DETAILED PROTOCOL: Treatment with Open-Label ZX008 (Fenfluramine Hydrochloride) in Epilepsy Patients with Sunflower Syndrome

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Version 8

I. BACKGROUND AND SIGNIFICANCE

Drug resistant epilepsy is a serious and potentially life-threatening condition that impacts the day to day functioning of those affected. Patients with drug resistant epilepsy are at a higher risk for Sudden Unexpected Death in Epilepsy (SUDEP), as frequency of generalized tonic-clonic seizures, poly therapy, number of anti-epileptic drugs (AED) used, and propensity for nocturnal seizures are the leading risk factors for SUDEP. Annual SUDEP risk for patients with epilepsy is 1/1000; whereas SUDEP risk for patients with drug resistant epilepsy is 1/150.

Patients with drug resistant epilepsy do not respond or respond incompletely to FDA approved AEDs. Children living with drug resistant epilepsy are particularly vulnerable, and urgently need more effective medications because those suffering from early-onset and high seizure burden epilepsies suffer the greatest neurodevelopmental problems, including intellectual disability and autism. In some syndromes such as Dravet Syndrome, recent evidence suggests that more effective early control of epilepsy is associated with better developmental outcomes than in children who were treated 20-30 years ago (Chieffo et al., 2011).

Sunflower Syndrome (also referred to as Self-induced Photosensitive Epilepsy) is a rare epileptic disorder characterized by a distinctive seizure that manifests itself in a highly stereotyped physical behavior. Seizure types associated with Sunflower Syndrome include absence seizures and generalized tonic-clonic seizures. Associated with these seizures, individuals with Sunflower Syndrome obsessively seek out a light source, stare at the light source, and wave one hand in front of their eye (Belcastro & Striano, 2014; Ames, 1971; Aicardi & Gastaut, 1985). Electroencephalogram (EEG) features include generalized spike and wave discharges interictally, and typically a strong photoparoxysmal response during photic stimulation (Belcastro & Striano, 2014; Ames & Saffer, 1983).

Currently, Sunflower Syndrome is poorly characterized in scientific literature and often misunderstood at the clinical level. The name self-induced photosensitive epilepsy may be a misnomer as research concerning the neurochemical and neuropsychological pathways have not been enough to truly characterize it as a self-induced (conscious behavior) as the name implies. Although some reports have concluded that the hand waiving induces the seizure, these findings are not consistent throughout scientific literature (Belcastro & Striano, 2014; Livingston & Torres, 1964). In fact, an EEG report found that the seizures can begin prior to the hand waving. This suggests that the hand waving may in fact be part of the seizure, not the cause (Livingston & Torres, 1964).

Preclinical Data:

Fenfluramine has been studied in young rats. In those neurochemical experiments, fenfluramine was shown to reduce activity and to induce learning and memory deficits. Fenfluramine was also shown to reduce certain chemicals in the brain, including serotonin, but the long-term effects of this are not known (Fuller, Snoddy, & Robertson, 1988).

The relevance of the animal data to humans is not known. Not many learning and memory studies have been conducted with fenfluramine in humans.

Clinical Data: Fenfluramine in Epilepsy

Aicardi and Gastaut wrote a letter to the NEJM in 1985 describing the successful use of fenfluramine in 3 children with self-induced photic sensitive epilepsy. The description of the first of the three patients matches that of Sunflower Syndrome (Aicardi & Gastaut, 1985). Additionally, there have been several published reports of fenfluramine's successful treatment of refractory childhood epilepsy in the 1980's, as well as, its successful treatment of 11 pediatric patients with refractory or self-induced epilepsy, not specifically Sunflower Syndrome, in Belgium.

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 & Casaer, 1996). Subjects were treated with fenfluramine at 0.5 to 1.0 mg/kg/day for 3 to 8.5 years. Sixty four percent of the subjects became seizure free and the remaining 36% of subjects experienced greater than or equal to 75% reduction in seizure frequency. By 2002, this study's population had been expanded to 22 patients with intractable or self-induced seizures who underwent

treatment between 1 to 12 years. Of the 22 patients treated, 27% (6) became seizure-free, 45% (10) patients had a 90% reduction in seizure frequency and 27% (6) patients were non-responders.

Zogenix, Inc. is currently evaluating fenfluramine hydrochloride (ZX008) in Dravet Syndrome (DS) in three Phase 3 double-blind, randomized, placebo-controlled studies, in which our site participated. Dravet Syndrome is a rare form of refractory epilepsy, which exhibits similar seizure types, as those seen in Sunflower Syndrome. This study enrolled 119 subjects across sites in the United States, Canada, Europe, and Australia. "The median age of subjects was 8 years (range, 2-18 years). Following a six-week baseline observation period, subjects were randomized to one of three treatment groups: ZX008 0.8 mg/kg/day (30 mg maximum daily dose; n=40), ZX008 0.2 mg/kg/day (n=39) and placebo (n=40) in which ZX008 or placebo was added to current regimens of antiepileptic drugs. Subjects were titrated to their target dose over two weeks and then remained at that fixed dose for 12 weeks. The mean baseline convulsive seizure frequency across the study groups was approximately 40 seizures per month.

