Pharmacokinetics of Fenfluramine and its Active Metabolite Norfenfluramine in Patients with Lennox-Gastaut Syndrome

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Question

What is the clinical pharmacokinetic (PK) profile of fenfluramine (FFA) and its active metabolite, norfenfluramine (nFFA) in Lennox-Gastaut syndrome (LGS) patients?

Investigation

- The population PK (PPK) model previously developed using data from healthy volunteers and patients with Dravet syndrome (DS) was refined to fit PK data from a randomized clinical trial of FFA in children and adults with LGS
- The model was used to estimate steady-state exposure to FFA and nFFA, variability, dose proportionality, and to determine if patient variables affect FFA and nFFA PK

Methods

- EP0214 (ZX008-1601) was a phase 3, double-blind, placebo-controlled trial where LGS patients 2-35 years of age were randomized (1:1:1) to placebo, 0.2 mg/kg/d FFA, or 0.7 mg/kg/d FFA
  - Per protocol, FFA dose was limited (capped) to the max 26 mg/d; in practice, includes participants randomized to 0.7 mg/kg/d with baseline body weight ≥37.5 kg

Results

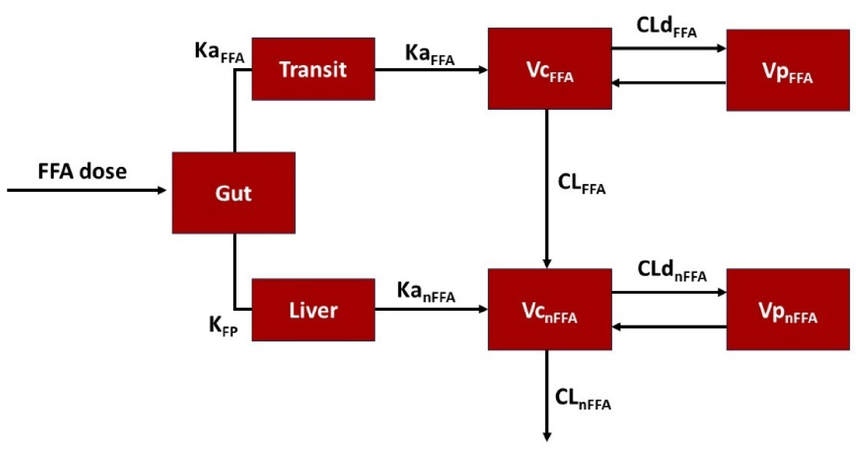
Table 1. Demographic Information and Baseline Characteristics

	FFA 0.2 mg/kg/d n = 84	FFA 0.7 mg/kg/d n = 80
Age, years		
Median, range	13, 3-33	13, 2-35
Weight (kg)		
Median, range	41.6, 13-108	39, 11-127
BMI, kg/m^2		
Median, range	19.4, 11.9-47.3	18.4, 9.9-37.2
CLcr, mL/min/1.73m^2		
Median, range	136, 76.3-252	134, 84.2-219
Male, n (%)	43 (51.2%)	76 (58.9%)
Race, n (%)		
White	64 (76.2%)	100 (77.5%)
Black	5 (5.6%)	7 (5.4%)
Asian	2 (2.4%)	5 (3.9%)
Native-Hawaiian/Other Pacific Islander	1 (1.2%)	1 (0.8%)
Other	12 (14.3%)	3 (8.6%)

BMI, body mass index; CLcr, creatinine clearance; FFA, fenfluramine.

- No changes to the structure of the previous model were necessary (**Fig 1**)

