A Post-Hoc Evaluation of Fenfluramine With or Without Vagus Nerve Stimulation in Lennox-Gastaut Syndrome Clinical Trials

Lieven Lagae, MD, PhD, FRCP[1]; Kelly G. Knupp, MD[2], Joseph Sullivan, MD[3]; James Wheless, BScPharm, MD[4]; Rima Nabbout, MD, PhD[5]; Ingrid E. Scheffer, MBBS, PhD, FRACP, FRS[6]; Renzo Guerrini, MD, FRCP[7]; Fawad A. Khan, MD[8]; Michael P. Macken, MD[9]; Sameer M. Zuberi, MD[10]; Antonio Gil-Nagel, MD, PhD[11]; Patrick Healy[12]; Jayne Abraham, PhD[12]; Melanie Langlois, PhD[13]; Amélie Lothe, PhD[13]; Nicola Specchio, MD, PhD, FRCP[14]

[1]Member of the European Reference Network EpiCARE, University of Leuven, Leuven, Belgium; [2]University of Colorado, Children's Hospital Colorado, Aurora, CO, USA; [3]University of California San Francisco Weill Institute for Neurosciences, Benioff Children's Hospital, San Francisco, CA, USA; [4]University of Tennessee Health Science Center, Le Bonheur Children's Hospital, Memphis, TN, USA; [5]Member of the European Reference Network EpiCARE, Reference Centre for Rare Epilepsies, Necker Enfants Malades Hospital, APHP, U 1163 Institut Imagine, Université Paris Cité, Paris, France; [6]University of Melbourne, Austin Hospital and Royal Children's Hospital, Florey and Murdoch Children's Research Institutes, Melbourne, Victoria, Australia; [7]Meyer Children's Hospital IRCCS, and University of Florence, Florence, Italy; [8]The International Center for Epilepsy at Ochsner, Ochsner Health, New Orleans, LA, USA; [9]Northwestern University, Chicago, Illinois, USA; [10]Paediatric Neurosciences Research Group, Royal Hospital for Children, Glasgow, UK; [11]Hospital Ruber Internacional, Madrid, Spain; [12]UCB, Smyrna, GA, USA; [13]UCB, Colombes, France; [14]Member of the European Reference Network EpiCARE, Bambino Gesù Children's Hospital, IRCCS, Rome, Italy, University Hospitals KU Leuven, Belgium

Introduction

- Lennox-Gastaut syndrome (LGS) is a developmental and epileptic encephalopathy characterized by multiple seizure types, cognitive and behavioral impairments, and abnormal electroencephalographic (EEG) features[1-3]
  - These, in addition to other comorbidities, contribute to high rates of morbidity, mortality, significant caregiver burden, and poor patient prognoses[2]
  - Seizures associated with a fall or drop are a feature of LGS and increase the risk of injury and decreased quality of life[4]
- Fenfluramine (FFA) is currently approved for the management of seizures associated with LGS in the US in patients ≥2 years old,[5] and as add-on treatment for patients ≥2 years old with seizures associated with LGS in the EU, UK, Japan, and Israel[6-9]
- Efficacy and safety of FFA were evaluated in patients with LGS in a randomized controlled trial (RCT)[10] followed by an open-label extension (OLE) study[11]
  - In the RCT (NCT03355209), treatment with FFA provided a significantly greater reduction in seizures associated with a fall compared with placebo as well as significant reductions in generalized tonic-clonic seizures (GTCS); in the OLE (NCT03355209), the frequencies of both seizures associated with a fall and GTCS were significantly reduced from baseline to end of study[10,11]
- Vagus nerve stimulation (VNS) is an adjunctive, nonpharmacological treatment option for patients with drug-resistant epilepsy that may reduce seizures in patients with LGS[2,12]
  - Use of VNS may serve as an indicator of the severity of seizures associated with LGS, since patients with VNS may have more drug-resistant seizures
- FFA exerts its effects through a novel, dual mechanism of increased serotonergic activity and positive modulation at sigma-1 receptors[13]
  - Similarly, among other mechanisms, VNS also helps to decrease seizures through increasing serotonin activity in the brain[14]
  - Combining FFA with VNS may, thus, have additive effects leading to greater reductions in seizures than either therapy alone

