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ZX008 (Fenfluramine HCl Oral Solution) in Dravet Syndrome: Results of a Phase 3, Randomized, Double-Blind, Placebo-Controlled Trial

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INTRODUCTION

- Dravet syndrome is a rare, severe, treatment-resistant, developmental epileptic encephalopathy
- Current standard of care for Dravet syndrome is treatment with multiple antiepileptic drugs (AEDs), but 45% of patients continue to experience ≥4 tonic-clonic seizures per month despite polytherapy[1]
- Currently, there are no FDA-approved medications to treat seizures associated with Dravet syndrome

ZX008 (Fenfluramine HCl Oral Solution)

- Observed efficacy of fenfluramine in pediatric patients with intractable seizures was initially reported in case reports (reviewed by Schoonjans, et al[2]) and 2 cohorts of Dravet syndrome patients treated for as long as 28 years[3-5]
- Here we report the results of a prospective merged analysis of 119 consecutive subjects randomized to treatment in either of 2 identical Phase 3, randomized, placebo-controlled, double-blind clinical trials of ZX008 in pediatric and young adult subjects with Dravet syndrome (NCT02682927, NCT02826863)

METHODS

Subjects

- Males and females 2 to 18 years old with a clinical diagnosis of Dravet syndrome whose seizures were not completely controlled by their current AED regimen
  - All medications or interventions for epilepsy (including ketogenic diet and vagal nerve stimulation) had to be stable for ≥4 weeks prior to screening
- All subjects had to meet minimum baseline convulsive seizure frequency entry criteria and be approved for entry by the Epilepsy Study Consortium and the cardiac monitoring group
- Key exclusion criteria included:
  - History of cardiovascular or cerebrovascular disease
  - Concomitant treatment with serotonergic activity or cannabinoid products
  - Treatment with stiripentol in the 21 days prior to screening
  - Any ongoing medical diagnosis that might alter risk-benefit ratio or impede participation in the trial

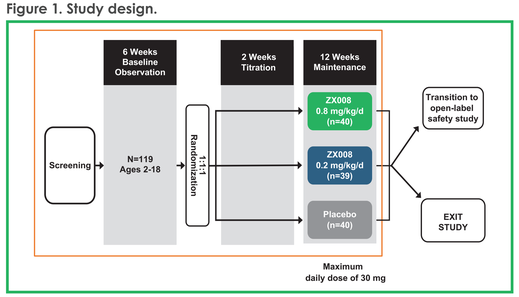
Study Design

- Study 1 was a prospective merged analysis of 2 identical double-blind, placebo-controlled, 14-week, fixed-dose clinical studies (**Figure 1**)

Safety

- Assessed by capture of adverse events (AEs), vital signs, chemistry, hematology, electrocardiogram, hormones, and cognition
- Cardiac valve structure and function and pulmonary hypertension were assessed by standardized Doppler echocardiography during screening, treatment, and post-treatment

Figure 1. Study design.



Outcomes Measured

- The primary efficacy endpoint was change in mean convulsive seizure frequency from baseline to the combined 14-week titration and maintenance periods between ZX008 0.8 mg/kg/day and placebo (**Figure 3**)
- Secondary efficacy endpoints included (*key secondary endpoints):
  - *Comparison of change in mean convulsive seizure frequency from baseline to the combined titration and maintenance periods between ZX008 0.2 mg/kg/day and placebo (**Figure 3**)
  - Proportion of subjects in each group who achieved ≥25%, *≥50%, or ≥75% reduction in convulsive seizure frequency compared with baseline
  - *Longest convulsive seizure-free interval between the treatment groups
- A hierarchical analysis plan was employed to control for multiplicity with the primary and key secondary endpoints

RESULTS

Figure 2. Subject disposition.

