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ZX008 (Fenfluramine Oral Solution) as Adjunctive Therapy for Dravet Syndrome Seizures: A Pharmacometric Approach to Quantify Potential Drug-Drug Interactions to Support Phase 3 Dose Selection

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RATIONALE

- Develop a physiologically-based pharmacokinetic (PBPK) model system that can be used to support the development of ZX008 (fenfluramine [FFA] oral solution) for the treatment of children with Dravet syndrome (DS)
- Specific aims include:
  - Predict the concentration-time profile of FFA and its major active metabolite norfenfluramine (norFFA) in normal, healthy adults and children after administration of ZX008
  - Quantify the impact of coadministration of the antiepileptic drugs (AEDs) stiripentol (STP), clobazam (CLB), and valproic acid (VPA), on the PK of FFA/norFFA
  - Quantify the impact of FFA on the other AEDs, as appropriate
  - Apply the model system to data collected from subjects in the Phase 3 studies in order to estimate FFA exposure in treated subjects

METHODS

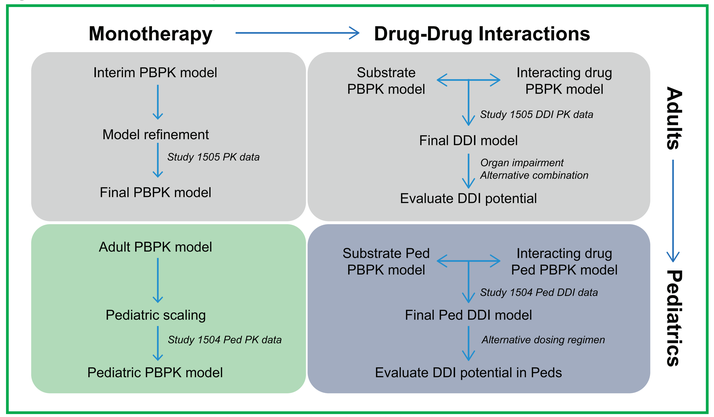
Study Design

- Adult Phase 1 PK (ZX008-1505):
  - Healthy adults
  - Single dose
  - Three-way crossover: ZX008 0.8 mg/kg, STP/CLB/VPA, and ZX008 plus STP/CLB/VPA
- Pediatric Phase 3 (ZX008-1504) Cohort 1:
  - Dravet syndrome subjects 2-18 years old
  - Single-dose PK cohort
  - 0.2 or 0.4 mg/kg ZX008 plus STP/CLB/VPA or plus CLB/VPA

PBPK Model Development and Application (Figure 1)

- Interim PPK model: develop independent models for FFA/norFFA, STP, CLB/norclobazam (NCLB), and VPA using published PBPK models or published data regarding drug properties
- Incorporate the contribution of various cytochrome P450 proteins (CYPs) into the FFA/norFFA model (substrate PBPK model) and combine the models together to allow for the impact of drug-drug interactions (DDIs) with coadministration of ZX008 and STP/CLB/VPA (interacting drug PBPK model)
- Qualify the models in adults using data from ZX008-1505
- Scale the model system to pediatric patients using accepted ontogeny of various facets of the PBPK model system
- Qualify the model system using data from Cohort 1 of ZX008-1504

Figure 1. PBPK model development schematic.



Note: VPA is not expected to impact the PK of FFA/norFFA and is therefore not included in the PBPK system (ie, a separate VPA model was developed but does not communicate with the DDI model system).

Table 1. Parameters Altered to Scale to Pediatric Patients

	Age-Dependent Anatomic Growth				CYP Maturation		Allometric Scaling			DDI
Drug	Blood flow	Tissue volume	Fup	GFR	CYP1A2	CYP2B6	Hepatic intrinsic clearance	Renal intrinsic clearance	Bio-availability	Hepatic intrinsic clearance[a]
FFA	•	•	•	•	•	•	•		•	•
NorFFA	•	•	•	•	•	•	•			•
CLB	•	•	•				•	•	•	
STP	•	•	•	•			•	•	•	

[a]In adults, the DDI effects of CLB + STP only influence the hepatic intrinsic clearance of FFA.

CLB, clobazam; CYP, cytochrome P450; DDI, drug-drug interaction; FFA, fenfluramine; Fup, fraction unbound in plasma; GFR, glomerular filtration rate; norFFA, norfenfluramine; STP, stiripentol.

