

Seizure Control With Fenfluramine vs Placebo in Children and Adults With CDKL5 Deficiency Disorder: A Post Hoc Time-To-Event Analysis of Data From a Phase III, Randomised, Placebo-Controlled Trial

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QUESTION

Did fenfluramine prolong the time to return to baseline seizure count vs placebo in patients with CDKL5 deficiency disorder (CDD)?

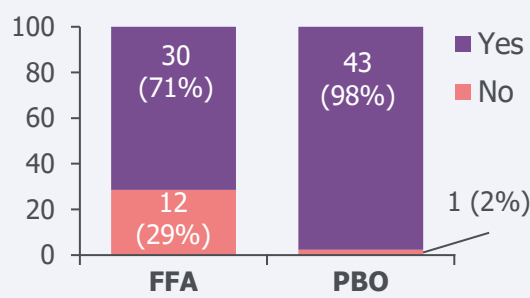
INVESTIGATION

Post hoc analysis of a Phase III trial (randomised, placebo-controlled portion of EP0216/NCT05064878) in patients (1-35 years of age) with CDD. Patients received fenfluramine 0.7 mg/kg/day or placebo for 14 weeks. Time to return to baseline seizure count (time to nth seizure) was evaluated for countable motor seizures (CMS) and across all seizure types.

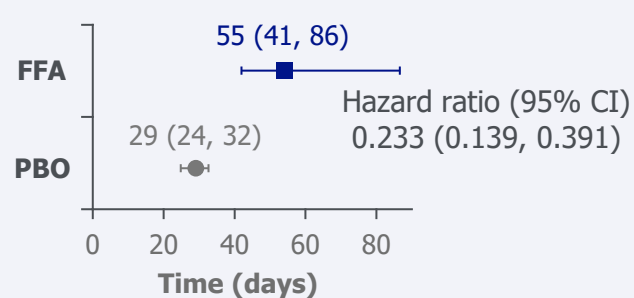
RESULTS

Countable motor seizures

Patients reaching baseline CMS count during 14-week T+M

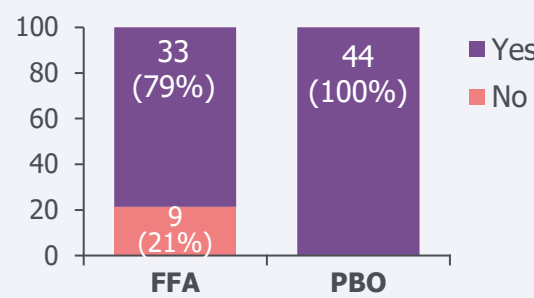


Kaplan-Meier estimated median time to nth CMS

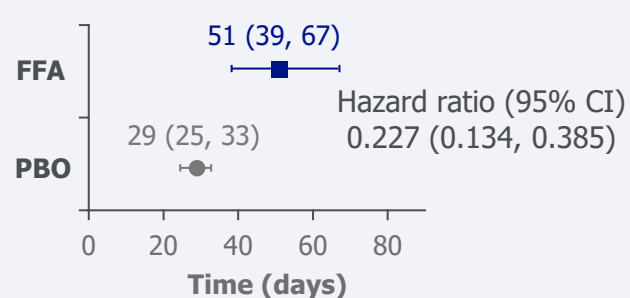


All seizures

Patients reaching baseline all-seizure count during 14-week T+M



Kaplan-Meier estimated median time to nth seizure



CI, confidence interval; CMS, countable motor seizure; FFA, fenfluramine; PBO, placebo; T+M, titration and maintenance.

CONCLUSIONS

- In this post hoc analysis, patients with CDD receiving fenfluramine took longer to return to their baseline CMS and all-seizure counts than those receiving placebo; 12 (29%) patients taking fenfluramine vs 1 (2%) taking placebo did not return to their baseline CMS count.
- These data suggest fenfluramine may provide longer windows of seizure reduction vs placebo, supporting this as a promising therapy for alleviating seizures in patients with CDD.

