Safety, Tolerability, Pharmacokinetics, and Efficacy of Fenfluramine in Combination With Cannabidiol: Results From an Exploratory Phase 1 Study

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Introduction

- Dravet syndrome (DS) and Lennox-Gastaut syndrome (LGS) are lifelong developmental and epileptic encephalopathies characterized by treatment-resistant seizures and developmental delay as well as cognitive and behavioral impairments[1-5]
- Fenfluramine (FFA) is currently approved for the management of seizures associated with DS and LGS in patients ≥2 years old in the US,[6] and as add-on treatment for patients ≥2 years old with seizures associated with DS and LGS in the EU, UK, and Japan,[7-9] among other countries[10,11]
- Multiple antiseizure medications (ASMs) are typically needed to manage seizures associated with both DS and LGS
  - FFA and CBD have different mechanisms of action,[6,12] increasing the likelihood that these drugs may be co-prescribed[13,14]
- Both FFA and CBD are metabolized by hepatic cytochrome P450 enzymes (CYP),[5,15,16] suggesting the potential for drug-drug interactions
  - CBD inhibits multiple CYP enzymes in vitro (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP3A4),[12] including CYPs implicated in FFA metabolism (CYP1A2, CYP2B6, and CYP2D6, with possible additional metabolism by CYP2C9, CYP2C19, and CYP3A4/5)[6]; thus, potential pharmacokinetic (PK) effects of these drugs combined should be evaluated
  - Over 75% of FFA is metabolized to a pharmacologically active metabolite, norfenfluramine (norFFA)[6]
- Cannabidiol (CBD, Epidiolex®) was not approved for use at the time this study was initiated, but has since been approved for the treatment of seizures associated with DS and LGS in the US and Europe[15,16]

Objective

- Here we assess the safety, tolerability, PK, and efficacy of FFA co-administered with CBD in patients 2–18 years of age with DS or LGS

Methods

- This phase 1, open-label study (NCT03467113) enrolled patients 2–18 years old, with DS or LGS, and receiving a stable dose of CBD
- At study initiation, pharmaceutical CBD (ie, Epidiolex®) was not yet FDA approved and available in the United States, so access to CBD was not controlled
- Patients had a 4-week baseline phase, ≤4-week titration phase, ≤104-week maintenance phase, and ≤6-month follow-up (**Figure 1**)
- FFA was initiated at 0.2 mg/kg/day and incrementally increased by 0.2 mg/kg/day to a target dose of 0.7 mg/kg/day (maximum 26 mg/day)
- Eligibility criteria included: a clinical diagnosis of DS or LGS where seizures were not completely controlled by current ASM regimen, patients must be receiving a stable dose of CBD for ≥4 weeks prior to first FFA dose, and the source of CBD was expected to remain consistent for ≥3 months; patients receiving stiripentol concomitantly or in the 28 days prior to screening were excluded
- The primary endpoint was incidence of treatment-emergent adverse events (TEAEs)
- Exploratory endpoints included: plasma concentrations of FFA and norFFA after ≥7 days of FFA treatment at the target dose, change from baseline in monthly convulsive seizure frequency (MCSF) for patients with DS and change from baseline in seizures associated with a fall for patients with LGS, percent of patients rated by investigators as demonstrating improvement on Clinical Global Impression–Improvement (CGI–I) scale at each visit

Figure 1. Study Design

Baseline Phase 4 weeks	Titration Phase ≤4 weeks	Maintenance Phase ≤104 weeks	Follow-up ≤6 months
• Day −28 and −15: baseline seizure frequency, ECHO, and CGI–I • Day −1: initiate 0.2 mg/kg/d FFA	• Day 1 to ≤21: titrate to target dose, 0.7 mg/kg/d FFA • Day ≤28: measure FFA, norFFA, and CBD PK	• Continued administration of FFA and CBD • CGI–I at Months 3, 6, 9, 12, 18, and 24 • Month 24: ECHO	• Physical exam and ECHO

CBD, cannabidiol; CGI–I, Clinical Global Impression–Improvement scale; d, day; ECHO, echocardiogram; FFA, fenfluramine; norFFA, norfenfluramine; PK, pharmacokinetics.

