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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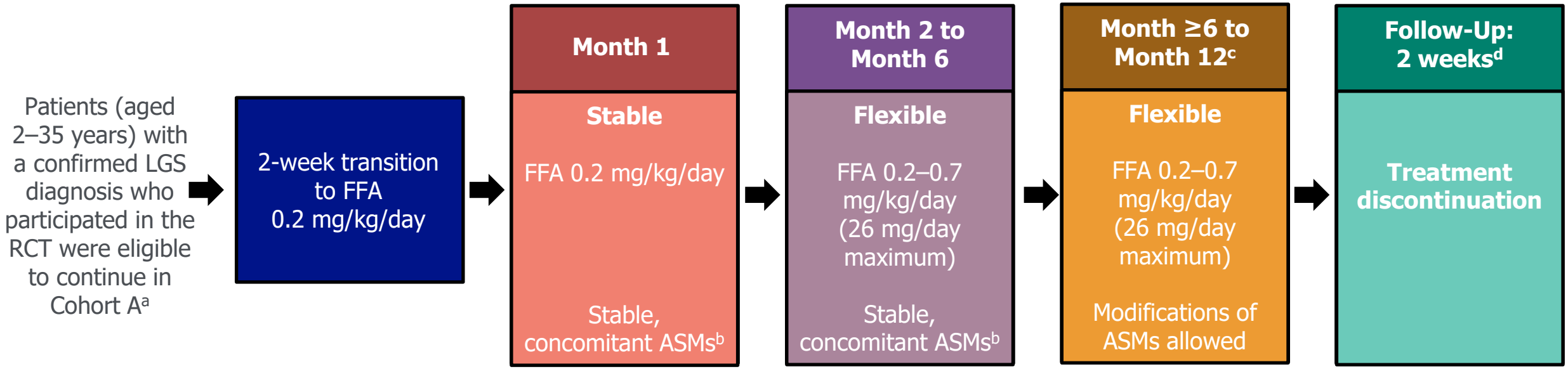
Introduction

- LGS is a rare developmental and epileptic encephalopathy
  - Characterized by various drug-resistant seizure types, abnormal electroencephalogram features, and cognitive and behavior impairments[1,2]
- Fenfluramine (FFA) is a serotonergic agent that also exhibits positive modulation at sigma-1 receptors[3]
- Adjunctive FFA 0.7 mg/kg/day has demonstrated statistically significant improvements in median frequency of seizures associated with a fall versus placebo in patients with LGS[4]
  - Common TEAEs reported: decreased appetite, somnolence, and fatigue; no cases of VHD or PAH were observed[4]
- FFA has been approved as adjunctive treatment for the management of seizures associated with LGS in patients ≥2 years old in the European Union[5] and United Kingdom[6]

Here we describe the long-term safety and effectiveness of FFA from the final analysis of an OLE study in pediatric and adult patients with LGS

1. Cross JH, et al. *Front Neurol.* 2017;8:505. 2. Specchio N, et al. *Epilepsia.* 2022;63(6):1398–442. 3. Martin P, et al. *Int J Mol Sci.* 2021;22(16):8416. 4. Knupp K, et al. *JAMA Neurol.* 2022;79(6):554–64. 5. Fintepla 2.2 mg/mL oral solution [summary of product characteristics]. UCB, Brussels, Belgium; 2024. 6. Fintepla 2.2 mg/ml oral solution [summary of product characteristics]. UCB, Slough, Berkshire, UK; April 2024.
LGS, Lennox-Gastaut syndrome; OLE, open-label extension; PAH, pulmonary arterial hypertension; RCT, randomized controlled trial; TEAEs, treatment-emergent adverse events; VHD, valvular heart disease.

