Poster #P508

Exposure-Response Relationships of Fenfluramine in Patients With Dravet Syndrome and Lennox-Gastaut Syndrome

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QUESTION

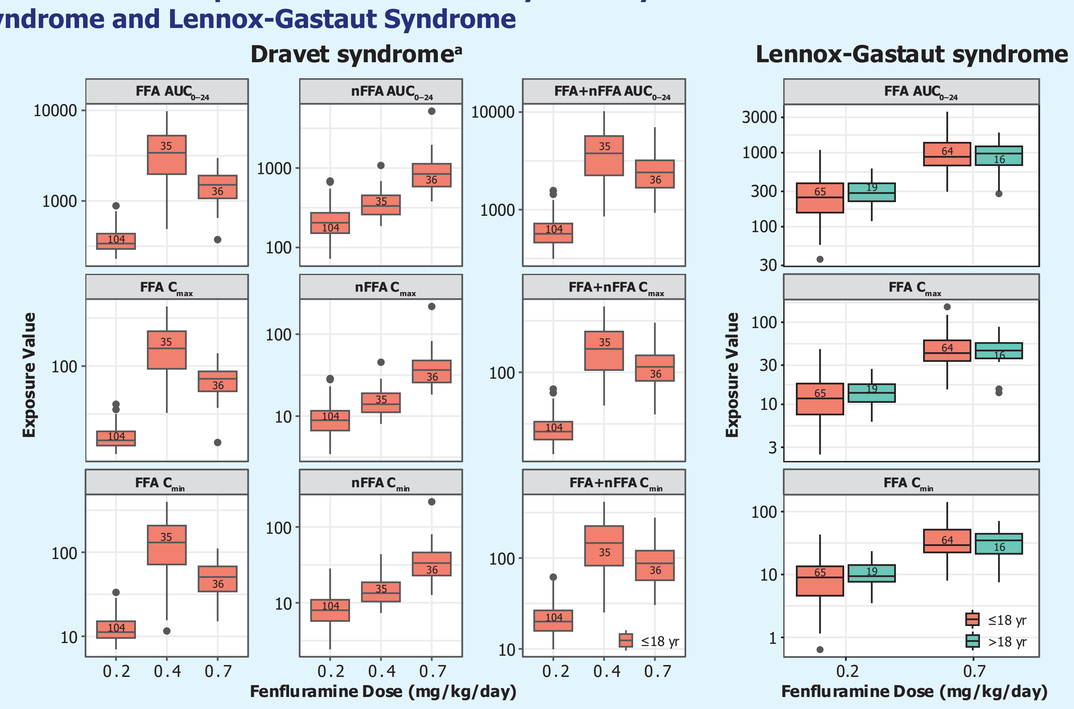
- In patients with Dravet syndrome (DS) or Lennox-Gastaut syndrome (LGS) treated with fenfluramine, what is the relationship of fenfluramine and norfenfluramine exposure with efficacy and safety?

INVESTIGATION

- A population pharmacokinetic (PK) model was developed using data acquired from patients enrolled in phase 3 clinical trials of fenfluramine in DS and LGS
- The PK model estimated exposures to fenfluramine and norfenfluramine in DS and LGS populations and correlated exposures with efficacy (seizure frequency) and safety outcomes

