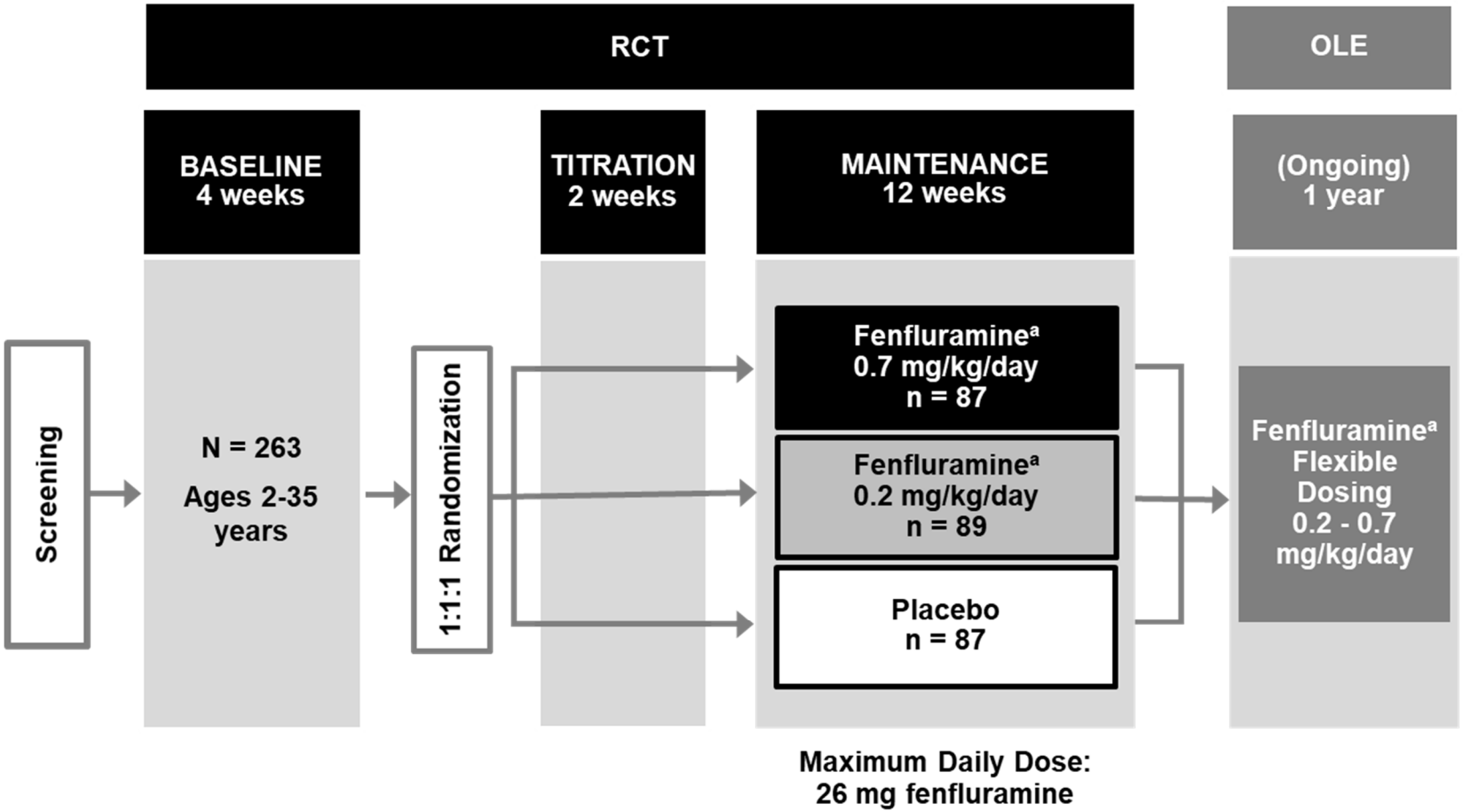
Supplementary Online Content

Knupp KG, Scheffer IE, Ceulemans B, et al. Efficacy and safety of fenfluramine for the treatment of seizures associated with Lennox-Gastaut syndrome: a randomized clinical trial. *JAMA Neurol*. Published online May 2, 2022. doi:10.1001/jamaneurol.2022.0829

This supplementary material has been provided by the authors to give readers additional information about their work.

