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 Behaviour 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 a patient's everyday executive function (EF),[2,3] 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 randomised controlled trial (RCT; NCT03355209) of fenfluramine demonstrated improvements in adults 18-35 years of age 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.

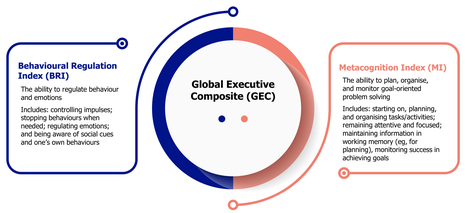
Objective

- 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 patients' everyday EF by BRIEF®—A scores in adults with LGS.

Methods

- In the 14-week RCT, adults with LGS (2-35 years of age) were randomised 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 of age) 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 Behavioural 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 everyday EF.
  - BRIEF®—A T-scores ≥65 (T≥65) are clinically meaningful 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, Figure 3**).
  - 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.
- Correlations between change in frequency of seizures associated with a fall and BRIEF®—A Indexes/Composite were negligible to weak (**Figure 4**).

Overview

QUESTION

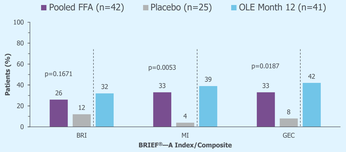
- Does treatment with fenfluramine in adults with LGS improve everyday caregiver-reported EF?
- Is there a relationship between change in frequency of seizures associated with a fall and change in everyday EF in adults?

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 meaningful score suggesting difficulties in everyday EF) at baseline, end of RCT, and OLE Month 12 was summarised.

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

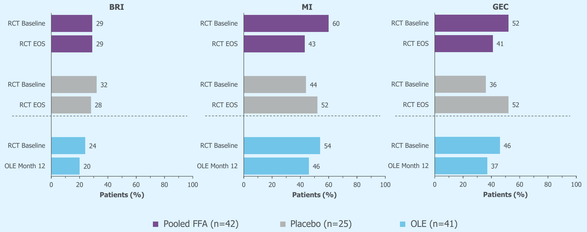


Fenfluramine 'per dose' analysis reported in Figures 2-4.

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



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 EOS to 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.

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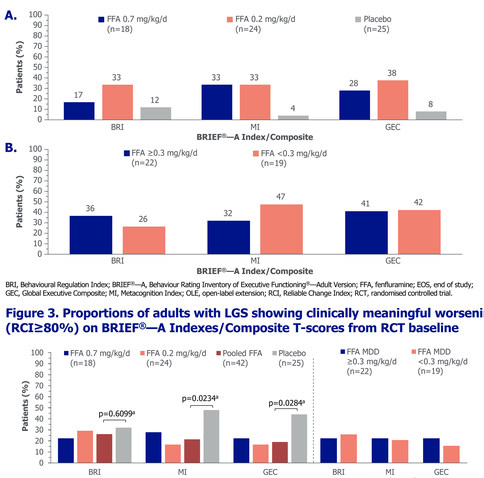
Abbreviations: BRI, Behavioural Regulation Index; BRIEF®—A, Behaviour Rating Inventory of Executive Functioning®—Adult Version; EF, executive functioning; EOS, end of study; FFA, fenfluramine; GEC, Global Executive Composite; LGS, Lennox-Gastaut syndrome; MI, Metacognition Index; OLE, open-label extension;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

