Modeling Systemic Exposure to Fenfluramine and its Active Metabolite, Norfenfluramine, in Patients With Dravet Syndrome

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Question

What is the potential impact of population characteristics and concomitant medications on the exposure of fenfluramine (FFA) and norfenfluramine (nFFA) in patients with Dravet syndrome (DS)?

Methods

- A post-hoc pooled analysis of two phase 1 studies and two phase 3 studies was conducted to develop a robust population pharmacokinetic (PPK) model (**Table 1**)

Table 1. Clinical Studies Used for the PPK Analysis

Study	Phase and Study Population	Treatment Arms
EP0200[a], Part 1	Phase 1 Healthy, adult volunteers n=25	• Single dose of FFA (0.35 mg/kg) alone • In combination with STP, CLB, and VPA
EP0210[b], Cohort 1	Phase 1 Children with DS n=18	• Single dose of FFA (0.2 or 0.35 mg/kg) in combination with existing ASM regimen, containing CLB + VPA • With or without STP and CLB + VPA
Study 1 (EP0208 and EP0209[c])	Phase 3 (sparse PK samples) Inclusion 2-18 years n=75	• Placebo • FFA 0.2 mg/kg/d or 0.7 mg/kg/d[§] • Without concomitant STP
EP0210[b], Cohort 2	Phase 3 (sparse PK samples) Inclusion 2-18 years n=65	• Placebo in combination with STP/CLB/VPA • FFA (0.4 mg/kg/d*) in combination with STP/CLB/VPA

[§]Maximum 26 mg/day. *Maximum 17 mg/day.
[a]ZX008-1505.
[b]ZX008-1504.
[c]ZX008-1501 and ZX008-1502.
ASM, antiseizure medications; CLB, clobazam; DS, Dravet syndrome; FFA, fenfluramine; PPK, population pharmacokinetic; STP, stiripentol; VPA, valproate.

- The model was used to estimate steady-state exposure (C_{min}, C_{max}, AUC_{0-24}) to FFA and nFFA, dose proportionality, and to determine if covariates and variables such as concomitant antiseizure medications (ASMs) affect FFA and nFFA pharmacokinetics (PK) in patients with DS

Results

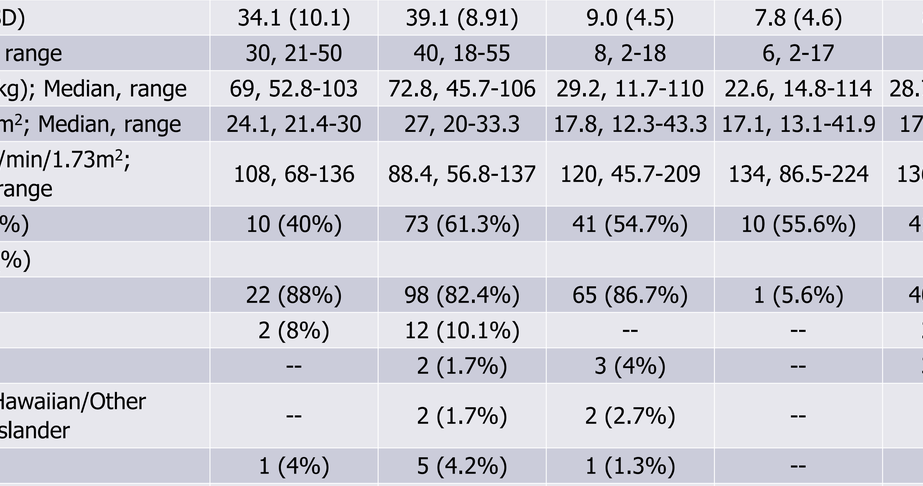
Table 2. Demographic Data

	Phase 1		Phase 3		
	EP0200[a] (Part 1) n=25	**EP0221[b] n=119**	**Study 1[c] n=75**	**EP0210[d], Cohort 1 n=18**	**EP0210[d], Cohort 2 n=65**
Age, years					
Mean (SD)	34.1 (10.1)	39.1 (8.91)	9.0 (4.5)	7.8 (4.6)	8.9 (4.8)
Median, range	30, 21-50	40, 18-55	8, 2-18	6, 2-17	9, 2-19
Weight (kg); Median, range	69, 52.8-103	72.8, 45.7-106	29.2, 11.7-110	22.6, 14.8-114	28.7, 12.9-90.6
BMI, kg/m^2; Median, range	24.1, 21.4-30	27, 20-33.3	17.8, 12.3-43.3	17.1, 13.1-41.9	17.1, 13.3-35
CLcr, mL/min/1.73m^2; Median, range	108, 68-136	88.4, 56.8-137	120, 45.7-209	134, 86.5-224	136, 83.8-202
Male, n (%)	10 (40%)	73 (61.3%)	41 (54.7%)	10 (55.6%)	41 (63.1%)
Race, n (%)					
White	22 (88%)	98 (82.4%)	65 (86.7%)	1 (5.6%)	40 (61.5%)
Black	2 (8%)	12 (10.1%)	--	--	2 (3.1%)
Asian	--	2 (1.7%)	3 (4%)	--	3 (4.6%)
Native-Hawaiian/Other Pacific Islander	--	2 (1.7%)	2 (2.7%)	--	--
Other	1 (4%)	5 (4.2%)	1 (1.3%)	--	--
Missing	--	--	4 (5.3%)	17 (94.4%)	20 (30.8%)

