

The Lack of Effect of Food on the Pharmacokinetics of ZX008 (Fenfluramine Oral Solution): Results of a Single-Dose, Two-Period Crossover Study

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INTRODUCTION

- Dravet syndrome (DS) and Lennox-Gastaut syndrome (LGS) are severe, drug-resistant, epileptic encephalopathies of childhood¹⁻³
- Pharmacotherapy in DS and LGS typically entails combinations of antiepileptic drugs (AEDs)^{2,3}
 - First line for DS: valproic acid, clobazam
 - Second line for DS: topiramate, stiripentol, levetiracetam, bromides; ketogenic diet
 - FDA-approved AEDs for LGS: felbamate, lamotrigine, topiramate, rufinamide, clobazam³
- Fenfluramine (FFA) has been shown to be effective in DS as an adjunctive treatment to AEDs^{4,5}
 - An oral formulation of FFA (ZX008) is currently being developed by Zogenix (Emeryville, CA)
- Interim findings from an ongoing dose-finding pilot study of ZX008 treatment for LGS (EudraCT Number 2015-004008-46) demonstrated that it was well tolerated and reduced major motor seizure frequency⁶
- Food can affect the rate and extent of AED drug absorption⁷
 - For example, stiripentol must be taken with a meal, but not with milk or dairy products, carbonated drinks, fruit juice, or food/drinks that contain caffeine or theophylline⁸
- Polypharmacy in DS patients presents a challenge to caregivers in establishing optimal administration in relation to meals and mealtimes

OBJECTIVE

- To determine the effect of food on the pharmacokinetics (PK) of FFA and its active metabolite norfenfluramine (norFFA) in the fasted or fed state

METHODS

Study Design and Treatments

- Open-label, randomized, single-dose, 2-period crossover study in healthy adults
- Key inclusion criteria
 - Healthy male/healthy nonpregnant, nonlactating female subjects 18-50 years old
 - Body mass index (BMI) 19.0-31.0 kg/m² and a minimum weight of 50.0 kg
 - Nonsmokers for at least 3 months
- Key exclusion criteria
 - Use of hepatic enzyme inducers or inhibitors within 30 days
 - History of alcohol or drug abuse
 - Positive drug screen for illegal drugs or nonprescription controlled substances
- Study regimens (9-day washout between treatment periods) were based on FDA guidance parameters⁹
 - Single oral dose (0.8 mg/kg ZX008) after an overnight fast of ≥10 hours
 - Single oral dose (0.8 mg/kg ZX008) 30 minutes after a high-fat breakfast (800-1000 calories, with fat comprising approximately 50% of total caloric content)

Pharmacokinetic Evaluations

- Venous blood samples were taken before each dose and at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 9, 12, 24, 36, 48, and 72 hours following each administration of ZX008
- FFA and norFFA plasma concentrations were determined by KCAS Bioanalytical Services (Shawnee, KS, USA) using a validated bioanalytical method (lower limit of quantification: 0.25 ng/mL)

- Plasma PK parameters were estimated by noncompartmental analysis using Phoenix WinNonlin v6.3 (Certara, Princeton, NJ, USA)
 - 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}, the terminal elimination half-life
 - CL/F, clearance, the apparent volume cleared of parent drug per unit time after extravascular administration

RESULTS

Patients

- A total of 14 patients were enrolled (Table 1) and 13 completed both treatment periods; 1 withdrew for a non-study related emergency
 - No current smokers; most had alcohol consumption of 1-7 units per week (1 unit = 10 mL of 200 proof [100%] alcohol, 0.5 pint beer, 25 mL of a 40% spirit, or a 125 mL glass of wine)