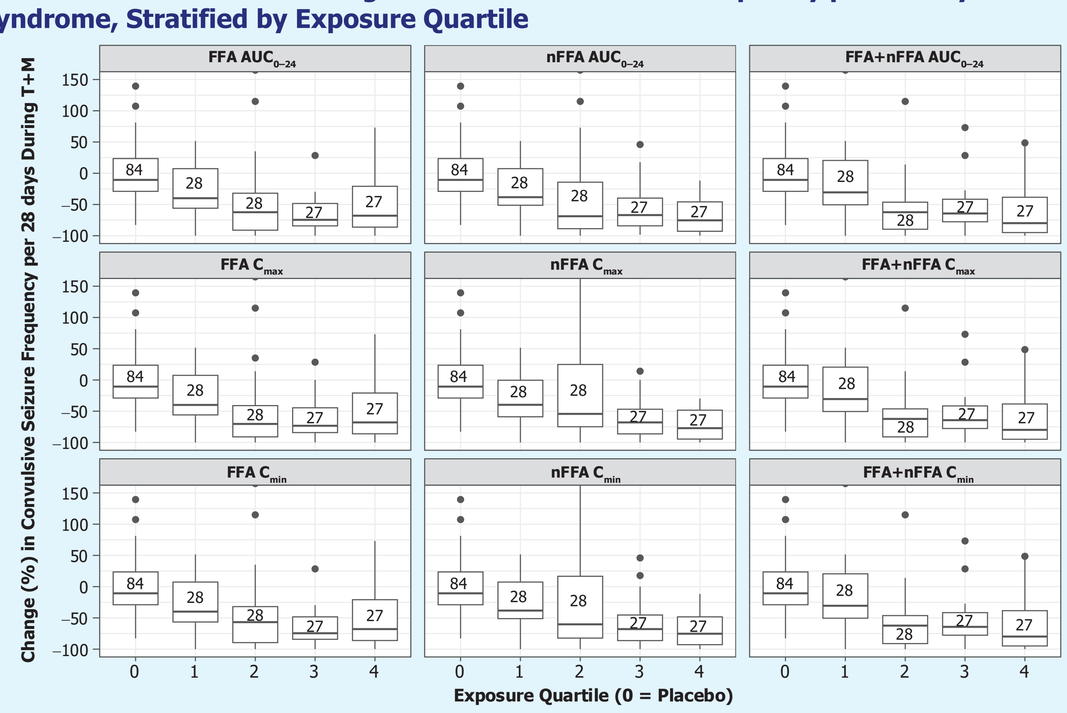
RESULTS

Distributions of Exposure Metrics at Steady State by Fenfluramine Dose for Dravet Syndrome and Lennox-Gastaut Syndrome



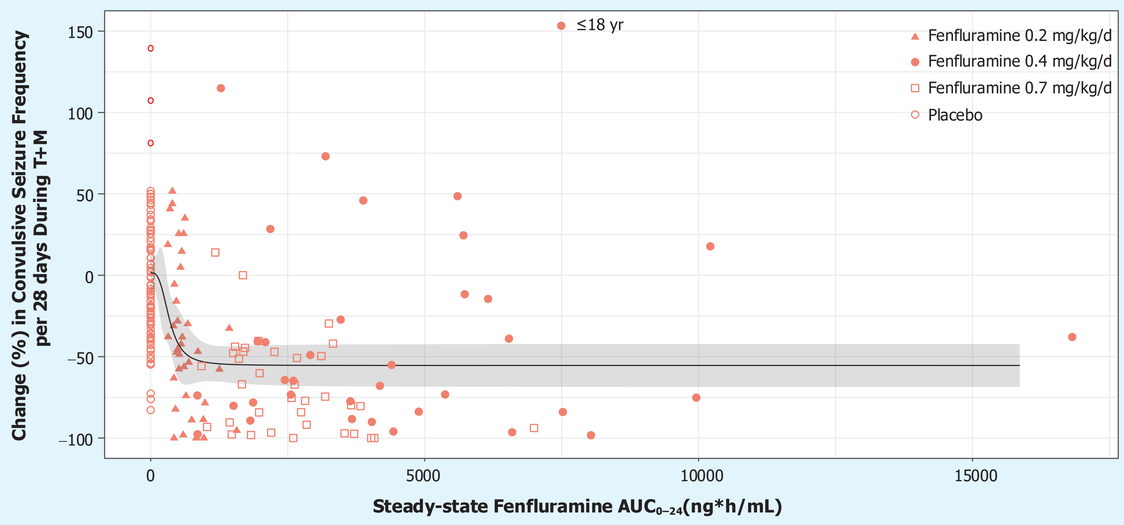
[a]Patients who received 0.2 or 0.7 mg/kg/d came from Study 1 and did not receive concomitant STP; the subjects who received 0.4 mg/kg/d came from Study 2 and received concomitant STP.
Numbers in each box show the count of patients in the respective group.
Fenfluramine dose has been adjusted to show the free base dosage.

Distributions of Percent Change in Convulsive Seizure Frequency per 28 Days in Dravet Syndrome, Stratified by Exposure Quartile



