seizure types and Total seizure burden. ZX008 may represent an effective new treatment option for Dravet syndrome.

doi:10.1016/j.yebeh.2019.08.064

Epilepsy & Behavior 101 (2019) 106790

Fenfluramine HCl Provides Long-Term Clinically Meaningful Reduction in Seizure Frequency: Results of an Open-Label Extension Study

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Introduction: Fenfluramine (FFA) has demonstrated superior efficacy compared to placebo for the reduction in frequency of convulsive seizures in children and young adults (2-18 years old) with Dravet syndrome in two recently completed Phase 3 clinical trials. Here we report the preliminary interim analysis of the effectiveness and tolerability of FFA in a long-term open label extension study.

Methods: Dravet syndrome patients completing one of the Phase 3 clinical trials were eligible to enroll in the open-label extension (OLE) study. All patients entering the OLE initiated FFA at a dose of 0.2 mg/kg/day regardless of what dose they were receiving in the core trial. After 4 weeks, the dose could be titrated up in 0.2 mg/kg/day increments up to a maximum of 0.8 mg/kg/day (max 30 mg/day; 0.5 mg/kg/day [max 20 mg/day] if patient was also on stiripentol). Effectiveness and safety were assessed at months 1, 2, and 3 and then 3-month intervals thereafter.

Results: A total of 232 patients have enrolled in the study as of March 13, 2018. A total of 128 (55.2%) were male, and the mean ± SD age was 9.1 ± 4.7 years. A total of 22 (9.5%) patients discontinued treatment: lack of efficacy (16), subject withdrawal (2), adverse event (1), death (1, SUDEP), physician decision (1), and withdrawal by caregiver (1). Median duration of treatment with FFA was 256 days (range, 58-634 days). The median percent reduction in monthly convulsive seizure frequency over the entire OLE treatment period as compared with the baseline frequency established in the core Phase 3 studies was 66.8%. A clinically meaningful reduction in convulsive seizure frequency was noted at the first observation (month 1) during OLE and continued over time (Figure). Over the entire observation period, 64.4% of patients demonstrated a 50% reduction in convulsive seizure frequency and 41.2% demonstrated a 75% reduction. At 12 months 70.4% of caregivers and 77.8% of investigators rated patients as "much improved" or "very much improved." The most common non-cardiovascular adverse events occurring in ≥10% of patients were pyrexia (21.6%), nasopharyngitis (19.4%), decreased appetite (15.9%), influenza (11.6%), diarrhoea (10.8%), and upper respiratory infection (10.3%). No patient showed echocardiographic or clinical signs of cardiac valvular heart disease or pulmonary hypertension at any time.

Conclusions: These preliminary OLE study results demonstrate FFA to provide clinically meaningful and substantial reductions in convulsive seizure frequency over time; while generally well tolerated. FFA represents a novel, highly effective antiepileptic treatment option for DS patients.

doi:10.1016/j.yebeh.2019.08.065

Epilepsy & Behavior 101 (2019) 106791

Long-Term Cardiovascular Safety of Fenfluramine HCl in the Treatment of Dravet Syndrome: Interim Analysis of an Open-Label Safety Extension Study

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Introduction: In two recently completed Phase 3 clinical trials, fenfluramine (FFA) has demonstrated superior efficacy vs placebo for convulsive seizure reduction in children and young adults (2-18 years old) with Dravet syndrome (DS). FFA, previously marketed for weight loss, was withdrawn from the market in 1997 following reports of cardiac valvular heart disease (VHD) and pulmonary hypertension in obese adults treated with ≥60 mg/day. Here we report the cardiovascular safety findings from an interim analysis of the long-term safety extension study of low-dose FFA for DS in children and young adults.

Methods: Patients with DS who successfully completed a Phase 3 study were eligible for this open-label extension (OLE) study. Patients with current cardiac VHD, pulmonary arterial hypertension, or any degree of aortic or mitral valve regurgitation were excluded from the Phase 3 trials. All patients in the OLE were started on FFA at 0.2 mg/kg/day, after 4 weeks the dose could be titrated 0.2 mg/kg/day every 2 weeks based on effectiveness and tolerability to 0.8 mg/kg/day to maximum 30 mg/day (0.5 mg/kg/day and 20 mg/day if they were taking concurrent stiripentol). Echocardiography was performed at extension study baseline, Week 6, and 3 monthly thereafter to assess cardiac valve function and pulmonary artery pressure. Cardiac VHD was defined as