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Overview

QUESTION

- What is the safety profile of fenfluramine (FFA) when co-administered with cannabidiol (CBD)?
- What are the plasma concentrations of FFA and norfenfluramine (norFFA) when co-administered with CBD?

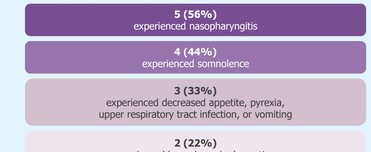
INVESTIGATION

- This phase 1, open-label study (NCT03467113) enrolled patients 2–18 years old with Dravet syndrome (DS) or Lennox-Gastaut syndrome (LGS) who were receiving unregulated products containing CBD (n=1 patient with LGS was receiving Epidiolex®)
- Patients had a 4-week baseline phase, ≤4-week titration phase, ≤104-week maintenance phase, and ≤6-month follow-up
- FFA was initiated at 0.2 mg/kg/day and incrementally increased by 0.2 mg/kg/day to a target dose of 0.7 mg/kg/day (maximum 26 mg/day) to be continued throughout the maintenance phase; patients receiving concomitant stiripentol were excluded

RESULTS

- A total of 9 patients were enrolled (4 DS; 5 LGS) and were included in the safety and PK populations; 8 patients were included in the efficacy population (n=3 DS, mean [SD] duration of FFA 587.3 [95.0] days; n=5 LGS, mean duration of FFA 525.5 [211.3] days)
- At least 1 treatment emergent adverse event (TEAE) was reported for each patient; nasopharyngitis (56%, n=2 DS; n=3 LGS) and somnolence (44%, n=2 DS; n=2 LGS) were most common (see **Figure**)
- No valvular heart disease or pulmonary arterial hypertension were observed during echocardiographic monitoring conducted routinely until 6 months after study drug discontinuation or end of study

Figure. TEAEs Reported in ≥2 Patients in the Overall Safety Population (N=9)



TEAEs, treatment-emergent adverse events.

- In DS, the median change from baseline in convulsive seizure frequency per 28 days was −65.6%
- In LGS, the median change from baseline in seizures associated with a fall per 28 days was −23.2%
- Six of 7 patients (86%) with measurements were rated as "improved" according to Clinical Global Impression–Improvement (CGI–I) scores at their final study visit (**Table**)

Table. CGI–I Ratings for Patients in the Efficacy Population

	Rated as Improved[a]	Rated as No Change[a]
Month 3 (n=8)	7 (88)	1 (13)
Month 6 (n=8)	8 (100)	0
Month 9 (n=7)	6 (88)	1 (14)
Month 12 (n=7)	7 (100)	0
Month 18 (n=5)	4 (80)	1 (20)
Month 24 (n=7)	6 (86)	1 (14)

[a]Percentages used the number of patients who completed CGI–I measurements at each visit as the denominator.
CGI–I, Clinical Global Impression–Improvement; EOS/ET, end of study/early termination.

CONCLUSIONS

- FFA was generally well tolerated at doses of 0.2 to 0.7 mg/kg/day (up to 26 mg/day) when administered with a stable, uncontrolled dose of CBD in children and young adults with DS and LGS
- Seizure reduction and CGI–I scores are within the range of those found in phase 3 trials of the same dose range of fenfluramine in patients with DS and LGS
- Plasma concentrations of FFA and norFFA are within normal ranges observed in phase 3 trials of FFA without concomitant CBD in patients with DS and LGS

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Results

DEMOGRAPHICS AND BASELINE CHARACTERISTICS

- A total of 9 patients (DS, n=4; LGS, n=5) were enrolled and received ≥1 dose of FFA and were included in the safety population
  - All 9 patients had ≥1 FFA plasma concentration measurement and were included in the PK population
  - The efficacy population included 8 patients; 1 patient with DS was excluded for not meeting criteria regarding seizure diary entries
- Seven patients completed the study with satisfactory medication diary entries, with a mean treatment duration of 552 days and mean compliance of 78.6%

