DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 125797

WRITTEN REQUEST

Zogenix, Inc.
Attention: AJ Acker, RAC
Vice President, Global Regulatory Affairs
5858 Horton Street
Suite 455
Emeryville, CA 94608

Dear Mr. Acker:

Reference is made to your July 13, 2018 Proposed Pediatric Study Request for ZX008 (fenfluramine HCl) oral solution.

BACKGROUND:

There are few anti-epileptic drugs (AEDs) approved for the treatment of seizures in pediatric patients with Dravet syndrome or Lennox-Gastaut syndrome. Fenfluramine hydrochloride was originally approved in 1973 for use as an appetite suppressant, and it was withdrawn from the US market in 1997 due to association with cardiac valvulopathy and pulmonary hypertension.

Adequate and controlled clinical trials in patients with Dravet syndrome or Lennox-Gastaut syndrome below 2 years of age, including neonates, are not feasible due to the small population available for recruitment, the difficulty in making a definitive diagnosis in patients younger than 2 years of age, and the need for patients to have failed at least one AED to be considered refractory. Although Lennox-Gastaut syndrome is typically diagnosed in early childhood, the seizures associated with this disorder tend to be refractory and lifelong; treatment for these seizures continues through childhood and adulthood. Therefore, clinical trials evaluating the safety and efficacy of a drug to treat seizures associated with Lennox-Gastaut syndrome generally enroll both pediatric and adult patients.

To obtain needed pediatric information on fenfluramine hydrochloride, the Food and Drug Administration (FDA) is hereby making a formal Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act (the Act), as amended by the Food and Drug Administration Amendments Act of 2007, that you submit information from the studies described below.

- *Nonclinical studies:*

Nonclinical studies are not required.

- *Clinical studies:*

Study 1: Pharmacokinetic and tolerability study in pediatric patients from 2 years to 18 years of age with Dravet syndrome taking concomitant stiripentol.

Study 2: Randomized, double-blind, placebo-controlled efficacy and safety study of two adjunctive doses of fenfluramine hydrochloride in pediatric patients from 2 years to 18 years of age with Dravet syndrome.

Study 3: Randomized, double-blind, placebo-controlled efficacy and safety study of adjunctive use of fenfluramine hydrochloride in pediatric patients from 2 years to 18 years of age with Dravet syndrome, taking concurrent stiripentol.

Study 4: Randomized, double-blind, placebo-controlled efficacy and safety study of two adjunctive doses of fenfluramine hydrochloride in pediatric patients and adults from 2 to 35 years of age with Lennox-Gastaut syndrome. Long-term (at least 1 year) safety will also be evaluated.

Study 5: A long-term, open-label, multicenter safety study in pediatric patients from 2 to 18 years of age with Dravet syndrome.

- *Objective of each study:*

Study 1: To characterize the pharmacokinetics of fenfluramine hydrochloride with concomitant stiripentol in pediatric patients from 2 years to 18 years of age with Dravet syndrome.

Study 2: To determine the efficacy and safety of high- and low-dose fenfluramine hydrochloride compared with placebo in treating convulsive seizures in pediatric patients from 2 years to 18 years of age with Dravet syndrome.

Study 3: To determine the efficacy and safety of fenfluramine hydrochloride compared with placebo in treating convulsive seizures in pediatric patients from 2 years to 18 years of age with Dravet syndrome, taking concurrent stiripentol.

Study 4: To determine the efficacy and safety of high- and low-dose fenfluramine hydrochloride compared with placebo in treating drop seizures in pediatric patients and adults from 2 to 35 years of age with Lennox-Gastaut syndrome, and to demonstrate long-term safety of fenfluramine hydrochloride in patients with Lennox-Gastaut syndrome. At least 50% of pediatric patients must receive the highest recommended dose for the pediatric population during the long-term safety phase.

Study 5: Evaluate the long-term safety of fenfluramine hydrochloride in pediatric patients from 2 to 18 years of age with Dravet syndrome. At least 50% of patients must receive the highest recommended dose for the pediatric population.