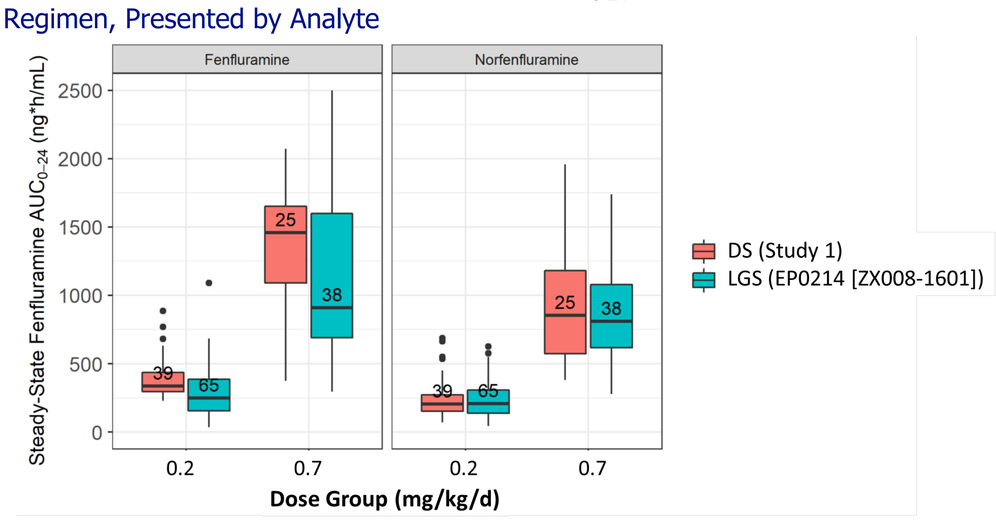
Figure 1. Schematic Representation of the Base Structural PK Model for Fenfluramine (FFA) and Norfenfluramine (nFFA)



CL_{FFA}, apparent oral systemic clearance fenfluramine (L/hr/70kg); CL_{nFFA}, apparent oral systemic clearance norfenfluramine (L/hr/70kg); CLd_{FFA}, apparent oral distributional clearance fenfluramine (L/hr/70kg); CLd_{nFFA}, apparent oral distributional clearance norfenfluramine (L/hr/70kg); Ka_{FFA}, absorption rate constant fenfluramine (hr^{-1}); Ka_{nFFA}, absorption rate constant norfenfluramine (hr^{-1}); K_{FP}, presystemic (first-pass) metabolism); Vc_{FFA}, apparent oral central volume of distribution fenfluramine (L/70kg); Vc_{nFFA}, apparent oral central volume of distribution norfenfluramine (L/70kg); Vp_{FFA}, apparent oral peripheral volume of distribution fenfluramine (L/70kg); Vp_{nFFA}, apparent oral peripheral volume of distribution norfenfluramine (L/70kg).

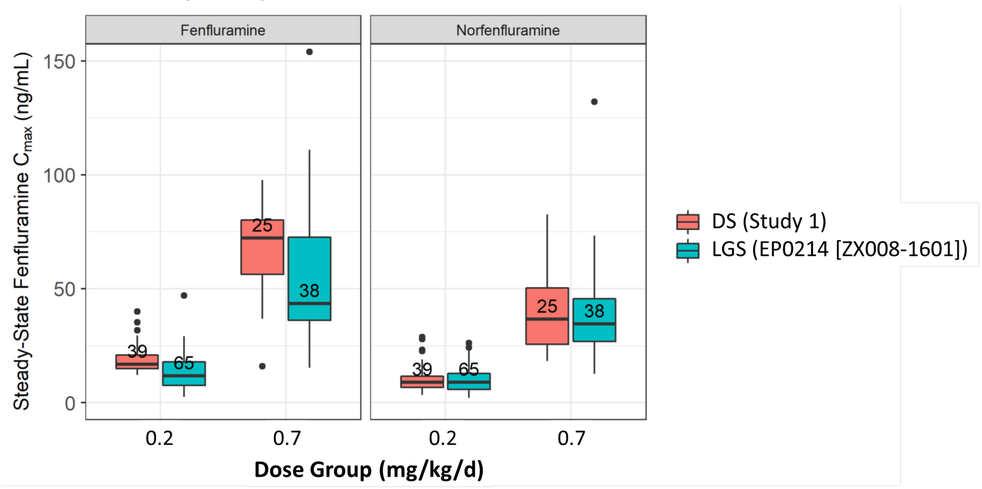
- After inclusion of body weight and concomitant use of stiripentol, the only covariate relationship of significance was between CLcr and clearance of nFFA
  - No other covariates were influential on PK
- FFA and nFFA PK profiles were similar and the distributions of steady-state FFA and nFFA exposures overlapped in the LGS and DS study populations (**Fig 2 and 3**)

Figure 2. Distributions of Estimates Steady-State $AUC_{0\text{-}24}$, Stratified by Indication/Study and Dose Regimen, Presented by Analyte