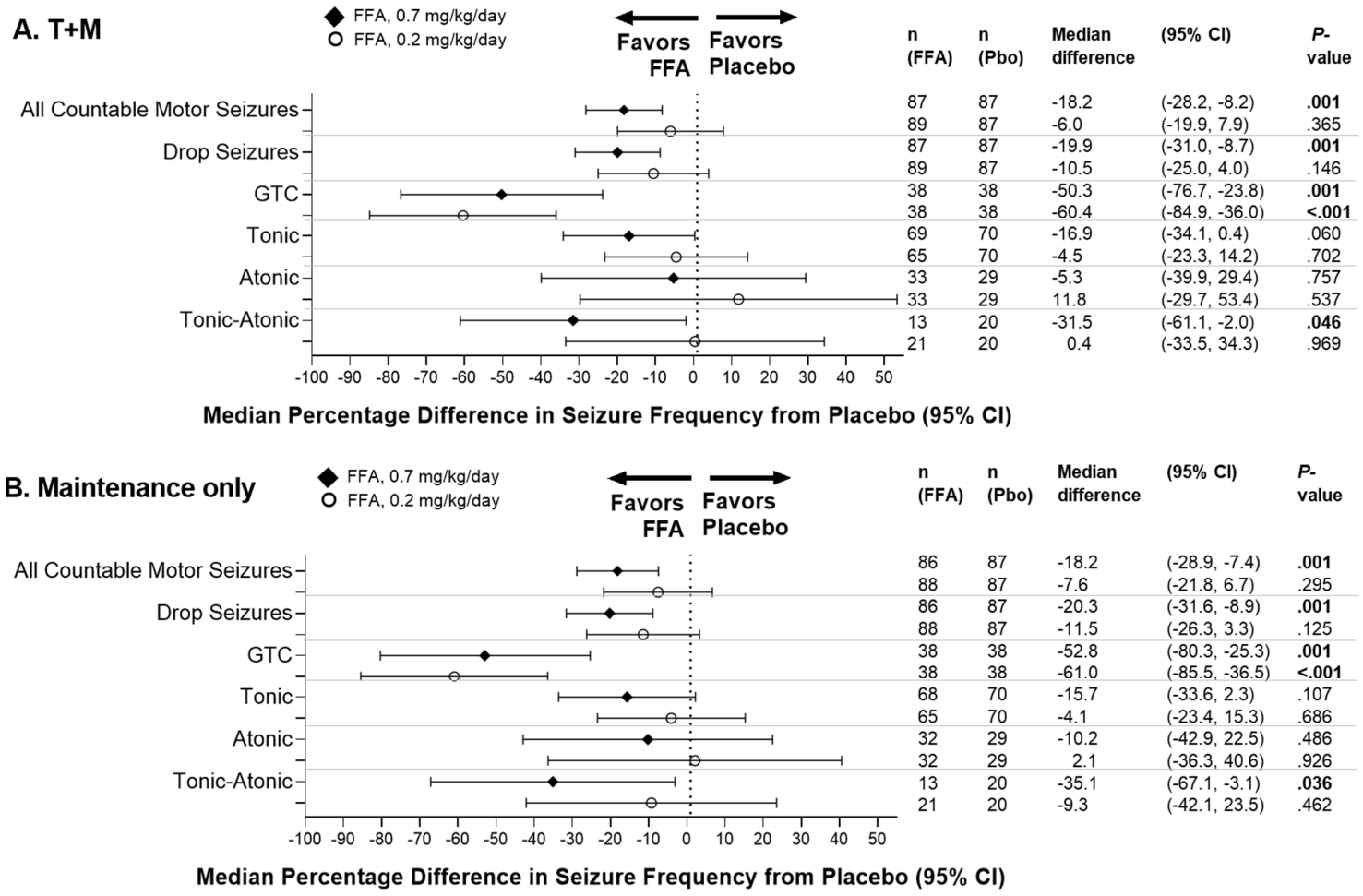
eFigure 1. Study Design



[a]Fenfluramine was administered orally twice daily as an oral solution of fenfluramine hydrochloride containing 2.2 mg/mL fenfluramine.
OLE, open-label extension; RCT, randomized clinical trial.

eFigure 2. Forest Plots: Distribution of Median Percentage Difference From Placebo in Seizure Frequency

(A) T+M period. (B) Maintenance only.



	n (FFA)	n (Pbo)	Median difference	(95% CI)	*P*-value
A. T+M					
All Countable Motor Seizures	87	87	-18.2	(-28.2, -8.2)	**.001**
	89	87	-6.0	(-19.9, 7.9)	.365
Drop Seizures	87	87	-19.9	(-31.0, -8.7)	**.001**
	89	87	-10.5	(-25.0, 4.0)	.146
GTC	38	38	-50.3	(-76.7, -23.8)	**.001**
	38	38	-60.4	(-84.9, -36.0)	**<.001**
Tonic	69	70	-16.9	(-34.1, 0.4)	.060
	65	70	-4.5	(-23.3, 14.2)	.702
Atonic	33	29	-5.3	(-39.9, 29.4)	.757
	33	29	11.8	(-29.7, 53.4)	.537
Tonic-Atonic	13	20	-31.5	(-61.1, -2.0)	**.046**
	21	20	0.4	(-33.5, 34.3)	.969
B. Maintenance only					
All Countable Motor Seizures	86	87	-18.2	(-28.9, -7.4)	**.001**
	88	87	-7.6	(-21.8, 6.7)	.295
Drop Seizures	86	87	-20.3	(-31.6, -8.9)	**.001**
	88	87	-11.5	(-26.3, 3.3)	.125
GTC	38	38	-52.8	(-80.3, -25.3)	**.001**
	38	38	-61.0	(-85.5, -36.5)	**<.001**
Tonic	68	70	-15.7	(-33.6, 2.3)	.107
	65	70	-4.1	(-23.4, 15.3)	.686
Atonic	32	29	-10.2	(-42.9, 22.5)	.486
	32	29	2.1	(-36.3, 40.6)	.926
Tonic-Atonic	13	20	-35.1	(-67.1, -3.1)	**.036**
	21	20	-9.3	(-42.1, 23.5)	.462