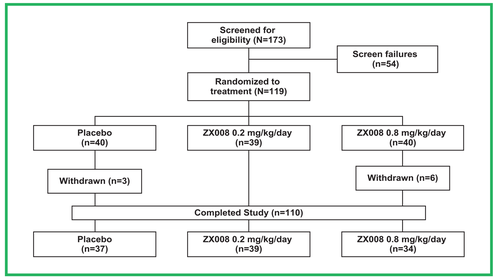
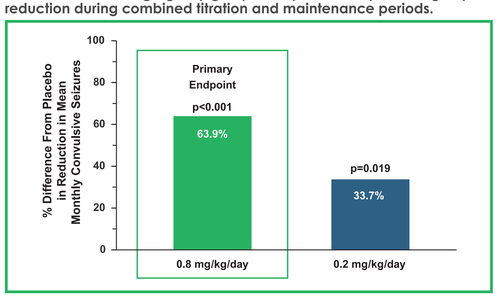


Table 1. Subject Demographics

	Placebo	ZX008 0.2 mg/kg/day	ZX008 0.8 mg/kg/day	Overall
n	40	39	40	119
Age, years, mean±SD (min, max)	9.2±5.1 (2, 18)	9.0±4.5 (2, 17)	8.8±4.4 (2, 18)	9.0±4.7 (2, 18)
Age group <6 years, n (%)	11 (27.5)	9 (23.1)	11 (27.5)	31 (26.1)
Males, n (%)	21 (52.5)	22 (56.4)	21 (52.5)	64 (53.8)
Race, n (%) Caucasian	31 (77.5)	33 (84.6)	34 (85.0)	98 (82.4)
BMI, kg/m^2, mean±SD	18.0±3.8	19.3±5.7	18.5±3.5	18.6±4.4
Baseline convulsive seizure frequency per 28 days, mean±SD (median)	46.1±40.7 (31.4)	47.2±99.6 (17.5)	33.0±31.5 (21.2)	41.9±65.0 (22.7)

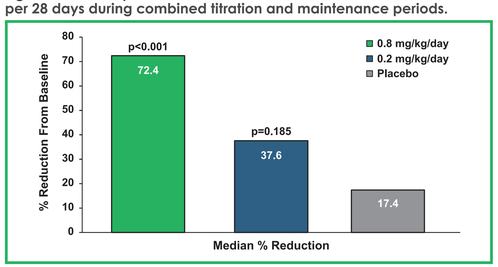
Efficacy

Figure 3. Percent reduction in mean monthly convulsive seizures for the ZX008 0.8 and 0.2 mg/kg/day groups compared with placebo group reduction during combined titration and maintenance periods.



p-values are derived from an ANCOVA with treatment group and age group as factors and baseline convulsive seizure frequency as a covariate.

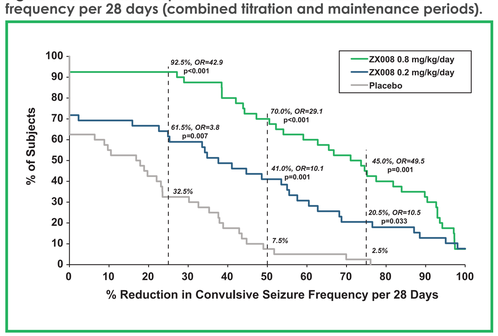
Figure 4. Median percent reduction from baseline in convulsive seizures per 28 days during combined titration and maintenance periods.



p-values are comparison vs placebo.

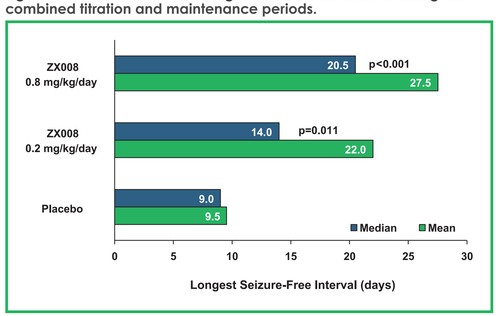
- Significantly more subjects treated with both doses of ZX008 achieved ≥25%, *≥50%, and ≥75% reduction in convulsive seizure frequency during treatment compared with baseline (**Figure 5**)
- The odds of achieving a clinically meaningful (ie, ≥50%) or substantial (ie, ≥75%) reduction in convulsive seizure frequency were 29 and 50 times higher, respectively, among subjects treated with ZX008 0.8 mg/kg than in subjects treated with placebo (**Figure 5**)
- *The median longest seizure-free interval was significantly longer in subjects treated with ZX008 0.8 mg/kg/day and ZX008 0.2 mg/kg/day compared with placebo (**Figure 6**)