The primary efficacy measure was a comparison of the change in mean monthly convulsive seizure frequency between ZX008 0.8 mg/kg/day and placebo during the 14-week treatment period compared with the 6-week baseline observation period. Subjects taking ZX008 0.8 mg/kg/day achieved a 63.9% reduction in mean monthly convulsive seizures compared to placebo ($p<0.001$). The median percent reduction in monthly convulsive seizure frequency was 72.4% among ZX008 0.8 mg/kg/day subjects compared to 17.4% in placebo subjects.

A key secondary endpoint was the same analysis for a comparison of ZX008 0.2 mg/kg/day and placebo. Subjects taking ZX008 0.2 mg/kg/day achieved a reduction in mean monthly convulsive seizures of 33.7% compared to placebo ($p=0.019$). Collectively, these top-line data suggest a dose-response relationship for ZX008 in the adjunctive treatment of convulsive seizures in Dravet syndrome" ("Zogenix Announces Positive Top-line Results from Pivotal Phase 3 Clinical Trial of ZX008 in Dravet Syndrome", September 2017).

There are no treatments specifically approved for the treatment of Sunflower Syndrome in the United States. Broad spectrum anticonvulsant medications, including sodium valproate, lamotrigine, levetiracetam, and clobazam, have not shown full efficacy in seizure

prevention in patients with Sunflower Syndrome. Accordingly, there remains a significant unmet need for an approved treatment for children and adults with Sunflower Syndrome.

As this epilepsy typically does not respond to anticonvulsant medications, and since Aicardi described the successful treatment with fenfluramine of at least one child with this syndrome, we would like to investigate if fenfluramine is an effective, safe and well tolerated treatment for Sunflower Syndrome.

II. SPECIFIC AIMS

The primary objective of this study is the determine the efficacy of ZX008 on seizure frequency in children and young adults with Sunflower Syndrome. The goal of treatment is to provide a 30 percent or greater reduction of generalized tonic-clonic seizures and/or hand waving associated with absence seizures.

Secondary objectives of the study include evaluation of the effect of ZX008 (fenfluramine hydrochloride) on EEG patterns and quality of life. Patients with Sunflower Syndrome often experience low self-esteem, bullying due to the unusual motor movements associated with their seizures, school performance issues, anxiety, and depression.

III. SUBJECT SELECTION

The study population will include pediatric and young adult patients seen by Elizabeth A. Thiele, M.D., Ph.D. at MGH's Pediatric Epilepsy Clinic who were identified as candidates. The Principal Investigator (PI) will follow up to 20 patients with Sunflower Syndrome who will be taking ZX008.

The inclusion criteria for enrollment in this study include:

- Subject is male or non-pregnant, non-lactating female, age 4 to 25 years, inclusive as of the day of the screening visit. Female subjects of childbearing potential must have a negative serum pregnancy test at screening. Subjects of childbearing or child-fathering potential must be willing to use medically acceptable forms of birth control, which includes abstinence, while in this study and for 90 days after the last dose of study drug.
- Subjects must have a diagnosis of Sunflower Syndrome, where seizures are not completely controlled by their current treatment plan.

- Subjects must experience seizures including absence seizures and/or generalized tonic-clonic seizures which involve seeking out a light source, staring at the light source, and waving one hand in front of their eye(s). Subject's must experience an average of 6 handwaving associated with absence seizures and/or generalized tonic-clonic seizures per week.
- Evidence of EEG in the medical history that shows generalized spike and wave discharges between seizures and a strong photoparoxysmal response during photic stimulation. Acceptable evidence includes a copy of the EEG trace, EEG report, or physician note that appropriately describes the EEG findings.
- All medications or interventions for epilepsy must be stable for at least 4 weeks prior to screening and are expected to remain stable until Month 3.
- Subject and/or parent/guardian has been informed of the nature of the study and informed consent has been obtained from the subject and/or legally responsible parent/guardian.
- Subject has provided assent in accordance with Institutional Review Board (IRB)/Ethics Committee requirements, if capable.
- Subjects parent/caregiver is willing and able to be compliant with diary completion, visit schedule, and study drug accountability.

The exclusion criteria for enrollment in this study include:

- Subject has a known hypersensitivity to fenfluramine hydrochloride or any other ingredients in the investigational drug.
- Subject's etiology of seizures is a degenerative neurological disease.
- Subject is pregnant.
- Subject is not willing to comply with a method of birth control acceptable to the LPI (Licensed Physician Investigator) during the study and for 90 days following completion of the study.
- Subject is breastfeeding.
- Subject has a history of drug or alcohol abuse.
- Subject has pulmonary arterial hypertension.
- 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: bicuspid valve 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).

- 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.
- Subject has a current or past history of glaucoma.
- Subject has had an anoxic episode requiring resuscitation within 6 months of the screening visit.
- *Subject has moderate or severe hepatic impairment. Asymptomatic subjects with mild hepatic impairment (elevated liver enzymes < 3x upper limit 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.*
- Subject has severe renal impairment (estimated glomerular filtration rate <30mL/min/1.73m^2)
- 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; other centrally-acting noradrenergic agonists, including atomoxetine; or cyproheptadine. (Note: Short-term medication requirements for prohibited medications will be handled on a per case basis by the medical monitor.)
- Subject is receiving a dose of Epidiolex that is above the labeled dosing recommendations for that product. (20 milligrams/kilogram/day)
- Subjects is using an artisanal formulation of CBD
- Subject has been taking felbamate for less than 1 year prior to screening and/or does not have stable liver function and hematology laboratory tests, and/or the dose has not been stable for at least 60 days prior to the screening visit.
- Subject is known to be human immunodeficiency virus (HIV) positive.
- Subject is known to have active viral hepatitis (B or C).
- Subject is currently receiving an investigational medicinal product.

