Fenfluramine Efficacy Trajectories in Placebo or Treatment Groups From Randomized Controlled Trial to Open-Label Extension in Patients With Lennox-Gastaut Syndrome

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Background

- Lennox-Gastaut syndrome (LGS) is a developmental and epileptic encephalopathy associated with pharmacoresistant seizures, developmental delay, and cognitive and behavioral deficits, that persist into adulthood
- Fenfluramine (FFA) is approved for the treatment of seizures associated with LGS in patients ≥2 years of age in the United States,[1] European Union,[2] United Kingdom, Japan,[3] and Israel[4]
- LGS is characterized by seizures associated with a fall (previously "drop seizures"), including generalized tonic-clonic seizures (GTCS), focal to bilateral tonic-clonic seizures, tonic, atonic, and myoclonic-atonic seizures[5,6]
  - GTCS is the highest risk factor for sudden unexpected death in epilepsy[7]
- In the pivotal phase 3 randomized controlled trial (RCT) of FFA for management of seizures associated with LGS, FFA treatment groups (FFA 0.2 and 0.7 mg/kg/day, maximum 26 mg/day) experienced a greater change in frequency of seizures associated with a fall from baseline compared to placebo[5]
  - This reduction was sustained in the open-label extension (OLE) study[6]
  - The most common treatment emergent adverse events during the RCT and OLE were decreased appetite, somnolence (RCT only), and fatigue

Objective

- Trajectories of FFA efficacy are described during the RCT and OLE in patients randomized to placebo or FFA during the RCT

Methods

- The RCT included baseline (4 wks), titration (2 wks), and maintenance periods (12 wks)
- After completing the RCT, patients were eligible to enroll in the OLE
  - All patients who enrolled in the OLE were transitioned to FFA 0.2 mg/kg/d; patients remained on this dose through the end of Month 1
  - Following Month 1, FFA was flexibly titrated to effect and tolerability through end of study (EOS); maximum dose 0.7 mg/kg/d (maximum daily dose, 26 mg/d)
- Trajectories of efficacy outcomes were assessed for patients who transitioned to the OLE from placebo ("RCT-Placebo"; "Prior RCT-Placebo" for OLE data) and any FFA dose in the RCT (**Figure 1**)
  - FFA dose groups (0.2 and 0.7 mg/kg/d, maximum 26 mg/d) were combined ("RCT-FFA")
- Timepoints assessed:
  - RCT: Baseline, Weeks 2, 6, 10, and 14, and combined titration and maintenance (T+M)
  - OLE: Months 1, 2, 3, 4–6, 7–9, 10–12, 13–15, 16–18, 19–21, and Month 1 to EOS
- The primary outcome in the RCT was the median percent change in frequency of seizures associated with a fall between RCT baseline and the RCT T+M period, and between RCT baseline and OLE Month 1–EOS
  - Seizures associated with a fall include GTCS, focal to bilateral tonic-clonic seizures, tonic seizures, atonic seizures, and myoclonic-atonic seizures confirmed by the Epilepsy Study Consortium
  - Efficacy was also assessed by days with no seizures associated with a fall, global functioning as assessed by the Clinical Global Impression—Improvement (CGI-I) scale using investigator and caregiver responses, responder rates, and time to sustained response (TTSR; **Table 1**)

Table 1. Outcomes Assessed in Patients Randomized to Placebo or FFA During the RCT and Transitioned to the OLE

Outcome Assessed	Description	Statistical Analysis[a]
Frequency of seizures associated with a fall; frequency of GTCS	Median percent change from baseline to T+M (RCT) and to Month 1–EOS (OLE)	Q1, median, and Q3 of percent change from baseline
Days with no seizures associated with a fall	Number of days with no seizures associated with a fall	Mean (SD)
CGI-I, investigator CGI-I, caregiver	Clinically meaningful improvement ("much improved" or "very much improved")	n (%) of patients with non-missing CGI-I, with clinically meaningful improvement
Responder rates	Number of patients with ≥50% and ≥75% reduction in seizures associated with a fall	n (%) Exact Clopper-Pearson 95% CI
TTSR	Day at which ≥50% or ≥75% responder rate in seizures associated with a fall, maintained through EOS, began	n (%) sustained responders Q1, median, and Q3 of TTSR, days KM estimate of median TTSR, days

[a]All outcomes include demographic analysis.
CGI-I, Clinical Global Impression—Improvement; EOS, end of study; FFA, fenfluramine; GTCS, generalized tonic-clonic seizures; KM estimate, Kaplan-Meier estimate; OLE, open-label extension; Q1, quartile 1; Q3, quartile 3; RCT, randomized controlled trial; SD, standard deviation; TTSR, time to sustained response.