Table 1. Patient Demographics

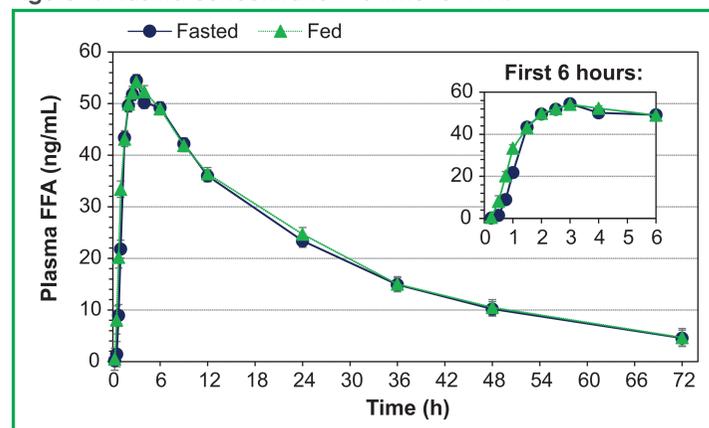
| Baseline Characteristic | Fasted/Fed (N=14) |
|--|-------------------------|
| Age, y, mean±SD (range) | 34.0±8.9 (20-44) |
| Race, n (%) | |
| White | 13 (93) |
| Other (White/Caribbean) | 1 (7) |
| Sex, n (%) | |
| Male | 9 (64) |
| Female | 5 (36) |
| Height, cm, mean±SD (range) | 172.3±9.8 (157.0-191.0) |
| Weight, kg, mean±SD (range) | 76.6±9.7 (56.2-90.4) |
| BMI, kg/m ² , mean±SD (range) | 25.9±3.6 (19.0-30.8) |

BMI, body mass index; SD, standard deviation.

Pharmacokinetics: FFA

- Plasma concentration-vs-time curves for FFA in the fed and fasted states were virtually overlapping (Figure 1, Table 2)
 - Plasma concentrations were quantifiable up to 72 hours post-dose in all subjects, in both fasted and fed states
 - Plasma terminal slopes were quantifiable in all subjects, resulting in terminal half-lives (t_{1/2}) ranging from 15.8-27.2 hours

Figure 1. Plasma concentration vs time for FFA.



Geometric mean (x/± geometric SD) plasma concentrations (ng/mL) following a single oral dose of 0.8 mg/kg ZX008. FFA, fenfluramine.

Table 2. Key Pharmacokinetic Parameters for FFA

| Measured Agent | n | T _{max} (h)* | C _{max} (ng/mL) | AUC _{0-inf} (ng·h/mL) | t _{1/2} (h) |
|----------------|----|-----------------------|--------------------------|--------------------------------|----------------------|
| FFA - Fasted | 14 | 3.0 (1.5-4.0) | 57.4±10.1 | 1610±338 | 21.2±3.6 |
| FFA - Fed | 13 | 3.0 (0.8-6.0) | 60.1±12.6 | 1680±417 | 21.3±3.3 |

*T_{max} values are median (range); remaining parameter values are mean±SD. FFA, fenfluramine.

Bioequivalence Analysis for FFA

- The presence of food had no effect on FFA rate or extent of absorption. The data met bioequivalence criteria (ie, 90% CIs of geometric mean ratio [GMR] of fed/fasted conditions were completely contained within 80%-125%) after a single dose of 0.8 mg/kg ZX008 (Table 3)

Table 3. Statistical Analysis of FFA Bioavailability

| PK Parameter | n | Treatment* | | Statistical Comparison | | |
|--------------------------------|----|------------|--------|------------------------|---------------|---------|
| | | Fed | Fasted | Ratio (%) | 90% CI (%) | P-value |
| C _{max} (ng/mL) | 13 | 59.1 | 56.7 | 104.2 | (97.9, 111.0) | NS |
| AUC _{0-inf} (ng·h/mL) | 13 | 1640 | 1600 | 102.7 | (98.9, 106.7) | NS |

