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NYU School of Medicine
NYU LANGONE MEDICAL CENTER

FENFLURMAINE IN CKDL5 DEFICIENCY DISORDER (CDD)

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Statement of Compliance

This study will be conducted in accordance with the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46), 21 CFR Parts 50, 56, 312, and 812 as applicable, any other applicable US government research regulations, and institutional research policies and procedures. The International Conference on Harmonisation ("ICH") Guideline for Good Clinical Practice ("GCP") (sometimes referred to as "ICH-GCP" or "E6") will be applied only to the extent that it is compatible with FDA and DHHS regulations. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection Training.

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List of Abbreviations

AE	Adverse Event/Adverse Experience
CFR	Code of Federal Regulations
CRF	Case Report Form
CSOC	Clinical Study Oversight Committee
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DSMB	Data and Safety Monitoring Board
FFR	Federal Financial Report
FWA	Federalwide Assurance
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
ISM	Independent Safety Monitor
MOP	Manual of Procedures
N	Number (typically refers to participants)
NIH	National Institutes of Health
OHRP	Office for Human Research Protections
OHSR	Office of Human Subjects Research
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event/Serious Adverse Experience
SOP	Standard Operating Procedure
US	United States

Protocol Summary

Title	*Fenfluramine in CKDL5 Deficiency Disorder (CDD)*
Brief Summary	*We will enroll 10 patients, ages 2-35 years old, with a confirmed genetic/clinical diagnosis of CDKL5 Deficiency Disorder (CDD) in an open label trial of fenfluramine for seizure control.* *Protocol – patients will be titrated over 14 days to a dose of ZX008 0.8 mg/kg/day (maximum dose 30 mg/d)*
Phase	*NA*
Objectives	*Decrease in seizure frequency and change in impression and quality of life*
Methodology	*Open label*
Endpoint	*Primary outcome:* *Median monthly convulsive seizure frequency* *Secondary outcomes:* 1. *Caregiver/Investigator Global Impression of Change (C/IGIC). The parent/caregiver and investigator rated change on a 7-point scale: 1-very much improved; 2-much improved; 3-minimally improved; 4-no change; 5-minimally worse; 6-much worse; and 7-very much worse* 2. *Quality of Life in Childhood Epilepsy Scale (13). A low-burden parent/caregiver completed assessment that looks at how epilepsy affects day-to-day functioning of their child in various life areas, including physical activities, well-being, cognition, social activities, behavior and general health.* 3. *Pediatric Quality Of Life Inventory (PEDS-QL). A parent/caregiver completed assessment that looks at how epilepsy affects day-to-day functioning of their child in various life areas, including physical activities, well-being, cognition, social activities, behavior and general health during a specific time frame*
Study Duration	*14 weeks with extension available*
Duration of IP administration	*14 weeks with extension available*
Population	*confirmed genetic/clinical diagnosis of CDKL5 Deficiency Disorder (CDD)*
Study Sites	*1: NYU Comprehensive Epilepsy Center.*
Number of participants	*10 patients: 7: ages 2-18 years old* *Max of 3: ages 18-35 years old*
Description of Study Agent	*Liquid*
Key Procedures	*Blood draws, questionnaires, Doppler echocardiogram, electrocardiogram*

Protocol Activity: Week (±7 days)	**Baseline Week 0**	**Safety call**	**Week 2**	**Week 6**	**Safety call**	**Week 10**	**Safety call**	**Week 14**	**Post Taper Follow up**
Visit	**1**	**Safety call**	**2**	**3**	**Safety call**	**4**	**Safety call**	**5/End of study/ End of treatment/ Withdrawal visit**	
Informed consent/assent	X								
Inclusion/exclusion criteria	X	X	X	X	X	X	X	X	
Medical history	X	X	X	X	X	X	X	X	X
Demographics	X								
Physical and neurological exam and Vital signs	X		X	X		X		X	
Adverse events	X	X	X	X	X	X	X	X	X
EKG	X			X				X	
Echo	X			X				X	
C/IGIC	X		X	X		X		X	
QOLCE	X		X	X		X		X	
PEDS-QOL	X		X	X		X		X	
Hematology & Chemistry (draw/handling) (CBC, CMP, LFTs, BUN, Creatinine), Coagulation	X		X	X		X		X	
HCG (urine and serum)	X		X	X		X		X	
THC (urine and serum)	X		X	X		X		X	
Urinalysis	X		X	X		X		X	
AED levels /Clobazam	X			X		X		X	
Study diary provided	X		X	X		X		X	
Study diary collected			X	X		X		X	
Study drug dispensed	X		X	X		X		X*	
Study Drug administration	X								
Study drug compliance dosing schedule and return dosing schedule	X	X	X	X	X	X	X	X	X
Concomitant/other medications/supplements	X	X	X	X	X	X	X	X	X

Extension								
Protocol Activity: Week (±7 days)	**Extension Visit**	**Safety call**	**Extension Visit**	**Safety call**	**Extension Visit**	**Safety call**	**End of Treatment/ Withdrawal**	**Post Taper Follow up**
Inclusion/exclusion criteria	X	X	X	X	X	X	X	
Medical history	X	X	X	X	X	X	X	X
Physical and neurological exam and Vital signs	X		X		X		X	
Adverse events	X	X	X	X	X	X	X	X
EKG	X		X		X		X	
Echo	X		X		X		X	
C/IGIC	X		X		X		X	
QOLCE	X		X		X		X	
PEDS-QOL	X		X		X		X	
Hematology & Chemistry (draw/handling) (CBC, CMP, LFTs, BUN, Creatinine), Coagulation	X		X		X		X	
HCG (urine and serum)	X		X		X		X	
THC (urine and serum)	X		X		X		X	
Urinalysis	X		X		X		X	
AED levels /Clobazam	X		X		X		X	
Study diary provided	X		X		X		X	
Study diary collected	X		X		X		X	
Study dispensed	X		X		X		X	
Study drug compliance dosing schedule and return dosing schedule	X	X	X	X	X	X	X	X
Concomitant/ other medications/supplements	X	X	X	X	X	X	X	X

***If subject continues to extension visit**

1. Key Roles

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2. Introduction, Background Information and Scientific Rationale

2.1Background Information and Relevant Literature: Name and Description of the Investigational Agent

Fenfluramine is an amphetamine analogue that was synthesized many years ago. It was approved in a large number of countries and widely prescribed as an appetite suppressant for the treatment of adult obesity. Brand names for fenfluramine formulations included Ponderax and Pondimin. Fenfluramine was also used extensively in an off-label combination with phentermine ("Fen-Phen") to treat adult obesity. Fenfluramine is a racemic compound and the single enantiomer D-fenfluramine (dexfenfluramine) was also approved and marketed for the treatment of obesity as Adifax, Redux, and others.

Fenfluramine was introduced in the USA in 1973. Products containing fenfluramine and D-fenfluramine were withdrawn from all markets between 1997 and 2000 after reports of heart valve disease and pulmonary hypertension (Connolly 1997; CDC 1997; Wong 1998). While the risk/benefit relationship for fenfluramine was considered unfavorable to treat obesity in adults, establishing seizure control in Dravet syndrome, Lennox-Gastaut syndrome (LGS) or other refractory catastrophic childhood epilepsies might lead to a more acceptable risk/benefit profile for fenfluramine. The high rate of mortality and severe intellectual and quality of life impairments in severe childhood epilepsies[1, 2] makes any effective drug or therapy a potentially life-saving option.

As a result of the earlier extensive use of fenfluramine in adult obesity, there is a large body of information in the public domain concerning its pharmacology, toxicology and use in the treatment of obesity. These data are summarized in the ZX008 Investigator Brochure (2017).[4] There is also a large body of information concerning its clinical safety profile.

2.1.1 Preclinical Data

The pharmacokinetics of fenfluramine, norfenfluramine and their respective isomers have been studied in mice, rats, dogs and humans. Fenfluramine and norfenfluramine were more slowly eliminated in humans than in other species. In vitro metabolism studies have shown considerable species differences in the metabolism of fenfluramine, with no single species having a profile similar to humans. No human-specific metabolites were detected and both rat and dog showed good coverage of the human fenfluramine metabolites. In humans, fenfluramine is metabolized primarily to norfenfluramine. Fenfluramine is partially metabolized by CYP1A2, CYP2B6, and CYP2D6, with additional metabolism by CYP2C9, CYP2C19, and CYP3A4. Norfenfluramine does not appear to be strong substrate of any CYP450 enzyme, but is metabolized by CYP1A2, CYP2B6, CYP2C19, and CYP2D6 in vitro. There is also some contribution of renal clearance to the elimination of dexfenfluramine (8%-16%) and nordexfenflurmaine (7%-8%) from the body. Because fenfluramine and its active metabolite

norfenfluramine have multiple pathways of elimination, interference with a single pathway is unlikely to cause a significant change in fenfluramine's clearance though the probability of an interaction increases if multiple elimination mechanisms are affected simultaneously.

