Effect of Low-Dose Fintepla® (Fenfluramine HCl Oral Solution) on Seizure and Non-Seizure Clinical Outcomes in Dravet Syndrome: A Case Series of 5 Pediatric Patients Receiving Fenfluramine Through Compassionate Use Protocols

Kelly Knupp[1]; Steven Phillips[2]; Annapurna Poduri[3]; Russell P. Saneto[4]; Elaine Wirrell[5]

[1]Children's Hospital Colorado, Department of Pediatrics and Neurology, University of Colorado – Anschutz Campus, Aurora, CO, USA; [2]Mary Bridge Children's Neurology Clinic, Olympia, WA, USA; [3]Department of Neurology, Harvard Medical School, Boston Children's Hospital, Boston, MA, USA; [4]Department of Neurology, Seattle Children's Hospital, Seattle, WA, USA; [5]Child and Adolescent Neurology, Mayo Clinic, Rochester, MN, USA

ZOGENIX

INTRODUCTION

- Dravet syndrome (DS) is a severe, treatment-resistant pediatric epilepsy syndrome with an incidence of approximately 1 in 15,700 infants[1-3]
  - Characterized by recurrent, treatment-refractory seizures of multiple types, intellectual disability, motor and language impairment, and developmental delay, with increased risk of mortality (7%-18%) in patients <18 years of age[4,5]
  - Caregivers of patients with DS report that non-seizure comorbidities (eg, speech/communication impairments, impacts on siblings, and cognitive impairment) rank among their top concerns after seizure control[6]
- Adjunctive fenfluramine (FFA) reduced convulsive seizure (CS) frequency in a recent phase 3, randomized, placebo-controlled clinical study[7]
  - Patients in the FFA groups also showed clinically meaningful improvement in the Behavior Regulation and Emotion Regulation Indices on the Behavior Rating Inventory for Executive Function (BRIEF®2) compared with those in the placebo group ($P<0.02$)

OBJECTIVE

- To present a case series of 5 children and adolescents with DS receiving adjunctive FFA under a compassionate use investigator-initiated investigational new drug (IND) program

METHODS

Study Design

- Patient Outcomes Report questionnaires were completed by 5 investigators who treated patients under a compassionate use IND program
  - FFA was dosed based on clinical response and tolerability up to a maximum of 0.8 mg/kg/day (maximum, 30 mg/day)
- A questionnaire was provided to report seizure and non-seizure outcomes and clinical global impression of patient disposition

RESULTS

Demographic and Clinical Characteristics

Table 1. Patient Characteristics at Time of Assessment (N=5)

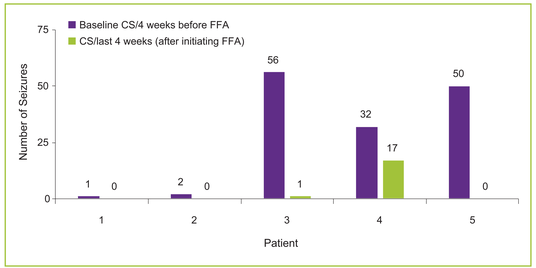
Patient	Sex	*SCN1A* Mutation? (Y/N)	Age at Inclusion	Age of Seizure Onset	Age of DS Diagnosis	Time on FFA (Weeks)	Failed Treatments	Current Treatments (With FFA)	Seizure Classification (Description)[a]
1	Male	Y[b]	2.5 years	7 months	9 months	19.0	Numerous AEDs and ketogenic diet	Not listed	C, GTC, M
2	Female	Not listed	9 years	6 months	11 months	39.7	Clobazam, cannabidiol, ethosuximide, levetiracetam, oxcarbazepine, phenobarbital, zonisamide	Not listed	C, dialeptic, FS, GTC
3	Male	Y[c]	12 years	9 weeks	6 years	21.4	Phenobarbital, topiramate, levetiracetam, stiripentol, rufinamide, felbamate, Epidiolex®, ketogenic diet, phenytoin, oxcarbazepine, carbamazepine	Zonisamide, clonazepam, clobazam, VNS	Absence, AS, GTC, M, TS
4	Female	N	10 years	6 months	Uncertain	27.3	Levetiracetam, topiramate, rufinamide, lamotrigine, carbamazepine, zonisamide, lacosamide, perampanel, felbamate, phenobarbital, ketogenic diet	Stiripentol, clobazam, valproic acid, gabapentin, VNS	AS, FS, GTC, M, TS
5	Female	Y[d]	15 years	6 months	3 years	20.6	Phenobarbital, oxcarbazepine, lamotrigine, zonisamide, valproic acid, IVIG, verapamil, acetazolamide, Epidiolex	VNS, modified Atkins diet, clobazam, levetiracetam, triple bromides	Atypical absence, C, GTC, M, TS

