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A Phase 1, Randomized, Open-Label, Single-Dose, 3-Period Crossover Study to Evaluate the Drug-Drug Interaction Between ZX008 (Fenfluramine Oral Solution) and a Regimen of Stiripentol, Clobazam, and Valproate in Healthy Volunteers

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RATIONALE

- An oral solution of fenfluramine (FFA), ZX008, is under development as a low-dose adjunctive treatment for seizures in patients with Dravet syndrome (DS) and Lennox-Gastaut syndrome (LGS)
- Current DS treatment regimens involve combinations of antiepileptics such as stiripentol (STP), clobazam (CLB), valproate (VPA), topiramate, and levetiracetam
- Assessment of potential drug-drug interactions when adding any new agent to DS treatment regimens is clinically important in this polypharmacy setting
- The anti-seizure activity of STP (labeled for administration with CLB and VPA) is based, at least in part, on its action as an enzyme inhibitor of metabolism of the labeled concomitant medications, making the potential interaction of FFA with STP of particular importance
- We assessed the pharmacokinetics (PK) and safety of ZX008 administered with and without a combination regimen of STP, CLB, and VPA (STP regimen), and the PK of STP, CLB, and VPA administered with and without ZX008

METHODS

Subjects

- Key inclusion criteria
  - Male or non-pregnant, non-lactating female subjects, 18-50 years old
  - Body mass index 19.0-31.0 kg/m^2 and weight of at least 50.0 kg
  - Non-smoker for at least 3 months
- Key exclusion criteria
  - Uncontrolled elevated blood pressure
  - Recent use (30 days prior to screening) of any medication that would induce or inhibit hepatic enzymes
  - Illicit drug use (positive screen) or history of alcohol abuse
  - History of cardiovascular, cerebrovascular, renal, hepatic, chronic respiratory, or gastrointestinal disease

Study Design, Treatments, and Outcomes

- Open-label, randomized, single-dose, 3-period crossover study
  - Treatment periods separated by 17 days
- Subjects were randomized to the following treatment regimens over 3 periods:
  - A: Single-dose ZX008 0.8 mg/kg
  - B: STP regimen: STP 3500 mg + CLB 20 mg + VPA 25 mg/kg
    - The maximum dose of VPA was 1500 mg, regardless of subject weight
  - C: ZX008 0.8 mg/kg + STP regimen
- Venous blood samples were withdrawn via an indwelling cannula or by venipuncture prior to dosing and at 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 9, 12, 24, 36, 48, and 72 hours following last administration of a study agent
- PK parameters included:
  - **T_{max}** (time from dosing to C_{max})
  - **C_{max}** (maximum observed plasma concentration)
  - **AUC_{0-t}** (area under the curve from 0 time to the last measurable concentration)
  - **AUC_{0-inf}** (area under the curve from 0 time to infinity)
  - **$t_{1/2}$** (terminal elimination half-life)
- Safety was assessed in all subjects who received at least 1 dose of an investigational agent

Statistical Analysis

- Statistical analysis used a bioequivalence approach performed on log-transformed PK parameters AUC_{0-inf}, AUC_{0-t} (analyzed because multiple AUC_{0-inf} values were noncalculable due to imprecision in quantifying the elimination phase), and C_{max} for each investigational agent
  - PK parameters were obtained via mixed-effects model with treatment, sequence, and period as fixed effects and subject nested within sequence as a random effect
  - Adjusted geometric mean ratios and 90% confidence intervals (CIs) for the ratios were calculated for the comparisons between ZX008 dosed with and without the STP regimen
  - The ratio was defined as the PK parameter from the combined treatment with ZX008 and the STP regimen, divided by the same parameter from treatment with ZX008 alone

RESULTS

Demographics

- Patient demographics (N=26) are shown in **Table 1**
  - Target enrollment was 24 healthy subjects to ensure 16 evaluable subjects at completion
- Seventeen subjects completed the study and 9 withdrew consent due to:
  - Inability to attend revised study dates (n=5)
  - Occurrence of an AE (depression, n=1)
  - Personal reasons (n=1)
  - Positive test for drugs of abuse (n=1)
  - AE requiring a prohibited medication for pain in an extremity (n=1)

