Fenfluramine in CDKL5 Deficiency Disorder: Primary Efficacy and Safety Results From a Phase 3, Randomized, Double-Blind, Placebo-Controlled Study

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Background

- Cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder (CDD) is an ultra-rare, drug-resistant, X-linked developmental and epileptic encephalopathy caused by *CDKL5* gene mutations[1,2]
- CDD is associated with infantile-onset epilepsy and global developmental delay[2,3]
- While the goal of antiseizure medication (ASM) treatment is to control seizures, seizure freedom is rare;[4] effective and well-tolerated ASM options are limited[5]
- Fenfluramine, a multimodal serotonergic and sigma-1 receptor modulator approved in the US to treat seizures in patients (≥2 years old) with Dravet syndrome (DS) and Lennox-Gastaut syndrome (LGS)[6], was safe and effective in an open-label, investigator-initiated, single-center trial in 6 patients with CDD (mean treatment duration of 5.3 months)[7]

Objective

- Here we report the primary results from the randomized placebo-controlled trial (RCT; NCT05064878) portion of an international, multicenter phase 3 study of fenfluramine in patients with CDD

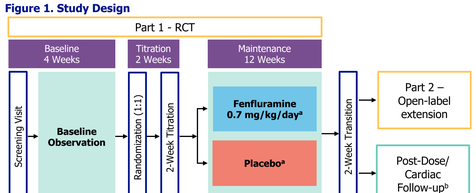
Methods

- Key patient eligibility criteria included: age 1–35 years, confirmed or likely pathogenic *CDKL5* mutation, clinical CDD diagnosis with epilepsy onset in the first year of life, ≥4 countable motor seizures/week as reported by caregivers, treatment with ≥1 antiseizure treatment and ≤4 concomitant ASMs, not including rescue
- After a 4-week baseline observation period, patients were randomized 1:1 to receive fenfluramine 0.7 mg/kg/d (maximum of 26 mg/d) or placebo over a 2-week titration (T) period, followed by a 12-week maintenance (M) period (**Figure 1**)
- The primary efficacy endpoint was the percentage change from baseline in countable motor seizure frequency (CMSF) over the 14-wk T+M period vs placebo
  - The mITT population comprised all patients who received ≥1 dose of study drug and for whom ≥1 week of post randomization seizure diary data was available
- Key secondary endpoints: achievement of a ≥50% CMSF reduction from baseline during T+M vs placebo; percentage of patients with ratings of clinically meaningful improvement ('much improved' or 'very much improved') on Clinical Global Impression–Improvement (CGI–I) by investigators at the end of T+M; percentage change from baseline in monthly generalized tonic-clonic seizure (GTCS) frequency over T+M vs placebo
- Additional secondary endpoints: achievement of ≥25%, ≥75%, and 100% CMSF reduction from baseline during T+M; percentage of patients with ratings of clinically meaningful improvement on CGI–I by caregivers at end of T+M; percentage change from baseline in monthly frequency of all seizures during T+M; mean change from baseline in monthly frequency of CMS-free days during T+M
- Safety and tolerability were evaluated in the safety population (all randomized patients who received ≥1 dose of study drug)

Results

- A total of 87 patients were randomized and comprised the safety population (fenfluramine, n=42; placebo, n=45); of these, 3 (7.1%) patients in the fenfluramine group discontinued treatment due to adverse events (AEs) and 1 (2.2%) patient in the placebo group discontinued due to an AE before the end of the RCT
  - Overall, 83 patients (38 and 44 in the fenfluramine and placebo groups, respectively) completed this RCT, all of whom intended to go onto Part 2/OLE

Figure 1. Study Design



[a]Added to existing standard of care. [b]Cardiac follow-up visit conducted 6 months after last FFA dose in patients discontinuing the study or not continuing FFA after study completion.

Overview

QUESTION

What is the efficacy and safety from the phase 3 randomized controlled trial to support the use of fenfluramine for the treatment of seizures in patients with CDD?