Methods: Study Design and Endpoints



Selected Endpoints:

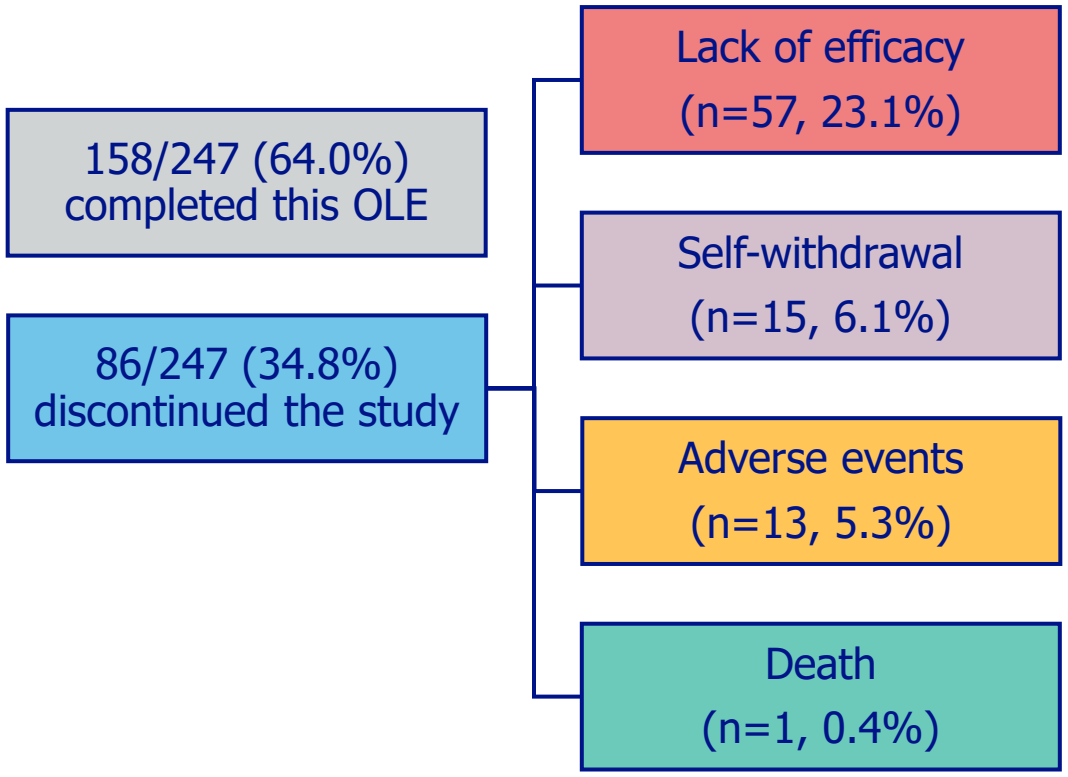
- Safety population[e]: Incidence of TEAEs occurring in ≥10% of patients and incidence of VHD and PAH
- mITT group[f]:
  - Median change from pre-RCT baseline in frequency of ESC-confirmed seizures associated with a fall from Month 1 to EOS and Month 2 to EOS
  - Ratings of any improvements (minimally, much, or very much improved) and clinically meaningful improvement (much improved or very much improved) on CGI-I scale by parents/caregivers and investigators at last visit
  - Change from baseline in anxiety, depression, and emotional distress using HADS in parents/caregivers
- Post hoc: Median percentage change from baseline in individual seizure types associated with a fall (GTCS, TS, AS, and TA)

[a]Study sites in North America, Europe, and Australia; Cohort B included patients enrolled from Japan, but were not included in this analysis. [b]Patients were required to be on ≥1 concomitant ASM (±vagus nerve stimulation and/or ketogenic diet) that must have remained stable for the first 6 months of the study. [c]Some patients remained in the study longer than 12 months due to COVID-19–related restrictions or limited access to in-clinic visits. [d]Patients continuing onto another extension study (ZX008-1900; NCT03936777) did not complete this follow-up visit. [e]All patients who received ≥1 dose of FFA during the OLE. [f]All patients who received ≥1 dose of FFA, had a valid baseline estimated frequency of seizures associated with a fall from the RCT, and provided at least 30 days of valid seizure data during the OLE.

AS, atonic seizures; ASMs, antiseizure medications; CGI-I, Clinical Global Impression-Improvement; EOS, end of study; ESC, Epilepsy Study Consortium; FFA, fenfluramine; GTCS, generalized tonic-clonic seizures; HADS, Hospital Anxiety and Depression Scale; LGS, Lennox-Gastaut syndrome; mITT, modified intent-to-treat; PAH, pulmonary arterial hypertension; RCT, randomized controlled trial; TA, tonic atonic seizures; TEAEs, treatment-emergent adverse events; TS, tonic seizures; VHD, valvular heart disease.

