Tolerability and Safety of Fenfluramine and Global Functioning of Patients in a Combined Open-label Extension Study of Children and Adults With Dravet and Lennox-Gastaut Syndromes

Poster #P150

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QUESTION

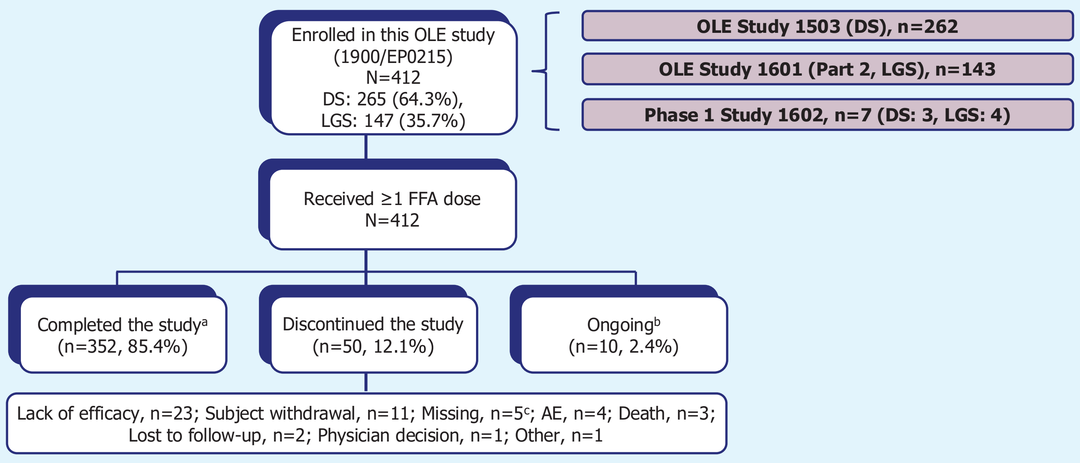
What are the key takeaways regarding long-term safety and global functioning in pediatric and adult patients with Dravet syndrome (DS) or Lennox-Gastaut syndrome (LGS) who continued treatment with fenfluramine in a combined open-label extension (OLE) study (NCT03936777) after participating in a previous open-label study?

INVESTIGATION

- Fenfluramine differs from other anti-seizure medications (ASMs) in its novel mechanism of action, which targets serotonergic and sigma-1 receptor pathways,[1] as well as its minimal risk for CYP450-related drug-drug interactions[2-4]
- The safety and efficacy of fenfluramine in DS and LGS has been demonstrated in 4 randomized controlled trials[5-8] and 2 open-label extension (OLE) studies,[9,10] leading to its approval for the management of seizures associated with DS and LGS in the United States[11] and in the European Union,[12] United Kingdom,[13] and Japan,[14,15] among other countries
- An additional phase 1, open-label study evaluated the safety, tolerability, and pharmacokinetics of fenfluramine when co-administered with cannabidiol (CBD) in patients (2–18 years old) with DS or LGS[16]
- After completion of a previous open-label study, patients still benefiting from fenfluramine were eligible to continue fenfluramine in this OLE study
- Here we report the long-term safety data and results from global functioning analyses from an interim report of a combined OLE study in patients with DS or LGS treated with fenfluramine through 26 July 2024

