A Physiological-based Pharmacokinetic (PBPK) Modeling Approach to Quantifying Drug-Drug Interactions: Applications to the Development of Fenfluramine (ZX008) for Treatment of Seizures in Dravet Syndrome (DS)

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INTRODUCTION

- Dravet syndrome (DS) is a severe form of childhood epilepsy in which seizures are often refractory to traditional antiepileptic drugs (AEDs).
- Low dose fenfluramine (ZX008; Zogenix, Inc.) has shown promise in DS patients and is currently under development as adjunctive therapy (top dose of 0.8 mg/kg/day, max of 30 mg/d), including combination with stiripentol/clobazam/valproic acid (STP/CLB/VPA) worldwide.
- Treatment of DS patients often requires a regimen of several AEDs that are metabolized via CYP450, which might result in potential drug-drug interactions (DDI).
  - Fenfluramine: mainly metabolized by CYP1A2, CYP2B6, CYP2D6; inhibits CYP2D6
  - STP: metabolized by CYP1A2, CYP2C19, CYP3A4; inhibits CYP1A2 and CYP3A4
  - CLB: metabolized by CYP 3A4, CYP2C19 and CYP2B6; inhibits CYP2D6
  - VPA: metabolized by UGT2B7, CYP2C9 and CYP2B6

OBJECTIVES

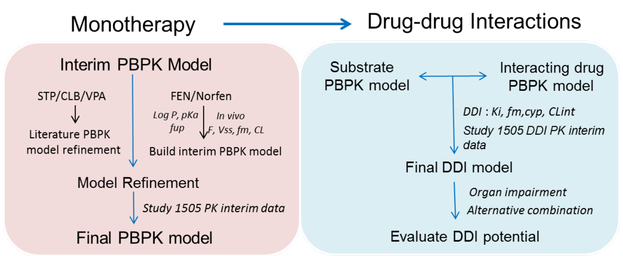
- The objective of this analysis was to construct a PBPK model system to quantify potential drug-drug interactions and facilitate dose justification for clinical trials of fenfluramine.

METHODS

Study 1505 Design

- Phase 1, single dose, three-way crossover study in healthy adults (N=20)
- Study arm (17 days wash out period):
  a. ZX008 0.8 mg/kg;
  b. STP 3500 mg, CLB 20 mg, and VPA 25 mg/kg (max 1500 mg);
  c. ZX008 0.8 mg/kg + STP 3500 mg / CLB 20 mg / VPA 25 mg/kg (max 1500 mg)
- Draft, pre-lock PK data were available at the time of this analysis

Figure 1. Flow Chart of PBPK DDI Model Development



METHODS

Monotherapy model

Fenfluramine

- Fenfluramine (FEN) PBPK model was comprised of ten perfusion-limited tissues.
- Tissue-to-plasma partition coefficients of FEN and its active metabolite norfenfluramine (norFEN) were calculated by integrating physiochemical and *in vitro* properties (e.g., LogP, pKa, *fup*).[1]
- FEN was eliminated by renal excretion and hepatic metabolism; 76% of hepatic intrinsic clearance (CL_{int}) was converted into norFEN.[2,3]

Stiripentol, Clobazam and Valproic acid

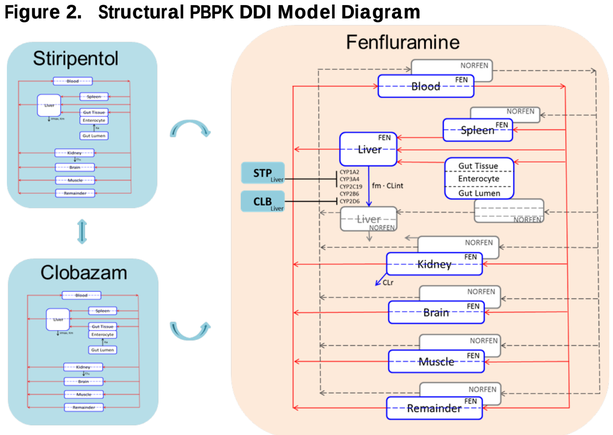
- STP PBPK model was developed by the refinement of a published PBPK model, where STP was only eliminated via liver metabolism[4].
- STP model refinement involved the incorporation of a secondary elimination route of renal clearance into the system.
- CLB and VPA PBPK model was developed by the refinement of published PBPK models.[4,5]

Drug-drug interaction models

- The inhibitory effect of STP and CLB on FEN elimination was described by reversibly inhibiting CYP1A2, CYP3A4, CYP2C19 and CYP2D6 – mediated FEN hepatic metabolism.
- The hepatic intrinsic clearance of FEN in combination ($CL_{int,\ DDI}$) is: $\frac{CLint_{,DDI}}{CLint} = \frac{fm_{,CYP1A2}}{1+\frac{C_{STP,liv}}{K_{I,1A2}}} + \frac{fm_{,CYP2D6}}{1+\frac{C_{CLB,liv}}{K_{I,2D6}}} + \frac{fm_{,other}}{1+\frac{C_{STP,liv}}{KI_{,other}}} + fm_{,CYP2B6}$ *$fm_{,other}$ includes $fm_{,CYP3A4}$ and $fm_{,CYP2C19}$
- Model development was conducted in Berkeley Madonna (v 8.3.18).

