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Fenfluramine-Associated Changes in Everyday Executive Functioning in Paediatric Patients With Lennox-Gastaut Syndrome: Post Hoc Analysis of a Phase III Trial

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Introduction and Objective

- Lennox-Gastaut syndrome (LGS) is a developmental and epileptic encephalopathy characterised by multiple types of treatment-resistant seizures, electroencephalogram abnormalities, neurodevelopmental delay, and profound cognitive and often behavioural impairments^{1,2}
- In addition to seizure control, reducing impairments in executive functioning is among the outcomes that matter most to patients with LGS and their caregivers³
 - A post hoc analysis of adults (18-35 years of age) with LGS in a randomised controlled trial and its open-label extension demonstrated caregiver-reported improvement in everyday executive functioning, as measured by the Behavior Rating Inventory of Executive Functioning®—Adult Version (BRIEF®-A), following fenfluramine treatment⁴
 - A separate post hoc analysis of data from the same study suggested fenfluramine may improve caregiver-perceived everyday executive functioning in some preschool-aged children (2 to <6 years) with LGS, as measured by the BRIEF®—Preschool Version (BRIEF®-P); however, larger studies are needed to better characterise the effects of fenfluramine⁵

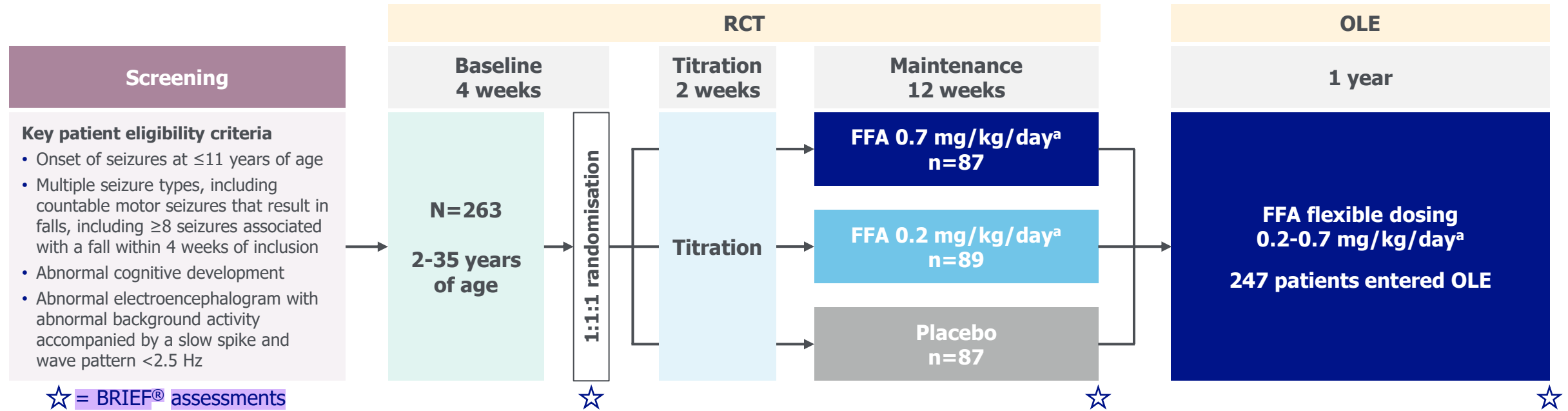
Here, we describe everyday executive functioning changes associated with fenfluramine treatment in school-age children with LGS

1. Cross JH, et al. *Front Neurol* 2017;8:505. 2. Specchio N, et al. *Epilepsia* 2022;63(6):1398-1442. 3. Kerr M, et al. *Epileptic Disord* 2011;13(suppl 1):S15-S26.

4. Breuillard D, et al. American Epilepsy Society 79th Annual Meeting 2025; Abstract 2.43. 5. Breuillard D, et al. 19th International Child Neurology Congress 2026; Abstract #847.

BRIEF®-A, Behavior Rating Inventory of Executive Functioning®—Adult Version; BRIEF®-P, Behavior Rating Inventory of Executive Functioning®—Preschool Version; LGS, Lennox-Gastaut syndrome.