While in vitro studies showed that both fenfluramine and norfenfluramine cause weak inhibition of CYP2D6 and fenfluramine causes weak induction of CYP3A4 and CYP2B6, further analysis based on the FDA's mechanistic static model shows that fenfluramine and its major metabolite norfenfluramine are unlikely to alter the pharmacokinetics of substrates of CYP450 enzymes in the range of ZX008 doses that will be administered in this study. A 10-week GLP juvenile toxicology and toxicokinetic study in rats, which included fenfluramine doses of 3.5, 9 and 20 mg/kg/day by oral gavage for 10 weeks (Days 7 to 76 pp). The data from the juvenile toxicology studies suggest that the effects of fenfluramine in juvenile animals (CNS-related clinical signs, effects on body weight and food consumption, and neurobehavioral deficits) are similar to effects previously reported in neonatal and adult rats (Morford, 2002; Williams, 2002). There was no evidence of CNS histopathology; importantly, there were also no histopathologic findings in aortic or mitral cardiac valves, and no adverse effects on any other tissues at necropsy.

The lowest-observed-adverse-effect level (LOAEL) of 3.5 mg/kg/day is a human equivalent dose (HED) of 0.833 mg/kg/day when converted on the basis of body surface in mg/m2, based on a reference body weight for a 20-kg child. No new target organs were identified in juvenile animals, and there were no permanent effects on sexual maturation or reproductive function when juvenile animals were administered fenfluramine from the neonatal period through adulthood.[4]

2.1.2 Clinical Data in Epilepsy

There have been several published reports of fenfluramine's successful treatment of refractory childhood epilepsy in the 1980s.(Aicardi and Gaustaut, 1985; Aicardi et al., 1988). In 1996, a Belgian group reported on the use of fenfluramine in 11 children (ages 18 months to 15.5 years old) with refractory or self-induced epilepsy (Boel and Casaer, 1996). Patients were treated with fenfluramine at 0.5 – 1 mg/kg/day for 3 to 8.5 years (average duration 5 years 7 months). Seven children (64%) became seizure-free and the remaining 4 patients experienced ≥75% reduction in seizure frequency.

In 2002, Casaer and Boel published an update of their fenfluramine study. The study population was expanded to 22 patients with intractable or self-induced seizures, including the previous 11 patients (Casaer and Boel, 2002). The duration of treatment was 1 to 12 years. Among the 22 patients treated, 6 (27%) became seizure-free, 10 (45%) had a 90% reduction in seizure frequency and 6 (27%) were non-responders. Fenfluramine was effective in multiple seizures types in Dravet syndrome (DS), a drug resistant pediatric epileptic encephalopathy syndrome (Ceulemans et al., 2012; Schoonjans 2015 et al,; Ceulemans et al,, 2016). [4]

Zogenix is currently evaluating ZX008 in DS in three Phase 3 double-blind, randomized, placebo-controlled studies (clinicaltrials.gov identifiers: NCT02826863, NCT02682927, and NCT02926898). Currently, a cohort of refractory Lennox-Gastaut syndrome (LGS) patients in Belgium are being treated in a Phase 2 open-label, pilot, dose-finding trial of fenfluramine as an add-on therapy to conventional therapy (Study S58545; clinicaltrials.gov identifier: NCT02655198). Subjects aged 3 to 18 years, fulfilling the diagnostic criteria for LGS as described by the International League Against Epilepsy (ILAE) in 1989, who have failed at least two AEDs (including vagal nerve stimulation (VNS), and have had at least 4 documented convulsive seizures (generalized tonic-clonic, tonic, atonic, and focal seizures with a motor

component and on at least 2 AEDs at stable doses in the prior 4 weeks are eligible for this study (Lagae et al., 2016). A similar study has been initiated in the United States.[4]

For the Belgium LGS study, subjects establish baseline convulsive seizure frequency over 4 weeks and are then treated with fenfluramine at a starting dose of 0.2 mg/kg/day. In non-responders (<50% convulsive seizure frequency decrease), the dose is up titrated every 4 weeks from 0.2 mg/kg/day to 0.4 mg/kg/day, and up to a maximum dose of 0.8 mg/kg/day for up to 20 weeks if the patient remains a non-responder per protocol definition.[4]

Interim results are available on the anticonvulsant effects of adjunctive treatment with ZX008 in the first 13 patients with LGS from Study S58545 (9 males, 4 female). Fenfluramine treatment was started at a mean age of 11.4 years (range 3 to 17 years), administered at a maximum of 0.8 mg/kg/day and added to each patient's current AED regimen. Prior to enrolling in the trial, all patients had failed on at least 3 other AEDs. By November 2016, 8 patients had completed all 20 weeks of the treatment period, 4 patients withdrew before study end, and 1 patient remained on treatment, having completed 16 weeks of treatment. Of the 4 patients who withdrew before study end, 1 withdrew due to worsening of seizures following elective surgery, and 3 withdrew due to adverse events (2 decreased alertness, 1 insomnia). Seven of the 13 patients (54%) achieved at least a 50% reduction in the number of convulsive seizures during the study at doses of 0.2mg/kg (3 patients), 0.4mg/kg (3 patients) and 0.6mg/kg (1 patient). Despite not attempting to dose to maximal efficacy 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. The most common treatment emergent adverse events to date include decreased appetite in 3 patients, decreased alertness/fatigue in 3 patients, and insomnia in 2 patients. ZX008 has been well tolerated in this small, open-label study, and no patients have exhibited any clinical signs of cardiovascular or cardiopulmonary adverse events as of the November 2016 data cut. (ZX008 IB 2017).[4]

2.1.3 Dose Rationale

Based on clinical data to date. Patient will be dosed up to 0.8 mg/kg/d or 30 mg/d maximum. It will be twice daily dosing. Fenfluramine was administered to over 500 children with neurobehavioral conditions, including autism and ADHD with good safety and tolerability, at doses in the range of 0.65 to 3.6 mg/kg/day (most common dose of 1.5 mg/kg/day) for up to 12 months.[4]

2.2 Rationale

The lack of consistent efficacy and individual tolerability and safety concerns with current treatments available have resulted in the continued significant unmet need for a new treatment with a novel mechanism of action for children and adults with CDD.

2.3 Potential Risks & Benefits

Fenfluramine is effective in multiple seizures types in Dravet syndrome (DS), another very drug resistant pediatric epileptic encephalopathy syndrome. In a recent Phase III study of 119 DS patients, the median reduction of convulsive seizures was 64% greater than placebo[3] in the group that received 0.8 mg/kg/day and 34% for the group that received 0.2 mg/kg/day of fenfluramine.

2.3.1Side effects

The most common AEs observed in children and young adults the ongoing studies of

ZX008 include decreased appetite, pyrexia, diarrhea, lethargy, and somnolence. However, there is limited data in the pediatric population, largely based on the Belgium and the more recent Phase 3 trial cited above.[4]

2.3.2 Echocardiogram findings

Findings from echocardiograms will be discussed between the investigator, local cardiologist and parent/caregiver/legal or authorized representative to determine risk versus benefit of the study to the subject.

ECHOs will be done at NYU. If caregivers/patients are not able to travel to NYU facility, doppler echocardiography can be done at a local facility. Readings will be sent back to site for evaluation. Findings related to pulmonary hypertension or valvulopathy on any of the four valves (aortic, mitral, pulmonary, tricuspid) will be reported to the investigator with grades of normal, trace, mild, moderate or severe. If the ECHO result has progressed in severity since the last reading, then new oversight measures will be enacted as described below in Levels 1-3. Table 12 describes the severity of ECHO findings with the level of increasing oversight if the subject is to remain in the study.