Objective

- This is a post-hoc analysis of the FFA RCT and OLE to evaluate the efficacy and safety of FFA with and without concomitant VNS in patients with LGS

Methods

- In the RCT, eligible patients with LGS (aged 2-35 years) were randomized (N=263) to placebo (PBO), FFA 0.2 mg/kg/day, or FFA 0.7 mg/kg/day (max: 26 mg/day)[10]
  - Patients were enrolled at 65 study sites in North America, Europe, and Australia
  - Following a 2-week titration period, patients remained on their dose throughout a 12-week maintenance phase
- After completing the RCT, patients could enroll in the OLE study and were transitioned to FFA 0.2 mg/kg/day for 1 month, then flexibly titrated to effectiveness and tolerability (max: 0.7 mg/kg/day or 26 mg/day)[11]
- No changes of VNS settings or concomitant ASMs were allowed during the RCT and the first 6 months of the OLE
  - Once patients were on a stable dose of FFA for ≥6 months with good seizure control, VNS stimulation parameters could be altered for those receiving VNS
- The following were evaluated according to use of FFA with concomitant VNS versus FFA without VNS:
  - Median percent change from baseline in seizures (seizures associated with a fall and GTCS)
  - Responder analyses (proportion of patients to achieve seizure reduction thresholds of ≥50%, ≥75%, and 100% reduction)
  - Incidence of treatment-emergent adverse events (TEAEs) occurring in ≥10% of patients in the RCT and OLE
- Descriptive analyses and Clopper-Pearson for confidence intervals were used
- *P*-values were based on a Wilcoxon rank-sum test assessing the difference in percent reduction in seizure frequency between FFA with VNS versus FFA without VNS for each treatment group; in the OLE, *P*-values were only calculated for any FFA dose combined, and FFA with VNS versus FFA without VNS

Results

- In the RCT, 82 patients had VNS at baseline prior to initiating FFA; 181 were started on FFA without baseline VNS
  - Of the 82 patients with VNS at baseline, 32 were randomized to placebo, 23 to FFA 0.2 mg/kg/day, and 27 to FFA 0.7 mg/kg/day (**Table 1**)

Overview

QUESTION

Does use of fenfluramine (FFA) with vagus nerve stimulation (VNS) result in any changes in efficacy and safety compared with FFA treatment without VNS in patients with Lennox-Gastaut syndrome (LGS)?

