Examining Seizure-Free Days With Fenfluramine in Children and Adults With CDKL5 Deficiency Disorder: A Post Hoc Analysis of a Phase 3, Randomized, Double-Blind, Placebo-Controlled Trial

Melinda Martin[1]; Ángel Aledo-Serrano[2]; Scott Demarest[3]; Heather Olson[4]; Eric Marsh[5,6]; Sam Amin[7]; Nadia Bahi-Buisson[8]; Amanda Jaksha[9]; Patrick Healy[10]; Brian Moseley[10]; Nicola Specchio[11,12]

1. UCB, Smyrna, GA, USA
2. Blua Sanitas Valdebebas University Hospital, Madrid, Spain
3. University of Colorado, Department of Pediatrics and Neurology, Precision Medicine Institute, Children's Hospital Colorado, Aurora, CO, USA
4. Department of Neurology, Boston Children's Hospital, Boston, MA, USA
5. Children's Hospital of Philadelphia, Philadelphia, PA, USA
6. Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA
7. University Hospitals Bristol and Weston, Bristol, UK
8. Hôpital Necker-Enfants Malades, Pediatric Neurology Department, Paris, France
9. Patient caregiver, Denver, CO, USA
10. UCB, Morrisville, NC, USA
11. Bambino Gesù Children's Hospital, IRCCS, Member of European Reference Network (ERN) EpiCARE, Rome, Italy
12. University Hospitals KU, Leuven, Belgium

OVERVIEW

QUESTION

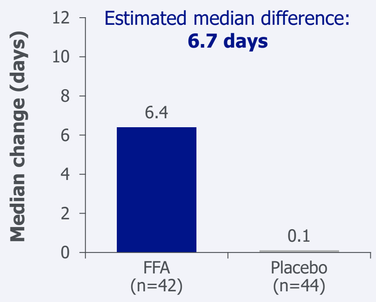
What effect does fenfluramine have on seizure-free days in children and adults with cyclin-dependent kinase-like 5 deficiency disorder (CDD)?

INVESTIGATION

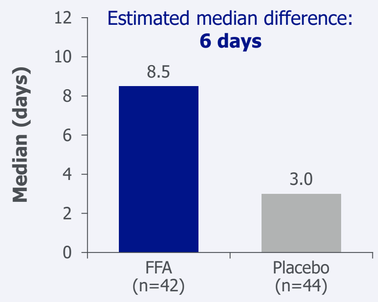
Post hoc analysis of a Phase III, randomized, placebo-controlled trial (EP0216/NCT05064878) in patients (1-35 years of age) with CDD.
Patients received fenfluramine 0.7 mg/kg/day (maximum 26 mg/day) or placebo over 14 weeks (2-week titration and 12-week maintenance).

RESULTS

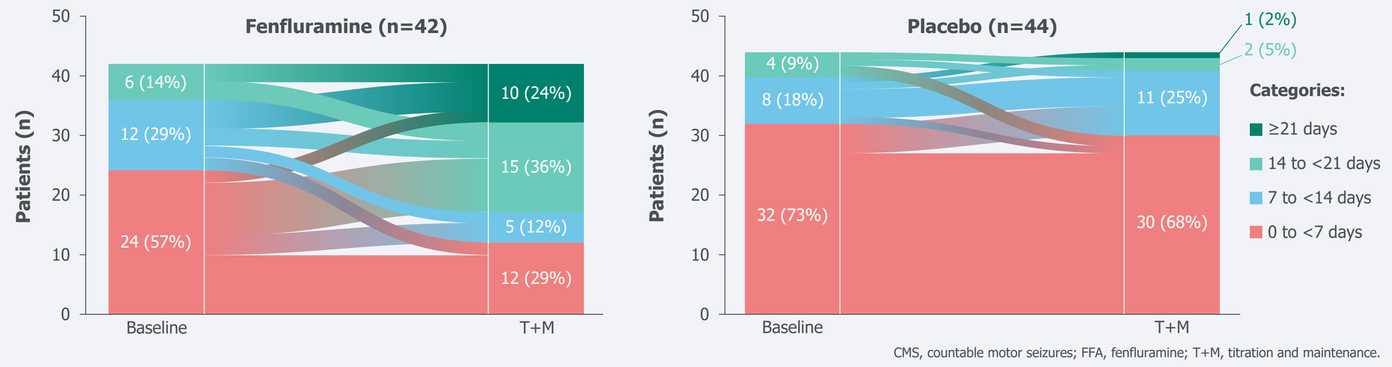
Change in CMS-free days per month from baseline to T+M



Longest interval of CMS-free days during T+M



Change in number of CMS-free days from baseline to T+M



CMS, countable motor seizures; FFA, fenfluramine; T+M, titration and maintenance.

