Onset and Duration of Adverse Events in Patients Treated With Fenfluramine in the Lennox-Gastaut Syndrome Clinical Trials

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Introduction

- Lennox-Gastaut syndrome (LGS) is a developmental and epileptic encephalopathy characterized by drug resistant seizures of multiple types[1,2]
- There are a range of anti-seizure medications (ASMs) available that vary in mechanism of action, efficacy, and safety and tolerability[3]
- Since a patient-focused approach involves a balance of ASM safety and efficacy, understanding adverse event (AE) characteristics is important for providers, patients and families[3]
- Fenfluramine (FFA) is currently approved for the management of seizures associated with LGS in the US in patients ≥2 years old,[4] and as add-on treatment for patients ≥2 years old with seizures associated with LGS in the EU, UK, Japan, and Israel[5-8]
- The FFA LGS clinical trial program involves a phase 3 trial of two parts: a randomized controlled trial (RCT)[9] and open-label extension (OLE)[10] (NCT03355209)

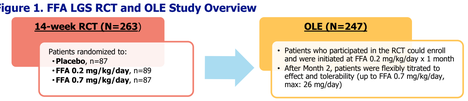
Objective

- This post-hoc analysis describes the time of onset and duration of treatment-emergent adverse events (TEAEs) reported in the FFA RCT and OLE

Methods

- In the RCT, patients with LGS (aged 2-35 years) enrolled from study sites in North America, Europe, and Australia were randomized to FFA 0.2 mg/kg/day or FFA 0.7 mg/kg/day (maximum 26 mg/day) or placebo
- After 2 weeks titration and 12 weeks maintenance in the RCT, patients could enroll in the OLE part where they were transitioned to FFA 0.2 mg/kg/day for 1 month, then were flexibly titrated to effect and tolerability ≥Month 2 (see overview in **Figure 1**)
  - Changes in concomitant ASMs were not permitted during the RCT
  - In the OLE, patients must have remained on a stable ASM regimen, including ≥1 concomitant ASM, for the first 6 months of the study; decreases in doses or discontinuation of ASMs were allowed after Month 6 but treatment with ≥1 concomitant ASM was required

Figure 1. FFA LGS RCT and OLE Study Overview



FFA, fenfluramine; LGS, Lennox-Gastaut syndrome; OLE, open-label extension; RCT, randomized controlled trial.

- For this post-hoc analysis, the following were reported:
  - Incidence of TEAEs occurring in ≥10% of patients in the RCT and OLE (previously reported,[9,10] reviewed in **Table 1**) by week of first onset of first occurrences
  - In the RCT, median time to onset and duration of first occurrences of TEAEs occurring in ≥10% of patients were reported by dose groups
  - Median time to onset of first occurrences of TEAEs occurring in ≥10% of patients in the OLE (any dose) and percent of patients who experienced resolution of those TEAEs were reported

Table 1. Overview of TEAEs Occurring in ≥10% of Patients per Treatment Group in the RCT and Any Dose in the OLE

FFA Study	Treatment Group	Patients Experiencing ≥1 TEAE, n (%)	Patients Experiencing TEAEs Occurring in ≥10% of Patients, n (%)	TEAEs Occurring in ≥10% of Patients
LGS RCT[9,11]	Placebo (n=87)	65 (74.7)	35 (40.2)	Decreased appetite (11.5%), pyrexia (11.5%), somnolence (10.3%), fatigue (10.3%)
	FFA 0.2 mg/kg/day (n=89)	69 (77.5)	42 (47.2)	Decreased appetite (20.2%), vomiting (13.5%), diarrhea (11.2%), pyrexia (10.1%), somnolence (10.1%)
	FFA 0.7 mg/kg/day (n=87)	78 (89.7)	52 (59.8)	Decreased appetite (35.6%), fatigue (18.4%), somnolence (17.2%), diarrhea (12.6%)
LGS OLE[10]	Any dose (N=247)	203 (82.2)	127 (51.4)	Decreased appetite (16.2%), fatigue (13.4%), nasopharyngitis (12.6%), seizure (10.9%)

FFA, fenfluramine; LGS, Lennox-Gastaut syndrome; OLE, open-label extension; RCT, randomized controlled trial; TEAE, treatment-emergent adverse event.

