Poster 1.408

Fenfluramine Efficacy Trajectories in Placebo or Treatment Groups From Randomized Controlled Trial to Open-Label Extension

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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, 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
  - 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 (RR), 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.

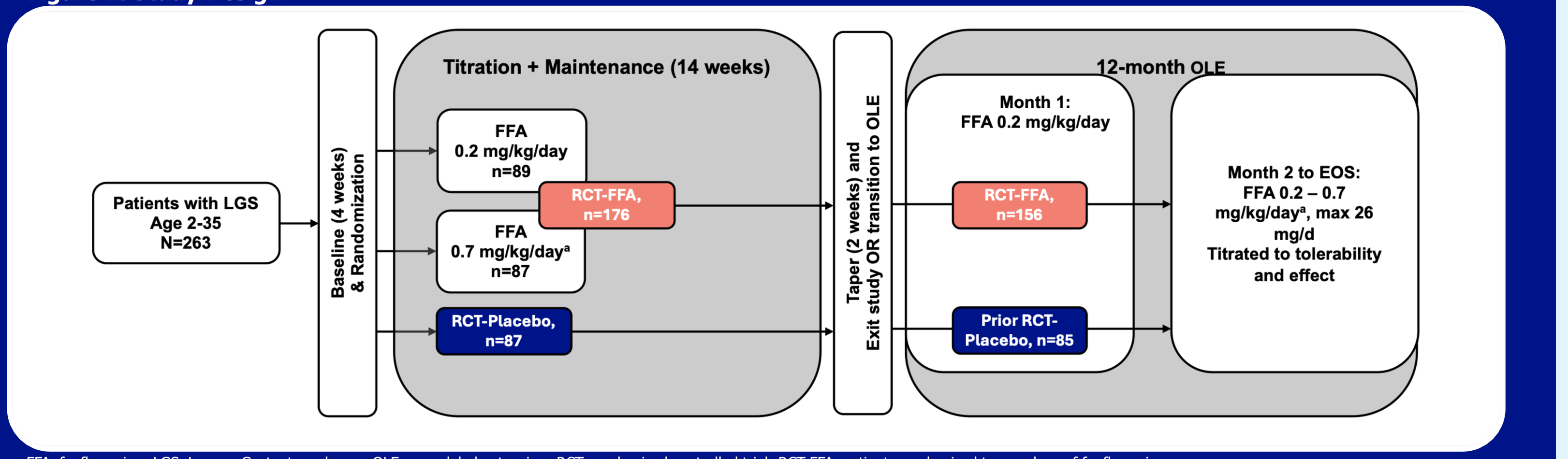
Overview

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 study (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; RCT, randomized controlled trial; RCT-FFA, patients randomized to any dose of fenfluramine during the randomized controlled trial; RCT-Placebo, patients randomized to placebo during the randomized controlled trial.

RESULTS

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

[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; RCT, randomized controlled trial; RCT-FFA, patients randomized to any dose of fenfluramine during the randomized controlled trial; RCT-Placebo, patients randomized to placebo during the randomized controlled trial.