[a]ZX008-1505.
[b]ZX008-1603.
[c]EP0208 and EP0209 (ZX008-1501 and ZX008-1502).
[d]ZX008-1504.
BMI, body mass index; CLcr, creatinine clearance.

- The PPK model consisted of 2 compartments for FFA and for nFFA, first-order absorption of FFA, allowance for pre-systemic formation of nFFA, and linear clearance for both compounds (**Fig 1**)

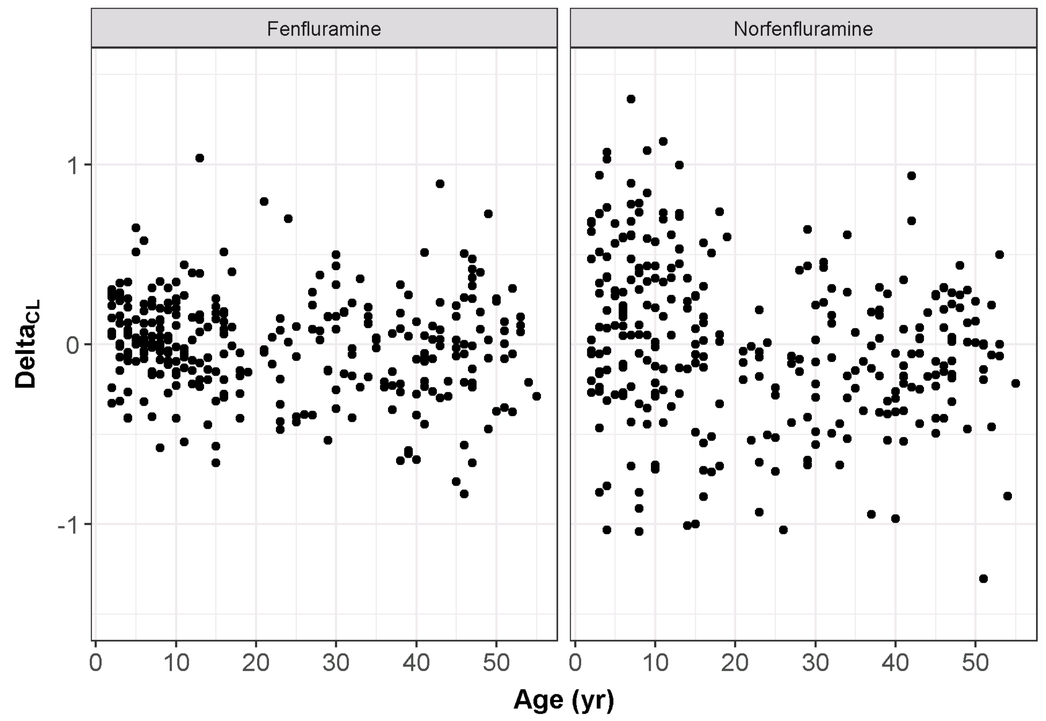
Figure 1. Schematic Representation of the Base Structural Model for Fenfluramine and Norfenfluramine Pharmacokinetics



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).

- Covariates of significance were body weight and concomitant STP
  - The lack of clear trends in the relationship between the interindividual variability in FFA and nFFA clearance and age indicates that clearance is similar in adults and children (**Fig 2**)

Figure 2. The Relationship Between $Delta_{CL}$ and Age Using the Fit of the PPK Model to the Observed Data



$Delta_{CL}$, difference between the population mean clearance and the participant's individual fitted estimate of clearance; PPK, population pharmacokinetics.

Conclusions

- A comprehensive modeling approach allowed for the evaluation of factors that could impact the PK of FFA and/or nFFA in patients with DS
- These results provide valuable information to aid prescribing clinicians in the selection of an optimal dose of FFA based on effectiveness and tolerability that can be added to current regimens for treatment of DS and other developmental and epileptic encephalopathies

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 2023.
3. Nippon Shinyaku Co. Ltd. Launch of Fintepla® (fenfluramine) for the treatment of seizures associated with Dravet syndrome in Japan. 2022.

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Disclosures

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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 Lennox-Gastaut syndrome (#238).

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

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