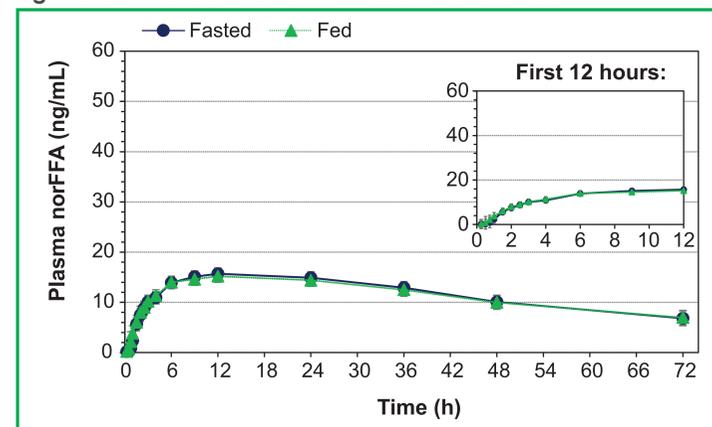
*Values are adjusted geometric means.

FFA, fenfluramine; NS, not significant.

Pharmacokinetics: NorFFA

- NorFFA, the active and major metabolite of FFA, showed overlapping concentration-vs-time curves in the fed and fasted states (Figure 2, Table 4)
 - Plasma concentrations were quantifiable to 72 hours under both dietary conditions
 - Decline in norFFA over 72 hours resulted in comparable median terminal half-lives in fasted and fed subjects

Figure 2. Plasma concentration vs time for norFFA.



Geometric mean (x/± geometric SD) plasma concentrations (ng/mL) following a single oral dose of 0.8 mg/kg ZX008. NorFFA, norfenfluramine.

Table 4. Key Pharmacokinetic Parameters for NorFFA

| Measured Agent | n | T _{max} (h)* | C _{max} (ng/mL) | AUC _{0-∞} ** (ng·h/mL) | t _{1/2} (h) |
|-----------------|----|-----------------------|--------------------------|---------------------------------|----------------------|
| NorFFA - Fasted | 14 | 12.0 (9.0-36.0) | 16.5±2.3 | 852±163 | 41.1±10.6 |
| NorFFA - Fed | 13 | 12.0 (6.0-36.0) | 16.1±2.3 | 843±162 | 48.0±20.2 (n=12) |

*T_{max} values are median (range); remaining parameter values are mean±SD.

**For norFFA, AUC_{0-t} was analyzed instead of AUC_{0-inf} because AUC_{0-inf} values were not consistently calculable.

NorFFA, norfenfluramine.

Safety

- Frequencies of treatment-emergent adverse events (TEAEs) in ≥10% of subjects are shown in Table 5
 - There were no deaths, severe AEs, or serious AEs, or withdrawals due to AEs
 - The most common TEAEs were dizziness, headache, and somnolence
- There were no notable food effects on TEAE frequency (Table 5)
 - Overall, 50% of subjects (7/14) reported 12 AEs, all mild in severity, with 9/12 possibly or probably drug-related
 - Slightly more instances of nervous system disorders (especially dizziness; n=3) were found in the fasted state (Table 5)
- There were no clinically significant laboratory, vital sign, or physical examination findings related to drug administration
- NOTE:** This study did not cap the ZX008 daily dose at 30 mg or titrate to a dose of 0.8 mg/kg/day, as will be done in clinical practice for the treatment of DS or LGS

Table 5. Incidence of TEAEs With a Frequency of ≥10%

| System/Organ Class | FFA Fasted (n=14) n (%) | FFA Fed (n=13) n (%) | Overall (N=14) n (%) |
|--------------------------|-------------------------|----------------------|----------------------|
| Subjects reporting TEAEs | 4 (28.6) | 4 (30.8) | 7 (50.0) |
| Nervous system disorders | 4 (28.6) | 2 (15.4) | 6 (42.9) |
| Dizziness | 3 (21.4) | 0 | 3 (21.4) |
| Headache | 2 (14.3) | 1 (7.7) | 3 (21.4) |
| Somnolence | 1 (7.1) | 1 (7.7) | 2 (14.3) |

CONCLUSIONS

- Food had no effect on the rate or extent of absorption of FFA, nor on the of systemic exposure of FFA and norFFA after a single dose of 0.8 mg/kg of ZX008
- A single oral dose of 0.8 mg/kg of ZX008 was generally well tolerated in both the fasted and fed states
- ZX008 may be administered without regard to meals

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DISCLOSURE

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

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