Study Design¹



- In the 14-week RCT (EP0214; NCT03355209), patients with LGS (2-35 years of age) were randomised to receive fenfluramine 0.7 mg/kg/day (maximum 26 mg/day), fenfluramine 0.2 mg/kg/day, or placebo
- Patients who completed the RCT were eligible to enter the OLE
 - Patients who received placebo in the RCT transitioned to fenfluramine 0.2 mg/kg/day and flexibly titrated up to 0.7 mg/kg/day (maximum 26 mg/day) based on effectiveness and tolerability after month 1

1. Knupp KG, et al. *JAMA Neurol* 2022;79(6):554-564.

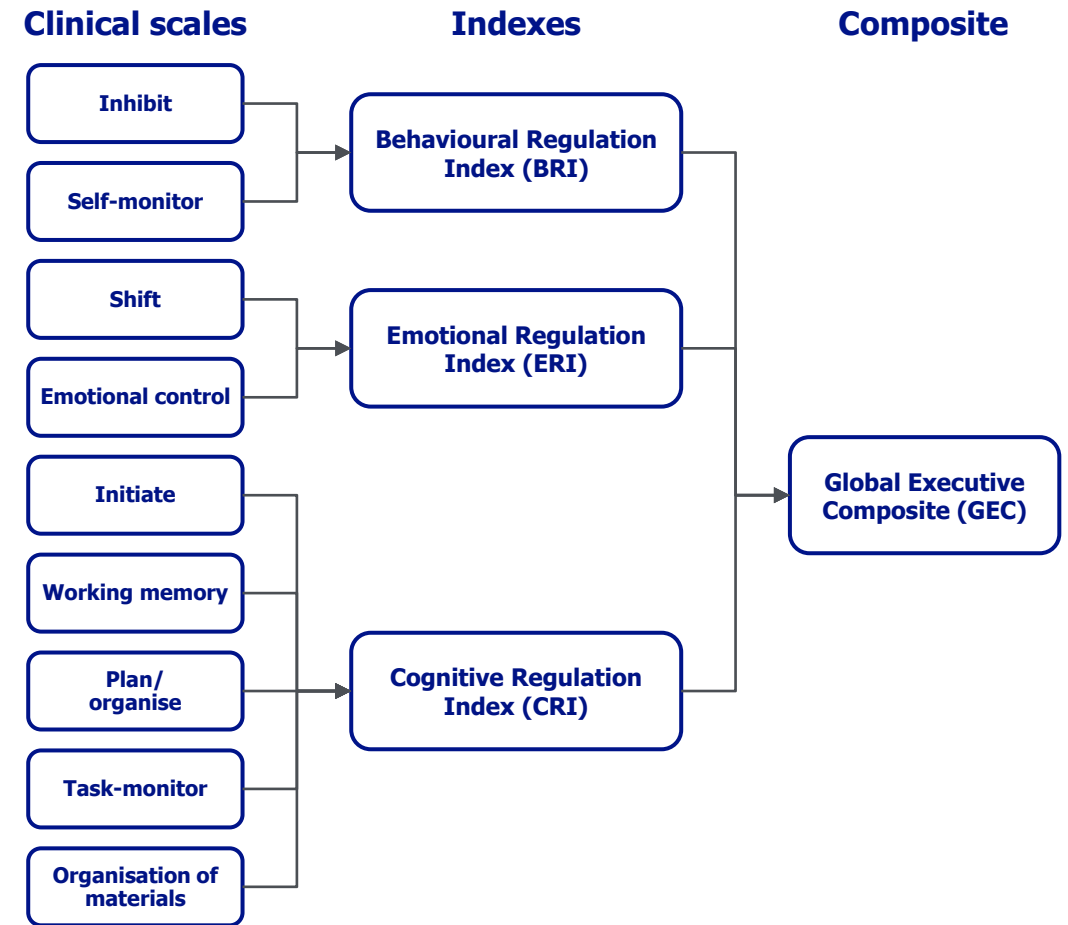
^aMaximum 26 mg/day.

BRIEF[®], Behavior Rating Inventory of Executive Functioning[®]; FFA, fenfluramine; LGS, Lennox-Gastaut syndrome; OLE, open-label extension; RCT, randomised controlled trial.