[a]Seizures listed in order of type.
[b]Patient had the following *SCN1A* gene mutation: c.4162G>T.
[c]Patient had early, profound Thr226Met phenotype, a much more severe form of *SCN1A*-related epilepsy.[8]
[d]Patient had the following *SCN1A* gene mutation: c.4928_4937delTTGGCinsCGTAGA truncation mutation.
AED, antiepileptic drug; AS, atonic seizures/drop attacks; C, clonic seizures; DS, Dravet syndrome; FFA, fenfluramine; FS, focal seizures; GTC, generalized tonic-clonic; IVIG, intravenous immunoglobulin for epilepsy; M, myoclonic seizures; N, no; TS, tonic seizures; VNS, vagus nerve stimulation; Y, yes.

Seizure Outcomes

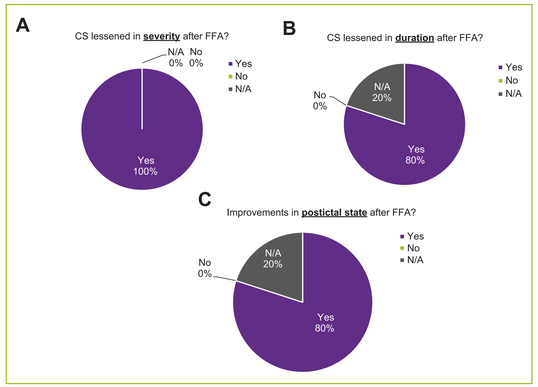
- Reduction in CS frequency during the last 4 weeks of treatment vs 4 weeks prior to FFA initiation ranged from 47%-100% (**Figure 1**)
  - 3 patients were seizure-free; 1 had a 98% reduction; and 1 had a 47% reduction
- CS were reported to be lessened in severity and duration after FFA, with improvements noted in postictal state (**Figure 2**)
- Qualitative assessments indicated that seizures were less intense and there were fewer episodes of status epilepticus and shorter clusters (**Table 2**)

Figure 1. CS Frequency at 4 Weeks Prior to FFA Treatment and During Last 4 Weeks on FFA Treatment



CS, convulsive seizures; FFA, fenfluramine.

Figure 2. Improvements in (A) CS Severity, (B) CS Duration, and (C) Postictal State After FFA Relative to Baseline



CS, convulsive seizures; FFA, fenfluramine; N/A, not applicable: patient is no longer having convulsive seizures.

Table 2. Qualitative Assessment of the Impact of FFA on CS

Patient	Severity	Duration	Postictal State
1	Initially no change in myoclonic seizures, but overall now less	N/A, no convulsive seizures	
2	--	No seizures for several months	Much improved unsteady gait and mental function
3	Fewer, shorter clusters	Shorter clusters	More alert; better eye contact
4	*Before FFA:* status epilepticus episodes requiring PICU admission every 4 weeks *After FFA:* used rescue medications only once in the last 4 weeks; last PICU admission was 7 weeks ago for observation, not treatment (seizures stopped before arrival)	*Before FFA:* 2-20 min *After FFA:* 0.5-2 min; last status epilepticus episode was a cluster of seizures, not a prolonged seizure	*After FFA:* shorter duration of postictal period; now able to function shortly after seizure
5	Seizure-free since 7 days after starting FFA		

CS, convulsive seizures; FFA, fenfluramine; N/A, not applicable; PICU, pediatric intensive care unit.

