Poster #P141

Post Hoc Analysis of Fenfluramine for Lennox-Gastaut Syndrome by Baseline Frequency Quartiles of Seizures Associated With a Fall

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QUESTION

- Are the efficacy and/or safety of fenfluramine (FFA) in patients with Lennox-Gastaut syndrome (LGS) affected by the disease severity at patient's pre-FFA baseline?

INVESTIGATION

- In LGS, various factors contribute to severity of the disease, including, but not limited to, high seizure frequency[1]
- In this post hoc analysis of the FFA randomized controlled trial (RCT)[2] in patients with LGS, baseline frequency of seizures associated with a fall was used as a surrogate marker of disease severity to evaluate efficacy and safety of FFA across a spectrum of patients who participated in that study

RESULTS

Quartiles (Q) of Baseline Seizures Associated With a Fall per 28 days (N=263)

Q1 (n=65): 2–34
- Placebo, n=26
- FFA 0.2 mg/kg/day, n=21
- FFA 0.7 mg/kg/day, n=18

Q2 (n=66): 35–76
- Placebo, n=26
- FFA 0.2 mg/kg/day, n=20
- FFA 0.7 mg/kg/day, n=20

Q3 (n=66): 77–175
- Placebo, n=14
- FFA 0.2 mg/kg/day, n=25
- FFA 0.7 mg/kg/day, n=27

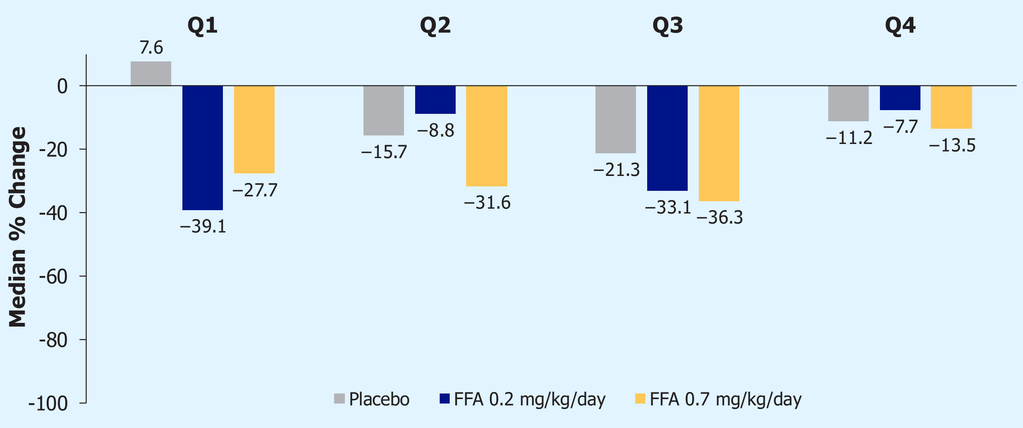
Q4 (n=66): 177–2943
- Placebo, n=21
- FFA 0.2 mg/kg/day, n=23
- FFA 0.7 mg/kg/day, n=22

Baseline Characteristics by Quartiles of Baseline Frequency of Seizures Associated With a Fall (N=263)

		Q1 n=65	Q2 n=66	Q3 n=66	Q4 n=66
Age, mean (SD), years		14.2 (7.1)	17.2 (7.4)	14.3 (6.9)	9.3 (7.0)
Sex					
Male, n (%)		38 (58.5)	40 (60.6)	38 (57.6)	30 (45.5)
Female, n (%)		27 (41.5)	26 (39.4)	28 (42.4)	36 (54.5)
Baseline weight, n (%)					
<37.5 kg		25 (38.5)	20 (30.3)	32 (48.5)	47 (71.2)
≥37.5 kg		40 (61.5)	46 (69.7)	34 (51.5)	19 (28.8)
BMI, mean (SD)		19.9 (4.8)	21.3 (5.2)	19.4 (5.7)	18.2 (4.0)[a]
Prior ASMs,[b] median (range)		8 (2-16)	8 (1–20)	8 (1–18)	7 (2–19)
Concomitant ASMs,[c] median (range)		3 (1–4)	3 (1–4)	3 (1–5)	3 (1–4)
Frequency of Seizures Associated With a Fall	Placebo, n	26	26	14	21
	Median (range)	23.8 (2–34)	47.5 (35-76)	105.5 (78–171)	348 (177–1761)
	FFA 0.2 mg/kg/day, n	21	20	25	23
	Median (range)	21.8 (4.1–32)	51.5 (35–75)	118 (77–175)	399 (199.8–2943)
	FFA 0.7 mg/kg/day, n	18	20	27	22
	Median (range)	20 (6.5–31)	56.5 (38–75)	111 (77–173)	460 (183–1803)

[a]BMI in 65 patients. [b]Prior ASMs are defined as any ASM with a start date prior to the first dose of FFA. [c]Concomitant ASMs are defined as any ASM with start or stop date after the first dose of FFA.