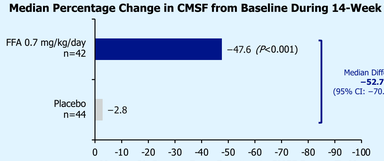
INVESTIGATION

- Eligible patients (1–35 years old) with confirmed/likely pathogenic *CDKL5* mutation, clinical CDD diagnosis, and ≥4 countable motor seizures/week as reported by caregivers were randomized to fenfluramine 0.7 mg/kg/day (max 26 mg/day) or placebo over 14 weeks (2-week T, 12-week M)
- The primary efficacy endpoint was percentage change in CMSF from baseline over T+M vs placebo
- Secondary endpoints included: achievement of ≥25%, ≥50%, ≥75%, and 100% CMSF reduction from baseline during T+M; ratings of clinically meaningful improvement ('much improved' or 'very much improved') on CGI–I by investigators and caregivers at end of T+M; and percentage change from baseline in monthly GTCS frequency over T+M

RESULTS

Efficacy (mITT, n=86)

Median Percentage Change in CMSF from Baseline During 14-Week T+M



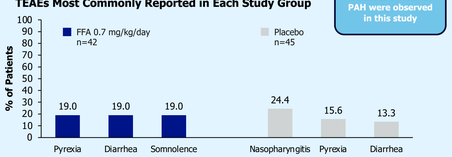
Overview of Secondary Efficacy Endpoint Results

		FFA 0.7 mg/kg/day n=42	Placebo n=44	*P* value
Key Secondary Endpoints	Achievement of ≥50% reduction in CMSF over T+M, n (%)	19 (45.2)	2 (4.5)	<0.001
	CGI–I rating of 'much improved' or 'very much improved' at end of T+M by investigator, n (%)	16 (38.1)	3 (6.8)	<0.001
	Percentage change in GTCS from baseline over T+M, median (n=32)	−61.5 (n=14)	−13.5 (n=18)	0.099[a]
Additional Secondary Endpoints	Achievement of ≥25% reduction in CMSF over T+M, n (%)	31 (73.8)	8 (18.2)	<0.001
	Achievement of ≥75% reduction in CMSF over T+M, n (%)	9 (21.4)	1 (2.3)	0.024
	Achievement of 100% reduction in CMSF over T+M, n (%)	2 (4.8)	0 (0.0)	Non-estimable[b]
	CGI–I rating of 'much improved' or 'very much improved' at end of T+M by caregiver, n (%)	22 (52.4[c])	1 (2.3)	<0.001

[a]The analysis of percentage change from baseline in monthly GTCS frequency was conducted in the subset of patients who had GTCS at baseline (n=32 out of 86); therefore, there was reduced statistical power for this analysis. [b]Non-estimable due to placebo group having no patients with 100% reduction in CMSF. [c]One patient had a missing CGI–I rating by caregiver at last visit and thus imputed as a non-responder (demonstrating no improvement); the percent reported in the abstract was 53.7% due to use of n=41 as denominator.

Safety (N=87)

TEAEs Most Commonly Reported in Each Study Group



No cases of VHD or PAH were observed in this study

CONCLUSIONS

- Fenfluramine provided significantly greater reduction in CMSF compared with placebo and was generally well tolerated; no new safety signals were identified
- A significantly greater number of patients demonstrated clinically meaningful improvement in global functioning when treated with fenfluramine vs placebo as rated by investigators and caregivers
- Fenfluramine may be a promising therapy for treating seizures in patients with CDD

For a copy of the poster and an accompanying PLS, scan:

Abbreviations: CDD, Cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder; CGI–I, Clinical Global Impression–Improvement; CI, confidence interval; CMSF, countable motor seizure frequency; FFA, fenfluramine; GTCS, generalized tonic-clonic seizure; mITT, modified intent-to-treat; PLS, plain language summary; PAH, pulmonary arterial hypertension; TEAE, treatment-emergent adverse event; T+M, titration+maintenance; VHD, valvular heart disease.

