Physiologically Based Pharmacokinetic (PBPK) Model of Sparsentan to Evaluate Drug-Drug Interaction Potential

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RESULTS

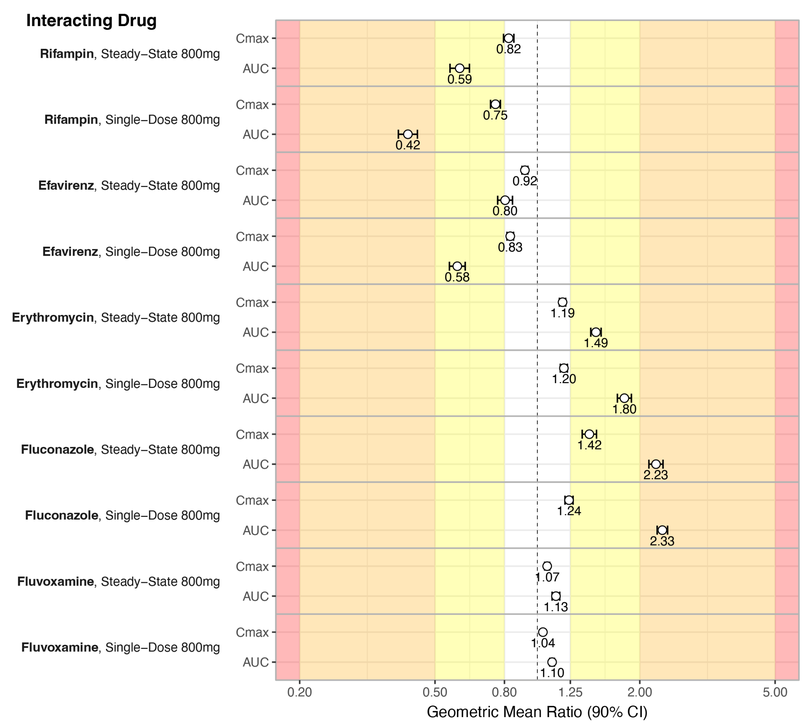
Sparsentan as a DDI victim and perpetrator of CYP3A4

- *In vitro*, F_m by CYP3A4 of 81.3% was able to predict itraconazole DDI within 0.8-1.25-fold of observed DDI
  - No further adjustments were required to *in vitro* F_m values

Sparsentan as a DDI victim

- The impact of CYP3A4 modulators on sparsentan exposure at steady state is less profound, with predicted DDI-to-control sparsentan C_{max} ratios of 0.82, 0.92, 1.19, 1.42, and 1.07 with and without rifampin, efavirenz, erythromycin, fluconazole, and fluvoxamine, respectively (**Figure 1**)
  - Predicted DDI-to-control sparsentan AUC ratios were 0.59, 0.80, 1.49, 2.23, and 1.13 with and without rifampin, efavirenz, erythromycin, fluconazole, and fluvoxamine, respectively
- After a single 800 mg sparsentan dose, the DDI-to-control sparsentan C_{max} ratios with and without rifampin, efavirenz, erythromycin, fluconazole, and fluvoxamine were predicted to be 0.75, 0.83, 1.20, 1.24, and 1.04, respectively (**Figure 1**)
  - DDI-to-control sparsentan AUC ratios with and without rifampin, efavirenz, erythromycin, fluconazole, and fluvoxamine were predicted to be 0.42, 0.58, 1.80, 2.33, and 1.10, respectively

Figure 1. Forest plot of metabolic drug-drug interaction of sparsentan as a victim with various probe perpetrators

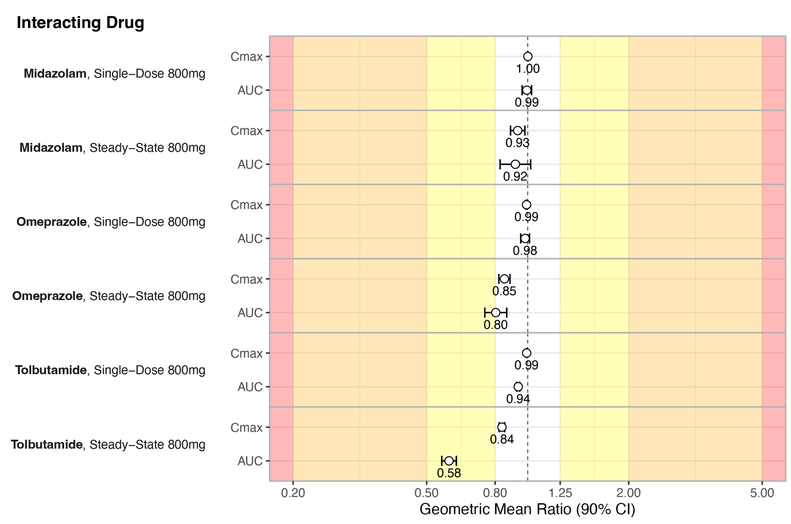


Geometric mean ratio of sparsentan AUC/C_{max} in presence of perpetrator over absence of perpetrator (control arm); Error bars indicate the simulated 90% confidence interval of the geometric mean ratio.
AUC, area under the curve of sparsentan plasma concentration profile over time; CI, confidence interval; C_{max}, maximum plasma concentration of sparsentan.