- Subject has participated in another clinical trial within the past 30 days (calculated from that study's last scheduled visit). Participation in non-treatment trials will be reviewed by the medical monitor.
- Subject is at imminent risk of self-harm or harm to others, in the investigator's opinion.
- Subject is unwilling or unable to comply with scheduled visits, drug administration plan, laboratory tests, other study procedures, and study restrictions.
- Subject is institutionalized in a general nursing home (i.e., in a facility that does not provide skilled epilepsy care).
- Subject does not have a reliable caregiver who can provide seizure diary information throughout the study.
- Subject has a clinically significant condition, or has had clinically relevant symptoms or a clinically significant illness in the 4 weeks prior to the Screening Visit, other than epilepsy, that would negatively impact study participation, collection of study data, or pose a risk to the subject.

IV. SUBJECT ENROLLMENT

This site will independently be studying the efficacy of ZX008 on seizure frequency in children and young adults with Sunflower Syndrome and the effects of ZX008 on EEG patterns and quality of life.

Informed consent will be obtained for each subject who participates in the study by the LPI and be documented in writing with the PHRC approved consent form. The LPI and/or the research nurse will initially explain the study, provide the informed consent form, and answer any questions from the subjects and their family members. Subjects will be given adequate time to make their decision. Subjects will have the opportunity to take the consent form home, and call back if they wish to participate. Subjects will also be encouraged to discuss any concerns they have with other health care providers. Informed consent for all subjects will be obtained by Elizabeth A. Thiele, M.D., Ph.D.. The potential for coercion will be avoided through ensuring the subject that participation in the study is completely voluntary, and that deciding not to take part in the study will not affect the care or benefits to which the subject is otherwise entitled. Subjects will be enrolled in the study once informed consent has been obtained. Only the LPI will be obtain consent from the subject, the subject's parent/guardian or the subject's surrogate

For subjects who are older than 18 years of age with impaired decision making, and subjects under 18 years of age, legal consent to participate in research will be provided by a parent or an individual authorized under applicable state or local law to provide consent on the subject's behalf to general medical care. When enrolling a subject who is younger than 18 it is sufficient for consent to be obtained from just one parent. Before the LPI allows an individual other than a parent to consent on behalf of a child, she will document the basis for the individual's authority to consent on behalf of the child to general medical care and place any relevant documentation in the research file.

In addition to permission of the parent(s) or guardian, assent to participate in the study must be obtained from each child age 7 to 17 years old who, in the opinion of the LPI, is able to provide assent based on their age, maturity or psychological state. When obtained, assent for subjects 14 through 17 years of age will be documented using the PHRC approved Consent Form and assent for subjects 7 through 13 years of age will be documented in writing using the PHRC approved Assent Form. When assent is not obtained, the LPI will document the rationale in the research records.

The following categories of surrogates (listed in general order of preference) may provide consent in writing on behalf of potential subjects incapable of providing informed consent:

1. Court appointed guardian with specific authority to consent to participation in research or authority to make health care decisions for a class of diagnostic and therapeutic decisions inclusive of the proposed research;
2. Health care proxy/person with durable power of attorney with specific authority for making health care decisions inclusive of the proposed research; or
3. Spouse, adult child, or other close family member who knows the subject well and has been involved in their care.

Assent of subjects will be a requirement for participation in the research unless the subject is incapable of giving assent due to his/her medical condition. If the individual objects to participation, s/he will not be enrolled. When surrogate consent is relied upon, the LPI will ensure that the surrogate understands that his or her decisions should be based on "substituted judgment." This means that the decision reflects a potential subject's own views when s/he had the capacity to express them. The PHRC preferred order of surrogates will be followed,

and the Investigator will document the relationship of the surrogate to the subject in the research record.

V. STUDY PROCEDURES

The investigational drug to be used in this study is fenfluramine hydrochloride (ZX008) manufactured by Zogenix, Inc..

ZX008 will be supplied as an oral solution in a concentration of 2.5 mg/mL. The subjects will be treated on an outpatient basis and will not require hospital admission. ZX008 will be administered on a twice daily basis.

The study will initially consist of a 4 week baseline period, during which handwaving associated with absence seizures and/or generalized tonic-clonic seizures will be recorded in a seizure diary on a daily basis. Subjects will meet enrollment criteria if they have an average of 6 generalized tonic-clonic and/or handwaving associated absence seizure per week.

If enrollment criteria is met, the subject will enter a titration period. The starting dose will be 0.2 mg/kg/day for the first 14 days. The dose will be increased every 2 weeks as tolerated by 0.2 mg/kg/day, to a maximum dose of 0.8 mg/kg/day, or a total maximum dose of 30 mg/day. The subject will remain on 0.8 mg/kg/day, 30 mg/day, or maximum tolerated dose for a 6 week maintenance period.

