# Safety and Effectiveness of Fenfluramine for the Treatment of Seizures in Lennox-Gastaut Syndrome: Results From the Final Analysis of an Open-Label Extension Study

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## Introduction

- Lennox-Gastaut syndrome (LGS) is a rare developmental and epileptic encephalopathy characterized by various drug-resistant seizure types, abnormal electroencephalogram findings, and cognitive and behavior impairment[1,2]
  - LGS accounts for 1%-10% of childhood epilepsies and has a heterogenous etiology with no biological marker[3,4]
  - Onset typically occurs before the age of 8 years, peaks between 3-5 years old, and persists into adulthood[2]
- Therapeutic strategies for LGS historically have involved valproate as a first line anti-seizure medication (ASM) followed by adjunctive ASMs such as lamotrigine, rufinamide, clobazam, cannabidiol, felbamate, and topiramate[4-6]
- Fenfluramine (FFA), also recommended as a treatment option for management of seizures associated with LGS,[4] was evaluated in a phase 3 randomized controlled trial (RCT; NCT03355209) of patients with LGS (N=263, aged 2-35 years), whereby adjunctive FFA 0.7 mg/kg/day reduced the median frequency of seizures associated with a drop by 26.5% compared to a 7.6% reduction in the placebo group[7]
- FFA exerts its effect through a novel, dual mechanism of action involving increased serotonergic activity and positive modulation at sigma-1 receptors[8] and was approved for the management of seizures associated with LGS in patients ≥2 years old in the United States in March 2022[9]; approval in other countries followed for use as adjunctive treatment in patients ≥2 years old with seizures associated with LGS[10-13]
- Various ASMs are associated with adverse events, drug-drug interactions, and are also associated with decreased efficacy as seen with the honeymoon effect; thus, there is a need for long-term effective and tolerable ASMs[5,14]

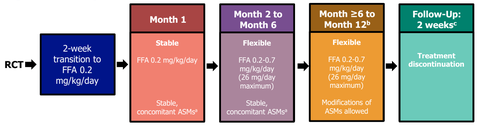
## Objective

- Here we describe the long-term safety and effectiveness of FFA from the final analysis of an open-label extension (OLE) study in children and adults with LGS

## Methods

- Patients (aged 2-35 years) with a confirmed LGS diagnosis who participated in the FFA RCT were eligible to continue in Cohort A of this OLE (study sites in North America, Europe, and Australia)
- At OLE start, patients were transitioned to FFA 0.2 mg/kg/day (**Figure 1**)
- Outcomes of interest:
  - Incidence of treatment-emergent adverse events (TEAEs) occurring in ≥10% of patients in safety population
  - Incidence of valvular heart disease (VHD) and pulmonary arterial hypertension (PAH) in safety population
  - Effectiveness outcomes are reported for the modified intent-to-treat (mITT) population, which includes all the patients who received at least one dose of FFA, had a valid pre-RCT baseline estimated frequency of seizures associated with a drop, and provided at least 30 days of valid seizure data during the OLE
    - Median change from pre-RCT baseline in frequency of Epilepsy Study Consortium (ESC)-confirmed seizures associated with a drop from Month 1 to end of study (EOS) and Month 2 to EOS
      - ESC-confirmed seizures associated with a drop included the following types: generalized tonic-clonic seizures (GTCS), secondary GTC seizures (focal-to-bilateral tonic-clonic), tonic seizures (TS), atonic seizures (AS), and tonic atonic seizures (TA)
      - Month 2 to EOS was analyzed to ensure data from the first month of the OLE, where each patient was kept at the lower dose of FFA 0.2 mg/kg/day, were excluded
    - Ratings of any improvements (minimally, much, or very much improved) and clinically meaningful improvement (much improved or very much improved) on Clinical Global Impression-Improvement (CGI-I) scale by parents/caregivers and investigators at last visit

### Figure 1. Study Design




[a]Patients were required to be on ≥1 concomitant ASM (+/- vagus nerve stimulation and/or ketogenic diet) that must have remained stable for the first 3 months of the study.
[b]Some patients remained in the study longer than 12 months due to COVID-19 related restrictions or limited access to in-clinic visits.
[c]Patients continuing onto another extension study (Study 1900) did not complete this follow-up visit.
ASMs, anti-seizure medications; FFA, fenfluramine; RCT, randomized controlled trial.