- *Patients to be Studied:*
  - *Age groups in which studies will be performed:*

    Studies 1, 2, and 3: patients ages 2 years to 18 years with Dravet syndrome

    Study 4: patients ages 2 years to 35 years with Lennox-Gastaut syndrome

    Study 5: patients ages 2 years to 18 years with Dravet syndrome

  - *Number of patients to be studied:*

    Study 1: At least 18 patients with Dravet syndrome on concomitant stiripentol.

    Study 2: Sufficient number randomized to provide at least 80% power to compare treatment arms and placebo based on ITT population for the primary endpoint. Patients must be enrolled in each of the two following age ranges: <6 years and 6 to 18 years, with at least 25% of these patients in each of the age subgroups.

    Study 3: Sufficient number randomized to provide at least 80% power to compare treatment arm and placebo based on ITT population for the primary endpoint. Patients must be enrolled in each of the two following age ranges: <6 years and 6 to 18 years, with at least 25% of these patients in each of the age subgroups.

    Study 4: The study must randomize a sufficient number of patients to provide at least 80% power to detect a difference between treatment arms and placebo for the primary endpoint. Patients must be enrolled in each of the two following weight groups: <37.5 kg and ≥37.5 kg, with at least 25% of these patients in each of the weight subgroups. A minimum of 100 patients less than 18 years of age will be studied. At least 30 patients less than 18 years of age must be exposed to fenfluramine hydrochloride for a period of at least 12 months.

    Study 5: At least 100 patients must be exposed to fenfluramine hydrochloride for a period of at least 12 months. At least 25% of patients must be enrolled in each of the two following age ranges: 2 to less than 6 years of age, and 6 to less than 18 years of age.

Representation of Ethnic and Racial Minorities: The studies must take into account adequate (e.g., proportionate to disease population) representation of children of ethnic and racial minorities. If you are not able to enroll an adequate number of these patients, provide a description of your efforts to do so and an explanation for why they were unsuccessful.

- *Study endpoints:*

(1) *Pharmacokinetic Endpoints (Studies 1-4):* The pharmacokinetic endpoints must include calculation of pharmacokinetic parameters such as average concentration at steady state (Css), apparent clearance (CL/F), and volume of distribution (V/F). Pharmacokinetic data from Study 1 should be combined with available pharmacokinetic data from other studies in pediatric and adult patients. Potential effects of covariates such as age, gender, body weight, and concomitant drugs (e.g., clobazam, stiripentol, and valproate) must be included in the analysis and used in the dosing selection of efficacy/safety studies, if deemed appropriate.

(2) *Efficacy Endpoints:*

Studies 2 and 3: The primary endpoint in this study must be a measure of the change in frequency of convulsive seizures per 28 days between the baseline and treatment periods. The treatment period will include the titration and maintenance periods. Analysis of non-convulsive seizures must be performed. You must include a simple descriptive breakdown of various types of seizures (e.g., tonic, tonic-atonic, tonic-clonic, clonic, partial onset, myoclonic, atypical absence). Routine demographic analysis must be included (e.g., age, sex, and race). Compliance must be monitored. Additional secondary efficacy endpoints may include responder rate and other evaluations.

Study 4: The primary endpoint in this study must be a measure of the change in frequency of drop seizures per 28 days between the baseline and treatment periods. The treatment period will include the titration and maintenance periods. Analysis of non-drop seizures must be performed. A simple descriptive breakdown of various types of seizures (e.g., tonic, tonic-atonic, tonic-clonic, clonic, partial onset, myoclonic, atypical absence) must be included. Routine demographic analysis must be included (e.g., age, sex, and race). Compliance must be monitored. Additional secondary efficacy endpoints may include responder rate analysis and other evaluations.