Site personnel will call the subject and/or their parent/caregiver every 11-14 days during the titration period before their next scheduled dose increase.

There will be 5 study visits within a 6 month period. After Visit 5, visits will occur every 6 months for an assessment in the clinic for subjects who respond to treatment with at least a 30% reduction in seizure frequency.

Seizure frequency will be tracked with the use of a daily seizure log. In the event that seizure frequency is markedly reduced compared to baseline after starting the study drug the LPI will discuss with the subject and/or their caregiver about adjusting the dose of concomitant seizure medications. If seizure frequency is markedly increased compared to baseline after discontinuing other medications which were taken as standard of care the LPI may decide to adjust dose of other seizure medications or reintroduce the medications that were taken as

part of standard of care. The use of these strategies will be decided on a case to case basis.

IND Visit Schedule		
Visit Number	**Visit Type**	**Time Point**
1	Baseline	Day -28
2	Titration	Day 1 (+14 days)
3	Titration and/or Maintenance	28 days from Visit 2 (±7 days)
4	Maintenance	56 days from Visit 2 (±14 days)
5	Maintenance	84 days from Visit 2 (±14 days)
Continuous	Maintenance	Each 6 Months following Visit 5 (±14 days)

When applicable, at each study visit, subjects will be given an information sheet detailing the potential risk for adverse events seen up to that point, along with any other relevant study updates, how they will be monitored and what measures will be taken if a subject does experience an adverse event.

For each blood draw, approximately 5 mL of blood will be drawn from the subject.

At Visit 1, 2, 3, 4, 5, (Day -28, Day 1, Day 28, Day 56, Day 84) and All Sequential Visits

For the period during which COVID-19 contingency plans are in place at Partners/MGH, all study visits, including the Screening Visit, will be conducted as telemedicine appointments through a PHS IS-approved Zoom software. A weblink will be provided to subjects ahead of each appointment.

For study visits conducted as telemedicine appointments, required study procedures will be performed at sites local to the subject. We will provide each subject with location and scheduling information for their respective local site. The required study procedures that will be performed locally are:

- Echocardiograms (Visits 1, 5 and Extension Visits 1 and 2)
- Labs (CBC, CMP, AED) (as required by Principal Investigator)

Echocardiograms, and labs (CBC, CMP, AED) conducted locally will be sent to the Principal Investigator to ensure patient safety, and, in the case of ECHOs returning positive results, will be sent to a central reader, BioMedical Systems, Inc. (BMS).

These visits will take about 2 hours. During these visits, the following will be conducted:

- All the study eligibility criteria will be reviewed to confirm that the subject is still eligible.
- The subjects past and current medical, neurological, and epilepsy history will be reviewed at Visit 1 only.
- The study doctor will review the subject's current epilepsy status from the previous visit including: the amount of seizures they had, the types of seizures they experienced, and the duration of each of their seizure types.
- The subject will be asked about their health and the medicines that they have taken or are currently taking.
- Perform a physical and neurological exam. These exams are a series of simple questions and tests that provide very important information about the subject's systems. During the neurological exam, the treatment doctor will ask the subject to stand straight and walk, see how well the subject can move during the visit, and talk to the subject to see how they are doing. The treatment doctor will also look at the subject's eyes and see how their face, arms, and legs feel when touched.
- Vital signs including: blood pressure, heart rate, respiratory rate, along with height, and weight will be measured.
- If the subject is a female and able to become pregnant, a urine or blood pregnancy test will be done at every visit. The subject will not be allowed to enter or continue in the study if they are pregnant. If given permission, we will tell their parents the results of the test. If no permission is given, the study doctor may decide, based on the subject's age, maturity, or medical condition, to tell the subjects parents this information.
- Laboratory tests will be done. Approximately 5 mL (approximately 1 teaspoons) of blood will be taken from the subject's arm using a needle. The blood sample will be tested for: complete blood count with differential (CBC with diff) and a complete metabolic panel on Visits 1, 2, 3, 4, 5, and all subsequent visits. Current anticonvulsant medication levels will be tested on Visits 1, 3, 5, and on other Visits as clinically indicated. Laboratory tests will be completed locally and results sent to the Principal Investigator to ensure patient safety.