CONCLUSIONS

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

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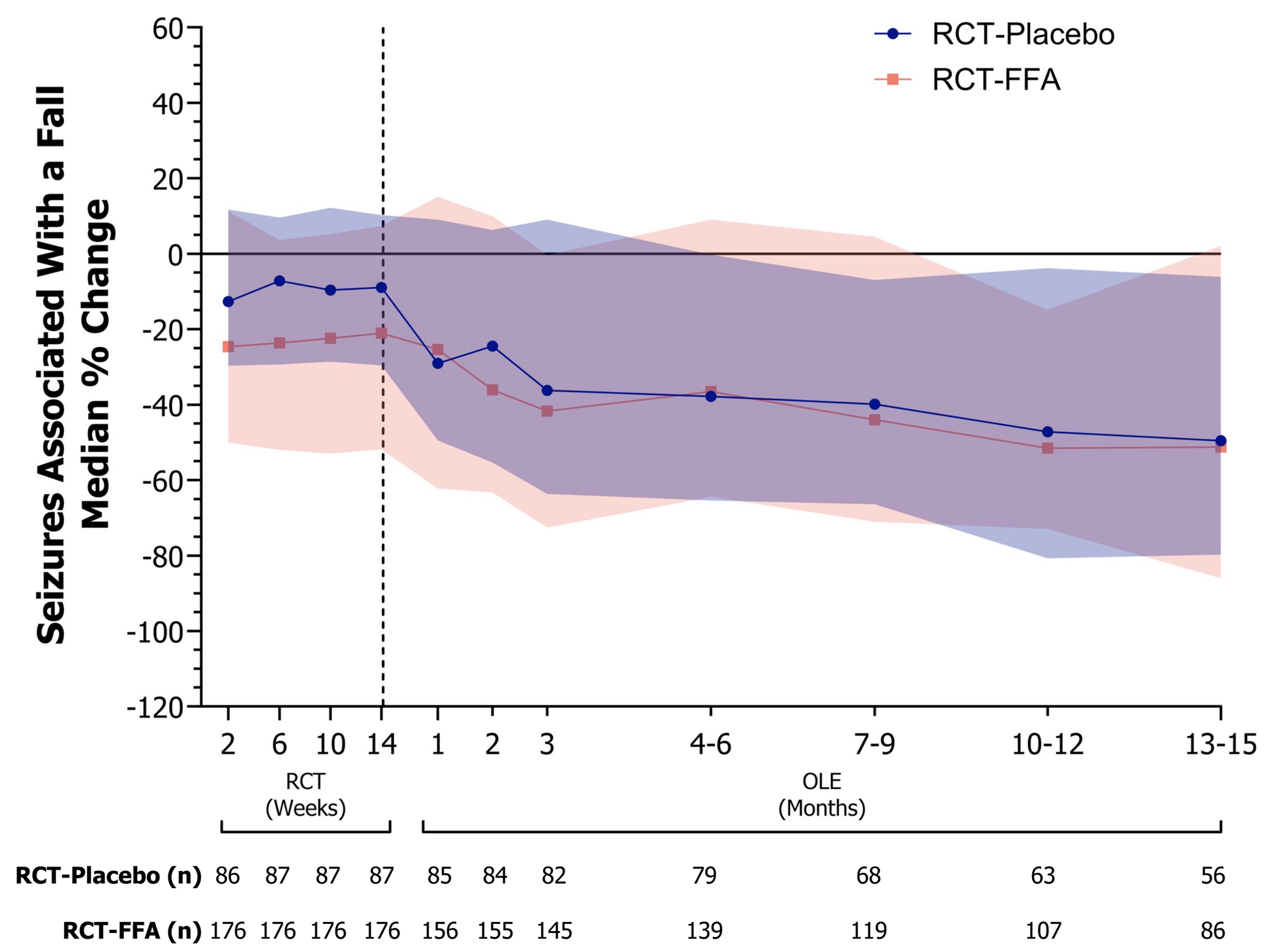
Results