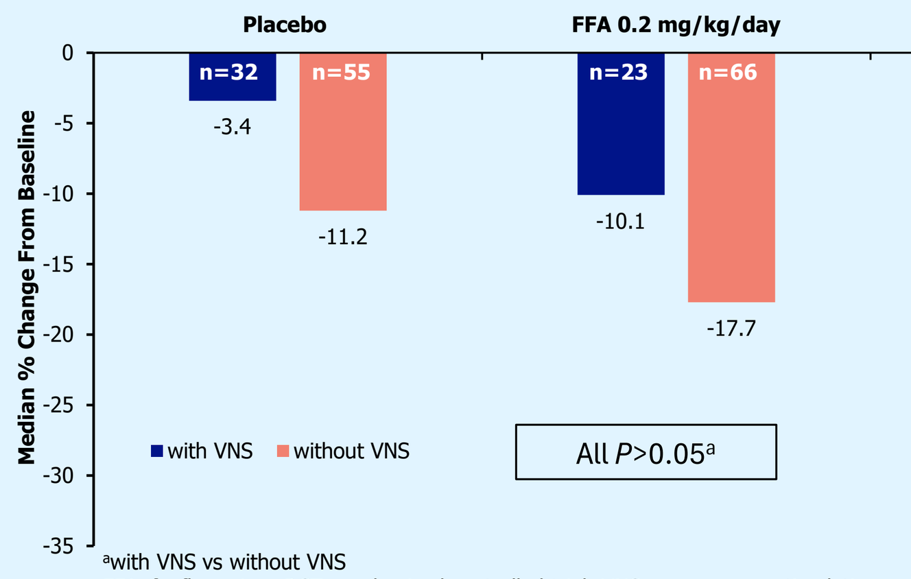
INVESTIGATION

The efficacy and safety of FFA were previously evaluated in a 14-week randomized-controlled trial (RCT) and subsequent open-label extension (OLE) study (NCT03355209) in patients with LGS. The current post-hoc analyses of those studies evaluated the effects of FFA with VNS compared with FFA without VNS on frequency of seizures associated with a fall, frequency of generalized tonic-clonic seizures (GTCS), percentage of patients who achieved ≥50%, ≥75%, and 100% reduction in seizures associated with a fall, and treatment-emergent adverse events (TEAEs).

RESULTS

- 263 patients were randomized to the RCT (n=82, FFA with VNS; n=181, FFA without VNS) and 241 patients entered the OLE (n=80, FFA with VNS; n=161, FFA without VNS)
- Reductions in both seizure types with FFA treatment did not change significantly based on concomitant VNS use (all *P*>0.05, see **Figure** and **Table**)
- For the combined FFA groups in the RCT and OLE, a numerically greater percentage of patients who achieved ≥50% and ≥75% reduction in seizures associated with a fall when treated without VNS compared to patients on FFA with VNS
  - A numerically greater proportion of patients receiving FFA without VNS achieved 100% reduction in seizures associated with a fall compared with FFA with VNS in the OLE
- The percentages of patients who experienced any TEAE were similar across groups for both the RCT and OLE, regardless of whether they received FFA with or without VNS
- Of the TEAEs reported in ≥10% of patients in the RCT and OLE, fatigue occurred more frequently in the patients on FFA with VNS versus those on FFA without VNS

Figure. Median Percent Change From Baseline in Seizures Associated With a Fall by Use of Concomitant VNS in RCT



[a]with VNS vs without VNS
FFA, fenfluramine; RCT, randomized controlled trial; VNS, vagus nerve stimulation.

Table. Median Percent Change From Baseline in GTCS by Use of Concomitant VNS in RCT and OLE

	With VNS (n, % change)	Without VNS (n, % change)	*P*-value[a]
Placebo	n=18, 8.7%	n=20, -14.7%	*P*>0.05
FFA 0.2 mg/kg/day	n=9, -69.6%	n=29, -57.0%	*P*>0.05
FFA 0.7 mg/kg/day	n=17, -50.1%	n=21, -41.2%	*P*>0.05
Any FFA dose in OLE	n=43, -37.9%	n=62, -56.3%	*P*>0.05

[a]with VNS vs without VNS.
FFA, fenfluramine; GTCS, generalized tonic-clonic seizures; OLE, open-label extension; RCT, randomized controlled trial; VNS, vagus nerve stimulation.

CONCLUSIONS

In these post-hoc analyses of the FFA LGS clinical trials, efficacy and safety of FFA remained consistent regardless of whether patients were already maintained on stable VNS therapy. Use of FFA with VNS did not result in any statistically significant difference in reduction of frequency of seizures associated with a fall or GTCS compared with FFA without VNS. The proportion of patients who experienced ≥50%, ≥75%, and 100% reductions in seizures associated with a fall did not increase when patients received FFA with VNS. Evaluation of VNS settings and duration of therapy may be needed; larger studies would provide insight into the combined use of FFA and VNS.

