

Association of Fenfluramine Treatment and Everyday Executive Functioning in Adults With Lennox-Gastaut Syndrome

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Introduction

- Most adults with Lennox-Gastaut syndrome (LGS) exhibit moderate to severe intellectual disabilities.¹
- The Behavior Rating Inventory of Executive Functioning[®]—Adult Version (BRIEF[®]—A) is a rating scale validated for adults 18-90 years of age used in clinical practice to evaluate the caregiver's perspective of everyday executive function (EF),^{2,3} the ability to engage in goal-oriented problem solving, and to accomplish everyday tasks.^{4,5}
- A previous post hoc analysis of a 14-week Phase III randomized controlled trial (RCT; NCT0335209) of fenfluramine demonstrated improvements in adults aged 18-35 years with LGS treated with fenfluramine on everyday EF as assessed by the BRIEF[®]—A.⁶
- Fenfluramine dose groups (0.7 mg/kg/d, 0.2 mg/kg/d) were pooled.

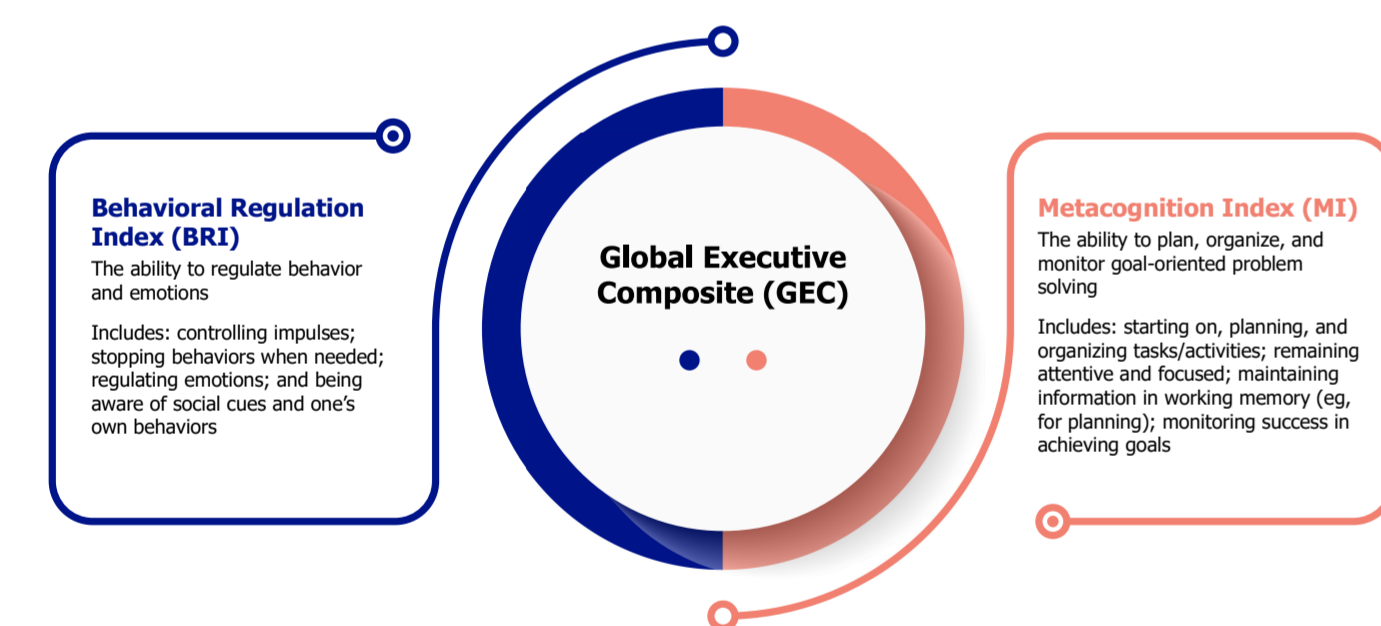
Objective

- In this post hoc analysis of the RCT and its open-label extension (OLE; final database lock), we describe fenfluramine-associated caregiver-reported changes in everyday EF by BRIEF[®]—A scores in adults with LGS.