- One patient had no countable motor seizures during the baseline period and thus, 86 patients made up the mITT population (fenfluramine, n=42; placebo, n=44)
- Most patients enrolled in this study were female and pediatric (**Table 1**)
- Valproate (fenfluramine, 45%; placebo, 47%) and clobazam (fenfluramine, 48%; placebo, 38%) were the most frequently used concomitant ASMs in both study groups
  - One (2%) and 2 (4%) patients randomized to fenfluramine and placebo, respectively, received concomitant ganaxolone
- Statistically significant differences in the primary and 2 key secondary efficacy endpoints were observed with fenfluramine compared with placebo (**Figure 2A**, **Figure 3**, **Figure 4A**); fenfluramine was associated with numerically greater reductions in GTCS compared with placebo (**Figure 2B**)
- The median percentage reduction from baseline in monthly frequency of all seizures during T+M was higher in the fenfluramine group compared with the placebo group: 43.7% vs 4.0%, respectively
- The median change from baseline in monthly frequency of CMS-free days during T+M was 6.4 days in the fenfluramine group compared with 0.1 day in the placebo group

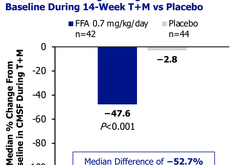
Table 1. Baseline Demographic and Clinical Characteristics (N=87)

	Fenfluramine 0.7 mg/kg/day n=42	Placebo n=45
Median age, years (range)	6.5 (1–29)	7.0 (1–35)
Age group, <18 years, n (%)	37 (88)	40 (89)
Female sex, n (%)	36 (86)	40 (89)
Weight, kg, mean (SD)	23.7 (12.9)	23 (10.2)
Tried ASMs, n (%)		
1–2	6 (14)	8 (18)
3–4	21 (50)	16 (36)
5–6	6 (14)	3 (7)
≥7	9 (21)	18 (40)
Concomitant ASMs, n (%)		
≤1	6 (14)	4 (9)
2	9 (21)	13 (29)
3	15 (36)	19 (42)
4	12 (29)	7 (16)
≥5[a]	0 (0)	2 (4)
Prior select surgical procedures, n (%)		
Epilepsy surgery	1 (2)	0 (0)
Corpus callosotomy	1 (2)	3 (7)
Gastrostomy	4 (10)	10 (22)
Vagal nerve stimulator implantation	1 (2)	7 (16)
CMSF per 28 days, median (range)	44 (16–290)	49 (0–1382)

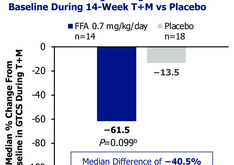
[a]Per protocol, patients could not be on >4 concomitant ASMs; two patients were on concomitant benzodiazepines for other indications.
ASMs, antiseizure medications; CMSF, countable motor seizure frequency; SD, standard deviation.

Figure 2. Median Percentage Change in CMSF and GTCS From Baseline Versus Placebo (mITT Population)[a]

A. Median Percentage Change in CMSF From Baseline During 14-Week T+M vs Placebo

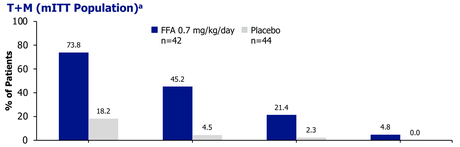


B. Median Percentage Change in GTCS From Baseline During 14-Week T+M vs Placebo



[a]*P* values for the differences in CMSF and GTCS between fenfluramine and placebo were calculated using nonparametric ANCOVA; the magnitude of differences were estimated using Hodges-Lehmann method. [b]Reduced statistical power due to 32 out of overall 86 patients having GTCS at baseline.
CI, confidence interval; CMSF, countable motor seizure frequency; FFA, fenfluramine; GTCS, generalized tonic-clonic seizure; mITT, modified intent-to-treat; T+M, titration and maintenance.

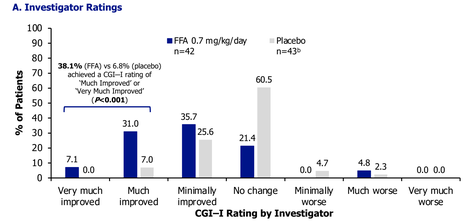
Figure 3. Proportion of Patients Who Achieved Specific Reductions in CMSF Over T+M (mITT Population)[a]



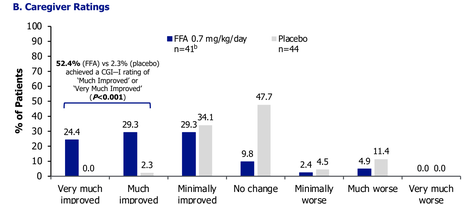
[a]*P* values, odds ratios and confidence intervals for the differences between fenfluramine and placebo were obtained via logistic regression. [b]Non-estimable due to placebo group having no patients with 100% reduction in CMSF.
CI, confidence interval; CMSF, countable motor seizure frequency; FFA, fenfluramine; NE, non-estimable; OR, odds ratio.