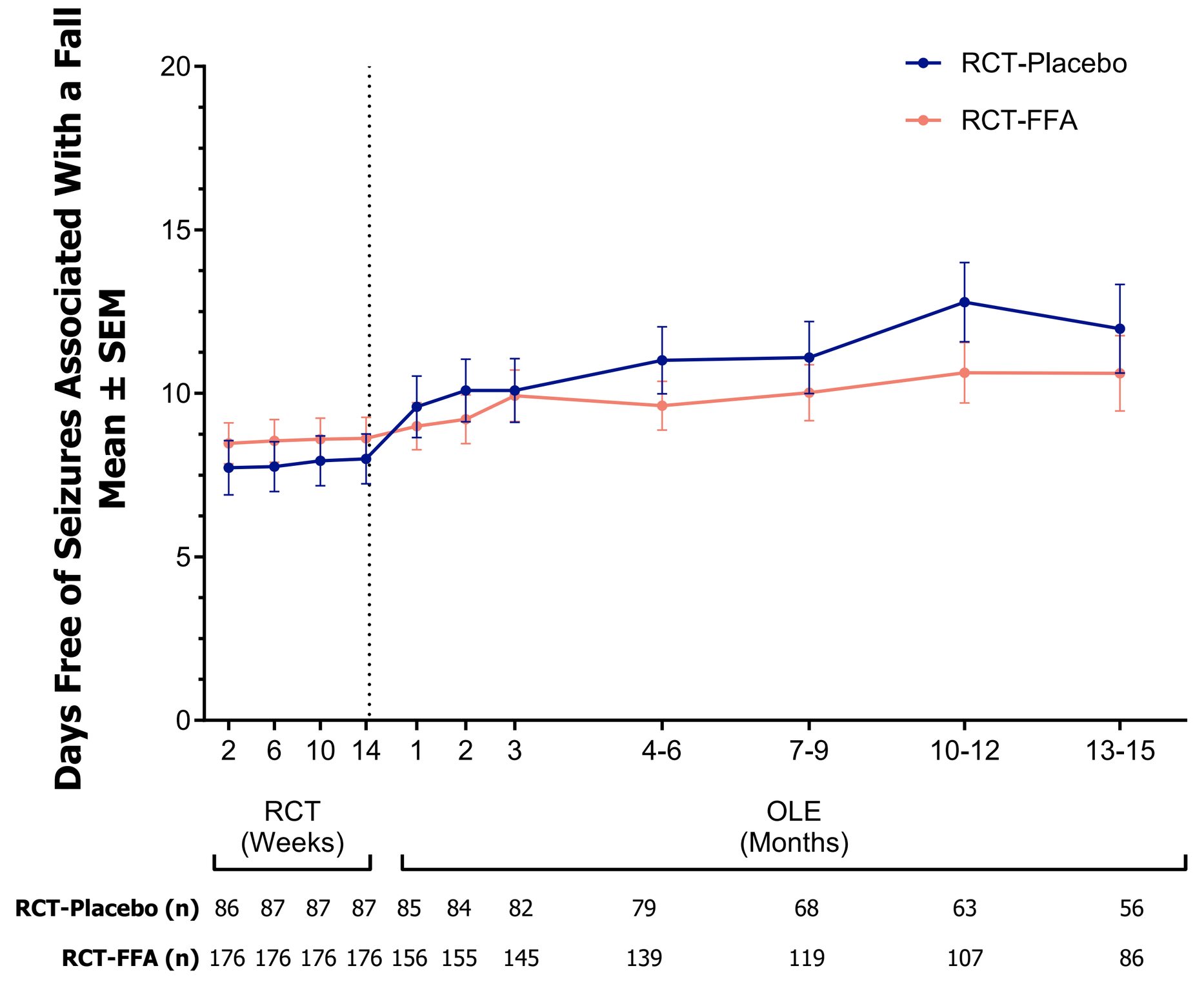
- During the RCT baseline (N=263), mean number of seizures associated with a fall per 28 days was 164.4 (SD=309.37; median=53.0) for RCT-Placebo and 209.2 (SD=377.44, median=83.5) for RCT-FFA
- During the RCT T+M, median percent change from baseline in seizures associated with a fall (-12.6% to -7.2%, **Figure 2**) remained consistent over the entire RCT for RCT-Placebo
- During Month 1 of the OLE, when all patients were treated with FFA 0.2 mg/kg/d, Prior RCT-Placebo patients (n=85) experienced a -29.0% median percent change in seizures associated with a fall compared to RCT baseline
  - This was numerically comparable to RCT-FFA patients (n=156), who experienced a median percent change of -25.4% in Month 1 of the OLE compared to RCT baseline
- Both Prior RCT-Placebo and RCT-FFA groups maintained a similar change from baseline in seizures associated with a fall through EOS
- Efficacy was numerically similar between the Prior RCT-Placebo and RCT-FFA groups 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 Prior RCT-Placebo and RCT-FFA Patients 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; RCT, randomized controlled trial; RCT-FFA, patients randomized to any dose of fenfluramine during the RCT; RCT-Placebo, patients randomized to placebo during the RCT.