Methods

- In the 14-week RCT, adults with LGS (2-35 years old) were randomized to receive fenfluramine 0.7 mg/kg/d (maximum [max] 26 mg/d), fenfluramine 0.2 mg/kg/d, or placebo.
- Adults who completed the RCT were eligible to enter the OLE.
 - Adults were transitioned to fenfluramine 0.2 mg/kg/d and flexibly titrated up to 0.7 mg/kg/d (max, 26 mg/d) based on effectiveness and tolerability after Month 1.
- In this post hoc analysis, adults (18-35 years old) with caregiver-completed BRIEF[®]—A at baseline and:
 - RCT end of study (EOS; Day 99) were included in the RCT analyses.
 - OLE Month 12 were included in the OLE analyses.
- BRIEF[®]—A Indexes/Composite include the Behavioral Regulation Index (BRI), Metacognition Index (MI), and Global Executive Composite (GEC) (Figure 1).

Figure 1. BRIEF[®]—A Indexes/Composite



- BRIEF[®]—A raw scores were transformed into T-scores (mean ± SD: 50 ± 10) based on a normative sample according to the Professional Manual.¹
- Higher BRIEF[®]—A T-scores are associated with greater caregiver-perceived impairment in executive EF.
- BRIEF[®]—A T-scores ≥65 (T≥65) are clinically significant and suggest difficulties in everyday EF.²
- Median changes in BRIEF[®]—A T-scores from baseline to RCT EOS and OLE Month 12 for the BRI, MI, and GEC were calculated.
- Reliable Change Indexes (RCIs) were used to determine clinically meaningful improvement (RCI≥90% certainty) and worsening (RCI≥80% certainty) in T-scores from baseline.
- Spearman's correlations were conducted to examine the relationships between change in BRIEF[®]—A T-scores and seizures associated with a fall per 28 days.
- The percentage of adults with T≥65 at baseline was compared with that at RCT EOS and OLE Month 12.

Results

- Data from 67 adults with LGS from the RCT (fenfluramine 0.7 mg/kg/d, max 26 mg/d, n=18; fenfluramine 0.2 mg/kg/d, n=24; placebo, n=25; Table 1) were evaluated.
- In the OLE, 41/67 adults with LGS were included (fenfluramine mean daily dose [MDD] ≥0.3 mg/kg/d, n=22; fenfluramine MDD <0.3 mg/kg/d, n=19).

BRIEF[®]—A T-SCORES AND CHANGE IN SEIZURES ASSOCIATED WITH A FALL

- Median changes in T-scores for all BRIEF[®]—A Indexes/Composite indicated improvement or no change in RCT fenfluramine groups and in the OLE, but worsening in the placebo group (Figure 2, Table 2).
- A significantly greater percentage of adults treated with fenfluramine (pooled) improved on MI (p=0.0053) and GEC (p=0.0187) vs placebo.
- A significantly lower percentage of adults treated with fenfluramine (pooled) worsened on MI (p=0.0234) and GEC (p=0.0284) vs placebo.

QUESTION

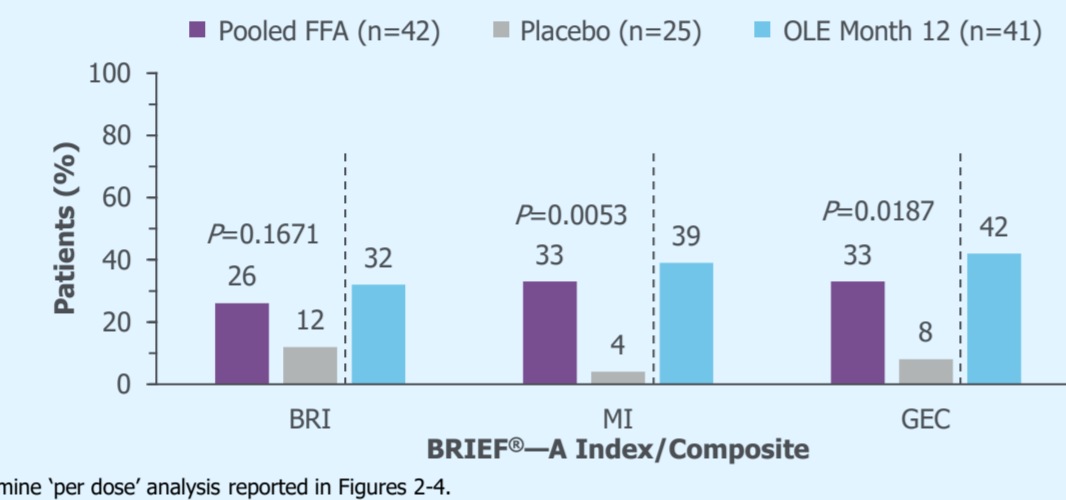
- Does treatment with fenfluramine in adults with LGS improve everyday caregiver-reported EF?
- Is there a relationship between change in frequency of seizures associated with a fall and change in everyday EF in adults?