Table 1. Subject Demographics (N=26)

Baseline Characteristic	
Age (y), mean±SD (range)	34.5±10.1 (21-50)
Race, n (%)	
Caucasian	23 (88)
Black	2 (8)
Asian	0
Other	1 (4)
Sex, n (%)	
Male	11 (42)
Female	15 (58)
Height (cm), mean±SD (range)	170.5±10.5 (157.0-188.0)
Weight (kg), mean±SD (range)	72.5±14.8 (52.8-103.0)
BMI (kg/m^2), mean±SD (range)	24.7±2.8 (21.4-30.0)

BMI, body mass index; SD, standard deviation.

Pharmacokinetics

- ZX008 did not have a significant impact on any of the PK profiles in the combination regimen (STP + CLB + VPA) (**Table 2**)
- Pharmacokinetics of STP, CLB, norclobazam (NCLB, the major metabolite of CLB), and VPA were not altered by the presence of FFA and norfenfluramine (norFFA, the major active metabolite of FFA) (**Table 3**)

Table 2. Key Pharmacokinetic Parameters for STP, CLB, NCLB, and VPA Following STP Regimen[a] Alone and in Combination With ZX008 (0.8 mg/kg)

Measured Agent in Combination	n	T_{max} (h)[b]	C_{max} (ng/mL)	AUC_{0-t} (ng·h/mL)	$t_{1/2}$ (h)
Stiripentol	19	6.0 (1.1-48.1)	3280±1390	81800±31100 (n=17)	16.0±4.2 (n=9)
Stiripentol + ZX008	24	6.0 (1.5-36.0)	3690±1210	76900±33800	16.7±7.5 (n=12)
Clobazam	19	3.0 (1.5-6.0)	231±38.9	7960±1120 (n=17)	28.9 (n=1)
Clobazam + ZX008	24	3.0 (1.5-6.0)	216±54.2	7750±1600	25.6±2.1 (n=4)
Norclobazam	19	72.0 (48.0-72.2)	97.4±30.9	4380±1500 (n=17)	NC
Norclobazam + ZX008	24	72.0 (71.6-72.2)	94.8±28.5	4420±1570	NC
Valproate	20	0.8 (0.5-3.0) (n=18)	100000±9140 (n=19)	1720000±415000 (n=17)	15.0±2.9 (n=17)
Valproate + ZX008	24	1.0 (0.5-3.0)	107000±17600	1890000±402000	14.8±2.5

[a]STP regimen: stiripentol 3500 mg + clobazam 20 mg + valproate 25 mg/kg (1500 mg maximum).
[b]T_{max} values are median (range); remaining values are mean±SD, except where SD is not calculated.
NC, not calculated. Pharmacokinetic abbreviations are as defined in Methods.

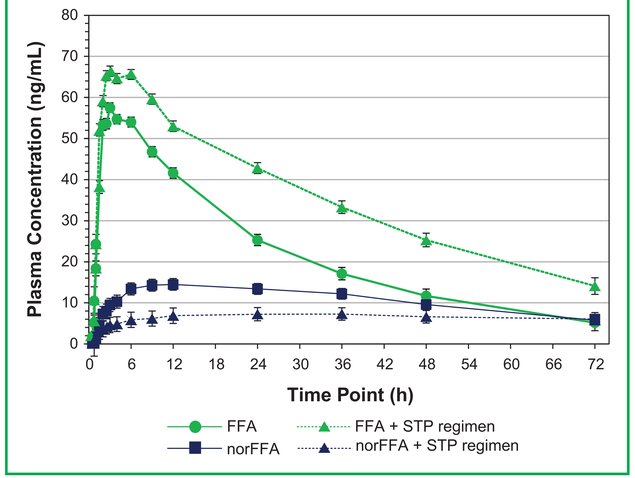
Table 3. Analysis of STP, CLB, NCLB, and VPA Following STP Regimen[a] Alone and in Combination With ZX008 (0.8 mg/kg)