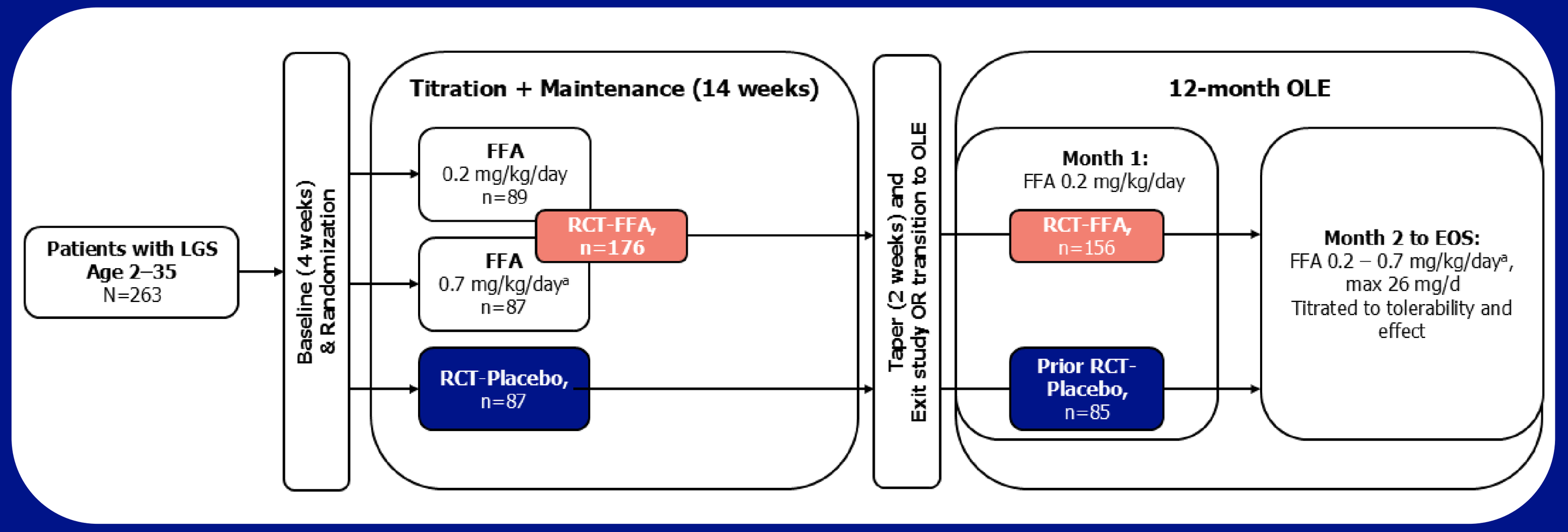
Overview

QUESTION

- What is the natural history of seizure frequency, as seen in placebo-treated patients, in patients with Lennox-Gastaut syndrome (LGS)?
- When do patients previously treated with placebo during a randomized controlled trial (RCT) experience efficacy of fenfluramine (FFA) treatment following initiation in the open-label extension (OLE), and when does efficacy reach a similar impact as seen in patients treated with FFA during the RCT?