(2) *Safety Endpoints (All Studies):* Routine safety evaluation must include monitoring for adverse events, clinical laboratories (hematology, blood chemistry, and urinalysis), vital signs and ECGs. Safety data must be summarized by age or weight cohort, as described above. In addition, growth must be assessed for this population by careful measurements of length or height (measured by a stadiometer in patients of appropriate age) and weight at each visit. Assessment of cardiac valves and pulmonary arterial pressure must be performed using a validated, age-appropriate metric (via echocardiography), along with clinical assessment of cardiac and pulmonary status. Doppler echocardiography must be performed, when feasible. Additional known safety concerns must be monitored as described in the section below.

Data Monitoring Committee: A Data Monitoring Committee (DMC) must be included because efficacy has not been established in the pediatric populations under study and because of significant cardiac and pulmonary adverse drug effects reported in adult patients with the use of fenfluramine hydrochloride. See Guidance: Establishment and Operation of

Clinical Trial Data Monitoring Committees
http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126578.pdf.

- *Known Drug Safety concerns and monitoring:*
  - *Cardiac Valvulopathy and Pulmonary Hypertension:*

    Because of serious or life-threatening cardiac valvular changes and pulmonary hypertension reported with use of fenfluramine hydrochloride, cardiac and pulmonary monitoring must be performed using a validated, age-appropriate metric (echocardiography), along with clinical assessment of cardiac function (via history and physical examination). Doppler echocardiography must be performed, when feasible. The risk of cardiac valvulopathy and pulmonary hypertension must be described in the informed consent. Agreement must be reached with the Agency on cardiac and pulmonary testing/monitoring.

  - *Suicidality:*

    Suicidality must be clinically assessed in patients ages 6 years and older at the time consent/assent and as appropriate throughout the study. The risk of suicidality must be described in the informed consent.

  - *Neurologic Effects:*

    Fenfluramine hydrochloride has been shown to enhance serotonergic activity and thus must be monitored for potential development of serotonin syndrome. Patients must be monitored for the following signs and/or symptoms: agitation, restlessness, confusion, increased heart rate and blood pressure, dilated pupils, muscle twitching, muscle rigidity, hyperhidrosis, diarrhea, headache, shivering, tremors, nausea and vomiting, hallucinations, psychosis, euphoria, mood disorders, and suicidality. These events can be monitored through adverse event reporting. The risk of neurologic effects must be described in the informed consent.

  - *Metabolic/Endocrine Effects:*

    Several metabolic and endocrine reactions have been potentially linked to fenfluramine hydrochloride, possibly related to its appetite suppressant effect. Patients must be monitored for elevated prolactin, galactorrhea, gynecomastia, hypoglycemia, and elevated fasting serum glucose. The risk of metabolic/endocrine effects must be described in the informed consent, and parents/guardians must be warned verbally about this risk. Additionally, a caution to investigators to consider diabetic medication changes in the setting of weight loss and potential hypoglycemia should be included.

  - *Vital Signs:*

    Weight loss has been observed with fenfluramine hydrochloride and must be monitored at baseline and at appropriate intervals during treatment.

    Height and/or length must be assessed at baseline and at appropriate intervals as agreed upon in the protocol during treatment using standardized and replicated techniques (such as stadiometry).

- *Extraordinary results:* In the course of conducting these studies, you may discover evidence to indicate that there are unexpected safety concerns, unexpected findings of benefit in a smaller sample size, or other unexpected results. In the event of such findings, there may be a need to deviate from the requirements of this Written Request. If you believe this is the case, you must contact the Agency to seek an amendment. It is solely within the Agency's discretion to decide whether it is appropriate to issue an amendment.

- *Drug information:*
  - *Dosage form:* an age appropriate dosage formulation must be used.
  - *Route of administration:* as appropriate to age and underlying disorder.
  - *Regimen:* an appropriate regimen as specified by the study protocol and agreed upon by the Agency.

  Use an age-appropriate formulation in the studies described above. If an age-appropriate formulation is not currently available, you must develop and test an age-appropriate formulation and, if it is found safe and effective in the studied pediatric populations, you must seek marketing approval for that age-appropriate formulation.