- Definitions:
  - Time to onset is measured from the first date of FFA initiation in either RCT or OLE
  - Duration of the event is based on the number of days from AE onset date to resolution date
- Descriptive statistics were used

Overview

QUESTION

What data are available related to the onset and duration of treatment-emergent adverse events (TEAEs) reported in the clinical trials of fenfluramine (FFA) in patients with Lennox-Gastaut syndrome (LGS)?

INVESTIGATION

The safety and effectiveness of FFA were evaluated in previously published studies, specifically a 14-week randomized-controlled trial (RCT) and subsequent open-label extension (OLE) study (NCT03355209). This post-hoc analysis of those studies describes the time of onset and duration of TEAEs occurring in ≥10% of patients in those studies.

RESULTS

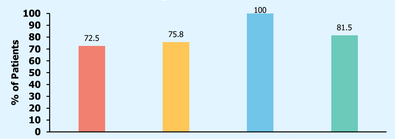
- TEAEs reported in ≥10% of patients per randomized treatment group of the RCT, median time to onset, and proportion of patients experiencing resolution of first occurrences of those TEAEs are reported in the **Table**
- In the OLE, TEAEs reported in ≥10% of patients included: decreased appetite (16.2%), fatigue (13.4%), nasopharyngitis (12.6%), and seizure (10.9%); percent of patients experiencing resolution of first occurrences are described in the **Figure**

Table. Median Time to Onset and Proportion of Patients Experiencing Resolution of First Occurrences of TEAEs Occurring in ≥10% of Patients in the FFA RCT

	Placebo n=87	FFA 0.2 mg/kg/day n=89	FFA 0.7 mg/kg/day n=87
Diarrhea, n (%) Median time to onset, days (range) % of patients with resolution	NA	10 (11.2) 9.5 (2-86) 90.0%	11 (12.6) 16 (2-86) 90.9%
Vomiting, n (%) Median time to onset, days (range) % of patients with resolution	NA	12 (13.5) 14 (1-101) 100%	NA
Fatigue, n (%) Median time to onset, days (range) % of patients with resolution	9 (10.3) 4 (1-99) 66.7%	NA	16 (18.4) 6.5 (1-41) 56.3%
Pyrexia, n (%) Median time to onset, days (range) % of patients with resolution	10 (11.5) 28.5 (2-92) 100%	9 (10.1) 20 (5-92) 100%	NA
Decreased appetite, n (%) Median time to onset, days (range) % of patients with resolution	10 (11.5) 10 (1-85) 80.0%	18 (20.2) 10 (1-69) 72.2%	31 (35.6) 11 (1-91) 45.2%
Somnolence, n (%) Median time to onset, days (range) % of patients with resolution	9 (10.3) 14 (1-96) 55.6%	9 (10.1) 17 (1-75) 77.8%	15 (17.2) 6 (1-95) 80.0%

FFA, fenfluramine; NA, not applicable, since the TEAE occurred in <10% of patients in that group; RCT, randomized controlled trial; TEAEs, treatment-emergent adverse events.

Figure. Proportion of Patients Experiencing Resolution of First Occurrences of TEAEs Occurring in ≥10% of Patients in the FFA OLE



Median time to onset, days (range)	51.5 (1-397)	60 (1-362)	87 (9-360)	92 (1-267)

FFA, fenfluramine; OLE, open-label extension; TEAEs, treatment-emergent adverse events.

CONCLUSIONS

First occurrences of TEAEs are reported early in FFA treatment and are associated with high percentages of resolution. FFA continues to be a well-tolerated treatment option for patients with LGS.

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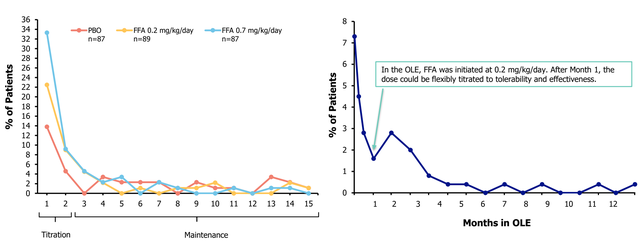
Results

- Incidence of TEAEs occurring in ≥10% of patients by week of first onset of first occurrences in the RCT and in the OLE are described in **Figure 2A** and **Figure 2B**, respectively

Figure 2. Pooled Incidence of TEAEs Occurring in ≥10% of Patients by Week of First Onset of First Occurrences



[a]TEAEs occurring in ≥10% of patients in either treatment group were: decreased appetite, somnolence, fatigue, pyrexia, diarrhea, and vomiting. [b]Two patients experienced TEAEs on the last day of FFA treatment in the RCT, a few days beyond 14 weeks (98 days), which accounts for TEAEs listed at Week 15. [c]TEAEs occurring in ≥10% of patients were: decreased appetite, fatigue, nasopharyngitis, and seizure; there were no first occurrences of these after Week 57.
FFA, fenfluramine; OLE, open-label extension; PBO, placebo; RCT, randomized controlled trial; TEAEs, treatment-emergent adverse events.