Table 1. Patient Characteristics, Demographics, and Concomitant ASMs

Characteristic	Dravet Syndrome n=4	Lennox-Gastaut Syndrome n=5	All N=9
Median age (range), years	7.45 (3.9–17.9)	8.30 (6.2–17.6)	8.30 (3.9–17.9)
Male, n (%)	1 (25)	3 (60)	4 (44)
White, n (%)	4 (100)	5 (100)	9 (100)
Weight, kg, mean ± SD (range)	26.6±12.3 (12.0–41.8)	28.0±9.8 (16.3–41.5)	27.4±10.3 (12.0–41.8)
BMI, mean ± SD (range)	15.8±2.5 (12.9–18.6)	15.6±2.7 (12.6–18.5)	15.7±2.4 (12.6–18.6)
Concomitant ASM use, n (%)[a]	4 (100)	5 (100)	9 (100)
Cannabidiol	4 (100)	5 (100)	9 (100)
Levetiracetam	2 (50)	2 (40)	4 (44)
Rufinamide	0	4 (80)	4 (44)
Clobazam	2 (50)	1 (20)	3 (33)
Valproate[b]	3 (75)	0	3 (33)

[a]Reported in ≥2 patients overall. [b]Including valproate or valproic acid.
ASM, antiseizure medication; BMI, body mass index; DS, Dravet syndrome; LGS, Lennox-Gastaut syndrome; SD, standard deviation.

SAFETY

- At least 1 TEAE was reported for each patient (**Table 2**); of 62 TEAEs reported, nasopharyngitis (56%; n=5) and somnolence (44%; n=4) were most common; no valvular heart disease or pulmonary arterial hypertension were observed during echocardiographic monitoring
- There was 1 serious adverse event (SAE) reported in the study that was not related to study treatment: a patient with DS experienced respiratory distress requiring hospitalization who recovered without dose modifications
- No deaths or discontinuations due to TEAEs were reported

Table 2. Total TEAEs and TEAEs Reported in ≥2 Patients Overall

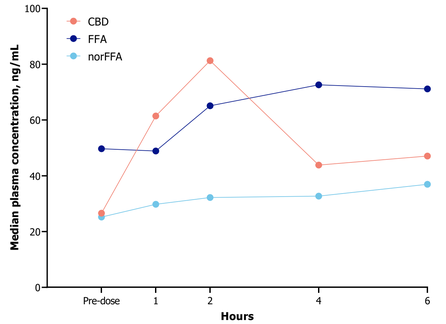
	DS n=4	LGS n=5	All N=9
Total reported TEAEs	34	28	62
Any TEAE, n (%)	4 (100)	5 (100)	9 (100)
Nasopharyngitis	2 (50)	3 (60)	5 (56)
Somnolence	2 (50)	2 (40)	4 (44)
Decreased appetite	2 (50)	1 (20)	3 (33)
Pyrexia	2 (50)	1 (20)	3 (33)
Upper respiratory tract infection	2 (50)	1 (20)	3 (33)
Vomiting	1 (25)	2 (40)	3 (33)
Hypoglycemia	1 (25)	1 (20)	2 (22)
Laceration	1 (25)	1 (20)	2 (22)
Lethargy	1 (25)	1 (20)	2 (22)
Rhinorrhea	2 (50)	0	2 (22)
Urinary tract infection	1 (25)	1 (20)	2 (22)

DS, Dravet syndrome; LGS, Lennox-Gastaut syndrome; TEAE, treatment-emergent adverse event.