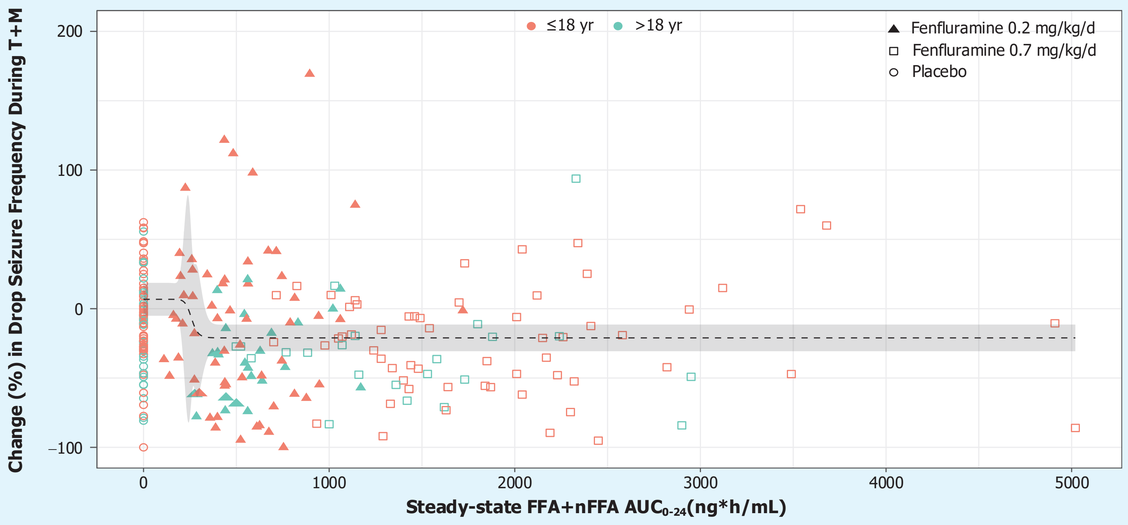
Data for one subject who received placebo and had a percent change of +435% and two subjects receiving 0.2 mg/kg/day who had percent changes of 198% and 165% are excluded from the above plot for visualization purposes. All participants were 2–18 years of age.

Percent Change in Convulsive Seizure Frequency per 28 Days in Dravet Syndrome During T+M Versus Steady-state Fenfluramine AUC_{0-24} With Fit of E_{max} Model Overlaid



Data for one patients who received placebo and had a percent change of +435% and two patients receiving 0.2 mg/kg/day who had percent changes of 198% and 165% are excluded from the above plot for visualization purposes. Points are observations, solid line and shaded region represent the mean (90% confidence interval) predicted values from the E_{max} model. All patients were 2–18 years of age.

Percent Change From Baseline in Drop Seizure Frequency in Lennox-Gastaut Syndrome During T+M Versus Steady-state FFA+nFFA AUC_{0-24} With Fit of E_{max} Model Overlaid



Points are observations, dashed line and shaded region represents the mean (90% CI) predicted values from the E_{max} model. Data for three patients who received placebo (percent changes of +245, +400, and +557%), one patient receiving 0.2 mg/kg/day (+250%), and one patient receiving 0.7 mg/kg/day (+402%) were excluded from the above plot for visualization purposes.

Log-linear Regression Models Relating the Maximum Percentage Change in the Respective Safety Variable to Steady-state $AUC_{0–24}$

	Safety Variable[a]	Steady-state $AUC_{0–24}$, ng·h/mL	Intercept	Coefficient	Adjusted r^2	*P* value	AIC
DS	Platelet count	Fenfluramine	−8.86	−1.31	0.059	<0.001	1662.2
		Norfenfluramine	−8.76	−1.56	0.060	<0.001	1661.9
		FFA+nFFA	−8.80	−1.25	0.059	<0.001	1662.1
	Weight loss	Fenfluramine	−0.57	−0.47	0.170	<0.0001	1045.8
		Norfenfluramine	−0.52	−0.56	0.176	<0.0001	1044.5
		FFA+nFFA	−0.55	−0.45	0.171	<0.0001	1045.6
LGS	Platelet count	Fenfluramine	−2.18	−0.25	−0.001	0.41	2281.1
		Norfenfluramine	−2.13	−0.27	−0.001	0.39	2281.1
		FFA+nFFA	−2.18	−0.23	−0.001	0.42	2281.2
	Weight loss	Fenfluramine	2.46	−0.38	0.100	<0.0001	1561.8
		Norfenfluramine	2.40	−0.38	0.095	<0.0001	1563.2
		FFA+nFFA	2.48	−0.35	0.098	<0.0001	1562.4
	Blood pressure, diastolic	Fenfluramine	1.35	−0.04	−0.004	0.85	2103.8
		Norfenfluramine	1.41	−0.06	−0.004	0.80	2103.8
		FFA+nFFA	1.39	−0.04	−0.004	0.82	2103.8
	Blood pressure, systolic	Fenfluramine	2.04	−0.36	0.004	0.17	2217.5
		Norfenfluramine	1.77	−0.33	0.002	0.23	2217.9
		FFA+nFFA	1.97	−0.32	0.003	0.19	2217.7
	Heart rate	Fenfluramine	0.24	−0.05	−0.004	0.81	2141.7
		Norfenfluramine	0.02	−0.01	−0.004	0.95	2141.7
		FFA+nFFA	0.15	−0.03	−0.004	0.88	2141.7
	Blood glucose	Fenfluramine	3.84	0.34	0.0006	0.29	2301.7
		Norfenfluramine	3.46	0.42	0.0027	0.20	2301.2
		FFA+nFFA	3.65	0.34	0.0013	0.25	2301.5

[a]Reported as maximum change in each safety variable during T+M period.
Exposure values were log-transformed (log-linear regression) for all safety variables except blood pressure.