Analysis

- In this post hoc analysis, paediatric patients (6-18 years of age) with caregiver-completed BRIEF® at RCT baseline and:
 - RCT end of study (day 99) were included in the RCT analyses
 - OLE month 12 were included in the OLE analyses
- BRIEF® data were mapped to BRIEF®, Second Edition (BRIEF®-2) scores for analysis
 - Data are presented for Behavioural Regulation Index, Emotional Regulation Index, Cognitive Regulation Index, and Global Executive Composite (GEC)
 - The GEC provides a summary measure incorporating all 9 scales
- BRIEF®-2 raw scores were transformed into T-scores based on a normative sample according to the Professional Manual¹
 - Higher BRIEF®-2 T-scores are associated with greater caregiver-perceived impairment in everyday executive functioning
 - BRIEF®-2 T-scores ≥ 65 are defined as potentially clinically significant and suggest difficulties in everyday executive functioning²
- Reliable change indexes (RCIs) were used to determine clinically meaningful improvement (RCI $\geq 90\%$ certainty) and worsening (RCI $\geq 80\%$ certainty) in T-scores from baseline
 - Somers' D was used to assess associations between treatment and clinically meaningful improvement (p-values are nominal)

Behaviour Rating Inventory of Executive Function®-2 (BRIEF®-2)



Demographics and Baseline Characteristics

- In the RCT, 138 patients had caregiver-completed BRIEF® assessments at baseline and end of study^a
- 58 patients had caregiver-completed BRIEF® assessments at RCT baseline and OLE month 12

	RCT (n=138)			OLE (n=58)	
	FFA 0.7 mg/kg/day (n=46)	FFA 0.2 mg/kg/day (n=42)	Placebo (n=50)	FFA MDD ≥0.6 mg/kg/day (n=23)	FFA <0.6 mg/kg/day (n=35)
Age, mean (SD), years	12.2 (3.5)	12.6 (3.7)	12.0 (3.4)	11.0 (3.1) ^b	13.0 (3.4) ^b
Female, n (%)	17 (37)	18 (43)	27 (54)	12 (52)	18 (51)
Weight, mean (SD), kg	40.3 (15.7)	43.2 (15.9)	39.9 (14.8)	32.0 (7.6) ^b	44.4 (16.7) ^b
Baseline frequency of seizures associated with a fall ^c per 28 days, median (range)	59.5 (6.5-893.0)	61.5 (5.0-1142.0)	40.0 (4.0-1495.4)	77.0 (4.0-1495.4)	44.0 (11.0-555.0)

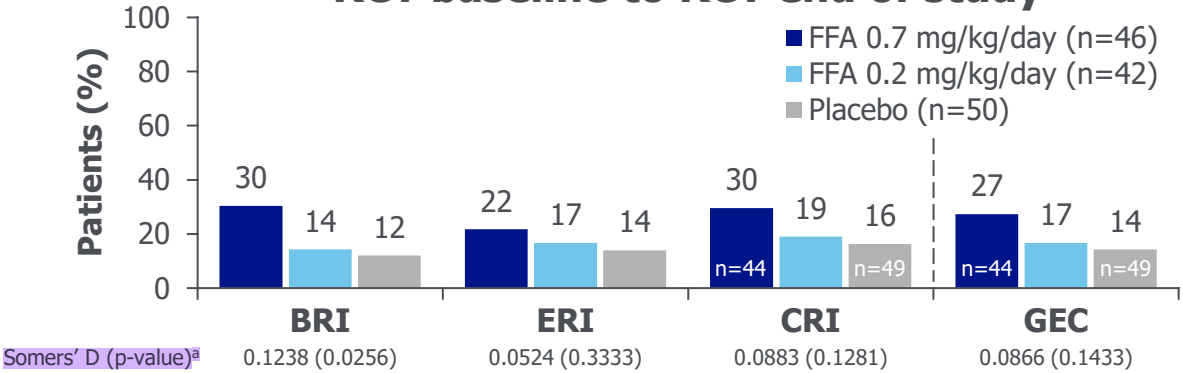
- Patients receiving FFA 0.7 mg/kg/day, FFA 0.2 mg/kg/day, and placebo had a median of 7 prior ASMs^d

