PL30. Long-Term (2-Year) Safety and Efficacy of Adjunctive ZX008 (Fenfluramine HCl) for Dravet Syndrome: Interim Results of an Ongoing Open-Label Extension Study

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Introduction

- Dravet syndrome (DS) is a rare, treatment-resistant epileptic encephalopathy characterized by disabling seizures and subsequent neurodevelopmental and psychomotor delay
- Patients with DS have a 6-fold higher risk of sudden unexpected death in epilepsy (SUDEP), for which the number one risk factor is generalized tonic-clonic seizures (GTCs)
- Fenfluramine (FFA) has been demonstrated to result in profound reductions in convulsive seizure frequency and prolonged periods of seizure freedom in 3 randomized, double-blind, placebo-controlled, phase 3 clinical studies[1-3]

Objective

- The aim of this interim analysis was to describe the long-term safety and efficacy of adjunctive fenfluramine for patients with DS

Methods

Study Design

- This is an ongoing international, multicenter, open-label, long-term study of FFA (Study 1503)
- FFA was administered as FINTEPLA®, an oral solution of fenfluramine hydrochloride containing 2.2 mg/mL FFA
- Patients with DS, aged 2-18 years, who successfully completed treatment in Study 1, 2, or 3 were eligible to participate (**Figure 1**)
  - In Studies 1 and 3 (NCT02682927 and NCT02826863), patients received FFA up to a maximum of 26 mg/day[1,3]
  - In Study 2 (NCT02926898), when stiripentol (STP) was used with FFA, dose range was 0.2-0.4 mg/kg/day with a maximum allowable dose of 17 mg/day[2]

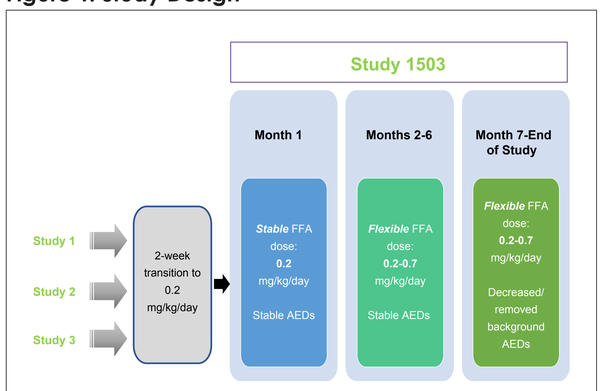
Endpoints

- Efficacy was assessed as the reduction in monthly convulsive seizure frequency (MCSF) from core study baseline
- The incidence of treatment-emergent adverse events (TEAEs) and cardiovascular safety were evaluated, as was the incidence of weight gain/weight loss

Statistical Analyses

- Descriptive statistics were used for demographic information
- Continuous data were summarized with n, mean, standard deviation, median, and range
- Categorical data were summarized using the frequency of patients within each category, n (%)

Figure 1. Study Design



AEDs, antiepileptic drugs; FFA, fenfluramine.

Results

Patients

- As of February 15, 2019 (interim analysis cutoff date), 330 patients had entered the open-label extension (OLE) with a median treatment duration of 445 days (**Table 1**)

Table 1. Patient Demographics and FFA Exposure

Demographic	N=330
Age, years	
Mean±SD	9.0±4.6
Median (min, max)	8.0 (2, 19)
Age group, n (%)	
<6 years	91 (27.6)
6-18 years	238 (72.1)
>18 years	1 (0.3)
Sex, n (%)	
Male	180 (54.5)
Race, n (%)	
White	245 (74.2)
Unknown[a]	44 (13.3)
Region, n (%)	
Canada or USA	150 (45.5)
Europe/Australia	180 (54.5)
Baseline convulsive seizure frequency per 28 days	
Median (min, max)[b]	15.3 (2.7, 2719.3)
Days of treatment with FFA in OLE	
Median (min, max)	445 (7, 899)
Patients discontinuing treatment, n (%)	56 (17)
Reasons for discontinuation, n (%)	
Lack of efficacy	35 (10.6)
Patient/caregiver withdrawal	9 (2.7)
Adverse event	4 (1.2)
Death (SUDEP)	2 (0.6)
Most common (>10%) concomitant AEDs, %	
Clobazam	72.4
Valproic acid	71.2
Stiripentol	29.1
Topiramate	24.8
Levetiracetam	24.2
Clonazepam	12.1
Duration of exposure by age group at core study entry, days	
Median (min, max)	
<6 years old	454 (57, 813)
≥6 years old	381 (7, 899)
Mean daily dose (FFA, mg/kg/day), n (%)	
Up to 0.2	26 (8)
>0.2 to <0.3	90 (27)
0.3 to 0.5	123 (37)
>0.5 to 0.7	91 (28)

[a]Privacy laws in some regions/countries preclude disclosure of certain personal information.