CONCLUSIONS

- In this post hoc analysis, fenfluramine provided marked increases in the number of seizure-free days and the duration of the longest period of consecutive seizure-free days vs placebo in children and adults with CDD.
- The results of this analysis further support fenfluramine 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 *CDKL5* gene mutations.[1-3]
- CDD is associated with early infantile-onset epilepsy, severe developmental impairment, and drug-resistant seizures of multiple types.[2,3]
- Seizure freedom is rare and 80% of patients with CDD have daily seizures.[2]
  - Effective and well-tolerated antiseizure medications (ASMs) are limited.[4]
- 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.[5,6]
- In a randomized, placebo-controlled trial (RCT) in patients with CDD, fenfluramine provided significantly greater reduction in the frequency of countable motor seizures (CMS) compared with placebo and was generally well tolerated; treatment-emergent adverse events were consistent with the known safety profile of fenfluramine in DS and LGS.[7]

Objective

- Here, we assess changes in the number of seizure-free days and the duration of the longest period of consecutive seizure-free days in patients with CDD receiving fenfluramine or placebo.

Methods

TRIAL DESIGN

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

ANALYSIS

- The safety population comprised all randomized patients who received ≥1 dose of study drug.
- The modified intent-to-treat (mITT) population comprised all patients who received ≥1 dose of study drug and for whom ≥1 week of post-randomisation seizure diary data was available.
- Outcomes were change in CMS-free days (pre-specified) and all-seizure-free days (post hoc) from baseline to titration and maintenance (T+M), longest intervals of CMS-free days and all-seizure-free days during T+M (post hoc), number of CMS-free and all-seizure-free days per month during baseline and T+M (post hoc), and investigator-assessed Clinical Global Impression-Improvement (CGI-I) ratings at end of T+M in patients receiving fenfluramine by responder status (post hoc).

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

Results

DEMOGRAPHICS AND DISPOSITION

- The safety population included 87 patients (fenfluramine, n=42; placebo, n=45).
- One patient (placebo group) had no CMS during baseline and was excluded from the mITT population.
- Overall, 83 patients (39 and 44 in the fenfluramine and placebo groups, respectively) completed this RCT, all of whom intended to go onto Part 2 (open-label extension).

Baseline demographics (safety population)

	Fenfluramine (n=42)	Placebo (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)

Additional baseline demographics have been previously presented.[7]

ASMs and clinical characteristics (safety population)

	Fenfluramine (n=42)	Placebo (n=45)
Tried ASMs,[a] 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[b]	0	2 (4)

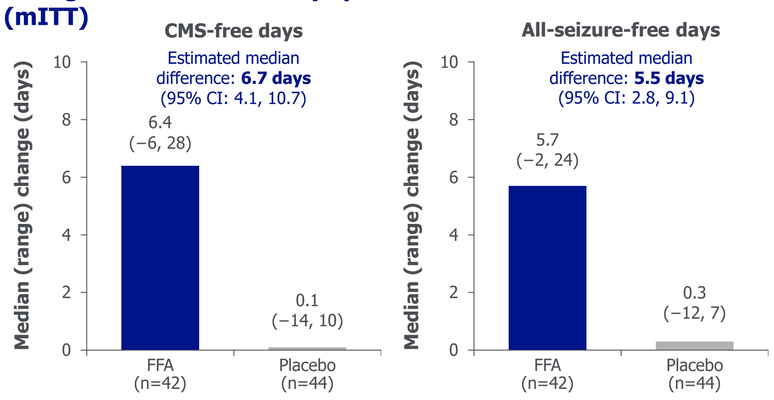
[a]Prior and concomitant ASMs; [b]Per protocol, patients could not be on >4 concomitant ASMs; 2 patients were on concomitant benzodiazepines for other indications. ASM, antiseizure medication.