- Baseline demographics and patient characteristics for DS and LGS populations are available in **supplementary data via QR code**
- Efficacy was associated with steady-state $AUC_{0–24}$ fenfluramine exposure (maximum effect [E_{max}]=−57.0%; half maximal effective concentration [EC_{50}]=342 ng·h/mL) in DS and fenfluramine+norfenfluramine exposure (E_{max}=−27.8%; EC_{50}=259 ng·h/mL) in LGS (**supplementary data available via QR code**)
  - Other exposure metrics including C_{max} and C_{min} were also related to efficacy (**supplementary data available via QR code**)
- Maximum change in body weight during the T+M period was statistically significantly related to steady-state exposures; however, the effect was small, unrelated to duration of fenfluramine treatment, and not different in the DS and LGS populations
- In DS and LGS, no relationship between any PK exposure variable and change in blood glucose concentration was observed during the T+M phase of the studies (**supplementary data available via QR code**)
- None of the covariates that were explored (such as drop seizure frequency at baseline, age, race, sex, concomitant medications, body weight below or above 37.5 kg, and various other measures of body size) showed visual relationships with the residuals from the models for efficacy and safety outcomes

Abbreviations: AIC, Akaike's Information Criterion; $AUC_{0–24}$, area under the plasma concentration-time curve from time zero to 24 hours; C_{max}, maximum plasma concentration; C_{min}, minimum plasma concentration; DS, Dravet syndrome; E_0, response at an exposure of zero; EC_{50}, exposure at which drug effect is half-maximal; E_{max}, maximal drug effect; FFA, fenfluramine; LGS, Lennox-Gastaut syndrome; nFFA, norfenfluramine; PK, pharmacokinetic; r^2, coefficient of determination; T+M, titration+maintenance; yr, years.

METHODS

- Population PK models were used to estimate fenfluramine and norfenfluramine exposure in DS phase 3 Study 1 and Study 2 (N=194) and LGS phase 3 Study 3 (N=251)
- Fenfluramine dose groups during the phase 3 studies were 0.2 or 0.7 mg/kg/day without concomitant stiripentol (Study 1 and Study 3) and 0.4 mg/kg/day with concomitant stiripentol (Study 2)
- The primary PK exposure metrics for the exposure-response analysis were fenfluramine, norfenfluramine, and fenfluramine+norfenfluramine plasma concentrations (C_{max}, C_{min}), and daily area under the concentration-time curve ($AUC_{0–24}$), which served as independent variables
- Efficacy and safety data collected during the titration and maintenance (T+M) periods for each study were used
- Primary efficacy endpoints were percentage change from baseline in monthly convulsive seizure frequency in DS and monthly frequency of seizures associated with a fall in LGS
- Safety endpoints included blood glucose concentration, platelet count, and weight loss (in DS and LGS), and blood pressure and heart rate (in LGS only)
  - Safety variables were based on available data from the T+M period of the phase 3 studies, the understanding of potential pharmacological effects at the time of the analysis, and if there were adequate data to perform the exposure-response analysis
- All data preparation, presentation, and statistical exposure-response analyses were performed using either SAS version 9.4 or later or R statistical software Version 2.15.1 or later
- Linear, log-linear, and non-linear regression models were utilized for continuous variables; ANOVA models were applied for categorical variables

CONCLUSIONS

- In patients with DS and LGS, a significant relationship between fenfluramine and norfenfluramine exposure and reductions in seizure frequency was observed
- Although seizure reductions were observed at relatively low exposures, corresponding to 0.2 mg/kg/day fenfluramine, reductions in seizure frequency were numerically greater at higher exposures
  - This supports titration to a maintenance dose based on individual efficacy, tolerability, and safety[1]
- In DS and LGS, fenfluramine, norfenfluramine and the sum of fenfluramine and norfenfluramine exposures had a weak relationship with maximum decrease in body weight
- In DS but not LGS, a weak relationship was observed between fenfluramine, norfenfluramine, and the sum of fenfluramine and norfenfluramine exposures and maximum decrease in platelet count
  - However further analysis doesn't suggest a clinically meaningful decrease in platelet count
- In DS and LGS, no relationships were evident between exposure and change in blood glucose concentration
  - In LGS, no relationships between exposure and change in blood pressure or heart rate were evident

References

1. UCB, Inc. FINTEPLA® (fenfluramine) oral solution [prescribing information]. Smyrna, GA April 2025.

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Disclosures

AM, BB: Employee and stock ownership, UCB.
CR: No disclosures.

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