INVESTIGATION

- In this post hoc analysis of an RCT and its OLE evaluating fenfluramine in the treatment of adults with LGS, everyday EF was examined via the BRIEF[®]—A Indexes/Composite: BRI, MI, and GEC.
- Adults with LGS in the study were rated on the BRIEF[®]—A by caregivers; T-scores from baseline, end of RCT (n=67), and OLE Month 12 (n=41) were used.
- The percentages of adults with clinically meaningful improvement/worsening and their relationships with change in frequency of seizures associated with a fall per 28 days were evaluated.
- The percentage of adults with T≥65 (a clinically significant score suggesting difficulties in everyday EF) at baseline, end of RCT, and OLE Month 12 was summarized.

RESULTS

A greater percentage of adults with LGS treated with fenfluramine showed clinically meaningful improvement (RCI≥90%) on BRIEF[®]—A Indexes/Composite vs adults in the placebo group at end of RCT



CONCLUSIONS

- A greater percentage of adults with LGS treated with fenfluramine during the RCT showed clinically meaningful improvement on everyday EF vs adults in the placebo group.
- These improvements were observed with a nominal increase from the RCT at OLE Month 12.
- Change in everyday frequency of seizures associated with a fall was not correlated with caregiver-reported EF, suggesting partially independent outcomes.
- The percentage of adults treated with fenfluramine who had caregiver-reported improvements on everyday EF suggest non-seizure benefits of fenfluramine in everyday life.

Abbreviations: BRI, Behavioral Regulation Index; BRIEF[®]—A, Behavior Rating Inventory of Executive Functioning[®]—Adult Version; EF, executive functioning; FFA, fenfluramine; GEC, Global Executive Composite; EOS, end of study; LGS, Lennox-Gastaut syndrome; MI, Metacognition Index; OLE, open-label extension; RCI, Reliable Change Index; RCT, randomized clinical trial; T≥65, T-score ≥65.

Overview

Correlations between change in seizures associated with a fall per 28 days and change in BRIEF[®]—A Indexes/Composite were negligible to moderate

	RCT POOLED FFA (n=42)	RCT PLACEBO (n=25)	OLE POOLED (n=41)
Change in number of seizures associated with a fall per 28 days, median (range)	-13.1 (-854.5 to 254.9)	-6.6 (-151.9 to 30.3)	-20.1 (-1194.2 to 36.8)
Change in BRI T-score, median (range)	-1 (-30 to 38)	2 (-10 to 22)	-2 (-30 to 37)
Correlation, ρ	-0.004	-0.126	-0.206
Change in MI T-score, median (range)	-1 (-47 to 48)	2 (-9 to 45)	-1 (-46 to 50)
Correlation, ρ	-0.101	0.178	-0.206
Change in GEC T-score, median (range)	-0.5 (-38 to 47)	2 (-7 to 37)	-2 (-37 to 48)
Correlation, ρ	-0.081	0.024	-0.239

The percentage of adults with LGS and T≥65 decreased on the MI and GEC following treatment with fenfluramine (pooled) and increased in the placebo group

