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Long-Term Cardiovascular Safety of Fintepla® (Fenfluramine HCl Oral Solution) in the Treatment of Dravet Syndrome: Interim Analysis of an Open-Label Safety Extension Study

ZOGENIX

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INTRODUCTION

- Dravet syndrome (DS) is a rare, severe, treatment-resistant epileptic encephalopathy
  - Despite use of multidrug regimens, 45% of patients with DS continue to experience ≥4 tonic-clonic seizures/month[1]
  - Generalized tonic-clonic seizures have been identified as a major risk factor for sudden unexpected death in epilepsy (SUDEP),[1] which occurs with a 2- to 6-fold higher incidence in patients with DS than in patients with other epilepsies[2]
- In 2 recently completed phase 3, double-blind, parallel-group, placebo-controlled clinical studies, low-dose fenfluramine (FFA) demonstrated profound reduction in frequency of convulsive seizures vs placebo in children and young adults with DS[3,4]
  - In the first study (Study 1), FFA 0.8 mg/kg/day (maximum 30 mg/day) demonstrated a 63.9% greater reduction in mean convulsive seizure frequency vs placebo ($P<0.001$)[3]
  - In the second study (Study 1504), FFA 0.5 mg/kg/day (maximum 20 mg/day) demonstrated a 54.0% greater reduction in mean convulsive seizure frequency vs placebo ($P<0.001$)
- FFA was previously marketed globally for weight loss in obese adults, with a total of 18 million prescriptions written in the US in 1996,[5] and was withdrawn following reports of valvular heart disease[6]
  - FFA was commonly used in combination with phentermine[6,7]
  - Doses up to 120 mg/day were reported[6,7]
  - The majority of reported cases had no pretreatment data[7]
- No studies have been published describing serial echocardiograms (ECHOs) conducted every 3 months over a period of 1 or more years in a pediatric population
- In the phase 3 studies of low-dose FFA in patients with DS, cardiac valve function and pulmonary arterial pressure were monitored prospectively with ECHOs performed during screening, after 6 weeks of treatment with FFA, and at the end of the study (14 or 15 weeks of treatment)
  - These ECHOs revealed no valvular heart disease (VHD) in any patient at any time
  - No patient demonstrated pulmonary arterial hypertension (PAH) during these studies
- Here we report an interim analysis of the cardiovascular safety findings from a long-term open-label extension (OLE) study (NCT02823145)

METHODS

- Upon completion of any of the program's phase 3 studies, patients were eligible to enroll in the OLE study
- All patients in the OLE study were started at a FFA dose of 0.2 mg/kg/day
  - After 4 weeks the dose could be titrated up to a maximum 0.8 mg/kg/day (maximum 30 mg/day), or in patients taking concurrent stiripentol, to a maximum dose of 0.5 mg/kg/day (maximum 20 mg/day)
- Color Doppler ECHO was performed at OLE study entry, Week 4-6, and every 3 months thereafter to assess cardiac valve function and pulmonary artery pressure
  - All ECHOs were performed with standardized views and machine settings
  - All ECHOs were read following a standardized blinded procedure with oversight from an independent expert review board
- VHD was defined using the FDA definition: ≥moderate mitral valve regurgitation and/or ≥mild aortic valve regurgitation[8]
- All grades of regurgitation (ie, absent, trace, mild, moderate, and severe) were captured on all 4 valves
  - Notably, the 2017 ECHO guidelines[9] classified grading of severity of regurgitation as mild, moderate, and severe, and considered "trace" regurgitation as physiological
- The threshold for potential PAH was set as pulmonary arterial systolic pressure >35 mmHg

RESULTS

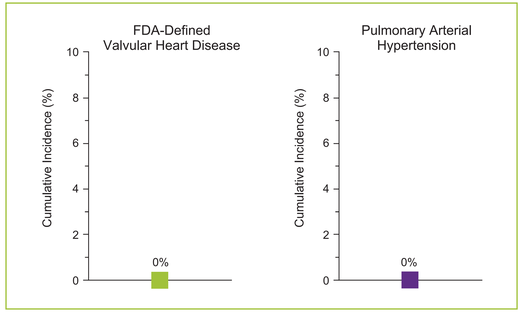
- 232 patients enrolled in the OLE study as of the interim cutoff date of March 13, 2018, and each received at least 1 dose of FFA
  - Median duration of treatment with FFA of 256 days (range, 58-634 days)
  - Approximately 161 patient-years
  - A total of 703 ECHOs have been performed and read
- OLE baseline patient characteristics are presented in **Table 1**
- No FDA-defined VHD or PAH was observed in any patient at any time during the study (**Figure 1**)