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Background

- Cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder (CDD) is a rare, X-linked developmental and epileptic encephalopathy caused by pathogenic *CDKL5* variants.¹⁻³
- CDD is associated with early infantile-onset epilepsy, severe developmental impairment, and multiple types of drug-resistant seizures.^{2,3}
- Seizure freedom is rare, with most patients experiencing daily seizures, with substantial impact on quality of life and caregiver burden.^{2,4}
 - Effective and well-tolerated treatment options are limited.⁵
 - Time-to-event analyses may complement efficacy results for healthcare professionals and families in a way that is meaningful for them.
- Fenfluramine, a multimodal serotonergic and sigma-1 receptor modulator, is approved for the treatment of seizures in patients (≥2 years of age) with Dravet syndrome (DS) and Lennox-Gastaut syndrome (LGS) in the European Union, United States, and many other countries worldwide.^{6,7}
- In a Phase III randomised controlled trial (RCT) in patients with CDD, fenfluramine provided significantly greater reduction of countable motor seizure (CMS) count compared with placebo; 7% of patients in the fenfluramine group and 2% of patients in the placebo group discontinued treatment due to adverse events.⁸

Objective

- This post hoc time-to-event analysis quantified time to return to baseline seizure count with fenfluramine vs placebo in patients with CDD in a Phase III trial.

Methods

TRIAL DESIGN

- EP0216 (ClinicalTrials.gov: NCT05064878) Part 1 was a Phase III RCT in children and adults (1-35 years of age) with confirmed pathogenic or likely pathogenic *CDKL5* variants, clinical CDD diagnoses with epilepsy onset in the first year of life, ≥4 countable motor seizures per week as reported by caregivers, treatment with ≥1 antiseizure medication (ASM), and ≤4 concomitant ASMs (not including rescue medications).
- After a 4-week baseline observation period, patients were randomised 1:1 to receive fenfluramine 0.7 mg/kg/day (maximum 26 mg/day) or placebo over a 2-week titration (T) period, followed by a 12-week maintenance (M) period.

ANALYSIS

- In this post hoc analysis, time to nth seizure was defined as the time required during the 14-week T+M period for each patient to reach a seizure count equivalent to that observed during the 4-week baseline.
- CMS (seizures with clear observable motor activity) and all seizures were assessed using the Kaplan-Meier method.
- The safety population comprised all randomised patients who received ≥1 dose of study drug.
- The modified intent-to-treat (mITT) population comprised all patients who received ≥1 dose of the study drug and had ≥1 week of post-randomisation seizure diary data available.
- Outcomes were time to nth seizure for CMS and all seizures over the T+M period.

CMS comprised distinct seizures of generalised tonic-clonic, bilateral clonic, bilateral tonic, atonic (drop), bilateral tonic/atonic (drop), and focal to bilateral tonic-clonic type (lasting approximately ≥3 seconds). CMS, countable motor seizures.

Results

DISPOSITION AND DEMOGRAPHICS

- The safety population included 87 patients (fenfluramine n=42; placebo n=45); of these, 3 (7%) patients receiving fenfluramine and 1 (2%) patient receiving placebo discontinued due to adverse events.
- One patient (placebo group) had no CMS during baseline and was excluded from the mITT population.
- Overall, 83 patients (fenfluramine n=39; placebo n=44) completed this RCT; all intended to continue to the open-label extension.

Baseline characteristics (safety population)

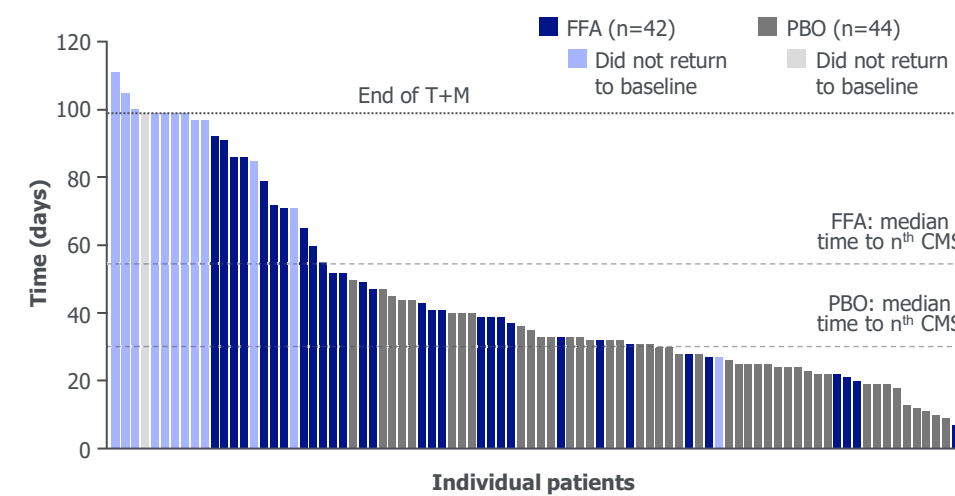
	FFA (n=42)	PBO (n=45)
Age, median (range), years	6.5 (1-29)	7.0 (1-35)
Age group, <18 years, n (%)	37 (88)	40 (89)
Female, n (%)	36 (86)	40 (89)
Weight, mean (SD), kg	23.7 (12.9)	23.0 (10.2)
Baseline CMS count, median	44.0 (16, 290)	51.5 (17, 1382)
Baseline all-seizure count, median	57.5 (16, 368)	82.5 (17, 2171)
Prior ASMs, n (%)		
0-3	33 (79)	24 (53)
4-6	6 (14)	12 (27)
≥7	3 (7)	9 (20)
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	2 (4)