INVESTIGATION

Figure 1. Study Design



Patients with LGS
Age 2–35
N=263
Baseline (4 weeks) & Randomization
Titration + Maintenance (14 weeks)
FFA
0.2 mg/kg/day
n=89
FFA
0.7 mg/kg/day[a]
n=87
RCT-FFA,
n=176
RCT-Placebo,
n=87
Taper (2 weeks) and Exit study OR transition to OLE
12-month OLE
Month 1:
FFA 0.2 mg/kg/day
RCT-FFA,
n=156
Prior RCT-Placebo,
n=85
Month 2 to EOS:
FFA 0.2 – 0.7 mg/kg/day[a],
max 26 mg/d
Titrated to tolerability and effect

FFA, fenfluramine; LGS, Lennox-Gastaut syndrome; OLE, open-label extension; Prior RCT-Placebo, patients who transitioned to the OLE from placebo; RCT, randomized controlled trial; RCT-FFA, patients randomized to any dose of FFA during the RCT; RCT-Placebo, patients randomized to placebo during the RCT.

RESULTS

Outcome	Summary of Results During the OLE
Median percent change from baseline, frequency per 28 days	
Seizures associated with a fall	Patients who received placebo in RCT reached numerically comparable reduction versus patients who received FFA
GTCS	Patients who received placebo in RCT trended toward reductions similar to those seen in patients who received FFA
Mean number of days free of seizures associated with a fall	Number of days for patients who received placebo and those who received FFA in RCT increased similarly during the OLE
Clinically meaningful improvement on the CGI-I scale, frequency	
Caregiver Investigator	Patients who received placebo in RCT reached numerically comparable improvement versus patients who received FFA
Responder rates for seizures associated with a fall	
≥50% reduction ≥75% reduction	Patients who received placebo and who received FFA in the RCT had similar responder rates during the OLE

[a]High variability was seen due to low group numbers in patients with GTCS at baseline.
CGI-I, Clinical Global Impression—Improvement; FFA, fenfluramine; GTCS, generalized tonic-clonic seizures; OLE, open-label extension; Prior RCT-Placebo, patients who transitioned to the OLE from placebo; RCT, randomized controlled trial; RCT-FFA, patients randomized to any dose of FFA during the RCT; RCT-Placebo, patients randomized to placebo during the RCT.

CONCLUSIONS

- Regression to the mean (natural variation that can be mistaken for real change) was not observed during the 14-week RCT treatment period in patients who received placebo during the RCT
- Rapid onset of FFA efficacy was displayed by the change in the median percent frequency of seizures associated with a fall during the first month of the OLE in patients who received placebo during the RCT
- Patients who had received placebo during the RCT improved across all analyzed efficacy outcomes following initiation of FFA treatment during the OLE