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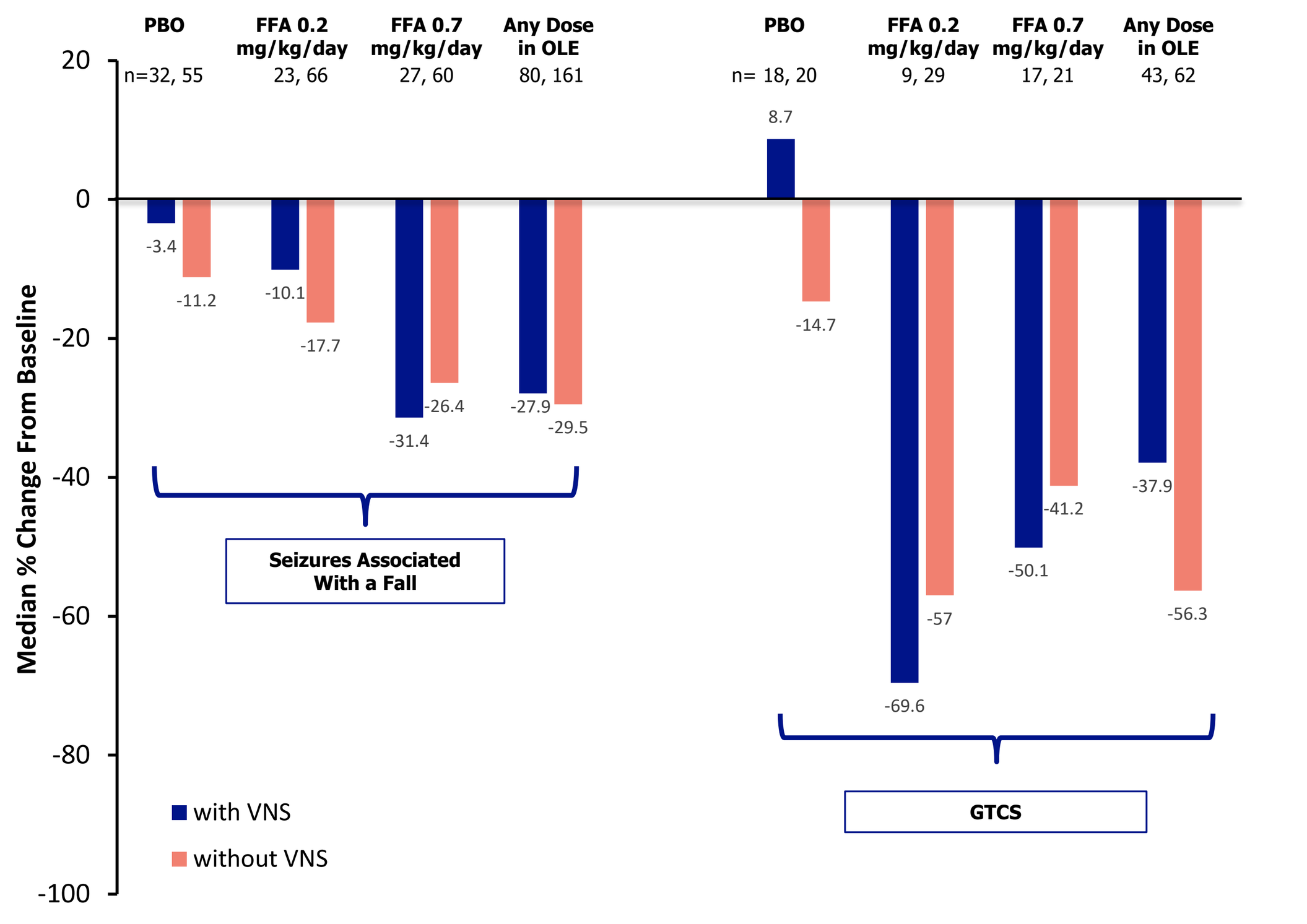
- In the OLE, 80/241 patients had VNS at RCT baseline (**Table 1**)
- There were no statistically significant differences in baseline seizure frequencies in groups by concomitant VNS use (all *P* >0.05)
  - Baseline median number of seizures associated with a fall was numerically higher in the RCT and OLE treatment groups on FFA without concomitant VNS compared with those on FFA with VNS (**Table 1**)

