2.284

A Pilot, Open-Label Study of the Effectiveness and Tolerability of Low-Dose Fenfluramine (ZX008) in Lennox-Gastaut Syndrome: Findings From a Long-Term Extension

Lieven Lagae[1]; An-Sofie Schoonjans[2]; Arnold Gammaitoni[3]; Bradley S. Galer[3]; Berten Ceulemans[2]

[1]Department of Paediatric Neurology, University of Leuven, Leuven, Belgium; [2]Division of Paediatric Neurology, Antwerp University Hospital, University of Antwerp, Edegem, Belgium; [3]Zogenix, Inc., Emeryville, CA, USA

RATIONALE

- Lennox-Gastaut syndrome (LGS) is a drug-resistant, childhood-onset, electroclinical epilepsy syndrome with multiple seizure types and diagnostic electroencephalogram (EEG) findings
  - Most typical seizures types are "drop attacks," which include axial tonic, atonic/tonic, and atonic seizures and atypical absences, with other generalized seizure types or focal seizures
- ZX008, an oral formulation of fenfluramine (FFA), is an adjunctive therapy with reported efficacy in Dravet syndrome, another drug-resistant childhood epilepsy syndrome[1,2]
- In a prior interim analysis of this study, the results of ZX008 treatment in 13 LGS patients demonstrated ≥50% seizure reduction in 8/13 patients (62%) after 12-20 weeks[3]

OBJECTIVE

- To report efficacy and safety results of ZX008 treatment in a subset of LGS Core study participants in an Extension study (beyond 20 weeks)

METHODS

Study Design

- Phase 2, pilot, open-label, dose-finding trial of ZX008 as adjunctive therapy for LGS in patients 3-18 years of age who failed multiple therapies (including vagal nerve stimulation, VNS)
- Key inclusion criteria
  - Diagnosed with LGS per International League Against Epilepsy (ILAE) diagnostic criteria
    - At least 4 documented major motor seizures (generalized tonic-clonic [GTC], tonic [TS], atonic [AS], and focal seizures [FS] with a motor component)
    - Receiving at least 2 antiepileptic drugs (AEDs) at stable doses in the 4 weeks prior to enrollment
- Core study (20 weeks)
  - Baseline (0 through Week 4): After enrollment, seizure number and type were recorded in patient diaries
  - Weeks 5 through 8: ZX008 administered at 0.2 mg/kg/day
  - Weeks 9 through 13: Responders with ≥50% reduction in major motor seizures from baseline remained at 0.2 mg/kg/day ZX008; nonresponders were considered for a dose increase to 0.4 mg/kg/day
  - Weeks 13 through 20: Responders remained at current dose; nonresponders were considered for dose escalation to 0.4-0.8 mg/kg/day
  - Maximum ZX008 dose was 30 mg/day; dose escalation stopped when seizure frequency reached ≥50% reduction from baseline
  - End of Week 20: Core study complete
  - Seizure frequencies were assessed at 4-week intervals via diary recordings made between visits
  - Echocardiograms were evaluated at screening and at end of the Core study
- Extension study (beyond 20 weeks)
  - Patients continued on the effective dose of ZX008 from week 20 of the Core study
  - Dose escalation was allowed if deemed necessary by the investigator in order to achieve optimal balance of efficacy and tolerability (maximum dose, 30 mg/day)
  - Seizure frequencies were assessed at 3-month intervals via diary entries and used to compare seizure frequency during the 4 weeks prior to each visit vs baseline
  - Efficacy was defined as ≥50% reduction in the frequency of countable seizures with a motor component (GTC, TS, AS, or FS) relative to baseline
  - Echocardiograms were evaluated every 3 months at the discretion of the investigator in the Extension study
- Summary data
  - Data are expressed as means±SD, medians, ranges, and percentages as appropriate

RESULTS

Demographics

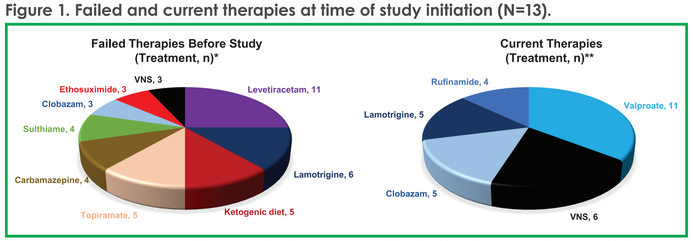
- Individual patient characteristics are shown in **Table 1** and **Figure 1**
- A total of 13 patients were enrolled and 9 completed the Core study
  - Average age, 11.7±4.4 years (mean±SD)
  - Average weight, 45.4±20.2 kg (mean±SD)
  - 69% male (9/13), 31% female
  - Duration of antiepileptic treatment prior to enrollment in the Core study, 2-15 years (median, 8 years)
    - Therapeutic failure on 23 different antiepileptic therapies (**Figure 1**)
    - Median of 5 failed antiepileptic therapies per patient (range 3-7)
  - Current treatment includes 14 different antiepileptic therapies (**Figure 1**)
    - Median of 4 concurrent antiepileptic therapies per patient at enrollment (range 2-4)
    - Most common antiepileptic therapies were valproate, VNS, clobazam, lamotrigine, and rufinamide
- Patient disposition is shown in **Figure 2**