Table 1. Baseline Patient Characteristics

N	232
Age, years; mean±SD (median) Min, max	9.1±4.7 (9.0) 2, 19
Age group, n (%) <6 years 6-18 years >18 years	 65 (28.0) 166 (71.6) 1 (0.4)
Sex, n (%) Male Female	 128 (55.2) 104 (44.8)
Race, n (%) White Black or African American Asian American Indian or Alaska native Other Not reported*	 172 (74.1) 1 (0.4) 9 (3.9) 2 (0.9) 13 (5.6) 35 (15.1)
Region, n (%) Canada or US Rest of world	 111 (47.8) 121 (52.2)
Baseline weight, kg Mean±SD (median)	 33.5±17.3 (28.7)
Baseline BMI, kg/m^2 Mean±SD (median)	 17.9±4.2 (17.0)
Patient disposition	
Days of treatment with FFA in OLE Median (min, max)	 256 (58, 634)
Patients discontinuing treatment n (%) Reasons Lack of efficacy Patient/caregiver withdrawal Adverse event Death (SUDEP) Physician decision	 22 (9.5) 16 3 1 1 1

*Not reported or missing. Privacy laws in some regions/countries preclude disclosure of certain personal information.

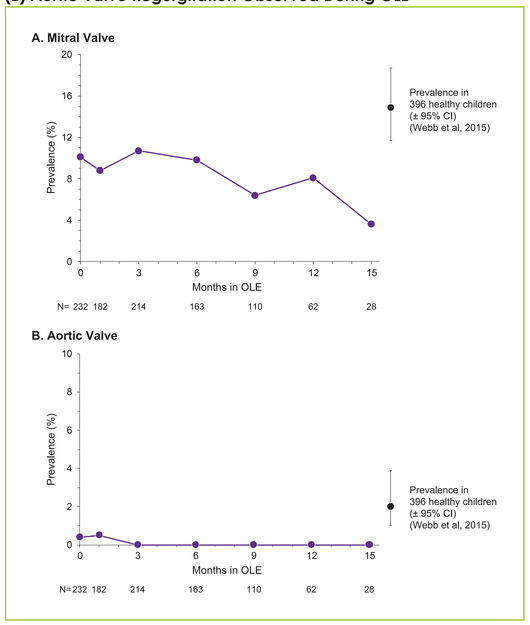
Figure 1. Cumulative Incidence of FDA-Defined Valvular Heart Disease or Pulmonary Arterial Hypertension in the OLE Study, N=232



Cardiac Valve Function

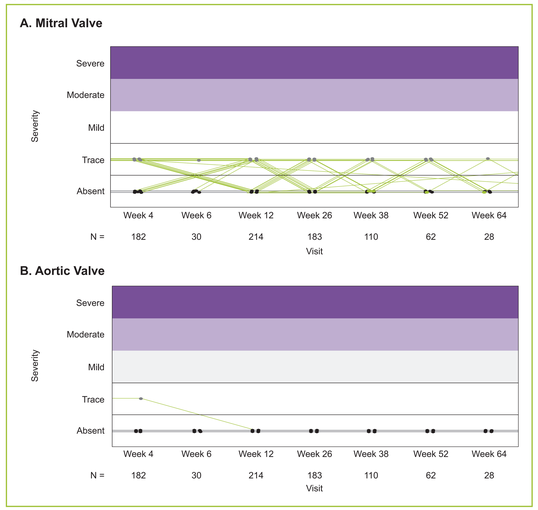
- During the OLE, all patients demonstrated mitral and aortic valve function within the normal range (**Figures 2 and 3**)
  - A low cross-sectional prevalence of "trace" mitral or aortic regurgitations was observed in this interim analysis (**Figures 2 and 3**)
    - These findings were considered physiologic and within the range of normal valve function[9]
    - "Trace" regurgitation was commonly transient or intermittent, a characteristic that supports its physiologic nature (**Figure 3**)
- The cross-sectional prevalence of trace mitral or trace aortic valve regurgitation did not increase with increased duration of exposure to FFA (**Figure 2**) and was less than observed in an echocardiographic study of 396 healthy children aged 10-12 years[10]

Figure 2. Cross-Sectional Prevalence of Trace (A) Mitral or (B) Aortic Valve Regurgitation Observed During OLE



The decrease in N is due to the staggered entry into the study and not due to patient withdrawals. The black points at the right of the x axis indicate the prevalence point estimate ± 95% CI for trace regurgitation in 396 normal healthy children aged 10-12 years, as reported by Webb et al (2015).[10]

Figure 3. (A) Mitral and (B) Aortic Valve ECHO Observations During OLE



Gray lines represent patients with "absent" regurgitation throughout the entire OLE study. The white zones in the plots represent normal physiologic findings. Green lines represent patients who had "trace" regurgitation at one or more times during the study.

CONCLUSION

- No VHD or PAH has been observed in this OLE study, during which 232 patients have been exposed to a median 256 days of treatment with low-dose FFA

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DISCLOSURES

WL, MP: Research funding, Zogenix.
GF, BSG, GM, ARG, AA: Employee, Zogenix; Stock ownership, Zogenix.
ML: Consultant, Zogenix.

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