Add-on Therapy with Low Dose Fenfluramine (ZX008) in Lennox Gastaut Syndrome

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INTRODUCTION

Lennox Gastaut Syndrome (LGS)

- A drug-resistant electroclinical epilepsy syndrome characterized by multiple seizure types
  - Most typical seizures are axial tonic, tonic/atonic and atonic seizures, and atypical absences
  - Other generalized seizure types and also focal seizures are possible
- Seizures typically start in early childhood between 2 and 6 years of age, though diagnosis is often made later as a clinical picture emerges
- Interictal EEG shows abnormal background with a generalized slow and spike wave pattern
- Diverse etiology; includes a variety of genetic causes as well as structural brain abnormalities
- Approximately 25% of LGS patients have no identified cause

Fenfluramine (FFA)

- Low dose FFA has been reported to be effective as an adjunctive anticonvulsant treatment in Dravet syndrome (DS),[1,2] another drug-resistant childhood epilepsy syndrome

Purpose

- Based on the observed effectiveness in DS, we conducted a dose-finding pilot study to determine the potential anticonvulsant effect of low dose FFA (ZX008) in LGS
  - Dose was titrated to achieve a ≥50% response, not the maximum response
- Here we report an interim analysis on the first 13 patients enrolled in the trial, treated for a minimum of 12 weeks and a maximum of 20 weeks

METHODS

- A single center Phase 2 pilot open-label, 20-week dose-finding trial of FFA as an add-on therapy
- Eligibility
  - LGS patients 3-18 years of age who had failed at least 2 AEDs (including vagal nerve stimulation [VNS])
  - LGS diagnosed as described by the International League Against Epilepsy (ILAE) diagnostic criteria
  - At least 4 documented convulsive seizures (generalized tonic clonic [GTC], tonic [TS], atonic [AS], and focal seizures [FS] with a motor component) and on at least 2 AEDs at stable doses in the prior 4 weeks
- After the initial 4-week baseline period to record seizure type and frequency, 0.2 mg/kg/day ZX008 was initiated
- An efficacy response was defined as a ≥50% reduction in major motor seizure frequency (GTC+TS+AS+FS)
- Dose titration was as follows:
  - At the 8-week visit, a non-responder could receive an increased dose of 0.4 mg/kg/day
  - At the 12-week visit, a non-responder could receive an increased dose of 0.8 mg/kg/day
  - At any visit, a responder (a patient with ≥50% reduction in major motor seizure frequency) remained at the currently administered dose
  - The maximum allowed dose was 30 mg/day
- **As this was a pilot dose-finding study, it is important to note that per protocol, dose escalation stopped when a patient's seizure frequency was reduced by ≥50% of baseline**
- Seizure types contributing to primary efficacy measure: GTC, TS, AS, FS

RESULTS

Demographics

- Individual patient demographics are provided in **Table 1**
- 13 patients were enrolled at the time of this interim report:
  - Mean age in years (±SD): 11.4 (±4.4)
  - 69% male
  - Mean weight in kg (±SD): 45.4 (±20.2)
- Subject disposition
  - 4 patients withdrew before end of study at 20 weeks
    - 1 experienced worsening of seizures following orthopedic surgery
    - 3 withdrew due to adverse events (AEs)
      - 2 decreased alertness
      - 1 insomnia
  - 8 patients completed all 20 weeks of the treatment period
  - 1 patient still enrolled and completed 16 weeks of study
- Patients had received a median of 5 failed antiepileptic therapies (range: 3-7) prior to this study (**Table 1**)
- At study initiation, patients were receiving a median of 4 antiepileptic therapies (range: 2-4; **Table 1**)
  - Most common therapies were valproate (11/13), VNS (6/13), clobazam (5/13), lamotrigine (5/13), and rufinamide (4/14)

Effectiveness

- Median seizure frequency during the baseline 4-week period was 60 (range: 21-1360; **Figure 1**)
- Median seizure frequency at endpoint (week 20) was 22 (range: 2-132; **Figure 1**)
- Once an effective dose was achieved, a ≥50% reduction in major motor seizure frequency typically occurred in 4-8 weeks (**Table 2**)