- The subject's seizure diary will be reviewed with the subject and/or their parent/caregiver. The subject and/or their parent/caregiver will record in their paper seizure diary daily. All of the subject's seizure types, along with the frequency and duration of each seizure, will be recorded in the subject's seizure diary. The subject and/or their parent/caregiver will record in the seizure diary if rescue medication was administered.
- Review of any current adverse events and/or adverse events of special interest experienced by the subject after the previous visit.
- The subject will be provided with new study drug bottles.
- During Visit 1, 5, and 7, a 4 to 6 hour electroencephalogram (EEG) will be performed (only for patients 1-10). This procedure will be done in order to analyze electrical activity in the brain. Changes in the brain wave patterns as well as photo paroxysmal response will be monitored.
- At Visit 1, 5 and all subsequent visits a Doppler echocardiogram (ECHO) will be done using ultrasound waves for examination of the heart. This will be performed at a cardiology clinic/office which may be separate from the study doctor's office, and may be done on a different day. The subject might receive a sedative medication for this procedure if they cannot be still for the test. In this test, the subject will be lying on a bed and a person will move a wand on their chest. This transmits information to a monitor to tell how well the subject's heart beats and moves inside their chest. It may also indicate if the subject has an increase in blood pressure in the arteries in their lungs. ECHOs will be completed locally and, if positive results are returned, it will be sent to a central reader, BioMedical Systems, Inc. (BMS) to ensure patient safety.
- At Visit 2, 5, and all subsequent visits, the subject and/or the subject's parent/caregiver will be asked to complete the following:
    - The Columbia-Suicide Severity Rating Scale (C-SSRS) questionnaire to see if they have ever thought about harming or killing themselves or behaved like they wanted to harm or kill themselves, if applicable.
    - Premonitory Urge Scale
    - If the subject is between 7-18 years he/she will be asked to complete:
        - the Beck Self Report Inventory – to assess self-concept, depression, anxiety, anger and disruptive behaviors
        - Children's Florida Obsessive-Compulsive Inventory

        - Children's Yale-Brown Obsessive-Compulsive symptoms
    - If the subject's age is 18 years or older he/she will be asked to complete:
        - Beck depression inventory.
        - Beck Anxiety inventory
        - Yale-Brown Obsessive-Compulsive symptoms
    - The subject's caregiver/parent will be asked to complete questionnaires to measure the subject's health as it relates to quality of life, and how their condition affects their day-to-day activities and health. The questionnaires that will be given include:
        - Behavioral Rating Inventory of Executive Function (BRIEF) – to assess executive function
        - Quality of Life in Childhood Epilepsy Questionnaire (QOLCE) – to assess mood, social relationships, behaviors)
        - Attention Deficit Hyperactivity Disorder (ADHD) checklist – to assess for hyperactivity and inattention
- At Visit 2, Visit 5, and Visit 7, Neuropsychological testing will be done to assess cognitive function using the following tests (only for patients 1-10):
        - Weschler Abbreviated Scale of Intelligence (WASI-II subtests)
    - If the subject is between 7-16 years he/she will be asked to complete:
        - Weschler Intelligence Scale for Children (WISC-IV) - Working Memory subtests
        - Weschler Intelligence Scale for Children (WISC-IV) - Processing Speed subtests
    - If the subject's age is 16 years or older he/she will be asked to complete:
        - Weschler Adult Intelligence Scales IV (WAIS-IV)
        - WAIS IV Coding and symbol search
    - If a study visit is conducted via virtual visit, we will send subjects and their parent/caregiver the questionnaires via mail and the subjects will return them back to us after completion at the study visit.

Safety Telephone Calls (Day 14, Day 42, Day 70)

At times during the study, the site personnel will call the subject and/or their parent/caregiver to see if they are adjusting well and whether they are having any difficulties on the medication. The subject will be

contacted by the study team by telephone at day 14, day 42, and day 70after the start of study drug and the following will be discussed:

1. Review of any current adverse events and/or adverse events of special interest that the subject has experienced.
2. Review of all medicines the subject is currently taking.

Virtual Visits

Virtual visits will be conducted in between scheduled clinic visits in the extension portion of the study to assess patient wellbeing. After a year of follow up in the extension period, virtual visits will be conducted as deemed necessary by the LPI. Partners enterprise platforms (Patient Gateway) will be used to conduct these visits.

Post-Dosing Telephone Follow-Up Visit (14 Days After Last Dose of ZX008)

After the subject has completed the study, or discontinues from the study early, the site personnel will call the subject and/or their parent/caregiver at the Post-Dosing Telephone Follow-Up Visit (14 days after the day of discontinuation):

- Review the subject's current epilepsy status since the previous visit including: the amount of seizures they had, the types of seizures they experience, and the duration of each of their seizure types.
- Review about how the subject is feeling and what medicines they have taken.
- Review of any current adverse events and/or adverse events of special interest experienced by them, after the previous visit.
- The subject's seizure diary will be reviewed with them or their parent/caregiver.

Cardiac Follow-up (3 Months After Last Dose of ZX008): to examine the heart

If the subject has taken study medication for longer than 14 days and then leaves the study, or if the subject completes the study, the study doctor will perform the following tests and procedures after 3 months of study treatment discontinuation. If a problem with the subject's

heart is detected, these procedures might be repeated after another 3 months:

- The study doctor will examine the subject (physical examination).
- A Doppler ECHO will be done using sound waves for examination of the heart. The subject may receive a sedative medication for this procedure if they cannot be still for the test.
- Review of any side effects related to heart safety experienced by the subject after the previous visit.

If the subject is found to have positive findings on ECHO and/or physical examination at the 3-month post dose follow-up the subject will have repeat examinations at 6 months post-dose and then every 3 months until the finding is resolved or stable and unlikely to change, with reports submitted to the ZX008 safety database.

Shipment of ZX008 study drug

If Study Visit 2 is conducted as a telemedicine appointment, we will ship a supply of ZX008 to the subject's home via FedEx to arrive on the day of the scheduled Study Visit 2. If it arrives prior to this visit, or if the visit is re-scheduled for any reason, the subject will be advised not to administer any study drug prior to the study visit and to store it in a cool, dry place at room temperature.