  In accordance with section 505A(e)(2), if

  1) you develop an age appropriate formulation that is found to be safe and effective in the pediatric population(s) studied (i.e. receives approval);
  2) the Agency grants pediatric exclusivity, including publishing the exclusivity determination notice required under section 505A(e)(1) of the Act; and
  3) you have not marketed the formulation within one year after the Agency publishes such notice,

  the Agency will publish a second notice indicating you have not marketed the new pediatric formulation.

  If you demonstrate that reasonable attempts to develop a commercially marketable formulation have failed, you must develop and test an age-appropriate formulation that can be prepared by a licensed pharmacist, in a licensed pharmacy, from commercially available ingredients. Under these circumstances, you must provide the Agency with documentation of your attempts to develop such a formulation and the reasons such attempts failed. If we agree that you have valid reasons for not developing a commercially marketable, age-appropriate formulation, then you must submit instructions for preparing an age appropriate formulation from commercially available ingredients that are acceptable to the Agency. If you conduct the requested studies using such a formulation, the following information must be provided for inclusion in the product labeling upon approval: active ingredients, diluents, suspending and sweetening agents; detailed step-by-step preparation instructions; packaging and storage requirements; and formulation stability information.

Bioavailability of any formulation used in the studies must be characterized, and, as needed, a relative bioavailability study comparing the approved drug to the age appropriate formulation may be conducted in adults.

- *Statistical information, including power of studies and statistical assessments:*

  Study 1: At least 18 patients from 2 years to 18 years of age must be studied in order to adequately characterize the pharmacokinetics of fenfluramine and to detect effects of covariates.

  Studies 2 and 3: The primary endpoint should be analyzed using an analysis of covariance (ANCOVA) model with age groups (< 6 years, > 6 years) as a factor and baseline convulsive seizure frequency as a covariate, or using an appropriate non-parametric method such as an ANCOVA on ranked data. All statistical tests must be at two-sided significance level of 0.05. The protocol must include provisions to limit missing data through the study design, monitoring and the education of investigators and patients, and pre-specify analysis methods to account for missing data for the primary and key secondary efficacy analyses. The statistical analysis plan must be reviewed and agreed upon by the Agency. Descriptive statistics should be used for the analysis of safety.

  Study 4: The primary endpoint should be analyzed using an analysis of covariance (ANCOVA) with weight group (< 37.5 kg, > 37.5 kg), and age group (<18 years, >18 years) as factors and baseline drop seizure frequency as a covariate, or using an appropriate non-parametric method such as an ANCOVA on ranked data. All statistical tests must be at two-sided significance level of 0.05. The protocol must include provisions to limit missing data through the study design, monitoring and the education of investigators and patients, and pre-specify analysis methods to account for missing data for the primary and key secondary efficacy analyses. The statistical analysis plan must be reviewed and agreed upon by the Agency. Descriptive statistics should be used for the analysis of safety.

  Study 5: Descriptive statistics should be used for the analysis of safety.

- *Labeling that may result from the studies:* You must submit proposed pediatric labeling to incorporate the findings of the studies. Under section 505A(j) of the Act, regardless of whether the studies demonstrate that perampanel is safe and effective, or whether such study results are inconclusive in the studied pediatric populations or subpopulations, the labeling must include information about the results of the studies. Under section 505A(k)(2) of the Act, you must distribute to physicians and other health care providers at least annually (or more frequently if FDA determines that it would be beneficial to the public health), information regarding such labeling changes that are approved as a result of the studies.
- *Format and types of reports to be submitted:* You must submit full study reports (which have not been previously submitted to the Agency) that address issues outlined in this request, with full analysis, assessment, and interpretation. In addition, the reports must include information on the representation of pediatric patients of ethnic and racial minorities. All

pediatric patients enrolled in the studies should be categorized using one of the following designations for race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander or White. For ethnicity, you should use one of the following designations: Hispanic/Latino or Not Hispanic/Latino. If you choose to use other categories, you should obtain agency agreement.