Table 1. Demographics and baseline characteristics

	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)
Age, years, mean (SD)	23.7 (4.3)	24.8 (4.6)	24.3 (4.5)	25.0 (4.9)	23.2 (3.5)[a]	25.4 (3.4)[a]
Sex, male, n (%)	14 (77.8)	16 (66.7)	30 (71.4)	15 (60)	17 (77.3)	14 (73.7)
Weight, kg, mean (SD)	63.9 (19.1)	60.2 (16.1)	61.8 (17.3)	62.7 (18.0)	52.5 (9.9)[a]	72.5 (13.2)[a]
Baseline frequency of seizures associated with a fall per 28 d, median (range)	68.5 (16-1556)	62.5 (4.1-343)	64 (4.1-1556)	53.0 (12-270)	59.5 (4.1-1556)	49.0 (16-285)
Number of prior ASMs						
Median (range)	10 (3-17)	11 (1-18)	10.5 (1-18)	8 (2-19)	NA	NA
Mean (SD)	10 (3.7)	10.3 (4.7)	10.2 (4.3)	9.3 (4.8)		
Number of concomitant ASMs						
Median (range)	3 (2-4)	3 (1-4)	3 (1-4)	3 (1-4)	3 (1-4)	3 (1-4)
Mean (SD)	3.2 (0.8)	2.8 (1.1)	2.9 (1.0)	3.2 (0.9)	3.0 (1.0)	3.1 (0.9)
Concomitant ASMs,[b] n (%)						
Valproate (all forms)	9 (50)	17 (70.8)	26 (61.9)	16 (64.0)	16 (72.7)	12 (63.2)
Lamotrigine	7 (38.9)	9 (37.5)	16 (38.1)	15 (60.0)	9 (40.9)	11 (57.9)
Clobazam	7 (38.9)	8 (33.3)	15 (35.7)	11 (44.0)	8 (36.4)	7 (36.8)
Lacosamide	6 (33.3)	4 (16.7)	10 (23.8)	3 (12.0)	6 (27.3)	3 (15.8)
Levetiracetam	6 (33.3)	3 (12.5)	9 (21.4)	3 (12.0)	4 (18.2)	1 (5.3)

[a]At entry to OLE. [b]For RCT, ASMs reported in ≥25% of any treatment group, and for OLE, reported in ≥20% of any dose group.
ASM, antiseizure medication; FFA, fenfluramine; MDD, mean daily dose; NA, not applicable; OLE, open-label extension; RCT, randomised controlled trial.

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

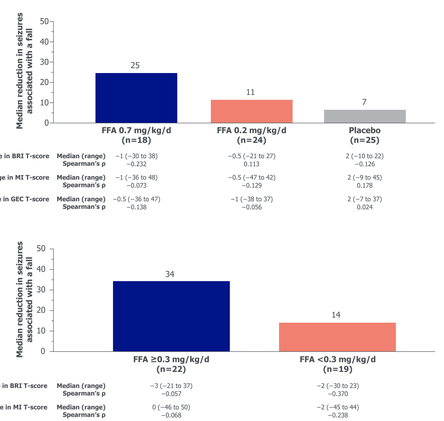


BRI, Behavioural Regulation Index; BRIEF®—A, Behaviour Rating Inventory of Executive Functioning®—Adult Version; FFA, fenfluramine; EOS, end of study; GEC, Global Executive Composite; MI, Metacognition Index; OLE, open-label extension; RCI, Reliable Change Index; RCT, randomised controlled trial.

Figure 3. Proportions of adults with LGS showing clinically meaningful worsening (RCI≥80%) on BRIEF®—A Indexes/Composite T-scores from RCT baseline

[a]p-value is the result of a chi-squared test, vs placebo. BRI, Behavioural Regulation Index; BRIEF®—A, Behaviour 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, randomised controlled trial.