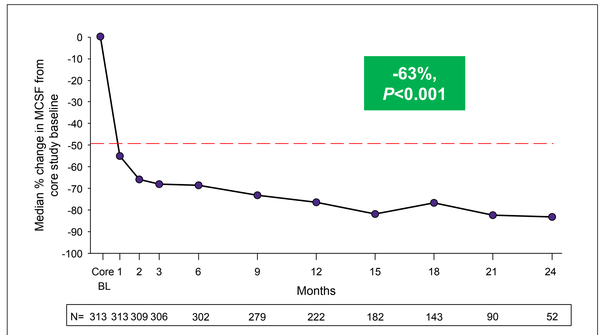
[b]Determined during the core study; does not include patients from Study 1504 Cohort 1.

AEDs, antiepileptic drugs; FFA, fenfluramine; OLE, open-label extension; SD, standard deviation; SUDEP, sudden unexpected death in epilepsy.

Median MCSF Reduction Over Time

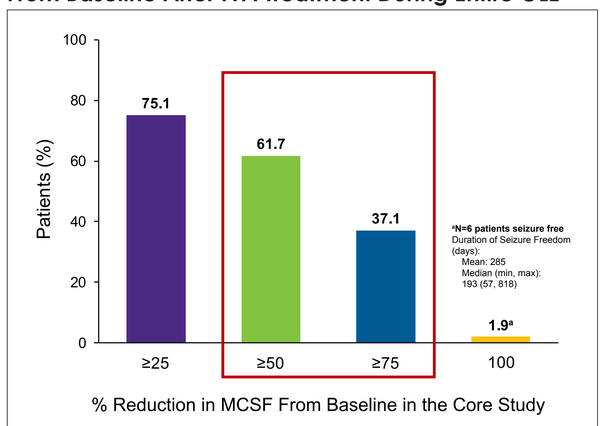
- Patients experienced a clinically meaningful and statistically significant reduction in MCSF over the entire treatment period (-63%; *P*<0.001) (**Figure 2**)
- A clinically meaningful (≥50%) MCSF reduction and a profound (≥75%) MCSF reduction were observed (**Figure 3**)

Figure 2. Reduction in Median MCSF Over Time During 24 Months' FFA Treatment in OLE



Core BL, core study baseline; MCSF, monthly convulsive seizure frequency; OLE, open-label extension.

Figure 3. Proportion of Patients With MCSF Reduction From Baseline After FFA Treatment During Entire OLE



FFA, fenfluramine; MCSF, monthly convulsive seizure frequency; OLE, open-label extension.

Safety

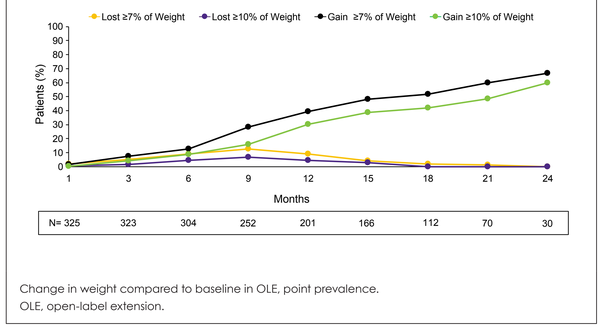
- No patient developed valvular heart disease or pulmonary hypertension (**Table 2**; **Figure 4**)

Table 2. Most Common Treatment-Emergent Adverse Events in OLE (N=330)

Patients with any TEAE, n (%)	308 (93.3)
TEAEs in ≥10% of patients, n (%)	
Nasopharyngitis	77 (23.3)
Pyrexia	76 (23.0)
Decreased appetite	70 (21.2)
Diarrhea	50 (15.2)
Upper respiratory tract infection	47 (14.2)
Seizure	43 (13.0)

OLE, open-label extension; TEAE, treatment-emergent adverse event.

Figure 4. Weight Change Over Time in OLE



Change in weight compared to baseline in OLE, point prevalence.
OLE, open-label extension.

Conclusions

- FFA provides a durable and sustained clinically meaningful seizure reduction, demonstrating a median of 63% reduction in MCSF throughout the entire OLE with 445 days' median treatment duration
- 61.7% and 37.1% had a ≥50% and a ≥75% MCSF reduction, respectively, during the entire OLE
- FFA was generally well tolerated; the most common TEAEs were nasopharyngitis, pyrexia, decreased appetite, and diarrhea
- No cases of valvular heart disease or pulmonary arterial hypertension were reported
- FFA represents an important new treatment option for patients with Dravet syndrome

References

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