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Effect of ZX008 (Fenfluramine HCl Oral Solution) on Total Seizures in Dravet Syndrome in a Phase 3 Clinical Trial

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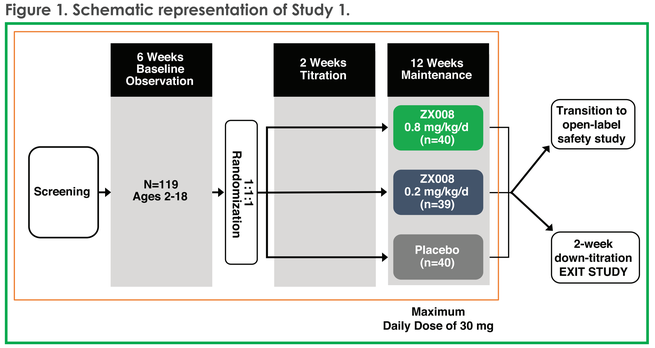
INTRODUCTION

- Dravet syndrome is a rare, severe, pediatric-onset, treatment-resistant epileptic encephalopathy
  - Characterized by different types of seizures, and neurodevelopmental and psychomotor disabilities
  - Current treatment most commonly involves polypharmacy with multiple antiepileptic drugs (AEDs)
  - 45% of patients continue to experience ≥4 seizures per month despite multi-AED regimens (1)
- ZX008 (fenfluramine hydrochloride oral solution) has recently been shown to substantially reduce the frequency of convulsive seizures (defined as tonic-clonic, tonic, clonic, hemiclonic, tonic-atonic, and focal motor seizures) in patients with Dravet syndrome compared with placebo in a phase 3 clinical trial (Study 1) (2)
  - Here we present a post hoc analysis of the effect of ZX008 in enrolled subjects (N=119) in Study 1 on the frequency of all seizure types studied
  - In addition to the convulsive seizures listed above, the following seizure types were also reported in some subjects (n=68): absence or atypical absence, myoclonic, atonic, and focal without clear observable motor signs

METHODS

- Study 1 (**Figure 1**) is a prospective merged analysis of two identical double-blind, placebo-controlled, fixed-dose clinical trials

Figure 1. Schematic representation of Study 1.



RESULTS

- Baseline demographics and seizure frequencies are presented in **Table 1**

Table 1. Demographics and Baseline Seizure Frequency

	Placebo n=40	ZX008 0.2 mg/kg/day n=39	ZX008 0.8 mg/kg/day n=40	Total N=119
Age, y				
Mean±SD	9.2±5.1	9.0±4.5	8.8±4.4	9.0±4.7
(Min, max)	(2, 18)	(2, 17)	(2, 18)	(2, 18)
Age group, <6 y, 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				
Caucasian, n (%)	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[a]				
Mean±SD	46.1±40.7	47.2±99.6	33.0±31.5	41.9±65.0
(Median)	(31.4)	(17.5)	(21.2)	(22.7)
Baseline total seizure frequency[b]				
n[c]	21	23	24	
Mean±SD	81.7±85.7	161.3±388.9	234.1±610.8	
(Median)	(53.9)	(40.7)	(52.9)	

BMI, body mass index; min, minimum; max, maximum; SD, standard deviation; y, years.

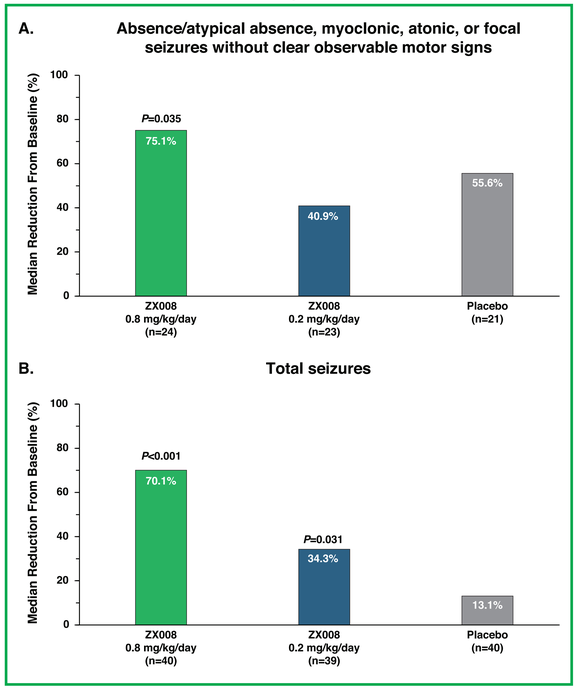
[a]Convulsive seizures included hemiclonic, tonic, clonic, tonic-atonic, generalized tonic-clonic, and focal with clear observable motor signs. Frequency was calculated per 28 days.

[b]Total seizures included convulsive seizures plus all other seizure types reported, which included: atonic, absence/atypical absence, myoclonic, and focal without clear observable motor signs. Frequency was calculated per 28 days.

[c]n represents the number of subjects in each treatment group who exhibited the other seizure subtypes.

- ZX008 significantly reduced total seizure frequency in a dose-related manner (**Figure 2**)

Figure 2. Median percentage reduction from baseline in (A) other seizure subtypes[a] and (B) total seizure frequency per 28 days during the combined titration and maintenance periods.



P values are for comparison to placebo and are based on a nonparametric analysis of covariance (ANCOVA) in both analyses.
[a]Other seizure subtypes included: atonic, absence/atypical absence, myoclonic, and focal without clear observable motor signs.