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

EFFICACY

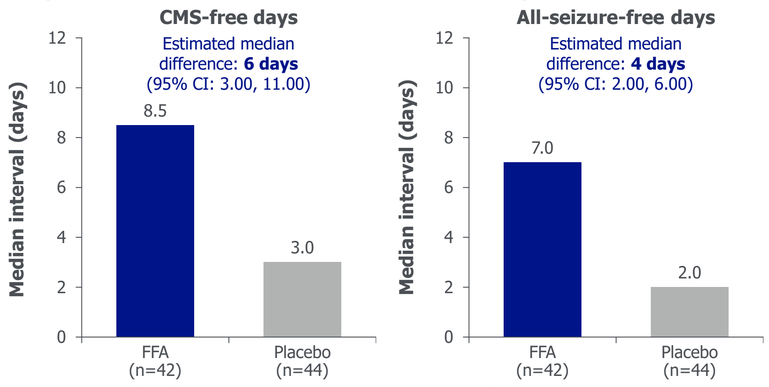
- At baseline, patients receiving fenfluramine (n=42) and placebo (n=44) had a median (range) of 5.4 (0-17) and 3.9 (0-17) CMS-free days/month, and 2.6 (0-17) and 1.0 (0-13) all-seizure-free days/month, respectively.

Change in seizure-free days per month from baseline to T+M (mITT)



Median difference and 95% CI were calculated using the Hodges-Lehmann method. CI, confidence interval; CMS, countable motor seizures; FFA, fenfluramine; mITT, modified intent-to-treat; T+M, titration and maintenance.

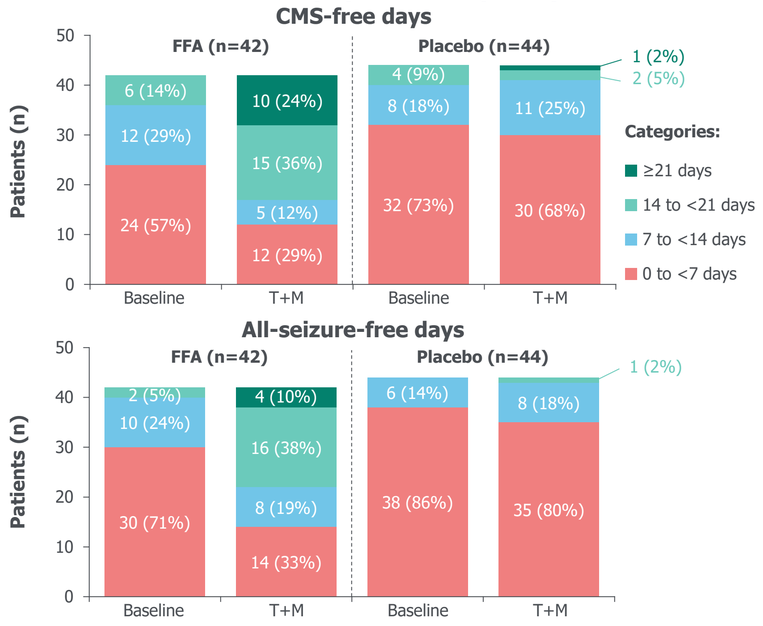
Longest intervals of seizure-free days during T+M (mITT)



Median difference and 95% CI were calculated using the Hodges-Lehmann method. CI, confidence interval; CMS, countable motor seizures; FFA, fenfluramine; mITT, modified intent-to-treat; T+M, titration and maintenance.