RESULTS

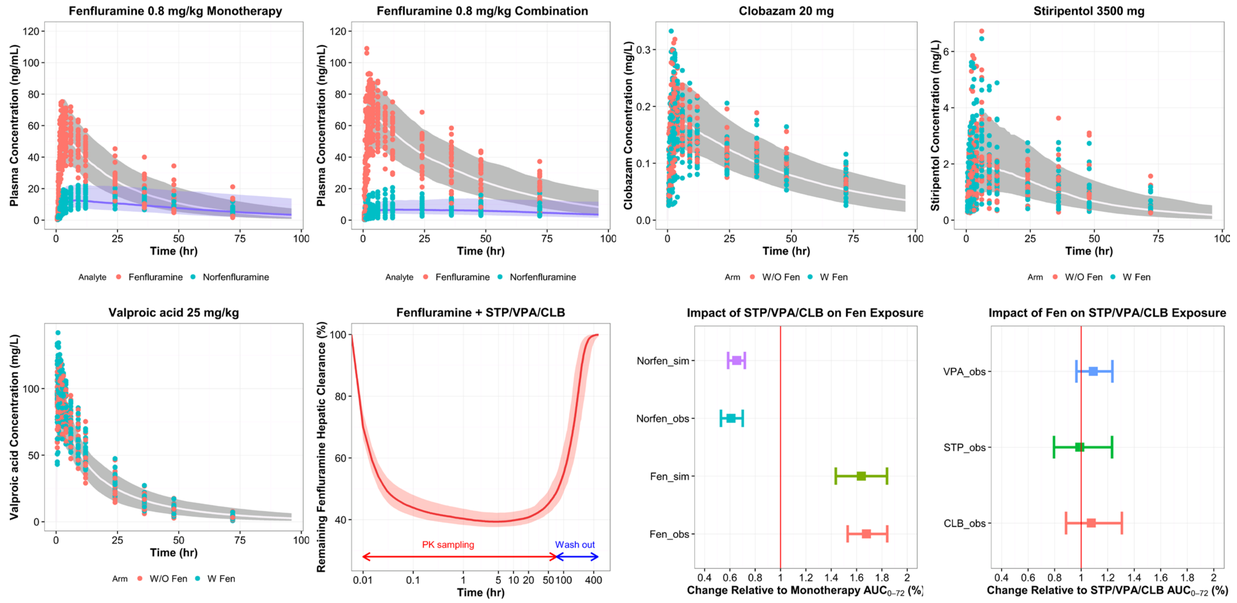
Figure 2. Structural PBPK DDI Model Diagram



- The PBPK DDI model predicted that the mean $AUC_{0\text{-}72}$ of FEN elevated 1.67 fold after co-administration with STP/CLB (Fig. 3), suggesting STP/CLB elicited only modest inhibition of FEN metabolism in healthy adults.
- The predicted increase in FEN AUC is less than 1.3 - fold when FEN is in combination with STP or CLB alone in healthy adults (Fig. 4).

RESULTS

Figure 3. PBPK DDI Model Qualification

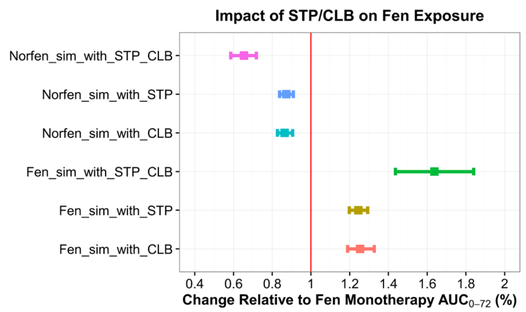


Note : $AUC_{0\text{-}72,obs}$ for all analytes was calculated using R (version 3.3.1)

Table 1. Model Predicted Change in Exposure of FEN and norFEN in Subjects with Renal Impairment

Renal Impairment	Mean $AUC_{0\text{-}72}$ Ratio			
	Monotherapy		Combination	
	FEN	norFEN	FEN	norFEN
Control	1.00	1.00	1.00	1.00
Mild	1.07	1.10	1.09	1.12
Moderate	1.12	1.17	1.16	1.20
Severe	1.16	1.24	1.22	1.28

Figure 4. Model Predicted Impact of STP or CLB Alone on Exposure of FEN in Healthy Subjects



CONCLUSIONS

- PBPK model describing the DDI between FEN and STP/CLB has been developed in healthy adults. The model predicted changes of FEN/norFEN exposure after combination treatment were in good agreement with clinical observations, qualifying the robustness of this model.
- The DDI model predicted the mean $AUC_{0\text{-}72}$ of FEN elevated 1.67-fold after in conjunctive with STP/CLB/VPA, suggesting that the DDI between FEN and STP/CLB is modest in healthy adults.
- The DDI model predicted the mean $AUC_{0\text{-}72}$ of STP/CLB/VPA are not significantly impacted by the co-administration of FEN in healthy adults.
- Model simulations suggest that FEN/norFEN exposure would be marginally increased in patients with renal impairment, suggesting that FEN dose adjustment might not be warranted in these sub-populations.
- This model can be further extrapolated to quantify potential DDIs and to facilitate dose justification for clinical trials of ZX008 in pediatric patients with DS.

REFERENCES

1) *Xenobiotica*. 2013;43:839. 2) *Arch Int Pharmacodyn Ther.* 1982;258:15. 3) *J Pharmacy Pharmcol.* 1967;19:49S. 4) *Pharm Res.* 2015 ; 32:144. 5) *Eur J Pharm Sci.* 2014 ; 63:45.