Table 1. Patient Characteristics at Study Initiation (N=13)

Patient	Sex	Age at Inclusion (y)	Weight (kg)	Etiology	No. of Failed Treatments	No. of Current Treatments	Seizure Classification (Description)**
0101*	M	16	49	*SCN2A* mutation; West syndrome	3	4	TS; Other (absences)
0102*	F	9	28	Intra-uterine toxoplasma	5	4	TS, M
0103	F	16	52	*ALG13* mutation	6	4	M, TS, GTC
0104	M	16	62	Unknown	4	4	TS, C, GTC
0105*	M	3	16	Unknown	4	3	TS
0106	M	14	63	Unknown	5	2	GTC, TS
0107*	M	11	35	Unknown; West syndrome	4	4	TS, Other (absences), FS (screaming; not clearly seizure episodes)
0108*	M	17	54	*STXBP1* mutation	7	4	AS, TS, M, Other (absences)
0109*	M	14	88	Unknown	7	4	TS, GTC, M, Other (absences)
0110*	M	5	20.8	Unknown	7	4	TS, C, M, GTC
0111*	M	11	56.9	Unknown	5	2	M, TS
0112	F	11	29.3	Cerebral palsy; lesional epilepsy	3	3	M, Other (absences), TC, Other (clonic seizures), FS
0113*	F	9	36.2	Ring chromosome 20	6	4	TS, AS, Other (atypical absences with jerking head and shoulders), Other (absences)

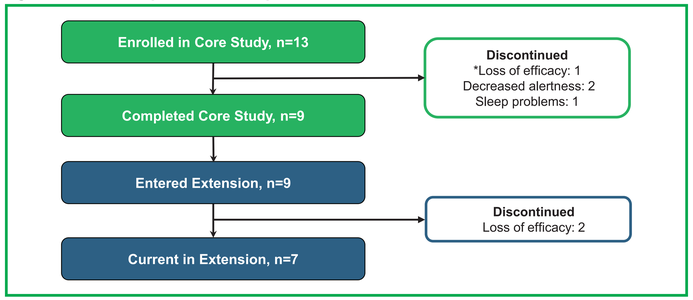
*Subjects who experienced drop attacks. **Seizures listed in order of type.
AS, atonic seizures/drop attacks; C, clonic seizures; FS, focal seizures; GTC, generalized tonic-clonic; M, myoclonic seizures; TS, tonic seizures.

Figure 1. Failed and current therapies at time of study initiation (N=13).



*Therapies not shown (n): valproate (2), gabapentin (2), oxcarbazepine (2), rufinamide (2), vigabatrin (2), phenytoin (2), clonazepam (2), ethyl loflazepate (1), surgery (1), zonisamide (1), felbamate (1), steroids (1), brivaracetam (1), phenobarbital (1).
**Therapies not shown (n): cannabidiol (2), clonazepam (2), ethyl loflazepate (2), topiramate (2), ethosuximide (1), felbamate (1), lorazepam (1), oxcarbazepine (1), perampanel (1). VNS, vagal nerve stimulation.

Figure 2. Patient disposition of LGS patients in the Core and Extension studies.

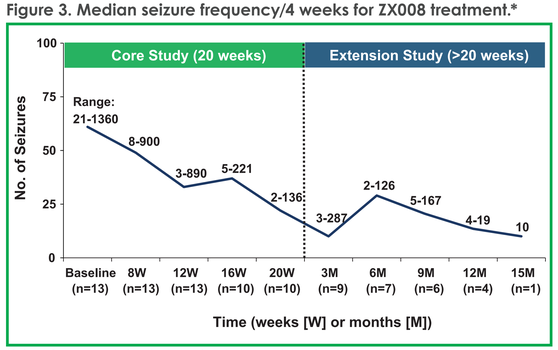


*Patient was a responder in study until underwent orthopedic surgery (protocol violation) when seizures increased, leading to discontinuation.