Table 1: Patient Demographics

Patient	Initials	Date of Birth (dd/mm/yy)	Sex	Age at Inclusion (y)	Weight (kg)	Etiology	Failed Treatments	Epilepsy Treatment at Inclusion
0101	NO	06/05/99	M	16	49	*SCN2A* mutation; West syndrome in infancy	TPM, LTG, VGB	VPA, RUF, VNS, lorazepam
0102	AE	24/12/06	F	9	28	Intrauterine toxoplasma	RUF, KD, LEV, CZP, ETS	VPA, LTG, VNS, ELF
0103	SL	03/12/99	F	16	52	*ALG13* mutation	KD, VNS, LTG, LEV, PB, PHT	VPA, TPM, CZP, perampanel
0104	JE	18/12/99	M	16	62	Not known	LEV, SUL, OXC, brivaracetam	VPA, LTG, CLB, VNS
0105	IK	19/06/12	M	3	16	Not known	TPM, CZP, LTG, LEV	VPA, CLB, ETS
0106	LJ	21/06/01	M	14	63	Not known	CLB, TPM, LEV, SUL, PHT	VPA, LTG
0107	BP	03/09/04	M	11	35	Not known; West syndrome in infancy	CBZ, LTG, LEV, VGB	VPA, RUF, VNS, ELF
0108	BN	01/07/98	M	17	54	Not known; possible *STXBP1* mutation	KD, LEV, RUF, TPM, VNS, felbamate, steroids	VPA, LTG, CBD, felbamate
0109	UF	12/05/01	M	14	88	Not known	KD, LTG, LEV, CBZ, OXC, zonisamide, gabapentin	VPA, RUF, CLB, VNS
0110	NA	26/02/11	M	5	20.8	Not known	CBZ, CLB, LEV, TPM, LTG, SUL, ETS	VPA, RUF, VNS, CZP
0111	BP	25/08/04	M	11	56.9	Not known	VPA, LTG, LEV, KD, VNS, surgery	TPM, CBD
0112	LE	26/04/05	F	11	29.3	Cerebral palsy; lesional epilepsy	LEV, CLB, ETS	VPA, CLB, RUF
0113	MC	06/09/06	F	9	36.2	Ring chromosome 20	VPA, LEV, CBZ, SUL, ELF, gabapentin	LTG, CLB, VNS, OXC

CBD, cannabidiol; CBZ, carbamazepine; CLB, clobazam; CZP, clonazepam; ELF, ethylloflazepate; ETS, ethosuximide; F, female; KD, ketogenic diet; kg, kilograms; LTG, lamotrigine; LEV, levetiracetam; M, male; OXC, oxcarbazepine; PB, phenobarbital; PHT, phenytoin; RUF, rufinamide; SUL, sulthiame; VGB, vigabatrin; VNS, vagal nerve stimulation; VPA, valproate; TPM, topiramate; y, years.

Figure 1. Effect of Add-on Treatment with ZX008 on Median Seizure Frequency in LGS