Results: Patient Disposition and Characteristics

247 patients continued into this OLE from the RCT[a]



	Patients (N=247)
Age group at RCT baseline, n (%) Pediatrics (2 to <18 years) Adults (18–35 years)	 174 (70.4) 73 (29.6)
Age, years, mean±SD	14.3±7.6
Number of prior ASMs, median (range)	7 (0–20)
Number of concomitant ASMs, median (range)	3 (1–7)
Pre-RCT baseline frequency of seizures associated with a fall per 28 days in the mITT group (n=241)[b], median (range)	75 (4–2943)

[a]Three patients who completed ≥1 year were not included as "completed" or "discontinued", but they continued FFA treatment after rolling into another extension study (ZX008-1900; NCT03936777).
[b]All patients who received ≥1 dose of FFA, had a valid baseline estimated frequency of seizures associated with a fall from the RCT, and provided at least 30 days of valid seizure data during the OLE.
ASMs, antiseizure medications; FFA, fenfluramine; mITT, modified intent-to-treat; OLE, open-label extension; RCT, randomized controlled trial; SD, standard deviation.

Safety Summary

	Pediatric Patients (2 to <18 years, n=174)	**Adult Patients** (18–35 years, n=73)	**All Patients** (N=247)
≥1 TEAE reported, 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)

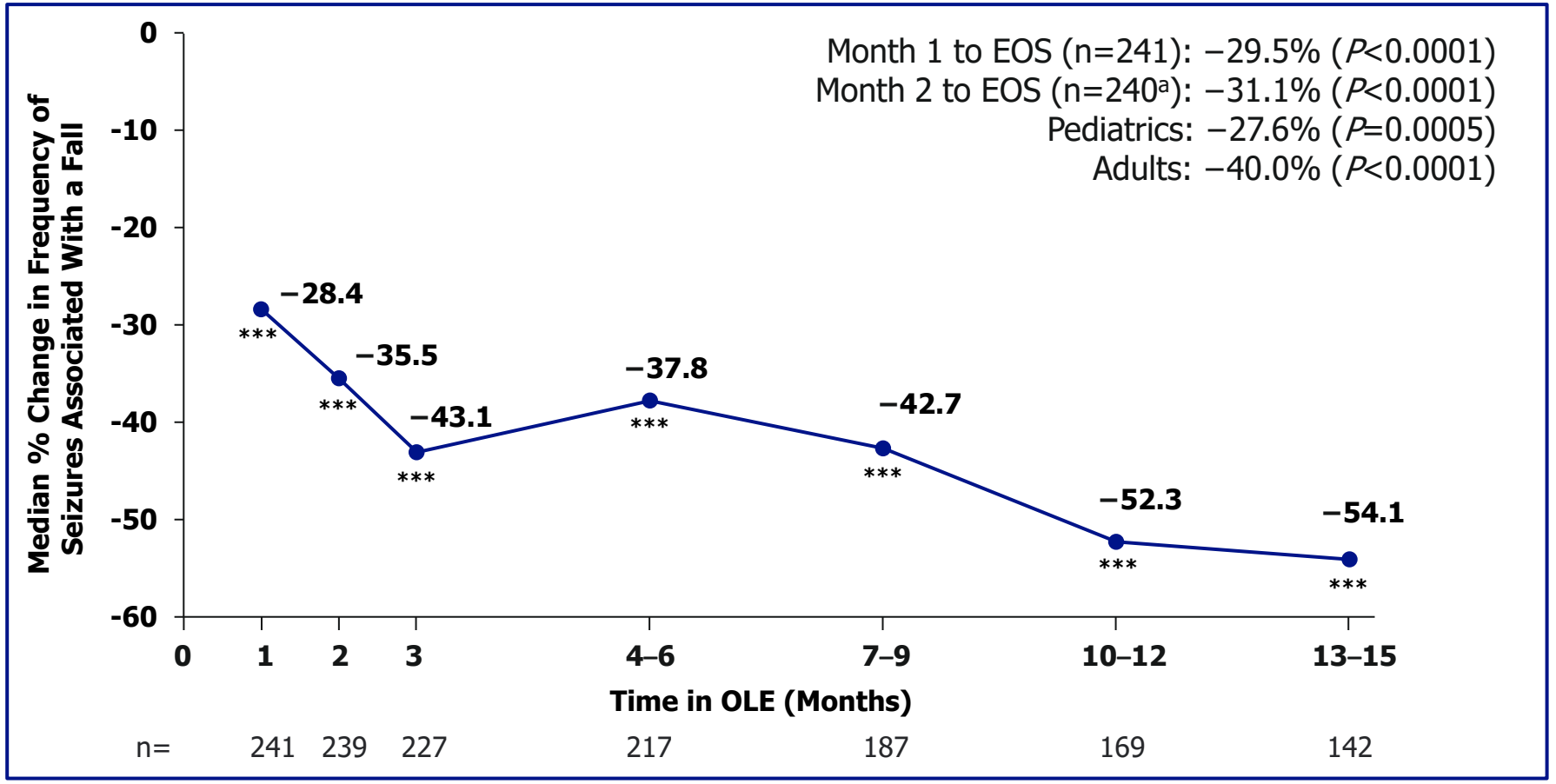
- ≥1 SAE was reported in 41/247 (16.6%) patients
  - ≥1 SAE deemed related to FFA was reported in 12/41 (29.3%) patients
- One patient died due to aspiration pneumonia, deemed unrelated to FFA by investigators