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

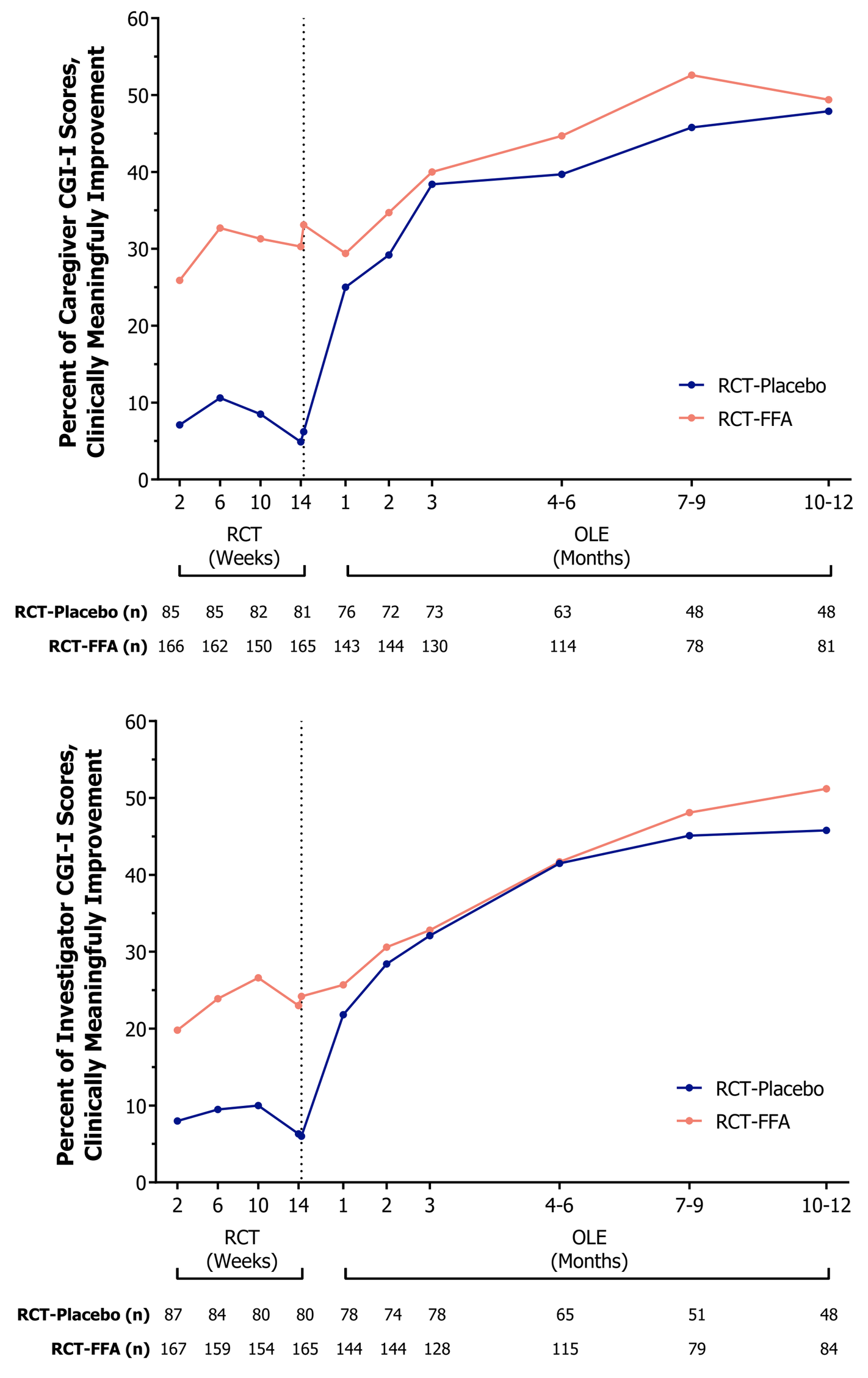


FFA, fenfluramine; OLE, open-label extension; RCT, randomized controlled trial; RCT-FFA, patients randomized to any dose of fenfluramine during the RCT; RCT-Placebo, patients randomized to placebo during the RCT; SEM, standard error of the mean.