Table 1. Characteristics of Patients by Concomitant VNS Use While on FFA in the LGS RCT and OLE

	LGS RCT Concomitant VNS			LGS RCT No Concomitant VNS			LGS OLE Concomitant VNS	LGS OLE No Concomitant VNS
Characteristic	**Placebo** n=32	**FFA 0.2 mg/kg/day** n=23	**FFA 0.7 mg/kg/day** n=27	**Placebo** n=55	**FFA 0.2 mg/kg/day** n=66	**FFA 0.7 mg/kg/day** n=60	**Any Dose** n=80	**Any Dose** n=161
Age, mean (SD), years	15.9 (6.2)	14.5 (6.5)	14.9 (6.3)	13.6 (8.4)	13.0 (8.2)	12.8 (7.6)	15.1 (6.3)	13.0 (8.1)
Sex								
Male, n (%)	20 (62.5)	10 (43.5)	19 (70.4)	26 (47.3)	36 (54.5)	35 (58.3)	49 (61.3)	86 (53.4)
Female, n (%)	12 (37.5)	13 (56.5)	8 (29.6)	29 (52.7)	30 (45.5)	25 (41.7)	31 (38.8)	75 (46.6)
Baseline weight, n (%)								
<37.5 kg	12 (37.5)	9 (39.1)	8 (29.6)	30 (54.5)	33 (50.0)	32 (53.3)	29 (36.3)	85 (52.8)
≥37.5 kg	20 (62.5)	14 (60.9)	19 (70.4)	25 (45.5)	33 (50.0)	28 (46.7)	51 (63.8)	76 (47.2)
BMI, mean (SD)	21.1 (5.3)	20.6 (3.9)[a]	19.7 (4.2)	18.9 (4.6)	19.3 (5.6)	19.7 (5.4)	20.3 (4.5)[b]	19.3 (5.3)
Number of prior ASMs, median (range)	8 (2-19)	9 (1-17)	11 (4-16)	7 (1-17)	7 (2-18)	8 (0-20)	NR	NR
Number of concomitant ASMs, median (range)	3 (1-4)	3 (1-5)	3 (2-4)	3 (0-4)[c]	3 (1-4)	3 (0-4)[c]	3 (1-5)	3 (0-4)[c]
Baseline frequency of seizures associated with a fall per 28 days, median (range)	48.5 (2-426)	67 (5-1142)	80 (10-1177)	70 (4-1761)	93.5 (4.1-2943)	85 (6.5-1803)	59.5 (4-1177)	80 (4-2943)
Baseline frequency of GTCS per 28 days, median (range), n	16.5 (1-132) 18	8.6 (1-91) 9	23 (1-188) 17	21.5 (1-64) 20	13 (1-78) 29	15 (1-198) 21	18 (1-188) 43	15 (1-198) 62

[a]Weight (and BMI) available in 22 patients. [b]BMI available in 79 patients. [c]n=2 patients (same 2 individuals in RCT and OLE) had no concomitant ASMs captured in the on-study dataset, but these patients may have been taking ASMs that do not fall into the same MedDRA classification.
ASM, antiseizure medication; BMI, body mass index; FFA, fenfluramine; GTCS, generalized tonic-clonic seizures; NR, not reported; LGS, Lennox-Gastaut syndrome; OLE, open-label extension; RCT, randomized controlled trial; SD, standard deviation; VNS, vagus nerve stimulation.