Table 1: Clinical Measures Enacted Upon Increasing Severity of ECHO Findings

	Valve			
Severity	Aortic	Mitral	Pulmonary	Tricuspid
Normal	Level 1	Level 1	Level 1	Level 1
Trace	Level 2	Level 2	Level 1	Level 1
Mild	Level 2	Level 2	Level 1	Level 1
Moderate	Level 3	Level 3	Level 3	Level 3
Severe	Level 3	Level 3	Level 3	Level 3

Level 1: Continue per protocol

Level 2:

1. If there is a desire to continue study medication:
    a. The investigator will evaluate the efficacy to date based on study diaries and consult with the parent/guardian, and determine whether study treatment was associated with significant, meaningful benefit in number, severity and/or duration of seizures and/or on the impact on daily functioning.
    b. The investigator will consider whether the subject has had reasonable trials (dose and duration) of other available anticonvulsants (e.g. valproic acid, clobazam, or topiramate), alone or in combination, and not maintained the level of seizure control achieved with study medication.
2. If the investigator feels consideration of continued treatment is warranted considering benefit and potential risk, and the parent/guardian feels strongly that the child be maintained on the study medication when understanding the risks, the parent/guardian must sign a new consent which describes the additional risk and the child should provide assent if appropriate.
    a. If both of these conditions are not met, the subject is discontinued from treatment.

3. Investigator and Institutional Cardiologist make a determination of appropriate path, including the possible outcomes:
    a. Discontinue study medication
    b. Increase frequency of ECHO and ECG monitoring
    c. Add additional ECG and/or ECHO measures to be monitored
    d. Reduce the dose of study medication

Level 3:

1. The investigator will evaluate efficacy to date based on study diaries and consult with the parent/guardian, and determine whether the achieved benefit justifies the consideration of continuing study treatment. MINIMAL efficacy criteria:
    a. Seizures must be more than 75% improved (number of convulsive seizures per 28 days) on treatment over baseline, and improvement must be consistent.
    b. The number, type, duration, and distribution of seizures at baseline should be of a severity, which justifies the risks of cardiopulmonary complications, considering the subject's age and overall health.
    c. Subject has had reasonable trials (dose and duration) of other available anticonvulsants (e.g., valproic acid, clobazam, topiramate), alone or in combination, and not maintained the level of seizure control achieved with study medication.
2. If the investigator feels consideration of continued treatment is warranted considering benefit and potential risks, and the parent/guardian feels strongly that the child be maintained on the study medication when understanding the risks, the parent/guardian must sign a new consent, which describes the additional risks and the child should provide assent if possible.
    a. If both of these conditions are not met, the subject is discontinued from treatment.
3. Investigator and Institutional Cardiologist make a determination of appropriate path, including these possible outcomes:
    a. Discontinue study medication
    b. Increase frequency of ECHO and ECG monitoring
    c. Add additional ECG and/or ECHO measures to be monitored
    d. Reduce the dose of study medication

3. Objectives and Purpose

3.1 Primary Objective

Median reduction in monthly convulsive seizure frequency

3.2 Secondary Objectives

- Caregiver/Investigator Global Impression of Change (C/IGIC). The parent/caregiver and investigator rated change on a 7-point scale: 1-very much improved; 2-much improved; 3-minimally improved; 4-no change; 5-minimally worse; 6-much worse; and 7-very much worse
- Quality of Life in Childhood Epilepsy Scale . A low-burden parent/caregiver completed assessment that looks at how epilepsy affects day-to-day functioning of their child in

various life areas, including physical activities, well-being, cognition, social activities, behavior and general health in comparison to other children their age,

- PEDS-QL. A parent/caregiver completed assessment that looks at how epilepsy affects day-to-day functioning of their child in various life areas, including physical activities, well-being, cognition, social activities, behavior and general health during a specific time frame.

4. Study Design and Endpoints

4.1 Description of Study Design

The study to be conducted is an expanded access program for intermediate size population use.

4.2 Study Endpoints

4.2.1 Primary Study Endpoints

Median reduction in monthly convulsive seizure frequency. For continuation after initial study period, patients must have a ≥ 40% reduction in convulsive seizure frequency over baseline.

4.2.2 Secondary Study Endpoints

Evaluate changes from Baseline in cognitive, motor, and behavioral function as well as QOL following fenfluramine treatment.

4.2.3 Safety Endpoints

The safety endpoints the study are:

- Adverse events
- Laboratory safety (hematology, chemistry, coagulation, urinalysis)
- Vital signs (blood pressure, heart rate, temperature, and respiratory rate)
- Physical examination
- Neurological examination
- Questionnaires to measure changes in cognition of the subject
- 12-lead ECGs
- Doppler ECHOs
- Body weight

5. Study Enrollment and Withdrawal

All subjects and/or their parent/legal guardian must sign the appropriate informed consent prior to beginning any study-related activities, including Screening procedures. Additionally, an assent form should be signed by subjects age 7 to 17 years old, unless lacking capacity.

5.1 Inclusion Criteria

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Confirmed clinical/genetic diagnosis of CDKL5 Deficiency Disorder CDD

2. Ages 2-35 years old. Subject is male or non-pregnant, non-lactating female. Female subjects of childbearing potential must not be pregnant or breast-feeding. Female subjects of childbearing potential must have a negative urine pregnancy test. Subjects of childbearing or child-fathering potential must be willing to use medically acceptable forms of birth control, which includes abstinence, while being treated on this study and for 30 days after the last dose of study drug.

3. Subject has been informed of the nature of the study and informed consent has been obtained from the legally responsible parent/guardian.

4. Subject has provided assent in accordance with Investigational Review Board/Independent Ethics Committee (IRB/IEC) requirements

5. Subject's caregiver is willing and able to be compliant with diary completion, visit schedule and study drug accountability.

6. Subjects must be receiving a therapeutically relevant and stable dose of anti-seizure medications, dietary therapies for epilepsy or vagus nerve stimulation settings for at least 4 weeks prior to screening and are expected to remain stable throughout the initial 14 weeks of the study. Medication changes are allowed during the extension portion.

7. ≥4 convulsive seizures (tonic-clonic, tonic, atonic, clonic, focal motor) per 4-week period; each convulsive seizure must last ≥3 seconds.

8. Subject is receiving at least 1 concomitant AED and up to 4 concomitant AEDs, inclusive. KD and VNS are permitted but do not count towards the total number of AEDs. Rescue Receiving at least 1 concomitant AED and up to 4 concomitant AEDs, inclusive. Rescue medications for seizures are not counted towards the total number of AEDs.

5.2 Exclusion Criteria

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Subject has a known hypersensitivity to fenfluramine or any of the excipients in the study medication.

2. Subject has current or past history of cardiovascular or cerebrovascular disease, myocardial infarction or stroke.

3. Subject has current or past history of cardiovascular or cerebrovascular disease, such as cardiac valvulopathy, myocardial infarction or stroke, or clinically significant structural cardiac abnormality, including but not limited to mitral valve prolapse, atrial or ventricular septal defects, patent ductus arteriosis, and patent foramen ovale

with reversal of shunt. (note: Patent foramen ovale or a bicuspid valve are is not considered exclusionary, but may be associated with the following diseases, which are exclusionary: coarctation of the aorta, Turner syndrome, supravalvular aortic stenosis, subvalvular aortic stenosis, patent ductus arteriosus, Sinus of Valsalva aneurysm, ventricular septal defect, Shone's complex, ascending aortic aneurysm, Loeys-Dietz syndrome, ACTA2 mutation familial thoracic aortic aneurysm syndrome, and MAT2A mutation familial thoracic aortic aneurysm syndrome).

4. Subject has current or recent history of Anorexia Nervosa, bulimia, or depression within the prior year that required medical treatment or psychological treatment for a duration greater than 1 month.

5. Subjects who are currently on formulations of CBD (other than Epidiolex) , CBD/THC or any MMJ.

6. Subject who have positive urine tetrahydrocannabinol (THC) Panel or whole blood cannabidiol (CBD) who have not been prescribed Epidiolex.

7. Subject has participated in another clinical trial within the past 30 days (calculated from that study's last scheduled visit).

8. Subject is at imminent risk of self-harm or harm to others, in the investigator's opinion, based on clinical interview.