Non-Seizure Outcomes

- Between 40%-60% of patients showed clinically meaningful improvement in all other non-seizure outcomes except for sensitivity to light/patterns (20%) (**Figure 3**)
- There were no reports of "Minimally Worse" to "Very Much Worse" in any category

Figure 3. Comparison of Seizure vs Non-Seizure Outcomes (N=5)

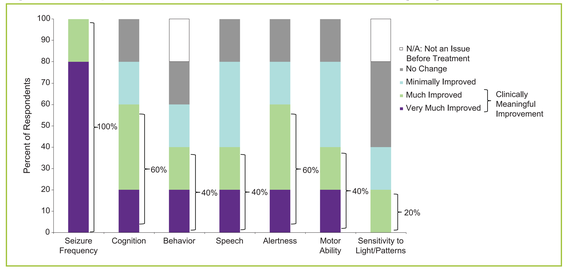
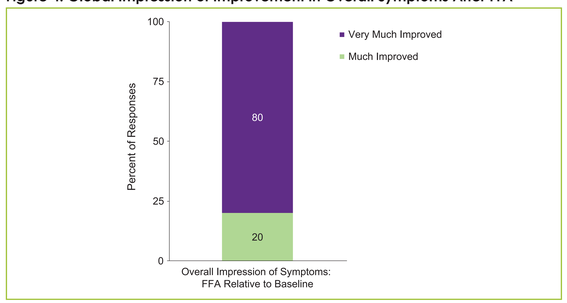


Figure 4. Global Impression of Improvement in Overall Symptoms After FFA



- Overall, investigators reported clinically meaningful improvements in all patients (**Figure 4**)
  - Global impression of improvement ratings were driven by both seizure and non-seizure improvements in 3/5 cases and seizure-only improvement in 2/5 cases

Table 3. Overall Qualitative Assessments by Investigators

Patient	Overall Observations
1	Cautiously optimistic: significant improvement in motor seizures, although he always does better in the summer months (need more time to assess); seizure freedom without ICU visits allows him to make some modest strides in development
2	Doing awesome: no more [ICU] admissions, with seizures resolved, improved balance and gait, improved social interactions
3	Marked reduction in CS with longer seizure-free durations, leading to a modest improvement in alertness; remains nonambulatory and nonverbal, but this patient has a severe mutation type (*SCN1A* Thr226Met)
4	Less frequent admissions to the ICU and decrease in seizure frequency
5	Seizure-free for the first time since age 6 months (currently age 15); more talkative and engaged during clinic visits, and she has developed a personality

CS, convulsive seizures; ICU, intensive care unit.

CONCLUSIONS

- In this case series of 5 treatment-refractory patients with DS being treated under a compassionate use IND program, FFA provided:
  - Clinically meaningful reduction in seizure frequency and improvements in both seizure and non-seizure outcomes
  - Clinically meaningful improvements in non-seizure outcomes, including cognition, behavior, speech, alertness, and motor ability, were noted in 40%-60% of patients
- FFA was generally well tolerated with no development of cardiac valve disease or pulmonary hypertension
- FFA may be an important and effective new DS treatment option with efficacy in improving both seizure and non-seizure outcomes

REFERENCES

1. Wirrell EC, et al. *Pediatr Neurol.* 2017;68:18-34.
2. Wu YW, et al. *Pediatrics.* 2015;136:e1310-e1315.
3. Ziobro J, et al. *Curr Treat Options Neurol.* 2018;20:52.
4. Dravet C. *Epilepsia.* 2011;52(suppl 2):3-9.
5. Skluzacek JV, et al. *Epilepsia.* 2011;52(suppl 2):95-101.
6. Villas N, et al. *Epilepsy Behav.* 2017;74:81-86.
7. Lagae L, et al. AES [poster 2.434]. Dec 1-5, 2017, Washington, DC.
8. Sadleir LG, et al. *Neurology.* 2017;89:1035-1042.

ACKNOWLEDGMENTS

This study was funded by Zogenix, Inc. (Emeryville, CA, USA). Medical writing and editorial assistance were provided by Danielle Ippolito, PhD, CMPP, MWC, and Courtney Breuel, ELS, of PharmaWrite (Princeton, NJ, USA) and were funded by Zogenix, Inc.

DISCLOSURES

All authors enrolled patients in ZX008 Study 1501 (NCT02682927, NCT02826863).

KK: Research support, West Pharmaceutical Services and Zogenix; Consultant (DSMB), Greenwich Biosciences.

AP: Consultant, Zogenix.

EW: Research support, Zogenix.

Presented as part of the Zogenix Scientific Exhibit during the American Epilepsy Society (AES) Annual Meeting, November 30–December 4, 2018, New Orleans, LA