



Fenfluramine Treatment Improves Everyday Executive Functioning in Patients With Lennox-Gastaut Syndrome: Analysis From a Phase 3 Clinical Trial

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Disclosures

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- Drs. Isquith and Gioia are associate consultants of Global Pharma Consultancy, LLC, which has received consultancy fees from Zogenix for research support; receives royalties from Psychological Assessment Resources (PAR, Inc.) for sale of the BRIEF® instruments.
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Introduction

- Lennox-Gastaut syndrome (LGS)¹⁻⁴
 - Treatment-resistant developmental and epileptic encephalopathy with high seizure burden
 - Associated with profound cognitive and neurodevelopmental impairment from seizures, underlying pathology, and antiseizure medications (ASMs)
- Assessing neurodevelopmental outcomes
 - Intellectual functioning and adaptive behavior deficits⁵
 - Executive function^{6,7}
- The Behavior Rating Inventory of Executive Function (BRIEF[®])
 - Most widely used validated rating scale for measuring executive function⁸
 - Designed to evaluate behavior regulation, emotion regulation, and cognitive regulation
 - Used to assess executive function in intractable epilepsy conditions⁹

Fenfluramine Treatment for Dravet Syndrome and LGS: Use of the BRIEF[®]2 to Assess Executive Function

- In Phase 3 studies and open-label extension studies, fenfluramine was shown to:
 - Significantly reduce convulsive seizure frequency in children and young adults with Dravet syndrome¹⁰⁻¹²
 - Be associated with improved everyday executive function at 14 weeks¹⁰ and at 1 year¹⁴ (open-label extension)
- Fenfluramine acts at 5-HT receptors and sigma-1 receptors affecting executive function^{15,16}
- In an LGS randomized clinical trial, fenfluramine reduced the frequency of seizures associated with a drop and generalized tonic-clonic seizures in patients aged 2 to 35 years¹⁷

Objective: To use the BRIEF[®]2 indexes and global executive composite to determine whether fenfluramine treatment improves everyday executive function in a 14-week RCT of children and young adults with LGS

Study Design

- Randomized clinical trial of fenfluramine for LGS (NCT03355209)¹⁷
 - N=263 patients with LGS aged 2-35 years
 - Prior antiseizure medications: mean, 7-8 (range: 1-20)
 - Concomitant antiseizure medications: mean, 3 (range: 1-5)
- Treatment schedule
 - 4-week baseline, then randomization to placebo or fenfluramine (0.2 or 0.7 mg/kg/day) for a combined 14-week titration and maintenance period
- BRIEF[®] Assessments
 - Age-appropriate versions of the BRIEF[®] Parent Form were completed by parents or caregivers at baseline and end of study
 - BRIEF[®] Parent Form was completed for 163 subjects aged 6-18 years
 - 137 individuals had both baseline and end-of-study BRIEF[®] assessments

Assessment of Executive Functions: Use of the BRIEF[®]2⁸

BRIEF [®] 2 Index/ Composite	Real-World Examples	RCI ≥95% ^a
Behavior Regulation Index (BRI)	Impulsive and socially intrusive <ul style="list-style-type: none"> • Controlling impulses • Stopping behavior when needed • Acknowledging how one’s behavior affects others 	9-11 points
Emotion Regulation Index (ERI)	Inflexible and not adaptive to new things, people, or situations and/or having strong emotional outbursts <ul style="list-style-type: none"> • Regulating or modulating emotional reactions • Moving flexibly or adaptively to new situations or activities 	9-11 points
Cognitive Regulation Index (CRI)	Inattentive, distractible, and disorganized <ul style="list-style-type: none"> • Getting started on tasks or activities • Remaining attentive or staying focused • Holding information in active memory • Planning and organizing activities or work • Monitoring success in achieving a goal • Noticing mistakes 	8-9 points
Global Executive Composite (GEC)	Overarching summary score of the three indexes	8-10 points

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Statistical Assessment of Change in Executive Functions

- BRIEF[®]2 raw scores were transformed to T-scores (mean T=50 ±10 SD) based on a normative population of 1400 neurotypical individuals^{8,9,18}
- Reliable Change Index (RCI)¹⁹
 - Determines clinically meaningful changes in T-scores over time at different levels of certainty
 - Used to compare clinically meaningful change in BRIEF[®]2 indexes/composite T-scores from baseline to Week 14 based on the following thresholds:
 - Improvement: Defined using a more stringent threshold of RCI ≥95% certainty
 - Worsening: Defined using a threshold of RCI ≥80% certainty
- Associations between change in BRIEF[®]2 scores and combined active (0.2 and 0.7 mg/kg/day fenfluramine) vs placebo treatment groups were evaluated in cross tabulations using Somers' D statistic