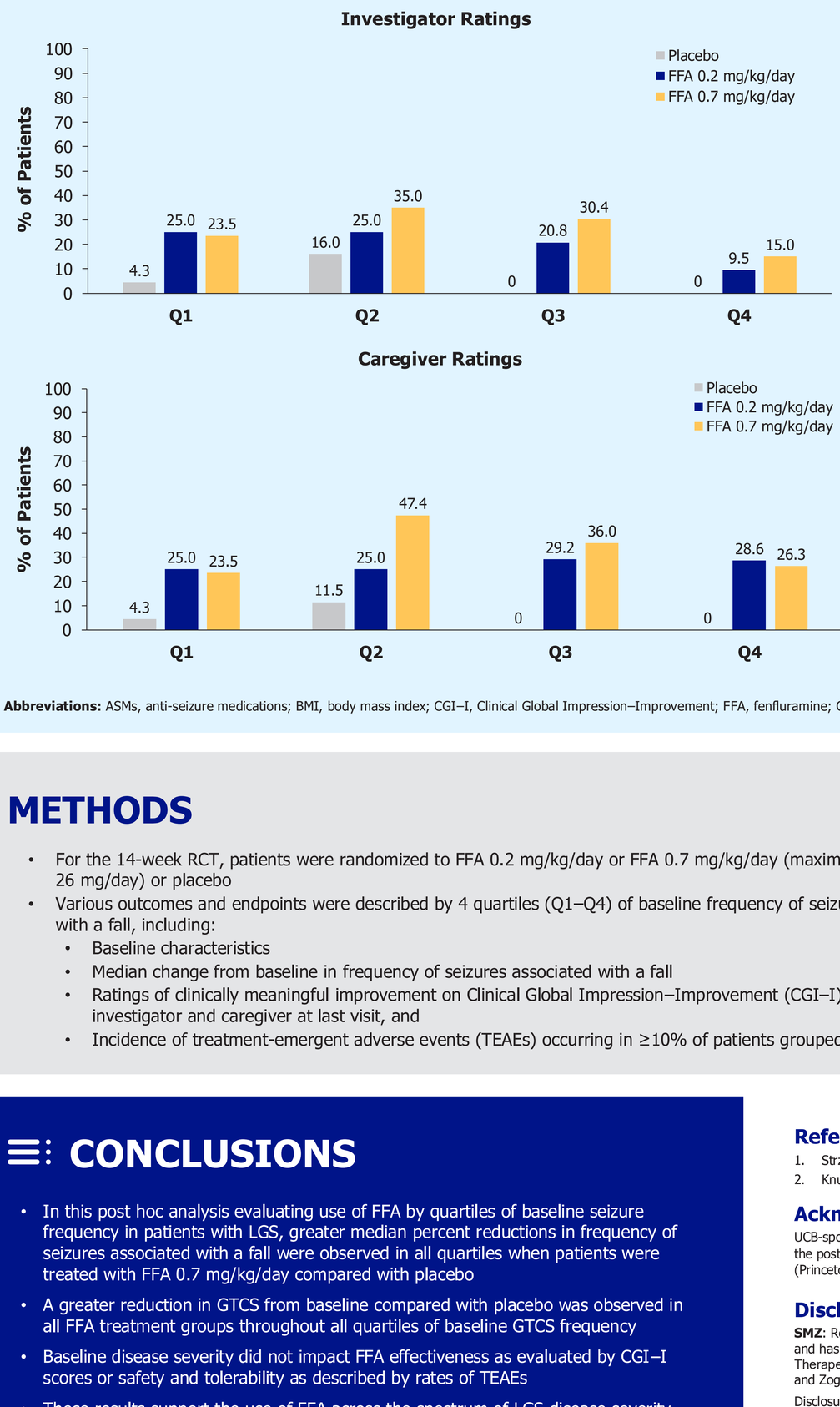
Median Percent Change From Baseline in Frequency of Seizures Associated With a Fall by Baseline Quartiles