Figure 5. Cumulative response curve for % reduction in seizure frequency per 28 days (combined titration and maintenance periods).



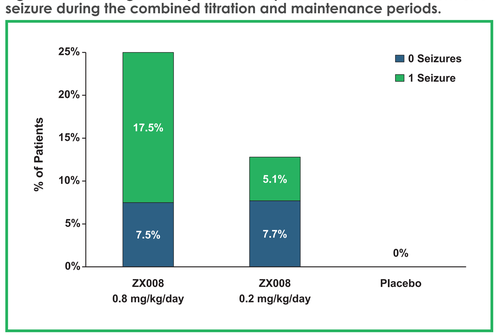
p-values are vs placebo. OR, odds ratio vs placebo.

Figure 6. Median* and mean longest seizure-free interval during the combined titration and maintenance periods.



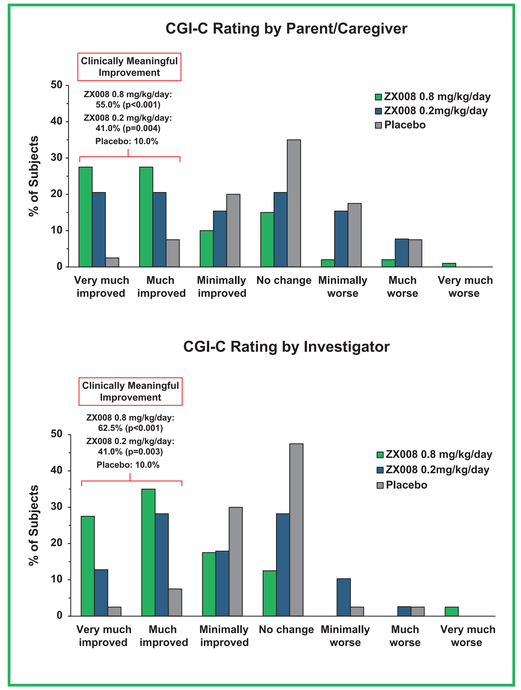
*Key secondary endpoint.

Figure 7. Percentage of subjects who experienced seizure freedom or 1 seizure during the combined titration and maintenance periods.



Seizure freedom was a prespecified secondary endpoint. Evaluation of 0 or 1 seizure was a post-hoc analysis.

Figure 8. Clinical Global Impression of Change (CGI-C) rated by parent/caregivers and investigators.



p-values are vs placebo.

Safety

Non-Cardiovascular Safety

Table 2. Most Common Non-Cardiovascular Treatment-Emergent AEs (≥10% in any treatment group)

	Placebo (n=40)	ZX008 0.2 mg/kg/day (n=39)	ZX008 0.8 mg/kg/day (n=40)
Subjects with ≥1 TEAE	26 (65.0%)	37 (94.9%)	38 (95.0%)
Subjects with ≥1 serious TEAE	4 (10.0%)	4 (10.3%)	5 (12.5%)
Diarrhea	3 (7.5%)	12 (30.8%)	7 (17.5%)
Vomiting	4 (10.0%)	4 (10.3%)	3 (7.5%)
Fatigue	1 (2.5%)	4 (10.3%)	4 (10.0%)
Pyrexia	8 (20.0%)	7 (17.9%)	2 (5.0%)
Nasopharyngitis	5 (12.5%)	4 (10.3%)	7 (17.5%)
Upper respiratory tract infection	5 (12.5%)	8 (20.5%)	0 (0.0%)
Fall	2 (5.0%)	4 (10.3%)	0 (0.0%)
Weight decreased	0 (0.0%)	5 (12.8%)	2 (5.0%)
Decreased appetite	2 (5.0%)	8 (20.5%)	15 (37.5%)
Lethargy	2 (5.0%)	4 (10.3%)	7 (17.5%)
Seizure	5 (12.5%)	4 (10.3%)	3 (7.5%)
Somnolence	3 (7.5%)	6 (15.4%)	4 (10.0%)