		Treatment		Statistical Comparison		
Measured AED[b]	n	STP regimen	STP regimen + ZX008	Ratio (%)	90% CI (%)	p-value
Stiripentol						
C_{max} (ng/mL)	18	3030	3500	115.6	97.9-136.5	NS
AUC_{0-t} (ng·h/mL)	16	85500	74200	86.7	68.0-110.6	NS
Clobazam						
C_{max} (ng/mL)	18	241	229	95.3	88.0-103.2	NS
AUC_{0-t} (ng·h/mL)	16	8130	7710	94.8	90.3-99.6	NS
Norclobazam						
C_{max} (ng/mL)	18	99.3	99.8	100.5	96.5-104.8	NS
AUC_{0-t} (ng·h/mL)	16	4410	4480	101.6	95.0-108.6	NS
Valproate						
C_{max} (ng/mL)	18	104000	105000	101.3	96.6-106.2	NS
AUC_{0-t} (ng·h/mL)	16	1760000	1750000	99.6	94.1-105.3	NS

[a]STP regimen: stiripentol 3500 mg + clobazam 20 mg + valproate 25 mg/kg (1500 mg maximum).
[b]C_{max} and AUC values are adjusted geometric means.
AED, antiepileptic drug; CI, confidence interval; NS, not significant. Pharmacokinetic abbreviations are as defined in Methods.

- The STP regimen had a moderate effect on FFA and norFFA PK (**Figure 1**, **Table 4**)
- The 3-drug combination increased the geometric mean C_{max}, AUC_{0-t}, and AUC_{0-inf} of FFA by 1.2-, 1.7-, and 1.7-fold, respectively (**Table 4**)
- The STP regimen reduced the AUC_{0-t} of norFFA by 41% (**Table 4**)
- Standard bioequivalence analysis showed both FFA and norFFA bioavailability were significantly altered by the co-administration of the STP regimen (**Table 5**)
- There was no obvious effect of CYP2D6 genotype status on FFA or norFFA PK (data not shown)

Figure 1. Geometric mean (×/÷ geometric SD) plasma concentrations (ng/mL) of FFA and norFFA following ZX008 (0.8 mg/kg) alone and in combination with STP regimen[a].



[a]STP regimen: stiripentol 3500 mg + clobazam 20 mg + valproate 25 mg/kg (1500 mg maximum).

Table 4. Key Pharmacokinetic Parameters for FFA and norFFA Following ZX008 (0.8 mg/kg) Alone and in Combination With STP Regimen[a]

Measured Agent	n	T_{max} (h)[b]	C_{max} (ng/mL)	AUC_{0-t} (ng·h/mL)	AUC_{0-inf} (ng·h/mL)	$t_{1/2}$ (h)
Fenfluramine	19	3.0 (2.0-12.0)	62.4±8.5	1670±497	1720±491 (n=17)	20.1±3.3 (n=17)
Fenfluramine + STP regimen	24	3.0 (1.0-9.0)	75.7±14.7	2700±762	2440±821 (n=12)	22.6±3.8 (n=12)
Norfenfluramine	19	12.1 (9.0-36.0)	16.4±4.4	804±199	839±79 (n=4)	23.5±2.3 (n=4)
Norfenfluramine + STP regimen	24	24.0 (2.0-72.2)	10.2±4.2	520±191	NC	NC

[a]STP regimen: stiripentol 3500 mg + clobazam 20 mg + valproate 25 mg/kg (1500 mg maximum).
[b]T_{max} values are median (range); remaining values are mean±SD.
NC, not calculated. PK abbreviations are as defined in Methods.

Table 5. Statistical Analysis of FFA and NorFFA Following ZX008 (0.8 mg/kg) Alone and in Combination With STP Regimen[a]

		Treatment		Statistical Comparison		
PK Parameter[b]	n	STP regimen + ZX008	ZX008	Ratio (%)	90% CI	p-value
Fenfluramine						
C_{max} (ng/mL)	19	73.7	62.4	118.10	109.43, 127.46	0.002
AUC_{0-t} (ng·h/mL)	19	2640	1590	166.19	152.00, 181.71	<0.001
AUC_{0-inf} (ng·h/mL)	9	2320	1370	168.53	154.83, 183.43	<0.001
Norfenfluramine						
C_{max} (ng/mL)	19	9.11	15.8	57.51	48.80, 67.77	<0.001
AUC_{0-t} (ng·h/mL)	19	459	782	58.71	50.40, 68.40	<0.001

[a]STP regimen: stiripentol 3500 mg + clobazam 20 mg + valproate 25 mg/kg (1500 mg maximum).
[b]C_{max} and AUC values are adjusted geometric means.
CI, confidence interval; PK, pharmacokinetic. PK abbreviations are as defined in Methods.