Echocardiographic evaluation revealed no cases of VHD or PAH

Median treatment duration (N=247): 364 days (range, 19–537 days)
Mean±SD FFA daily dose over the duration of this OLE (n=246[a]): 0.4±0.1 mg/kg/day

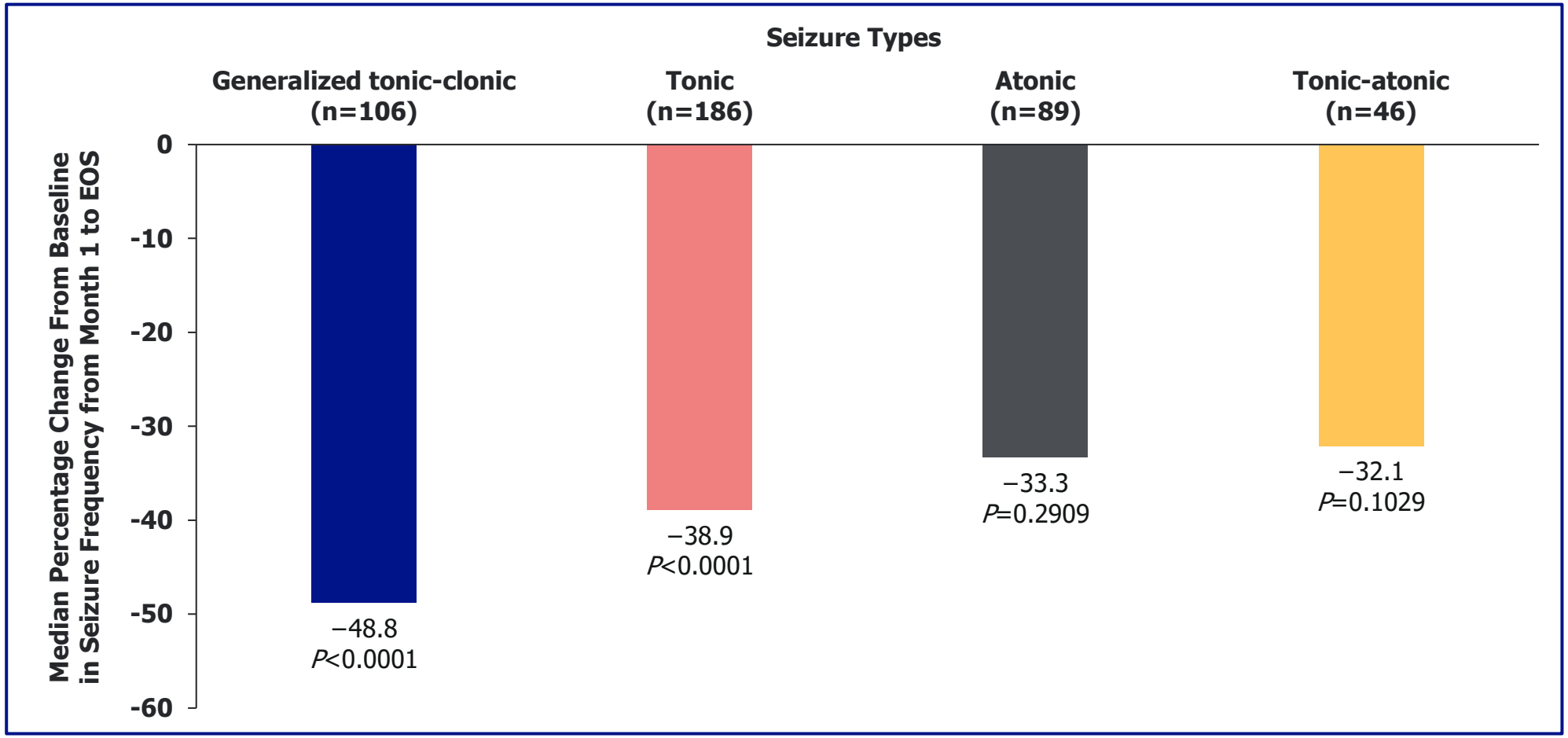
[a]Daily dosing diary was not available for one patient.
FFA, fenfluramine; OLE, open-label extension; PAH, pulmonary arterial hypertension; SAE, serious adverse event; SD, standard deviation; TEAEs, treatment-emergent adverse events; VHD, valvular heart disease.