Shipments of ZX008 will be sent to subject's homes via FedEx as they require new supply. Study staff will review the schedule of these shipments with the subject as they may vary for each subject.

VI. BIOSTATISTICAL ANALYSIS

The data variables to be collected from each subject will include:

- The number and type of seizures occurring per day
- The duration of the seizures
- Complete blood count with differential (CBC with diff), a complete metabolic panel, and current levels of anticonvulsant medication levels
- EEG patterns
- Quality of life assessments

VII. RISKS AND DISCOMFORTS

Risks of Taking ZX008

Any research study has risks, which may include things that could make the subject sick, make the subject feel uncomfortable, or harm them. The subject might experience side effects related to the treatment drug while participating in the treatment. The subject will be watched carefully for any side effects; however, the study team does not know all the effects that ZX008 may have on the subject. The study team may give the subject medicines to help reduce side effects. These side effects may be mild or serious. In some cases, these side effects might be long lasting, or permanent, and may even be life threatening.

Allergic Reaction:

Any drug has a possible risk for an allergic reaction. If the subject has any symptoms that could be an allergic reaction such as feeling faint, having skin swelling, or having difficulty breathing, or experience any worrying health issue, they should seek immediate local medical assistance and then contact the study site.

Thickening of Heart Valves; Pulmonary Hypertension:

When the active ingredient in ZX008, fenfluramine, was on the market for the treatment of obesity in adults who were overweight from the 1970s through the 1990s, some adults developed thickening of heart valves and pulmonary hypertension (high pressure in blood vessels in the lung that makes it difficult to breathe normally). After stopping the medication, some patients' heart valves returned to normal, some remained stable but abnormal, and some had surgery to correct the condition. Generally, if these problems do occur, they develop slowly over time. The subject will be administered ECHOs during the study to very carefully watch for early signs that the subject's heart valves are thickening and to look for early signs of pulmonary hypertension. If there are heart valve changes, the subject will re-review the risk and potential benefit of the study medication with the study doctor and discuss further options. The subject may withdraw at this or any other time. If the subject experiences any chest pain, persistent cough, shortness of breath, wheezing, extreme fatigue, or dizziness, they should contact the study staff immediately to discuss whether they should have a clinic visit or other tests.

If a Subject Has a Positive Finding on Their Echocardiogram:

A positive finding on one of the echocardiograms may indicate that one or more of the subject's heart's valves are not functioning normally. This detected abnormality may not be associated with any physical symptoms. There are four valves in the heart: the aortic, mitral, tricuspid, and pulmonary. If one or more of these valves are not working properly and the subject continues in this study, they may be at an increased risk. We cannot know for certain whether a positive finding is the result of ZX008 and we do not know for certain whether the condition will worsen with continued use of ZX008. Some adults who have taken the same medication components in ZX008 and developed heart abnormalities have remained stable for years, while some adults who have taken the medication for obesity (excess overweight) developed heart problems that interfered with daily activities, and a small number have needed surgery or a procedure to improve heart function.

All ECHOs will be evaluated by a central reader from BioMedical Systems, Inc. (BMS). The primary investigator and local cardiologist will receive notification in the event of any ECHO findings consistent with pulmonary hypertension or valvulopathy on any of the four valves (aortic, mitral, pulmonary, tricuspid) 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 1 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
Trace (≤18 years)	Level 2	Level 2	Level 1	Level 1
Trace (>18 years)	Level 1	Level 1	Level 1	Level 1
Mild (≤18 years)	Level 2	Level 2	Level 1	Level 1
Mild (>18 years)	Level 2	Level 1	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 principal 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 principal investigator will consider whether the subject has had reasonable trials (dose and duration) of other available anticonvulsants, alone or in combination, and not maintained the level of seizure control currently achieved with study medication.
2. If the principal 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 statement acknowledging their understanding of the positive findings and possible risks associated with continuing in the study. The child should provide assent if appropriate. If both of these conditions are not met, the subject is discontinued from treatment.
3. The principal investigator prepares a case history and rationale for continuation to review with the local cardiologist, including consideration of effects on seizures and comorbidities.
4. The principal investigator and local cardiologist will 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 principal 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 for consideration:

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, alone or in combination, and not maintained the level of seizure control achieved with study medication.

2. If the principal 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 statement acknowledging their understanding of the positive findings and possible risks associated with continuing in the study. The child should provide assent if appropriate. If both of these conditions are not met, the subject is discontinued from treatment.
3. The principal investigator prepares a case history and rationale for continuation to review with the local cardiologist, including consideration of effects on seizures and comorbidities.
4. The principal investigator and local cardiologist will evaluate the risks and proposed monitoring plan, if applicable.
5. The principal investigator and local cardiologist will 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

Weight Decrease or Appetite Decrease

The study staff will take precautions against the possibility of weight loss and/or decreased appetite by monitoring weight at each study visit. If there is a notable decrease in weight or appetite, the study staff will refer the subject to a licensed dietician or gastrointestinal specialist. If it is determined that the weight loss is related to the study drug the LPI may decide to decrease the dose of study drug. This will be determined on a case to case basis.

