

Final Results From a Long-Term Open-Label Extension Study (Up to 4 Years): Tolerability of Fenfluramine and Global Functioning of Pediatric and Adult Patients With Dravet or Lennox-Gastaut Syndromes

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Introduction

- Dravet syndrome (DS) and Lennox-Gastaut syndrome (LGS) are rare, lifelong developmental and epileptic encephalopathies characterized by high seizure burden and cognitive and behavioral impairments¹⁻³
- Fenfluramine differs from other antiseizure medications (ASMs) in its mode of action, as it targets the serotonergic (5-HT) system and the sigma-1 receptor⁴ and is also associated with minimal risk for CYP450-related drug-drug interactions⁵⁻⁷
- Fenfluramine is currently approved in the US for the management of seizures associated with DS and LGS patients ≥2 years old⁸; its safety and efficacy has been demonstrated in randomized controlled trials (RCTs)⁹⁻¹² and open-label extension (OLE) studies^{13,14}

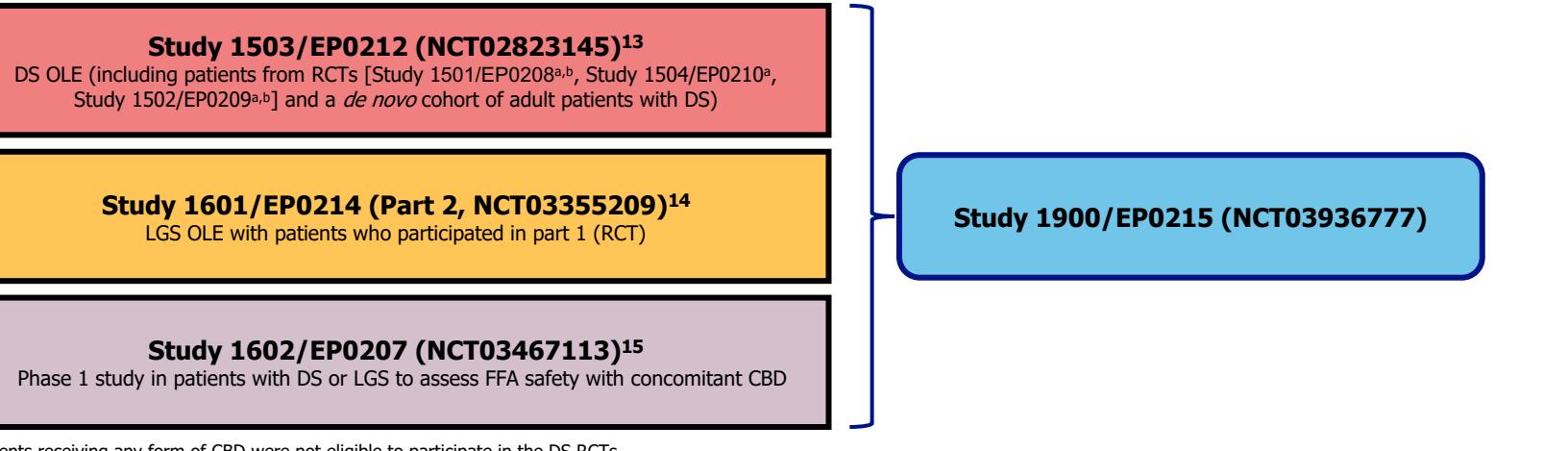
Objective

- Here we report the final long-term safety and global functioning analyses from an OLE study in pediatric and adult patients with DS or LGS treated with fenfluramine

Methods

- Patients who had participated in a prior fenfluramine open-label study were eligible to enroll in this international, multicenter OLE study (NCT03936777) (Figure 1)
- The latest fenfluramine dose from the previous study was continued; doses could then be flexibly titrated
 - Fenfluramine 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 receiving concomitant STP
- ≥1 ASM was required to be given concomitantly with fenfluramine; dose changes in concomitant ASMs were permitted as clinically necessary
- The primary objective was to assess the long-term safety and tolerability of fenfluramine, including cardiovascular safety
 - Echocardiograms (ECHOs) were performed at baseline, then scheduled every 6 months (every 3 months in France) and required 6 months after the last fenfluramine dose
- A secondary objective was to evaluate patient global functioning using Clinical Global Impression—Improvement (CGI-I) ratings, globally and relative to Clinical Global Impression—Severity (CGI-S) scores obtained at study baseline (entrance into this OLE) by caregiver and investigator
- Outcomes are presented by DS or LGS and by age group, where applicable; some age group analyses were conducted post hoc, as were analyses of mean daily dose and overall treatment exposure
- Descriptive statistics were used