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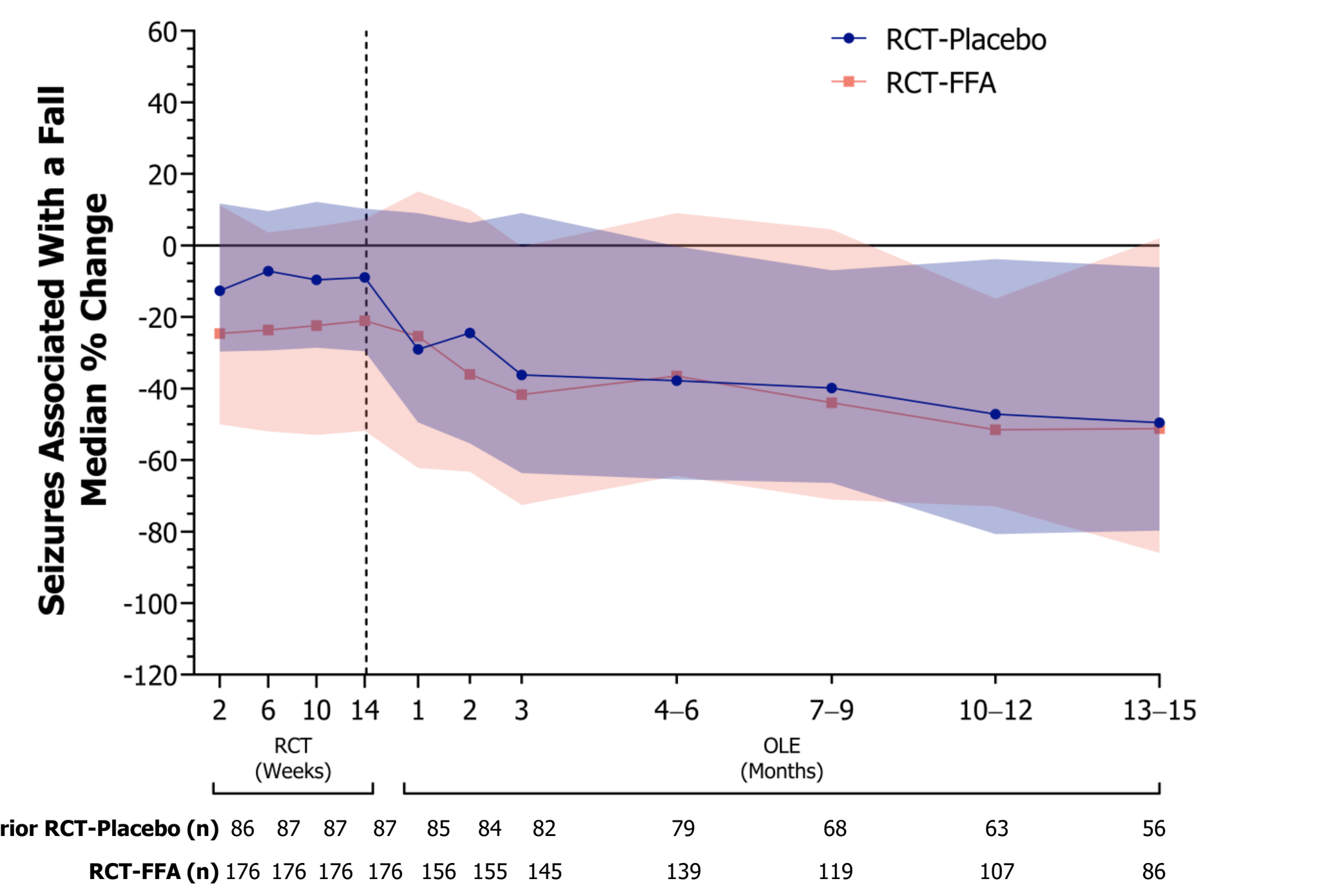
Results