^aPer protocol, patients could not be on >4 concomitant ASMs; 2 patients were on concomitant benzodiazepines for other indications. ASM, antiseizure medication; CMS, countable motor seizure; FFA, fenfluramine; PBO, placebo.

- The most frequently used concomitant ASMs in both study groups were valproate (fenfluramine 45%; placebo 47%) and clobazam (fenfluramine 48%; placebo 38%).

EFFICACY: CMS (mITT)

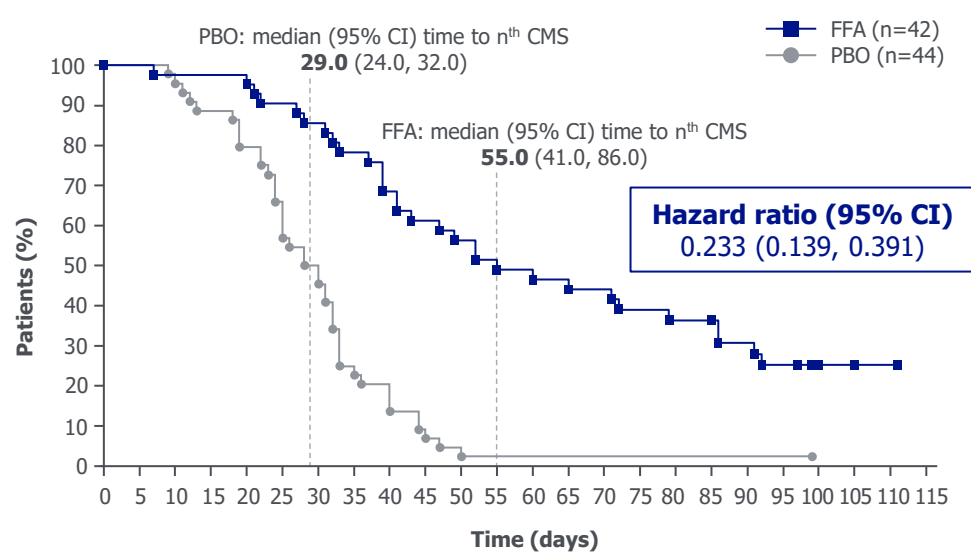
Time to nth CMS



CMS, countable motor seizure; FFA, fenfluramine; mITT, modified intent-to-treat; PBO, placebo; T+M, titration and maintenance.

- Twelve (29%) patients receiving fenfluramine did not return to their baseline CMS count during T+M, compared with 1 (2%) patient receiving placebo.