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

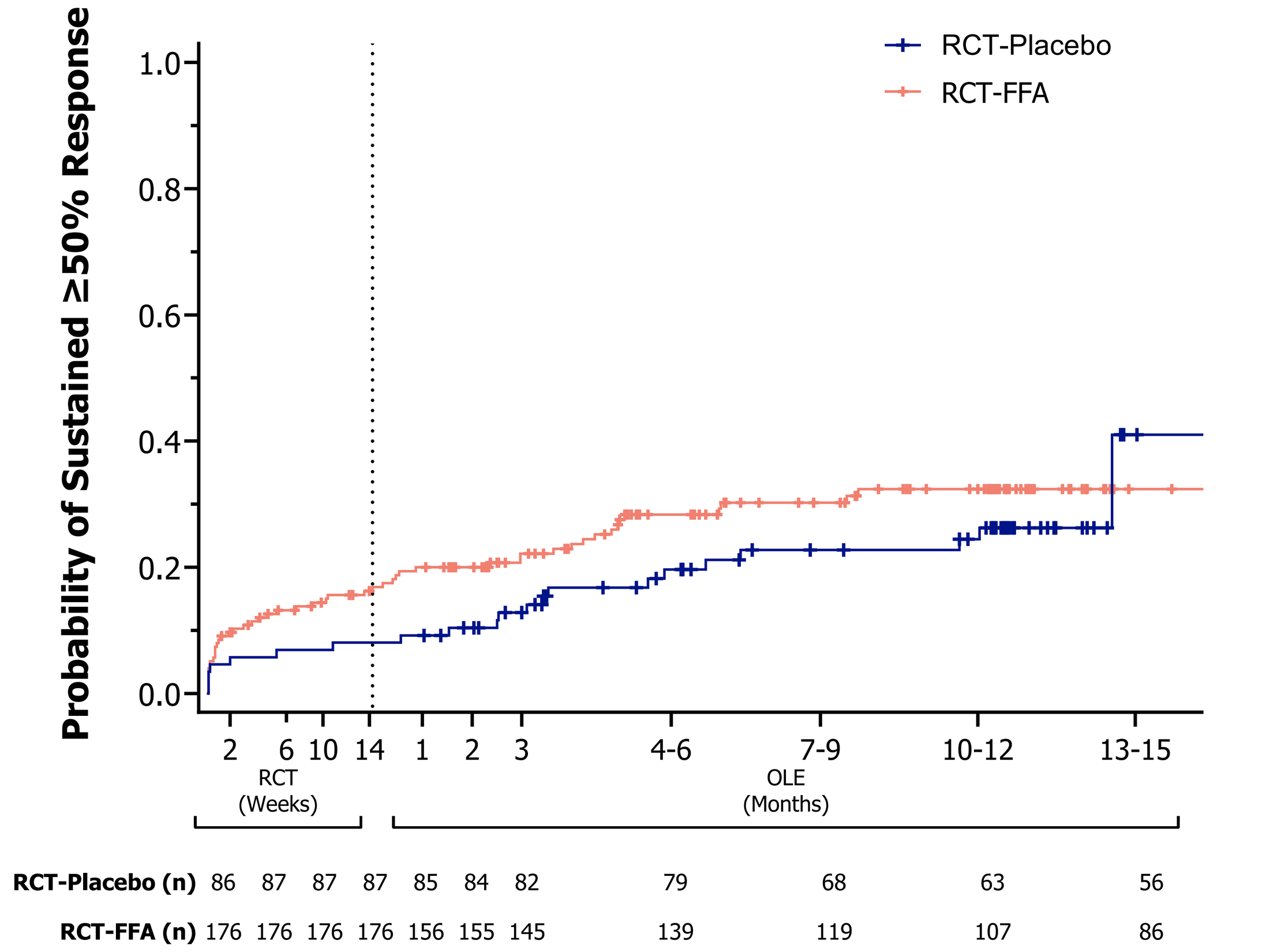
A.