RESULTS

Patient Disposition

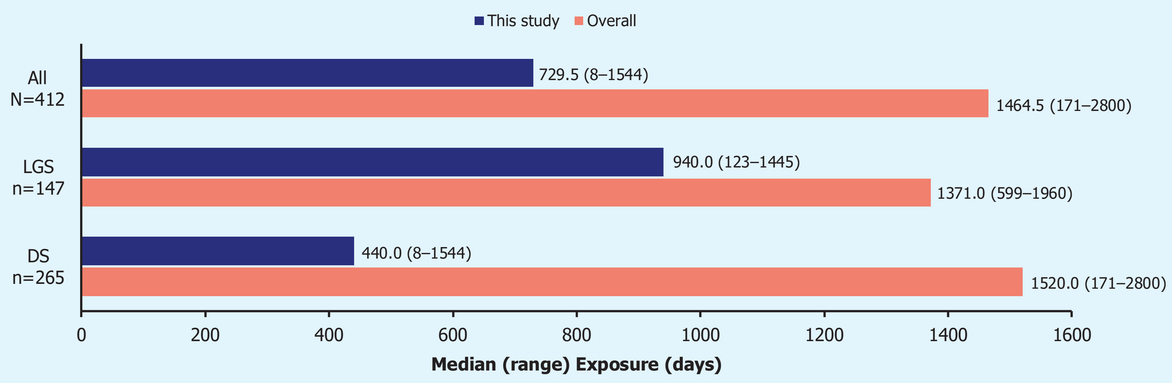


[a]Completed means completed 36 months of treatment (24 months in Denmark), or transitioned to commercial fenfluramine.
[b]Ten patients are either ongoing in the cardiovascular safety follow-up period or final disposition was not yet available.
[c]Five patients with "missing" disposition data were incorrectly reported as having completed the study but had not completed 36 months of treatment (or 24 months in Denmark), so have no reported reason for discontinuation.

Baseline Characteristics

	DS n=265	LGS n=147	All N=412
Age at Visit 1 of this OLE, years			
Mean (SD)	13.4 (6.1)	15.3 (7.7)	14.1 (6.8)
Median (range)	13.0 (3–33)	15.0 (3–37)	13.0 (3–37)
Adult patients (≥18 yrs), n (%)	72 (27.2)	55 (37.4)	127 (30.8)
Male, n (%)	144 (54.3)	77 (52.4)	221 (53.6)
BMI (kg/m²), n	261	142	403
Mean (SD)	18.3 (4.4)	18.8 (4.7)	18.4 (4.5)
Median (range)	17.3 (11.5–38.7)	17.6 (10.3–38.5)	17.4 (10.3–38.7)
Region, n (%)			
North America	111 (41.9)	72 (49.0)	183 (44.4)
Europe	140 (52.8)	70 (47.6)	210 (51.0)
Australia	14 (5.3)	5 (3.4)	19 (4.6)
Prior ASMs at Visit 1 of this OLE, number			
Mean (SD)	2.9 (1.2)	3.3 (1.2)	3.1 (1.2)
Median (range)	3.0 (0–7)	3.0 (0–6)	3.0 (0–7)

Treatment Exposure in This Study and Overall Exposure Since the Start of Fenfluramine



Overview of TEAEs and Serious TEAEs

	DS n=265	LGS n=147	All N=412
Patients with any TEAE, n (%)	183 (69.1)	128 (87.1)	311 (75.5)
Patients with serious TEAEs, n (%)	29 (10.9)	38 (25.9)	67 (16.3)
Patients with TEAEs leading to study discontinuation, n (%)	0 (0.0)	4 (2.7)	4 (1.0)
Patients with treatment-related TEAEs[a], n (%)	29 (10.9)	22 (15.0)	51 (12.4)
Patients with treatment-related serious TEAEs[a], n (%)	1 (0.4)	4 (2.7)	5 (1.2)
Deaths[b], n (%)	1 (0.4)	2 (1.4)	3 (0.7)
TEAEs Reported in ≥10% of Patients, n (%)			
Coronavirus infection	43 (16.2)	42 (28.6)	85 (20.6)
Seizure	26 (9.8)	37 (25.2)	63 (15.3)
Pyrexia	39 (14.7)	15 (10.2)	54 (13.1)
Nasopharyngitis	34 (12.8)	15 (10.2)	49 (11.9)

[a]Treatment-related is based on the investigator's assessment.
[b]3 deaths were attributed to cardiac arrest, left ventricular dysfunction, and status epilepticus; none were deemed by the investigator to be related to fenfluramine.

TEAEs were reported at similar rates among pediatric and adult groups (*supplementary data available via QR code*)

Overview of Cardiovascular Safety *(supplementary data available via QR code)*

No evidence of a clinically significant effect of FFA on ECG parameters (QTcF) observed

No patients with VHD[a,b]

No patients with PAH (PASP >35 mmHg)

[a]Per the agreement with the FDA, VHD is defined as mild, moderate or severe aortic regurgitation (AR) or moderate or severe mitral regurgitation (MR), with additional characteristics and/or physical signs or symptoms attributable to VHD (eg, valve thickening, restricted valve motion).
[b]Three patients presented with mild AR during the study without any other clinical or anatomical abnormality attributable to valve disease, which is not classified as VHD.