^aThe BRIEF® version administered at randomisation was used at all subsequent study visits, regardless of changes in the patient’s age; ^bAt entry into the OLE; ^cIncludes atonic, tonic, tonic/tonic, generalised tonic-clonic, and secondarily generalised tonic-clonic seizures resulting in falls; ^dASMs with a stop date prior to the first randomised dose in the RCT.
ASM, antiseizure medication; BRIEF®, Behavior Rating Inventory of Executive Functioning®; FFA, fenfluramine; MDD, mean daily dose; OLE, open-label extension; RCT, randomised controlled trial; SD, standard deviation.

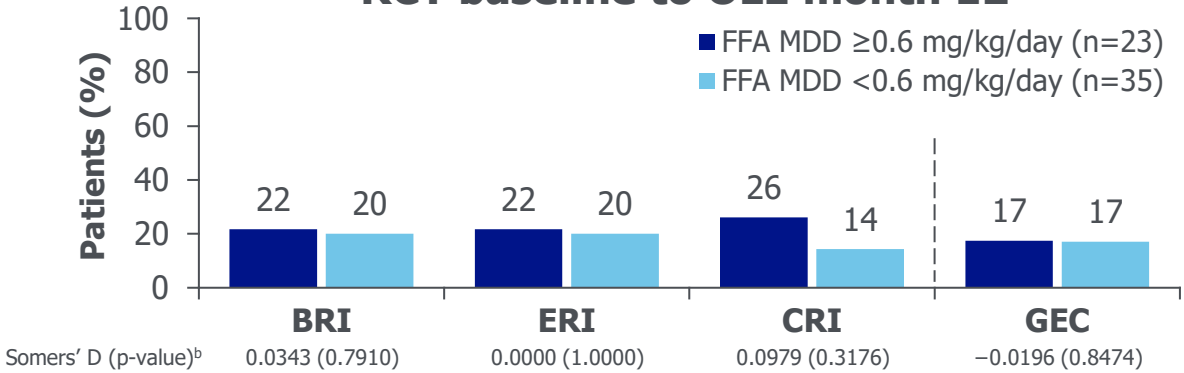
Percentage of Patients With Clinically Meaningful Improvement (RCI ≥90%) on BRIEF®-2 Indexes/Composite

- A clinically meaningful improvement in GEC was reported in:
 - 27%, 17%, and 14% of patients receiving FFA 0.7 mg/kg/day, FFA 0.2 mg/kg/day, and placebo, respectively, at RCT end of study
 - 17% of patients in each FFA dose group at OLE month 12

RCT baseline to RCT end of study



RCT baseline to OLE month 12



Percentage of patients with clinically meaningful worsening (RCI ≥80%) on BRIEF®-2 indexes/composite