Figure 1. Median Percent Change From Baseline in Seizures Associated With a Fall and GTCS by Use of Concomitant VNS



PBO
FFA 0.2 mg/kg/day
FFA 0.7 mg/kg/day
Any Dose in OLE
n=32, 55
23, 66
27, 60
80, 161
PBO
FFA 0.2 mg/kg/day
FFA 0.7 mg/kg/day
Any Dose in OLE
n= 18, 20
9, 29
17, 21
43, 62
20
0
-20
-40
-60
-80
-100
Median % Change From Baseline
-3.4
-11.2
-10.1
-17.7
-31.4
-26.4
-27.9
-29.5
8.7
-14.7
-69.6
-57
-50.1
-41.2
-37.9
-56.3
Seizures Associated With a Fall
GTCS
with VNS
without VNS

FFA, fenfluramine; GTCS, generalized tonic-clonic seizures; OLE, open-label extension; PBO, placebo; VNS, vagus nerve stimulation.

- Median percent reductions in seizures associated with a fall were similar for FFA treatment groups regardless of VNS use in both the RCT and OLE parts (**Figure 1**; *P*>0.05 for all)
  - In the RCT, patients on FFA with VNS exhibited numerically greater reductions in GTCS than patients on FFA without VNS (**Figure 1**; *P*>0.05)
  - A numerically higher median reduction in GTCS was observed in the OLE when FFA was given without concomitant VNS (**Figure 1**; *P*>0.05)

- For the combined FFA groups in the RCT, a numerically greater percentage of patients achieved ≥50% and ≥75% reduction in seizures associated with a fall when on FFA without VNS compared to patients on FFA with VNS; in patients who achieved a 100% seizure reduction, a numerically greater percentage was observed for the FFA without VNS group vs FFA with VNS
  - ≥50% reduction: 24.0% (FFA with VNS) vs 27.8% (FFA without VNS)
  - ≥75% reduction: 4.0% (FFA with VNS) vs 11.1% (FFA without VNS)
  - 100% reduction: 2.0% (FFA with VNS) vs 1.6% (FFA without VNS)
- In the OLE, numerically more patients on FFA (any dose) without VNS achieved reductions in seizures associated with a fall compared to those on FFA with VNS
  - ≥50% reduction: 27.5% (FFA with VNS) vs 32.9% (FFA without VNS)
  - ≥75% reduction: 7.5% (FFA with VNS) vs 13.7% (FFA without VNS)
  - 100% reduction: 0% (FFA with VNS) vs 1.2% (FFA without VNS)
- The percentages of patients who experienced any TEAE were similar, regardless of VNS use (**Table 2**)
  - Of the TEAEs reported in ≥10% of patients in the RCT and OLE, fatigue occurred more frequently in the patients on FFA with VNS versus those on FFA without VNS
  - Within the OLE, a higher proportion of patients who were on FFA with concomitant VNS experienced upper respiratory tract infection
  - Irritability and asthenia were reported in ≥10% of patients with VNS in an FFA treatment group in the RCT; these were not reported in ≥10% of patients in any treatment group within the original RCT and are also not typically associated with VNS[10,11]
- Percentages of patients experiencing serious adverse events (SAEs) are shown in **Table 2**
  - The percentages of patients experiencing SAEs in the RCTs showed no pattern based on concomitant VNS use; similar percentages of patients in the OLE experienced SAEs regardless of VNS
  - One patient in the RCT FFA 0.7 mg/kg/day group (without VNS) died due to SUDEP, deemed unrelated to FFA

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Table 2. Summary of Adverse Events