Sparsentan as a DDI perpetrator

- Concomitant use of sparsentan 800 mg has no or minimal impact on the exposure of midazolam and omeprazole (**Figure 2**)
  - DDI-to-control C_{max} ratios with and without sparsentan was predicted to be 0.93 and 0.85 for midazolam and omeprazole, respectively
  - DDI-to-control AUC ratios with and without sparsentan was predicted to be 0.92 and 0.80 for midazolam and omeprazole, respectively
- DDI-to-control sparsentan C_{max} and AUC of tolbutamide were predicted to be 0.84 and 0.58, respectively

Figure 2. Forest plot of metabolic drug-drug interaction of sparsentan as perpetrator with various probe victim substrates



Geometric mean ratio of probe victim substrate AUC/C_{max} in presence of perpetrator over absence of perpetrator (control arm); Error bars indicate the simulated 90% confidence interval of the geometric mean ratio.
AUC, area under the curve of victim plasma concentration profile over time; CI, confidence interval; C_{max}, maximum plasma concentration of victim.

Effect of P-gp inhibition on sparsentan exposure

- Removal of P-gp transport in the gut and liver has no or limited impact with 200 or 800 mg single sparsentan dose exposure within 10% of control

CONCLUSIONS

- PBPK model simulations with sparsentan as a victim showed that the exposure of sparsentan could increase with coadministration of strong CYP3A4 inhibitors
- Potential for other DDIs either with sparsentan as a victim or perpetrator were negligible

DISCLOSURES

NKP and KFC: Employees of Certara, Inc. and may have an equity or other financial interest in Certara, Inc.

KL: Employee of Travere Therapeutics, Inc. and may have an equity or other financial interest in Travere Therapeutics, Inc.

SCC: Former employee of Travere Therapeutics, Inc. and may have an equity or other financial interest in Travere Therapeutics, Inc.

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BACKGROUND

- Sparsentan (Travere Therapeutics, Inc., San Diego, CA), a novel Dual Endothelin Angiotensin Receptor Antagonist (DEARA), is a dual-acting, highly selective, single molecule antagonist of both the endothelin type A receptor and the angiotensin II subtype 1 receptor being investigated for the treatment of focal segmental glomerulosclerosis (FSGS) and IgA nephropathy[1-3]
- *In vitro* inhibition and induction studies of sparsentan suggest that inhibition of CYP3A4 and induction of CYP3A4, CYP2C9, and CYP2C19 are likely to occur at therapeutic concentrations
- Clinical pharmacokinetic data for sparsentan are available from healthy volunteers as well as FSGS patients ≥8 years
  - In a clinical drug-drug interaction (DDI) study, 800 mg sparsentan at steady state had no meaningful interaction with 2 mg oral midazolam (CYP3A4/5 substrate)
- The objective of this study was to develop a bottom-up, physiologically based pharmacokinetic (PBPK) model of sparsentan based on *in vitro* data of, drug formulation solubility, dissolution, permeability, metabolic pathways, and inhibition and induction potential on major metabolic enzymes
  - After verification, the model was applied to simulate the potential DDI risk of sparsentan as a victim and a perpetrator

METHODS

Model Development

- A mechanistic bottom-up absorption and full body disposition PBPK model that incorporated auto-induction and auto-inhibition of metabolic pathways was developed in Simcyp™ Simulator V19
  - *In vitro* data and physiochemical parameters of sparsentan used for model development are summarized in **Table 1**