RESULTS

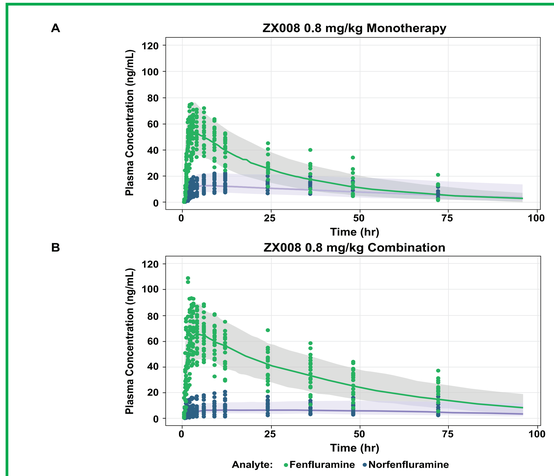
Adult Phase 1 Data

- Concentration-time data were available for 25 healthy volunteers (10 male and 15 female subjects) enrolled in the DDI portion of ZX008-1505
- All 25 subjects completed Regimen C (concomitant ZX008 and CLB/STP/VPA); 20 out of 25 subjects completed Regimen A and were available for the comparison of FFA/norFFA AUC with and without concomitant CLB/STP/VPA
- Mean (CV%) body weight was 71.7 (20.1) kg and the subjects ranged in age from 21 to 50 years (mean, 34.1)

Qualification of the PBPK Model System in Adults

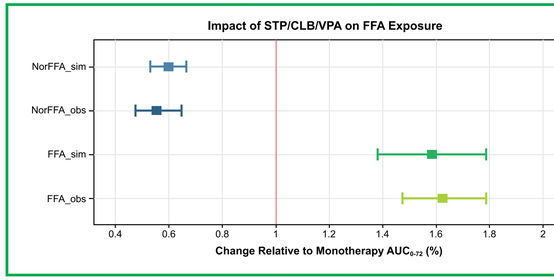
- The PBPK model system was able to reliably capture the FFA/norFFA concentration-time data from ZX008-1505 after both mono- and combination therapy (**Figure 2**)
- The model-predicted changes of FFA/norFFA exposure after combination treatment were in good agreement with clinical observations, qualifying the robustness of this model (**Figure 3**)

Figure 2. Comparison of optimized PBPK model predictions to observed single-dose data from ZX008-1505 after treatment with ZX008 alone (top panel) and in combination with STP/CLB/VPA (bottom panel).



Note: Solid line is the median predicted concentrations over time (green is FFA, purple is norFFA), shaded regions are the 90% prediction intervals, and solid dots are the observed concentrations from ZX008-1505 (green is FFA, blue is norFFA).

Figure 3. Comparison of observed to model-predicted impact of concomitant STP/CLB/VPA on FFA/norFFA using the ratio of $AUC_{0\text{-}72}$



Note: The squares above show the geometric mean $AUC_{0\text{-}72}$ ratio and the whiskers extend from the 5th to the 95th confidence (for observed data) or prediction (for the simulation) intervals.

Qualification Using Pediatric PK Data

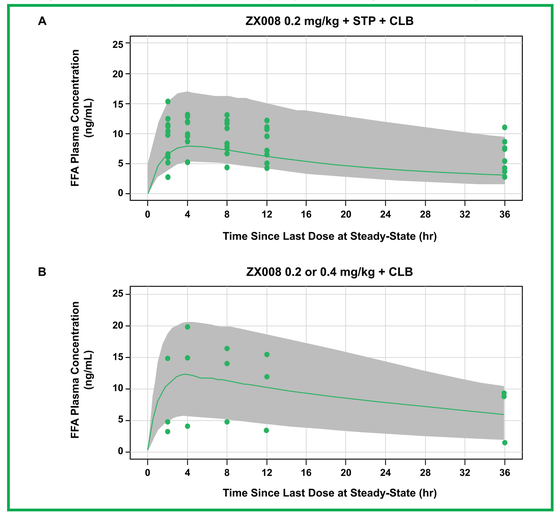
- Data available from 13 subjects with DS (**Table 2**)
- Each subject provided up to 5 blood samples for PK analysis at approximately 2, 4, 8, 12, and 36 hours after the dose
- After scaling to pediatrics and adjusting for concomitant doses of STP and/or CLB, the model provided an adequate description of the observed data (**Figure 4**)

Table 2. Demographic and Dosing Data for Pediatric Subjects from ZX008-1504

				CLB Dose (mg)		STP Dose (mg)	
Subject ID	Age (y)	Arm	ZX008 Single Dose (mg/kg)	AM	PM	AM	PM
1	6	C+V	0.2	1	1	–	–
2	3	S+C+V	0.2	2.5	2.5	150	200
3	13	S+C+V	0.2	5	10	500	500
4	9	S+C+V	0.2	2.5	2.5	500	500
5	16	C+V	0.2	–	20	–	–
6	6	S+C+V	0.2	5	10	1000	1000
7	9	S+C+V	0.2	5	7.5	500	750
8	3	S+C+V	0.2	–	5	300	300
9	5	S+C+V	0.2	2.5	5	500	500
10	11	C+V	0.4	–	7.5	–	–
11	11	S+C+V	0.2	–	10	500	500
12	6	S+C+V	0.2	5	5	500	500
13	4	S+C+V	0.2	–	2.5	500	500

Treatment arm abbreviations: C, clobazam; S, stiripentol; V, valproic acid.
CLB, clobazam; STP, stiripentol.