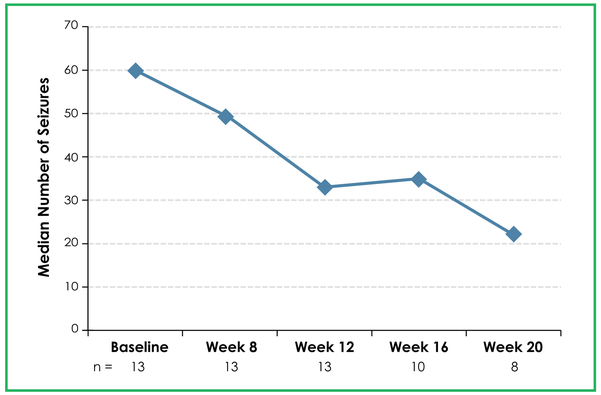


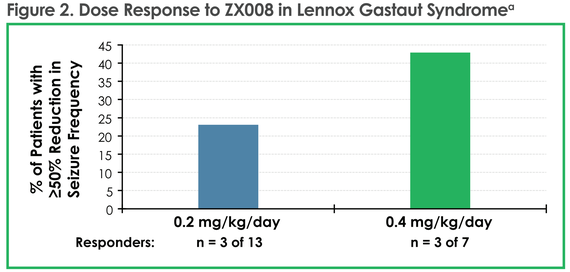
Table 2. Dose and Time on Effective Dose

Patient ID	Dose at ≥50% Response	Weeks on Effective Dose to Response
0101	W[1]	W[1]
0102	0.4	4
0103	W	W
0104	0.2	4
0105	W	W
0106	0.2	4
0107	0.4	4
0108	30 mg (0.6)	8
0109	0.8	[2]
0110	0.4	4
0111	W	W
0112	0.2	8
0113	[3]	[3]

W, withdrew due to AE or lack of effect (see text).
Highlighted rows are responders.
[1]Patient achieved responder status after 4 weeks at 0.4 mg/kg/day and then lost control following orthopedic surgery; withdrew after 20 weeks.
[2]Awaiting 20-week evaluation.
[3]Patient achieved responder status after 4 weeks at 0.4 mg/kg/day but became a non-responder at week 16 (visit 5); patient is still in trial.

- In the Intent-to-Treat (ITT) patient population (n=13) there was a median 50% reduction in seizure frequency over the 20-week study period compared to baseline (range: +74% to –90%)
  - The subject with a 74% increase had been a responder at 0.4 mg/kg/day (61% reduction in major motor seizure frequency at week 12) but lost control after undergoing orthopedic surgery between the visits at week 12 and week 16 in the trial
- 7 of the 13 patients (54%) achieved at least a 50% reduction in the number of major motor seizures
- There was approximately a 2-fold increase in the number of responders (≥50% reduction) on a dose of 0.4 mg/kg/day vs. 0.2 mg/kg/day (**Figure 2**)

Figure 2. Dose Response to ZX008 in Lennox Gastaut Syndrome[a]



[a]As of this interim analysis, 1 patient was titrated to the maximum allowable dose of 30 mg/day and became a responder.

Tolerability

- The most common treatment-emergent AEs reported to date include:
  - Decreased appetite (n=3; 23%)
  - Decreased alertness/fatigue (n=3; 23%)
  - Insomnia (n=2; 15%)

CONCLUSIONS

- In this pilot study evaluating ZX008 for the treatment of uncontrolled seizures in LGS, interim results (n=13) after at least 12 weeks of treatment suggest that ZX008 provides clinically meaningful improvement in major motor seizure frequency in patients with severely refractory LGS, despite not attempting to dose to maximal efficacy and is generally well tolerated
  - 7/13 patients (54%) achieved a ≥50% reduction in the number of major motor seizures (range: 50%-90%)
  - In responders (patients with a ≥50% decrease in major motor seizures), efficacy was apparent by 4-8 weeks of treatment at the effective dose level
- In this open-label dose-finding pilot study, submaximal doses of FFA (0.2 and 0.4 mg/kg/day) provided a ≥50% decrease in major motor seizures in 54% of patients. Greater seizure reductions might be seen at higher doses of FFA
- A dose response appears to be emerging with a 2-fold increase in the number of responders at the 0.4 mg/kg/day vs. 0.2 mg/kg/day dose (**Figure 2**)
- Patients in this study who are responders will be invited to enter a long-term extension study where doses will be further titrated to 0.8 mg/day (with a maximum of 30 mg/day) in order to assess maximal efficacious dose

REFERENCES

1. Ceulemans B, et al. *Epilepsia*. 2012;53:1131-9.
2. Schoonjans AS, et al. *Eur J Neurol*. 2016;doi:10.1111/ene.13195. [Epub ahead of print]

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