9. Subject has a current or past history of glaucoma.

10. Subject is receiving concomitant therapy with: centrally-acting anorectic agents; monoamine-oxidase inhibitors; any centrally-acting compound with clinically appreciable amount of serotonin agonist or antagonist properties, including serotonin reuptake inhibition; atomoxetine, or other centrally-acting noradrenergic agonist; or cyproheptadine. (see appendix 1)

11. Subject has moderate or severe hepatic impairment. Asymptomatic subjects with mild hepatic impairment (elevated liver enzymes <3x upper limited of normal [ULN] and/or elevated bilirubin <2x ULN) may be entered into the study after review and approval by the Medical Monitor in conjunction with the sponsor, in consideration of comorbidities and concomitant medications.

5.3 Strategies for Recruitment and Retention

During a routine visit at the NYU Comprehensive Epilepsy Center, subjects who meet criteria for the study (or their parents/legal guardians) will be asked if they would like to participate in the study. Note: some subjects may hear of this study from other parents with CDD or from the International Foundation for CDKL5 Research (https://www.cdkl5.com), which lists studies for patients with CDD. Such subjects who contact the Principal Investigator or research staff will be screened for their potential to participate based on inclusion and exclusion criteria.

Male and female subjects of any ethnicity between ages of 2 and 35 (inclusive) will be

assessed for inclusion, with no more than 3 patients between the ages of 18-35.

During the routine visit, the investigator will inform each prospective subject/parent/legal guardian of the nature of the study, and explain the potential risks and study-related procedures. If the subject/parent/legal guardian agrees, they will be given the informed consent documents to read and sign prior to starting any study procedures. Only the Principal Investigator, sub-investigators, and other research personnel listed on the study will have access to subject information. Once the study subject/parent/legal guardian has signed the informed consent, the investigator will explain the study during the routine visit. If necessary, the investigator will inform the subject and surrogate that a capacity assessment will be performed to determine whether the subject is capable of providing an informed decision to participate in the study. At this time, a capacity assessment will be conducted if the subject does not refuse the assessment. Capacity will be assessed through neurological examinations and neuropsychology reports conducted by the physician as well as learning and/or development delays that have been documented. If there is already documentation of lack of capacity, no assessment will be needed. If it has been determined by the investigator that the subject has capacity, they will be given the assent form to review. The investigator will go over the study as described in the assent form including study visits and procedures. The subject will be allowed time to ask questions. If the subject is comfortable, then they can sign the assent. All documentation will be placed in the study binder and documented in the study visit note. A copy of the informed assent and consent documents will be given to the subject and the subject's parent/legal guardian. Screening procedures may begin. The Screening Period is 4 weeks, during which study candidates must complete a diary documenting the frequency and duration of seizures.

Refer to Section 7 for the Schedule of Events and specific requirements for each study visit.

5.4 Duration of Study Participation

Subject participation will be a total of 14 weeks with extension available.

5.5 Total Number of Participants and Sites

Approximately 10 patients with a confirmed genetic/clinical diagnosis of CDKL5 Deficiency Disorder (CDD) will be recruited for the study from the Principal Investigator's and co-investigator's clinical practice at New York University Comprehensive Epilepsy Center (NYUCEC) or from families that contact the Principal Investigator. Male and female subjects of any ethnicity between ages of 2 and 35 (inclusive) will be assessed for inclusion, with no more than 3 patients between the ages of 18-35.

5.6 Participant Withdrawal or Termination

5.6.1 Reasons for Withdrawal or Termination

A subject may be discontinued from study drug at any time if the subject, subject's legal guardian, or the investigator feels that it is not in the subject's best interest to continue. The following is a list of possible reasons for study drug discontinuation:

1. Parental/legal guardian withdrawal of consent.

2. Subject is not compliant with study procedures.

3. Protocol violation requiring discontinuation of study drug.

4. Severe adverse events, including significant toxicity such as severe cognitive or behavioral toxicity, impaired liver and renal function, or impaired hematopoiesis

5. Seizure exacerbation not attributable to other known provocative factors.

6. Interaction with concomitant AED regimen that leads to unacceptable toxicity. Medication adjustments will be avoided, if possible, and may require the subject to exit the study, at the discretion of the Investigator.

Specific drug-related toxicities will be assessed and managed by the Principal Investigator.

Depending on the nature of the signs (eg, changes in serum chemistries, liver function tests) or symptoms (eg, rash), the subject will be assessed to determine the severity and likelihood of relation to study medication. Based on this assessment, the medication may be discontinued, the dose may be reduced, or the drug may be continued with ongoing assessment. If the study drug is discontinued due to a suspected toxicity, it will only be restarted if there is strong evidence that the toxicity was likely not related to the study medication (eg, liver tests were elevated due to a cytomegalovirus infection).

If a subject must discontinue study drug, the method for discontinuation from study drug will be determined based on the type of reaction and/or reason for withdrawal. For example, if the subject experiences a rapidly progressive rash, it would lead to abrupt cessation of study drug, but if subject experiences excess tiredness, study drug may be tapered off. A discussion of the method of cessation will occur between the subject and/or subject's parent/legal guardian and the physician.

5.6.2 Handling of Participant Withdrawals or Termination

For all subjects who withdraw from the study, there will be 1 final telephone/email follow-up 4 weeks after the last dose of study drug (Post taper Follow-up Visit). If the subject/parent/legal guardian cannot be contacted after 4 phone calls to subject/parent/legal guardian, a certified letter will be sent to the subject/parent/legal guardian.

Refer to Section 7 for the Schedule of Events and specific requirements for each study visit.

5.7 Premature Termination or Suspension of Study

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to Principal investigator. If the study is prematurely terminated or suspended, the PI will promptly inform the IRB and will provide the reason(s) for the termination or suspension.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable

- Determination of futility

Study may resume once concerns about safety, protocol compliance, data quality is addressed and satisfy the sponsor, IRB and/or FDA.

6 Study Agent

Investigational Medicinal Product – ZX008	
Substance Code	ZX008
Active Substance (INN)	Fenfluramine Hydrochloride
Trade Name	Not applicable
Formulation (including dosage form and strength)	Solution 2.5mg/mL
Route/Mode of Administration	Oral
Manufacturer	Andersonbrecon, Inc. on behalf of Zogenix International Limited

6.1 Study Agent Description

ZX008 drug product is an oral aqueous solution of fenfluramine hydrochloride buffered to pH 5 and provided in concentrations of 2.5 mg/mL. The excipients selected have been approved for use in the formulations of currently marketed drug products and are considered to be safe. The solution formulations will be suitably flavored, and will contain preservatives and a thickening agent. The product is sugar free and is intended to be compatible with a ketogenic diet. The doses to be studied will be 0.8 mg/kg/day divided into two daily doses, up to a maximum of 30 mg/day.

6.1.1 Acquisition

The investigational medicinal product (IMP) will be supplied to the study site by the sponsor or its delegate.

All IMP will be transported, received, stored, and handled strictly in accordance with the container or product label, the instructions supplied to the research site and its designated pharmacy, the site's standard operating procedures, and applicable regulations. IMP must be stored separately from normal hospital or practice inventories, in a locked facility with access limited to the investigator and authorized personnel. The investigator must ensure that the IMP is dispensed only to subjects enrolled in this study according to this study protocol.

6.1.2 Formulation, Appearance, Packaging, and Labeling

ZX008 drug product will be provided in a concentration of 2.5 mg/mL in 1 bottle size with nominal fill volume of 120 ml. The ZX008 product will be packaged and labeled according to current International Conference on Harmonization (ICH), Good Manufacturing Practices (GMP), and Good Clinical Practices (GCP) guidelines, and national legal requirements.

Dosing directions for the product can be found in the IMP handling instructions for the study subjects and for the investigator.

6.1.3 Product Storage and Stability

Appropriate storage temperature and transportation conditions will be maintained for the study drug from the point of manufacture up to delivery of the study drug. Study medication must be stored at 15-25°C (59-77°F) with excursions of 5-30°C (41-86°F) permitted; do not

refrigerate or freeze. Storage and handling instructions of the IMP maintained at the subject's home are described in the subject's IMP handling instructions.

All unused IMP will be saved by the site for final disposition according to the sponsor's directive.

6.1.4 Dosing and Administration

Study medication will be administered as equal doses BID in the morning and in the evening approximately 12 hours apart. Each dose should be separated by a minimum of 8 hours and a maximum of 12 hours.

6.1.5 Route of Administration

Medication is given orally.

6.1.6 Starting Dose and Dose Escalation Schedule

Patients will be titrated over 14 days to a dose of ZX008 0.8 mg/kg/day (maximum dose 30 mg/d).