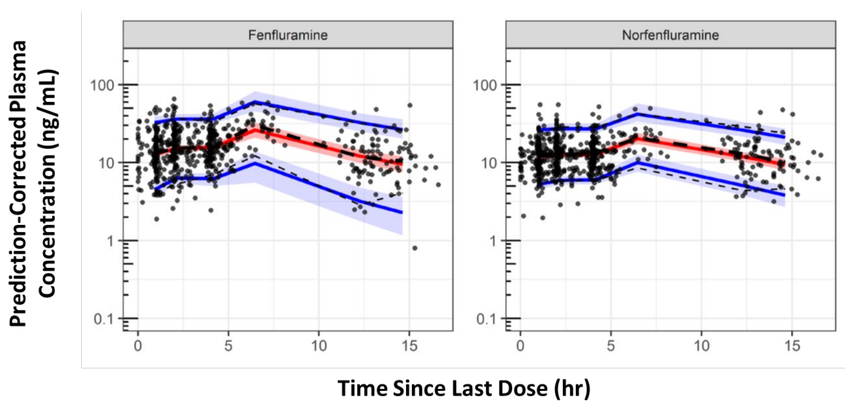
Numbers in each box show the number of patients in the respective group.
Only patients <18 years of age are included. For the 0.7 mg/kg/day regiment, only patients with body weight <37.5 kg are included.
$AUC^{0\text{-}24}$, area under the concentration-time curve from time 0 to 24 hours; DS, Dravet syndrome; LGS, Lennox-Gastaut syndrome.

Figure 3. Distribution of Estimated Steady-State C_{max}, Stratified by Indication/Study and Dose Regimen, Presented by Analyte



Numbers in each box show the number of patients in the respective group.
Only patients <18 years of age are included. For the 0.7 mg/kg/day regiment, only patients with body weight <37.5 kg are included.
C_{max}, maximum concentration; DS, Dravet syndrome; LGS, Lennox-Gastaut syndrome.

Figure 4. Prediction-Corrected Visual Predictive Check for the Final PPK Model for FFA and nFFA for the Entire Study Population on a Log-Linear Scale



Circles are observed concentrations; thick black dashed lines are the median observed concentration; thin black dashed lines are the 5th and 95th percentiles of the observed concentrations. Red and blue shaded regions are the 90% confidence intervals for the median, 5th, and 95th percentiles from the simulations. Red and blue lines are the medians of the 50th, 5th, and 95th percentiles of the simulated values.

Conclusions

- Alternative dosing regimens are not required for subpopulations of LGS based on age, BMI, CLcr, sex, or race
- Systemic exposures overlapped between LGS and DS patients, although the former experienced lower geometric mean exposures which are not clinically meaningful; the recommended doses of FFA are the same for LGS and DS patients
- These results provide information to aid prescribing clinicians in selecting an optimal dose of FFA for effectiveness and tolerability that can be added to current regiments for treatment of LGS

References

1. UCB Inc. FINTEPLA® (fenfluramine) oral solution [prescribing information]. Smyrna, GA March 2023.
2. Zogenix ROI Limited. Fintepla 2.2 mg/mL oral solution [summary of product characteristics]. Dublin, IE April 20 2023.
3. Nippon Shinyaku Co. Ltd. Launch of Fintepla® (fenfluramine) for the treatment of seizures associated with Dravet syndrome in Japan. 2022.
4. Savic RM, Karlsson MO. *AAPS J.* 2009;11(3):558-69.

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Disclosures

AM and BB: Employees of UCB Biosciences. **CR:** Employee of ICPD. **JW:** Speaker or a member of a speakers bureau for Cyberonics Inc., Eisai Inc., Lundbeck Inc., Mallinckrodt, Neurelis Inc., Supernus Pharmaceuticals Inc., and Upsher-Smith Laboratories Inc.; Received grants for clinical research from Acorda Therapeutics, GW Pharma (now Jazz Pharmaceuticals), Insys Therapeutics Inc., Lundbeck Inc., Mallinckrodt, Neurelis Inc., NeuroPace Inc., Upsher-Smith Laboratories Inc., and Zogenix Inc. (now a part of UCB).

This poster is a part of a larger project, and we have prepared a companion poster which provides the PK of FFA and nFFA in patients with Dravet syndrome (#198).

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This is a summary of the main findings. Please use the QR code to download the full poster.

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