	LGS RCT Concomitant VNS			LGS RCT No Concomitant VNS			LGS OLE Concomitant VNS	LGS OLE No Concomitant VNS
	Placebo n=32	**FFA 0.2 mg/kg/d** n=23	**FFA 0.7 mg/kg/d** n=27	**Placebo** n=55	**FFA 0.2 mg/kg/d** n=66	**FFA 0.7 mg/kg/d** n=60	**Any Dose** n=80	**Any Dose** n=161
Any TEAE, n (%)	22 (68.8)	20 (87.0)	25 (92.6)	43 (78.2)	49 (74.2)	53 (88.3)	66 (82.5)	135 (83.9)
Any Serious TEAE, n (%)	1 (3.1)	2 (8.7)	2 (7.4)	3 (5.5)	2 (3.0)	8 (13.3)	13 (16.3)	26 (16.1)
TEAEs in ≥10% of patients in any group by study and concomitant VNS, n (%)								
Asthenia	1 (3.1)	1 (4.3)	3 (11.1)	2 (3.6)	3 (4.5)	2 (3.3)	NR	NR
Change in seizure presentation	NR	NR	NR	NR	NR	NR	9 (11.3)	14 (8.7)
Constipation	1 (3.1)	1 (4.3)	2 (7.4)	4 (7.3)	4 (6.1)	6 (10.0)	5 (6.3)	13 (8.1)
Decreased appetite	4 (12.5)	5 (21.7)	12 (44.4)	6 (10.9)	13 (19.7)	19 (31.7)	11 (13.8)	29 (18.0)
Diarrhea	2 (6.3)	4 (17.4)	4 (14.8)	2 (3.6)	6 (9.1)	7 (11.7)	3 (3.8)	10 (6.2)
Fatigue	4 (12.5)	4 (17.4)	6 (22.2)	5 (9.1)	4 (6.1)	10 (16.7)	15 (18.8)	18 (11.2)
Irritability	1 (3.1)	3 (13.0)	0 (0.0)	4 (7.3)	4 (6.1)	3 (5.0)	NR	NR
Nasopharyngitis	3 (9.4)	0 (0.0)	2 (7.4)	5 (9.1)	3 (4.5)	4 (6.7)	10 (12.5)	21 (13.0)
Pyrexia	2 (6.3)	0 (0.0)	3 (11.1)	8 (14.5)	9 (13.6)	4 (6.7)	8 (10.0)	16 (9.9)
Seizure	0 (0.0)	4 (17.4)	2 (7.4)	6 (10.9)	4 (6.1)	2 (3.3)	12 (15.0)	14 (8.7)
Somnolence	2 (6.3)	4 (17.4)	4 (14.8)	7 (12.7)	5 (7.6)	11 (18.3)	8 (10.0)	16 (9.9)
Upper respiratory tract infection	1 (3.1)	1 (4.3)	2 (7.4)	2 (3.6)	6 (9.1)	4 (6.7)	8 (10.0)	8 (5.0)
Vomiting	1 (3.1)	3 (13.0)	3 (11.1)	4 (7.3)	9 (13.6)	4 (6.7)	4 (5.0)	9 (5.6)
Weight decreased	2 (6.3)	1 (4.3)	3 (11.1)	0 (0.0)	1 (1.5)	4 (6.7)	6 (7.5)	6 (3.7)

FFA, fenfluramine; LGS, Lennox-Gastaut syndrome; NR, not reported (may have been reported in <5% of patients and therefore data not available); OLE, open-label extension; RCT, randomized controlled trial; TEAE, treatment-emergent adverse event; VNS, vagus nerve stimulation.

Conclusions

- In this analysis, use of FFA in the LGS clinical trials was effective and demonstrated an acceptable safety profile irrespective of whether FFA was given with or without baseline VNS
- Overall, reductions in both seizures associated with a fall and frequency of GTCS with FFA treatment did not differ significantly based on baseline concomitant VNS
  - The proportions of patients who experienced ≥50%, ≥75%, or 100% reduction in seizures associated with a fall were similar regardless of whether patients received FFA treatment with VNS or if FFA was given without VNS
  - Notably, baseline frequency of seizures associated with a fall were numerically higher in the RCT and OLE treatment groups that received FFA without VNS versus those on FFA with VNS
- Evaluation of VNS settings and duration of therapy may be needed, and larger studies would provide insight into the combined use of FFA and VNS
- An analysis of FFA use with other non-pharmacological treatments (eg, ketogenic diet) may be useful

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Disclosures

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