Titration schedule			
	Day 1-4	*Day 5-8*	*Day 9-14*
	ZX008 0.2 mg/kg/day	ZX008 0.4 mg/kg/day	ZX008 0.8 mg/kg/day

After completion of the Titration Period, subjects will enter the Maintenance Period and continue to receive this dose of ZX008 and be treated for an additional 12 weeks. Study medication will continue to be administered BID in the morning and in the evening, approximately 12 hours apart. Each dose should be separated by a minimum of 8 hours and a maximum of 12 hours. A missed dose of study medication may be taken later up to 8 hours before the next scheduled dose; otherwise, the missed dose should not be given.

6.1.7 Taper Period

Subjects will decrease from 0.8 mg/kg BID to a dose of 0.4 mg/kg BID (maximum 30 mg/day or). After 4 days at this dose level, subjects will decrease their dose to 0.2 mg/kg/day. On Study Day 9, all subjects will stop taking study medication. The taper is expected to take a total of 8 days.

Taper schedule		
	Day 5-8 after end of study/ study withdrawal	*Day 9-14 after end of study/ study withdrawal*
	ZX008 0.4 mg/kg/day	ZX008 0.2 mg/kg/day

6.1.8 Dose Adjustments/Modifications/Delays

A missed dose of study medication may be taken later up to 8 hours before the next scheduled dose; otherwise, the missed dose should not be given.

If the parent/caregiver is unable to administer the full dose due to spillage (eg, dose was spilled during measuring, subject spit dose out during administration), he/she should attempt to give the full dose noting the extra amount used to fulfill the dose. If the subject vomits within the first 15 minutes of administration the dose may be re-administered. Care must be taken not to overdose. If the amount spilled is not known, the parent/caregiver should not give additional

medication to avoid potential overdose.

6.1.9 Duration of Therapy

Duration of therapy will be14 weeks with extension available.

6.1.10 Tracking of Dose

The study team will assess and track subject compliance with the study drug regimen via clinical evaluations and follow-up email or phone calls.

7 Study Procedures and Schedule

7.1 Study Specific Procedures

-Medical history: Any medical problems/conditions throughout subject's body system, relevant medical events and/or procedures/surgery

-Medication history: complete medication history of any anti-epileptic medications; current history other prescription and over-the-counter medications.

-Physical examination: vital signs including temperature, height and weight and organ systems to be assessed

-Neurological examination: examination of sensory neurons, motor responses and reflexes

-Biological specimen collection and laboratory evaluations.

-Procedures: Doppler Echocardiography and Electrocardiograms

-Questionnaires and seizure diary

7.2 *Clinical Laboratory Evaluations*

-Hematology: hemoglobin, hematocrit, white blood cells (WBC) with differential count, platelet count.

-Coagulation: Prothrombin time (PT)/International normalized ratio (INR), activated partial thromboplastin time (PTT)

-Biochemistry: comprehensive metabolic panel, creatinine, total bilirubin, alanine aminotransferase (ALT), aspartate and aminotransferase (AST) albumin (ALB), alkaline phosphatase (AP), alanine aminotransferase (ALT; SGPT), aspartate aminotransferase (AST; SGOT), bicarbonate, blood urea nitrogen (BUN), calcium (Ca), carbon dioxide (CO2),chloride (Cl), creatinine, creatine kinase, gamma-glutamyl transferase (GGT), globulin, glucose, lactate dehydrogenase (LDH), phosphorus, potassium (K), sodium (Na), thyroid function (T3, T4, and thyroid stimulating hormone [TSH]), total bilirubin, direct bilirubin, total cholesterol, total protein, triglycerides, uric acid.

-**Urinalysis:** dipstick urinalysis, including protein, hemoglobin and glucose; if dipstick is abnormal, complete urinalysis with microscopic evaluation is required.

-Urine or serum pregnancy test: usually to be done within 24 hours prior to study intervention and results must be available prior to administration of study product.

- Urine or serum THC test: usually to be done within 24 hours prior to study intervention and results must be available prior to administration of study product.

-Plasma Sample for Concomitant Antiepileptic Drug(s): Plasma samples to ensure that concomitant AEDs dosing is within an acceptable range will be conducted during the study as outlined.

Blood work will be about 8.0 – 20.0mL (about 2-4 teaspoons) of blood depending on the amount of concomitant medications**.**

If caregivers/patients are not able to travel to the NYU facility due to COVID-19 travel restrictions, clinical laboratory evaluations can be completed at a local facility.

7.3 Procedures

Electrocardiograms: Twelve-lead ECGs will be conducted during study as outlined after the subject has been in the supine position resting for ≥5 minutes. Heart rate, PR duration, QRS duration, QT duration, and the investigator's overall interpretation will be recorded.

Doppler Echocardiography: Doppler echocardiography will be conducted at the hospital facility with experience for the subject's age. If caregivers/patients are not able to travel to NYU facility, doppler echocardiography can be done at a local facility. Doppler echocardiography can be done +/- 7 days from study visit. Doppler echocardiography uses ultrasound technology to examine the heart or blood vessels. An ECHO uses high frequency sound waves to create an image of the heart while the use of Doppler technology allows determination of the speed and direction of blood flow by utilizing the Doppler effect. Predetermined standard guidelines on the proper evaluation of certain measurements, as well as abnormality thresholds, were constructed by the sponsor prior to study initiation. Readings will be sent back to site to determine the appropriate benefit is and any findings consistent with cardiac valvopathy or pulmonary hypertension.

7.4 Questionnaires

*Given the profound intellectual disability of this population (ie, adults have intelligence of <age 5), the pediatric versions will be used for both children and adults. *

-**Caregiver Global Impression of Change (CGIC).** The parent/caregiver rated change on a 7-point scale: 1-very much improved; 2-much improved; 3-minimally improved; 4-no change; 5-minimally worse; 6-much worse; and 7-very much worse

-**Investigator Global Impression of Change (IGIC).** The investigator rated change on a

7-point scale: 1-very much improved; 2-much improved; 3-minimally improved; 4-no change; 5-minimally worse; 6-much worse; and 7-very much worse

-**Quality of Life in Childhood Epilepsy Scale (13)**. A low-burden parent/caregiver completed assessment that looks at how epilepsy affects day-to-day functioning of their child in various life areas, including physical activities, well-being, cognition, social activities, behavior and general health in comparison to other children their age,

-**Pediatric Quality of Life Inventory (PEDS-QL**). A parent/caregiver completed assessment that looks at how epilepsy affects day-to-day functioning of their child in various life areas, including physical activities, well-being, cognition, social activities, behavior and general health during a specific time frame

7.5 Study Schedule

7.5.1 *Core study*

7.5.1.1 Baseline

Visit 1 Baseline (Week 0)

Baseline (Visit 1) will occur at NYU CEC. Procedures will proceed as follows:

- Obtain written informed consent/assent.
- Determine if the subject meets the preliminary eligibility criteria:
    - Collect demographic information
    - Collect current and relevant medical history
    - Identify concomitant medications used
    - Identify and confirm stable use AED medications
    - ≥4 convulsive seizures (tonic-clonic, tonic, atonic, clonic, focal motor) per 4-week period; each convulsive seizure must last ≥3 seconds.