Safety

- No deaths, severe adverse events (AEs), or serious AEs (SAEs) were reported
- **Table 6** presents treatment-emergent AEs (TEAEs) with an incidence ≥10% in the overall patient population or in the separate treatment groups
- **NOTE:** The single administration of these relatively high doses of ZX008, STP, CLB, and VPA in these healthy patients is unlike the clinical treatment of DS and LGS, where the dose would be gradually titrated to effect. In addition, the ZX008 dose would be capped at no greater than 30 mg.

Table 6. Incidence of TEAEs With a Frequency of ≥10% for ZX008 Alone, STP Regimen[a] Alone, and ZX008 + STP Regimen

System/Organ Class	ZX008 (n=20) n (%)	STP Regimen (n=21) n (%)	ZX008 + STP Regimen (n=25) n (%)	Overall (n=26) n (%)
Subjects reporting TEAEs	13 (65.0)	16 (76.2)	22 (88.0)	25 (96.2)
Nervous system disorders	9 (45.0)	14 (66.7)	20 (80.0)	24 (92.3)
Somnolence	1 (5.0)	12 (57.1)	19 (76.0)	20 (76.9)
Headache	6 (30.0)	3 (14.3)	7 (28.0)	13 (50.0)
Dizziness	3 (15.0)	1 (4.8)	2 (8.0)	5 (19.2)
Gastrointestinal disorders	6 (30.0)	4 (19.0)	9 (36.0)	14 (53.8)
Nausea	2 (10.0)	1 (4.8)	7 (28.0)	10 (38.5)
Vomiting	1 (5.0)	2 (9.5)	4 (16.0)	6 (23.1)
General disorders and administration site conditions	5 (25.0)	2 (9.5)	4 (16.0)	11 (42.3)
Fatigue	3 (15.0)	2 (9.5)	2 (8.0)	7 (26.9)
Psychiatric disorders	2 (10.0)	1 (4.8)	5 (20.0)	7 (26.9)
Anxiety	2 (10.0)	0	2 (8.0)	3 (11.5)
Euphoric mood	0	1 (4.8)	2 (8.0)	3 (11.5)
Metabolism and nutrition disorders	2 (10.0)	0	3 (12.0)	3 (11.5)
Decreased appetite	2 (10.0)	0	3 (12.0)	3 (11.5)

[a]STP regimen: stiripentol 3500 mg + clobazam 20 mg + valproate 25 mg/kg (1500 mg maximum).
TEAEs, treatment-emergent adverse events.

CONCLUSIONS

- ZX008 did not have any significant impact on the PK of the individual agents in the STP regimen (STP, CLB, and VPA)
  - ZX008 had no appreciable effect on the PK of the CLB metabolite NCLB
- The STP regimen had a significant effect on the PK of FFA and norFFA. When administering these drugs together, a 35%-40% downward dose adjustment of FFA and a slower titration to reach a therapeutic dose are required.
- FFA was generally well tolerated alone and in combination with the STP regimen in these healthy volunteers

DISCLOSURE

BB, AG, BSG, GMF: Employee, Zogenix; Stock ownership, Zogenix.
SS: Consultant, Zogenix.

ACKNOWLEDGEMENTS

This study was funded by Zogenix, Inc. (Emeryville, CA). Medical writing and editorial assistance was provided by Gregory Kopia, PhD and Donald Fallon, ELS of PharmaWrite, LLC (Princeton, NJ, USA) and was funded by Zogenix, Inc.

Presented at the 71st Annual Meeting of the American Epilepsy Society, December 1-5, 2017, Washington, DC