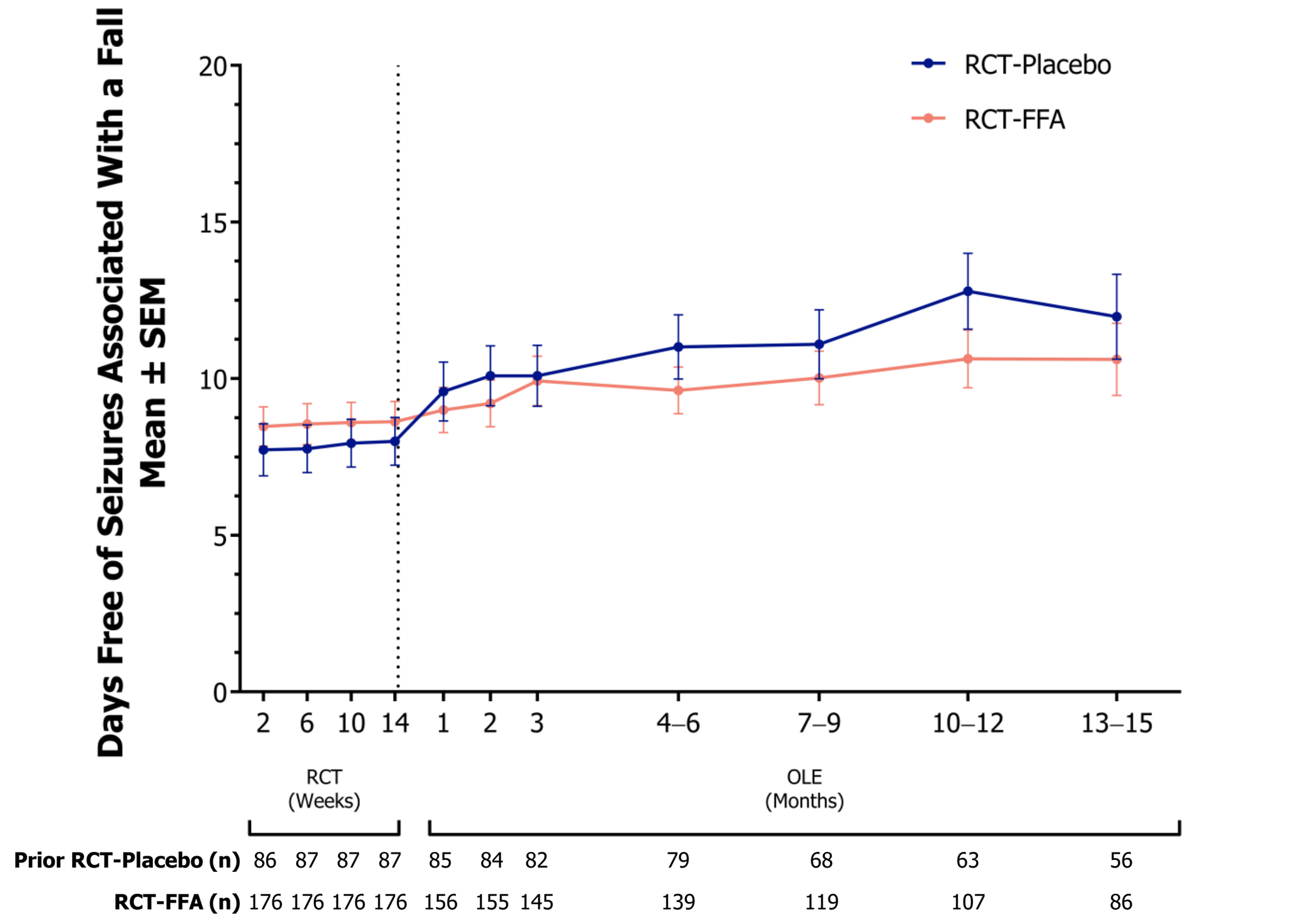
- During the RCT baseline (N=263), the mean number of seizures associated with a fall per 28 days was 164.4 (SD=309.37; median=53.0) for patients in the RCT-placebo group and 209.2 (SD=377.44, median=83.5) for patients in the RCT-FFA group
- During the RCT T+M, median percent change from baseline in seizures associated with a fall (−12.6% to −7.2%, **Figure 2**) remained consistent over the entire RCT for patients receiving placebo
- During Month 1 of the OLE, when all patients were treated with FFA 0.2 mg/kg/d, patients in the RCT-placebo group (n=85) experienced a −29.0% median percent change in seizures associated with a fall compared to RCT baseline
  - This was numerically comparable (median percent change of −25.4%) to patients in the RCT-FFA group (n=156)
- Both Prior RCT-Placebo and RCT-FFA groups maintained a similar change from baseline in seizures associated with a fall through OLE EOS
- Efficacy was numerically similar between patients who received placebo and patients who received FFA during the RCT across multiple measures (**Figures 3, 4, and 5**), with a similar trend in changes in median percent change in GTCS from RCT baseline (patient subset at RCT baseline, RCT-Placebo: n=38; RCT-FFA: n=76)

Figure 2. Change in Seizures Associated With a Fall in Patients in Prior RCT-Placebo and RCT-FFA Groups During the RCT and During the OLE



Envelope plot of the median percent change from baseline in frequency of seizures associated with a fall by randomized group in the RCT. Lower and upper boundary of each shaded region represents the 25th and 75th percentiles, respectively.
FFA, fenfluramine; OLE, open-label extension; Prior RCT-Placebo, patients who transitioned to the OLE from placebo; RCT, randomized controlled trial; RCT-FFA, patients randomized to any dose of FFA during the RCT; RCT-Placebo, patients randomized to placebo during the RCT.