If the subject meets the preliminary eligibility criteria, the following assessments will be performed:

- Vital signs (including systolic and diastolic blood pressure, radial pulse rate, and body temperature): perform in sitting position
- Physical and neurological examination including Height and weight
- EKG and echocardiogram
- Complete the following assessments:
    - Caregiver and Investigator Global Impression of Change
    - QOLCE
    - PEDS-QOL
- Blood draw for clinical laboratory evaluations:
    - Complete blood count (CBC), comprehensive metabolic panel (CMP) Serum/Urine human chorionic gonadotropin (HCG), as applicable (sample taken only for female subjects of childbearing potential), and antiepileptic medication levels

- Urinalysis
- Urine or serum THC
- Record any AEs occurring since signing the ICF and any that occur during this visit
- Instruct subject or subject's caregiver to keep a seizure diary for the next 2 weeks, including the following information:
    - Seizure type and duration
    - Use of rescue medications
- Dispense study drug and review administration instructions and titration schedule
- First dose given in office
- Instruct subject to return in 2 weeks for Visit 2

Safety call telephone

The safety call will occur between visit 1 and visit 2. It will proceed as follows:

- Record any AEs occurring since last visit and any that occur during this visit
- Issues with titration schedule
- Record any changes in concomitant medications

Visit 2 (Week 2)

Visit (Week 2) as follows:

- Physical and neurological examination and height and weight
- Vital signs (including systolic and diastolic blood pressure, radial pulse rate, and body temperature): performed after the subject has been in a sitting position for 3–5 minutes
- Collect seizure diary and review entries
- Record any AEs occurring since last visit and any that occur during this visit
- Record any changes in concomitant medications
- Complete the following assessments:
    - Caregiver and Investigator Global Impression of Change
    - QOLCE
    - PEDS-QOL
- Blood draw for Complete blood count (CBC), comprehensive metabolic panel (CMP) Serum/Urine human chorionic gonadotropin (HCG), as applicable (sample taken only for female subjects of childbearing potential)
- Urinalysis
- Urine or serum THC
- Dispense new seizure diary and review instructions for completion
- Dispense study drug and review administration instructions
- Instruct subject to return in 4 weeks for Visit 3

Visit 3 (Week 6)

The subject will return to the site for Visit 3. Procedures at Visit 3 will proceed as follows:

- Physical and neurological examination and height and weight
- Vital signs (including systolic and diastolic blood pressure, radial pulse rate, and body temperature): performed after the subject has been in a sitting position for 3–5 minutes
- EKG and echocardiogram
- Collect seizure diary and review entries
- Record any AEs occurring since last visit and any that occur during this visit
- Blood draw for Complete blood count (CBC), comprehensive metabolic panel (CMP) Serum/Urine human chorionic gonadotropin (HCG), as applicable (sample taken only for female subjects of childbearing potential) , and antiepileptic medication levels
- Urinalysis
- Urine or serum THC
- Complete the following assessments:
    - Caregiver and Investigator Global Impression of Change
    - QOLCE
    - PEDS-QOL
- Record any changes in concomitant medications
- Dispense new seizure diary and review instructions for completion
- Review returned study drug and compliance
- Dispense study drug and review administration instructions
- Instruct subject to return in 4 weeks for Visit 4

Safety call telephone

The safety call will occur between visit 3 and visit 4. It will proceed as follows:

- Record any AEs occurring since last visit and any that occur during this visit
- Record any changes in concomitant medications

Visit 4 (Week 10)

The subject will return to the site for Visit 4. Visit 4 will proceed as follows:

- Physical and neurological examination and height and weight
- Vital signs (including systolic and diastolic blood pressure, radial pulse rate, and body temperature): performed after the subject has been in a sitting position for 3–5 minutes
- Collect seizure diary and review entries
- Record any AEs occurring since last visit and any that occur during this visit
- Record any changes in concomitant medications
- Complete the following assessments:
    - Caregiver and Investigator Global Impression of Change
    - QOLCE
    - PEDS-QOL

- Blood draw for Complete blood count (CBC), comprehensive metabolic panel (CMP) Serum/Urine human chorionic gonadotropin (HCG), as applicable (sample taken only for female subjects of childbearing potential), and antiepileptic medication levels
- Urinalysis
- Urine or serum THC
- Dispense new seizure diary and review instructions for completion
- Dispense study drug and review administration instructions
- Instruct subject to return in 4 weeks for Visit 5

Safety call telephone

The safety call will occur between visit 4 and visit 5. It will proceed as follows:

- Record any AEs occurring since last visit and any that occur during this visit
- Record any changes in concomitant medications

Visit 5/End of study/ End of treatment/ Withdrawal visit (Week 14)

Visit 5 will proceed as follows:

- Physical and neurological examination and height and weight
- Vital signs (including systolic and diastolic blood pressure, radial pulse rate, and body temperature): performed after the subject has been in a sitting position for 3–5 minutes
- EKG and echocardiogram
- Collect seizure diary and review entries
- Record any AEs occurring since last visit and any that occur during this visit
- Record any changes in concomitant medications
- Complete the following assessments:
    - Caregiver and Investigator Global Impression of Change
    - QOLCE
    - PEDS-QOL
- Blood draw for Complete blood count (CBC), comprehensive metabolic panel (CMP) Serum/Urine human chorionic gonadotropin (HCG), as applicable (sample taken only for female subjects of childbearing potential), and antiepileptic medication levels
- Urinalysis
- Urine or serum THC
- For those subjects who have responded (response level ≥ 40%) and will like to continue in to the extension study:
    - Dispense new seizure diary and review instructions for completion
    - Dispense study drug and review administration instructions
    - Instruct subject to return in 12 weeks for Extension visit 1
- For those subjects who have not responded and will not continue in to the extension study:
    - Taper schedule will be given
    - Subject have final post taper follow up in 4 weeks after the last dose

7.5.2 Extension

Extension visits

If study medication provide benefit to the subject (response level ≥ 40%), study medication will be provided until FDA approval or program discontinuation by Zogenix. The subject will return to the site every 12 weeks for extension visits. This includes:

- Physical and neurological examination and height and weight
- Vital signs (including systolic and diastolic blood pressure, radial pulse rate, and body temperature): performed after the subject has been in a sitting position for 3–5 minutes
- EKG and echocardiogram
- Collect seizure diary and review entries
- Record any AEs occurring since last visit and any that occur during this visit
- Record any changes in concomitant medications
- Complete the following assessments:
    - Clinical Caregiver/Investigator Global Impression of Change
    - QOLCE
    - PEDS-QOL
- Blood draw for Complete blood count (CBC), comprehensive metabolic panel (CMP) Serum/Urine human chorionic gonadotropin (HCG), as applicable (sample taken only for female subjects of childbearing potential), and antiepileptic medication levels
- Urinalysis
- Urine or serum THC
- Dispense new seizure diary and review instructions for completion
- Dispense masked study drug and review administration instructions
- Instruct subject to return in 12 weeks for next visit

Safety call telephone

The safety call will occur between extension visit. It will proceed as follows:

- Record any AEs occurring since last visit and any that occur during this visit
- Record any changes in concomitant medications

7.5.3 End of treatment

End of treatment/ Withdrawal visit

End of treatment/withdrawal will proceed as follows:

- Physical and neurological examination and height and weight
- Vital signs (including systolic and diastolic blood pressure, radial pulse rate, and body temperature): performed after the subject has been in a sitting position for 3–5 minutes
- EKG and echocardiogram
- Collect seizure diary and review entries
- Record any AEs occurring since last visit and any that occur during this visit

- Record any changes in concomitant medications
- Complete the following assessments:
    - Clinical Caregiver/Investigator Global Impression of Change
    - QOLCE
    - PEDS-QOL
- Blood draw for Complete blood count (CBC), comprehensive metabolic panel (CMP) Serum/Urine human chorionic gonadotropin (HCG), as applicable (sample taken only for female subjects of childbearing potential), and antiepileptic medication levels
- Urinalysis
- Urine or serum THC
- Subject have final post taper follow up in 4 weeks after the last dose

Post Taper Follow-up

The Follow-up visit is to occur 4 weeks after the last dose of study drug,
It will proceed as follows:

- Record any AEs occurring since last visit and any that occur during this visit
- Record any changes in concomitant medications
- Return any study medications

7.5.4 Unscheduled Visit

- Record any AEs occurring since last visit and any that occur during this visit
- Record any changes in concomitant medications

7.6 Concomitant Medications

All concomitant prescription medications taken during study participation will be recorded on the case report forms (CRFs). For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician. Medications to be reported in the CRF are concomitant prescription medications, over-the-counter medications and non-prescription medications. Epidiolex is only acceptable CBD preparation that may be included. All other formulations are excluded.

7.7 Prohibited Medications, Treatments, and Procedures

Treatment with other investigational medications will not be permitted.

7.8 Participant Access to Study Agent at Study Closure

Zogenix will continue to supply study medication to those subjects that received benefit from the study after participant are no longer enrolled in the study.

8 Assessment of Safety

8.1 Specification of Safety Parameters

- Treatment-emergent adverse events will be continuously reported throughout the study

- Each patient will undergo a Doppler echocardiographic (ECHO) and ECG examinations during the baseline period and again at weeks 6, 14, and every 3 months thereafter during the extension study and End of treatment/withdrawal visits.
- All ECHOs readings will be sent to the site for evaluation and will be graded as to presence and severity of cardiac valve regurgitation

8.1.1 Definition of Adverse Events (AE)

An ***adverse event*** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

8.1.2 Definition of Serious Adverse Events (SAE)

Serious Adverse Event

Adverse events are classified as serious or non-serious. A ***serious adverse event*** is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious should be regarded as ***non-serious adverse events***.