B.


Percent of Caregiver CGI-I Scores, Clinically Meaningfuly Improvement
RCT-Placebo
RCT-FFA
2 6 10 14 1 2 3 4-6 7-9 10-12
RCT (Weeks)
OLE (Months)
RCT-Placebo (n) 85 85 82 81 76 72 73 63 48 48
RCT-FFA (n) 166 162 150 165 143 144 130 114 78 81
Percent of Investigator CGI-I Scores, Clinically Meaningfuly Improvement
RCT-Placebo
RCT-FFA
2 6 10 14 1 2 3 4-6 7-9 10-12
RCT (Weeks)
OLE (Months)
RCT-Placebo (n) 87 84 80 80 78 74 78 65 51 48
RCT-FFA (n) 167 159 154 165 144 144 128 115 79 84

CGI-I, Clinical Global Impression – Improvement; FFA, fenfluramine; OLE, open-label extension; RCT, randomized controlled trial; RCT-FFA, patients randomized to any dose of fenfluramine 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; RCT, randomized controlled trial; RCT-FFA, patients randomized to any dose of fenfluramine 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 in RCT placebo-treated patients during the 14-week RCT period
  - 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 randomized to placebo exhibited numerical improvements in all efficacy outcomes analyzed following transition to the OLE and initiating FFA treatment
- The change in frequency of seizures associated with a fall in the RCT-Placebo group occurred during Month 1 of the OLE, confirming rapid onset of 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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Acknowledgements

UCB-sponsored. The authors acknowledge Tom Grant, PhD (UCB, Slough, UK), for managing the development of the poster, and Mari Willeman, PhD, and Scott Bergfeld, PhD, of PharmaWrite (Princeton, NJ) for writing assistance, which was funded by UCB.