Figure 4. Comparison of PBPK model predictions to observed data from ZX008-1504 Cohort 1 after treatment with ZX008 plus STP and CLB (top panel) or ZX008 0.2 mg/kg or 0.4 mg/kg plus CLB (bottom panel).

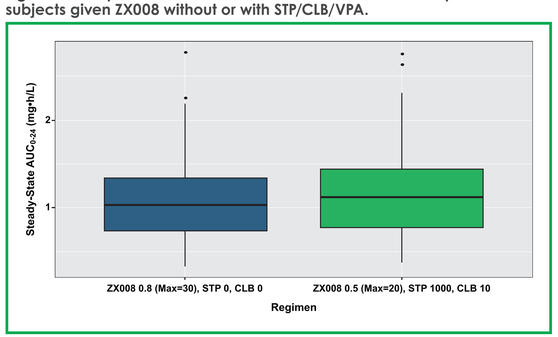


Note: Solid line (green) is the median predicted FFA concentrations over time, shaded regions (gray) are the 90% prediction intervals, and green dots are the observed concentrations from ZX008-1504.

Model-Based Simulations

- Simulated population of 1,000 children 2-18 years old (50% female)
- Age- and sex-appropriate height and weight assigned using CDC growth charts
- PBPK model including age-dependent factors
- Steady-state $AUC_{0\text{-}24}$ generated for each subject using various combinations of FFA, STP, and CLB
- Ultimately, when used in combination with STP/CLB/VPA, a ZX008 dose of 0.5 mg/kg/day (administered BID), with a daily maximum of 20 mg, is expected to provide FFA exposures that are reasonably similar to that predicted for ZX008 at a dose of 0.8 mg/kg/day (administered BID), with a daily maximum of 30 mg, without concomitant STP/CLB/VPA (**Figure 5**)
- The use of mg/kg dosing tends to result in lower exposures in the youngest age subjects, likely due to the fact that drug clearance does not scale linearly with body weight (**Figure 6**)

Figure 5. Comparison of the distributions of simulated FFA exposure in subjects given ZX008 without or with STP/CLB/VPA.

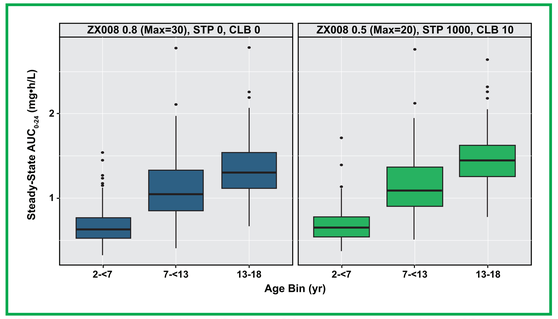


ZX008 doses are mg/kg/day (administered BID), STP and CLB doses are mg/day (administered BID). Max, maximum daily dose (mg).

Solid lines in middle of boxes represent the medians, boxes represent the interquartile range, whiskers extend to 1.5-times the interquartile range, and solid circles represent outlier values that occur outside the whiskers.

VPA was not expected to impact the PK of FFA/norFFA and is therefore not included in the model.

Figure 6. Comparison of the distributions of simulated FFA exposure in subjects given ZX008 without (left panel) or with (right panel) STP/CLB/VPA, stratified by age category.



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VPA was not expected to impact the PK of FFA/norFFA and is therefore not included in the model.

CONCLUSIONS

- Use of a pharmacometric-based strategy allowed for prediction of potential DDI in patients
- These simulations, in combination with safety data from the described clinical studies, supported dose selection for a Phase 3 trial of ZX008 when used as an adjunctive treatment to a STP-based treatment regimen
- These data and simulations will help clinicians select the safest dose of ZX008 that can be added to current regimens for treatment of DS and other pediatric-onset epilepsies

DISCLOSURES

CR: Consultant/advisor, Zogenix; Research grant, Zogenix; Patent (no royalties).
CR, LZ, MI, MT: Employees of ICPD, which contracted with Zogenix to do this analysis.
BB, GMF: Employee, Zogenix; Stock ownership, Zogenix.

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