- **Table 2** describes median time to onset and duration of first occurrences of TEAEs occurring in ≥10% of patients in the RCT
  - Decreased appetite and somnolence occurred in ≥10% of patients in all RCT groups (placebo and FFA)
  - Of the FFA treatment groups, earliest median time to onset of TEAEs occurred in patients treated with FFA 0.7 mg/kg/day who experienced somnolence (n=15; median, 6 days; range, 1-95) and fatigue (n=16; median, 6.5 days; range 1-41)
  - First occurrence of pyrexia and vomiting resolved in all patients
    - Vomiting resolved in 12/12 patients on FFA 0.2 mg/kg/day within a median duration of 1.5 days (range, 1-54)
    - Pyrexia resolved in 10/10 patients in the placebo group within a median of 2.5 days (range, 1-6) and in 9/9 patients treated with FFA 0.2 mg/kg/day within a median of 3 days (range, 1-10)
- Of the patients randomized to an FFA treatment group who experienced a TEAE occurring in ≥10% of patients, resolution occurred in 45.2%-100% of patients

Table 2. Median Time to Onset and Duration of First Occurrences of TEAEs Occurring in ≥10% of Patients in the FFA RCT by Dose Group

		Diarrhea		Vomiting		Fatigue		Pyrexia		Decreased Appetite		Somnolence	
		Onset	Duration	Onset	Duration	Onset	Duration	Onset	Duration	Onset	Duration	Onset	Duration
Placebo n=87	n Median, days (range)	NA	NA	NA	NA	9 4 (1-99)	6 20.5 (3-71)	10 28.5 (2-92)	10 2.5 (1-6)	10 10 (1-85)	8 28 (8-65)	9 14 (1-96)	5 37 (4-42)
FFA 0.2 mg/kg/day n=89	n Median, days (range)	10 9.5 (2-86)	9 2 (1-60)[a]	12 14 (1-101)	12 1.5 (1-54)[a]	NA	NA	9 20 (5-92)	9 3 (1-10)	18 10 (1-69)	13 15 (4-98)	9 17 (1-75)	7 18 (1-42)
FFA 0.7 mg/kg/day n=87	n Median, days (range)	11 16 (2-86)	10 5 (1-32)	NA	NA	16 6.5 (1-41)	9 51 (4-101)	NA	NA	31 11 (1-91)	14 25.5 (4-97)	15 6 (1-95)	12 14.5 (4-75)

[a]The maximum end of the range was due to one patient.
FFA, fenfluramine; LGS, Lennox-Gastaut syndrome; NA, not applicable, since the TEAE occurred in <10% of patients in that group; OLE, open-label extension; RCT, randomized controlled trial; TEAEs, treatment-emergent adverse events.

- In the OLE, median time to TEAE onset and percent of patients experiencing resolution of first occurrences was reported for the following TEAEs:
  - **Decreased appetite** (n=40): median time to onset, 51.5 days (range, 1-397); resolution in 29 patients (72.5%)
  - **Fatigue** (n=33): median time to onset, 60 days (range, 1-362); resolution in 25 patients (75.8%)
  - **Nasopharyngitis** (n=31): median time to onset, 87 days (range, 9-360); resolution in 100% of patients
  - **Seizure** (n=27): median time to onset, 92 days (range, 1-267); resolution in 22 patients (81.5%)
- Flexible dosing in the OLE limited analysis of time to resolution
- Late-onset first occurrence of TEAEs could be related to other ASMs introduced or dose increases that took place during the OLE study

Conclusions

These results provide further insight on TEAEs reported by ≥10% of patients in the LGS clinical trials. Incidence of first onset of TEAEs was most common during the RCT titration phase and the flexible dose phase in the OLE. Of the first occurrences of TEAEs, a high proportion of patients experienced resolution regardless of FFA dose received in either the RCT or OLE. These data demonstrate that FFA is generally well tolerated, which may contribute to health-related quality of life outcomes in patients with LGS.

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