INTRODUCTION

CDKL5 deficiency disorder (CDD) is an X-linked disorder resulting from mutations in the CDKL5 gene, which encodes a kinase involved in synaptic plasticity, glutaminergic signaling, and dendrite formation. Girls are ~4-fold more often affected, but boys are more severely affected. The incidence is ~1 per 50,000 births. CDD typically presents in the first 3 months of life with treatment-resistant epilepsy (TRE) and hypotonia followed by global developmental delays and cortical visual impairment. Infantile spasms and other generalized or mixed generalized/focal epilepsies may be the initial seizure type, with evolution to multiple seizure types that often straddle or fail to conform to standard classifications. Seizures often respond initially but recur, and most children have daily seizures despite multiple antiseizure medication (ASM) regimens.

Fenfluramine (FFA) enhances serotonin release, positively modulates sigma-1 receptors, and has potent, durable efficacy in treating convulsive seizures in Dravet syndrome and other epilepsies. Our preliminary results suggest that FFA may be a promising ASM for CDD. Randomized clinical trials are warranted.
drop seizures in Lennox-Gastaut syndrome,\textsuperscript{4,5} with approval for Dravet syndrome by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA). Long-term open-label extension studies and the Belgium experience demonstrated durable reduction in convulsive seizure frequency for up to 30 years in patients with Dravet syndrome, with no observations of pulmonary arterial hypertension or valvular heart disease in any patient at any time.\textsuperscript{6,7}

We studied FFA in patients with CDD and treatment-resistant epilepsy.

2 | MATERIALS AND METHODS

This open-label, investigator-initiated trial was performed at the NYU Epilepsy Center and was designed to enroll up to 10 patients (NCT03861871). Inclusion criteria included confirmed pathogenic CDKL5 mutation and clinical diagnosis of CDD, ages 2–35 years inclusive, ≥4 convulsive seizures lasting ≥3 s (tonic-clonic, tonic, atonic, clonic, focal motor) during the 4-week baseline period, and therapy with ≥1 ASM with stable doses of ASMs, dietary therapies, or vagus nerve stimulation settings for ≥4 weeks before screening and expected stability throughout the study.

Patients were titrated to effect and were treated with FFA for ≥14 weeks, followed by a long-term follow-up phase. FFA was administered twice daily as an oral solution of FFA hydrochloride containing 2.2 mg/mL FFA. The primary outcome was median monthly convulsive seizure frequency on seizure diary. Secondary outcomes included caregiver ratings on the Clinical Global Impression of Improvement (CGI-I) scale, a 7-point Likert scale; Quality of Life in Childhood Epilepsy (QOLCE), a 91-item survey assessing five functional domains; and the Pediatric Quality of Life Inventory (PedsQL), a 23-item survey assessing five functional domains in children and adolescents. Echocardiography were performed at baseline before treatment with FFA and then 6 weeks after FFA therapy was initiated. We did not assess fine motor skills, stereotypies, or eye contact.

Descriptive statistics included medians, means, ranges, and standard deviations for continuous variables, and frequencies and percentages for categorical variables. The study was approved by the NYU Langone Medical Center Institutional Review Board.

3 | RESULTS

Patient characteristics are presented in Table 1. Six children with CDD with TRE were enrolled; five were female. Age at enrollment ranged from 2–26 years (median: 6.5 years). Patients had failed 5–12 ASMs. All patients’ epilepsy therapies were stable except for one patient who had valproate added while on FFA treatment for myoclonic seizures. Doses were titrated to effect, and patients were treated for ≥14 weeks (2 months) at the maintenance dose. Mean treatment duration was 5.3 months (range: 2–9 months). The maximum dose of 0.7 mg/kg/day (maximum daily dose: 26 mg/day) was reached in four patients and 0.4 mg/kg/day (maximum and maintenance dose) in two patients.

Among five patients with generalized tonic-clonic seizures (GTCS), there was a median 90% (range: 86%–100%) reduction in GTCS (Figure 1A). Among two patients with tonic seizures, there was a median 55% (range: 50%–60%) reduction in tonic seizures (Figure 1B). The only patient with myoclonic seizures had a 71.4% reduction. One additional patient developed new-onset myoclonic seizures while on FFA, and valproate was added, which resulted in reduced myoclonic seizures.

Treatment-emergent adverse events were reported in two patients. One had decreased appetite and flatus, and the other had lethargy after valproate was added. Decreased appetite resolved after 20 days, flatus resolved after 5 months, and lethargy persisted with valproate. No patient developed signs or symptoms of valvular heart disease or pulmonary arterial hypertension.

Secondary outcomes improved after FFA treatment in most patients. Most caregivers (4/6; 67%) rated patients as having clinically meaningful improvement overall on the CGI-I scale (“Much Improved” or greater). Four patients (67%) showed overall improvement on the QOLCE, and half (3/6; 50%) showed improvement on the PedsQL. Individual patient scores showed consistent improvement, no change, or worsening across all three metrics.

