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

Abstract number : 2.393
Submission category : 7. Anti-seizure Medications / 7D. Drug Side Effects
Year : 2024
Submission ID : 1129
Source : www.aesnet.org
Presentation date : 12/8/2024 12:00:00 AM
Published date :

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Rationale: Lennox-Gastaut syndrome (LGS) is a developmental and epileptic encephalopathy characterized by pharmacoresistant seizures of multiple types. There are a range of anti-seizure medications (ASMs) available that vary in mechanism of action, efficacy, and safety and tolerability. 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. This post-hoc analysis describes the time of onset and duration of treatment-emergent adverse events (TEAEs) reported in the fenfluramine (FFA) randomized controlled trial (RCT, NCT03355209) and open-label extension (OLE, NCT03355209) study in patients with LGS.

Methods: In the RCT, patients 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 study where they were transitioned to FFA 0.2 mg/kg/day for 1 month, then were flexibly titrated to effect and tolerability during Month 2-Month 6. Incidence of TEAEs occurring in ≥5% of patients and in ≥10% of patients by week of first onset, median time to onset and resolution of TEAEs are reported; duration of TEAEs will be described. Time to onset is measured from FFA initiation in either study. Descriptive statistics were used.

Results: Median time to onset of TEAEs occurring in ≥5% of patients are described in **Table 1**. Of these patients receiving FFA 0.2 mg/kg/day and FFA 0.7 mg/kg/day in the RCT, 79.6% and 64.5% experienced TEAE resolution, respectively; **Figure 1A** displays incidence of TEAEs occurring in ≥5% of patients by week of first onset in the RCT. In the OLE, TEAEs occurring in ≥5% of patients resolved in 82.6% of patients. Of the TEAEs occurring in ≥10% of patients in either RCT FFA treatment group (decreased appetite, somnolence, fatigue, pyrexia, diarrhea, and vomiting), fatigue (n=24) was associated with the earliest median time to onset (4 days after FFA start). In the RCT FFA groups, first occurrence of pyrexia (n=16) and vomiting (n=19) resolved in all patients. In the OLE, TEAEs occurring in ≥10% of patients included decreased appetite, fatigue, nasopharyngitis and seizure; all first instances of nasopharyngitis (n=31) in the OLE resolved with a median time to resolution of 94 days (range, 13-368). Incidence of the two most commonly reported TEAEs, decreased appetite and fatigue, by week of first onset in the OLE is displayed in **Figure 1B**.

Conclusions: These results provide insight on time of onset and duration of AEs associated with FFA in the LGS clinical trials. Incidence of first onset of AEs was most common during the RCT titration phase and flexible dose phase in the OLE. These data further highlight that long-term FFA is generally well-tolerated, which may contribute to health-related quality of life outcomes in patients with LGS.

Funding: UCB Pharma

Anti-seizure Medications

Table 1. Median Time to Onset of Commonly Reported TEAEs Occurring in ≥5% of Patients in the Fenfluramine RCT and OLE[a]

	FFA LGS RCT			FFA LGS OLE
Treatment Group	Placebo N=87	FFA 0.2mg/kg/day N=89	FFA 0.7 mg/kg/day N=87	Any dose N=247
Patients Experiencing Commonly Reported TEAEs Occurring in ≥5% of Patients, n (%)	47 (54.0)	54 (60.7)	62 (71.3)	138 (55.9)
Median Time to Onset, days (range)	14 (1-99)	11 (1-101)	7.5 (1-98)	48.5 (1-297)

[a]Only the first occurrence (earliest onset) of a TEAE is counted.

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