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## Overview

### QUESTION

What are the long-term safety and effectiveness data of fenfluramine (FFA) use in children and adults with Lennox-Gastaut syndrome (LGS)?

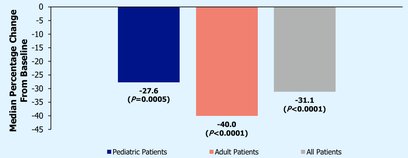
### INVESTIGATION

- Patients with a confirmed LGS diagnosis were continued in an open-label extension (OLE) study if they participated in the randomized controlled trial (RCT)
- Incidence of treatment-emergent adverse events (TEAEs) and median percentage change from baseline in frequency of seizures associated with a drop compared to pre-RCT baseline among pediatric, adult and overall patient populations are reported
- Ratings of patients' improvements by caregivers and investigators from baseline at the last visit on the Clinical Global Impression-Improvement (CGI-I) scale and change from pre-RCT baseline in affective symptoms of parents/caregivers using the Hospital Anxiety and Depression Scale (HADS) were also described

### RESULTS

- 247 patients were continued in this OLE and the overall mean±SD age was 14.3±7.6 years
  - At RCT baseline, 73 patients were adults (18 to 35 years)
- Mean±SD FFA daily dose over the duration of this OLE was 0.4±0.1 mg/kg/day; median treatment duration was 364 days (range, 19-537)
- 158 (64.0%) patients completed this OLE
  - 86 (34.8%) patients discontinued the study due to lack of efficacy (n=57, 23.1%), self-withdrawal (n=15, 6.1%), adverse events (n=13, 5.3%) and death (n=1, 0.4%)
- 83.0% of patients experienced ≥1 TEAE; TEAEs occurring in ≥10% of patients were decreased appetite, fatigue, nasopharyngitis, seizure, and pyrexia
- Key effectiveness results for the mITT population (n=241) are described in the **Figure** and **Table**

**Figure. Median Percentage Change From Baseline in Seizures Associated With a Drop From Month 2 to EOS[a]**




[a]Month 2 to EOS was used to ensure data from the first month of the OLE, where each patient was kept at the lower dose of FFA 0.2 mg/kg/day, were excluded; one patient from mITT (n=241) discontinued the study early and is therefore not included in the Month 2 to EOS assessment.
EOS, end of study; FFA, fenfluramine; OLE; open-label extension.

**Table. CGI-I Ratings of Any Improvement or Clinically Meaningful Improvement ("Much Improved" or "Very Much Improved") by Caregivers and Investigators at Last Visit**

| | Pediatric (2 to <18 yr, n=167) | Adult (18-35 yr, n=70) | All Patients n=237 |
|---|---|---|---|
| **Any improvements on CGI-I, n (%)** | | | |
| Parents/caregivers | 95 (56.9) | 47 (67.1) | 142 (59.9) |
| Investigators | 95 (56.9) | 40 (57.1) | 135 (57.0) |
| **Clinically meaningful improvement on CGI-I, n (%)** | | | |
| Parents/caregivers | 57 (34.1) | 27 (38.6) | 84 (35.4) |
| Investigators | 56 (33.5) | 27 (38.6) | 83 (35.0) |

CGI-I; Clinical Global Impression-Improvement.