Figure 4. 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



		FFA 0.7 mg/kg/d (n=18)	FFA 0.2 mg/kg/d (n=24)	Placebo (n=25)
Change in BRI T-score	Median (range)	−1 (−30 to 38)	−0.5 (−21 to 27)	2 (−10 to 22)
	Spearman's ρ	−0.232	0.113	−0.126
Change in MI T-score	Median (range)	−1 (−36 to 48)	−0.5 (−47 to 42)	2 (−9 to 45)
	Spearman's ρ	−0.073	−0.129	0.178
Change in GEC T-score	Median (range)	−0.5 (−36 to 47)	−1 (−38 to 37)	2 (−7 to 37)
	Spearman's ρ	−0.138	−0.056	0.024

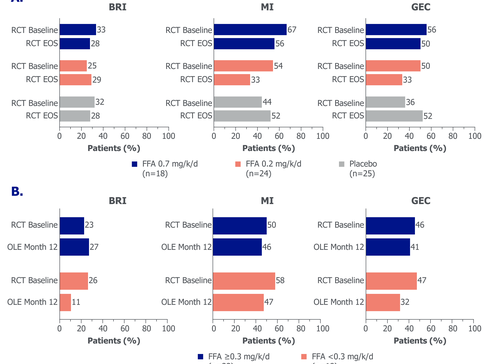
		FFA ≥0.3 mg/k/d (n=22)	FFA <0.3 mg/k/d (n=19)
Change in BRI T-score	Median (range)	−3 (−21 to 37)	−2 (−30 to 23)
	Spearman's ρ	−0.057	−0.370
Change in MI T-score	Median (range)	0 (−46 to 50)	−2 (−45 to 44)
	Spearman's ρ	−0.068	−0.238
Change in GEC T-score	Median (range)	−0.5 (−37 to 48)	−2 (−36 to 37)
	Spearman's ρ	0.003	−0.382

BRI, Behavioural Regulation Index; EOS, end of study; FFA, fenfluramine; GEC, Global Executive Composite; MI, Metacognition Index; OLE, open-label extension; RCT, randomised controlled trial.

CLINICALLY MEANINGFUL SCORES

- The percentage of adult patients with T≥65 decreased from baseline to RCT EOS on all Indexes/Composite with 0.7 mg/kg/d fenfluramine treatment and increased on MI and GEC in the placebo group (**Figure 5A**).
- 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 5B**).

Figure 5. 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, Behavioural Regulation Index; BRIEF®—A, Behaviour 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, randomised 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 patients who reported clinically meaningful executive dysfunction decreased following fenfluramine treatment at RCT Day 99 and OLE Month 12 vs RCT baseline.
- 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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UCB-sponsored. The authors acknowledge Katerina Kumpan, PhD, CMPP (UCB, Slough, UK) for managing the development of the poster, and Mari Willeman, PhD, and Courtney Breuel, ELS, of the Sensified Division of Woven Health Collective, LLC, for writing and editorial assistance (funded by UCB). Author disclosures: D Breuillard: Honoraria for consulting and lecture from Biocodex, Eisai, and Jazz Pharmaceuticals. KG Knupp: Research grants from Encoded Therapeutics, Stoke, and Zogenix (now part of UCB). Consulting fees from Biocodex, BioMarin, and Epygenix. Other support as a Data and Safety Monitoring Board member from Epygenix and GW Pharma (now Jazz Pharmaceuticals). A Strzelczyk: Personal fees and grants from Angelini Pharma, Biocodex, Desitin Arzneimittel, Eisai, Jazz Pharmaceuticals, Takeda, UCB, and UNEEG medical. DM Andrade: Unrestricted educational grants from Biocodex. Participated as an advisor and/or consultant for Biocodex, Epygenix, Marinus, Stoke, and UCB. Conducted research for UCB. P Healy, J Abraham, A Lothe: Employee and stockholder of UCB. R Nabbout: Research funding from Biocodex, GW Pharma (now Jazz Pharmaceuticals), Neuraxpharma, and UCB. Consultancy and/or lectures fees from Advicenne, Biogen, BioMarin, Eisai, GW Pharma (now Jazz Pharmaceuticals), Longboard, Novartis, Nutricia, Orion, Servier, Stoke, Takeda, and Zogenix (now part of UCB). An investigator (last 5 years) for Eisai, Jazz Pharmaceuticals, Nutricia, Takeda, and UCB.

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