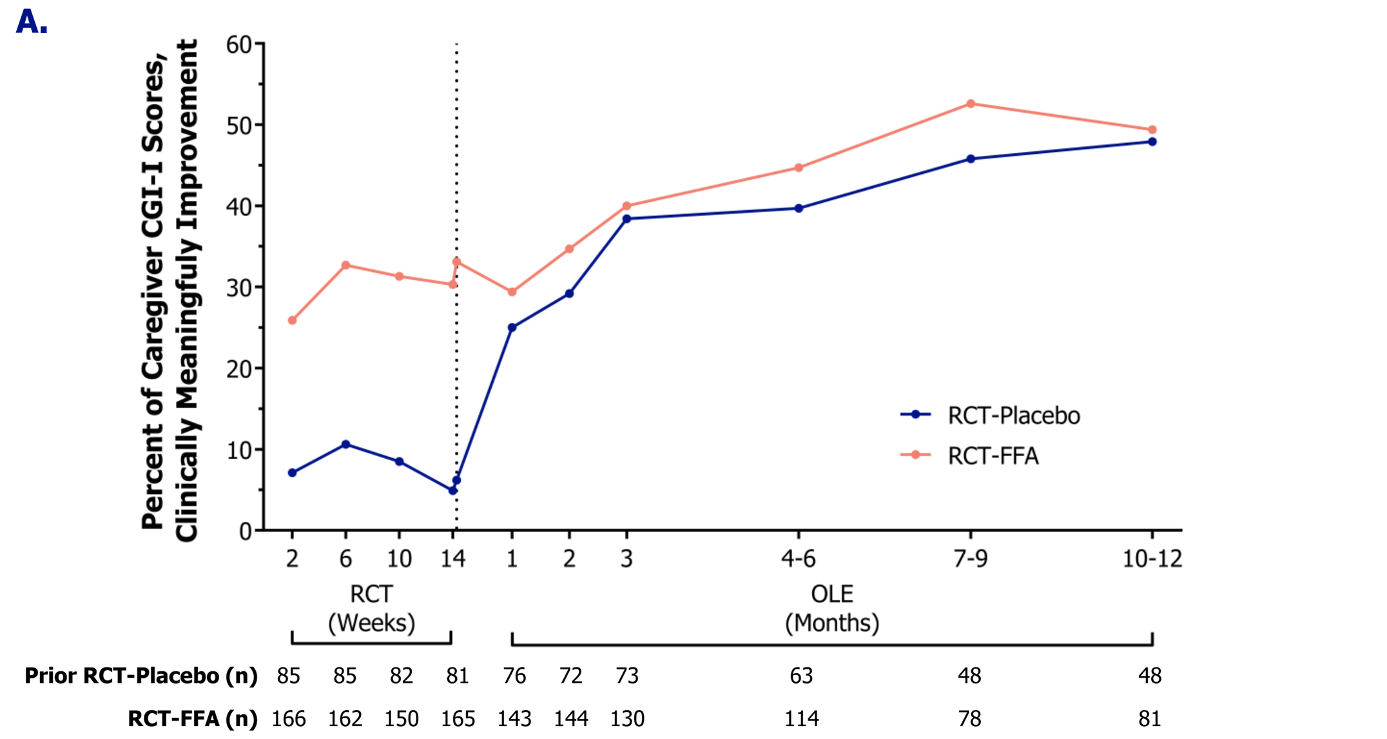
Figure 3. Days With No Seizures Associated With a Fall in Patients in Prior RCT-Placebo and RCT-FFA Groups During the RCT and During the OLE