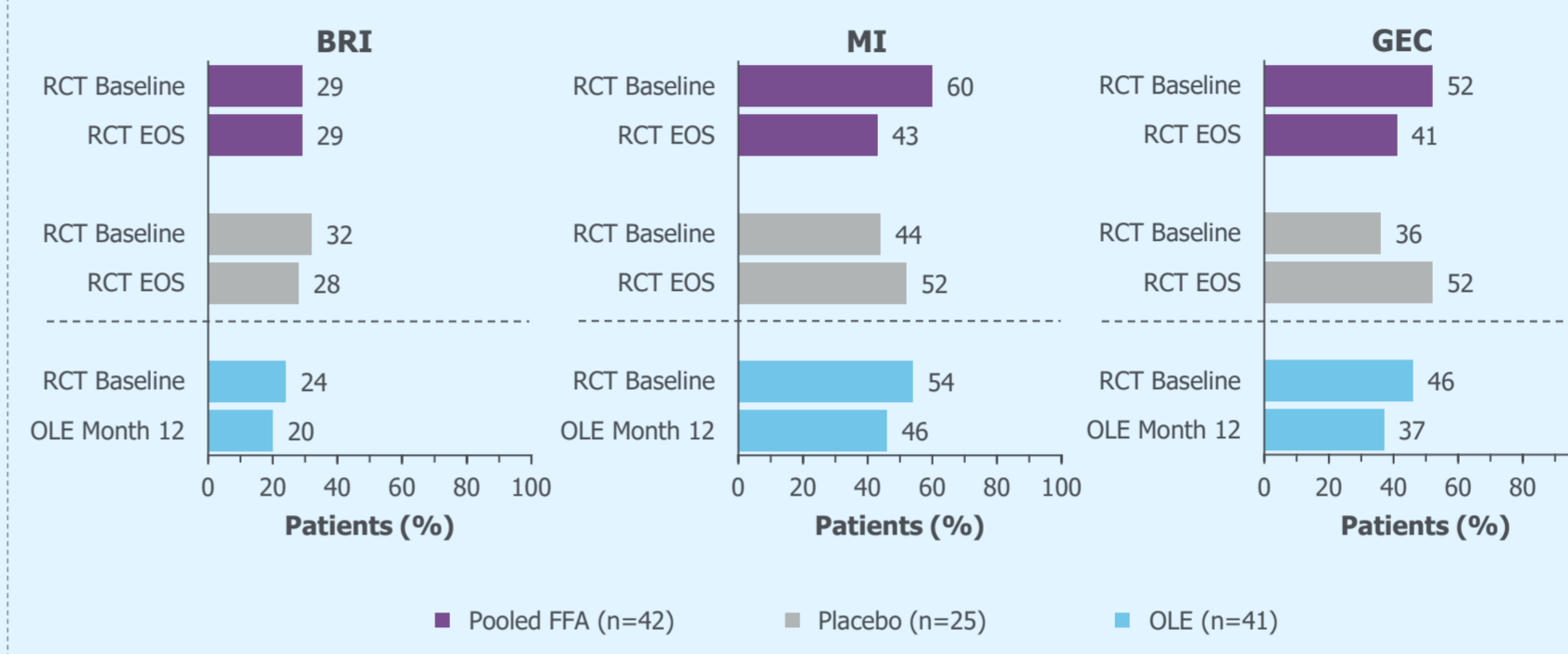


Figure 2. Percentage of adults with clinically meaningful improvement (RCI≥90%) on BRIEF[®]—A Indexes/Composite at A. RCT EOS (Day 99, n=67) and B. OLE Month 12 (n=41) – by fenfluramine dose