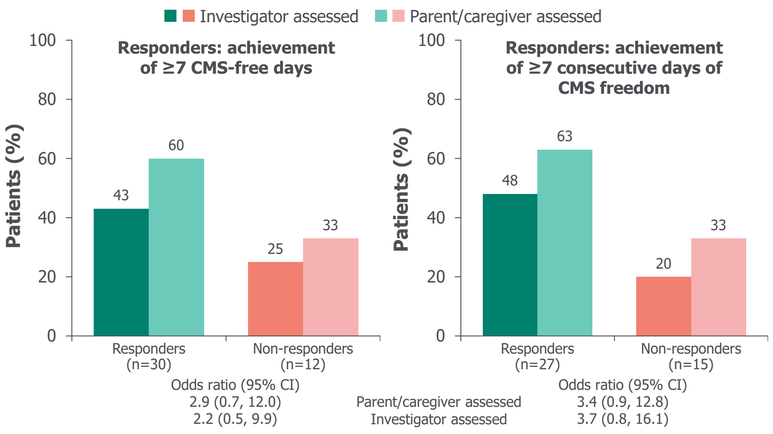
UCB-sponsored. UCB was involved in the design of the analysis, the collection, analysis, and interpretation of data, and review of the poster. The authors thank the patients and their caregivers in addition to the investigators and their teams who contributed to this trial. The authors acknowledge Katerina Kumpan, PhD, CMPP (UCB, Slough, UK) for managing the development of the poster, and Michaela Fuchs, PhD, CMPP (Envision Medical Communications, Horsham, UK) for writing assistance, which was funded by UB. Author contributions: M Martin, S Demarest, H Olson, N Bahi-Buisson, B Moseley, and N Specchio designed the study. P Healy analyzed the data. M Martin, Á Aledo-Serrano, S Demarest, H Olson, E Marsh, S Amin, A Jaksha, B Moseley, and N Specchio interpreted the data. All authors critically reviewed the poster and approved the final version for presentation. Author disclosures: M Martin, P Healy, and B Moseley are employees of UCB. Á Aledo-Serrano received funding for research and educational activities from Arvelle, Bial, Eisai, GW Pharmaceuticals (now Jazz Pharmaceuticals), Neuraxpharm, Sanofi, UCB, and Zogenix (now part of UCB). S Demarest has consulted for BioMarin, Capsida, Encoded, Longboard, Mahzi, Marinus, Neurogene, Ovid, Tysha, UCB, and Ultragenyx; received funding from Mila's Miracle Foundation, the National Institutes of Health, and Project 8P; and is an advisory board member for non-profit foundations FamilieSCN2A, N of 1 Collaborative, Project 8P, Rare X, Ring14 USA, and SLC6A1 Connect. H Olson has consulted for Marinus and served on an advisory board for UCB. E Marsh received research funding from Zogenix (now part of UCB). S Amin received funding from BioMarin, Boston Scientific, CDKL5 UK, Desitin, Ipsen, Jazz Pharmaceuticals, LivaNova, Medtronic, National Institute for Health Research, Novartis, Nutricia, PTC Therapeutics, TSA, and UCB. N Bahi-Buisson has served on an advisory board for Acadia and has been a scientific advisor for Jazz Pharmaceuticals and LivaNova. A Jaksha reports no conflicts of interest. N Specchio has served on scientific advisory boards for Arvelle, BioMarin, GW Pharmaceuticals (now Jazz Pharmaceuticals), Marinus, and Takeda; has received speaker honoraria from BioMarin, Eisai, LivaNova, and Sanofi; and has served as an investigator for BioMarin, Marinus, Roche, and UCB.

Number of seizure-free days per month (mITT)



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

CGI-I ratings of "much/very much improved" at end of T+M in patients receiving fenfluramine (mITT)



Odds ratio (95% CI) comparing responders vs non-responders are based on logistic regression controlling for age group.
CI, confidence interval; CGI-I, Clinical Global Impression-Improvement; CMS, countable motor seizures; mITT, modified intent-to-treat; T+M, titration and maintenance.

- Among fenfluramine-treated patients, responders achieved CGI-I ratings of "much/very much improved" at a greater rate relative to non-responders.

LIMITATIONS

- Formal comparisons of the longest intervals of seizure-free days during T+M with baseline were not possible because baseline data were unavailable (the screening period lasted 4 weeks).

CONCLUSIONS

- In this post hoc analysis, fenfluramine provided marked increases in the number of seizure-free days and the duration of the longest period of consecutive seizure-free days vs placebo in children and adults with CDD.
- The results of this analysis further support fenfluramine as a promising treatment in patients with CDD.

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