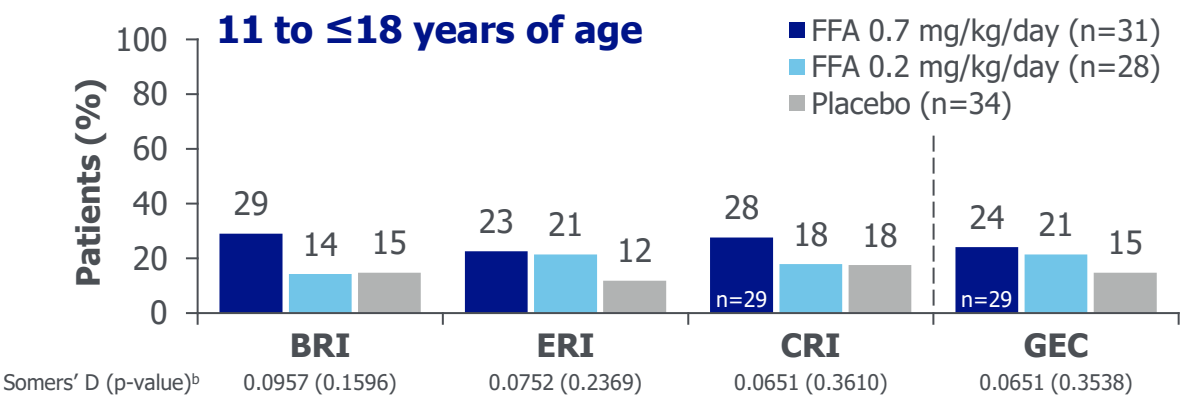
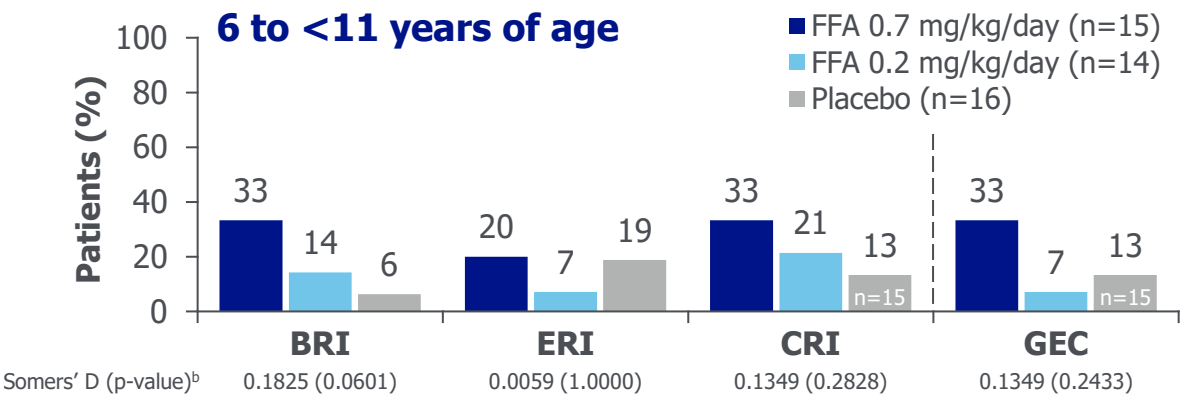
Patients, n (%)	RCT baseline to RCT end of study				RCT baseline to OLE month 12		
	FFA 0.7 mg/kg/day (n=46)	FFA 0.2 mg/kg/day (n=42)	Placebo (n=50)	Somers' D (p-value) ^a	FFA MDD ≥0.6 mg/kg/day (n=23)	FFA MDD <0.6 mg/kg/day (n=35)	Somers' D (p-value) ^b
BRI	9 (20)	10 (24)	13 (26)	-0.0436 (0.4529)	8 (35)	6 (17)	0.1861 (0.0689)
ERI	8 (17)	8 (19)	11 (22)	-0.0316 (0.5791)	2 (9)	9 (26)	-0.1665 (0.0765)
CRI	8 (18) ^c	8 (19)	8 (16) ^d	0.0132 (0.8517)	4 (17)	12 (34)	-0.1420 (0.1751)
GEC	10 (23) ^c	12 (29)	10 (20) ^d	0.0181 (0.7469)	6 (26)	11 (31)	-0.0588 (0.6422)

^aSomers' D assessing association between treatment group and clinically meaningful improvement (p-values are nominal); ^bSomers' D assessing association between MDD group and clinically meaningful improvement (p-values are nominal); ^cn=44; ^dn=49. BRI, Behavioural Regulation Index; BRIEF®-2, Behavior Rating Inventory of Executive Functioning®, Second Edition; CRI, Cognitive Regulation Index; ERI, Emotional Regulation Index; FFA, fenfluramine; GEC, Global Executive Composite; MDD, mean daily dose; OLE, open-label extension; RCI, reliable change index; RCT, randomised controlled trial.