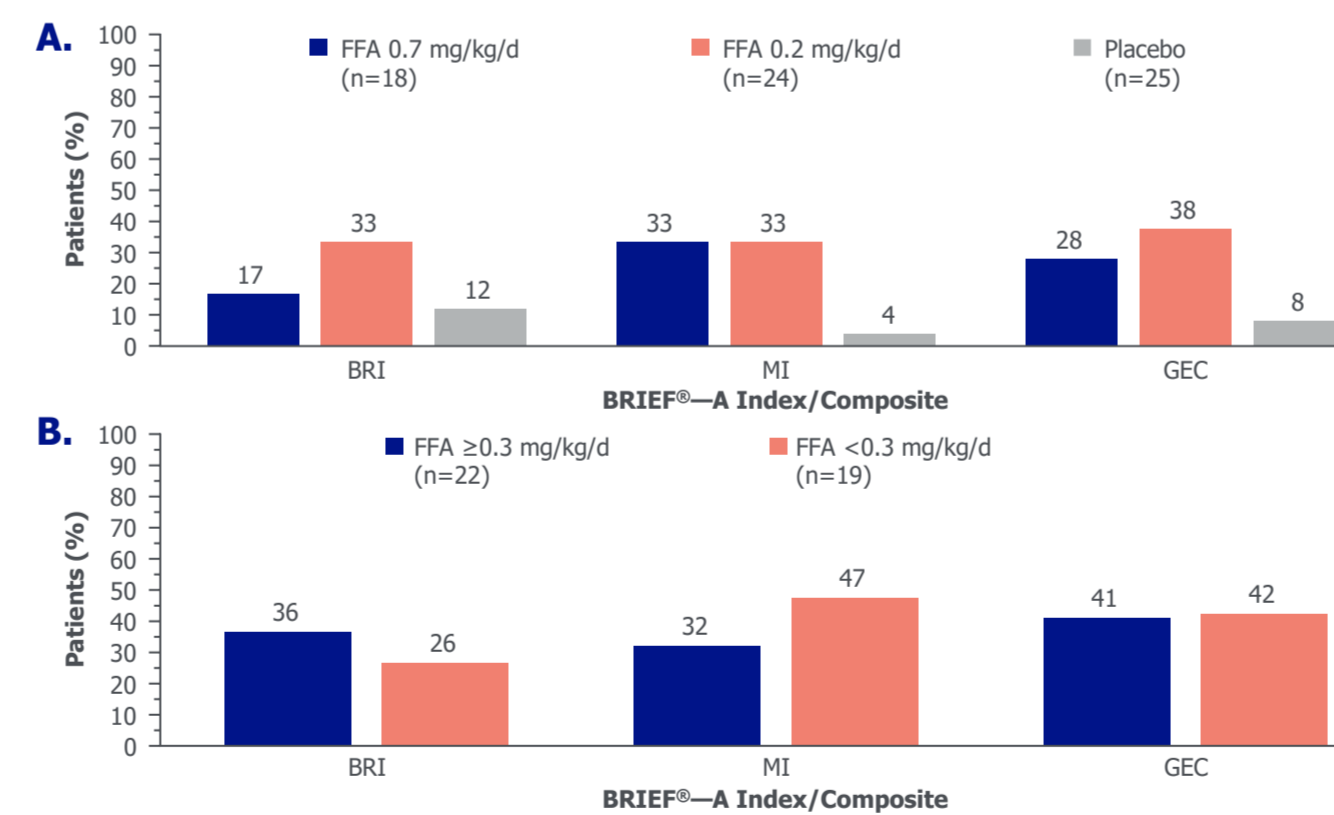


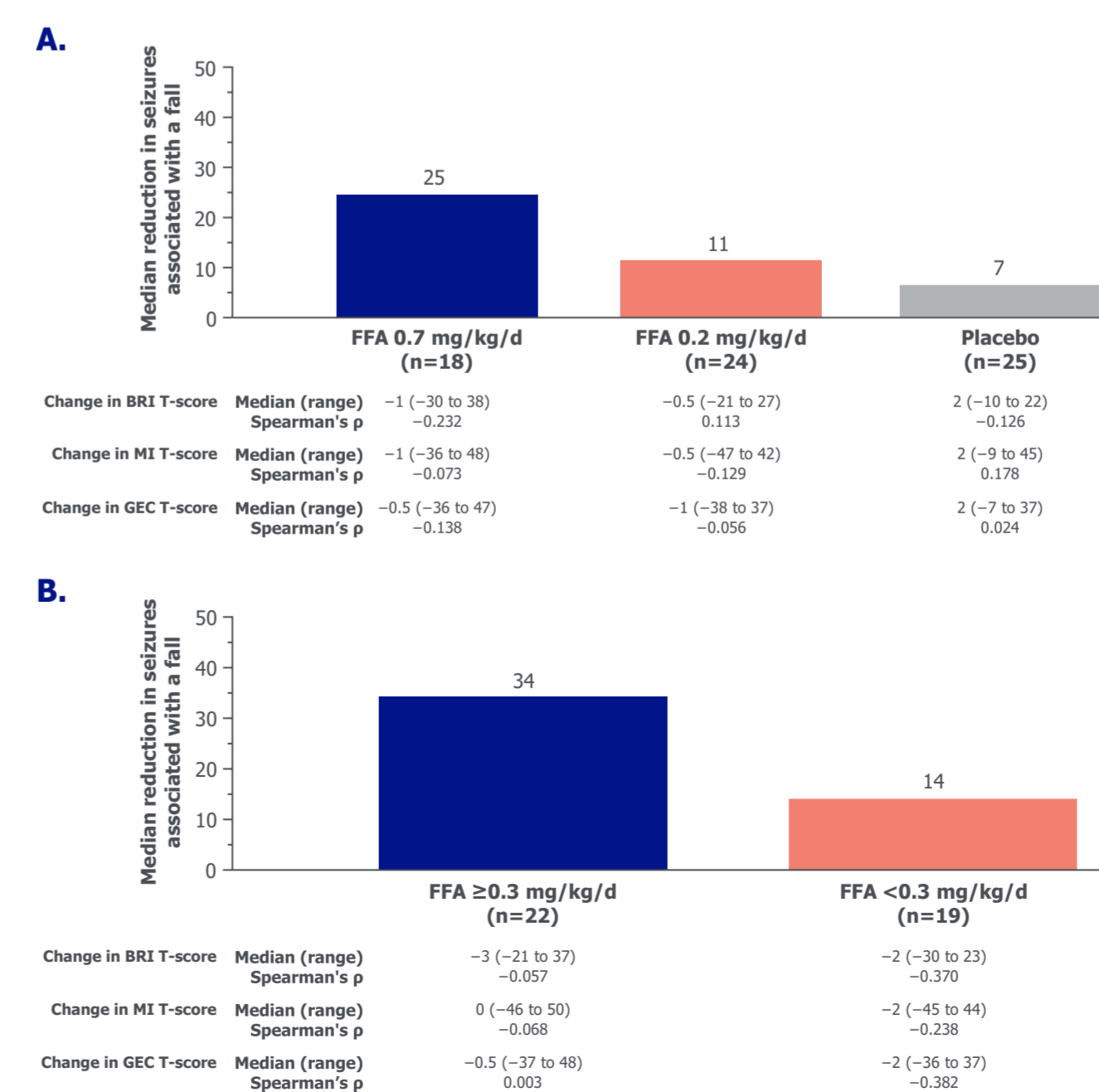
Table 2. Proportions of adults with LGS showing clinically meaningful worsening (RCI≥80%) on BRIEF[®]—A indexes/composite T-scores from RCT baseline