Figure 4. CGI–I Ratings at End of T+M (mITT)[a]

A. Investigator Ratings



B. Caregiver Ratings



[a]*P* values for the CGI–I rating comparisons were calculated with Fisher's exact test.
[b]Data missing for one patient.
CGI–I, Clinical Global Impression–Improvement; FFA, fenfluramine; mITT, modified intent-to-treat; T+M, titration+maintenance.

Table 2. Safety Summary (N=87)

	Fenfluramine 0.7 mg/kg/day n=42	Placebo n=45
Patients with any TEAE, n (%)	32 (76.2)	35 (77.8)
Patients with related TEAEs[a], n (%)	17 (40.5)	13 (28.9)
Patients with serious TEAEs[b,c], n (%)	6 (14.3)	3 (6.7)
Patients with related serious TEAEs[a], n (%)	2 (4.8)	0 (0.0)
Patients with TEAEs of special interest[d], n (%)	0 (0.0)	0 (0.0)
Patients with TEAEs with outcome of death, n (%)	0 (0.0)	0 (0.0)
Patients with TEAEs leading to discontinuation of the study[e], n (%)	3 (7.1)	3 (6.7)
TEAEs reported in ≥10% of patients in either treatment group, n (%)		
Pyrexia	8 (19.0)	7 (15.6)
Diarrhea	8 (19.0)	6 (13.3)
Somnolence	8 (19.0)	2 (4.4)
Decreased appetite	7 (16.7)	5 (11.1)
Nasopharyngitis	4 (9.5)	11 (24.4)

[a]Treatment-related is based on the investigator's assessment. [b]Serious TEAEs included urinary tract infection (n=2), metapneumovirus infection (n=1), RSV pneumonia (n=1), decreased appetite (n=1), and dyskinesia (n=1) in patients on fenfluramine, and gastroenteritis, pneumoperitoneum, and hypoxia in the 3 patients on placebo. [c]After re-analysis, one additional patient in the placebo group was found to have a serious TEAE (hypoxia); therefore, this percent differs from the abstract (4.4%). [d]TEAEs of special interest included: suicidal thoughts, ideation, or gestures; valvular heart disease; pulmonary arterial hypertension. [e]Aside from the 4 total patients who discontinued this RCT, another 2 patients had a TEAE with onset during the RCT that led to discontinuation during the open-label extension part (which is ongoing).
RCT, randomized controlled trial; RSV, respiratory syncytial virus; TEAEs, treatment-emergent adverse events.

- Additional TEAEs reported by ≥5% of patients in each group were:
  - Fenfluramine: upper respiratory tract infection (9.5%); seizure, urinary tract infection and insomnia (each reported in 7.1% of patients)
  - Placebo: seizure, insomnia, and irritability (each reported in 8.9% of patients); upper respiratory tract infection, cough, vomiting, conjunctivitis, gastroenteritis, and viral infection (each reported in 6.7% of patients)
- Rates of patients with any TEAEs were similar in both groups (**Table 2**); no new safety signals were identified in patients on fenfluramine
  - No cases of valvular heart disease or pulmonary arterial hypertension were observed
- Overall, gastrointestinal TEAEs were reported in 12 (28.6%) patients in the fenfluramine group and 12 (26.7%) patients in the placebo group
- At last visit, weight loss of ≥7% was reported in 0 and 3 (6.7%) patients in the fenfluramine and placebo groups, respectively; weight loss of ≥10% was reported in no patients receiving fenfluramine and 1 (2.2%) receiving placebo

Conclusions

- In this first RCT evaluating fenfluramine in patients with CDD, fenfluramine provided significantly greater reduction in CMSF compared with placebo
- A significantly higher proportion of patients receiving fenfluramine demonstrated clinically meaningful improvement in global functioning vs placebo
- Fenfluramine was generally well tolerated; no new safety signals were identified in this RCT
- TEAEs were consistent with those reported and known from the DS and LGS clinical trials,[8–13] including no cases of valvular heart disease or pulmonary arterial hypertension
- The results of this study suggest that fenfluramine may be a promising therapy for treating seizures in patients with CDD

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