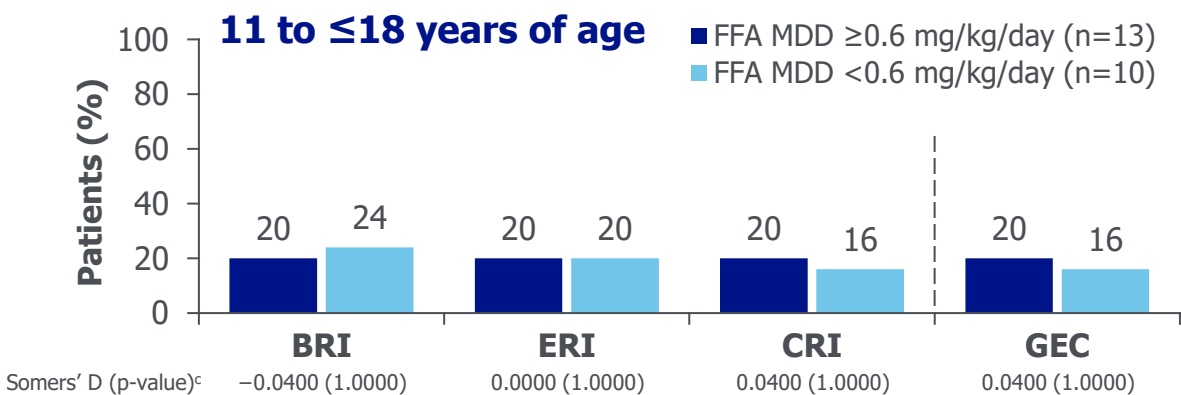
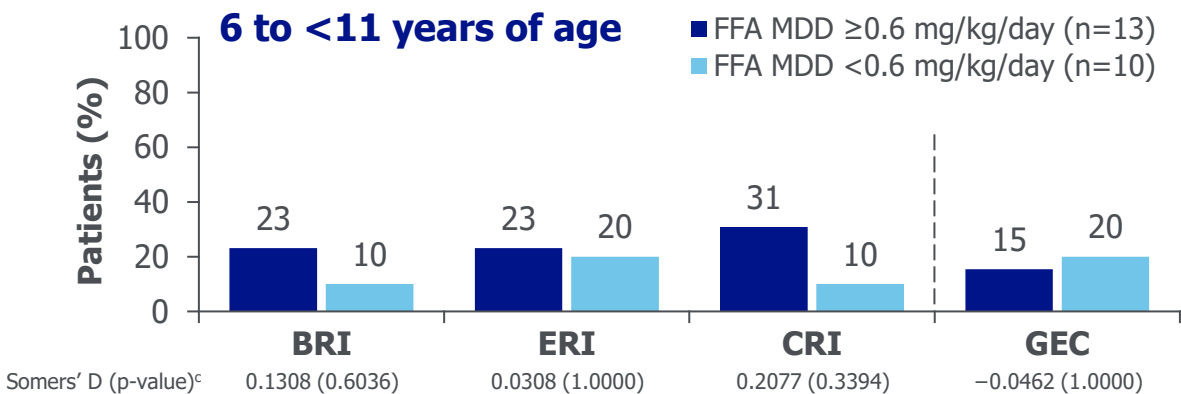
Percentage of Patients With Clinically Meaningful Improvement (RCI ≥90%) on BRIEF®-2 Indexes/Composite – Subgroup Analysis

- Changes in everyday executive functioning were consistent across subgroups defined by patient age^a at RCT entry