Cardiovascular Safety

Table 3. FDA Definition of Cardiac Valvulopathy

Valve	Grade of Blood Regurgitation (Back-Flow) at Valve Measured by Echocardiogram				
	Absent	Trace	Mild	Moderate	Severe
Aortic					
Mitral					
Tricuspid					
Pulmonic					

Blue cells are findings that are not considered evidence of a cardiac valve disorder. The gray cells in the table meet the FDA definition of cardiac valvulopathy.

- Valvulopathy
  - No cases of FDA-defined cardiac valvulopathy were observed during the trial
- Trace mitral regurgitation (MR) or aortic regurgitation (AR)
  - During the study, 5 (12.5%), 7 (17.9%), and 9 (22.5%) subjects had at least one echocardiogram finding with trace MR and/or AR in the placebo, 0.2 mg/kg/day, and 0.8 mg/kg/day groups, respectively
    - These findings all fell within the blue cells of **Table 3**
  - Clinical guidelines categorize absent and trace echocardiogram findings as normal and do not represent evidence of cardiac valve disease[6]
  - 21/179 subjects (12.1%) were excluded from participation in the study due to a screening echocardiogram finding of trace MR or trace AR with no symptoms of CV disease, illustrating the common occurrence of this finding in normal children and young adults
- Pulmonary hypertension
  - No echocardiographic findings or clinical symptoms suggesting pulmonary hypertension were noted

CONCLUSIONS

- ZX008 (Fenfluramine HCl oral solution) demonstrated robust efficacy in this Phase 3 clinical trial for adjunctive treatment of convulsive seizures in Dravet syndrome, as evidenced by achieving statistically significant improvement vs placebo on the primary and all key secondary endpoints
- ZX008 was generally well tolerated at doses ≤30 mg/day and no clinical and/or echocardiographic signs of cardiac valvulopathy or pulmonary hypertension were observed
- ZX008 may represent a significant advance over existing treatment options and serve as an important novel adjunct therapy for the treatment of convulsive seizures in children and young adult patients with Dravet syndrome

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DISCLOSURE

LL: Consultant/advisor: LivaNova, Novartis, Ovid, Shire, UCB, Zogenix.
JS: Contracted research, Zogenix; Consultant, Epygenix, Epilepsy Study Consortium; Advisor, Dravet Syndrome Foundation.
JHC: Consultant/advisor and Speaker (remuneration to institution), Eisai, GW Pharma, Nutricia, Shire, Takeda, UCB, Vitaflo; Investigator, GW Pharma, Vitaflo, Zogenix.
GMF, BSG, AG, AM, GM: Employee, Zogenix; Stock ownership, Zogenix.
RG, LCL, MN, TP, DT: Research support, Zogenix.
KGK: Research support, Zogenix, Colorado Department of Public Health and Environment.
IM: Consultant/advisor, Dravet Syndrome Foundation, Greenwich, INSYS, Neurelis, NeuroPace, Tuberous Sclerosis Alliance, Ultragenyx, Visualase, Zogenix.
OD: Research support, Zogenix.
ML: Consultant, Zogenix.
BC: Consultant/advisor and Investigator: Brabant, Novartis, UCB, Zogenix.

LL, **BC**, and the KU Leuven University/Antwerp University Hospital may benefit financially from a royalty arrangement that is related to this research if Zogenix is successful in marketing its product, fenfluramine. The terms of this arrangement have been reviewed and approved by the KU Leuven University/Antwerp University Hospital.

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