- Mean change in HADS assessment scores from baseline to Month 12 for anxiety, depression, and emotional distress were -0.8 (*P*=0.0418), -0.7 (*P*=0.5257), and -1.4 (*P*=0.0986), respectively

### CONCLUSIONS

- These results highlight no new safety signals and a consistent safety profile from previous studies. Effectiveness was observed via sustained reductions in seizures associated with a drop and ratings of patients' improvements on CGI-I by investigators and caregivers. Parents/caregivers also experienced significant improvements in anxiety from baseline to Month 12.

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- Outcomes of interest (continued):
  - A post-hoc analysis was conducted to evaluate median percentage change from baseline in individual seizure types associated with a drop (GTCS, TS, AS, and TA)
  - Change from baseline in anxiety, depression, and emotional distress using the Hospital Anxiety and Depression Scale (HADS)
- Data were presented by pediatric (2 to <18 years) and adult age groups (18-35 years) at RCT baseline where applicable
- Statistical Analyses
  - Wilcoxon signed-rank tests were used to assess the statistical significance in median percentage change from pre-RCT baseline in seizures associated with a drop and seizure subtypes, along with changes in HADS score, where statistical significance was defined a priori as *P*<0.05
  - Descriptive statistics were used for other outcomes
- Additional details on the study methodology have been previously published[15]

## Results

- 247 patients continued in this OLE study; mean±SD age was 14.3±7.6 years
  - At RCT baseline, 174 patients were pediatric and 73 were adults
- Median number of prior ASMs was 7 (range, 1-20)[15] and median number of concomitant ASMs was 3 (range, 1-7)
- Median pre-RCT baseline frequency of seizures associated with a drop per 28 days in the mITT group (n=241) was 75 (range, 4-2943)
- 158/247 (64.0%) completed this OLE
  - 86/247 (34.8%) discontinued the study due to lack of efficacy (n=57, 23.1%), self-withdrawal (n=15, 6.1%), adverse events (n=13, 5.3%) and death (n=1, 0.4%)
- Mean±SD FFA daily dose over the duration of this OLE was 0.4±0.1 mg/kg/day (n=246)

### *Safety*

- 205/247 (83.0%) patients experienced ≥1 TEAE
- TEAEs reported in ≥10% of patients are described in **Table 1**, also described by pediatric and adult age groups
- 41/247 (16.6%) patients experienced ≥1 serious adverse event (SAE)
  - 12/41 (29.3%) patients experienced ≥1 SAE deemed related to FFA, including change in seizure presentations (n=3), status epilepticus (n=2), somnolence (n=2), decreased appetite (n=2), and weight decrease, hypoalbuminemia, and asthenia in one patient each
  - One patient died due to aspiration pneumonia, unrelated to FFA
- No cases of VHD or PAH were observed

**Table 1. Incidence of Treatment-Emergent Adverse Events Reported by ≥10% of Patients Treated With Fenfluramine**

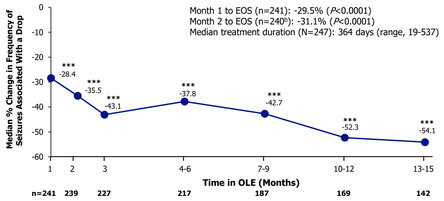
| | Pediatric (2 to <18 yr, n=174) | Adult (18-35 yr, n=73) | All Patients (N=247) |
|---|---|---|---|
| Patients experiencing ≥1 TEAE, n (%) | 140 (80.5) | 65 (89.0) | 205 (83.0) |
| TEAEs reported in ≥10% of patients, n (%) | | | |
| Decreased appetite | 28 (16.1) | 12 (16.4) | 40 (16.2) |
| Fatigue | 23 (13.2) | 10 (13.7) | 33 (13.4) |
| Nasopharyngitis | 23 (13.2) | 8 (11.0) | 31 (12.6) |
| Seizure | 16 (9.2) | 11 (15.1) | 27 (10.9) |
| Pyrexia | 21 (12.1) | 4 (5.5) | 25 (10.1) |

TEAEs, treatment-emergent adverse events.