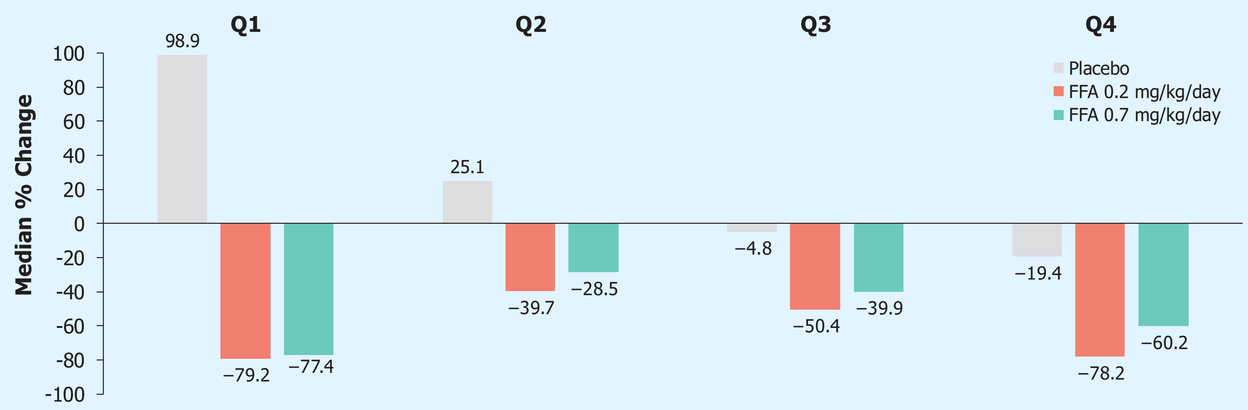
Baseline GTCS Frequencies by RCT Treatment Group (N=114)

	Q1 (1–7) n=28	Q2 (7.3–15) n=29	Q3 (15.5–30) n=28	Q4 (32–198) n=29
Placebo, n	6	11	11	10
Median (range)	1.5 (1–6)	13 (8–15)	23 (16–29)	50 (34–132)
FFA 0.2 mg/kg/day, n	13	10	8	7
Median (range)	3 (1–7)	10 (7.3–15)	20 (16–29)	63 (32–91)
FFA 0.7 mg/kg/day, n	9	8	9	12
Median (range)	4 (1–6)	11.5 (9–15)	21.8 (17–30)	83 (32–198)

Proportion of Patients Rated as Having Clinically Meaningful Improvement ("Much Improved" or "Very Much Improved") on CGI–I by Treatment Group and Quartiles of Baseline Seizures Associated With a Fall



Median Percent Change From Baseline in Frequency of GTCS by Baseline GTCS Quartiles



Incidence of TEAEs reported by ≥10% of patients in either group over the course of the RCT (decreased appetite, somnolence, fatigue, pyrexia, diarrhea, vomiting) was similar across baseline quartiles of seizures associated with a fall. In each of the 4 quartiles, decreased appetite and fatigue occurred in ≥10% of patients in the group treated with FFA 0.7 mg/kg/day.

Abbreviations: ASMs, anti-seizure medications; BMI, body mass index; CGI–I, Clinical Global Impression–Improvement; FFA, fenfluramine; GTCS, generalized tonic-clonic seizures; Q, quartile; RCT, randomized controlled trial; SD, standard deviation; TEAEs, treatment-emergent adverse events.

METHODS

- For the 14-week RCT, patients were randomized to FFA 0.2 mg/kg/day or FFA 0.7 mg/kg/day (maximum = 26 mg/day) or placebo
- Various outcomes and endpoints were described by 4 quartiles (Q1–Q4) of baseline frequency of seizures associated with a fall, including:
  - Baseline characteristics
  - Median change from baseline in frequency of seizures associated with a fall
  - Ratings of clinically meaningful improvement on Clinical Global Impression–Improvement (CGI–I) scale by investigator and caregiver at last visit, and
  - Incidence of treatment-emergent adverse events (TEAEs) occurring in ≥10% of patients grouped by quartiles
- Quartiles of baseline frequency of generalized tonic-clonic seizures (GTCS; Q1–Q4) were also used to describe median change from baseline in frequency of GTCS
  - These were included as part of the Epilepsy Study Consortium (ESC)-confirmed seizures associated with a fall and also reported alone as a separate outcome
  - In the FFA LGS RCT, ESC-confirmed seizures associated with a fall included the following types: generalized tonic-clonic, focal to bilateral tonic-clonic, tonic, or atonic
- Descriptive statistics were used

CONCLUSIONS

- In this post hoc analysis evaluating use of FFA by quartiles of baseline seizure frequency in patients with LGS, greater median percent reductions in frequency of seizures associated with a fall were observed in all quartiles when patients were treated with FFA 0.7 mg/kg/day compared with placebo
- A greater reduction in GTCS from baseline compared with placebo was observed in all FFA treatment groups throughout all quartiles of baseline GTCS frequency
- Baseline disease severity did not impact FFA effectiveness as evaluated by CGI–I scores or safety and tolerability as described by rates of TEAEs
- These results support the use of FFA across the spectrum of LGS disease severity

References

1. Strzelczyk A, et al. *Orphanet J Rare Dis*. 2023;18(1):42.
2. Knupp K, et al. *JAMA Neurol*. 2022;79(6):554-64.

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Disclosures for all authors can be found in the full poster at the QR code.

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