Additional Risk

The subject taking part in this treatment involves some risks and possible discomfort as noted below:

- If the treatment does not work for the subject, the subject may see no change or an increase in their seizures. If there is an increase in seizure frequency the LPI may decide to lower the dose of the study drug or other seizure medications.
- The treatment drug may cause unpleasant side effects or reactions, as described below.
- Since ZX008 is investigational, there may be risks and side effects that are unknown. Any drug has a possible risk of an allergic reaction.

ZX008 (Fenfluramine Hydrochloride)

Animal Models:

Fenfluramine has been studied in young rats. In those studies, fenfluramine was given in doses similar to those the subject may receive and was shown to reduce activity and to induce learning and memory deficits. Fenfluramine was also shown to reduce certain chemicals in the brain, including serotonin, but the long-term effects of this are not known.

The relevance of the animal data to humans is not known. Not many learning and memory studies have been conducted with fenfluramine in humans. Of those that are published, the results are variable with some studies reporting no effect while other studies report some decrements or some improvements. Two studies have been conducted in children. Children were dosed daily for four weeks in one study and for four months in the other study. At the highest dose, which was 1.5 mg/kg/day in both studies, no adverse effects of fenfluramine were found on learning and memory tasks in either study.

In Human Trials:

The possible side effects of fenfluramine (as observed in 3 open-label studies involving pediatric and young adult populations with Dravet Syndrome at doses of up to 30 mg/ day) were:

- Somnolence (sleepiness/ drowsiness)

- Anorexia
- Status Epilepticus (a seizure lasting more than five minutes or when seizures occur close together and the person is not able to recover in between seizures for more than five minutes)
- Decreased appetite
- Abnormal behavior
- Mild heart valve thickening without clinical significance
- Seizures/Seizure cluster (seizure clusters are when seizures occur in groups over several hours or days)
- Vomiting

In addition, fenfluramine has been studied in 13 clinical trials in an obese adult population at doses of 60-120 mg/day. The commonly reported adverse events from these trials were**:**

Most Common Adverse Events (15-16% of study subjects had these symptoms):

- Diarrhea
- Drowsiness

Less Frequent Adverse Events (2-7% of study subjects):

- Dizziness
- Elevated mood
- Frequent urination
- Headache
- Insomnia
- Tiredness

Fenfluramine has also been studied in small trials in children and adolescents with autism and/or ADHD (attention deficit hyperactivity disorder). The commonly reported adverse events from these trials were:

- Drowsiness
- Increased withdrawal symptoms
- Irritability
- Lack of energy
- Sleeplessness (insomnia)
- Weight Loss

Risks from the study procedures:

- **Blood Sample Collection**: Taking blood from the subject's arm may sometimes cause pain/discomfort at the site where the blood is drawn, bruising, bleeding, occasional lightheadedness, redness, and/or swelling, and, rarely, feeling faint or infection.
- **EEG (electroencephalogram)**: Skin irritation is rare but could occur during or after an EEG from the sensors, gel, or glue that is used.
- **ECHO (echocardiogram)**: An ECHO is a test that uses sound waves to examine the subject's heart. A technician will place sensors on the subject's chest that are connected by wires to a machine and the technician will then move a wand over their chest. The wand may have a small amount of cool gel on the end to make it move more easily. The subject may feel some pressure on the chest during this procedure. If they need to receive a sedative because they are unable to stay still for this procedure, the subject may experience extra sleepiness, slow or difficult breathing, a drop in blood pressure, feeling sick to their stomach, vomiting (throwing up), restlessness, or not knowing where they are when they wake up.
- **Questionnaires**: A questionnaire may contain questions that are sensitive in nature. The subject and/or their caregiver/parent may refuse to answer any question that makes them feel uncomfortable. If the subject has concerns after completing the questionnaire, they should talk to their study doctor.
- **Reproductive risks**: The subject should not become pregnant or father a baby while on this study because it is not known whether the drugs in this study can affect an unborn baby. Females should not breastfeed a baby while on this study. It is important to understand that if the subject is able to become pregnant or father a baby they need to use birth control while on this study. The subject should check with their study doctor about what kind of birth control methods to use and how long to use them. Some methods might not be approved for use in this study. If the subject is capable of having a baby, their blood will be tested to confirm that they are not pregnant.
- **Unknown Risks**: The experimental treatment may have side effects that no one knows about yet. The study staff will let the subject know if they learn anything that might make the subject change their mind about participating in the study.

As with all studies, there is a potential to breach confidentiality. Assigning a study number and keeping the log in a safe physical or electronic place will reduce the risk.

Additionally, if the study treatment does not work for the subject, they may see no change or an increase in their seizures. ZX008 may cause unpleasant side effects or reactions. Since ZX008 is an investigational medication, there may be risks and side effects that are unknown.

Pregnancy/Birth Control

Women

If this subject is a female who is not able to have children, i.e. they are permanently sterile (when a female is unable to have children after surgical removal of female reproductive organ), they do not need to use any birth control methods.

Taking ZX008 may involve unknown risks to a pregnant female, an embryo, fetus (unborn baby), or nursing infant. Therefore, if the subject is pregnant, planning to become pregnant, or are breastfeeding a child, the subject cannot take part in this study.