	RCT (n=67)				OLE (n=41)	
	FFA 0.7 mg/kg/d (n=18)	FFA 0.2 mg/kg/d (n=24)	POOLED FFA (n=42)	PLACEBO (n=25)	FFA MDD ≥0.3 mg/kg/d (n=22)	FFA MDD <0.3 mg/kg/d (n=19)
BRI, n (%)	4 (22.2)	7 (29.2)	11 (26.2) P=0.6099 ^a	8 (32)	5 (22.7)	5 (26.3)
MI, n (%)	5 (27.8)	4 (16.7)	9 (21.4) P=0.0234 ^a	12 (48)	5 (22.7)	4 (21.1)
GEC, n (%)	4 (22.2)	4 (16.7)	8 (19) P=0.0284 ^a	11 (44)	5 (22.7)	3 (15.8)

^aP value is the result of a chi-squared test, vs placebo.
 BRI, Behavioral Regulation Index; BRIEF[®]—A, Behavior Rating Inventory of Executive Functioning[®]—Adult Version; FFA, fenfluramine; GEC, Global Executive Composite; LGS, Lennox-Gastaut syndrome; MDD, mean daily dose; MI, Metacognition Index; OLE, open-label extension; RCI, Reliable Change Index; RCT, randomized controlled trial.

- Correlations between change in frequency of seizures associated with a fall and BRIEF[®]—A Indexes/Composite were negligible to weak (Figure 3).

