its metabolites on metformin pharmacokinetics is not clinically significant
- No dose adjustment of metformin is necessary when coadministered with FTR

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References: 1. Burt et al. *Eur J Pharm Sci.* 2016;88:70-82. **2.** Umehara et al. *Biopharm Drug Dispos.* 2018;39:152-163.

Presenting author: Dung Nguyen; dung.2.nguyen@gsk.com