Figure 1. Study Design



Results

- A total of 412 patients were enrolled (DS: 265 [64.3%], LGS: 147 [35.7%]) and comprised the safety population; modified intent-to-treat (mITT) population comprised 410 patients
 - Respectively, 262 (63.6%) and 143 (34.7%) patients enrolled from Study 1503 (DS OLE)¹³ and Study 1601 (LGS OLE)¹⁴
 - Of 412 enrolled patients, 285 (69.2%) were pediatric (2 to <18 years old) and 127 (30.8%) were adult (≥18 years old)
- Most baseline characteristics were balanced between the DEE diagnoses (Table 1)
 - A higher proportion of patients with LGS (37.4%) vs those with DS (27.2%) enrolled as adults
 - In both DEE groups, a median of 3.0 ASMs had been previously tried (DS: range, 0-7; LGS: range, 0-6)
 - Of the patients with DS, 143 (54.0%) previously tried 3-4 ASMs and 23 (8.7%) previously tried ≥5 ASMs; 97 (66.0%) patients with LGS had previously tried 3-4 ASMs and 20 (13.6%) had previously tried ≥5 ASMs

Table 1. Baseline Characteristics

Age group	DS n=265		LGS n=147		All n=412	
	2 to <18 y n=193	≥18 y n=72	2 to <18 y n=92	≥18 y n=55	2 to <18 y n=285	≥18 y n=127
Completed, n (%)	186 (96.4)	71 (98.6)	65 (70.7)	38 (69.1)	251 (88.1)	109 (85.8)
Discontinued, n (%)	7 (3.6)	1 (1.4)	27 (29.3)	17 (30.9)	34 (11.9)	18 (14.2)
Reason for discontinuation, n (%)						
Adverse event	0	0	2 (2.2)	1 (1.8)	2 (0.7)	1 (0.8)
Death	1 (0.5)	0	1 (1.1)	1 (1.8)	2 (0.7)	1 (0.8)
Lack of efficacy	4 (2.1)	0	13 (14.1)	7 (12.7)	17 (6.0)	7 (5.5)
Lost to follow-up	0	0	1 (1.1)	2 (3.6)	1 (0.4)	2 (1.6)
Physician decision	0	0	1 (1.1)	0	1 (0.4)	0
Subject withdrawal	1 (0.5)	1 (1.4)	5 (5.4)	4 (7.3)	6 (2.1)	5 (3.9)
Other	0	0	0	1 (1.8)	0	1 (0.8)
Missing	1 (0.5)	0	4 (4.3)	1 (1.8)	5 (1.8)	1 (0.8)
Mean daily dose (SD), mg/kg/day	0.5 (0.2)	0.4 (0.1)	0.6 (0.1)	0.4 (0.1)	0.5 (0.2)	0.4 (0.1)
FFA exposure in this study, days	449.0 (8-1544)	370.0 (189-1431)	993.0 (123-1445)	894.0 (8-1544)	730.0 (123-1445)	722.0 (8-1544)
Median (range)	449.0 (8-1544)	370.0 (189-1431)	993.0 (123-1445)	894.0 (8-1544)	730.0 (123-1445)	722.0 (8-1544)

*Completed or discontinued 36 months of treatment (24 months in Denmark) or transitioned to commercial fenfluramine. [†]Deaths were attributed to cardiac arrest (n=1), non-compaction cardiomyopathy (n=1), and status epilepticus (n=1); none were deemed by the investigator to be related to FFA. [‡]Six 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.

DEE, developmental and epileptic encephalopathy; DS, Dravet syndrome; FFA, fenfluramine; LGS, Lennox-Gastaut syndrome; SD, standard deviation; y, years.

• Mean fenfluramine (SD) daily dose throughout this OLE study: 0.5 (0.2) mg/kg/day

• In both DEE groups, mean daily dose was lower in adult (0.4 [0.1] mg/kg/day) vs pediatric patients (0.5 [0.2] mg/kg/day). **Table 2**

• Median fenfluramine exposure in this study was 2 years (729.5 days [range, 8-1544]; **Figure 2**)

• Median exposure in patients with DS was 440.0 days (range, 8-1544) and in patients with LGS was 940.0 days (123-1445)

• Exposure in either DEE was higher in pediatric patients (**Table 2**)

^aWeight available in 283/285 pediatric and 124/127 adult patients.

ASMs, antiseizure medications; DS, Dravet syndrome; LGS, Lennox-Gastaut syndrome.

^bWeight available in 283/285 pediatric and 124/127 adult patients.

ASMs, antiseizure medications; DS, Dravet syndrome; LGS, Lennox-Gastaut syndrome.

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