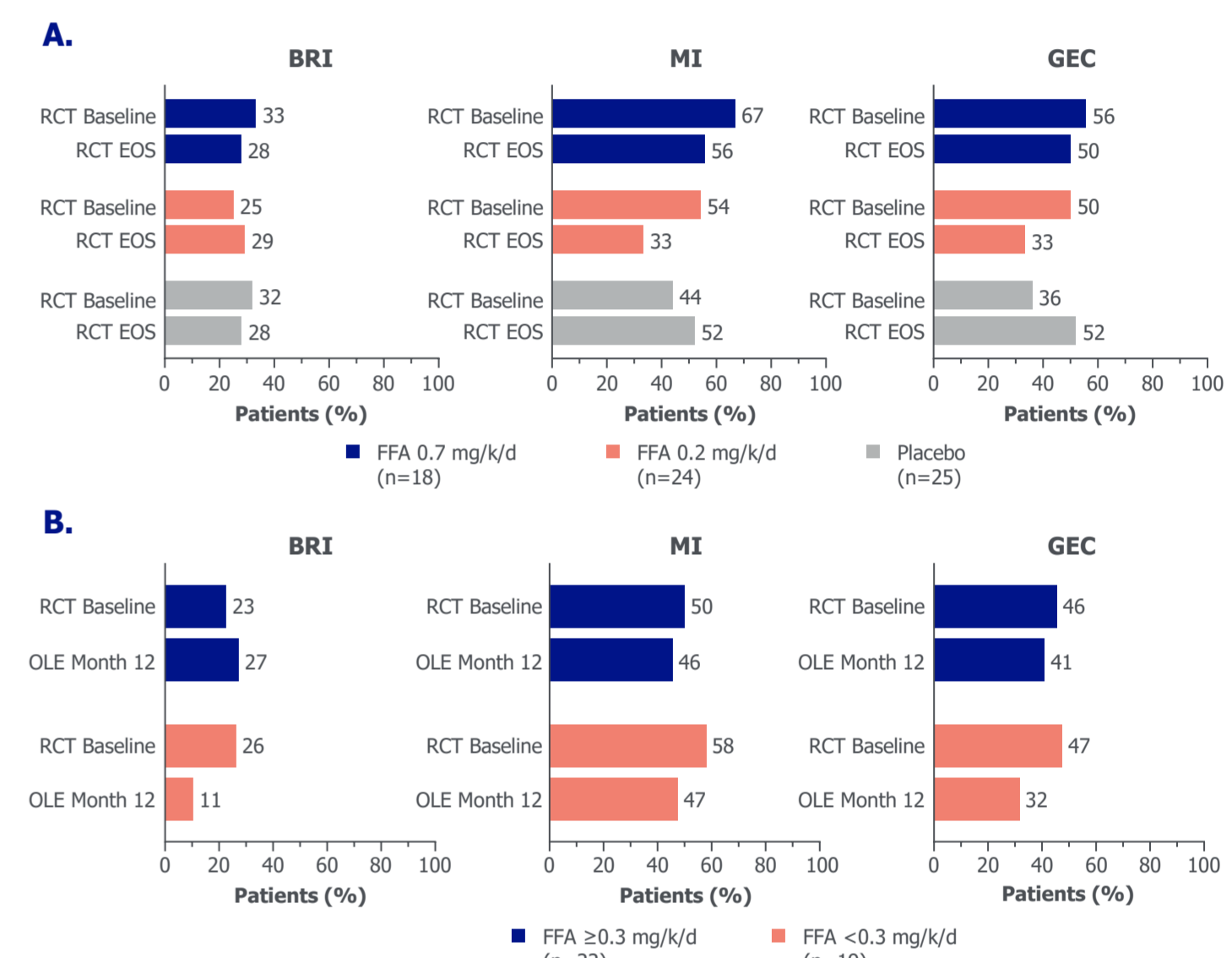
Figure 3. Median reduction in frequency of seizures associated with a fall per 28 days and correlation with T-scores in adults at A. RCT EOS (Day 99, n=67) and B. OLE Month 12 (n=41) – by fenfluramine dose



CLINICALLY SIGNIFICANT SCORES

- The percentage of adult patients with T≥65 decreased from baseline to RCT EOS on all Indexes/Composite with fenfluramine treatment and increased on MI and GEC in the placebo group (Figure 4A).
- In the OLE, the percentage of adults with T≥65 treated with fenfluramine MDD <0.3 mg/kg/d decreased on all Indexes/Composite (Figure 4B).

Figure 4. Percentage of adults with T≥65 on BRIEF[®]—A Indexes/Composite at RCT baseline and at A. RCT EOS (Day 99, n=67) and B. OLE Month 12 (n=41) – by fenfluramine dose



Higher T-scores are associated with greater impairment in everyday EF. Scores of T≥65 are clinically elevated and associated with potential difficulties. BRI, Behavioral Regulation Index; BRIEF[®]—A, Behavior Rating Inventory of Executive Functioning[®]—Adult Version; EF, executive functioning; EOS, end of study; FFA, fenfluramine; GEC, Global Executive Composite; MI, Metacognition Index; OLE, open-label extension; RCT, randomized controlled trial; T≥65, T-score ≥65.

Conclusions

- In this post hoc analysis, clinically meaningful improvements in everyday EF were reported by a significantly greater percentage of caregivers to adults with LGS treated with fenfluramine at the end of the RCT (Day 99) compared with those in the placebo group.
- Improvements were reported at OLE Month 12 in up to 47% (MI) of adults with LGS.
- The percentage of adults with clinically significant scores in everyday EF on the BRIEF[®]—A decreased following fenfluramine treatment at RCT Day 99 and OLE Month 12.
- There were no strong correlations between reductions in seizures associated with a fall per 28 days and everyday caregiver-reported EF, suggesting that everyday EF improvements were not secondary to improved seizure outcomes.

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