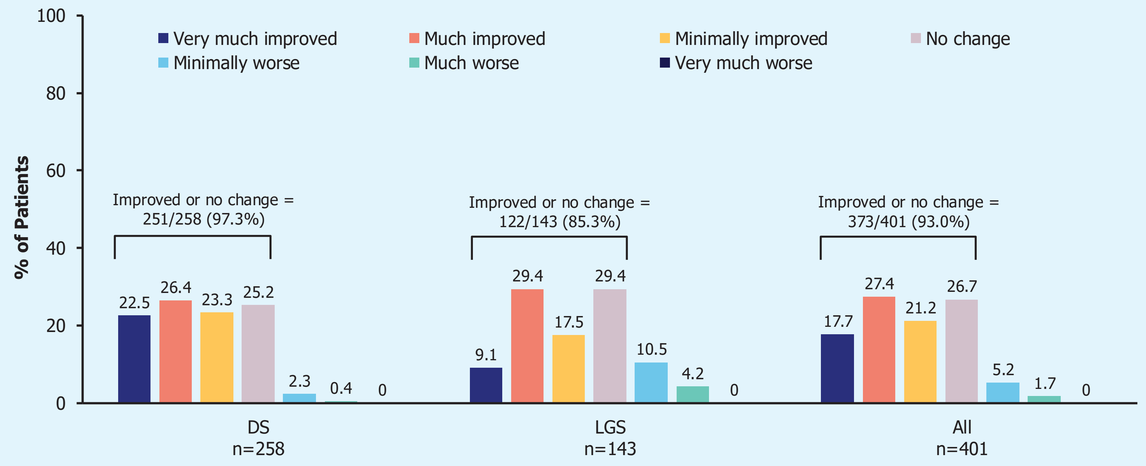
Clinical Global Impression–Severity Scores at Baseline of This OLE

	DS N=265		LGS n=147		All N=412	
	Caregiver, n (%)	Investigator, n (%)	Caregiver, n (%)	Investigator, n (%)	Caregiver, n (%)	Investigator, n (%)
1=Normal, not at all ill	21 (7.9)	13 (4.9)	19 (12.9)	16 (10.9)	40 (9.7)	29 (7.0)
2=Borderline ill	17 (6.4)	11 (4.2)	1 (0.7)	3 (2.0)	18 (4.4)	14 (3.4)
3=Mildly ill	31 (11.7)	35 (13.2)	14 (9.5)	17 (11.6)	45 (10.9)	52 (12.6)
4=Moderately ill	52 (19.6)	106 (40.0)	26 (17.7)	35 (23.8)	78 (18.9)	141 (34.2)
5=Markedly ill	74 (27.9)	54 (20.4)	39 (26.5)	46 (31.3)	113 (27.4)	100 (24.3)
6=Severely ill	40 (15.1)	30 (11.3)	33 (22.4)	23 (15.6)	73 (17.7)	53 (12.9)
7=Among the most extremely ill	14 (5.3)	5 (1.9)	8 (5.4)	5 (3.4)	22 (5.3)	10 (2.4)
Missing	16 (6.0)	11 (4.2)	7 (4.8)	2 (1.4)	23 (5.6)	13 (3.2)

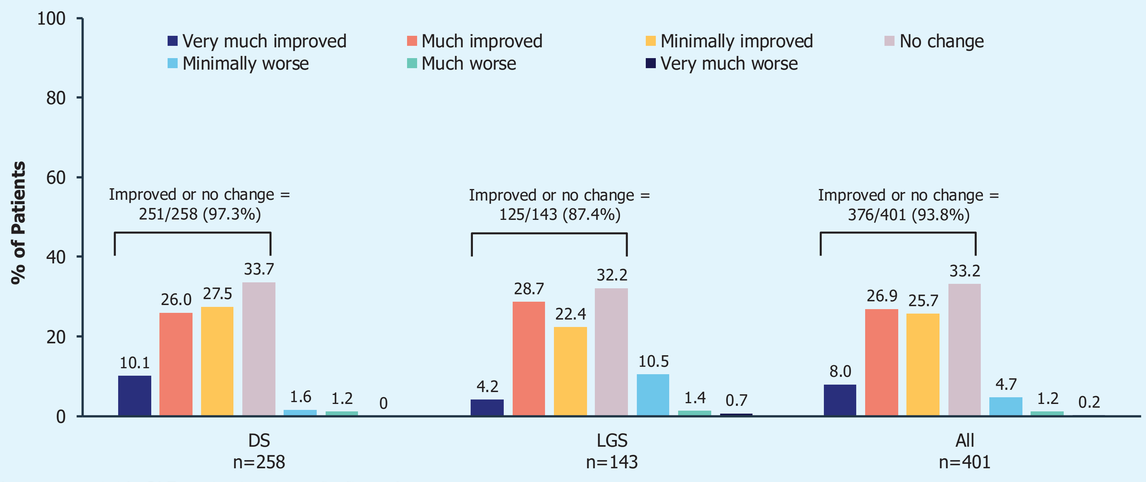
CGI–I Ratings at Last On-Treatment Visit Compared to This OLE Baseline[a]