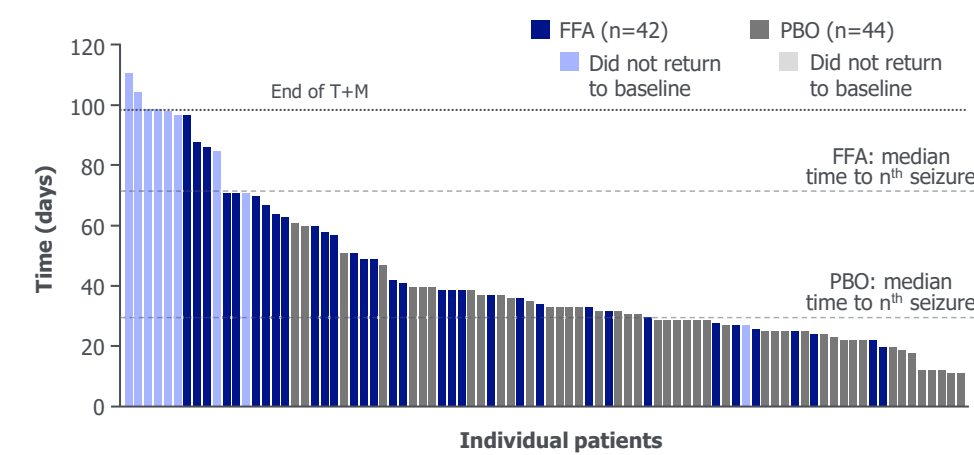
Kaplan-Meier estimated time to nth CMS



Patients who discontinued or completed the T+M period before reaching baseline seizure count were censored. Statistical tests, hazard ratios, and confidence intervals are based on a proportional hazards model with an effect for treatment. CI, confidence interval; CMS, countable motor seizure; FFA, fenfluramine; mITT, modified intent-to-treat; PBO, placebo; T+M, titration and maintenance.

EFFICACY: ALL SEIZURES (mITT)

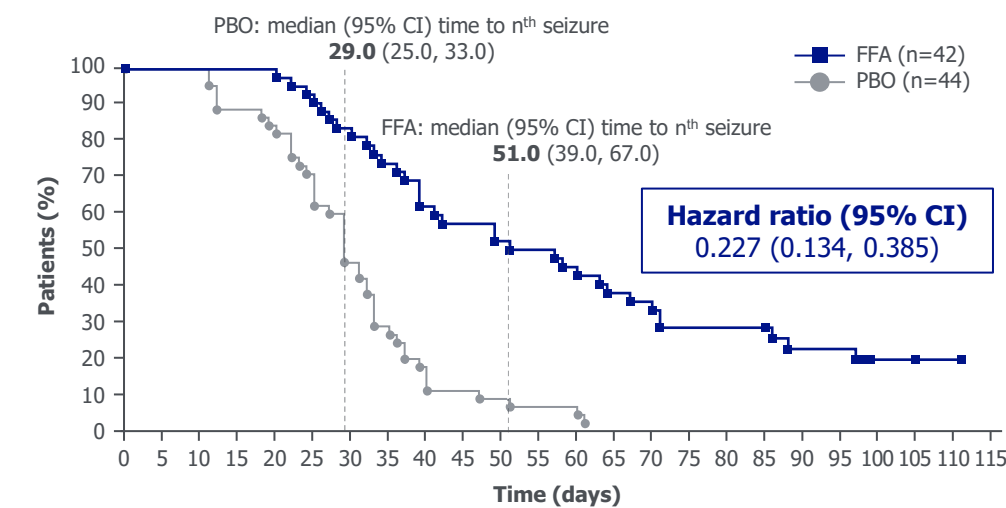
Time to nth seizure of any type



^aAll patients who received placebo returned to their baseline seizure count. FFA, fenfluramine; mITT, modified intent-to-treat; PBO, placebo; T+M, titration and maintenance.

- Nine (21%) patients receiving fenfluramine did not return to their baseline all-seizure count during T+M, compared with no patients receiving placebo.

Kaplan-Meier estimated time to nth seizure of any type



Patients who discontinued or completed the T+M period before reaching baseline seizure count were censored. Statistical tests, hazard ratios, and confidence intervals are based on a proportional hazards model with an effect for treatment. CI, confidence interval; FFA, fenfluramine; mITT, modified intent-to-treat; PBO, placebo; T+M, titration and maintenance.

CONCLUSIONS

- In a Phase III RCT in patients with CDD, fenfluramine reduced CMS count vs placebo and was generally well tolerated.⁷
- In this post hoc analysis, patients with CDD receiving fenfluramine took longer to return to their baseline CMS and all-seizure counts than those receiving placebo; 12 patients taking fenfluramine vs 1 taking placebo did not return to their baseline CMS count.
- These data suggest fenfluramine may provide longer windows of seizure reduction vs placebo, supporting this as a promising treatment in patients with CDD.

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