Under section 505A(d)(2)(B) of the Act, when you submit the study reports, you must submit all postmarketing adverse event reports regarding this drug that are available to you at that time. All post-market reports that would be reportable under section 21 CFR 314.80 should include adverse events occurring in an adult or a pediatric patient. In general, the format of the post-market adverse event report should follow the model for a periodic safety update report described in the Guidance for Industry E2C Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs and the Guidance addendum. You are encouraged to contact the reviewing Division for further guidance.

Although not currently required, we request that study data be submitted electronically according to the Study Data Tabulation (SDTM) standard published by the Clinical Data Interchange Standards Consortium (CDISC) provided in the document "Study Data Specifications" which is posted on the http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM199759.pdf and referenced in the FDA Guidance for Industry, Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications at http://www.fda.gov/Cder/guidance/7087rev.htm.

- *Timeframe for submitting reports of the studies:* Reports of the above studies must be submitted to the Agency on or before August 31, 2021. Please keep in mind that pediatric exclusivity attaches only to existing patent protection or exclusivity that would otherwise expire nine (9) months or more after pediatric exclusivity is granted, and FDA has 180 days from the date that the study reports are submitted to make a pediatric exclusivity determination. Therefore, to ensure that a particular patent or exclusivity is eligible for pediatric exclusivity to attach, you are advised to submit the reports of the studies at least 15 months (9 moths plus 6 months/180 days for determination) before such patent or exclusivity is otherwise due to expire.

- *Response to Written Request:* Under section 505A(d)(2)(A)(i), within 180 days of receipt of this Written Request you must notify the Agency whether or not you agree to the Written Request. If you agree to the request, you must indicate when the pediatric studies will be initiated. If you do not agree to the request, you must indicate why you are declining to conduct the studies. If you decline on the grounds that it is not possible to develop the appropriate pediatric formulation, you must submit to us the reasons it cannot be developed.

  Furthermore, if you agree to conduct the studies, but have not submitted the study reports on or before the date specified in the Written Request, the Agency may utilize the process discussed in section 505A(n) of the Act.

Submit protocols for the above studies to an investigational new drug application (IND) and clearly mark your submission "**PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY"** in large font, bolded type at the beginning of the cover letter of the submission.

Reports of the studies must be submitted as a new drug application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF PEDIATRIC STUDY REPORTS - PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED**" in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. Please also send a copy of the cover letter of your submission to the Director, Office of Generic Drugs, CDER, FDA, Document Control Room, Metro Park North VII, 7620 Standish Place, Rockville, MD 20855-2773. If you wish to fax it, the fax number is 240-276-9327.

In accordance with section 505A(k)(1) of the Act, *Dissemination of Pediatric Information*, FDA must make available to the public the medical, statistical, and clinical pharmacology reviews of the pediatric studies conducted in response to this Written Request within 210 days of submission of your study report(s). These reviews will be posted regardless of the following circumstances:

1. The type of response to the Written Request (i.e., complete or partial response);
2. The status of the application (i.e., withdrawn after the supplement has been filed or pending);
3. The action taken (i.e., approval, complete response); or
4. The exclusivity determination (i.e., granted or denied).

FDA will post the medical, statistical, and clinical pharmacology reviews on the FDA website at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM049872.

If you wish to discuss any amendments to this Written Request, please submit proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request should be clearly marked "**PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES**" in large font, bolded type at the beginning of the cover letter of the submission. You will be notified in writing if any changes to this Written Request are agreed upon by the Agency.

Please note that, if your trial is considered an "applicable clinical trial" under section 402(j)(1)A)(i) of the Public Health Service Act (PHS Act), you are required to comply with the provisions of section 402(j) of the PHS Act with regard to registration of your trial and submission of trial results. Additional information on submission of such information can be found at www.ClinicalTrials.gov.

If you have any questions, contact Stephanie N. Parncutt, M.H.A., Senior Regulatory Health Project Manager, at (301) 796-4098 or Stephanie.Parncutt@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Ellis Unger, M.D.
Director
Office of Drug Evaluation 1
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ELLIS F UNGER
11/09/2018