Disclosures

RN: Research funding from Eisai, GW Pharma (now Jazz Pharmaceuticals), Novartis, Shire, UCB, and Zogenix Inc; consultant/advisor for Eisai, Biogen, GW Pharma (now Jazz Pharmaceuticals), Novartis, Shire, and Zogenix Inc (now a part of UCB); speaker for Advicenne, Eisai, BioMarin, GW Pharma (now Jazz Pharmaceuticals), Novartis, and Zogenix Inc (now a part of UCB). **OD:** Grant support from National Institute of Neurological Disorders and Stroke (NINDS), National Institute of Mental Health (NIMH), Multidisciplinary University Research Initiative (MURI), Centers for Disease Control and Prevention (CDC), and National Science Foundation (NSF); equity and/or compensation from Tilray, Receptor Life Sciences, Qstate Biosciences, Hitch Biosciences, Tevard Biosciences, Regel Biosciences, Script Biosciences, Actio Biosciences, Empatica, SilverSpike, and California Cannabis Enterprises (CCE); consulting fees from Zogenix, Ultragenyx, BridgeBio, GeneMedicine, and Marinus; patents for the use of cannabidiol in treating neurological disorders (owned by GW Pharmaceuticals, now Jazz Pharmaceuticals) for which he has waived any financial interests; other patents in molecular biology; managing partner of the PhiFundVentures. **LL:** Has received grants and is a consultant and/or speaker for Zogenix (now a part of UCB), LivaNova, UCB, Shire, Eisai, Novartis, Takeda/Ovid, NEL, and Epihunter. **IES:** Served on scientific advisory boards for BioMarin, Chiesi, Eisai, Encoded Therapeutics, GlaxoSmithKline, Knopp Biosciences, Nutricia, Rogcon, Takeda Pharmaceuticals, UCB, Xenon Pharmaceuticals; has received speaker honoraria from GlaxoSmithKline, UCB, BioMarin, Biocodex, Chiesi, Liva Nova and Eisai; has received funding for travel from UCB, Biocodex, GlaxoSmithKline, Biomarin and Eisai; has served as an investigator for Anavex Life Sciences, Cerebral Therapeutics, Cereval Therapeutics, Eisai, Encoded Therapeutics, EpiMinder Inc, Epygenyx, ES-Therapeutics, GW Pharma (now Jazz Pharmaceuticals), Marinus, Neurocrine BioSciences, Ovid Therapeutics, Takeda Pharmaceuticals, UCB, Ultragenyx, Xenon Pharmaceutical, Zogenix (now a part of UCB) and Zynerba; and has consulted for Atheneum Partners, Care Beyond Diagnosis, Epilepsy Consortium, Ovid Therapeutics, Stoke Therapeutics, Praxis, UCB, and Zynerba Pharmaceuticals; and is a Non-Executive Director of Bellberry Ltd. and a Director of the Australian Academy of Health and Medical Sciences. **RG:** Research grants, Zogenix (now a part of UCB) during conduct of the study; Speaker/Consultant, Zogenix (now a part of UCB), outside the submitted work; Investigator for studies with Biocodex, UCB, Angelini, and Eisai Inc; Speaker/Advisory Boards for Biocodex, Novartis, Biomarin, and GW Pharma (now Jazz Pharmaceuticals), outside the submitted work. **JS:** Research grants, Stoke, Marinus, Zogenix (now a part of UCB), Biopharm; Consultant/Advisor, Dravet Syndrome Foundation, Epygenix, Encoded, GW Pharma (now Jazz Pharmaceuticals), Asceneuron, Longboard Pharmaceuticals, Knopp Biosciences, Neurocrine; Stock options, Epygenix; Travel support, Zogenix (now a part of UCB); Reviewer, Epilepsy Study Consortium. **AGN:** Served on speaker bureau, advisory boards, or committees for Angelini Pharma, Bial, Biocodex, Eisai, Esteve, GW Pharma (now Jazz Pharmaceuticals), Oils 4 Cure, Pharvaris, PTC Therapeutics, Rapport Therapeutics, Stoke, UCB Pharma, and Zogenix (now a part of UCB). Has received research support from Biogen, Jazz Pharmaceuticals, PTC Therapeutics, and UCB Pharma. **SMZ:** Research support: Epilepsy Research UK, Dravet Syndrome UK, Zogenix (now a part of UCB). Consultancy, advisory and speaker support: GW Pharma (now Jazz Pharmaceuticals), Encoded Therapeutics, Stoke Therapeutics, Eisai, UCB, Jaguar Gene Therapy, Arvelle, Zogenix (now a part of UCB). **KR:** Honoraria for educational symposia, advisory boards, and/or consultancy work from Eisai, LivaNova, MedLink Neurology, Novartis, and UCB Australia. Her institution has supported clinical trials for Biogen Idec Research, DSLP, Eisai, Epigenyx Therapeutics, GW Research, Janssen-Cilag, Longboard Pharmaceuticals, Marinus Pharmaceuticals, Medicure International, LivaNova, Neurocrine Biosciences, Noema Pharma, Novartis, SK Lifesciences, Takeda Pharmaceutical Company Limited, UCB Australia, UCB Biopharma, and Zogenix (now a part of UCB). **PH, ML, JA, AL:** Employment/Stock Ownership: UCB. **KGK:** Research grants, Zogenix (now a part of UCB), Stoke, Encoded Therapeutics; consulting fees from Biomarin, Epygenix, and Biocodex; and other support as a Data and Safety Monitoring Board member from Greenwich Pharmaceuticals and Epygenix.

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American Epilepsy Society 78th Annual Meeting
Los Angeles, CA, USA | December 6–10, 2024