Model Verification

- Data available from 4 sparsentan clinical studies were used to verify the model
  - Absorption and disposition parameters for sparsentan 50, 100, 200, 400, 800, and 1600 mg dose levels after a single dose and at steady state were verified via "Open-Label, Parallel Group, Fixed Dose Study to Assess the Pharmacokinetic Profile and Safety of Sparsentan Following Single-Dose Administration Under Fed and Fasted Conditions, and Following Multiple Doses Administered Once Daily for 14 Days Under Fasted Conditions in Healthy Adult Subjects"
  - Sparsentan absorption parameters, including food effects, after a single 200 and 800 mg dose were verified via "A Phase 1, Open-label, Randomised, Single-dose (200 mg and 800 mg), Four-period, Crossover Study to Investigate the Effect of Food on the Pharmacokinetics of Sparsentan in Healthy Subjects"
  - Sparsentan fraction metabolized (F_m) by CYP3A4 *in vivo* was verified via "A Study to Evaluate the Effects of Itraconazole on the PK, Safety, and Tolerability of Sparsentan in Healthy Male Subjects"
  - Sparsentan CYP3A4 inhibition and induction parameters were verified via "A Study to Evaluate the Effects of Steady State Sparsentan (QD dosing for 7 days) on the Single Dose Pharmacokinetics of Midazolam in Healthy Male Subjects"

Parameter	Value	Source
Physiochemistry and plasma protein binding		
Molecular weight (g/mol)	592.76	Internal data
log P	4.26	
Compound type	Ampholyte	
pKa (acid)	5.31	
pKa (base)	4.09	
B:P	0.612	
Fu_p	0.009	
Distribution		Full body 14-organ distribution model
V_{SS} (L/kg)	0.16	Predicted (Method 2) with PerL model
Absorption		ADAM model
Formulation type	Solid IR formulation	
Mean particle size (µm)	16 (tablet)	Internal data
Disintegration rate constant	0.12 (tablet)	Estimated by modelling *in vitro* dissolution data for the corresponding formulation
Intrinsic solubility (mg/mL)	0.0019	SIVA solubility model
Log $K_{m:w,\ unionized}$	4.61	
Log $K_{m:w,\ ionized}$	3.39	
Fu_{gut}	0.022	Predicted by Simcyp™ Simulator
Precipitation model	Model 2	Accounts for lag time for nucleation
Critical supersaturation ratio	10	Simcyp default
Precipitation rate constant (h^{-1})	4	
Permeability model	MechPeff model	
P_{trans0} ($x10^{-4}$ cm/s)	54.4	Derived from SIVA permeability model
$P_{eff,man}$ (jej) ($x10^{-4}$ cm/s)	6.29	
P-gp J_{max} (pmol/min/pmol)	5.56	
P-gp K_m (µM)	8.03	
Elimination		
CYP3A4 CL_{int} (µl/min/pmol)	0.497	CYP CL_{int} calculated by assigning HLM CLu_{int} based on enzyme contribution and abundance
CYP2C9 CL_{int} (µl/min/pmol)	0.212	
CYP2EI CL_{int} (µl/min/pmol)	0.00275	
Interaction		
CYP3A4 K_i (µM)	6.33	Internal data
CYP3A4 $K_{app,u}$ (µM)	4.04	
CYP3A4 k_{inact} (h^{-1})	3.168	
CYP3A4 Ind_{max} (fold-change)	7.86	
CYP3A4 $IndC_{50}$ (µM)	1.83	
CYP3A4 gamma	2.88	
CYP2C9 Ind_{max} (fold-change)	3.67	
CYP2C9 $IndC_{50}$ (µM)	2.25	
CYP2C9 gamma	1	
CYP2C19 Ind_{max} (fold-change)	1.97	
CYP2C19 $IndC_{50}$ (µM)	1.75	
CYP2C19 gamma	1.57	

Model Application

- Sparsentan as a victim was simulated with:
  - Rifampin (strong CYP3A4 inducer)
  - Efavirenz (moderate CYP3A4 inducer)
  - Erythromycin (moderate CYP3A4 mechanism-based interaction)
  - Fluconazole (moderate CYP3A4 competitive inhibitor)
  - Fluvoxamine (weak CYP3A4 competitive inhibitor)
  - As an inducer and mechanism-based inhibitor of CYP3A4, sparsentan was co-dosed with perpetrators for 14 days to steady state
- Sparsentan as a perpetrator was simulated with:
  - Midazolam (CYP3A4 probe substrate)
  - Tolbutamide (CYP2C9 probe substrate)
  - Omeprazole (CYP2C19 probe substrate)
  - CYP3A4, CYP2C9, and CYP2C19-mediated induction and/or autoinhibition were simulated after 14-day dosing of sparsentan to ensure the induction effect reached steady state
- For each substrate drug, the geometric mean ratios of the maximum plasma concentration (C_{max}) and area under the curve (AUC) with/without perpetrator were provided
- The effect of P-glycoprotein (P-gp) inhibition on the absorption and disposition of sparsentan was predicted by knocking out P-gp transport from the gut and liver tissues

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