- **Table 2** presents the median percentage reductions for seizure subtypes during treatment in Study 1

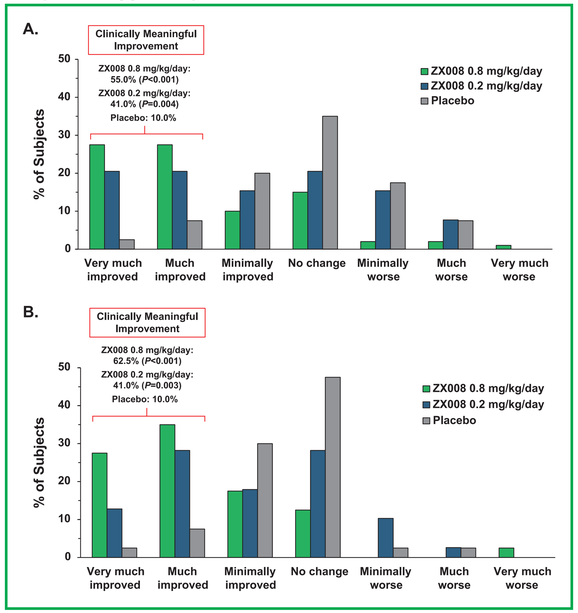
Table 2. Median Percentage Reduction From Baseline in Seizure Frequency per 28 Days During Combined Titration and Maintenance Periods: Additional Seizure Subtypes[a]

Seizure Type	Placebo	ZX008 0.2 mg/kg/day	ZX008 0.8 mg/kg/day
Focal without clear observable motor signs	-62.5%	-78.4%	-77.2%
n[b]	3	7	6
Absence or atypical absence	-54.8%	-3.8%	-78.6%
n[b]	14	8	10
Myoclonic	-34.8%	-62.2%	-64.0%
n[b]	14	18	19
Atonic	-70.5%	-100%	-100%
n[b]	2	3	3
Total additional seizure subtypes	-55.6%	-40.9%	-75.1%
n[b]	21	23	24
P-value			0.035

[a]Additional seizure subtypes not included in the definition of convulsive seizure for the primary endpoint included: atonic, absence/atypical absence, myoclonic, and focal without clear observable motor signs.

[b]n represents the number of subjects in each treatment group demonstrating the specific seizure subtype.

Figure 3. Clinical Global Impression of Improvement rated by (A) parent/caregiver and (B) investigator in the entire study population.



P values are vs placebo.

Safety

Table 3. Most Common Non-Cardiovascular Treatment-Emergent Adverse Events (TEAEs) Occurring in ≥10% of Subjects in any Group

TEAE, n (%)	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)
Decreased appetite	2 (5.0)	8 (20.5)	15 (37.5)
Diarrhea	3 (7.5)	12 (30.8)	7 (17.5)
Fall	2 (5.0)	4 (10.3)	0 (0.0)
Fatigue	1 (2.5)	4 (10.3)	4 (10.0)
Lethargy	2 (5.0)	4 (10.3)	7 (17.5)
Nasopharyngitis	5 (12.5)	4 (10.3)	7 (17.5)
Pyrexia	8 (20.0)	7 (17.9)	2 (5.0)
Seizure	5 (12.5)	4 (10.3)	3 (7.5)
Somnolence	3 (7.5)	6 (15.4)	4 (10.0)
Upper respiratory tract infection	5 (12.5)	8 (20.5)	0 (0.0)
Vomiting	4 (10.0)	4 (10.3)	3 (7.5)
Weight decreased	0 (0.0)	5 (12.8)	2 (5.0)

Cardiovascular Safety

- Valvulopathy
  - No cases of FDA-defined cardiac valvulopathy were observed during the trial (**Table 4**)
- Pulmonary hypertension
  - No echocardiographic findings or clinical symptoms suggesting pulmonary hypertension were noted
- Trace mitral regurgitation (MR) or aortic regurgitation (AR)
  - Current guidelines do not recognize echocardiographic trace AR or MR as pathology as they are considered a normal physiologic variant (3)
  - In the entire study population, regular echocardiographic monitoring during the study identified 5 (12.5%), 7 (17.9%), and 9 (22.5%) subjects who had at least one echocardiogram finding with trace MR and/or trace AR in the placebo, ZX008 0.2 mg/kg/day, and ZX008 0.8 mg/kg/day groups, respectively, which were all clinically benign
  - Of 173 subjects, 23 (13.3%) were excluded from participation in the study due to a screening echocardiogram with a finding of trace MR or trace AR with no symptoms of cardiovascular disease, illustrating the common occurrence of this finding in children and young adults

Table 4. US Food and Drug Administration (FDA) Definition of Cardiac Valvulopathy

	Severity of Blood Regurgitation (Back-Flow) at Valve Measured by Echocardiogram				
Valve	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.

CONCLUSIONS

- ZX008 significantly improved both total and convulsive seizure frequency in this phase 3 trial for adjunctive treatment of seizures in subjects with Dravet syndrome
- Despite large observed reductions in the placebo group, highlighting the difficulty in counting these other seizure subtypes, subjects treated with ZX008 0.8 mg/kg/day (max 30 mg/day) demonstrated a greater median reduction in seizure frequency compared with placebo-treated subjects
- ZX008 was generally well tolerated, and no echocardiographic signs of cardiac valvulopathy or pulmonary hypertension were observed in any subject during the study
- ZX008 may represent an important and effective new treatment option for patients with Dravet syndrome

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DISCLOSURES

JS: Contracted research for Zogenix; Consultant for Epygenix and the Epilepsy Study Consortium; Advisor for the Dravet Syndrome Foundation.

LL: Consultant/advisor for LivaNova, Novartis, Ovid, Shire, UCB, and Zogenix.

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GMF, BSG, AG, GM: Employees of Zogenix; Stock ownership with Zogenix.

LL 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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