Before entering the study, a blood pregnancy test will be done for all women who are able to become pregnant. This test might not detect an early pregnancy. Pregnancy tests will be repeated during the study.

Any female in the study who is sexually active and is able to have children must use, with her partner, approved methods of highly effective birth control from the time of signing informed consent through 90 days after the last dose of study drug. If the subject is already using a method of birth control, the study doctor or study staff will discuss with the subject whether their current method of birth control is acceptable for use during this study. Methods of effective birth control include surgical sterilization (for example, "vasectomy"); hormonal contraceptives such as birth control pills, the patch, intrauterine device, etc.

If during the study, the subject becomes pregnant, they should tell the study doctor as soon as possible. The study medication will be stopped, the subject will be discontinued from the study, and the study doctor will ask that the subject give updates about the outcome of the pregnancy.

Men

If the subject is a male and sexually active with a partner who is able to have children, the subject and his partner should be compliant with

a highly effective method of birth control consistently from the time of signing informed consent through 90 days after the last dose of study drug. Acceptable methods of birth control include condom for the subject plus hormonal contraceptives, such as birth control pills, the patch, intrauterine device, etc. for their partner; or surgical sterilization (for example, "vasectomy"). The study doctor will discuss and suggest the appropriate method of birth control for the subject while they are in this study.

If during the study, the subject's partner becomes pregnant, they should tell the study doctor as soon as possible. In this situation, the study doctor can either withdraw the subject from the study or if not, he/she will ask the subject to give updates about the outcome of their partner's pregnancy.

Alternatively, true abstinence is acceptable when it is in line with the subject's preferred and usual lifestyle. If a subject is usually not sexually active but becomes active, they, with their partner, they must comply with the contraceptive requirements detailed above.

Male subjects should not donate sperm and female subjects should refrain from egg donation for the duration of the study and for at least 90 days after the last day of study medication administration.

VIII. POTENTIAL BENEFITS

Potential benefits to participating subjects include the possibility for a reduction in seizure frequency and/or severity.

This study will elucidate the effects of fenfluramine hydrochloride (ZX008) on the improvement of seizures in children and young adults with Sunflower Syndrome. Additionally, should the investigation drug be effective, this study will provide new information about the safety, tolerability, and appropriate dosing for ZX008 in the treatment of Sunflower Syndrome.

IX. MONITORING AND QUALITY ASSURANCE

The LPI and clinical research nurses will review all data relating to safety and tolerability throughout the study to monitor compliance and assess subject safety.

Reporting of Adverse Events: The Institution and Investigator shall follow the same standards as a normal healthcare professional to report observed or reported adverse events to the FDA (https://www.accessdata.fda.gov/scripts/medwatch/) and notification regarding any serious adverse events (SAEs) or ECHO findings consistent with cardiac valvulopathy or pulmonary hypertension to ZOGENIX either by phone at 1-866-964-3649 or via email Zogenix@druginfo.com

All problems having to do with subject safety related to the treatment drug will be documented, including adverse events (AE) and serious adverse events (SAE). Some SAEs might necessitate withdrawing from the study. Serious adverse events would be those which could result in death, are life threatening, require inpatient hospitalization, result in a persistent or significant disability/incapacity, or any other adverse event that, based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention. If the subject is withdrawn from the treatment due to an adverse event, the subject will be followed as frequently as necessary until resolution of the event.

Unexpected serious related adverse reactions will be reported to FDA as soon as possible, but no later than 15 calendar days following the initial receipt of information, as per FDA regulations. Unexpected fatal or life-threatening suspected adverse reactions will be reported to FDA as soon as possible, but no later than 7 calendar days following the initial receipt of the information, as per FDA regulations. Included in the report, will be:

- A detailed description of the adverse event
- The basis for determining that the event is unexpected in nature, severity, or frequency
- The basis for determining that the event is related or possibly related to the research procedures
- The basis for determining that the research places subjects at an increased risk of harm (i.e., a serious adverse event)
- Whether any changes to the research or other corrective actions are warranted

In addition to reporting adverse events to the Partner's IRB, the LPI will also report them to the FDA in the form of a written IND safety report. The IND safety report will be submitted on form 3500A and accompanied by form 1571.

The LPI will also monitor the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and make sure that study drug is being stored, dispensed, and accounted for according to specifications. The subjects will be closely monitored for side effects during the treatment period.

Parents/subjects are instructed how to administer the study drug at each study visit.
The subject will be withdrawn from the treatment for any of the following reasons:

1. Development of signs or symptoms indicative of cardiac valvulopathy or regurgitation (mitral, aortic, tricuspid, pulmonary valves), or pulmonary hypertension for which the local cardiologist and the investigator believe the benefit of continued participation does not outweigh the risk.
2. Subject is noncompliant with procedures set forth in the protocol in an ongoing or repeated manner.
3. Subject experiences an AE or SAE that warrants withdrawal from the treatment.
4. Clinically significant worsening of seizures, judged by investigator or caregiver such that treatment outside of the protocol and treatments other than ZX008 are assumed to be in the subject's best interest. Frequent or increased use of rescue medication may be considered indicative of worsening seizures.
5. It is the investigator's opinion that it is not in the subject's best interest to continue in the treatment.

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