8.1.3 Definition of Unanticipated Problems (UP)

Unanticipated Problems Involving Risk to Subjects or Others

Any incident, experience, or outcome that meets <u>all</u> of the following criteria:

- <u>Unexpected in nature, severity, or frequency</u> (i.e. not described in study-related documents such as the IRB-approved protocol or consent form, the investigators brochure, etc)
- <u>Related or possibly related to participation in the research</u> (i.e. possibly related means there is a reasonable possibility that the incident experience, or outcome may have been

caused by the procedures involved in the research)

- Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm).

8.2 Classification of an Adverse Event

8.2.1 Severity of Event

The following grading system will be used to describe severity.

- **Grade 1: Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Grade 2: Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Grade 3: Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating.

8.2.2 Relationship to Study Agent

The clinician's assessment of an AE's relationship to study agent (drug, biologic, device) is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event should be reported. All AEs must have their relationship to study agent assessed. In a clinical trial, the study product must always be suspect. To help assess, the following guidelines are used:

- **Related** – The AE is known to occur with the study agent, there is a reasonable possibility that the study agent caused the AE, or there is a temporal relationship between the study agent and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study agent and the AE.
- **Not Related** – There is not a reasonable possibility that the administration of the study agent caused the event, there is no temporal relationship between the study agent and event onset, or an alternate etiology has been established.

For all collected AEs, the clinician who examines and evaluates the participant will determine the AE's causality based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below:

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to drug administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.
- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the drug, is unlikely to be

attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.

- **Possibly Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related," as appropriate.
- **Unlikely to be related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to drug administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the trial medication) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
- **Not Related** – The AE is completely independent of study drug administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

8.2.3 Expectedness

Principal Investigator will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study agent.

8.3 Time Period and Frequency for Event Assessment and Follow-Up

The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor. All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate CRF. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE. UPs will be recorded in the data collection system throughout the study.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The PI will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

All unresolved adverse events should be followed by the investigator until the events are

resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study. The investigator should notify the study sponsor of any death or adverse event occurring at any time after a subject has discontinued or terminated study participation that may reasonably be related to this study. The sponsor should also be notified if the investigator should become aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a subject that has participated in this study.

8.4 Reporting Procedures – Notifying the IRB

Federal regulations require timely reporting by investigators to their local IRB of unanticipated problems posing risks to subjects or others. The following describes the NYULMC IRB reporting requirements, though Investigators at participating sites are responsible for meeting the specific requirements of their IRB of record.

Report Promptly, but no later than 5 working days:
Researchers are required to submit reports of the following problems promptly but no later than 5 working days from the time the investigator becomes aware of the event:
• Unanticipated problems including adverse events that are unexpected and related
– *Unexpected:* An event is "unexpected" when its specificity and severity are not accurately reflected in the protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document and other relevant sources of information, such as product labeling and package inserts.
– *Related to the research procedures*: An event is related to the research procedures if in the opinion of the principal investigator or sponsor, the event was more likely than not to be caused by the research procedures.
– *Harmful:* either caused harm to subjects or others, or placed them at increased risk

Other Reportable events:
The following events also require prompt reporting to the IRB, though no later than 5 working days:
• Complaint of a research subject when the complaint indicates unexpected risks or the complaint cannot be resolved by the research team.
• Protocol deviations or violations (includes intentional and accidental/unintentional deviations from the IRB approved protocol) for any of the following situations:
– *one or more participants were placed at increased risk of harm*
– *the event has the potential to occur again*
– *the deviation was necessary to protect a subject from immediate harm*
• Breach of confidentiality
• Incarceration of a participant when the research was not previously approved under Subpart C and the investigator believes it is in the best interest of the subject to remain on the study.
• New Information indicating a change to the risks or potential benefits of the research, in terms of severity or frequency. (e.g. analysis indicates lower-than-

expected response rate or a more severe or frequent side effect; Other research finds arm of study has no therapeutic value; FDA labeling change or withdrawal from market).

Reporting Process

The reportable events noted above will be reported to the IRB using the form: "Reportable Event Form" or as a written report of the event (including a description of the event with information regarding its fulfillment of the above criteria, follow-up/resolution and need for revision to consent form and/or other study documentation).

8.4.1 Adverse Event Reporting and Serious Adverse Event Reporting

Adverse events and serious adverse events will be reported to the IRB on a spreadsheet including timeframe, severity, relatedness and action during annual reporting.

8.4.2 Unanticipated Problem Reporting

Incidents or events that meet the OHRP criteria for UPs require the creation and completion of an UP report form. It is the site investigator's responsibility to report UPs to their IRB and to the study sponsor. The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are SAEs will be reported to the IRB and to the study sponsor within 7 days of the investigator becoming aware of the event.
- Any other UP will be reported to the IRB and to the study sponsor within 7 days of the investigator becoming aware of the problem.
- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and OHRP within7 days of the IR's receipt of the report of the problem from the investigator.

8.4.3 Reporting of Pregnancy

The investigator should also be notified of pregnancy occurring during the study but confirmed after completion of the study. In the event that a subject/subject's partner is subsequently found to be pregnant after the volunteer is included in the study, then consent will be sought from the partner and, if granted, any pregnancy will be followed

and the status of mother and/or child will be reported to the sponsor after delivery.

Any subject reporting a pregnancy during the study will be withdrawn from the study and should complete the taper schedule.

8.5 Reporting Procedures – Notifying the Study Sponsor

The study clinician will complete a SAE Form within the following timelines:

- All deaths and immediately life-threatening events, whether related or unrelated, will be recorded on the SAE Form and submitted to the DCC/study sponsor within 24 hours of site awareness. See Section 1, Key Roles for contact information.
- Other SAEs regardless of relationship will be submitted to the DCC/study sponsor within 72 hours of site awareness.

All SAEs will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the adherence to be stable. Other supporting documentation of the event may be requested by the DCC/study sponsor and should be provided as soon as possible.

As a follow-up to the initial report, within the following 48 hours of awareness of the event, the investigator shall provide further information, as applicable, on the unanticipated event or the unanticipated problem in the form of a written narrative. This should include a copy of the completed Unanticipated Problem form, and any other diagnostic information that will assist the understanding of the event. Significant new information on ongoing unanticipated adverse effects shall be provided promptly to the study sponsor.

8.6 Reporting Procedures – Notifying the FDA

The drug sponsor is required to report certain study events in an expedited fashion to the FDA. These written notifications of adverse events are referred to as IND safety reports. The following describes the IND safety reporting requirements by timeline for reporting and associated type of event:

- ***Within 7 calendar days*** *(via telephone or facsimile report)*
  Any study event that is:
  - associated with the use of the study drug
  - unexpected,
  - fatal or life-threatening

- ***Within 15 calendar days*** *(via written report)*
  Any study event that is:
  - associated with the use of the study drug,
  - unexpected, and
  - serious, but not fatal or life-threatening
    -or-
  - a previous adverse event that was not initially deemed reportable but is later found to fit the criteria for reporting (reporting within 15 calendar days from when event was deemed reportable).

  Any finding from tests in laboratory animals that:

- suggest a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity.

Additional reporting requirements
Sponsors are also required to identify in IND safety reports all previous reports concerning similar adverse events and to analyze the significance of the current event in light of the previous reports.

Reporting Process
Adverse events may be submitted on FDA Form 3500A or in a narrative format. If supplied as in a narrative format, the minimum information to be supplied is noted above at the beginning of section 8.3. The contact information for submitting IND safety reports is noted below:

[Include the FDA Division, contact person, telephone number and fax number here]

8.7 Study Halting Rules

If the investigator becomes aware of conditions such as adverse events that if additional similar events occurred may warrant halting or termination of the clinical study, the investigator will notify Zogenix within 24 hours. They will convene an ad hoc meeting by teleconference or in writing as soon as possible so that both parties can discuss and agree on the best path forward which may include:

- Modification to the study protocol
- Modification to safety monitoring
- Steps to be taken if additional similar adverse events are observed

8.8 Safety Oversight

It is the responsibility of the Principal Investigator to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan. Medical monitoring will include an assessment of the number and type of serious adverse events.