Effectiveness

- ZX008 therapy resulted in significant reduction in patient seizure frequency over time (**Figure 3**)
  - Core study:
    - Median seizure during the 4-week baseline period was 60 (range 21-1360, n=13)
    - By 20 weeks median seizure frequency had fallen to 22/4 weeks (range 2-136, n=9)
    - 8/13 patients (62%) responded to ZX008 during Core study (≥50% seizure reduction from baseline)
  - Extension study:
    - 9/13 (69%) continued into the extension study
      - 8/9 patients were responders
      - 1/9 (Patient 109, **Figure 4**) had an initial reduction in seizures during the Core study that was lost by week 20; patient continued into the Extension study at request of parents to see if seizure control could be regained
        - Patient later discontinued by month 3 of the Extension study
    - Median % reduction in seizure frequency from last visit during the extension study compared to baseline was 58% (**Table 2**)
    - 6/9 patients (67%) responded to ZX008 during Extension study (≥50% seizure reduction from baseline)
  - Individual patient seizure frequencies over time are provided in **Figure 4**

Figure 3. Median seizure frequency/4 weeks for ZX008 treatment.*



*Seizure frequency during the Extension study was determined as total seizures during the 4 weeks prior to each visit vs baseline.

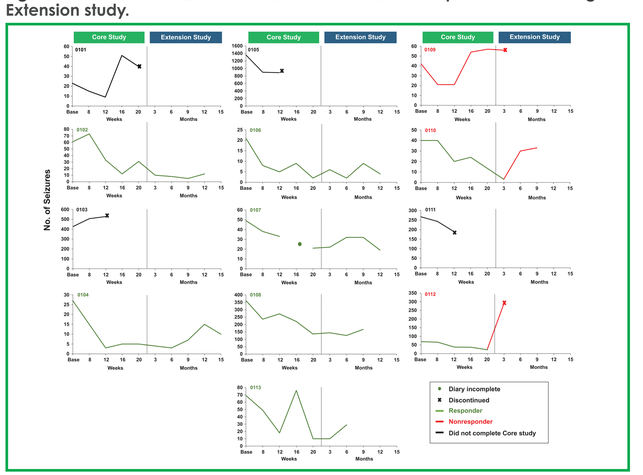
Decreasing n due to not reaching visit time point as yet, not to patient discontinuation.

Table 2. Percent Change in Seizure Frequency From Last Visit in the Extension Study Compared to Baseline (N=9)

Patient ID	Last Visit**	Dose at Last Visit (mg/kg/day or max 30 mg)	Change in Seizure Frequency vs Baseline
0102	12M	0.8	-80.3%
0104	15M	30 mg	-63.0%
0106	12M	0.4	-81.0%
0107	12M	0.4	-61.2%
0108	9M	30 mg	-53.9%
0109*	3M	30 mg	+33.3%
0110	9M	0.4	-17.5%
0112*	3M	0.4	+315.9%
0113	6M	0.4	-58.0%
Median seizure reduction			**-58.0%**
Patients with ≥50% reduction in seizure frequency			**n=6 (67%)**
Patients with ≥75% reduction in seizure frequency			**n=2 (22%)**

*Patient discontinued.
**Months (M) from end of 20-week Core study.

Figure 4. Number of seizures recorded for individual LGS patients continuing into Extension study.



Safety

- AEs are shown in **Table 3**

Table 3. Adverse Events Reported in the Core and Extension Studies (N=13)

Adverse Event*	No. of Patients (%)
Decreased appetite	4 (31%)
Decreased alertness	2 (15%)
Sleep problems	1 (8%)
Fatigue	1 (8%)
Tiredness	1 (8%)
Sleepiness	1 (8%)
Cardiac abnormalities	(0%)

*Frequencies of AEs were comparable in the Core and Extension studies.

CONCLUSIONS

- ZX008 provided sustained, clinically meaningful seizure reduction in a cohort of refractory LGS patients enrolled in a Core and long-term Extension study, treated for up to 15 months
  - 9/13 (69%) enrolled in the Core study continued into the Extension, with 6/9 (67%) experiencing a ≥50% reduction in seizure frequency and 2/9 (22%) experiencing a ≥75% reduction
- ZX008 was generally well tolerated and there were no clinical and/or echocardiographic signs of cardiac valvulopathy or pulmonary hypertension
- A phase 3 randomized, controlled study is underway to validate these findings

REFERENCES

1. Schoonjans A, et al. *Eur J Neurol*. 2017;24(2):309-314.
2. Ceulemans B, et al. *Epilepsia*. 2016;57(7):e129-e134.
3. Lagae L, et al. Presented at: American Epilepsy Society 2016 Conference, December 2-6, Houston, TX. Abstract 1.369.

DISCLOSURES

LL: Consultant/advisor and Speaker, LivaNova, Novartis, Ovid, Shire, UCB, Zogenix.
AS: Consultant/advisor, Brabant, Zogenix.
AG, BSG: Employee, Zogenix; Stock ownership, 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.

ACKNOWLEDGEMENTS

This study was funded by Zogenix, Inc. (Emeryville, CA). Medical writing and editorial assistance was provided by Gregory Kopia, PhD, Danielle Ippolito, PhD, and Donald Fallon, ELS, of PharmaWrite, LLC (Princeton, NJ, USA) and was funded by Zogenix, Inc.

Presented at the 71st Annual Meeting of the American Epilepsy Society, December 1-5, 2017, Washington, DC