Patient Baseline Characteristics (N=137)^a

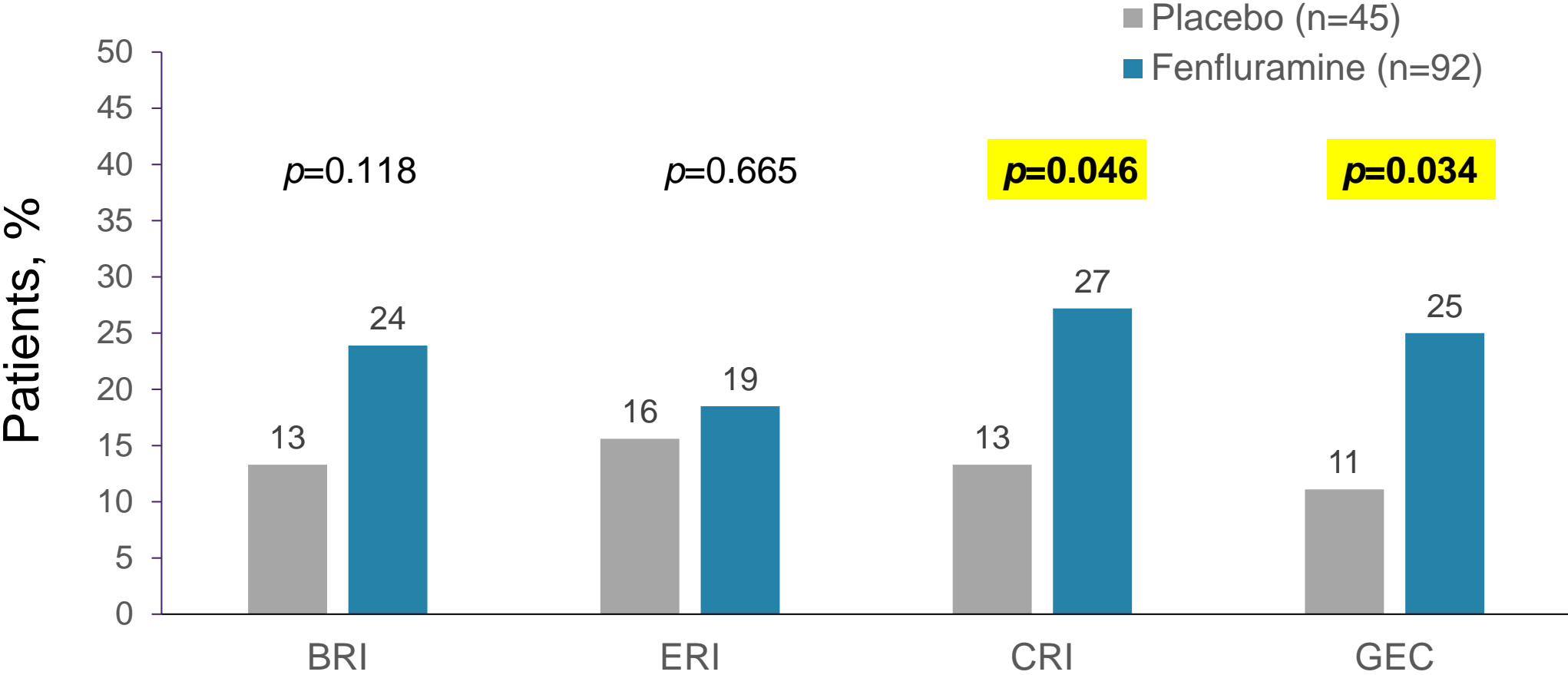
Characteristic	Placebo (n=45)		Fenfluramine (n=92)	
	Baseline T-score, median (range) ^b	T≥65 at baseline, n (%)	Baseline T-score, median (range) ^b	T≥65 at baseline, n (%)
Age, years, mean (SD) Median	11.8 (3.5) 12		12.3 (3.6) 13	
Sex, n (%) Female Male	24 (53%) 21 (47%)		40 (44%) 52 (56%)	
BRIEF [®] 2 Index/Composite				
BRI	65 (37-87)	23 (51%)	68 (35-90)	51 (55%)
ERI	62 (40-85)	19 (42%)	60 (39-90)	36 (39%)
CRI	64 (38-85)	22 (49%)	66 (36-85)	50 (54%)
GEC	66 (38-85)	23 (51%)	68 (36-88)	49 (53%)

^aPrerandomization baseline and end-of-study BRIEF[®] scores available from caregivers of 137 of 163 total enrolled patients aged 6-18.

^bNo statistically significant differences in T-scores among treatment groups at baseline.

BRI, Behavior Regulation Index; BRIEF[®], Behavior Rating Inventory of Executive Function; BRIEF[®]2, Behavior Rating Inventory of Executive Function, 2nd edition; CRI, Cognitive Regulation Index; ERI, Emotion Regulation Index; GEC, Global Executive Composite; SD, standard deviation.

Percentage of Patients Showing Clinically Meaningful Improvement (RCI ≥95% Certainty) in Active vs Placebo Treatment Groups



- Active treatment was not associated with greater worsening of T-scores than placebo (RCI ≥80% certainty)

p-values are active vs placebo; calculated by Somers' D.

9 BRI, Behavior Regulation Index; BRIEF®2, Behavior Rating Inventory of Executive Function, 2nd edition; CRI, Cognitive Regulation Index; ERI, Emotion Regulation Index; GEC, Global Executive Composite; RCI, Reliable Change Index.



Conclusions

- Prior studies have shown improvements in executive function in Phase 3 and long-term studies with fenfluramine in patients with intractable epilepsy
- In this 14-week Phase 3 study, children and young adults with LGS treated with fenfluramine were more likely to show clinically meaningful improvement in executive functioning
 - These improvements may be the result of improved seizure control and/or fenfluramine's mechanism of action at 5-HT and sigma-1 receptors,^{16,20} both of which have been implicated as having positive effects on memory, learning, and executive function^{15,16,21}
- Future directions include evaluating the impact of fenfluramine on everyday executive function:
 - Long-term (≥ 1 year) outcomes
 - Adults > 18 years and children ≤ 5 years
 - Associations between seizure frequency and/or type

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