PLASMA CONCENTRATIONS

- Median pre-dose plasma concentrations for FFA and CBD were 49.7 and 26.6 ng/mL, respectively, and the highest concentrations were 72.6 (4 hours post dose) and 81.3 ng/mL (2 hours post dose), respectively (**Figure 2**)
  - Median pre-dose norFFA plasma concentration was 25.2 ng/mL and the highest concentration was 37.0 ng/mL at 6 hours post dose

Figure 2. Median Plasma Concentration vs Time Profiles of FFA, norFFA, and CBD at Day 28[a] (PK Population)

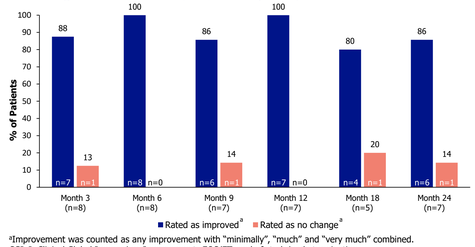


[a]After ≥7 days of treatment with FFA.
CBD, cannabidiol; FFA, fenfluramine; norFFA, norfenfluramine.

EFFICACY

- In the titration and maintenance periods, median change from baseline in convulsive seizure frequency per 28 days was −65.6% in DS (n=3) and median change from baseline in seizures associated with a fall per 28 days was −23.2% in LGS (n=5)
- During the maintenance period, ≥80% of patients with CGI–I measurements were rated as improved at all maintenance visits (**Figure 3**)
- No patients worsened according to investigator-rated CGI–I scores

Figure 3. Patients Rated as "Improved[a]" or "No Change" by Investigator According to CGI–I (Efficacy Population, N=8)



[a]Improvement was counted as any improvement with "minimally", "much" and "very much" combined.
CGI–I, Clinical Global Impression–Improvement; EOS/ET, end of study/early termination.

LIMITATIONS

- Interpretation of these data is limited by the small numbers of patients
- There were significant missing seizure diary and study medication diary data, thus, all efficacy data should be interpreted with caution
- At the time of this study, pharmaceutical CBD (Epidiolex®) was not yet approved, thus patients received unregulated products containing CBD
  - Therefore, patients may not have achieved therapeutic doses of CBD or could have experienced variable CBD doses
- Enrollment in this study was terminated after a Canadian clinical trial examined safety, PK, and efficacy of FFA and CBD using pharmaceutical CBD (Epidiolex®) at controlled therapeutic doses[17]

Conclusions

- FFA was generally well tolerated at doses of 0.2 to 0.7 mg/kg/day (up to 26 mg/day) when administered with a stable dose of CBD in children and young adults with DS and LGS
  - Among the TEAEs observed, most were consistent with the spectrum of central nervous system-related adverse events observed in other studies with FFA
- Efficacy endpoints measured in this study were within the range of those found in phase 3 trials of the same dose range of FFA in patients with DS and LGS
  - However, these results should be interpreted with caution due to the low number of patients in the study, and the extent of missing data for seizure diary entries
- Plasma FFA and norFFA concentrations were within the range of phase 3 DS and LGS trials of the same FFA dose without concomitant CBD or stiripentol
  - There is no need for dose adjustments when FFA is administered with CBD
- Plasma concentrations of CBD in this study were in the range reported in phase 2 and phase 3 trials of Epidiolex (5, 10, 20 mg/kg/d) in DS and LGS[18,19]

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Acknowledgements

UCB-sponsored. The authors acknowledge Glenn Morrison, PhD (UCB), for his contribution to the current work, Katerina Kumpan, PhD (UCB), for managing the development of the poster, and Eric Scocchera, PhD, and Scott Bergfeld, PhD, of PharmaWrite, LLC (Princeton, NJ, USA), for writing assistance, which was funded by UCB.

Disclosures

RZR, AM, BB, ML, SE, DM: Employees and stock ownership: UCB.
SP: No relevant disclosures.

Previously presented at American Academy of Neurology 2025 Annual Meeting
San Diego, CA, USA | 5–9 April 2025
Presented at the 16th European Paediatric Neurology Society Congress
Munich, Germany | 8–12 July 2025