In this OLE study (after a median 729 days of FFA exposure; mean[SD] FFA daily dose 0.5[0.2] mg/kg/day), most patients were rated as demonstrating improvement or no change from this OLE study baseline (entrance into this OLE) in CGI–I by both caregivers and investigators.

A. Caregiver



B. Investigator



[a]Patients entered this OLE study already on fenfluramine.

Proportions of patients with CGI–I ratings of improved or no change (since entering this OLE) were similar among pediatric and adult groups by DS or LGS (*supplementary data available via QR code*)

Abbreviations: ASMs, anti-seizure medications; CGI–I, Clinical Global Impression–Improvement; DS, Dravet syndrome; ECG, electrocardiogram; FFA, fenfluramine; LGS, Lennox-Gastaut syndrome; OLE, open label extension; PAH, pulmonary arterial hypertension; PASP, pulmonary arterial systolic pressure; QTcF, QT interval corrected for heart rate using Fridericia's formula; RCT, randomized controlled trial; SD, standard deviation; TEAEs, treatment-emergent adverse events; VHD, valvular heart disease.

METHODS

- Patients could enroll in this OLE (Study 1900/EP0215) after participating in a fenfluramine open-label study:
  - Study 1503/EP0212: NCT02823145 (DS)[9]
  - Study 1601/EP0214 (Part 2): NCT03355209 (LGS),[10] or
  - Study 1602/EP0207: NCT03467113 (DS/LGS, phase 1 study assessing safety of fenfluramine+CBD)[16]
- Patients continued onto this OLE study with the latest fenfluramine dose from the previous studies; doses could then be flexibly titrated
  - Dose caps applied: maximum 0.7 mg/kg/day (26 mg/day) without stiripentol (STP) or 0.4 mg/kg/day (17 mg/day) if on concomitant STP
- All patients had to remain on ≥1 concomitant ASM; dose changes in concomitant ASMs permitted as clinically necessary
- The primary objective was to assess the long-term safety and tolerability of fenfluramine
  - Outcomes reported were: incidence of TEAEs, incidence of serious TEAEs, and incidence of VHD and PAH
  - ECGs and echocardiograms (ECHOs) were performed at baseline, then scheduled every 6 months (ECGs as clinically indicated and ECHOs were mandatory); ECHO was required 6 months after the last fenfluramine dose
- A secondary objective was to evaluate patient global functioning using CGI–I global ratings at last treatment visit from baseline (entrance into this OLE) by investigator and caregiver
- Outcomes are presented by developmental and epileptic encephalopathy (DS or LGS) and by age group (pediatric: 2 to <18 years; adult: ≥18 years), where applicable
- Descriptive statistics were used

CONCLUSIONS

- The results of this combined OLE study demonstrate that long-term use of fenfluramine in children and adult patients with DS or LGS was well tolerated
- In this study, TEAEs were consistent with the known safety profile of fenfluramine; no new safety signals were identified and no cases of VHD or PAH were observed
- CGI–I ratings by caregivers and investigators, which may encompass both seizure and non-seizure effectiveness, suggest that pediatric and adult patients with DS or LGS treated with long-term fenfluramine (median overall FFA exposure = 4 years) had a sustained clinical benefit
- Data from this combined OLE study support the continued clinical benefit of fenfluramine and its positive risk/benefit profile observed in prior studies[5-10]

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Disclosures

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Disclosures for all authors can be found in the supplementary slide deck at the QR code.

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