Estimated median difference from placebo (Hodges-Lehmann Estimate) in percentage reduction in seizure frequency. The *P*-values are statistically significant for the primary efficacy outcome (drop seizure frequency, 0.7 mg/kg/day FFA); all other *P*-values are considered nominal. CI, confidence interval; FFA, fenfluramine; GTC, generalized tonic-clonic; Pbo, placebo; T+M, combined titration and maintenance periods.

eTable 1. Titration and Tapering Algorithms

All patients were titrated to their randomized dose over a 2-week titration period. A tapering protocol was administered to patients who discontinued early or who completed the study but did not continue to the OLE. Patients who transitioned from the double-blind study to the OLE were titrated to a dose of fenfluramine 0.2 mg/kg/day and were then titrated to effect, including those patients who entered the OLE early without completing the double-blind study.

	STEP 1	**STEP 2**	**STEP 3**
Titration[a,b]	**Study Days 1-4**	**Study Days 5-8**	**Study Days 9-14**
Placebo Fenfluramine 0.2 mg/kg/day Fenfluramine 0.7 mg/kg/day	Placebo Fenfluramine 0.2 mg/kg/day Fenfluramine 0.2 mg/kg/day	Placebo Fenfluramine 0.2 mg/kg/day Fenfluramine 0.4 mg/kg/day	Placebo Fenfluramine 0.2 mg/kg/day Fenfluramine 0.7 mg/kg/day
Tapering[a]	**Days 1-4 after study completion or early termination**	**Days 5-8 after study completion or early termination**	
Placebo Fenfluramine 0.2 mg/kg/day Fenfluramine 0.7 mg/kg/day	Placebo Placebo Fenfluramine 0.4 mg/kg/day	Placebo Placebo Fenfluramine 0.2 mg/kg/day	
Transition to OLE from dose group in double-blind study[a]	**Days 1-4 after Visit 12**[c]	**Days 5-14 after Visit 12**[c]	

Placebo	Fenfluramine 0.2 mg/kg/day	Fenfluramine 0.2 mg/kg/day
Fenfluramine 0.2 mg/kg/day	Fenfluramine 0.2 mg/kg/day	Fenfluramine 0.2 mg/kg/day
Fenfluramine 0.7 mg/kg/day	Fenfluramine 0.4 mg/kg/day	Fenfluramine 0.2 mg/kg/day

BID, twice daily; OLE, open-label extension.
[a]Maximum daily dose of fenfluramine, 26 mg.
[b]The dosing regimen, BID for all doses.
[c]Visit 12 is Maintenance Period Study Day 99 (Week 12), or early termination/end of study visit.

eTable 2. Sequential Gatekeeping Procedure to Maintain Type 1 Error Rate at α = 0.05 for Pairwise Comparisons Between Active Treatment and Placebo[1]

Step	Outcome	Definition	Dosage Comparison vs. Placebo
1	Primary	Change in the frequency of drop seizures between baseline and T+M	FFA 0.7 mg/kg/day
2	Second key secondary	Proportion of subjects who achieve a ≥50% reduction from baseline in the frequency of seizures that result in drops	FFA 0.7 mg/kg/day
3	Third key secondary	Clinical Global Impression of Improvement (CGI-I) rating, as assessed by the principal investigator – Any Improvement	FFA 0.7 mg/kg/day
4	Fourth key secondary	Change in frequency of drop seizures between baseline and T+M	FFA 0.2 mg/kg/day
5	Fifth key secondary	Proportion of subjects who achieve a ≥50% reduction from baseline in the frequency of drop seizures	FFA 0.2 mg/kg/day
6	Sixth key secondary	Clinical Global Impression of Improvement (CGI-I) rating, as assessed by the principal investigator – Any Improvement	FFA 0.2 mg/kg/day

[1]Primary outcome-defined Epilepsy-Study-Consortium-confirmed seizure subtypes that resulted in a drop were: GTC, secondary GTC, tonic, atonic, and tonic-atonic. If the comparison was statistically significant at the α=0.05 (2-sided) level, hypothesis testing proceeded to the next step; if not, p-values were considered nominal.
CGI-I: Clinical Global Impression—Improvement; GTC, generalized tonic-clonic; T+M, combined titration and maintenance periods.