4 | DISCUSSION

FFA was a safe and effective ASM in these six patients with CDD. FFA, with its novel mechanism of action involving both serotonergic and sigma-1 activity,\textsuperscript{3} may be a promising ASM treatment option to achieve durable clinically meaningful seizure frequency reduction in patients with CDD. Our preliminary results suggest that FFA is very effective in controlling GTCS and is effective in controlling tonic seizures in CDD patients. All five patients with GTCS had previously been on 5–12 ASMs, often in three to four medication combinations, without achieving comparable efficacy in seizure control. We only counted seizures with motor activity lasting 3 seconds or longer, and likely included some of the hypermotor–tonic spasm seizures within the tonic group but did not include isolated epileptic spasms. Because myoclonic seizures are brief and difficult to accurately count, we planned not to include these. Although we had planned to recruit 10 subjects, enrollment stalled after six subjects were enrolled, and given the positive data, we decided to halt enrollment, as a randomized, placebo-controlled clinical trial
**TABLE 1**  Patient characteristics

| Patient | Age at diagnosis | CDKL5 pathogenic Variant | Prior ASM$^a$ | ASM at FFA initiation$^b$ | Predominant seizure type, BL (seizure history)$^c$ | CGI | QOLCE | PedsQL |
|---------|-----------------|--------------------------|--------------|--------------------------|-----------------------------------------------|-----|-------|--------|
|         |                 |                          |              |                          |                                               |     |       |        |
| 1       | 2 months        | p.Glu449LeufsX38         | Levetiracetam, oxcarbazepine, pentobarbital, topiramate | Diazepam, valproate | TC (AA, MC) | Much Impr | Fair | Very Good | 200 | 425 |
| 2       | 3 months        | p.Arg550Ter             | Ataluren, cannabidiol, clobazam, levetiracetam, lamotrigine, lorcaserin, valproate | Diazepam, midazolam, perampanel, quetiapine, zonisamide | A (MC, TC) | Slt Worse | Very Good | Fair | 500 | 450 |
| 3       | 6 weeks         | p.Glu416ValfsX2         | Clonazepam, levetiracetam, topiramate | Clonazepam, diazepam, valproate, vigabatrin | TC (A, ES) | Much Impr | Good | Good | 650 | 1100 |
| 4       | 6 weeks         | p.His127Tyr            | Acetazolamide, cannabidiol, ezogabine, felbamate, lorcaserin, lacosamide, phenytoin, prednisone, primidone, rufinamide, topiramate, vigabatrin | Clonazepam, diazepam, midazolam, valproate | T (A, MC, TC, TA) | Much Impr | Fair | Very Good | 450 | 800 |
| 5       | 5 weeks         | p.Arg558ThrfsTer9      | Clonazepam, lacosamide, levetiracetam, lorzepam, phenobarbital, phenytoin, vigabatrin | Cannabidiol, clobazam, midazolam, perampanel, valproate | T (A, AA, TA, FWMC, MC, TC) | Slt Impr | Poor | Fair | NC | NC |
| 6       | 7 months        | Xp22.2p22.13           | Brivaracetam, clobazam, felbamate, lacosamide, levetiracetam, perampanel, prednisone, topiramate, valproate | Lorazepam, cannabidiol, clonazepam, midazolam | TC (AA) | Much Impr | Poor | Fair | NC | NC |

| Median  | (range)        | 6.5 (5-12) | 3.5 (2-5) | 3 (2-7) | — | — | — | — | — | — | — |

Note: Seizure types: A, atonic; AA, atypical absence; ES, epileptic spasm; FWMC, focal impaired with motor components; MC, myoclonic; T, tonic; TA, typical absence; TC, tonic-clonic.

Abbreviations: ASM, antiseizure medication; BL, baseline; CGI, clinical global impression; FFA, fenfluramine; Impr, improved; N/A, not applicable; NC, not calculated (N/A listed too many times); QOLCE, Quality of Life Childhood Epilepsy; Slt, slightly; VNS, vagus nerve stimulation.

$^a$Patient 2 was also on ketogenic diet as a prior ASM.

$^b$Patient 1 was also on ketogenic diet at FFA initiation; Patient 4 was also on VNS at FFA initiation.

$^c$Nonseizure symptoms at baseline in ≥2 patients: constipation ($n = 4$), hypotonia ($n = 3$), sleep issues ($n = 3$), tiredness ($n = 3$), unsteadiness ($n = 3$), headaches ($n = 2$), kidney stones ($n = 2$), and scoliosis ($n = 2$).
with FFA was planned and is currently being initiated in this population.

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CONFLICT OF INTEREST
OD: Research funding, Novartis, PTC Therapeutics, Zogenix; Equity interest, Rettco, Pairnomix, Tilray, and Egg Rock Holdings; LK, DP: No disclosures. We confirm that we have read the Journal’s position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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