RCT baseline to RCT end of study



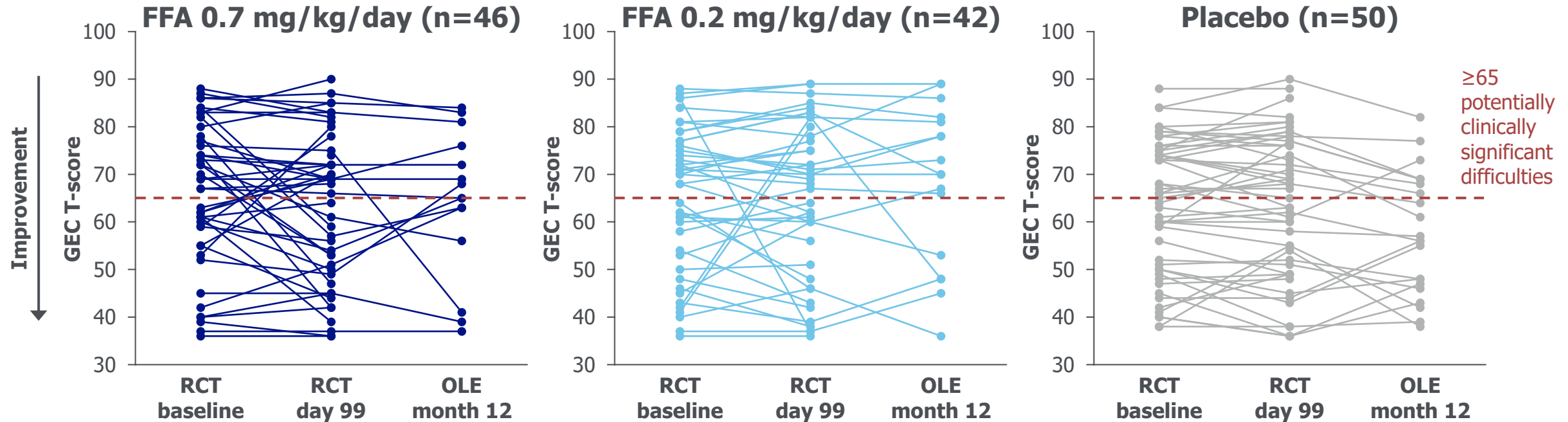
RCT baseline to OLE month 12



^aThe 6 to <11 years and 11 to ≤18 years age groups were selected due to the developmental transition associated with adolescence, which is accompanied by biological and psychological changes and during which environmental expectations increase, potentially making age-related differences in executive function more apparent; ^bSomers' D assessing association between treatment group and clinically meaningful improvement (p-values are nominal); ^cSomers' D assessing association between MDD group and clinically meaningful improvement (p-values are nominal).
 BRI, Behavioural Regulation Index; BRIEF®-2, Behavior Rating Inventory of Executive Functioning®, Second Edition; CRI, Cognitive Regulation Index; ERI, Emotional Regulation Index; FFA, fenfluramine; GEC, Global Executive Composite; MDD, mean daily dose; OLE, open-label extension; RCI, reliable change index; RCT, randomised controlled trial.

Individual Patient Trajectories on BRIEF®-2 GEC T-Scores

- Individual **patient trajectories** of GEC T-scores showed variable responses, with both improvements and worsening observed over time



Correlations of BRIEF®-2 T-Scores With Seizure Frequency

- Correlations between change in BRIEF®-2 index/composite T-scores and change in the frequency of seizures associated with a fall were negligible

RCT end of study is defined as day 99 of the RCT. Higher T-scores on the BRIEF®-2 are associated with greater caregiver-perceived impairment on everyday executive functioning.

BRIEF®-2 T-scores ≥65 are defined as potentially clinically significant and suggest difficulties in everyday executive function.

BRIEF®-2, Behavior Rating Inventory of Executive Functioning®, Second Edition; FFA, fenfluramine; GEC, Global Executive Composite; OLE, open-label extension; RCT, randomised controlled trial.

Conclusions

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- Published literature indicates that patients with LGS experience developmental slowing, plateauing, or regression over time¹; consequently, BRIEF®-2 scores in school-age children (6-18 years of age) are also expected to progressively worsen
- In this post hoc analysis, 14-30% of children aged 6-18 years with LGS experienced clinically meaningful improvement in everyday executive functioning with fenfluramine, suggesting potential beneficial effects despite the expected regression over time
 - Similar effects on executive functioning were observed in both the 6 to <11 years and 11 to ≤18 years age groups
 - In the RCT, clinically meaningful improvement across multiple executive functioning indices/composites was more common with the higher fenfluramine dose, suggesting a potential dose-response relationship; however, this pattern was not observed in the OLE
 - Worsening of executive functioning was also observed across all dose groups, highlighting the complexity of the evolution of these outcomes
- Limitations of these analyses include their post hoc nature and the small sample size
- Further investigation is needed to better understand the effects of fenfluramine on executive function in patients with LGS

1. Specchio N, et al. *Epilepsia* 2022;63(6):1398-1442.

BRIEF®-2, Behavior Rating Inventory of Executive Functioning®, Second Edition; LGS, Lennox-Gastaut syndrome; OLE, open-label extension; RCT, randomised controlled trial.