### *Effectiveness*

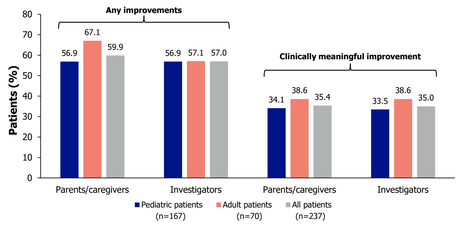
- Median percentage change in frequency of ESC-confirmed seizures associated with a drop from baseline from Month 2 to EOS was -31.1% (*P*<0.0001)
  - -27.6% in pediatric patients (*P*=0.0005) and -40.0% in adult patients (*P*<0.0001)
  - Median percentage change in frequency of ESC-confirmed seizures associated with a drop over the OLE study in patients who remained in the study is presented in **Figure 2**
- Proportion of patients with CGI-I ratings of any improvements and clinically meaningful improvements reported by parents/caregivers and investigators at last visit are described in **Figure 3**, also described by pediatric and adult age groups
- Post-hoc analysis of median percentage change in frequency in the following seizure subtypes over the OLE:
  - GTCS: -48.8% (*P*<0.0001; n=106)
  - TS: -38.9% (*P*<0.0001; n=186)
  - AS: -33.3% (*P*=0.2909; n=89)
  - TA : -32.1% (*P*=0.1029; n=46)
- Mean change in HADS assessment scores from pre-RCT baseline to Month 12 for anxiety, depression, and emotional distress were -0.8, -0.7, and -1.4, respectively (**Figure 4**)

**Figure 2. Percentage Change in Frequency of Seizures Associated With a Drop in Patients Treated With Fenfluramine[a]**



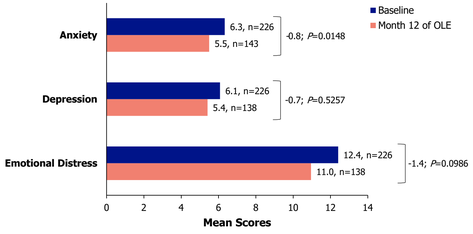

***P<0.0001 by Wilcoxon signed-rank test.
[a]At Months 16-18 (n=10), the median percentage change in seizure frequency was -27.9% (*P*=0.1602).
[b]One patient discontinued the study early and is therefore not included in the Month 2 to EOS assessment.
EOS, end of study; OLE, open-label extension.

**Figure 3. CGI-I Ratings of Any Improvement or Clinically Meaningful Improvement ("Much Improved" or "Very Much Improved") by Caregivers and Investigators at Last Visit**




CGI-I, Clinical Global Impression-Improvement.

**Figure 4. Change From Baseline at Month 12 in HADS Scores[a] in Parents/Caregivers of Patients Treated With Fenfluramine**




[a]HADS is a 14-item self-reported scale that evaluates parent/caregiver anxiety and depression. Higher scores indicate greater severity, and mean scores are classified as normal (0-7), borderline (8-10), or abnormal (11-21). The sum of anxiety and depression scores result in "emotional distress" scores.
HADS, Hospital Anxiety and Depression Scale; OLE, open-label extension.

## Conclusions

- In this final analysis of an FFA OLE in children and adults with LGS, FFA was well tolerated over a median treatment duration of 364 days
  - There were no new safety signals identified
  - No cases of VHD and PAH were observed
- Median percentage change in seizures associated with a drop from Month 1 to EOS was -29.5 (*P*<0.0001; n=241) and -31.1% (*P*<0.0001; n=240) from Month 2 to EOS, demonstrating sustained reduction of frequency of seizures associated with a drop
- On CGI-I, caregivers and investigators both rated >50% of patients as improved while on FFA treatment
- Among the seizure subtypes evaluated, GTCS had the greatest median percentage reduction in frequency
- FFA also provided statistically significant benefits to caregivers in reducing anxiety and demonstrated a numerical benefit in reducing depression and emotional distress

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