Effectiveness: Median Percentage Change in Frequency of Seizures Associated With a Fall



***P<0.0001 by Wilcoxon signed-rank test.
At Months 16–18 (n=10), the median percentage change in seizure frequency was −27.9% (P=0.1602).
[a]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.

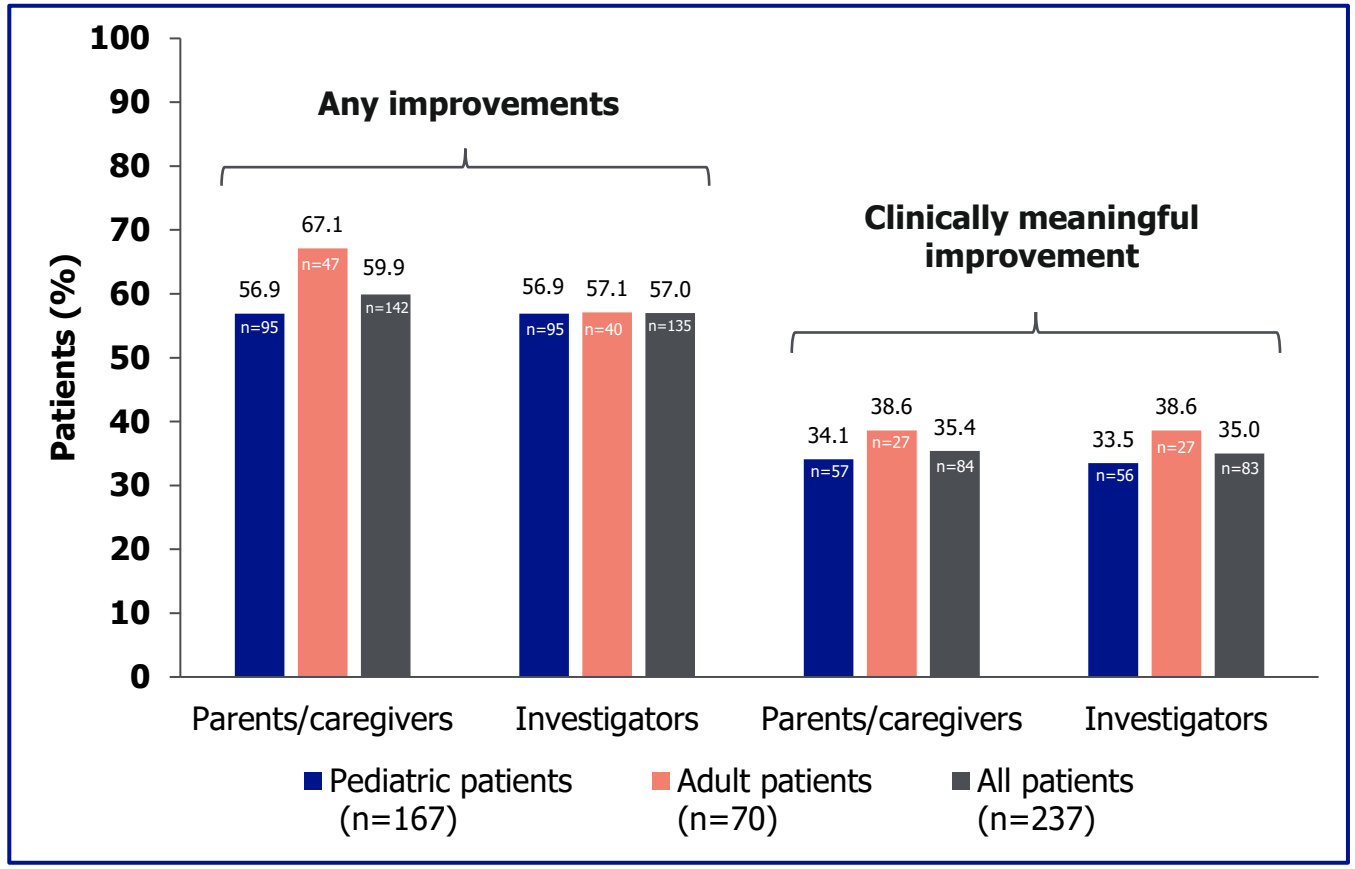
Effectiveness: Median Percentage Change in Frequency by Seizure Types (Post Hoc Analysis)



EOS, end of study.

Effectiveness: Patient Global Functioning and Caregiver Anxiety and Depression

CGI-I ratings of any improvement or clinically meaningful improvement ("much improved" or "very much improved") by parents/caregivers and investigators at last visit



HADS[a] scores at baseline and at Month 12 in parents/caregivers of patients treated with FFA

	Pre-RCT Baseline	Month 12 of OLE
Anxiety	6.3 (n=226)	5.5 (n=143)
Depression	6.1 (n=226)	5.4 (n=138)
Emotional distress	12.4 (n=226)	11.0 (n=138)

Mean change in HADS assessment scores from baseline at Month 12

Anxiety: −0.8 (*P*=0.0148)

Depression: −0.7 (*P*=0.5257)

Emotional distress: −1.4 (*P*=0.0986)

[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 results in "emotional distress" scores.

CGI-I, Clinical Global Impression-Improvement; FFA, fenfluramine; HADS, Hospital Anxiety and Depression Scale; OLE, open-label extension; RCT, randomized controlled trial.

Summary

- The results of this OLE study highlight a consistent safety profile of FFA
  - No cases of VHD or PAH were observed
- FFA was associated with a median percentage change in seizures associated with a fall from Month 2 to EOS of −31.1% (P<0.0001; n=240)
- GTCS had the greatest median percentage reduction in frequency
- On CGI-I, parents/caregivers and investigators both rated >50% of patients as improved while receiving FFA
- A statistically significant improvement in parent/caregiver anxiety was also noted from baseline to Month 12

In this final analysis of an FFA OLE study in pediatric and adult patients with LGS, FFA was well tolerated with no new safety signals identified, and provided sustained reductions in seizures associated with a fall, as well as improvements in global functioning

CGI-I, Clinical Global Impression-Improvement; EOS, end of study; FFA, fenfluramine; GTCS, generalized tonic-clonic seizures; LGS, Lennox-Gastaut syndrome; OLE, open-label extension; PAH, pulmonary arterial hypertension; VHD, valvular heart disease.

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