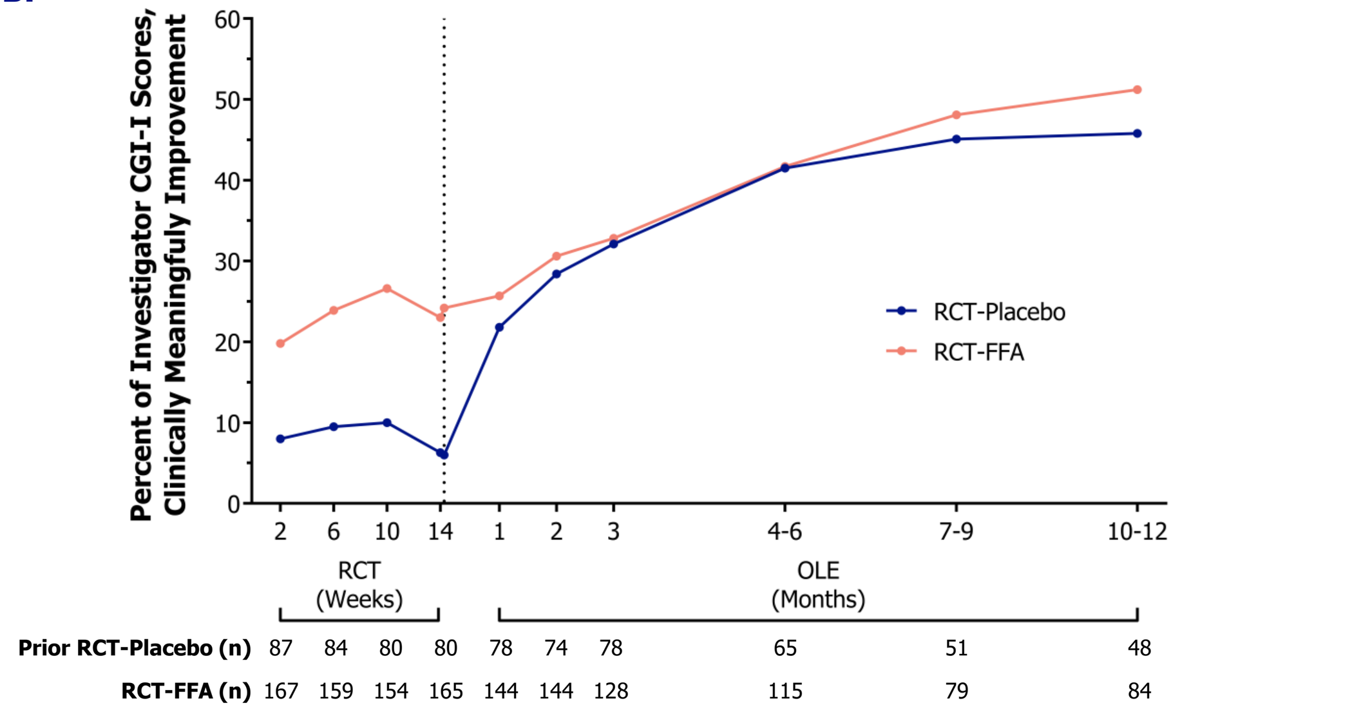
FFA, fenfluramine; OLE, open-label extension; Prior RCT-Placebo, patients who transitioned to the OLE from placebo; RCT, randomized controlled trial; RCT-FFA, patients randomized to any dose of FFA during the RCT; RCT-Placebo, patients randomized to placebo during the RCT; SEM, standard error of the mean.

Figure 4. CGI-I Scores Assessed in Patients in Prior RCT-Placebo and RCT-FFA Groups Through the RCT and OLE by A. Caregivers and B. Investigators

A.