9 Statistical Considerations

9.1 Statistical and Analytical Plans (SAP)

There will be no formal statistical methodology but rather descriptive statistics to quantify the primary and secondary outcome measures as well as the frequency and severity of adverse effects. All subjects participating in this study will have their data analyzed with descriptive statistics for both the primary and secondary analyses.

9.2 Sample Size

No statistical methods were used to determine the sample size for this study. The principal investigator has requested for expanded access use, 21 CFR 312.315 in an intermediate size patient population of 10. The total number of subjects expected to participate at NYU Comprehensive Epilepsy Center is 10.

10 Source Documents and Access to Source Data/Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial. It is acceptable to use CRFs as source documents. If this is the case, it should be stated in this section what data will be collected on CRFs and what data will be collected from other sources.

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. DO NOT ERASE OR WHITE OUT ERRORS. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.

Access to study records will be limited to IRB-approved members of the study team. The investigator will permit study-related monitoring, audits, and inspections by the IRB/EC, the sponsor, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

11 Ethics/Protection of Human Subjects

11.1 Ethical Standard

The investigator will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Subjects of Research codified in 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and/or the ICH E6.

11.2 Institutional Review Board

The protocol, informed consent/assent forms, recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent/assent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether previously consented participants need to be re-consented.

11.3 Informed Consent Process

11.3.1 Consent/Assent and Other Informational Documents Provided to Participants

Consent forms describing in detail the study agent, study procedures, and risks are given to the participants. Capacity assessment will be conducted by Dr. Orrin Devinsky. He is board certified Neurologist and Epileptologist and Director of both the NYU Comprehensive Epilepsy Center and St. Barnabas Institute for Neurology & Neurosurgery. He is experienced in dealing with various neurological diseases and multiple clinical trials.

Capacity will be assessed through neurological examinations conducted by the physician as well as documented learning and/or development delays. Previous neurological records and neuropsychological assessments will be used to determine whether the subject has t the capacity to assent. Consent forms describing in detail the study agent, study procedures, and risks will be given to the parent/guardian and written documentation of informed consent is required prior to starting intervention/administering study product. Dr. Orrin Devinsky will obtain consent and explain and/or answer any questions that should arise. This will be done in a private patient examination room at the NYU Comprehensive Epilepsy Center. The consent materials are submitted with this protocol. Study participant and written documentation of informed consent is required prior to starting intervention/administering study product.

11.3.2 Consent Procedures and Documentation

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of participation will be provided to the participants and their families. Consent forms will be IRB-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. The participants may withdraw consent at any time throughout the course of the trial. A copy of the signed informed consent document will be given to the participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study. For individuals under 18 years of age, assent will be obtained using an IRB approved age-appropriate assent form. If a subject turns 18 during study participation, he or she will be re-consented as an adult. For subjects 18 or older, consent will be obtained with the IRB approved consent form.

A copy of the signed informed consent document will be stored in the subject's research record. The consent process, including the name of the individual obtaining consent, will be thoroughly documented in the subject's research record. Any alteration to the standard consent process (e.g. use of a translator, consent from a legally authorized representative, consent document presented orally, etc.) and the justification for such

alteration will likewise be documented.

11.4 Participant and Data Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their agents. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The study monitor, other authorized representatives of the sponsor, representatives of the IRB or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB and Institutional regulations.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at NYU Langone Medical Center. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by NYU Langone Medical Center research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the NYU Langone Medical Center.

12 Data Handling and Record Keeping

12.1 Data Collection and Management Responsibilities

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site PI. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Black ink is required to ensure clarity of reproduced copies. When making changes or corrections, cross out the original entry with a single line, and initial and date the

change. We will not: ERASE, OVERWRITE, OR USE CORRECTION FLUID OR TAPE ON THE ORIGINAL.

Copies of the electronic CRF (eCRF), if used, will be provided for use as source documents and maintained for recording data for each participant enrolled in the study. Data reported in the eCRF derived from source documents should be consistent with the source documents or the discrepancies should be explained and captured in a progress note and maintained in the participant's official electronic study record.

Clinical data (including AEs, concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into study site database. Clinical data will be entered directly from the source documents.

12.2 Study Records Retention

Study documents will be retained for the longer of 3 years after close-out, 5 years after final reporting/publication, or 2 years after the last approval of a marketing application is approved for the drug for the indication for which it is being investigated or 2 years after the investigation is discontinued and FDA is notified if no application is to be filed or if the application has not been approved for such indication. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

12.3 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, GCP, or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH E6:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site PI/study staff to use continuous vigilance to identify and report deviations. Protocol deviations must be reported to the local IRB at the annual continuation.

13 Study Finances

13.1 Funding Source

Zogenix will provide study medication and funding to support this study.

13.2 Costs to the Participant

Zogenix will provide the study medicine free of charge to participating research subjects for the duration of this study.

The subjects will be receiving medical care as a part of this research study. Subjects or their insurance company will not be charged or held responsible or the costs of that care. All costs related to procedures and assessments associated with participating in this study will be free of charge.

Procedures that are part of routine care or to assess the subject's health but are not mandatory for the study will not be covered. The subject's individual insurance or government health

insurance program may not cover certain services, items, or procedures. This may be discussed with the subject's insurance carrier in advance. The subject/parent/legal guardian will be responsible for any co-payments and/or deductibles for services rendered.

The subject and/or the subject's health insurance may be billed for the costs of medical care during this study if these expenses would have happened even if the subject was not in the study, or if the subject's insurance agrees in advance to pay. If the subject has health insurance, the cost of these services will be billed to the subject's insurance company. If the subject's insurance does not cover these costs or the subject does not have insurance, these costs will be the subject's responsibility.

14 Conflict of Interest Policy

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the trial. All study group members will disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by the NYU Langone Conflict of Interest Management Unit (CIMU) with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor prior to participation in this study. All NYULMC investigators will follow the applicable conflict of interest policies.

15 References

1. Devinsky, O, Hesdorffer DC, Thurman DJ, Lhatoo S, Richerson G. Sudden unexpected death in epilepsy: epidemiology, mechanisms, and prevention. Lancet Neurol. 2016 Sep;15(10):1075-88.

2. Guerrini R, Parrini E.Epilepsy in Rett syndrome, and CDKL5- and FOXG1-gene-related encephalopathies. Epilepsia. 2012 Dec ;53(12):2067-78.

3. Lagae ,Lieven; Sullivan, Joseph E.; Cross ,J. Helen; Devinsky,Orri,; Guerrini,Renzo, Meyer ,Anna; Knupp,Kelly G.; Laux, Linda C.,; Miller, Ian; Nikanorova,Marina; Polster,Tilman; Talwar ,Dinesh; Farfel,Gail M.; Galer,Bradley S.; Gammaitoni,Arnold; Morrison,Glenn; Mistry,Arun; and Ceulemans, Berten. ZX008 (Fenfluramine) in Dravet Syndrome: Results of a Phase 3, Randomized, Double-Blind, Placebo-Controlled Trial. Abstract. Abst. 2.434), 2017.

4. ZX008. Fenfluramine Hydrochloride. Investigator's Brochure, Edition 5. Zogenix International Limited: A Wholly Owned Subsidiary of Zogenix, Inc. 28 Apr 2017.

16. APPENDIX

APPENDIX 1 – LIST OF PROHIBITED CONCOMITANT MEDICATIONS

Generic Name	Generic Name
alfentanil	naratriptan
almotriptan	nefazodone
alprenolol	nortriptyline
amitriptyline	ondansetron
amphetamine	oxcarbazepine
astemizole	oxycodone
atomoxetine	paroxetine
bufuralol	pergolide
bupropion	perphenazine
buspirone	phenacetin
cafergot	phenobarbital
Cannabidiol: that is not Epidiolex	phenytoin
carbamazepine	promethazine
cerivastatin	propafenone
cabergoline	retigabine/ezogabine
citalopram	risperidone
clomipramine	ritonavir
codeine	rizatriptan
cyproheptadine	selegiline
dasatinib	sertraline
desipramine	sumatriptansertraline
dextromethorphan	telaprevir
duloxetine	THC and derivatives
eletriptan	tramadol
encainide	trazodone
ergotamine tartrate	vortioxetine
eslicarbazepine	zolmitriptan
felbamate	zuclopenthixol
fentanyl	
fluoxetine	
fluvoxamine	
frovatriptan	
imipramine	
interferon	
levacetylmethadol (LAAM)	

linezolid	
meperidine	
methadone	
metoclopramide	
mexiletine	