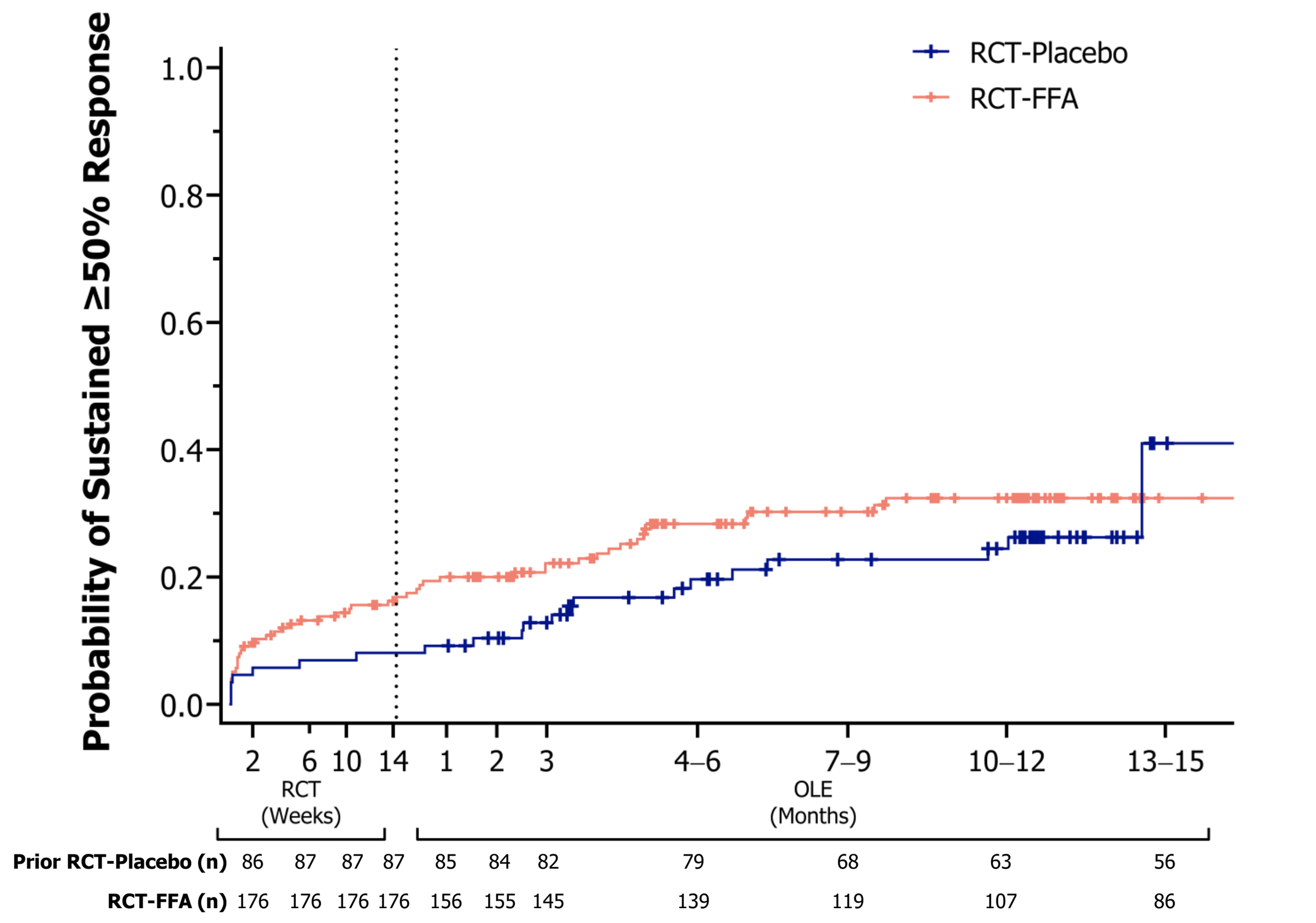


B.



CGI-I, Clinical Global Impression—Improvement; FFA, fenfluramine; OLE, open-label extension; Prior RCT-Placebo, patients who transitioned to the OLE from placebo; RCT, randomized controlled trial; RCT-FFA, patients randomized to any dose of FFA during the RCT; RCT-Placebo, patients randomized to placebo during the RCT.

Figure 5. Probability of Sustained Response of Seizures Associated With a Fall for ≥50% Reduction Through OLE EOS



CGI-I, Clinical Global Impression – Improvement; EOS, end of study; FFA, fenfluramine; OLE, open-label extension; Prior RCT-Placebo, patients who transitioned to the OLE from placebo; RCT, randomized controlled trial; RCT-FFA, patients randomized to any dose of FFA during the RCT; RCT-Placebo, patients randomized to placebo during the RCT.

Conclusions

- Regression to the mean (natural variation in a repeated measure [seizure frequency] that can be mistaken for real change [treatment response]) was not observed during the 14-week RCT T+M period in patients in the RCT-Placebo group
- Baseline seizure frequency severity was not just a reflection of the relatively short baseline period
  - This result suggests that changes were not due to extreme events and could be attributed to FFA treatment
- Patients previously receiving placebo exhibited numerical improvements in all efficacy outcomes analyzed following transition to the OLE and initiating FFA treatment, providing a natural history of FFA's effect on patients with LGS
- The change in frequency of seizures associated with a fall in patients who received placebo during the RCT occurred during Month 1 of the OLE, confirming rapid onset of FFA efficacy
- Further analyses on the time to efficacy in a larger population of patients with LGS who may have been excluded from the RCT/OLE would be beneficial

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